Towards the Total Synthesis of Lactonamycin

A Thesis submitted by

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In partial fulfilment of the requirements for the degree of

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Declaration of Originality

I, Sylvain JACQUES, hereby confirm that I solely produced the presented thesis under the supervision of Professor Anthony G. M. Barrett at the Department of Chemistry, Imperial College London, and that I did not use any other material that cited or known to the public domain. Information derived from the published and unpublished work of others has been acknowledged in the text and a list of references is given in the bibliography

London, 23rd June 2011

Sylvain Jacques

Abstract

The natural product lactonamycin (**1**) was isolated in Japan by Matsomoto *et al.*. Biological evaluation of lactonamycin (**1**) against *Gram*-positive bacteria such as *Staphylococcus aureus* showed significant levels of antimicrobial activity and it was especially active against clinically isolated-MRSA and -VRE. In addition to interesting biological properties, lactonamycin (**1**) possesses an intriguing molecular architecture (Figure 1). The novel, highly functionalized hexacyclic aglycone core, known as lactonamycinone (**2**) contains, in the western half, a highly-oxygenated fused perhydrofuran-furanone bicycle connected to a labile tertiary methoxy group, and in the eastern half, a naphtha[*e*]isoindole ring system. Adding to the structural complexity of lactonamycin (**1**), a 2,3,6-trideoxy sugar unit is connected to the core *via* a highly hindered tertiary glycosidic linkage.

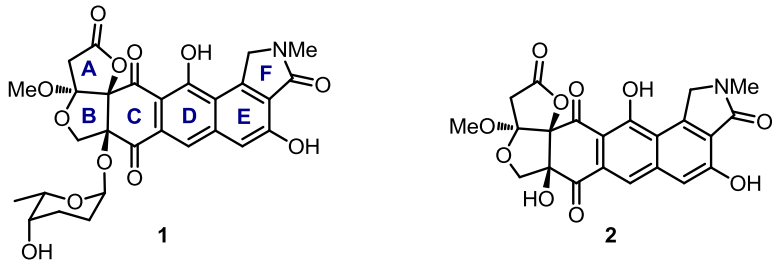

Figure 1 - Structures of lactonamycin (1) and lactonamycinone (2)

A key step in the current strategy is an electrodecarboxylation reaction to introduce the angular methoxy group. Various experiments towards this electrodecarboxylation reaction are described using simple model substrates. In particular, the synthesis of model system (**3**) and investigations towards ABCD tetracycle model system (**4**) are described alongside our efforts towards the synthesis of lactonamycin (**1**) (Figure 2). Finally, a new synthesis of known boronic ester **5** was investigated using the biomimetic resorcylate methodology developed in the group.

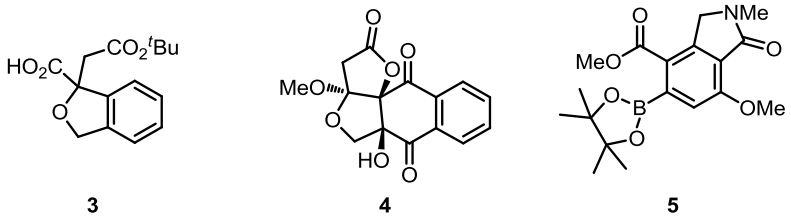

Figure 2 – Structures of carboxylic model system 3, ABCD tetracycle model system 4 and boronic ester 5

Acknowledgements

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Contents

Abbreviations

A	Ampere
Å	Angström
Ac	Acetyl
ACCN	1,1′-Azobis(cyclohexanecarbonitrile)
AIBN	Azobisisobutyronitrile
Anal.	Analysis
Aq.	Aqueous
Bn	Benzyl
BOC	*tert*-Butyl carbonate
BOM	Benzyloxymethyl
brsm	Based on recovered starting material
bs	Broad singlet
Bt	Benzotriazole
Bu	Butyl
Bz	Benzoate
°C	Degrees Celcius
CAN	Ceric ammonium nitrate
cat.	Catalytic
Cbz	Benzyl formate
CI	Chemical ionization
conc.	Concentrated
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
CuTC	Copper(I)-thiophene-2-carboxylate
δ	Chemical shift
d	Day
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIAD	Diisopropyl azodicarboxylate

DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
E	Electrophile
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	Electron ionization
EOM	Methyl ethyl ether
eq.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
et al.	*et alii*
g	Gram
GCSM	Gas chromatography–mass spectrometry
h	Hour
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
Hz	Hertz
i	*iso*
i.e.	*id est*
IC_{50}	Half maximal inhibitory concentration
IBX	2-Iodoxybenzoic acid
IR	Infra-red
J	Coupling constant
L	Litre
LDA	Lithium diisopropylamide
M	Molar
m	Mass
m/z	Mass-to-charge ratio

*m*CPBA	*meta*-Chloroperbenzoic acid
min	Minute
mL	Millilitre
Me	Methyl
mol	Mole
Mp	Melting point
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Mass spectrometry
N	Normal
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Ns	Nosyl
Ph	Phenyl
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PMB	*Para*-methoxy benzyl
PPA	Polyphosphoric acid
ppm	Parts per million
Pr	Propyl
psi	Pound per square inch
*p*TSA	*p*-Toluenesulfonic acid
Py	Pyridine
q	Quartet
R	General substituents
RAL	Resorcylic acid lactone
R*f*	Retention factor
rt	Room temperature
sat.	Saturated
SES	2-(Trimethylsilyl)ethanesulfonamide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl

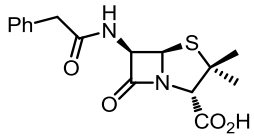
tert	Tertiary
Tf	Trifluoromethanesulfonyl (triflic)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFPAA	Trifluoroperacetic acid
THF	Tetrahydrofuran
TIPS	Tri-*iso*-propylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
o-tol	*o*-Tolyl
TTMSS	Tris(trimethylsilyl)silane
VRE	Vancomycin-resistant *Enterococcus*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
WSCI	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride

Chapter I General Introduction

1. Project background

1.1 The need for new antibiotics

One of the greatest discoveries of modern times was that of β-lactam penicillin (**6**) by Sir Alexander Fleming in the 1920s (Figure 3).[1] Unfortunately, Fleming was not able to isolate penicillin (**6**) and it was only in 1939 that Howard Florey, Ernst Chain, and Norman G. Heatley succeeded in the isolation of its active agent and they produced enough penicillin to conduct the first clinical tests.[2-4] Prior to the clinical introduction of penicillin in the 1940s and its development as an antimicrobial agent, bacteria were responsible for many of the world's most lethal diseases including pneumonia, plague, gangrene and tuberculosis.



6

Figure 3 – Structure of penicillin (6)

Unfortunately, it was not long before *Staphylococcus aureus* (*S. aureus*) strains became resistant and in the 1950s, up to 85% of clinically isolated *Staphylococci* were found to be penicillin resistant.[5] The pharmaceutical industry responded to this challenge with the synthesis of methicillin (**7**) (Figure 4), a β-lactamase stable agent, but once again the bacteria fought back to give methicillin resistant *Staphylococcus aureus* (MRSA).[6] Since then, despite the isolation and development of new antibacterial agents such as the cephalosporins,[7] glycopeptides,[8] the macrolide erythromycin B (**8**)[9] and tetracycline (**10**),[10] bacterial strains resistant to virtually all known antibiotics have emerged.[7]

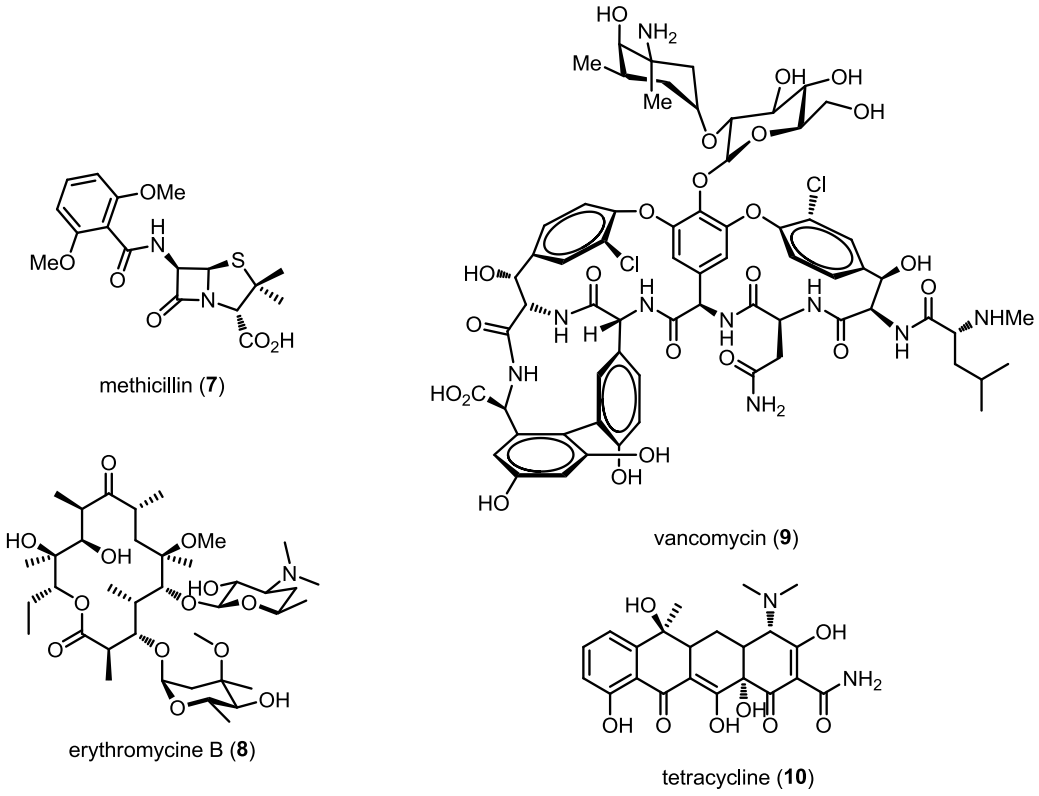


Figure 4 – Structures of different antibacterial agents

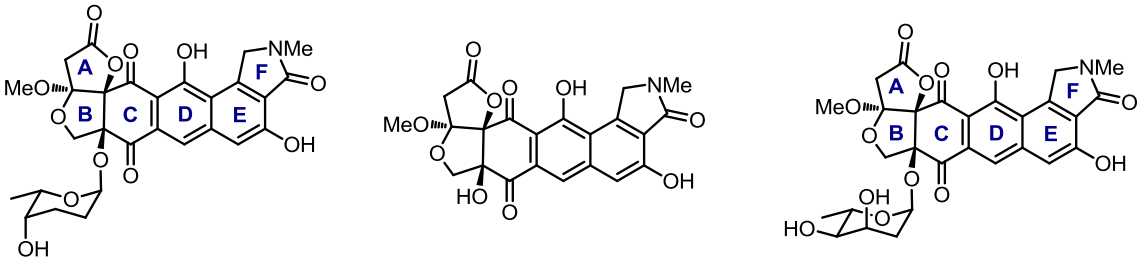
The emergence of MRSA as a major worldwide problem resulted in an increased use of vancomycin (**9**) (Figure 4), the only agent that effectively treats these bacteria.[11] However, in 1987, the hope that vancomycin would be a "cure-all" antibiotic came to an end when vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE) were discovered in hospitals.[12]

It is therefore evident that the continued evolution of bacteria must be matched by the discovery and development of new classes of antibiotics, or combination of antibiotic therapies, that are effective against resistant bacteria.

1.2 Lactonamycin (1)

The natural product (+)-lactonamycin (**1**) was first isolated from a culture broth of *Steptomyces rishiriensis* MJ773-88K4 obtained from a soil sample collected near Yokohama City, Japan in 1996 by

Matsomoto and co-workers (Figure 5).[13] Biological evaluation of lactonamycin (**1**) against *Gram*-positive bacteria such as *Staphylococcus aureus*, *Micrococcus luteus* or *Bacillus anthracis* showed significant levels of antimicrobial activity while lactonamycin (**1**) exhibited no antimicrobial activity against *Gram*-negative bacteria.[14] Remarkably, it was especially active against clinically isolated-MRSA and -VRE with minimum inhibitory concentration levels of 0.39 and 0.20 μg/mL, respectively. In addition, lactonamycin (**1**) showed significant levels of cytotoxicity against various tumor cell lines such as EL-4 (Leukemia), Ehrlich (Carcinoma) or S180 (Sarcoma) with IC_{50} values ranging from 0.06 to 3.30 μg/mL.[14]



1 **2** **11**

Figure 5 – Structures of lactonamycin (1), lactonamycinone (2) and lactonamycin-Z (11)

The interesting biological properties combined with the intriguing molecular architecture of lactonamycin (**1**) have generated considerable interest in the total synthesis of this complex and fascinating molecule. The novel, highly functionalized hexacyclic aglycone core, known as lactonamycinone (**2**) contains, in the western half, a highly-oxygenated fused perhydrofuran-furanone ring connected to a labile tertiary methoxy group, and in the eastern half, a naphtha[*e*]isoindole ring system (Figure 5). The natural products also each contain a 2-deoxy sugar unit (**1**, α-L-rhodinopyranose; **11**, α-L-2,6-dideoxyribopyranose) attached through a tertiary α-keto glycosidic linkage.[15]

In 2003, a closely related structure to that of lactonamycin (**1**), lactonamycin-Z (**11**) was reported. It was isolated from a culture of *Streptomyces sanglieri* AK 623 collected from a pine wood sample at Hamsterley Forest, UK by Fiedler and co-workers.[16] The structure of **11** was elucidated after NMR analysis as a new derivative of lactonamycin (**1**) with a 2,4,6-dideoxyribohexose as the sugar moiety. Weak activity against *Gram*-positive bacteria was found during analysis of the antibacterial properties of this compound.[16]

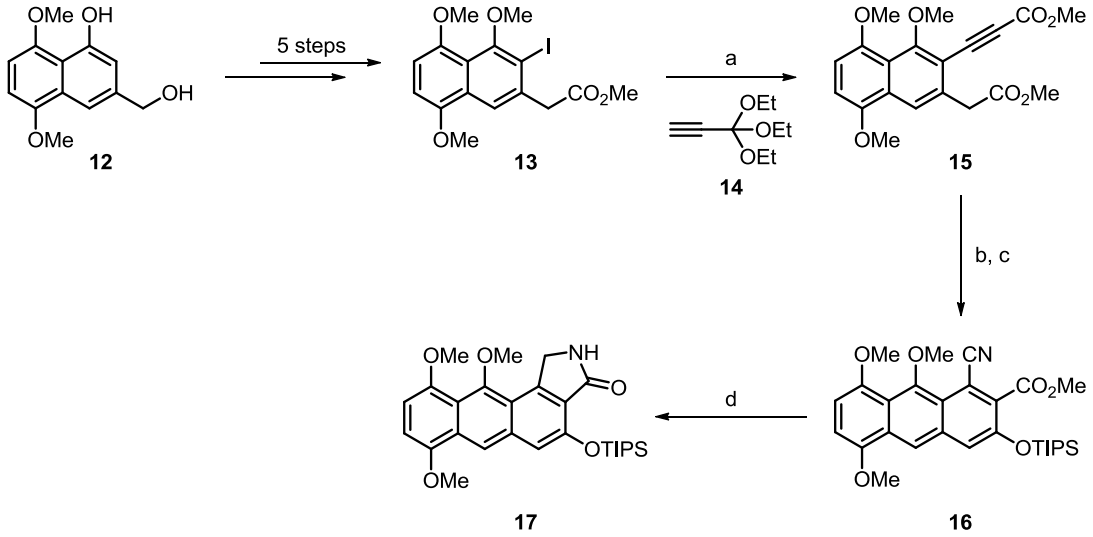
2. Published synthetic studies

Since the isolation of lactonamycin (**1**), synthetic studies have been reported by seven groups. Their investigations have focused on the construction of the ABCD[22,24,31] and CDEF[17,18,28,32a,32b] ring systems and more recently on the total synthesis of lactonamycinone (**2**) by Danishefsky and co-workers.[25,26] In 2010, Tatsuta *et al.* published the first total synthesis of lactonamycin (**1**).[30]

2.1 Behar's synthesis of the eastern aromatic core of lactonamycin (1)

In 2002, Behar and co-workers were the first of two groups to report the construction of the CDEF-ring system of lactonamycin (**1**).[17] Their approach was based on the construction of the isoindole ring through a conjugate cyanide addition into alkyne ester **15** followed by a Dieckmann condensation to give **16** after aromatisation. Selective reduction of the cyanide moiety and subsequent lactamisation allowed the formation of the eastern aromatic core of lactonamycin (**1**).

The synthesis started from the known naphthalene system **12** which was transformed in five steps to iodoester **13** (Scheme 1). Sonogashira coupling followed by *ortho* ester hydrolysis afforded substrate for cyclisation **15**. Cyclisation of **15** under the optimized conditions proceeded smoothly and the resultant phenol was protected as its TIPS ether, due to the instability of the phenol intermediate. Reduction of cyanide **16** followed by lactam formation gave anthracene **17** in 52% yield.

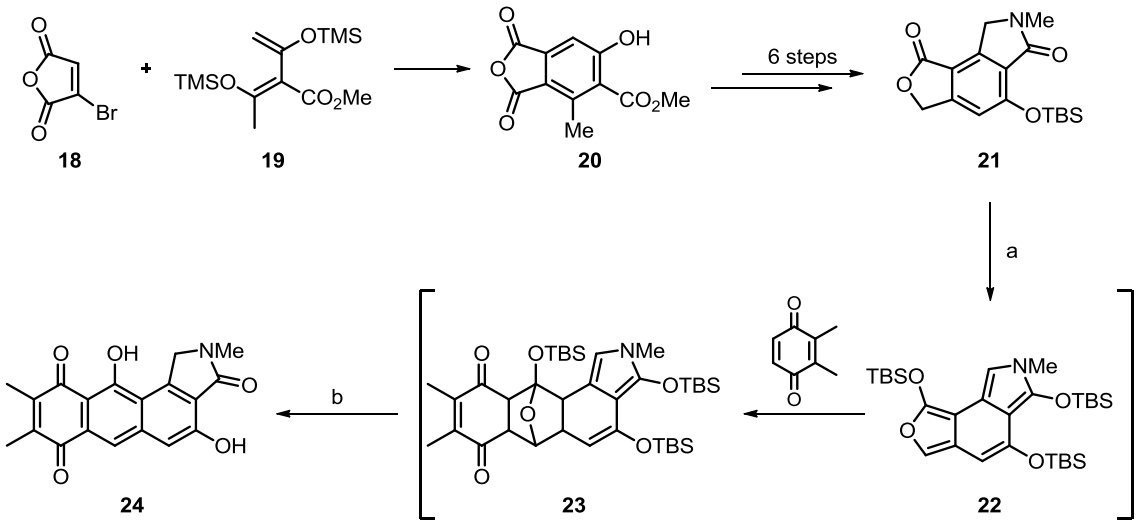


Scheme 1 – Behar's synthesis of CDEF ring system of lactonamycin (1)

Reagents and conditions: a) i) **14**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, MeCN, 0 °C to rt; ii) *p*TSA, MeOH, 97%; b) NaCN, DMSO; c) NaH, TIPSCl, DMF, 68% over 2 steps; d) $CoCl_2$, $NaBH_4$, MeOH/THF, 50 °C, 52%.

2.2 Kelly's approach towards CDEF ring system of lactonamycin (1)

In the same year, Kelly and co-workers published a short synthesis of the CDEF ring system of lactonamycin (**1**) using a key Diels-Alder reaction between tricycle **22** and 2,3-dimethylbenzoquinone.[18] Known anhydride **20** was prepared from bromide **18** and silyl enol ether **19** *via* a Diels-Alder reaction (Scheme 2) and transformed into **21** in six steps. Treatment of **21** with $KN(TMS)_2$ and TBSCl gave key intermediate **22** that reacted with 2,3-dimethylbenzoquinone to afford **23**. Direct treatment of **23** with trifluoroacetic acid resulted in the formation of desired product **24**.

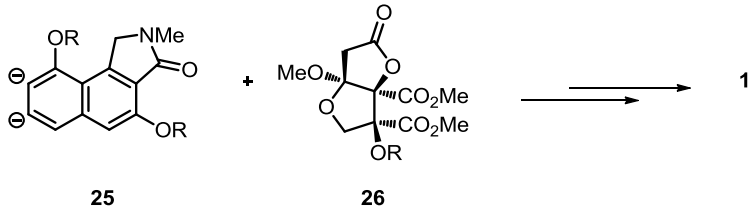


Scheme 2 – Kelly's approach to the CDEF ring system of lactonamycin (1)

Reagents and conditions: a) $KN(TMS)_2$, TBSCl; b) TFA, 74% over 2 steps.

2.3 Kelly's asymmetric synthesis of the AB ring system of lactonamycin (1)

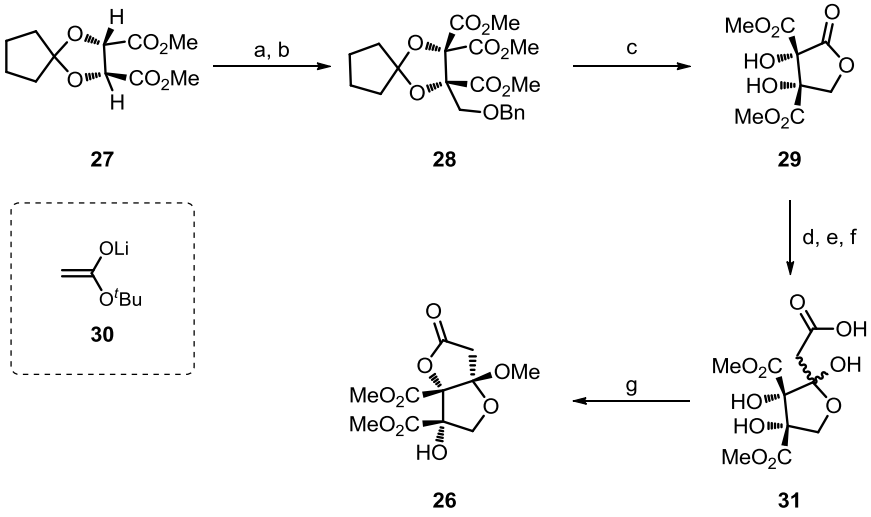
Two years after their first paper, Kelly and co-workers described their efforts towards the asymmetric synthesis of the AB ring system of lactonamycin (**1**).[19] Indeed, Kelly suggested that one possible approach could be the reaction between di-anion **25** and enantiomerically pure ester **26** (Scheme 3).



Scheme 3 – Kelly's approach for the application of enantiomerically pure diester 26 in the total synthesis of lactonamycin (1)

In eight steps, an enantiospecific synthesis of **26** was achieved starting from dimethyl D-tartrate (Scheme 4). Dimethyl D-tartrate was readily converted to the cyclopentylidene acetal **27**. The choice of this protecting group had proven to be crucial. Alkylation by LDA and BOMCl selectively gave one stereoisomer. Deprotonation of the remaining enolisable centre, followed by trapping of the resulting

enolate with methyl chloroformate yielded triester **28**. TFA deprotection of **28** followed by reprotection using benzaldehyde resulted in the formation of two diastereoisomers that reacted with the lithium enolate of *tert*-butylacetate in the presence of $TiCl_4$ to give desired lactol **31** after catalytic hydrogenation cleavage of the acetal protecting group. Treatment of **31** with CSA in methanol initiated a cascade reaction (methyl acetate formation, anomeric equilibration and lactone closure) to afford **26**.



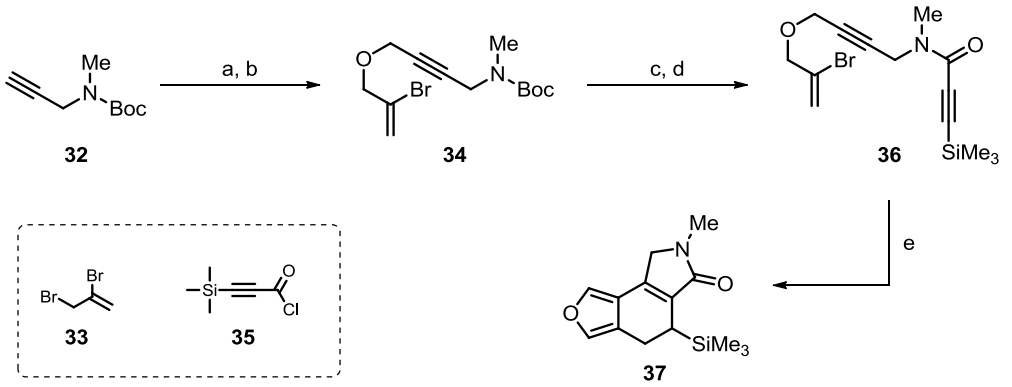
Scheme 4 – Synthesis of enantiomerically pure diester 26

Reagents and conditions: a) LDA, BOMCl, THF/HMPA, −78 °C, 60%; b) i) LDA, THF, −78°C; ii) MeO_2CCl, 66%; c) TFA, H_2O, CH_2Cl_2, sealed tube, 65 °C, 50-60%; d) PhCHO, PhH, *p*TSA, reflux, minor 30%, major 60%; e) **30**, $TiCl_4$, Et_2O, −40 °C, 62% (for minor), 41% (for major); f) H_2, Pd/C, MeOH; g) CSA, MeOH, reflux, 63% over 2 steps.

2.4 Parsons' strategy for the synthesis of lactonamycin (1)

Parsons and co-workers recently developed a new metal-free thermally induced cascade reaction for the synthesis of 3,4-disubstituted furans.[20] Key cyclisation precursor **36** was synthesized in four steps starting from *N*-Boc-*N*-methylpropargylamine **32** (Scheme 5). Treatment of **32** with *n*-BuLi and *para*-formaldehyde followed by reaction with sodium hydride and 2,3-dibromopropene **33** afforded ether **34**. Removal of the Boc protecting group with TFA followed by *N*-acylation with

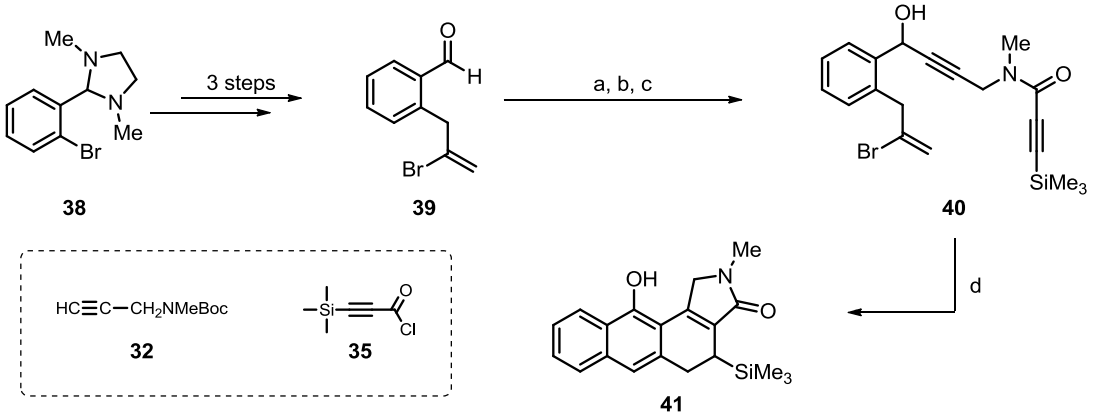
trimethylsilylpropyonyl chloride **35** gave the desired cyclisation precursor **36**. Refluxing **36** in toluene in the presence of ten equivalents of 1-epoxyhexene gave cyclized product **37** in 90%.



Scheme 5 – Parson's cascade synthesis of 3,4-disubstituted furan 37

Reagents and conditions: a) *n*-BuLi, $(CH_2O)_n$, −78 °C, 85%; b) **33**, NaH, THF, 81%; c) TFA, CH_2Cl_2; d) **35**, Et_3N, CH_2Cl_2, 85%; e) PhMe, 1-epoxyhexene, 110 °C, 1 h, 90%.

This novel cyclisation strategy was applied towards the construction of the CDEF ring system of lactonamycin (**1**) (Scheme 6).[21a,21b] Aldehyde **39** was obtained in three steps from known aminal **38**. Addition of **32** onto aldehyde **39** followed by removal of the *N*-Boc protection group and addition of trimethylsilylpropyonyl chloride **35** successfully gave the radical cyclisation precursor **40**. Refluxing **40** in toluene in the presence of 1-epoxyhexene gave the desired tetracycle **41** in 76% yield.



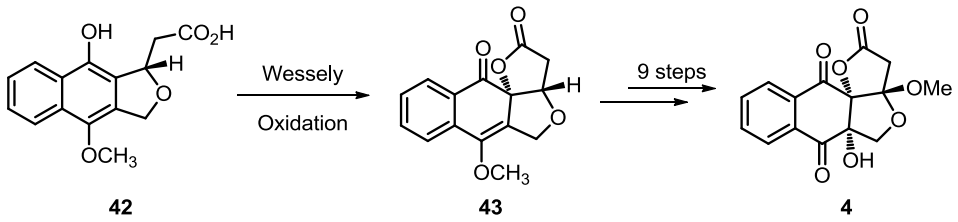
Scheme 6 – Parson's cascade reaction for the synthesis of CDEF ring system of lactonamycin (1)

Reagents and conditions: a) i) **32**, *n*-BuLi, THF, –90 °C; ii) *tert*-BuBr, –90 °C to rt, 83%; b) HCl [2 M in Et_2O]; c) **35**, Et_3N, CH_2Cl_2, 79%; d) PhMe, 1-epoxyhexene, 110 °C, 1 h, 76%.

2.5 Danishefsky's work on lactonamycin (1)

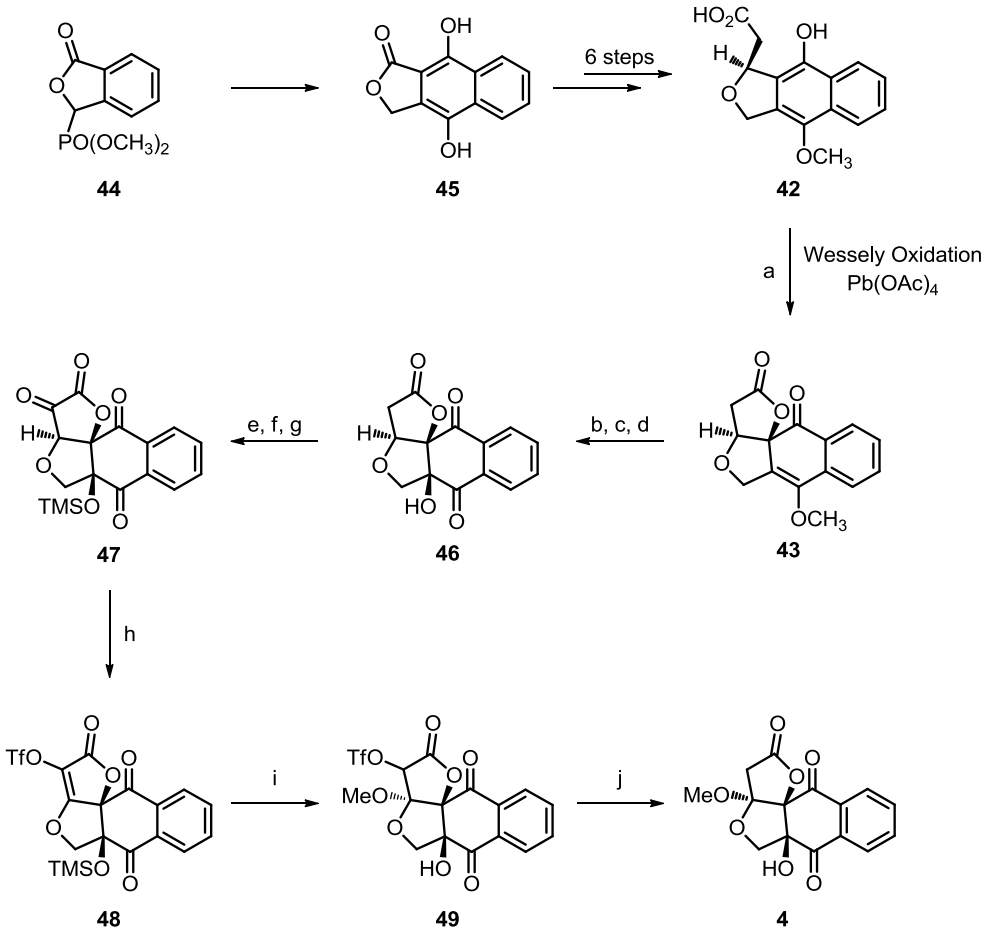
2.5.1 First synthesis of ABCD model system

One year after the isolation of lactonamycin (**1**), Danishefsky and Cox published their first results on the synthesis of the functionalized tricyclic core of lactonamycin (**1**).[22] The key step in the synthesis featured an intramolecular Wessely oxidative lactonization[23] of acid **42** followed by a hydroxyl-directed epoxidation (Scheme 7).



Scheme 7 – Wessely oxidation of acid 42

The Wessely precursor **42** was prepared from known phosphonate **44** *via* a Michael addition-cyclisation. **42** underwent stereospecific oxidative cyclisation upon exposure to $Pb(OAc)_4$ to afford stable lactone **43** (Scheme 8). Treatment of **43** with lithium methoxide provided the allylic alcohol, which under epoxidation conditions using TFPAA successfully gave rise to **46** in 51%. After protection of the hydroxyl group, treatment with NIS provided α-iodolactones as a 2:1 mixture. Treatment of the mixture with DMDO successfully gave rise to a single product identified as α-ketolactone **47**. Conversion of **47** to enol triflate **48** followed by conjugate addition of methanol in the presence of a catalytic amount of CSA afforded **49** as a single diastereomer. Finally, removal of the α-triflate with lithium iodide provided target system **4**.



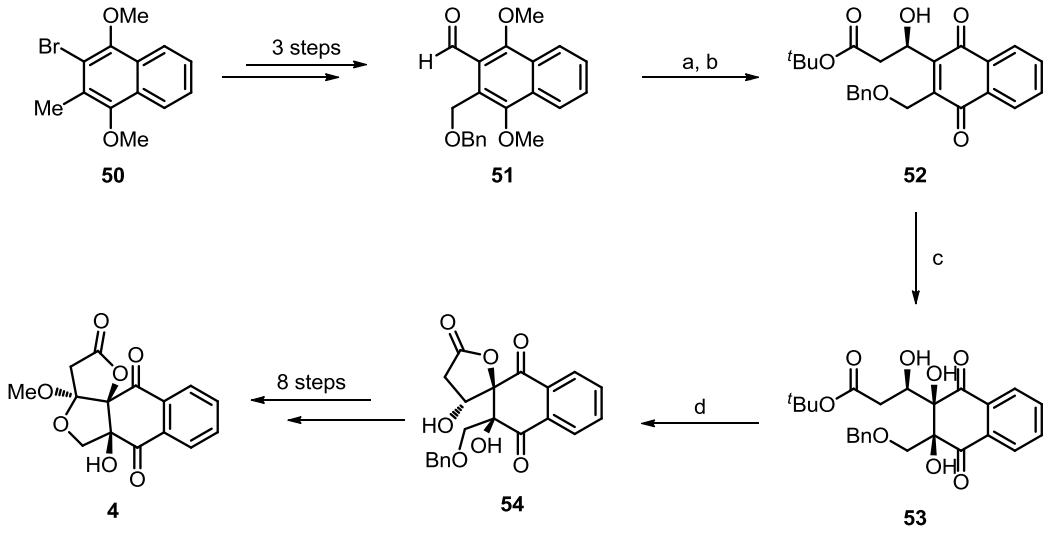
Scheme 8 – Danishefsky's approach to the ABCD ring system of lactonamycin (1)

Reagents and conditions: a) $Pb(OAc)_4$, CH_2Cl_2, 74%; b) LiHMDS, MeOH, CH_2Cl_2, –35 °C, 51% (+ 41% recovered **43**); c) TFPAA, Na_2CO_3, CH_2Cl_2, 0 °C; d) TsOH, benzene, reflux, 51% over 2 steps; e) HMDS, imidazole, TMSCl, CH_2Cl_2, 84%; f) NIS, 86%; g) DMDO, CH_2Cl_2, 71% (+ 17% recovered sm); h) Tf_2O, Hünig's base, CH_2Cl_2, 60%; i) CSA, MeOH, 88%; j) LiI, THF, HOAc, reflux, 55%.

2.5.2 Second synthesis of ABCD model system

One year later, Danishefsky and Cox published a second communication concerning a concise synthesis of the lactonamycin model system **4**. The methodology behind Danishefsky's approach was an unprecedented highly stereoselective dihydroxylation which gave **53** following an acid-promoted deprotection-cyclisation sequence.[24]

Aldehyde **51** was easily prepared from readily available bromide **50** (Scheme 9). Addition of the lithium enolate of *tert*-butylacetate followed by CAN oxidation provided α-hydroxyquinone **52**. Treatment of **52** with catalytic OsO_4 and stoichiometric NMO successfully afforded triol **53** in 71% yield. Treatment of **53** with TFA served to accomplish deprotection and concomitant cyclisation to provide spirocyclic lactone **54**. The methodology developed in the previous paper afforded model system **4** in eight steps.



Scheme 9 – Danishefsky's second approach to the ABCD ring system of lactonamycin (1)

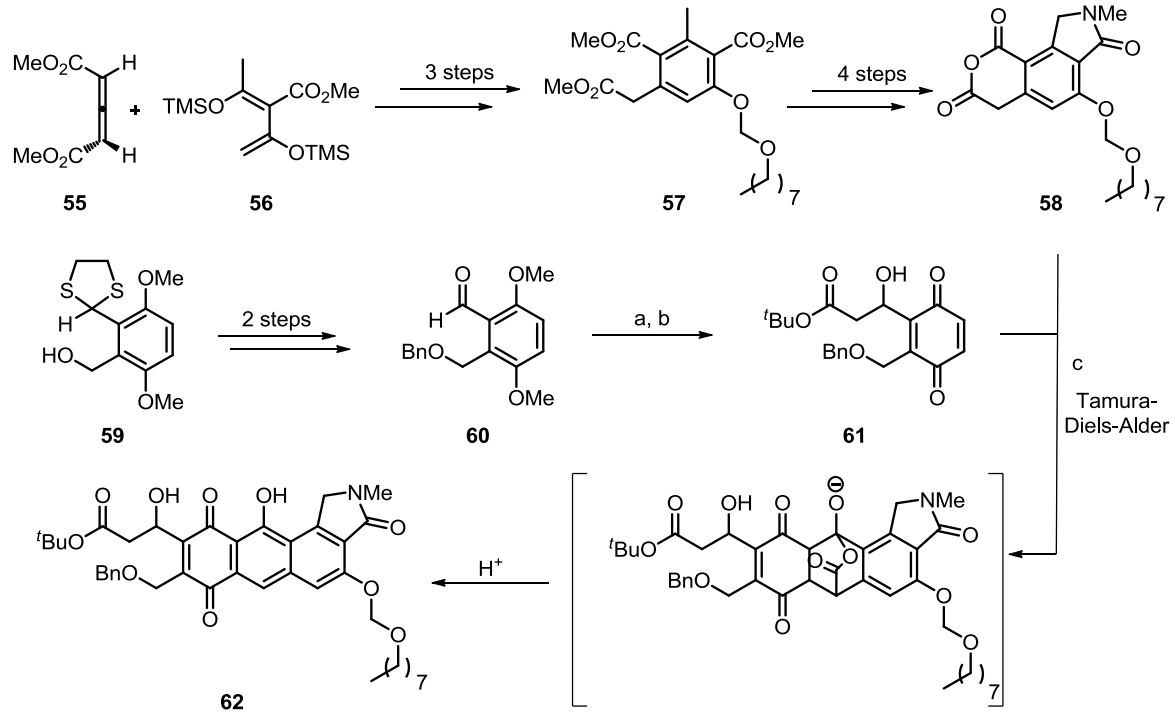
Reagents and conditions: a) LDA, *tert*-BuOAc, THF, −78 °C, 100%; b) CAN, CH_3CN/H_2O, 97%; c) OsO_4, NMO, Me_2CO/H_2O, 71%; d) 90% TFA/H_2O, CH_2Cl_2, 83%.

2.5.3 Total synthesis of lactonamycinone 2 by Danishefsky

In 2003, Danishefsky and Cox published a series of papers directed towards the total synthesis of lactonamycinone (**2**) the novel, highly functionalized hexacyclic aglycone domain of lactonamycin (**1**).[25-26] Their strategy depended upon the condensation of homophthalic anhydride **58** with quinone **61** *via* a process initiated by an anionically-mediated Tamura-Diels-Alder reaction (Scheme 10).[27]

2.5.3.1 First approach

Synthesis of protected pyrrolo homophthalic anhydride **58** was achieved in seven steps and began with the cycloaddition of known bis(silyl enol ether) **55** with 1,3-dicarbomethoxyallene **56** (Scheme 10).[25] Subsequent protection of the phenolic hydroxyl function with an octyloxymethyl ether (to avoid solubility problems) afforded **57**. Bromination of **57** and subsequent amination gave rise to the lactam functionality. Hydrolysis of the ester linkages and dehydration of the diacid formed afforded the protected pyrrolo homophthalic anhydride **58**. The synthesis of the second coupling partner **61** was achieved in four steps from known thioacetal **59**. Protection of the alcohol functionality and deprotection of the dithiane gave benzylic aldehyde **60**. Chain extension by treatment with LDA and *tert*-BuOAc, followed by CAN oxidation afforded α-hydroxyquinone **61**. Treatment of **58** with two equivalents of NaH at −78 °C followed by addition of two equivalents of quinone **61** and warming to 0 °C provided highly-substituted tetracycle **62** after decarboxylation in 40% yield. Unfortunately, all attempts to complete the synthesis of lactonamycinone (**2**) based on the chemistry described in the two previous papers were unsuccessful despite its similarities to the model **52**.



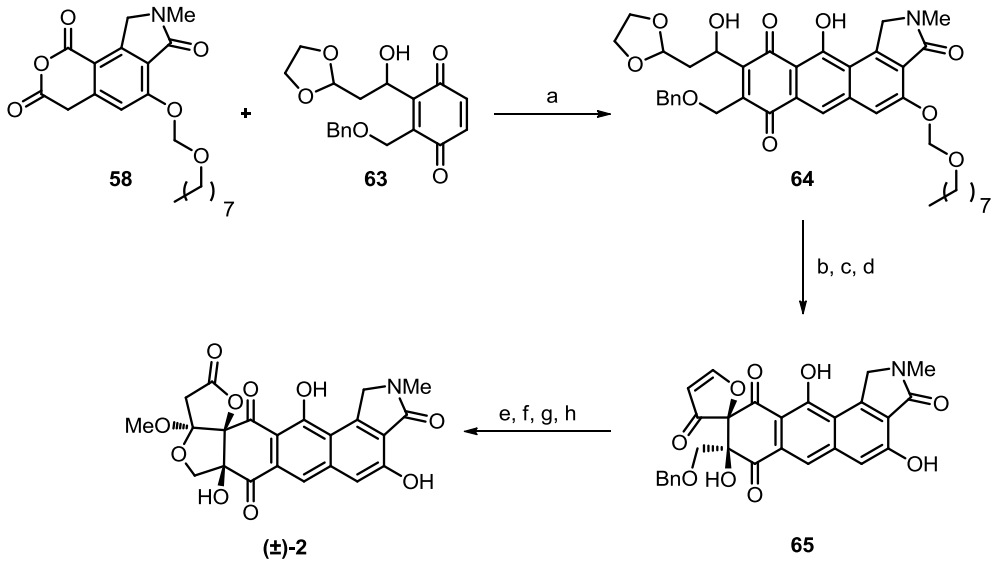
Scheme 10 - Danishefsky's approach towards the total synthesis of lactonamycinone 2

Reagents and conditions: a) LDA, *tert*-BuOAc, THF, −78 °C, 99%; b) CAN, CH_3CN/H_2O (9:1), 0 °C, 96%; c) NaH, THF, −78 °C to 0 °C, 40%.

Given that the total synthesis project now appeared to be almost complete, Danishefsky and co-workers revised the quinone concept.

2.5.3.2 Second approach and completion of the synthesis

Coupling between readily available quinone **63** with homophthalic anhydride **58** gave the tetracyclic product **64** in 42% yield (Scheme 11).[26] Oxidation of the secondary alcohol followed by dihydroxylation and HCl deprotection of the octyloxymethyl ether gave **65**. Deprotection of the benzyl ether with BBr_3 followed by HCl methanolysis led to intramolecular acetalization and addition of methanol to the resulting enol ether. TEMPO-mediated oxidation completed the transformation to lactonamycinone (**2**).

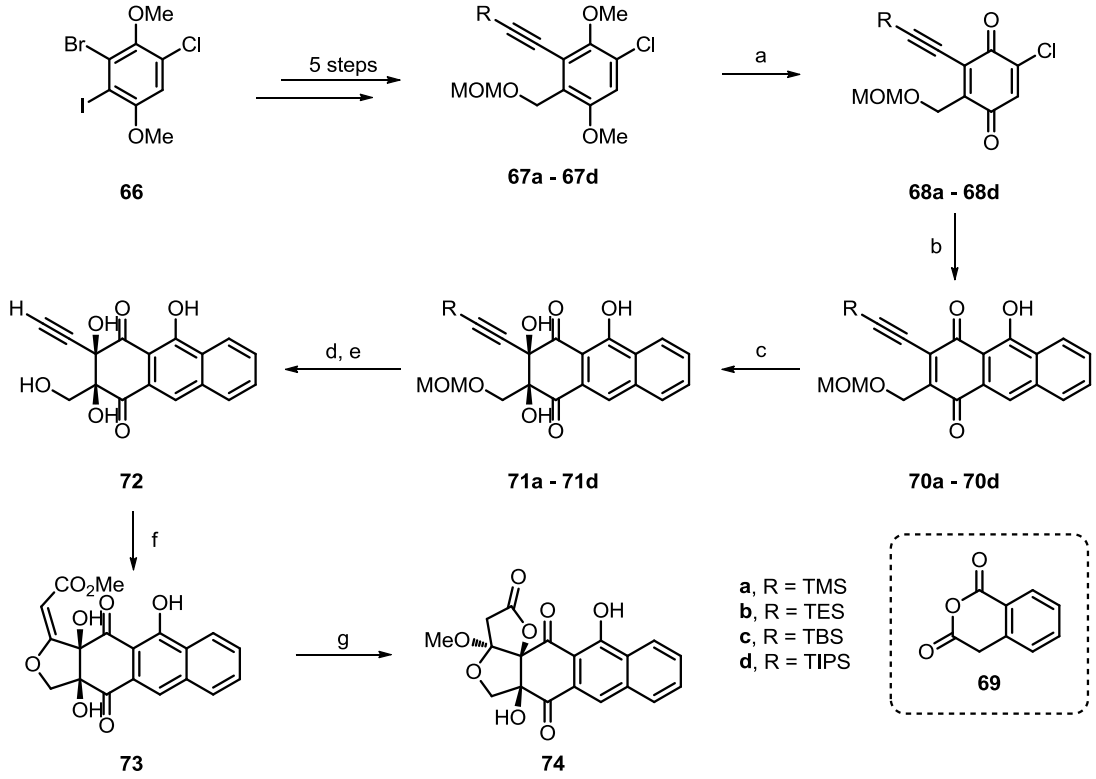


Scheme 11 – Completion of the total synthesis of lactonamycinone 2

Reagents and conditions: a) NaH, THF, −78 °C to 0 °C, 42%; b) DMP, CH_2Cl_2, quantitative; c) i) OsO_4, NMO, CH_2Cl_2; ii) HCl [1 N], $NaHSO_3$, THF, 89%; d) HCl [3 N], Me_2CO/THF, reflux, 82% (brsm); e) BBr_3, CH_2Cl_2, −78 °C; f) HCl [4 N], dioxane/MeOH, 65 °C, 51% (brsm); g) HCl [1 N], THF, quantitative; h) TEMPO, $PhI(OAc)_2$, 58%.

2.6 Synthetic studies of the model BCDEF aglycone by Saikawa and Nakata

In 2010, Saikawa and Nakata published a synthesis of the model BDCEF aglycone of lactonamycin (**1**)[28] in which the E-ring was formed *via* a palladium-catalyzed cyclization-methoxycarbonylation.[29] The four acetylenes **67a**–**67d** were synthesized from trihalogenated benzene derivative **66** using elegant selective halogen-metal exchange reactions and formylation as key steps (Scheme 12). The key transformation was the cycloaddition of the quinones **68a**–**68d** with homophthalic anhydride (**69**) to reveal anthraquinones **70a**–**70b** in low to moderate yield. The dihydroxylation proved to be challenging but oxidation using ruthenium tetraoxide generated *in situ*, successfully gave the expected products **71a**–**71d** albeit in modest yields. Diols **71a**–**71d** were converted into crucial diol **72** using standard deprotection conditions. Diol **75** was converted into the aglycone model **74** *via* tetracyclic ester **73** using a key palladium-catalyzed cyclisation- methoxycarbonylation-lactonisation sequence.



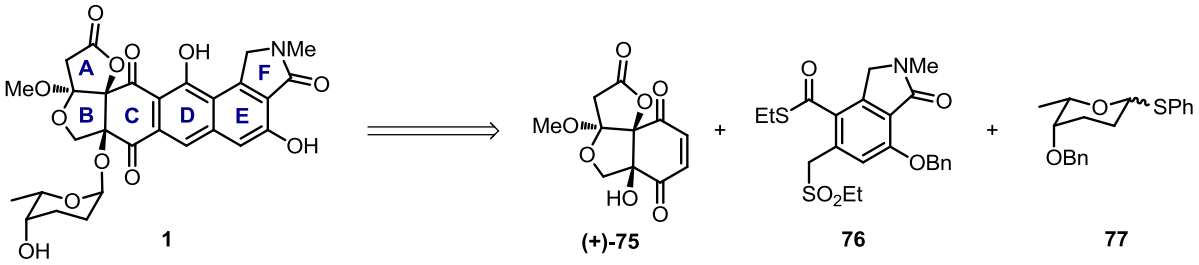
Scheme 12– Saikawa's synthesis of ABCDE ring system of lactonamycin (1)

Reagents and conditions: a) CAN, H_2O/MeCN, **67a**: 92%, **67b**: 92%, **67c**: 85%, **67d**: 54%; b) **69**, LDA, THF, **70a**: 51%, **70b**: 52%, **70c**: 58%, **70d**: 22%; c) $RuCl_3$, $NaIO_4$, MeCN/EtOAc/H_2O, 0 °C, **71a**: 18%, **71b**: 16%, **71c**: 33%, **71d**: 35%; d) TBAF, THF, 0 °C, from **71a**: 93%, from **71b**: 94%,

from **71c**: 98%, from **71d**: 98%; e) TFA, CH_2Cl_2, 98%; f) $PdCl_2$, 1,4-benzoquinone, CO, MeOH, 62%; g) CSA, MeOH, 80 °C, 5 d, evaporation in benzene, 75 °C, 93%.

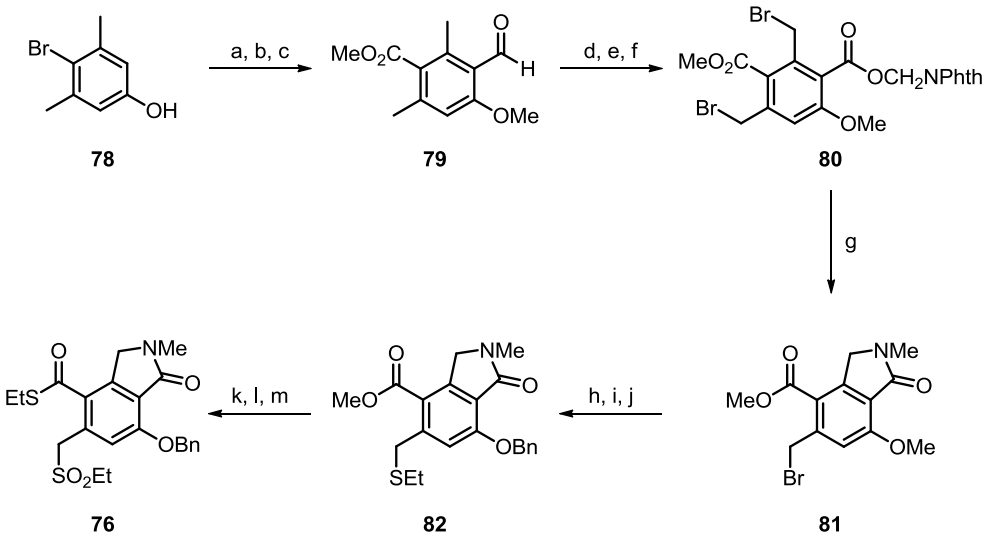
2.7 First total synthesis of lactonamycin (1) by Tatsuta

In 2010, Tatusta *et al.* reported the first total synthesis of lactonamycin **1**.[30] Their retrosynthetic plan is depicted in Scheme 13. They envisaged that lactonamycin **1** could be synthesized starting from three key building blocks, including ABC ring system **(+)-75**, thioester **76** and rhodinose derivative **77**.



Scheme 13 – Tatsuta's retrosynthetic approach towards the total synthesis of lactonamycin 1

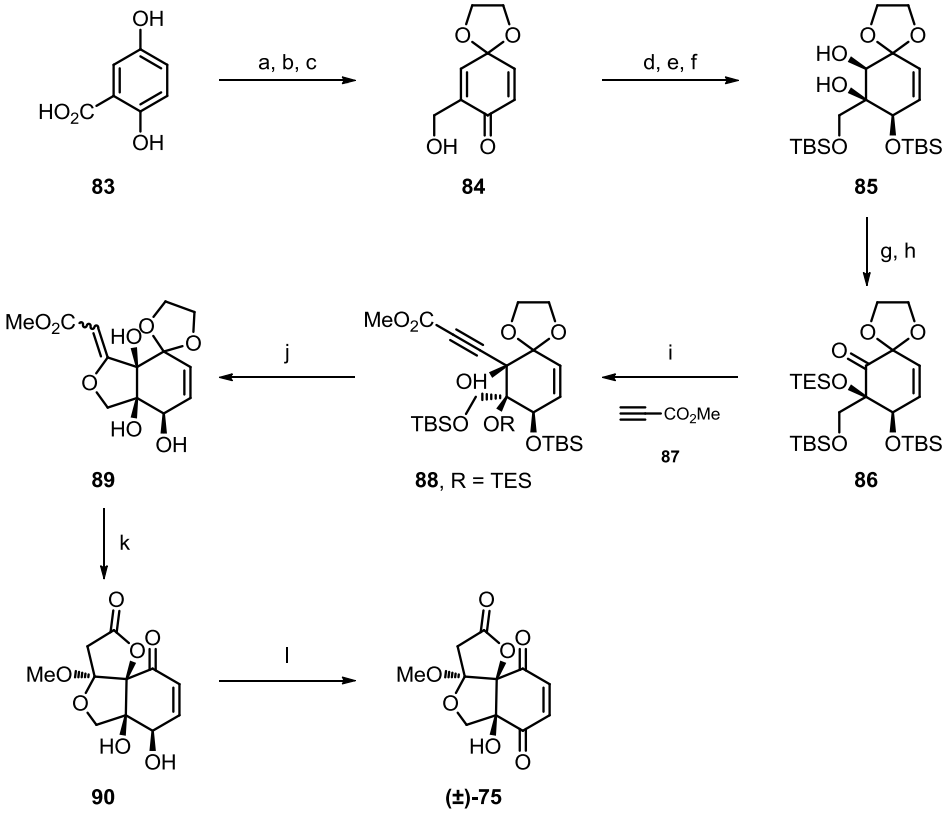
Thioester **76** was synthesized in 13 steps starting from 4-bromo-3,5-dimethylphenol **78** (Scheme 14). The synthesis began with the *O*-methylation of **78** followed by lithiation, subsequent methoxycarbonylation and Friedel-Crafts formylation to give ester **79**. The aldehyde moiety in **79** was successfully oxidized to the corresponding carboxylic acid *via* a Pinnick oxidation and converted into phthalimidylmethyl ester. **80** was obtained after subsequent bromination. Treatment of **80** with methylamine promoted the sequential lactamization to form bicycle **81**. The methoxy ether in **81** was cleaved and the free phenol was immediately reprotected as a benzyl ether and the bromide moiety was displaced by ethanethiol to give **82**. Finally, the methyl ester was hydrolyzed, condensed with ethanethiol and the thioether moiety was oxidized to form thioester **76**.



Scheme 14 – Synthesis of thioester 76

Reagents and conditions: a) Me_2SO_4, K_2CO_3, Me_2CO, 40 °C, 99%; b) *n*-BuLi, $ClCO_2Me$, THF, −78 °C, 88%; c) Cl_2CHOMe, $SnCl_4$, CH_2Cl_2, 0 °C, 95%; d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *tert*-BuOH, rt; e) $PhthNCH_2Br$, K_2CO_3, Me_2CO, 40 °C; f) NBS, AIBN, CCl_4, 80 °C, 40% (over 3 steps); g) $MeNH_2$, THF, rt, 42%; h) BCl_3, CH_2Cl_2, 0 °C to rt, 78%; i) BnBr, Ag_2O, MeCN, rt, 78%; j) EtSH, DBU, PhMe, 60 °C, 89%; k) $LiOH{\cdot}H_2O$, aq. THF, 70 °C; l) EtSH, WSCI·HCl, DMAP, CH_2Cl_2, rt, 87% (over 2 steps); m) *m*CPBA, CH_2Cl_2, rt, 73%.

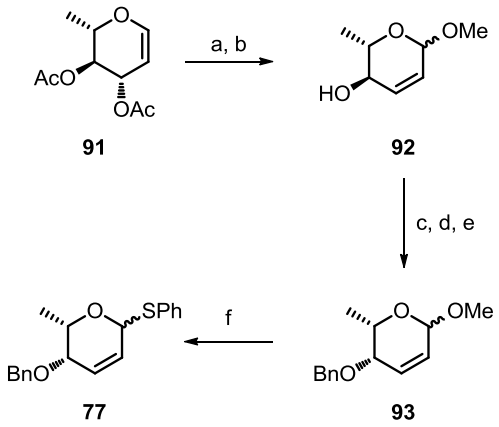
The ABC ring system **(±)-75** was synthesized starting from 2,5-dihydroxybenzoic acid **83** (Scheme 15). The synthesis began with the selective *O*-methylation of **83** followed by successive reduction of the methyl ester moiety and oxidation of the aromatic ring in the presence of ethylene glycol to give quinone mono-acetal **84**. Dihydroxylation of the tri-substituted olefin in **84** gave the corresponding triol which was subjected to a stereoselective reduction and TBS-protection to obtain diol **85**. The secondary alcohol in **85** was oxidized to the corresponding ketone and the tertiary alcohol was protected as the corresponding TES-ether to form **86**. Methyl propionate **87** was successfully added stereospecifically under basic conditions and **88** was obtained in excellent yield. Desilylation using 0.5 equivalent of TBAF and conjugate addition of the resulting primary alcohol proceeded smoothly and bicycle **89** was obtained. Finally, ester **89** was treated in methanol under acidic conditions to give tricyclic **90**, which was oxidized to key precursor **(±)-75**.



Scheme 15 – Synthesis of ABC ring system (±)-75

Reagents and conditions: a) Me_2SO_4, K_2CO_3, Me_2CO, 50 °C, 94%; b) $LiBH_4$, THF, 50 °C; c) ethylene glycol, PIFA, CH_2Cl_2, 0 °C, 84% (over 2 steps); d) OsO_4, NMO·H_2O, Me_2CO, rt, 48%; e) $NaBH_4$, MeOH, 0 °C, ds 13:1; f) TBSCl, imidazole, DMF, 0 °C to rt, 67% (over 2 steps); g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 71%; h) TESOTf, pyridine, rt, 93%; i) **87**, NaHMDS, THF, −100 °C, 93%; j) TBAF, THF, rt; k) AcCl, MeOH, 0 °C to rt, addition of PhMe and concentration, 55% (over 2 steps); l) IBX, $(CH_2Cl)_2$, 70 °C, 94%.

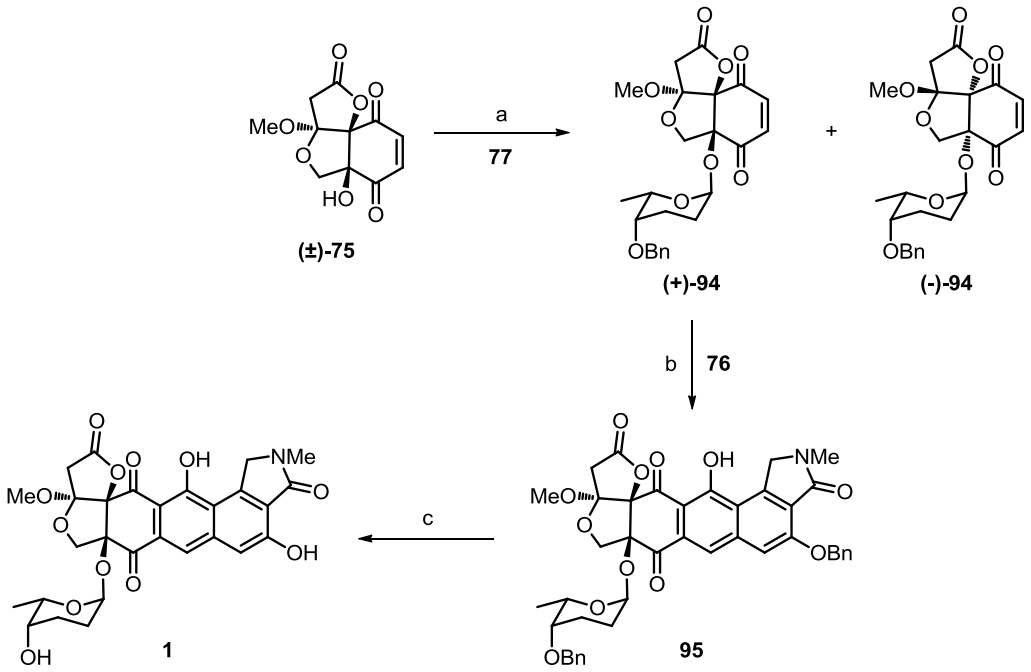
Rhodinose derivative **77** was synthesized from L-rhamnal **91** (Scheme 16). **91** was subjected to a Ferrier reaction in MeOH and allyl alcohol **92** was obtained after deacetylation. The stereochemistry of the secondary alcohol in **92** was inversed *via* a Mitsunobu reaction. Hydrogenation and concomitant solvolysis of formyl ester followed by treatment with BnBr successfully afforded **93**. Finally, the methoxy ether at the C1-position of the saccharide was displaced with thiophenol and thioether **77** was obtained.



Scheme 16 – Synthesis of rhodinose derivative 77

Reagents and conditions: a) MeOH, $BF_3 \cdot OEt_2$, CH_2Cl_2, rt, 73%; b) NaOMe, MeOH, rt; c) HCO_2H, PPh_3, DEAD, THF, rt, 84% (over 2 steps); d) NaOMe, MeOH, rt, CG 50, H_2, Pd–C, MeOH, rt; e) BnBr, NaH, THF, 60 °C, 64% from **92**; (f) PhSH, CSA, CH_2Cl_2, rt, 93%.

Racemic **(±)-75** was subjected to glycosidation with **77** in the presence of silver triflate and gave a mixture of diastereoisomers **(+)-94** and **(-)-94** which could be separated by column chromatography. Michael-Dieckman type condensation of **(+)-94** and **76** successfully gave **95** albeit in a modest 37% yield. Finally, both benzyl ethers in **95** were cleaved and lactonamycin **1** was obtained in 40% yield. The physico-chemical data of synthetic lactonamycin **1** were identical of those of the natural product.



Scheme 17 – Resolution of (±)-75 and completion of the synthesis

Reagents and conditions: a) **77** (10.0 eq.), 2-cyclohexen-1-one (11.0 eq.), AgOTf, MS-4Å, CH_2Cl_2, –40 °C to rt, 40% for **(+)-94**, 35% for **(-)-94**; b) **76**, KHMDS, THF, –78 °C to reflux, 37%; c) H_2, Pd-black, THF, rt, 40%.

3. Previous efforts by the Barrett group

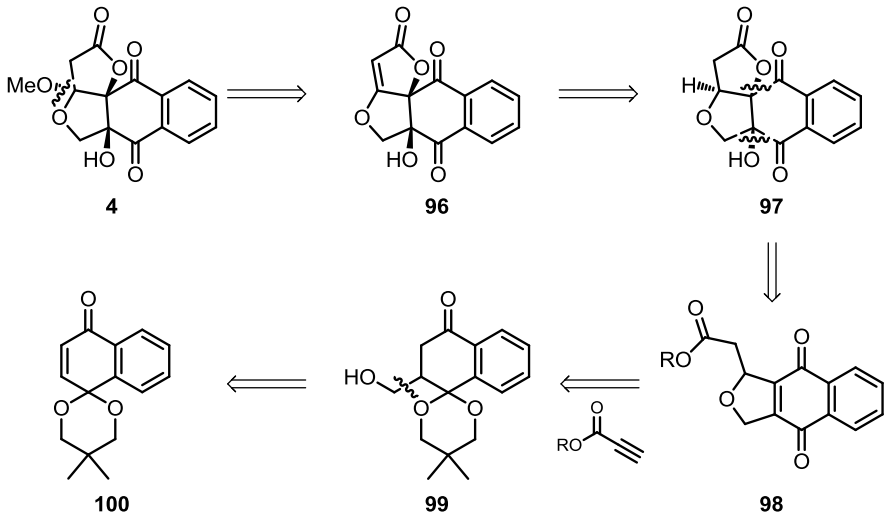
3.1 Construction of a model of the ABCD ring system

In 2005, Barrett and co-workers published their first paper, detailing their studies towards the synthesis of lactonamycin (**1**), which described the construction of a model of the ABCD ring system.[31]

3.1.1 First approach

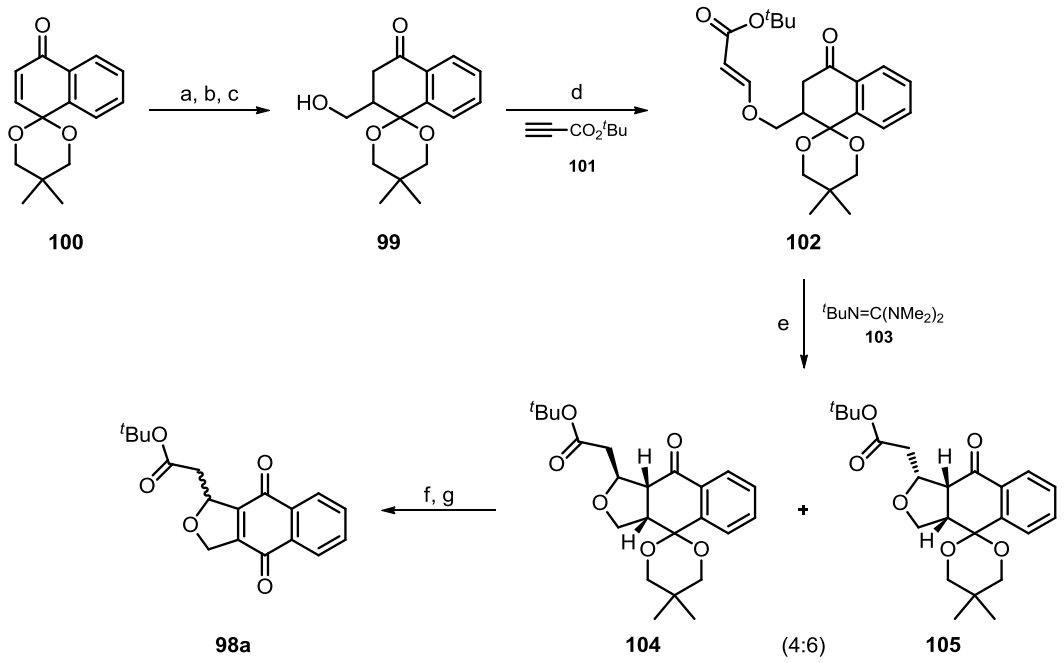
The tetracycle **4** was primarily disconnected by the loss of the angular methoxy group to reveal butenolide **96** (Scheme 18) which in turn could be obtained from oxidation of lactone **97**. Oxidation of

naphthoquinone **98** should give **97** after dihydroxylation or epoxide formation. Quinone **98** should be available *via* a double Michael addition sequence and subsequent transformations from alcohol **99** and a propionate ester. Finally, alcohol **99** should be available from quinone monoketal **100** *via* a further Michael addition sequence.



Scheme 18 – Barrett's first retrosynthesis towards ABCD ring system of lactonamycin (1)

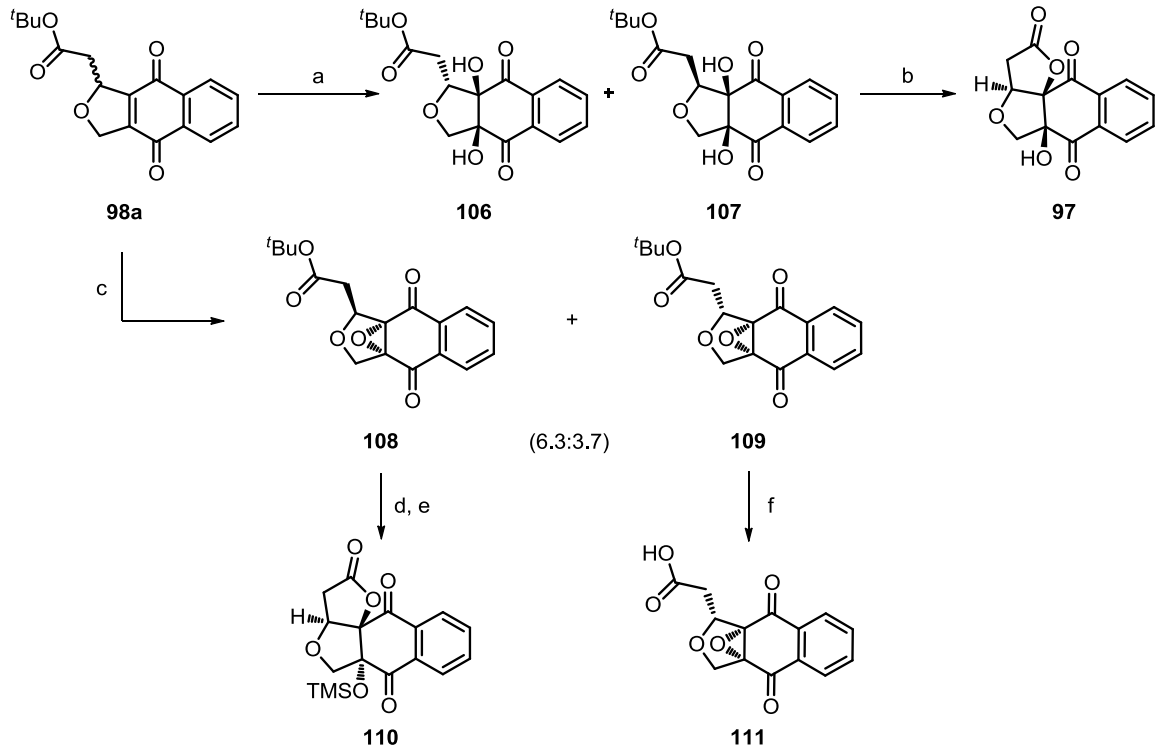
Quinone monoketal **100** was easily synthesized in multigram-scale quantities from 4-methoxy-1-naphthol using $PhI(OCOCF_3)_2$ and 2,2-dimethyl-1,3-propanediol. Quinone monoketal **100** was transformed into the corresponding nitroalkane by the Et_3N-catalysed Michael addition of nitromethane (Scheme 19). Subsequent Nef oxidation followed by reduction of the aldehyde formed furnished the corresponding alcohol **99**. Michael addition of alcohol **99** to *tert*-butylpropynoate **101** successfully yielded vinyl ether **102** as a single isomer. Formation of the B ring was achieved by using *N-tert*-butyl-*N',N',N'',N''*-tetramethylguanidine **103** as a base *via* a second Michael addition and gave the corresponding esters **104** and **105** in 96% yield as a mixture of diastereoisomers (4:6). Treatment of **104** and **105** with aqueous acetic acid in the presence of air resulted in the formation of naphthoquinone **98a**.



Scheme 19 – Synthesis of precursor 98a

Reagents and conditions: a) $MeNO_2$, Et_3N, MeOH, 83%; b) KOH, $KMnO_4$, MeOH, 0 °C, 55%; c) $NaBH_4$, MeOH, −5 °C, 77%; d) **101**, *N*-methylmorpholine, Et_2O, 68%; e) **103**, CH_2Cl_2, 0 °C, 96%; f) Ac_2O, H_2O, 60 °C; g) Ac_2O, H_2O, air, 57% (over 2 steps).

Dihydroxylation of **98a** using Danishefsky's previously established methodology[24] (NMO, OsO_4) yielded a mixture of diols **106** and **107** (Scheme 20). Treatment of the mixture of **106** and **107** with TFA gave lactone **97** but only in low yield. It was thought that only the minor isomer was able to undergo the γ-lactonization. An alternative route was explored by converting **98a** into epoxides **108** and **109** using H_2O_2 and Na_2CO_3 Treatment of **108** with TFA gave the γ-lactone **110** after TMS protection. Treatment of the second isomer **109** with TFA resulted only in the deprotection forming the epoxy acid **111**.



98a 106 107 97

108 109

110 111

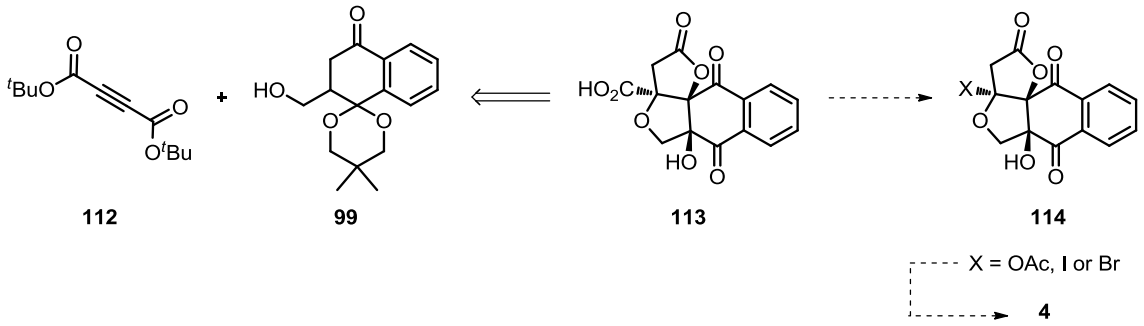
Scheme 20 – Dihydroxylation and epoxidation of 98a

Reagents and conditions: a) OsO_4, NMO, Me_2CO/H_2O, 0 °C, 70%; b) TFA, CH_2Cl_2, 0 °C, 27%; c) H_2O_2, Na_2CO_3, THF, 93%; d) TFA, CH_2Cl_2, 0 °C, 97%; e) TMSCl, CH_2Cl_2, 95%; f) TFA, CH_2Cl_2, 0 °C, 91%.

However, all attempted oxidations of γ-lactone **110** to provide the corresponding butenolide in order to introduce the angular methoxy group failed. In light of the difficulties with this initial approach, it was thought that the methoxy group could be masked as a carboxylic acid and could be revealed *via* a late stage halodecarboxylation, decarboxylative acetoxylation, or through the intermediacy of a methyl perester.

3.1.2 Second approach

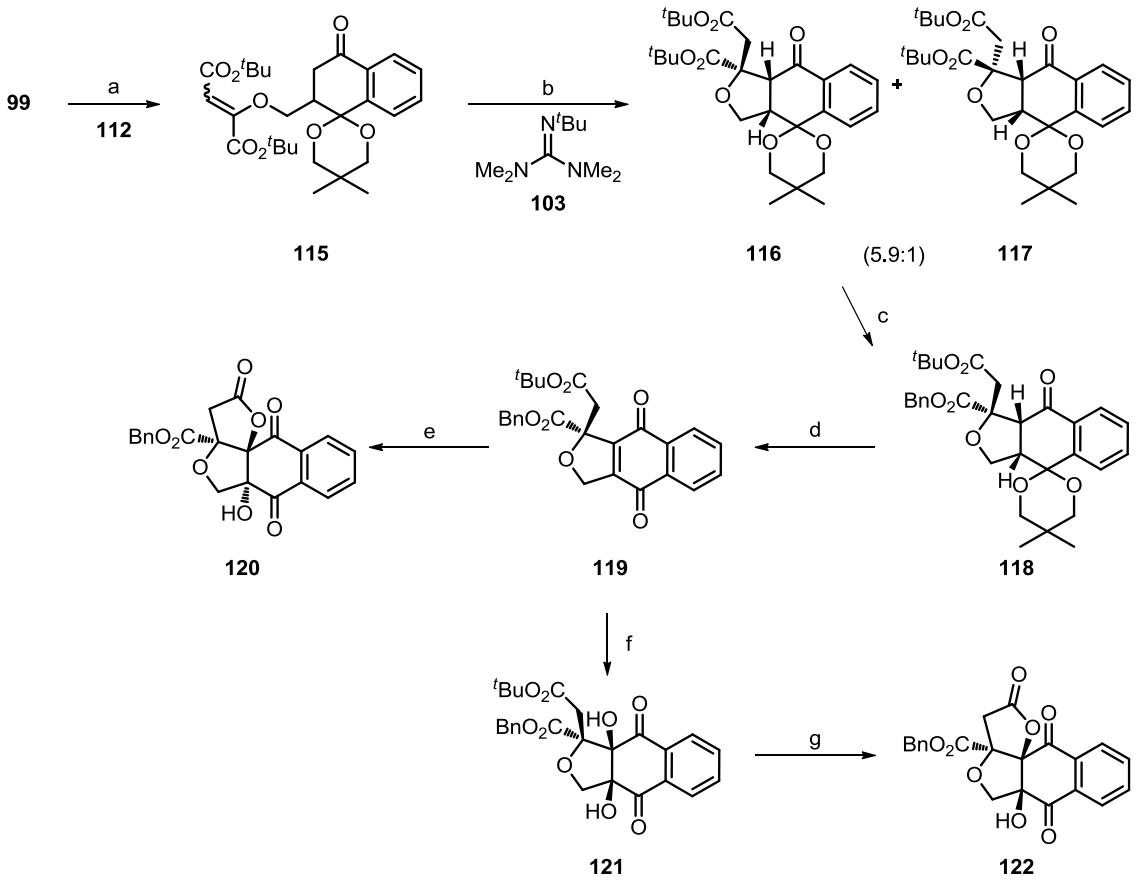
As a result, the retrosynthetic route was slightly modified with the use of di-*tert*-butyl acetylene dicarboxylate **112** as the initial Michael acceptor for reaction with alcohol **99** (Scheme 21).



112 **99** **113** **114**

Scheme 21 – Barrett's second retrosynthesis towards ABCD ring system of lactonamycin (1)

Michael addition of alcohol **99** to di-*tert*-butyl acetylene dicarboxylate **112** afforded adduct **115** (Scheme 22). Cyclisation *via* a second Michael addition reaction gave both tetrahydrofurans **116** and **117**. Selective saponification of di-ester **116** followed by benzylation gave differentially-functionalized di-ester **118**. Treatment of **118** with AcOH in water in the presence of air gave quinone **119** which underwent epoxidation with H_2O_2 followed by direct cyclisation with TFA to give *trans*-lactone **120**. Unfortunately, attempted epimerization of the tertiary alcohol of **120** to give the *cis*-ring fused lactone under basic or acidic conditions failed. Ruthenium(III) chloride catalyzed dihydroxylation of quinone **119** gave diol **121**. Treatment of **121** with TFA gave *cis*-lactone **122**.



Scheme 22 – Synthesis of ABCD ring system of lactonamycin (1)

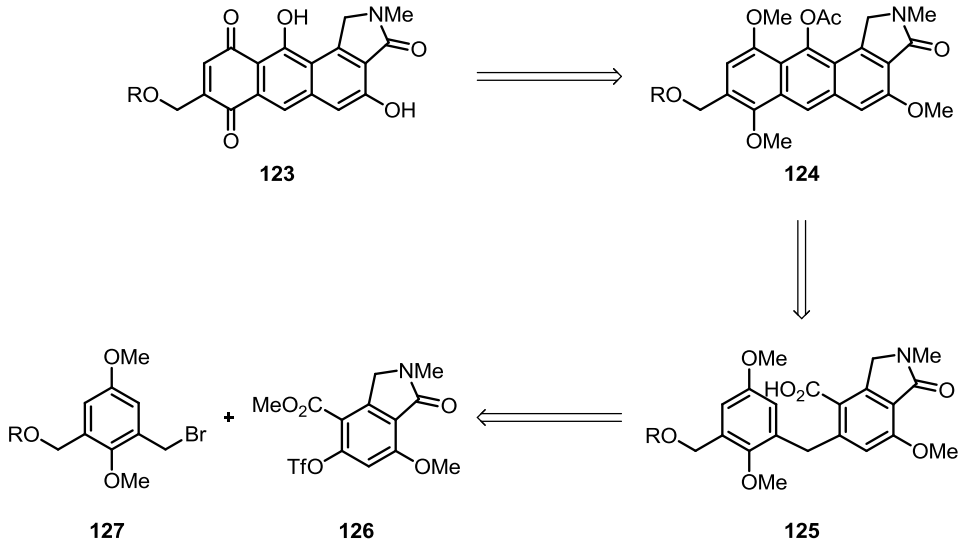
Reagents and conditions: a) **112**, DMAP, CH_2Cl_2, 86%; b) **103**, CH_2Cl_2, 76%; c) i) KOH, dioxane; ii) BnBr, DMF, 78% over 2 steps; d) AcOH, H_2O, air, 55 °C, 70%; e) i) H_2O_2, K_2CO_3, THF; ii) TFA, CH_2Cl_2, 0 °C, 42%; f) $RuCl_3$, $NaIO_4$, EtOAc/CH_3CN/H_2O, 0 °C, 64%; g) TFA, CH_2Cl_2, 0 °C, 26%.

This system was an accurate model for investigation into unmasking the tertiary methoxy group. However, none of the conditions surveyed afforded this key transformation.

3.2 Construction of a model of the CDEF ring system

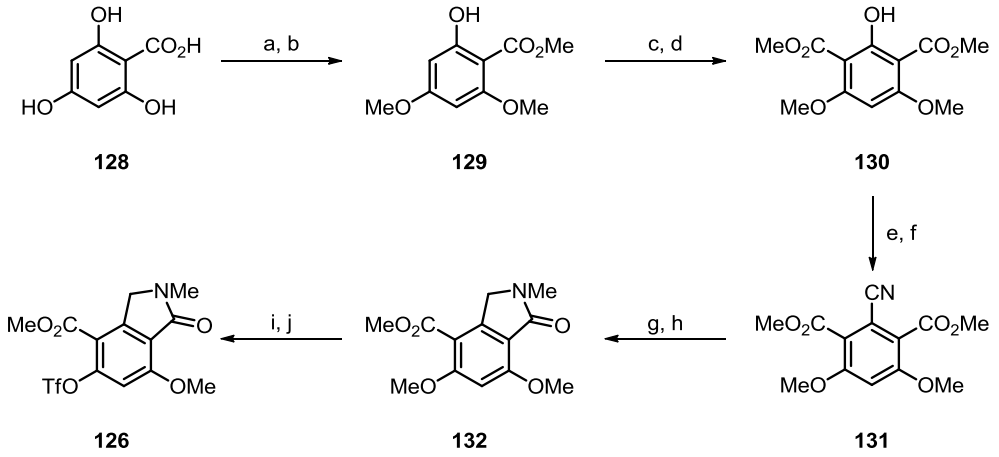
3.2.1 First approach

In 2006, Barrett and co-workers published the first of two papers on studies on the CDEF ring system of lactonamycin (**1**).[32a] The methodology involved the Lewis acid mediated, intramolecular Friedel-Crafts acylation of carboxylic acid **125** to produce the tetracyclic CDEF core of target **123**. The synthesis of **125** was carried out using a high yielding Negishi coupling of benzyl bromide **127** and triflate **126** (Scheme 23).



Scheme 23 – Barrett's retrosynthesis towards CDEF ring system of lactonamycin (1)

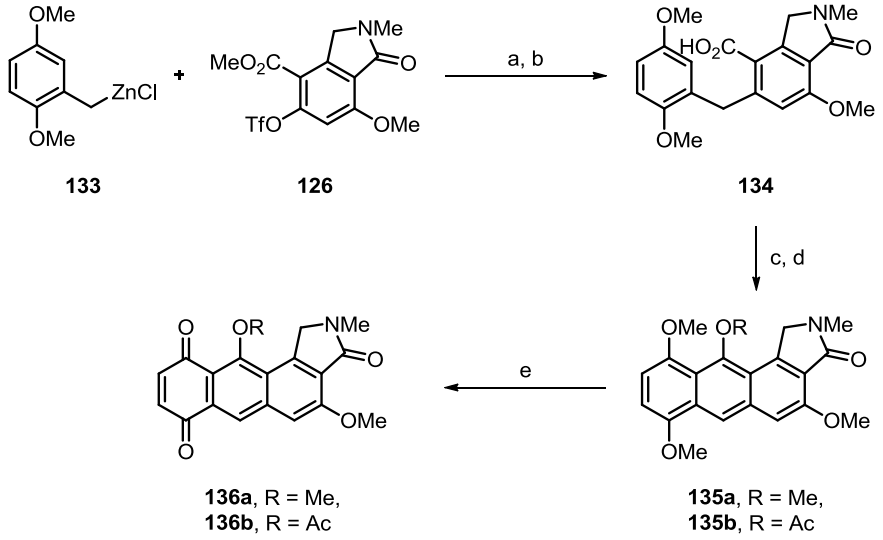
Global protection of **128** using Me_2SO_4 and K_2CO_3 followed by selective monodeprotection of one of the *ortho* methoxy group gave phenol **129** (Scheme 24). Subsequent Vilsmeier-Haack formylation, oxidation with sodium chlorite in the presence of sulfamic acid and subsequent methylation afforded di-ester **130**. Condensation of phenol **130** with triflic anhydride followed by palladium-mediated Negishi cross-coupling with zinc cyanide gave nitrile **131**. Reduction of the nitrile and methylation yielded ether **132** which was demethylated using BCl_3 and subsequently triflated to furnish key intermediate **126**.



Scheme 24 - Synthesis of triflate 126

Reagents and conditions: a) Me_2SO_4, K_2CO_3, Me_2CO, 84%; b) BCl_3, CH_2Cl_2, −78 °C, 91%; c) $POCl_3$, DMF, MeCN, 0 °C to 25 °C, 75%; d) i) $NaClO_2$, NH_2SO_3H, 2-methylbutene, THF/H_2O/DMSO; ii) $KHCO_3$, Me_2SO_4, DMF, 94% over 2 steps; e) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 95%; f) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 60 °C, 95%; g) PtO_2, THF, AcOH, H_2, 70 psi, 94%; h) NaH, MeI, DMF, 0 °C, 91%; i) BCl_3, CH_2Cl_2, −78 °C, 82%; j) $PhNTf_2$, Et_3N, CH_2Cl_2, reflux, 92%.

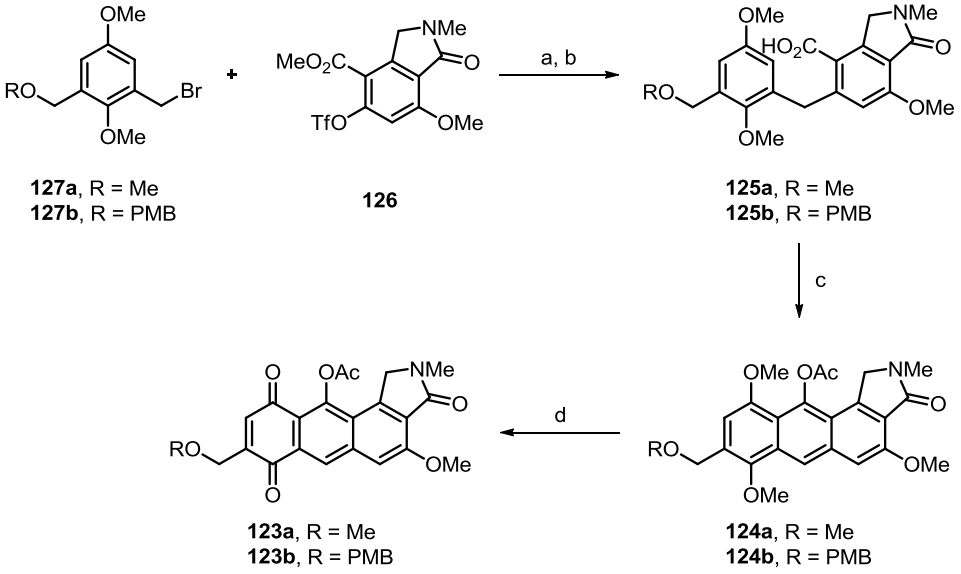
Negishi coupling of triflate **126** with 2,5-dimethoxybenzylzinc chloride **133** gave methyl ester **134** in high yield (Scheme 25). Saponification of the ester moiety with LiOH, Friedel-Crafts acylation and subsequent protection of the resulting phenol as a methyl ether or as the corresponding acetate to avoid air oxidation to the anthraquinone gave tetracyclic products **135a** and **135b** respectively. Selective oxidation of **135a** with CAN afforded only traces of expected quinone **136a**. However, CAN oxidation of **135b** gave the expected quinone **136b** in 65% yield.



Scheme 25 – Synthesis of CDEF ring model system of lactonamycin (1)

Reagents and conditions: a) $Pd(PPh_3)_4$, THF, 94%; b) LiOH, THF/MeOH/H_2O, 37-64%; c) **135a**: PPA, 110 °C, 5 h. **135b**: $Me_2C{=}C(Cl)NMe_2$, CH_2Cl_2, $ZnCl_2$; d) **135a**: K_2CO_3, Me_2SO_4, Me_2CO, 50 °C, 3 h, <30% over 2 steps, **135b**: Ac_2O, pyridine, DMAP, 80% over 2 steps; e) **135b**: CAN, MeCN/H_2O, 65%.

It was thought to prepare the tetracyclic ring system **123a** or **123b** with a protected hydroxymethyl side chain attached to the quinone *C*-ring (Scheme 26). Negishi coupling of triflate **126** with the organozinc derivative of the methyl **127a** or PMB-protected **127b** derivative and subsequent saponification of the ester moiety with LiOH afforded coupling products **125a** and **125b** in excellent yields. The use of PPA as previously described resulted in total decomposition of starting material. However, treatment of **125a** or **125b** with 1-chloro-*N*,*N*-2-trimethyl-1-propylenamine and $ZnCl_2$ gave the tetracyclic products **124a** and **124b** after direct protection. CAN oxidation afforded quinone **123a** and **123b** in 61% and 71% yield respectively.



Scheme 26 – Second synthesis of CDEF ring model system of lactonamycin (1)

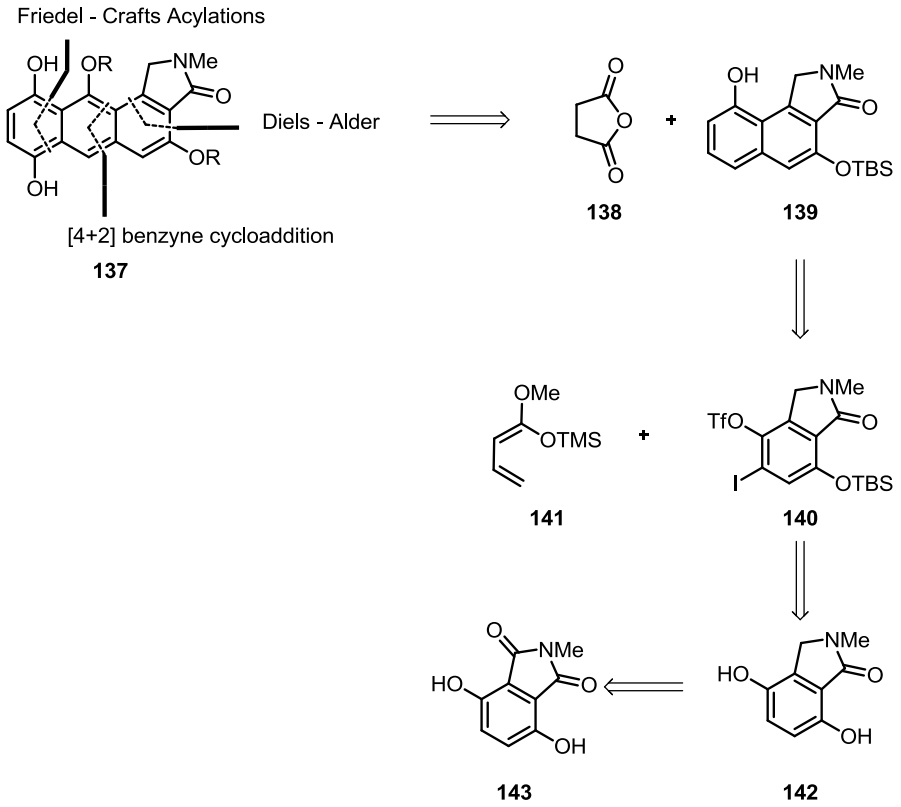
Reagents and conditions: a) **127a** or **127b** (2.2 eq.), Zn, $(BrCH_2)_2$, $Pd(PPh_3)_4$, THF; b) LiOH, THF/MeOH/H_2O, 85% for **125a**, 92% for **125b (**over 2 steps); c) i) $Me_2C{=}C(Cl)NMe_2$, $ZnCl_2$, CH_2Cl_2, 0 °C; ii) Ac_2O, pyridine, DMAP, 82% for **124a** (over 2 steps), 92% for **124b** (over 2 steps); d) CAN, MeCN/H_2O, 61% for **123a**, 71% for **123b**.

3.2.1 Second approach

In the same year, Barrett and co-workers published a second paper on synthetic studies on the CDEF ring system of lactonamycin (**1**) using notably benzyne-furan and maleimide-furan cycloaddition reactions, Suzuki coupling reaction, and electrophilic aromatic substitutions.[32b]

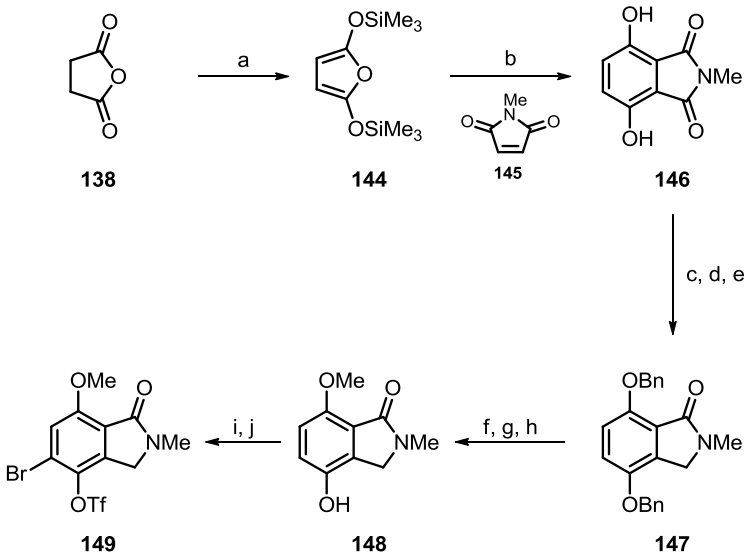
3.2.1.1 Benzyne cycloaddition strategy

The lactonamycin CDEF ring system **137** could be synthesized using a double Friedel-Crafts acylation of naphthol **139** using succinic anhydride **138** (Scheme 27). Naphthalene **139** could be available from a [4+2] cycloaddition of the aryne derived from iodotriflate **140** and diene **141** with subsequent aromatization. Iodotriflate **140** should be available from imide **142** *via* reduction, iodination and triflation.



Scheme 27 – First retrosynthesis towards CDEF ring of lactonamycin (1)

Diels-Alder reaction of **144** with *N*-methylmaleimide **145** and *in situ* aromatization gave imide **146** in excellent overall yield (Scheme 28). Protection of the phenolic alcohols followed by a two-step imide reduction resulted in the formation of the corresponding lactam **147**. Selective mono-debenzylation using $MgBr_2$, protection with MeI and debenzylation by hydrogenolysis afforded methyl ether **148**. Reaction of **148** with bromine in the presence of sodium acetate followed by condensation of the phenol with triflic anhydride yielded **149**. However, the attempted conversion of the derived bromo-triflate **149** into the corresponding benzyne and trapping with 2-methoxyfuran using several conditions gave only intractable mixtures of products. As a result, the benzyne strategy was abandoned.



Scheme 28 – Synthesis of bromo-triflate precursor 147

Reagents and conditions: a) Et_3N, $ZnCl_2$, TMSCl, CH_2Cl_2, 100%; b) **145**, CH_2Cl_2, 40 °C, 92%; c) Cs_2CO_3, BnBr, DMF, 92%; d) $NaBH_4$, MeOH/$CHCl_3$, 0 °C, 100%; e) Et_3SiH, TFA, CH_2Cl_2, 0 °C, 81%; f) $MgBr_2 \cdot Et_2O$, PhMe/Et_2O, 75 °C, 73%; g) K_2CO_3, MeI, Me_2CO, reflux, 91%; h) H_2, Pd/C, MeOH/EtOAc, 91%; i) Br_2, NaOAc, AcOH, 52%; j) Tf_2O, Et_3N, CH_2Cl_2, –78 °C, 55%.

3.2.1.2 Palladium coupling and Friedel – Crafts cyclisation strategy

Barrett and co-workers now focussed on an approach whereby the lactonamycin CDEF ring system core would be assembled using either a sequential Michael addition, or a palladium coupling reaction and subsequent Friedel-Crafts hydroxyalkylation (Figure 6).

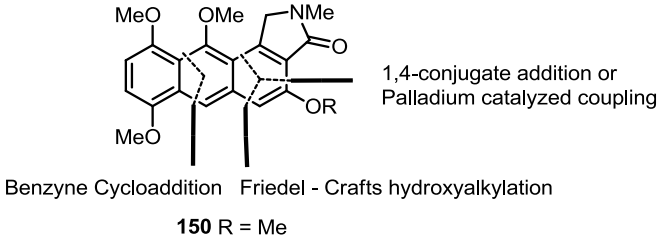
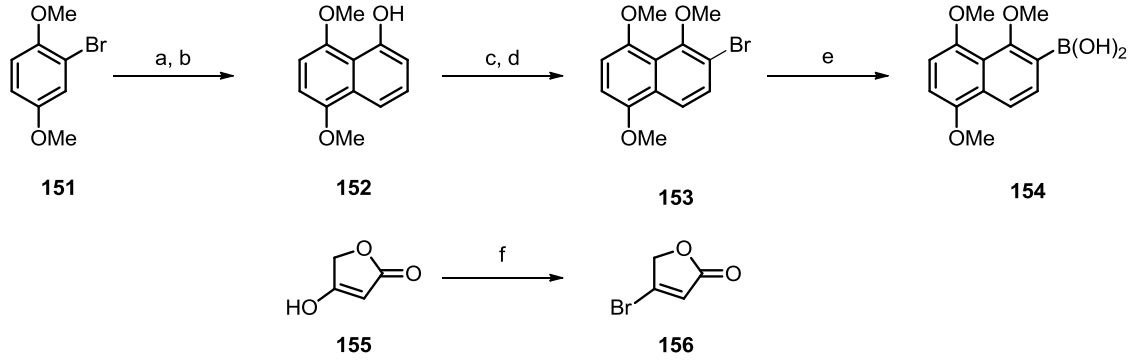


Figure 6 – Retrosynthetic approach using palladium coupling and Friedel – Crafts cyclisation

Coupling partners **154** and **156** were synthesized as described in Scheme 29. Naphthalene **154** was prepared from **151** using a benzyne-furan cycloaddition reaction to provide naphthalene **153** after regioselective *ortho*-bromination. Boronic acid **154** was readily prepared from bromide **153** by sequential bromine-lithium exchange, condensation with $B(O^iPr)_3$ and subsequent hydrolysis. Bromobutenolide **156** was readily prepared from tetronic acid **155** using oxalyl bromide.

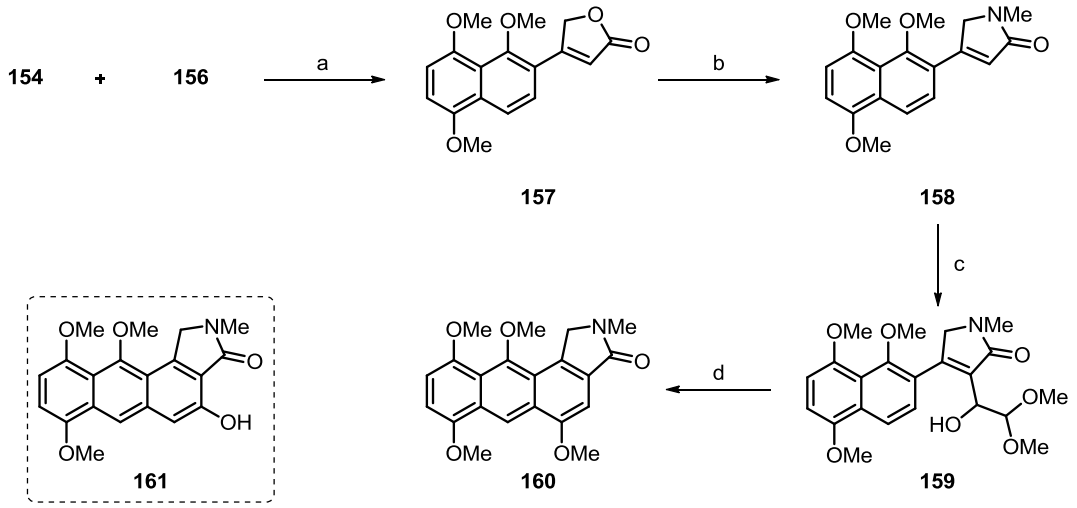


Scheme 29 – Synthesis of key intermediates 154 and 156

Reagents and conditions: a) Furan, $NaNH_2$; b) HCl, 93% over 2 steps; c) Br_2, CH_2Cl_2, −78 °C, 84%; d) K_2CO_3, MeI, Me_2CO, reflux, 94%; e) i) *n*-BuLi, B(O*i*-Pr)$_3$, THF, −78 °C; ii) HCl, H_2O, 92%; f) $(COBr)_2$, DMF, CH_2Cl_2/DMF, 0 °C, 81%.

The introduction of the pyrrolinone unit was envisioned to be achieved by either Michael addition of organometallic reagents derived from bromide **153** to a 2-pyrrolinone derivative, or by a palladium-catalyzed coupling of **154** with a related 4-bromo-2-pyrrolinone or synthetic equivalent.

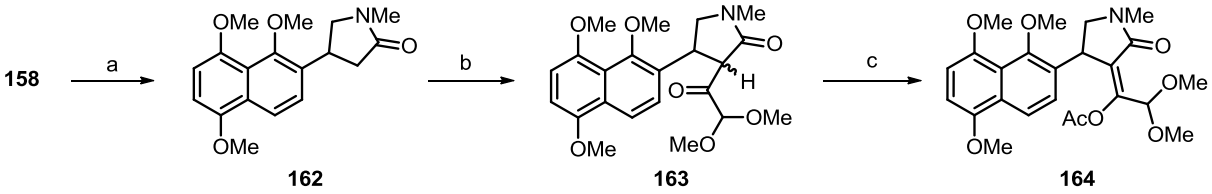
Suzuki coupling between **154** and **156** provided alkene **157** which reacted with methylamine to give lactam **158** (Scheme 30). Transformation of **158** into the corresponding aldol product **159** proceeded smoothly. However, all attempts to cyclize directly acetal **159** to the desired anthracene **161** failed, probably due to deactivation of the electron withdrawing pyrrolinone carbonyl group. In order to alleviate this deactivation, pyrrolinone **159** was converted into the corresponding pyrrole and subsequent reaction with $ZnBr_2$ gave the isomeric anthracene lactam **160** rather than the required tetracycle **161**.



Scheme 30 – Synthesis of anthracene 160

Reagents and conditions: a) $Pd_2(dba)_3$, KF, P(*tert*-Bu)$_3$, THF, 60 °C, 64% or $PdCl_2(PPh_3)_2$, KF [2 M], THF, 60 °C, 91%; b) i) NH_2Me, 65 °C; ii) HCl [4 M], reflux, 76%; c) i) Et_3N, Bu_2BOTf, CH_2Cl_2, −78 °C; ii) $(MeO)_2CHCHO$, −78 °C, 65%; d) i) *tert*-$BuMe_2SiOTf$, $^iPr_2NEt$, CH_2Cl_2, −78 °C; ii) $ZnBr_2$, 32% over 2 steps.

As an alternative, a second route to the desired anthracene **161** was followed beginning with the reduction of **158** with Mg in MeOH to give **162** (Scheme 31). **162** was converted into the corresponding keto-lactam **163** by a crossed-Claisen condensation reaction. Treatment of **163** with LDA and *O*-acylation reaction gave the *Z*-enol acetate **164**. However, attempted cyclisation of **164** under several conditions failed to give the desired anthracene **161**.

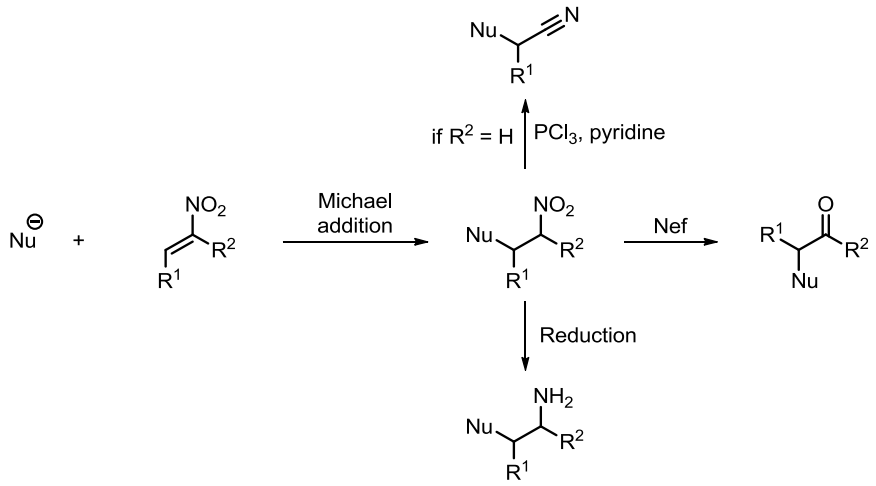


Scheme 31 – Synthesis of *Z*-enol acetate 164

Reagents and conditions: a) Mg, MeOH, 0 °C, 93%; d) i) *n*-BuLi, $^iPr_2NH$, THF, 0 °C; ii) **162**, −78 °C; iii) $(MeO)_2CHCO_2Me$, −78 °C, 69%; e) i) *n*-BuLi, $^iPr_2NH$, THF, 0 °C; ii) AcCl, −78 °C, 40%.

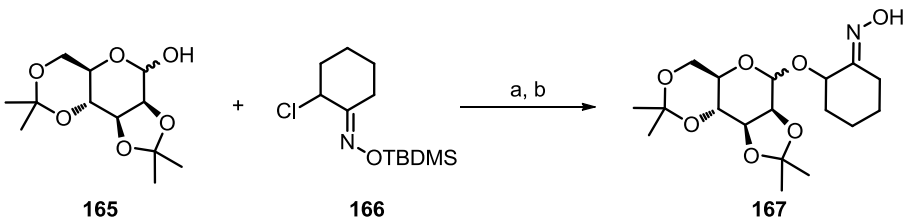
3.3 Studies towards glycosidation *via* conjugate addition of anomeric alkoxides to nitroalkenes and nitrosoalkenes

As part of the total synthesis of lactonamycin (**1**), the introduction of (L)-α-rhodinose residue was required. However, since the direct glycosidation of a sterically hindered α-hydroxy-ketone would be problematic, a novel non-traditional method was explored. This strategy was based on the known potent reactivity of both nitroalkenes and nitrosoalkenes as conjugate addition acceptors,[33] alongside the facile conversion of nitro or nitroso groups into ketones,[34] nitriles[35] and amines[36] (Scheme 32).



Scheme 32 – Reactivity of nitroalkene and their facile conversion

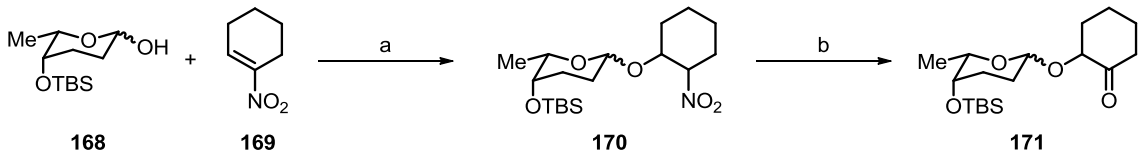
A wide range of anomeric alcohols (glucose derivatives, fucose, mannose, xylose) were prepared and used as nucleophiles on α-chloro-ketoxime **166** (Scheme 33).[37] Deprotonation of alcohol **165** followed by addition of **166** and treatment with TBAF successfully gave the desired glycoside **167** (Scheme 33).



Scheme 33 – Preparation of *O*-glycoside 167

Reagents and conditions: a) *n*-BuLi, THF, −10 °C, AcOH; b) TBAF, THF, −78 °C, 69% (over 2 steps) (mixture of isomers).

Of particular importance was the effective glycosidation of 2-deoxysugar (Scheme 34). **168** was prepared in seven steps from methyl (*S*)-lactate and subjected to the same glycosidation conditions as described above to give **170**. 2-Nitroakyl glycoside **170** was converted into the corresponding 2-oxoalkyl glycoside **171** using an oxidative Nef reaction.



168 **169** **170** **171**

Scheme 34 – Synthesis of 2-oxoalkyl glycoside 171

Reagents and conditions: a) *n*-BuLi, THF, –10 °C, AcOH, 55% α:β, 3:1; b) $KMnO_4$, KOH, $MgSO_4$, 50%.

3.4 Conclusion

The efforts made towards the total synthesis of lactonamycin (**1**) highlight the synthetic complexity associated with the construction of its highly functionalized hexacyclic core and significant challenges are still to be met.

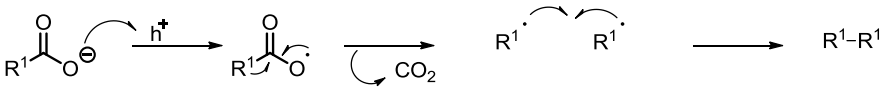
Chapter II Electrodecarboxylation Reactions and their Applications to Natural Product Synthesis

1. Introduction

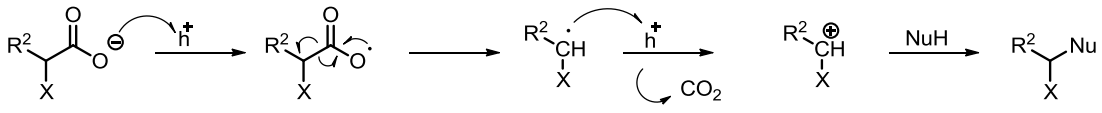
Enormous progress has been made in the study of oxidative processes in recent years and many valuable anodic reactions have been described in the literature. It was discovered early in the 19th-century that electrochemical oxidation of carboxylic acid affords dimeric products. This first electrochemical reaction is now widely known as the *Kolbe Synthesis*. It was first described by Faraday who observed the evolution of ethane during electrolysis of aqueous acetate solutions at smooth platinum electrodes.[38] Kolbe later studied the electrolytic decarboxylation of organic acids in the mid-19th century,[39] although neither he nor Faraday clearly grasped the oxidative reaction mechanism as it is accepted today.

Brown and Walker first proposed the generally accepted mechanism of the Kolbe reaction,[40] which consists of a one-electron oxidation of an organic acid, followed by decarboxylation yielding a radical that dimerises to a homocoupling product (Scheme 35). It was later determined by Hofer and Moest that depending on the structure of the carboxylic acid and the electrolyte, the reaction became a two-electron oxidation (*i.e.*, two successive one-electron oxidations) with a carbocation being formed as an intermediate before nucleophilic addition of the solvent.[41]

Kolbe mechanism:



Hofer-Moest mechanism:



h+ symbolises an anode
X = Electron-donating group

Scheme 35 – The Kolbe reaction and Hofer-Moest decarboxylation

The large amount of literature in connection with the Kolbe or Hofer-Moest (non-Kolbe) electrolysis is covered in a number of reviews[42] and chapters in books.[43] Electrodecarboxylation reactions have been examined in a variety of electrolysis systems, and a suitable combination of solvents, supporting electrolytes, electrode material, pH, concentration of salt and substrate. Other variables have to be chosen according to the synthetic requirements.

2. Radical reaction (One-electron oxidation)

2.1 Kolbe electrolysis

The yield and selectivity of the Kolbe electrolysis is determined by the reaction conditions and the structure of the carboxylate.

Coupling reactions are in general limited to primary carboxylic acids ($R^1CH_2CO_2H$) or when the intermediate radical is substituted by electron-withdrawing groups ($R^1CHX^{\cdot}$ or $R^1CX_2^{\cdot}$ X = CO_2R^2, COR^2). However, there are really few restrictions on the nature of the R^1 group which is submitted to Kolbe oxidation: hydroxyl, alkoxy, keto, carboalkoxy, cyano, amido, halo, nitro, olefinic, acetylenic and ketal acids have all been successfully dimerized *via* the Kolbe reaction.[42,43]

The Kolbe reaction is usually performed with constant current density. A high current density (higher than 0.25 and often up to 1.0 $A.cm^{-2}$) is in general recommended for the Kolbe dimerisation. This is due to a high radical concentration at the electrode surface that promotes dimerisation.[42,43]

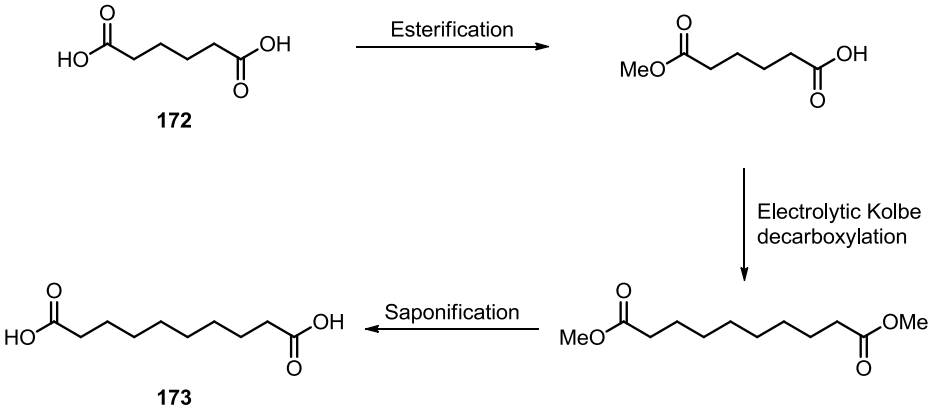
The Kolbe reaction can be performed in a neutral or preferentially in a weakly acidic medium. This is achieved by neutralizing the carboxylic acid to an extent of 2 to 5% by an alkali metal hydroxide or alkoxide. The concentration of carboxylate remains constant during the electrolysis and when the carboxylate is consumed at the anode, base is continuously formed at the cathode and this way the carboxylate is regenerated from the acid. The end point of the electrolysis is indicated by a change of the electrolyte to an alkaline pH. This procedure is called the salt-deficit method. Water is rarely used alone and methanol or aqueous methanol are considered as the best choice as solvent.[42b] The following electrolytes with methanol as solvent have been used: MeOH-MeONa, MeOH-NaOH and MeOH-H_2O-NaOH.[44] In a few cases, aprotic media, such as DMF-KOH, MeCN-Et_3N and Py-H_2O-Et_3N have been used.[45] More recently, Tajima *et al.* developed a novel electrolytic system for Kolbe carbon-carbon coupling electrosynthesis based on the acid-base reaction between carboxylic acids as substrates and solid-supported bases.[46]

Additives can strongly influence the Kolbe-reaction. Foreign anions should be definitely excluded because they seem to disturb the formation of the necessary carboxylate layer at the anode and their negative effect increases with the charge of the anion.[47] In a similar manner, cations can increasingly lower the yield of the reaction possibly due to the formation of oxide layers at the anode.[42f]

The influence of the anode materials in the electrodecarboxylation in aqueous solutions has been well documented and platinum, iridium and vitreous carbon electrodes favor the coupling product.[42f] In contrast, in non-aqueous solvents, a variety of anode materials may be employed and the choice of electrode material is less critical although platinum is still recommended.[42f]

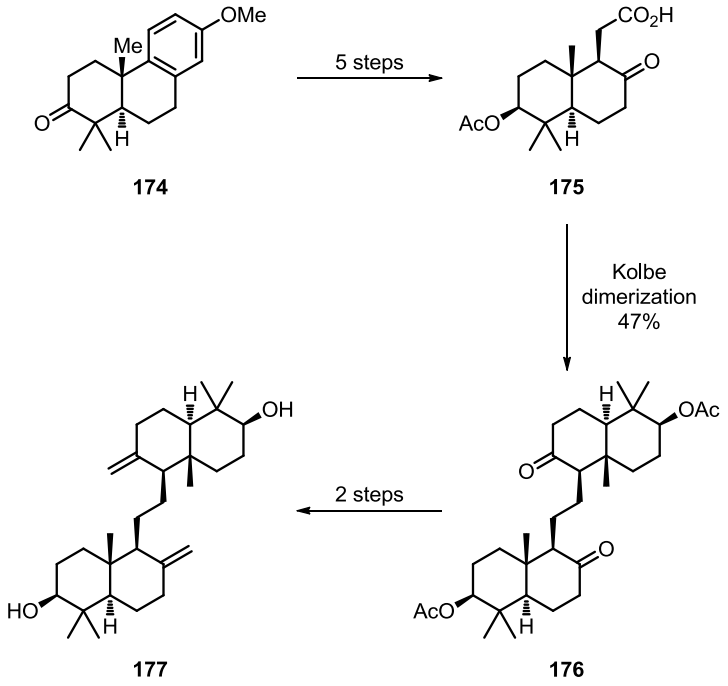
The Kolbe synthesis is a versatile and practical method which has been widely used for the synthesis of a great variety of organic compounds.

Sebacic acid **173** has been produced on an industrial scale by the Kolbe method.[48] The industrial process started with the mono-esterification of adipic acid (**172**) with methanol to obtain mono-methyl ester which is submitted to an electrolytic Kolbe decarboxylation to give the dimethyl ester of sebacic acid (Scheme 36). A final saponification gave sebacic acid **173**.



Scheme 36 – Synthesis of sebacic acid 173

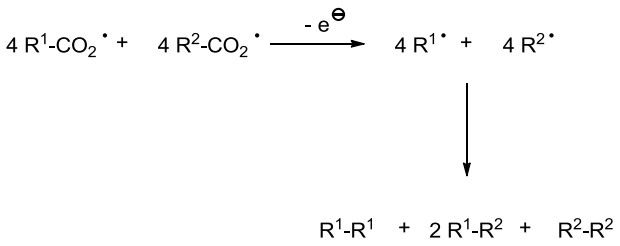
The Kolbe dimerization has also been used as a key step in the synthesis of natural products and this strategy was applied by Davies and co-workers towards the synthesis of (+)-α-onocerin **176** (Scheme 37).[49] Starting from tricyclic ketone **174**, key hydroxyl keto acid **175** was synthesized in five steps. Hydroxyl keto acid **175** was treated with sodium methoxide in methanol and electrolysis to give di-keto dimer **176** in a moderate yield. The latter was converted to the natural product **177** in two steps.



Scheme 37 – Synthesis of (+)-α-onocerin 177

2.2 Kolbe cross-coupling of carboxylic acids

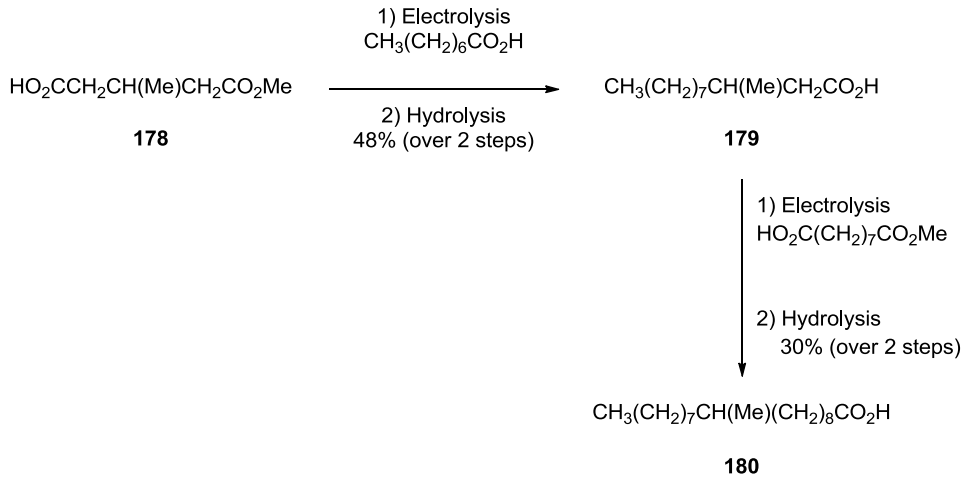
In 1855, Wurts showed that a mixture of carboxylate can be electrolyzed[50] and the reaction was further developed by Crum-Brown and Walker.[51] This cross-coupling method has been widely used for the synthesis of unsymmetrical compounds. However, the intermediate radicals combine statistically and the mixed product is always accompanied by two symmetrical dimers as major side products (Scheme 38). To make this coupling more attractive for synthesis, the less expensive acid is often taken in excess.



Scheme 38 – Kolbe cross-coupling of carboxylic acids

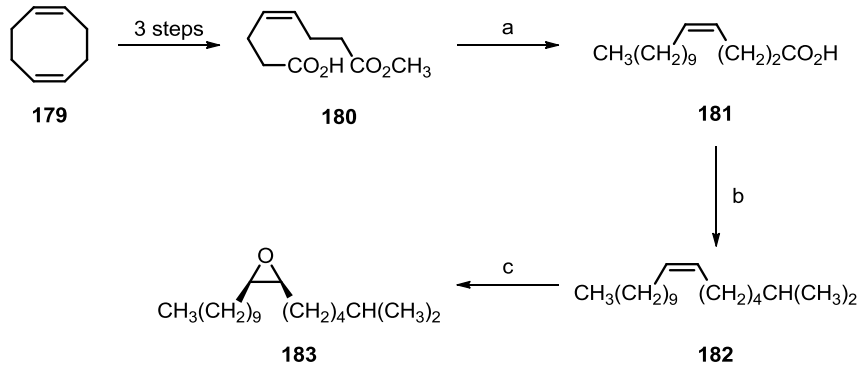
Despite of the disadvantage that at least one symmetrical dimer is formed as a side product, mixed Kolbe electrolysis has turned out to be a powerful synthetic method. It enabled the efficient synthesis of rare fatty acids, pheromones and chiral building blocks.

In the 1950's, Weedon and co-workers reported the synthesis of many fatty acids using this methodology and the synthesis of (±)-tuberculostearic acid **180** is illustrated in Scheme 39.[52] Octanoic acid and (±)-methyl hydrogen β-methylglutarate **178** were electrolyzed in methanol using platinum electrodes and acid **179** was obtained in 48% after hydrolysis. Finally, a second Kolbe electrolysis using the same conditions in the presence of methyl hydrogen azelate gave (±)-tuberculostearic acid **178** in 30% yield after hydrolysis.



Scheme 39 – Synthesis of (±)-tuberculostearic acid 178

Disparlure **183**, the sex attractant of the gypsy moth Lyrnantria dispur, has been synthesized following two successive Kolbe electrolysis.[53] Starting from 1,5-cyclooctadiene **179**, key carboxylic acid **180** was synthesized in three steps (Scheme 40). Acid **180** was subjected to a Kolbe electrolysis in the presence of nonanoic acid and acid **181** was formed in 48% yield. Acid **181** was subjected to a second Kolbe electrolysis with 4-methylvaleric acid as co-reactant and coupling product **182** was obtained in 62% yield. Finally, the double bond in **182** was epoxidized to yield disparlure **183**.

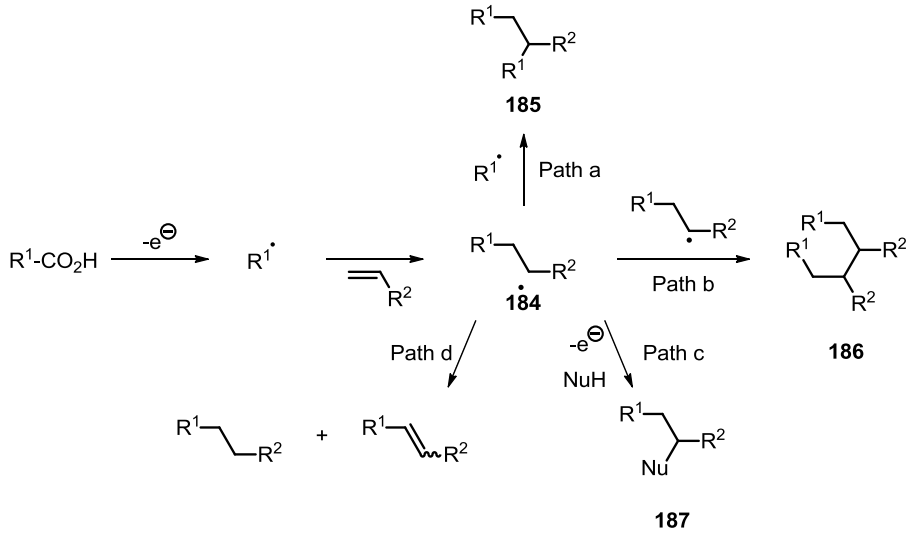


Scheme 40 – Synthesis of disparlure 183

Reagents and conditions: a) $CH_3(CH_2)_7CO_2H$, Pt anode, MeOH; MeOH, KOH; H^+, 48%; b) $(CH_3)_2CH(CH_2)_2CO_2H$, Pt anode, MeOH, 62%; c) m-Cl-$C_6H_4CO_3H$, 89%.

2.3 Addition of Kolbe radicals to double bonds

Kolbe radicals can be added to olefins that are present in the electrolyte (Scheme 41). The primary adduct **184**, a new radical, can further react with the Kolbe radical to form an additive monomer **185** (Path a), it can dimerize to form an additive dimer **186** (Path b), it can be further oxidized to a carbocation, that reacts with a nucleophile to give **187** (Path c), or it can disproportionate (Path d).

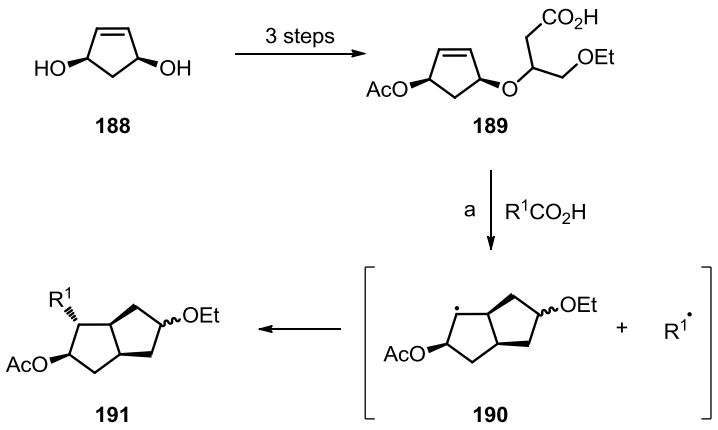


Scheme 41 - Addition of Kolbe radicals to double bonds

Oligomerization and polymerization of the olefin by addition of the primary adduct to further monomers occurs only in a few cases. The radical concentration is so high that the termination step and not the propagation step of the polymerization predominates.

To some degree, the ratio of additive monomer to additive dimer can be influenced by the current density. High current densities favor the formation of additive monomers **185**, whereas low current densities favor the formation of additive dimers **186**. At high current densities, which correspond to a high radical concentration, the olefin can only trap a part of the Kolbe radical formed. This leads to a preferred coupling to the Kolbe dimer and a combination of the Kolbe radical with the primary adduct to form the additive monomer **185**. At low current densities, the majority of the Kolbe radicals are scavenged by the olefin, which leads to a preferential formation of the additive dimer **186**.

This reaction has been applied to the synthesis of a prostaglandine precursor **191** by Schäfer and co-workers.[54] Starting from diol **188**, key precursor **189** was synthesized in three steps (Scheme 42). Kolbe electrolysis of **189** with a co-acid successfully gave **191**. The reaction proceeds *via* anodic decarboxylation to a radical that undergo a 5-exo-trig cyclization to form a secondary alkyl radical **190** that couples with another radical, generated by co-electrolysis from a second acid.



Scheme 42 – Synthesis of 191

Reagents and conditions: a) MeOH, 5% neutralization, electrolysis, 40–45 °C, $R^1 = CH_3$, 35%, $R^1 = (CH_2)_2CO_2Me$, 33%.

3. Carbenium ion reaction (Two-electron oxidation)

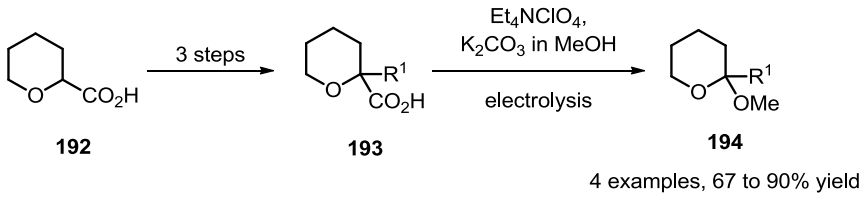
The two-electron process in the electrodecarboxylation has been intensively investigated and the yield and selectivity of this pathway is determined by the reaction conditions and the structure of the carboxylate.

It has been shown that low current densities suppress Kolbe-dimerization[47b] and non-Kolbe electrolysis is favored when graphite or porous carbon are used as the electrode material.[55]

Addition of certain salts, such as perchlorate, fluoroborate, sulfate, dihydrogen phosphate, bicarbonate, and fluoride, tends to inhibit the radical reaction and favor the formation of cation intermediates.[47b,56] The shift from the radical to the carbocation pathway by perchlorate is due to the blocking of the anode surface by perchlorate adsorption, which lowers the radical concentration at the electrode. This disfavors the bimolecular radical dimerisation and favors the second electron transfer to form the carbenium ion.

Electrogenerated carbenium ions, which are stabilized by neighboring heteroatom (electron donating groups), such as, oxygen, nitrogen, sulphur, and others, can be trapped by nucleophiles. For example, acetoxylation and methoxylation proceed *via* electrolysis in acetic acid or methanol, respectively while acetamidation occurs in wet acetonitrile, in which the nucleophilic attack of the nitrile group on the carbenium ion R^+ tends to give iminium cation, the hydrolysis of which gives the acetimidate. Based on their previous results for Kolbe electrolysis, Tajima *et al.* showed that their methodology based on the acid-base reaction between carboxylic acids as substrates and solid-supported bases could afford methylated and acetoxylated products when the reaction was conducted in methanol,[57] or acetic acid,[58] respectively.

Spiroketals often constitute key fragment in the structure of natural products and antibiotics and Wuts *et al.* investigated the synthesis of simple ketal.[59] Acid **192** was chosen as a model substrate and key precursor **193** was synthesized in three steps. Treatment of **193** in anhydrous methanol with tetraethylammonium perchlorate and potassium carbonate afforded ketal **194** in good to excellent yields.



Scheme 43 – Ketal formation using electrodecarboxylation

4. Conclusion

Carboxylic acids can be converted by anodic oxidation into radicals and/or carbocations. Experimental variables affecting the course of the electrolytic decarboxylation of carboxylic acids are summarized in Table 1.

Variables	One-electron process	Two-electron process
Current	High current density	Low current density
Electrode material	Pt electrode	Graphite electrode
Electrolyte	Slightly acid or neutral	Basic
Additive	None	ClO_4^-, SO_4^{2-}, HCO_3^-…
Temperature	< 50 °C	Not critical

Table 1 – Conditions to use in order to favor the one-electron or the two-electron pathway

The conditions specified for a one-electron process are recommended for the Kolbe dimerisation; otherwise the reaction through carbenium ion (non-Kolbe reaction) may occur predominantly. It should be emphasized that even under the conditions most favorable for the Kolbe dimerisation, the cation-derived products are usually formed to some extent or, in particular cases, as a major product, depending on the structure of the carboxylic acid used.

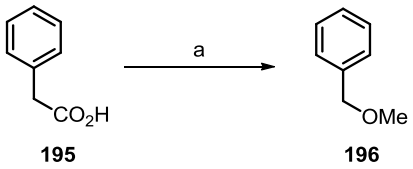
Chapter III Results and Discussion

Electrodecarboxylation Reactions on Simple Substrates and Model Studies

1. Electrodecarboxylation on simple substrates

1.1 Electrodecarboxylation reactions using phenylacetic acid 195

Electrolytic decarboxylations were set up using simple substrates to optimize the conditions for this chemistry. Commercially available phenylacetic acid **195** was used first to model the carboxylic acid and was expected to give (methoxymethyl)benzene **196** (Scheme 44).



Scheme 44 – Synthesis of (methoxymethyl)benzene 196 *via* electrodecarboxylation

Reagents and conditions: a) MeOH (see Table 2), NaOMe (5.4 M in MeOH, see Table 2), 2 graphite electrodes.

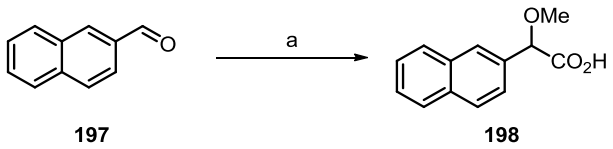
Entry	MeOH (mL)	NaOMe (mL)	Additives (eq.)	Results
a	15	0.3	None	No reaction after 6 hours
b	5	0.3	None	8% conversion after 6 hours
c	5	2	None	50% **196**
d	5	2	NH_4Cl (10)	84% **196**

Table 2 – Optimization for the formation of 196 *via* an electrodecarboxylation reaction

Following the procedure described by Vogel *et al*,.[60] phenylacetic acid **195** was treated with a mixture of sodium methoxide in methanol [0.1 M]. Unfortunately, the reaction seemed to be very slow under these conditions (Table 2, entry a). In order to address this issue, the reaction was performed at a concentration of 0.3 M and 8% conversion was observed by ^{1}H-NMR after six hours (Table 2, entry b). The reaction mixture was further concentrated and the reaction was repeated at a concentration of 1.54 M and **196** was successfully isolated in moderate yield after six hours (Table 2, entry c). The addition of ten equivalents of the inert salt NH_4Cl improved the yield to 84% after six hours (Table 2, entry d).

1.2 Electrodecarboxylation reactions using 2-methoxy-2-(naphthalen-2-yl)acetic acid 197

With these promising results, the reaction was further studied using 2-methoxy-2-(naphthalen-2-yl)acetic acid **198** as substrate. Based on previous results within the literature,[42] it was expected that the methoxy group would act a as electron donating group and therefore stabilize the carbocation formed and favor the two-electron pathway. Synthesis of **198** was achieved in one step starting from 2-naphthaldehyde **197** (Scheme 45).[61] Treatment of 2-naphthaldehyde **197** with bromoform in methanol and subsequent addition of potassium hydroxide in methanol successfully gave 2-methoxy-2-(naphthalen-2-yl)acetic acid **198** in 68% yield.

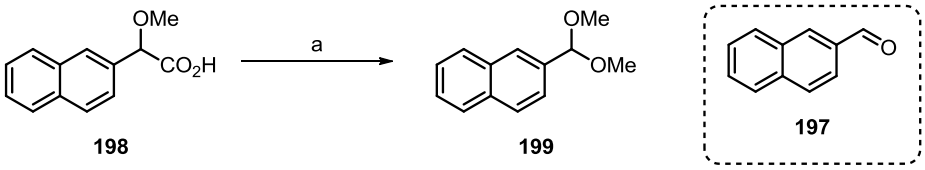


197 **198**

Scheme 45 – Synthesis of 2-methoxy-2-(naphthalen-2-yl)acetic acid 198

Reagents and conditions: a) $CHBr_3$, KOH, MeOH, 0 °C to rt, 12 h, 68%.

A series of electrodecarboxylation reactions were pursued utilizing **199** (Scheme 46).



Scheme 46 – Synthesis of 199 *via* electrodecarboxylation

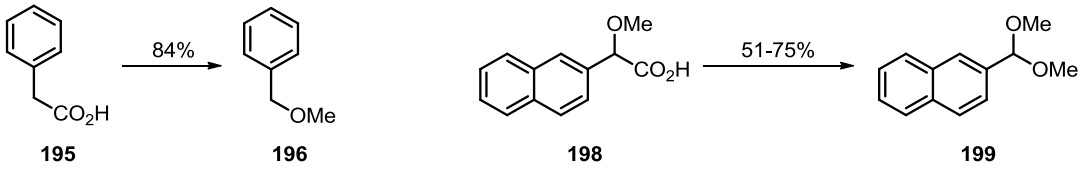
Reagents and conditions: a) MeOH, NaOMe, graphite electrodes.

Electrochemically induced oxidative decarboxylation in methanol proceeded smoothly and starting material **198** was consumed after four hours as seen by ^{1}H-NMR and GCMS analysis. Unfortunately, after HCl quench and aqueous work-up, product **199** was isolated in a poor 18% yield alongside 2-naphthaldehyde **197** (6% yield). As a result, it was thought that using milder conditions during the work-up may decrease the amount of aldehyde **197** and therefore increase the yield of the reaction. Upon quench with AcOH [1 M in MeOH] or after addition of an acidic resin (Dowex 50WX2), acetal **199** was isolated in 31% and 75% yields, respectively and aldehyde **197** was obtained in 7% and 15% yields, respectively. Recently, Tajima *et al.* reported the development of an electrolysis system based on the acid-base reaction between carboxylic acids and solid-supported bases.[57] These polymer-supported bases could be easily filtrated and product could be isolated cleanly after concentration. Treatment of **198** with polymer-supported piperidine in methanol successfully gave pure product **199** in 51% yield after a single filtration. In this case, no formation of 2-naphthaldehyde **197** was observed by ^{1}H-NMR.

1.3 Conclusion

The electrodecarboxylation reaction was successfully attempted on simpler substrates such as phenylacetic acid **195** and 2-methoxy-2-(naphthalen-2-yl)acetic acid **198** (Scheme 47). Starting from phenylacetic acid **195**, the corresponding product **196** was isolated in 84% yield when the reaction was conducted in the presence of ammonium chloride.

In a similar manner, acetal **199** was successfully obtained from acid **198**. In this case, aldehyde **197** was formed alongside the desired product and its formation could be reduced depending on the work-up conditions. Its formation could be avoided by the use of a polymer supported base.



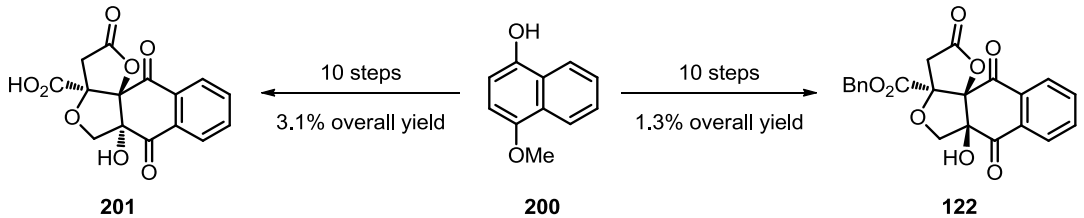
Scheme 47 – Electrodecarboxylation attempts on substrates 196 and 199

With these promising results, the synthesis of a model system closer to lactonamycin (**1**) was investigated in order to further experiment this reaction.

2. Towards a new synthesis of ABCD ring system of lactonamycin (1)

2.1 Introduction

The successful total synthesis of lactonamycin (**1**) will require an efficient electrodecarboxylation reaction for the introduction of the angular methoxy group. With the aim of carrying out such a reaction, a model carboxylic acid that displayed similar chemical reactivity to that of lactonamycinone (**2**) was necessary. The synthesis of ABCD model system had previously been conducted within the Barrett group in order to develop chemistry for the construction of the ABCD ring system of lactonamycin (**1**) (Scheme 48).[31] Model system **122** was synthesized in ten steps starting from 4-methoxy-1-naphthol **200** in 1.3% overall yield. A different model system **201** bearing the anti-diol configuration was also synthesized in ten steps with an overall yield of 3.1%. In order to synthesize large quantities of model system **201**, a new route had to be investigated.

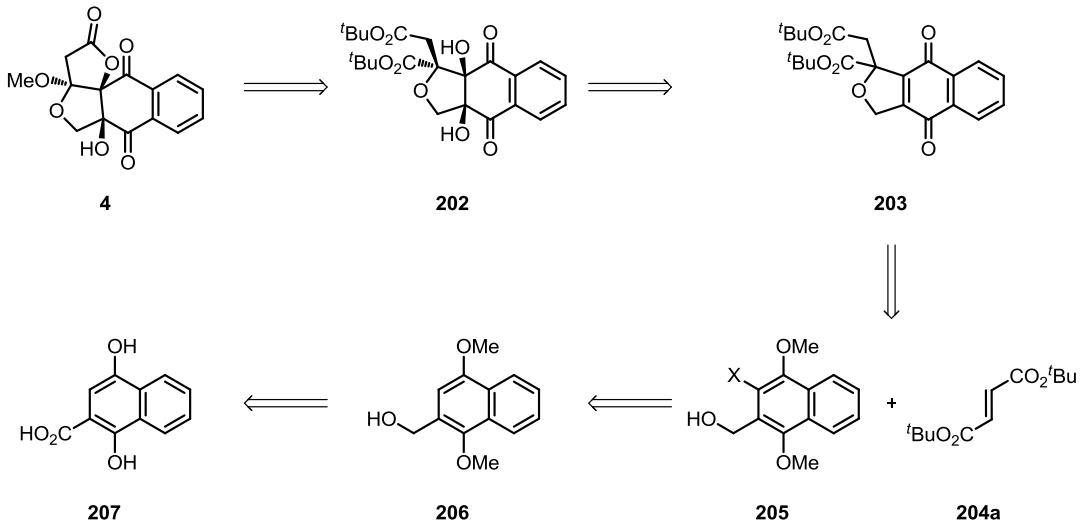


Scheme 48 – Previous synthesis of model systems 201 and 122

2.2 Retrosynthetic approach *via* a tandem Heck coupling/Michael addition sequence

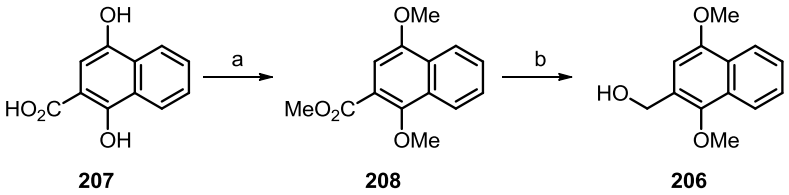
2.2.1 First retrosynthetic approach

Retrosynthetically, model system **4** could be obtained from diol **202** after cleavage of the *tert*-butyl esters and subsequent lactonisation followed by electrodecarboxylation (Scheme 49). Diol **202** could be synthesized from quinone **203** *via* a dihydroxylation. Quinone **203** could be obtained from halide alcohol **205** and di-ester **204a** after a tandem Heck coupling/Michael addition sequence followed by oxidation. Halide alcohol **205** could be obtained from alcohol **206**. Finally, alcohol **206** could be synthesized from commercially available dihydroxy acid **207**.



Scheme 49 – First retrosynthetic approach towards ABCD ring system of lactonamycin (1)

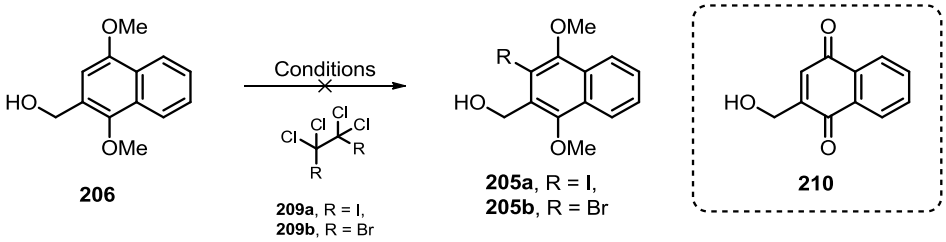
The initial approach to halide alcohol **205** was inspired by the chemistry carried out by Borch and co-workers.[62] The synthesis began with global protection of dihydroxy acid **207** to afford **208** (Scheme 50). The ester moiety in **208** was reduced using lithium aluminium hydride to afford alcohol **206**.



Scheme 50 – Synthesis of alcohol 206

Reagents and conditions: a) MeI, K_2CO_3, Me_2CO, reflux, 12 h, 96%; b) $LiAlH_4$, THF, reflux, 3 h, 94%.

Following the retrosynthetic approach, the key step of the synthesis will be the tandem Heck coupling/Michael addition sequence[63a] to form tricycle **203** after oxidation. It was thought that this sequence will give higher yields and will proceed faster if the halide in **205** will be an iodide. To this aim, the conversion into iodide derivative **205a** was investigated first (Scheme 51). Unfortunately, treatment with *n*-BuLi followed by 1,1,2,2-tetrafluoro-1,2-diiodoethane **209a** did not yield any expected product **205a** compared to the 50% previously reported by Borch and co-workers. (Table 3, entry a).[62] The reaction was repeated and the reaction mixture was warmed up to room temperature after addition of *n*-BuLi and the electrophile was added at this temperature. Unfortunately, the outcome of the reaction did not improve (Table 3, entry b). The reaction was repeated with more reactive lithium species (*s*-BuLi and *t*-BuLi with TMEDA) and a different electrophile **209b**. Unfortunately, none of the conditions tested successfully afforded the desired products **205a** and **205b** (Table 3, entries c to e). Ag(I)-assisted iodination using a mixture of iodine and silver trifluoroacetate only afforded quinone derivative **210** in modest yield (Table 3, entry f).[64] Upon treatment with iodine monochloride, no reaction occurred (Table 3, entry g).[65] Bedekar and co-workers demonstrated that electron-rich aromatic compounds could be iodinated using a mixture of potassium iodide and potassium iodate.[66] Unfortunately, no reaction was observed and alcohol **206** could be recovered (Table 3, entry h).

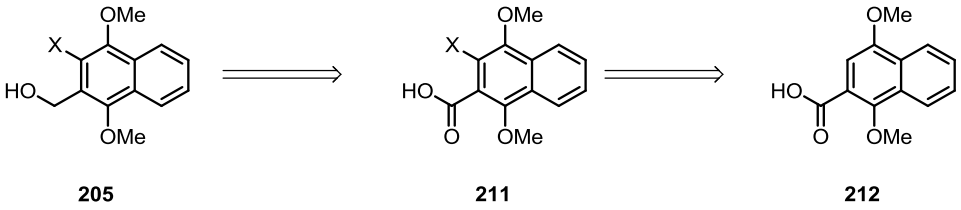


Scheme 51 – Attempts to synthesize halide alcohol 205a or 205b

Entry	Reagents (eq.)	Solvent	Temperature	Results
a	*n*-BuLi (4.0), **209a** (1.2)	THF	–78 °C	No reaction
b	*n*-BuLi (4.0), **209a** (1.2)	THF	–78 °C to rt	No reaction
c	*s*-BuLi (4.0), TMEDA (2.0), **209a-b** (1.2)	THF	–78 °C	No reaction
d	*s*-BuLi (4.0), TMEDA (2.0), **209a-b** (1.2)	THF	–20 °C	No reaction
e	*t*-BuLi (4.0), TMEDA (2.0), **209a-b** (1.2)	THF	–78 °C	No reaction
f	I_2 (1.05), $Ag(O_2CCF_3)$ (1.5)	$CHCl_3$	0 °C to rt	**210** (38%)
g	ICl (1.1)	CH_2Cl_2	rt	No reaction
h	i) KI (0.7) , KIO_3 (0.35); ii) HCl	$MeOH/H_2O$	rt	No reaction

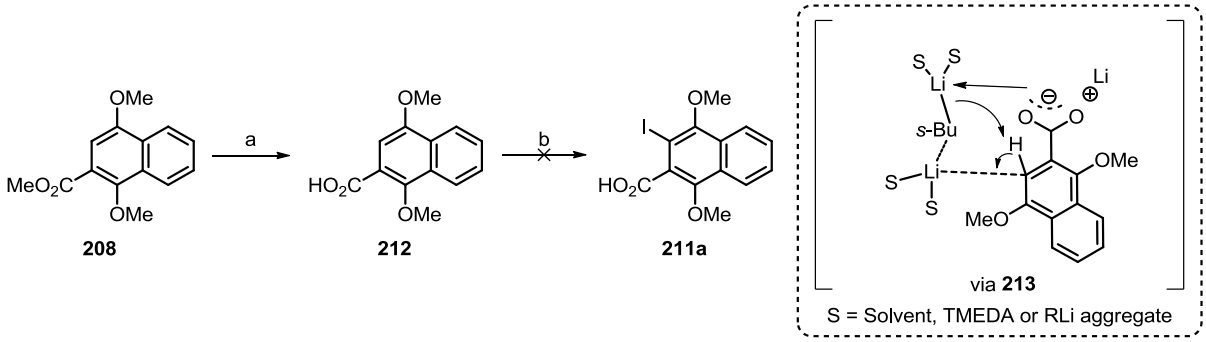
Table 3 – Attempts to introduce the halogen in 206

Based on a similar strategy developed by Mortier and co-workers who showed that unprotected 2-methoxybenzoic acid are deprotonated exclusively in the position *ortho* to the carboxylate by treatment with a mixture of *s*-BuLi/TMEDA at –78 °C,[67] it was thought that key halide alcohol **205** could be obtained from the corresponding carboxylic halide **211** after directed *ortho*-metalation and reduction of the carboxylic moiety (Scheme 52).



Scheme 52 – Second method for the introduction of the halogen group

Starting from already synthesized ester **208**, the ester moiety was saponified using sodium hydroxide in water/methanol (Scheme 53) to give carboxylic acid **212**.[68] Following Mortier's precedent,[67] carboxylic acid **212** was treated with the 1:1 complex *s*-BuLi/TMEDA in tetrahydrofuran for 2 h at −78 °C and quenched with a solution of iodine in tetrahydrofuran. Unfortunately, no reaction was observed and none of the desired product **211a** could be detected by ^{1}H and ^{13}C NMR spectroscopy. The lithiation was also attempted at −20 °C but again no reaction occurred.

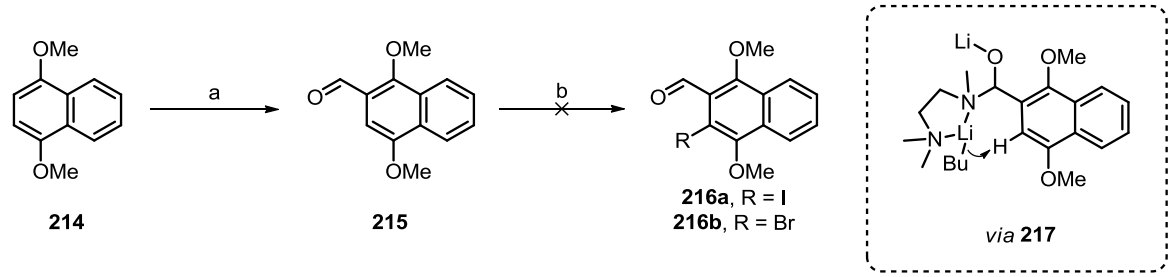


Scheme 53 – Synthesis of 212 and attempt to introduce the halogen group

Reagents and conditions: a) NaOH (20% in H_2O), MeOH, reflux, 3 h, 95%; b) i) *s*-BuLi (2.2 eq.), TMEDA (2.2 eq.); ii) I_2, THF, −78 °C or −20 °C.

As a last effort, the halogen could be introduced using Comins' methodology for directed *ortho*-lithiation of aryl aldehydes.[69] Comins showed that the addition of aromatic aldehydes to certain lithium dialkylamides in THF at low temperatures gave α-amino alkoxides which were *ortho* lithiated with excess of *n*-BuLi. Subsequent alkylation and hydrolysis provided *ortho*-substituted aromatic aldehydes *via* a *one*-pot reaction. The synthesis began from 1,4-dimethoxynaphthalene **214** which was converted to aldehyde **215** *via* a Vilsmeier–Haack formylation (Scheme 54).[70] Unfortunately, addition of **215** into a premixed solution of *N,N,N',N'*-trimethylethylenediamine and *n*-BuLi at −20 °C

followed by a second addition of *n*-BuLi and quench with iodine or carbon tetrabromide failed to give the expected adduct **216a** or **216b** and only starting material **215** was recovered.[69]



214 **215** **216a**, R = I **216b**, R = Br *via* **217**

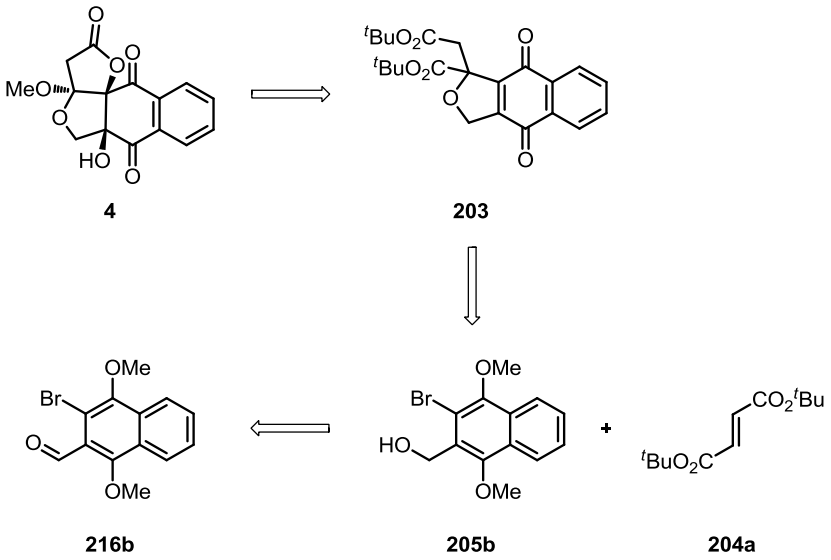
Scheme 54 – Synthesis of aldehyde 215 and attempt to introduce the halogen group

Reagents and conditions: a) i) $POCl_3$, DMF, 0 °C, 30 min; ii) **214** (1.0 eq.) in $CHCl_3$, reflux, 53%; b) i) *N*,*N*,*N'N'*-trimethylethylenediamine (1.07 eq.), *n*-BuLi (1.03 eq.), –20 °C, 15 min; ii) **215** in THF, –20 °C, 20 min; iii) *n*-BuLi (3.0 eq.), 1 h; iv) I_2 or CBr_4, –78 °C.

Given the difficulties associated with introduction of the halogen group *via* lithiation, this route was no longer investigated and was consequently abandoned.

2.2.2 Second retrosynthetic approach

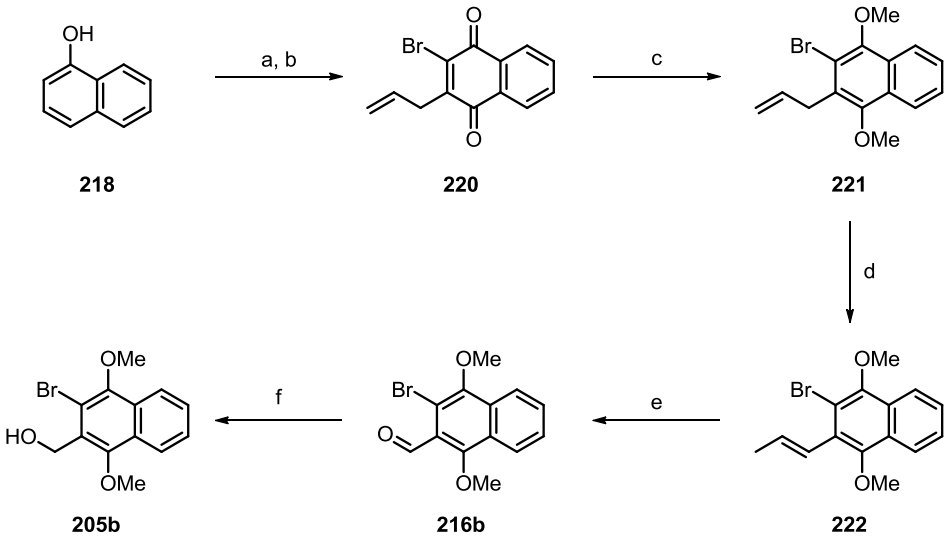
As the introduction of the halogen onto the naphthalene ring tended to be problematic, a new route where the bromine was already in place was examined and the synthesis of bromo-aldehyde naphthoquinone **216b** was investigated. Retrosynthetically, tricycle **203** could be obtained from aldehyde **205b** after reduction of the carbonyl moiety to form the corresponding alcohol **205b**. As suggested in the first retrosynthetic route, a tandem Heck coupling/Michael addition sequence with di-ester **204a** could give tricycle **203** after oxidation (Scheme 55).[63a] The stereochemistry of the double bond was not relevant and di-*tert*-butyl fumarate **204a** was chosen arbitrarily.



Scheme 55 – Second retrosynthetic approach towards ABCD ring system of lactonamycin (1)

2.2.2.1 Synthesis of bromo-alcohol naphthoquinone 205b

The synthesis of intermediate **205b** started with the oxidation of 1-naphthol **218** with *N*-bromosuccinimide to give 2-bromo naphthoquinone **219**,[71] upon which radical allylation using a silver persulfate catalyzed oxidative decarboxylation of vinylacetic acid, effected the introduction of the allyl side chain to afford **220** in 73% yield (Scheme 56).[72] Reductive methylation of **220**, followed by isomerization of the double bond gave **222**. Oxidative cleavage of the double bond using osmium tetraoxide and sodium periodate provided aldehyde **216b**. Finally, treatment with sodium borohydride afforded bromo-alcohol naphthoquinone **205b** in 43% steps over six steps.

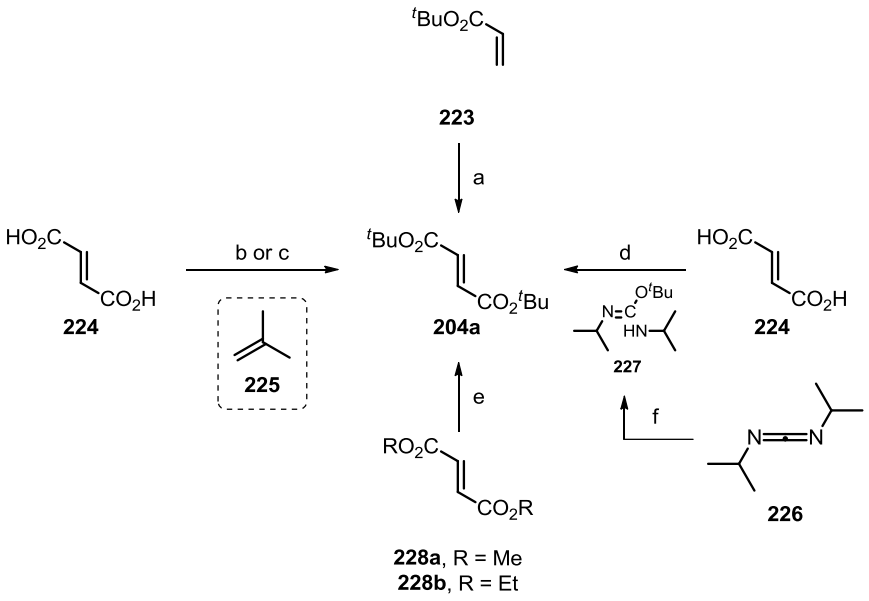


Scheme 56 – Synthesis of bromo-alcohol naphthoquinone 205b

Reagents and conditions: a) NBS, AcOH/H_2O (1:2), 45 °C, 1 h, 91%; b) i) 3-butenoic acid, $AgNO_3$, MeCN, 65 °C; ii) $(NH_4)_2S_2O_8$, H_2O, 65 °C, 2 h, 73%; c) i) TBAI, $Na_2S_2O_4$, THF/H_2O (2.5:1), 30 min; ii) KOH, H_2O, rt, 1 h; iii) Me_2SO_4, 4 h, 93%; d) *tert*-BuOK, THF, 0 °C, quantitative; e) OsO_4, $NaIO_4$, THF/H_2O (2:1), 65 °C, 12 h, 73%; f) $NaBH_4$, MeOH, rt, 1 h, 95%.

2.2.2.2 Investigations towards the synthesis of di-tert-butyl fumarate 204a

Di-*tert* butyl fumarate **204a** could be synthesized in many different ways such as: dimerisation of *tert*-butyl acrylate **223** with Grubbs catalyst (pathway a),[73] acid catalyzed esterification of fumaric acid **224** under high pressure (pathway b),[74] esterification with *tert*-BuOH (pathway c)[75] or with **227** (pathway d)[76] and finally transesterification of di-ester **228a** or **228b** with *tert*-BuOK (pathway e).[77]

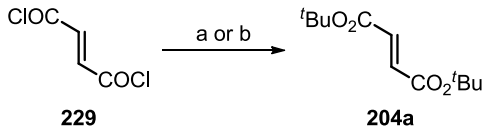


Scheme 57 – Synthesis of di-*tert*-butyl fumarate 204a

Reagents and conditions: a) Grubbs II (5 mol%), CH_2Cl_2 [0.4 M], reflux, 3 h, 88%; b) **225**, Et_2O, 0 °C to rt, pressure, 4%; c) *tert*-BuOH, DMAP, DCC, CH_2Cl_2 or DMF, 0 °C to rt; d) **227**, CH_2Cl_2, reflux, 48 – 66%; e) *tert*-BuOK, Et_2O, 0 °C to rt; f) *tert*-BuOH, CuI, rt, 3 d, 85%.

Following a procedure developed by Grubbs,[73] di-*tert*-butyl acrylate **223** was successfully dimerized using Grubb's II catalyst in refluxing dichloromethane and **204a** was isolated in 88% yield (Scheme 57, pathway a). However, this methodology was not suitable for scale-up. As a result, alternative strategies were investigated. Treatment of **224** with 2-methyl-prop-1-ene **225** in Et_2O with catalytic amount of sulphuric acid afforded the expected product albeit in only 4% yield (pathway b).[74] This low yield can be explained by the loss of pressure within the reaction flask over time. Esterification using a mixture of DCC/DMAP in CH_2Cl_2 only afforded starting material **224**.[75] Because of the poor solubility of **224** in CH_2Cl_2, the reaction was repeated in DMF, but this time only decomposition was observed (pathway c). Upon treatment of a suspension of **224** in CH_2Cl_2 with freshly prepared **227**,[76b] the expected product **204a** was isolated in a variable yield of 48% to 66% (pathway d). As reported in the literature,[76a] it was necessary to use a larger excess of reagent **227** to drive the reaction to completion due to the tendency of this reagent to form isobutene *via* an E1-type side reaction. Finally, transesterification of **228a** and **228b** with potassium *tert*-butoxide resulted in complete decomposition (pathway e).[77]

A new strategy using more reactive fumaryl chloride **229** was investigated (Scheme 58). Treatment of **229** with *tert*-BuOH and *N*,*N*-dimethylaniline in diethyl ether afforded the expected di-ester **204a** in 38% yield.[78] Gratifyingly, upon treatment with potassium *tert*-butoxide, **204a** was obtained in 57% yield.



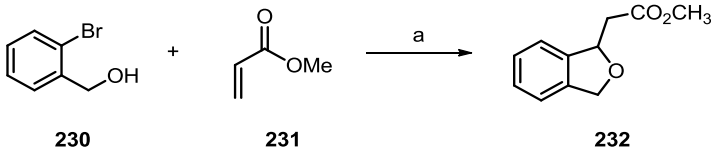
229 **204a**

Scheme 58 - Synthesis of di-*tert*-butyl fumarate 204a starting from fumaryl chloride 229

Reagents and conditions: a) *tert*-BuOH, *N*,*N*-dimethylaniline, Et_2O, 0 °C to rt, 38%; b) *tert*-BuOH, *tert*-BuOK, Et_2O, 0 °C to rt, 57%.

2.2.2.3 Tandem Heck coupling/Michael addition sequence

With coupling partners **204a** and **205b** in hand, the key coupling reaction was investigated. This tandem Heck coupling/Michael addition was inspired by the chemistry developed by Heck and co-workers on the palladium-catalyzed synthesis of 2-quinolone derivatives from 2-iodoanilines.[63a] Of particular importance, Heck and co-workers described the synthesis of **232** starting from 2-bromo benzyl alcohol **230** and methyl acrylate **231** (Scheme 59).



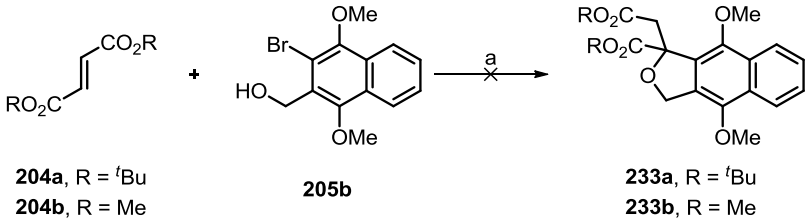
230 **231** **232**

Scheme 59 – Synthesis of 232 following Heck's methodology

Reagents and conditions: a) **230** (1.0 eq.), **231** (1.25 eq.), $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, 100 °C, 72 h, 68%.

Unfortunately, upon treatment with palladium acetate, tri(*o*-tolyl)phosphine and triethylamine, no reaction was observed after 12 hours and only unreactive starting materials could be recovered (Scheme 60). It was thought that the Heck coupling did not proceed due to the possible steric hindrance from both *tert*-butyl esters. As a result, commercially available di-methyl fumarate **204b**

was used under the same reaction conditions, however, only unreactive starting materials were recovered.



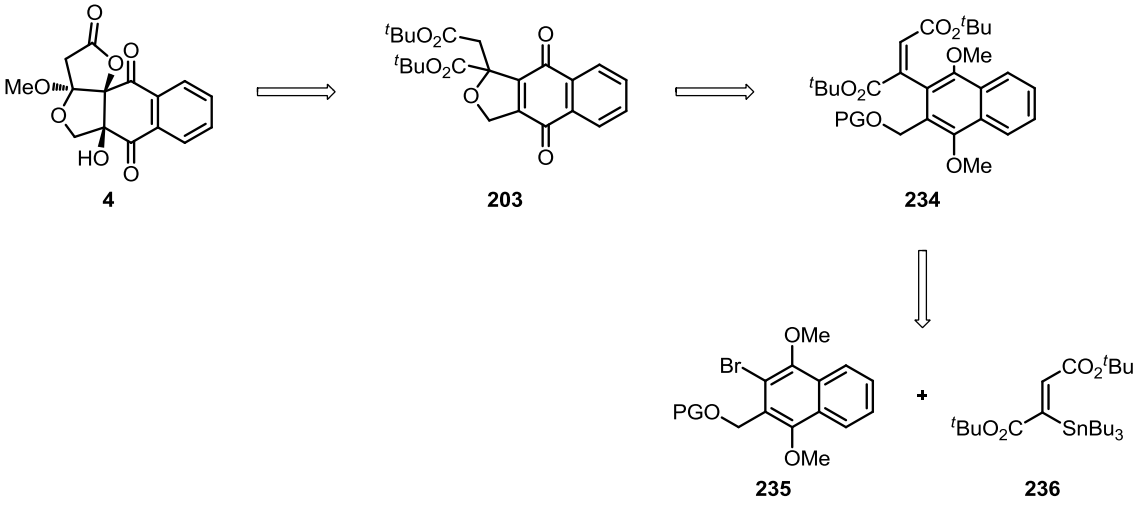
Scheme 60 – Tandem Heck coupling/Michael addition sequence towards tricycle 233

Reagents and conditions: a) $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, 85 °C, 12 h.

As a result, the synthesis of tricycle **233** *via* the tandem Heck coupling/Michael addition sequence was abandoned and a new strategy was investigated.

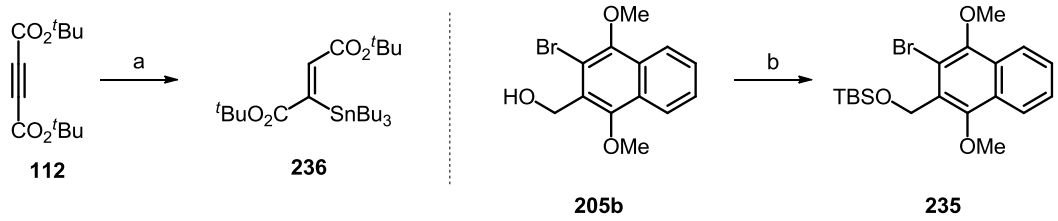
2.3 Retrosynthetic approach *via* a Stille coupling

It was thought that key tricycle **203** could be obtained from alkene **234** after deprotection of the alcohol, subsequent Michael addition and oxidation (Scheme 61). Alkene **234** could be synthesized *via* a Stille coupling between protected-alcohol bromo naphthoquinone **235** and stannane **236**.



Scheme 61 – Retrosynthetic approach *via* a Stille coupling

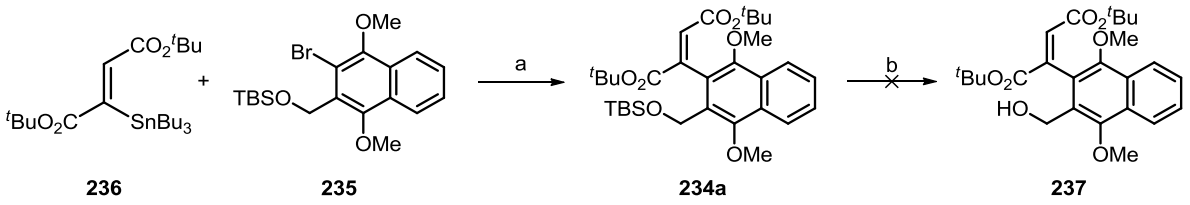
Stannane **236** was prepared starting from the corresponding alkyne **112** by hydrostannation (Scheme 62).[79] The use of 1.1 equivalents of fresh tributyltin hydride led to complete conversion after three hours to afford **236**, which was used immediately in the Stille coupling. Only one product was obtained during the hydrostannation, the stereochemistry of which was assigned as *trans* as the authors suggested that addition of trialkyltin hydrides to disubstituted ethynes affords mainly the trans-addition product.[79] Alcohol **205b** was protected as the corresponding TBS-ether upon treatment with TBSCl and imidazole and **235** was isolated in 97% yield.



Scheme 62 – Preparation of precursors 235 and 236

Reagents and conditions: a) Bu_3SnH, PhH, rt, 3 h, 99%; b) TBSCl, imidazole, 0 °C to rt, 12 h, 97%.

TBS-protected alcohol **235** and freshly prepared stannane **236** were treated with tetrakis(triphenylphosphine)palladium and copper(I) iodide and coupling product **234a** was obtained in moderate yield alongside the corresponding reduced product (Scheme 63). Based on previous results within the group that showed that TBS-deprotection of similar compounds with TBAF resulted in decomposition,[80] the deprotection was attempted under acidic conditions. Unfortunately, TBS-deprotection of **234a** with concentrated HCl failed and only a complex mixture of highly polar by-products was obtained probably due to the steric hindrance of the *tert*-butyl groups preventing the removal of the silyl group. Unexpectedly, other attempts to couple **235** and **236** were not reproducible, no coupling product **234a** was formed and as a result, the Stille route was abandoned.

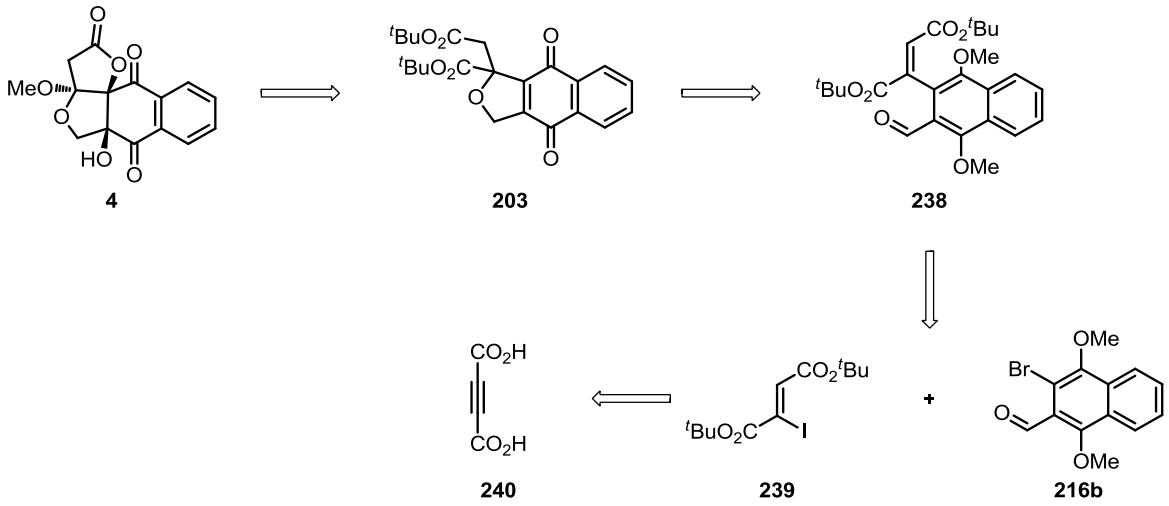


Scheme 63 – Stille coupling and TBS-deprotection

Reagents and conditions: a) **236** (1.2 eq.), $Pd(PPh_3)_4$ (5 mol%), CuI, PhMe, reflux, 12 h, 45%; b) conc. HCl, THF, 0 °C.

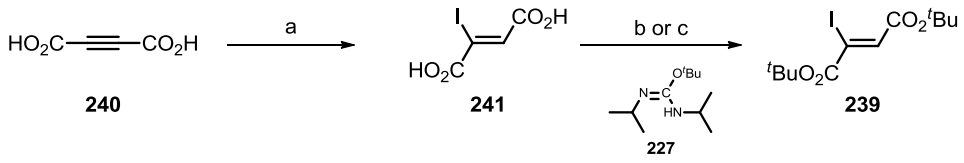
2.4 Retrosynthetic approach *via* a Pd(0)-mediated Ullmann coupling

It was envisaged that tricycle **203** could be obtained from **238** after reduction of the aldehyde moiety, subsequent Michael addition and oxidation (Scheme 64). Aldehyde **238** could be synthesized from already synthesized bromide **216b** and iodide **239** *via* a modified Ullmann coupling.[71,81] Finally, iodide **239** could be obtained from acetylene dicarboxylic acid **240**.



Scheme 64 – Retrosynthetic approach *via* a Pd(0)-mediated Ullmann coupling

The synthesis of the iodide derivative **239** began with the iodination of acetyl dicarboxylic acid **240** upon treatment with hydriodic acid (Scheme 65).[82] The synthesis continued with esterification of iodo di-acid **241** and the use of freshly prepared **227** seemed the most convenient. Treatment of **241** with three equivalents of **227** in dichloromethane afforded **239** in a moderate yield.[76b] The yield could be increased to 85% by slow addition of **227** in a suspension of **241** in dichloromethane.

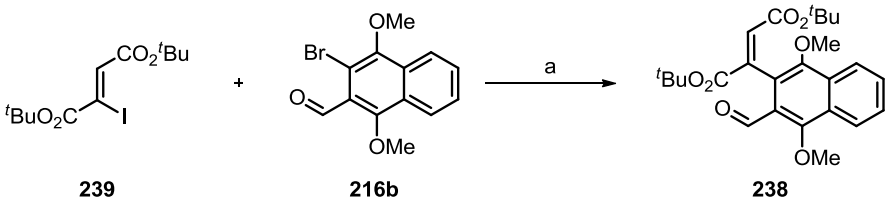


Scheme 65 – Synthesis of iodide 239

Reagents and conditions: a) HI (57% in H_2O), 0 °C to rt, 2 h,78%; b) **227**, CH_2Cl_2, rt, 12 h, 52%; c) **227**, syringe pump addition over 1 h, CH_2Cl_2, rt, 12 h, 85%.

Based on the work developed by Banwell *et al.*[81] and successfully used by Nicolaou *et al.* towards the total synthesis of the monomeric unit of the lomaiviticin aglycone,[72] the key palladium(0)-mediated Ullmann coupling was investigated (Scheme 66).

Upon treatment of an equimolar quantity of **239** and **216b** with activated copper,[83] copper iodide and tris(dibenzylideneacetone)dipalladium(0) in hot DMSO, coupling product **238** was isolated albeit in a modest 31% yield (Table 4, entry a). Because the synthesis of iodine partner **239** was shorter and larger quantities could be easily prepared, the quantity of vinyl iodide **239** was gradually increased and pleasingly, the use of 1.5, 2 and 3 equivalents of iodide **239** significantly improved the yield to 40, 55 and 58%, respectively (Table 4, entries b to d). Based on these results, large scale synthesis of aldehyde **238** was conducted using three equivalents of iodide **239**.



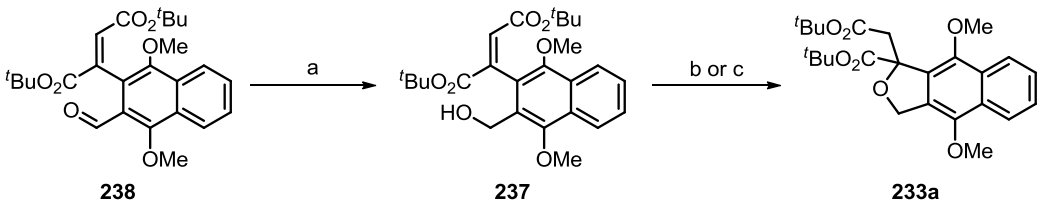
Scheme 66 – Palladium(0) modified Ullmann coupling investigations

Reagents and conditions: a) **239** (see Table 4), **216b** (see Table 4), Cu (10.0 eq), CuI (0.4 eq.), $Pd_2(dba)_3$ (0.1 eq.), DMSO, 65 °C.

Entry	**Vinyl iodide 239** (eq.)	**Bromide 216b** (eq.)	**Yield of 238**
a	1.0	1.0	31%
b	1.5	1.0	40%
c	2.0	1.0	55%
d	3.0	1.0	58%

Table 4 – Optimization for the formation of aldehyde 238

The synthesis continued with the reduction of the aldehyde moiety using sodium borohydride to afford **237**, precursor for the intramolecular Michael addition (Scheme 67). Treatment of alcohol **237** with sodium hydride under high dilution successfully gave tricycle **233a** in 43% yield. Upon treatment with potassium *tert*-butoxide, tricycle **233a** was isolated in a moderate 53% yield.



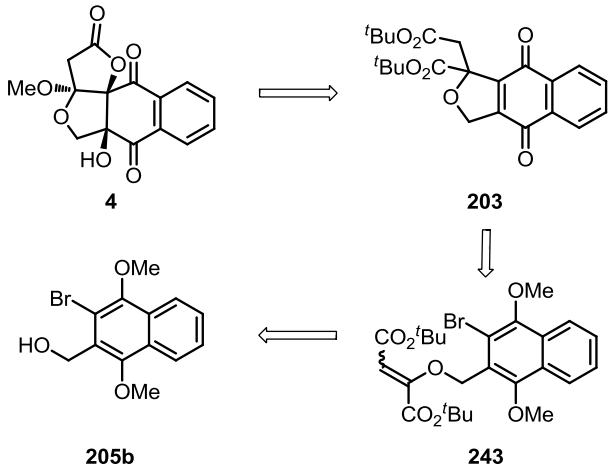
Scheme 67 – Synthesis of tricycle 233a

Reagents and conditions: a) $NaBH_4$, MeOH, 0 °C to rt, 88%; b) NaH, THF, [0.01 M], 0 °C to rt, 43%; c) *tert*-BuOK, THF [0.01 M], 0 °C to rt, 53%.

Although this route was satisfactory enough for the synthesis of a large quantity of tricycle **233a**, a last approach was investigated using a radical cyclization.

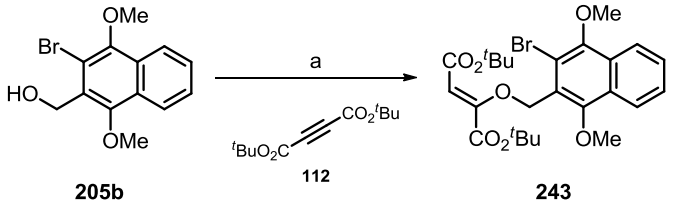
2.5 Retrosynthetic approach *via* a radical cyclization

As a last effort, it was thought tricycle could be obtained from **203** after radical cyclization[84] and subsequent aromatization. Michael addition of **205b** onto the triple bond of di-*tert*-butyl acetylene dicarboxylate **112** could furnish precursor **243**.



Scheme 68 – Retrosynthetic approach *via* a radical cyclization

The synthesis started with the Michael addition of **205b** onto di-*tert*-butyl acetylene dicarboxylate **112** in the presence of DMAP as catalyst and the *O*-alkylated product **243** was isolated in good yield (Scheme 69).[31]

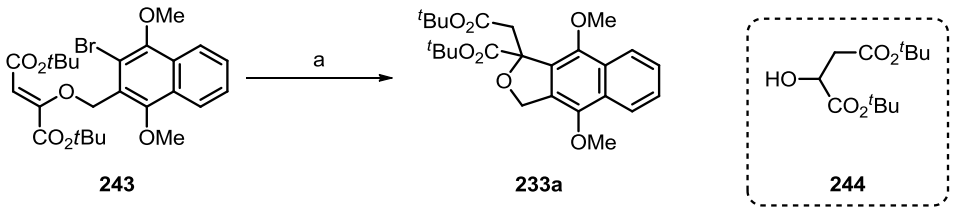


Scheme 69 – Synthesis of precursor 243

Reagents and conditions: a) DMAP, CH_2Cl_2, 0 °C to rt, 12 h, 88%.

Treatment of **243** under classical radical reaction (Bu_3SnH and AIBN in refluxing benzene) afforded the expected product in good yield on small scale (Table 5, entry a).[85] The reaction was also attempted in a microwave and product **233a** was isolated in similar yield (Table 5, entry b). Unfortunately, the reaction failed to be reproducible when scaling-up (Table 5, entry c). Moreover, it appeared that an inseparable side-product **244** was isolated alongside the desired product **233a**. In order to reduce the concentration of radical species in the mixture, a mixture of Bu_3SnH and AIBN was added over six hours *via* a syringe pump. However, the yield did not improve and the side-product **244** was still present albeit in a lesser extent (Table 5, entry d).

Different radical initiators such as ACCN[86] or benzoyl peroxide were tested. Treatment of **243** with either ACCN or benzoyl peroxide with Bu_3SnH gave the desired product **233a** in moderate yields and the side product **244** was still present (Table 5, entries e and f).



Scheme 70 – Attempts for the formation of tricycle 233a *via* radical cyclization

Reagents and conditions: a) Radical initiator (0.1 eq, see Table 5), hydride (1.1 eq, see Table 5), PhMe [see Table 5], Conditions A: reflux, 12 h; Conditions B: μW (120 °C, 5 min x 2), Conditions C: micro-syringe addition over 6 h.

Entry	Conditions	Radical initiator	Hydride	Concentration	Yield and Ratio 233a/244	Scale (mmol)
a	A	AIBN	Bu_3SnH	[0.01 M]	78% (3:1)	0.09
b	B	AIBN	Bu_3SnH	[0.01 M]	76% (3:2)	0.09
c	B	AIBN	Bu_3SnH	[0.01 M]	47% (3:1)	0.8
d	C	AIBN	Bu_3SnH	[0.01 M]	40% (3:0.7)	0.47
e	B	ACCN	Bu_3SnH	[0.01 M]	34% (3:1)	0.47
f	B	$(C_6H_5CO)_2O_2$	Bu_3SnH	[0.01 M]	45% (3:1)	0.09

Table 5 – Optimization for the formation of 233a

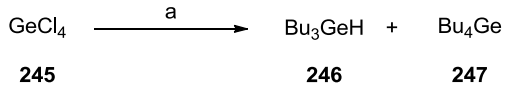
It was envisaged that the formation of alcohol **244** was induced by the use of Bu_3SnH. Consequently, different hydrides were screened. Tris(trimethyl)silane[87] and tributylgermanium hydride have also been widely used as replacements for tributyltin hydride in radical chemistry and in addition to their lower toxicities, several other advantages have been documented.[88] Of particular importance is the difference of reactivity between these three hydrides: the Si-H and Ge-H bonds in $(Me_3Si)_3SiH$ and Bu_3GeH are 5 and 8 kcal/mol stronger than the Sn-H bond, respectively (74, 79, 82 kcal/mol, respectively). As a result, their use can therefore minimize the formation of side products, because the reduction of the initially formed radical is retarded, facilitating a higher rate of cyclization.

As expected, no formation of alcohol **244** was observed when TTMSS was used and pure tricycle **233a** was isolated in moderate yield (Table 6, entry a). When the reaction was scaled-up, the yield decreased but not as much as when Bu_3SnH was used (Table 6, entry b).

Entry	Conditions	Radical initiator	Hydride	Concentration	Yield	Scale (mmol)
a	B	AIBN	$(Me_3Si)_3SiH$	[0.01 M]	51%	0.09
b	B	AIBN	$(Me_3Si)_3SiH$	[0.01 M]	44%	0.68

Table 6 – Optimization for the formation of 233a

Due to the high cost of Bu_3GeH, it was synthesized in one step from germanium(IV) chloride **245** (Scheme 71).[89] The reaction of $GeCl_4$ with *n*-BuMgCl in presence of a catalytic amount of Cp_2TiCl_2 successfully gave *n*-Bu_3GeH **246** in a moderate 44% yield. The formation of **246** was accompanied by the formation of side product **247** but the mixture of products could be purified by careful distillation.



Scheme 71 – Synthesis of Bu_3GeH 246

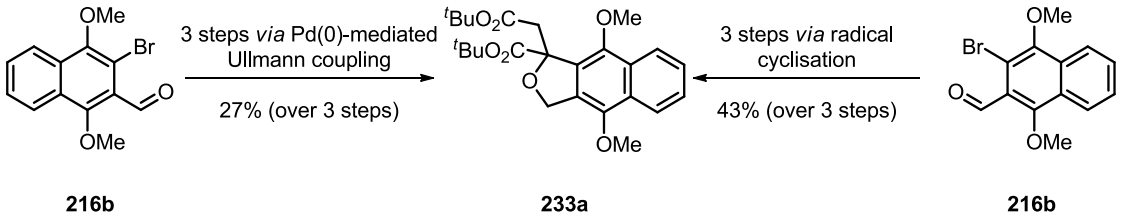
Reagents and conditions: a) i) Cp_2TiCl_2, Et_2O, −78 °C, ii) *n*-BuMgCl [2 M in Et_2O], −78 °C to rt and reflux, 12 h, 44%.

In a similar manner, upon treatment with Bu_3GeH and different radical initiators no formation of alcohol **244** was observed (Table 7, entries a to c).[90] As previously observed, benzoyl peroxide gave lower yield (53%) compared to AIBN and ACCN which gave good yields (86 and 80%, respectively) on small scale. When the reaction was scaled up, the yield dropped to 52% yield (Table 7, entry d). For practical reasons, the concentration was also increased in order to synthesize more material in one batch. Increasing the concentration from 0.01 M to 0.02 M, in a microwave, slightly decreased the yield from 52% to 47% (Table 7, entry e). A further increase of concentration to 0.05 M under classical benzene reflux or in a microwave afforded tricycle **233a** in a comparable yield of 42 and 52%, respectively (Table 7, entries f and g).

Entry	Conditions	Radical initiator	Hydride	Concentration	Yield	Scale (mmol)
a	B	$(C_6H_5CO)_2O_2$	Bu_3GeH	[0.01 M]	53%	0.09
b	B	AIBN	Bu_3GeH	[0.01 M]	86%	0.09
c	B	ACCN	Bu_3GeH	[0.01 M]	80%	0.09
d	B	AIBN	Bu_3GeH	[0.01 M]	52%	1.0
e	B	ACCN	Bu_3GeH	[0.02 M]	47%	3.8
f	B	ACCN	Bu_3GeH	[0.05 M]	42%	3.8
g	A	ACCN	Bu_3GeH	[0.05 M]	52%	4.8

Table 7 – Optimization for the formation of 233a

As a summary, tricycle **233a** was successfully synthesized from bromo aldehyde **216b** either *via* a Pd(0)-mediated Ullmann coupling in 27% (over the last three steps) or *via* a radical cyclization in 43% (over the last three steps) (Scheme 72). The used of Bu_3GeH and ACCN successfully afforded tricycle **233a** and the formation of side product **244** could be prevented. Even if the yield of the radical cyclization was still moderate, the overall yield of this route was higher than *via* the Pd(0)-mediated Ullmann coupling and a large amount of tricycle **233a** was synthesized *via* radical cyclization.



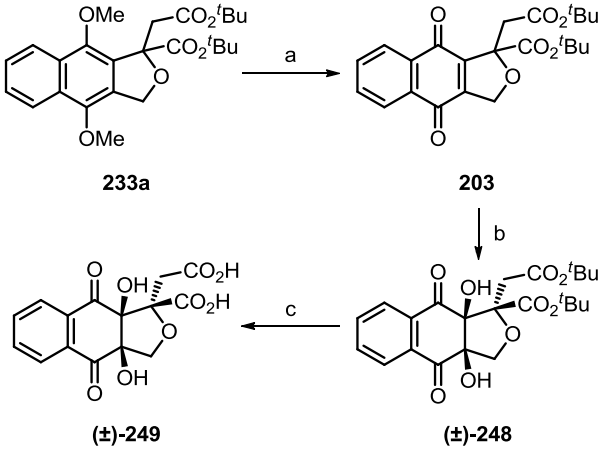
Scheme 72 – Synthesis of tricycle 233a *via* the Pd(0)-mediated Ullmann coupling and *via* radical cyclization

2.6 Oxidation to the quinone system and diol formation

The synthesis continued with the oxidation of tricycle **233a** with CAN and quinone **203** was obtained in good yield (Scheme 73).[91] With quinone **203** in hand, the synthesis of the A ring was investigated. Following the Danishefsky precedent,[24] and previous studies within the Barrett group[31] dihydroxylation of **203** using catalytic quantities of osmium tetraoxide in the presence of NMO was attempted first. Surprisingly, despite many similarities with previous model systems, only a complex mixture was observed with no expected products identifiable (Table 8, entry a). Pleasingly, upon treatment with ruthenium(VIII) oxide (RuO_4), which was prepared *in situ* from ruthenium(III) chloride and sodium periodate, diol **(±)-248** was successfully isolated in good yield (Table 8, entry b).[92] The relative stereochemistry in diol **(±)-248** was further confirmed by a relative X-ray crystallography (Figure 7). Unfortunately at this stage, the isolation of the minor diastereoisomer was not possible. As expected, treatment of **(±)-231** with excess trifluoroacetic acid in dichloromethane gave di-acid **(±)-232** in excellent yield.

S*yn* dihydroxylation are also described in the literature using Woodward's procedure in which alkenes are treated with a mixture of I_2-AgOAc in $AcOH/H_2O$.[93] Unfortunately, upon treatment with a combination of I_2 and AgOAc in AcOH (classical Prevost-Woodward's conditions)[93] or under

modified conditions ($NaIO_4$, LiBr in AcOH)[94] no reaction occurred and unreacted quinone **203** was recovered.



Scheme 73 – Attempts to form the A ring

Reagents and conditions: a) CAN, $MeCN/H_2O$ (2:1), 0 °C to rt, 30 min, 73%; b) Catalyst (see Table 8), co-oxidant (see Table 8), solvent (Table 8), 0 °C; c) TFA, CH_2Cl_2, 0 °C to rt, 2 h, quantitative.

Entry	Catalyst	Co-oxidant (eq.)	Solvents	Results
a	OsO_4 (0.05 eq.)	NMO (1.1)	Me_2CO/H_2O (10:1)	Complex mixture
b	$RuCl_3$ (0.5 mol%)	$NaIO_4$ (1.5)	EtOAc/MeCN/H_2O (3:3:1)	77% of **(±)-248**

Table 8 – Dihydroxylation attempts

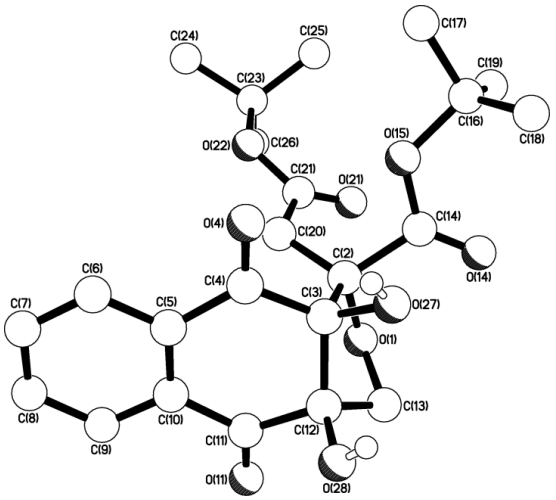
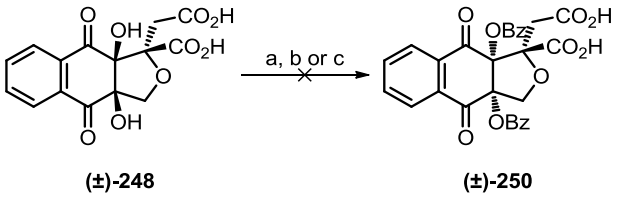


Figure 7 – Relative X-ray structure of (±)-248

The diastereoselectivity of the dihydroxylation reaction could not be improved in favor of the desired precursor for the formation of the A ring and therefore alternative methods to invert the diastereoselectivity were investigated.

2.7 Alternative methods to invert the diastereoselectivity

In general, tertiary alcohols are less reactive towards Mitsunobu reactions, and only few examples have been reported.[95] In 2003, Shi *et al.* successfully reported the stereospecific synthesis of chiral tertiary alkyl-aryl ethers *via* a Mitsunobu reaction with complete inversion of configuration.[95d] Based on this result, a Mitsunobu reaction was attempted on diol **(±)-248**. Unfortunately, upon treatment with a mixture of DIAD, PPh_3 and benzoic acid at room temperature no reaction occurred. Shi *et al.* emphasized in their communication the importance of the temperature for the success of the reaction.[95d] As a result, the reaction was repeated in THF at 60 °C and in toluene at 90 °C. Unfortunately, an increase of temperature on this rather sensitive substrate only afforded a complex mixture and no expected products could be identifiable (Scheme 74).

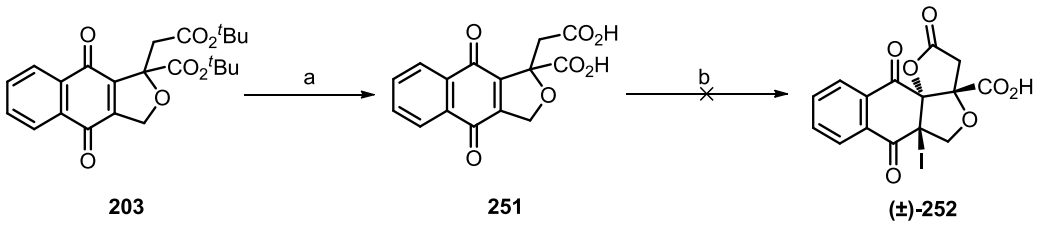


(±)-248 **(±)-250**

Scheme 74 – Mitsunobu reaction on (±)-250

Reagents and conditions: a) PPh_3, DIAD, BzOH, THF, rt; b) PPh_3, DIAD, BzOH, THF, 60 °C; c) PPh_3, DIAD, BzOH, PhMe, 90 °C.

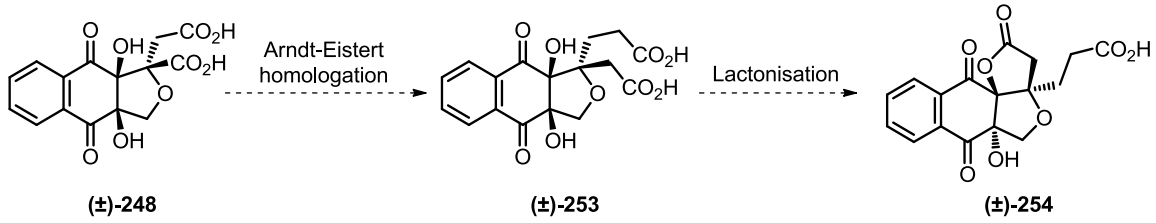
Alternatively, the A ring could be formed *via* an iodolactonisation[96] and if successful, further modifications could convert the resulting iodine into the corresponding alcohol. Starting from already synthesized naphthoquinone **203**, treatment with excess trifluoroacetic acid in CH_2Cl_2 successfully gave di-acid **251** (Scheme 75). Unfortunately, upon exposure to a mixture of I_2, KI in THF/H_2O,[96] only a complex mixture was obtained and no expected product **(±)-252** could be identifiable.



Scheme 75 – Synthesis of naphthoquinone 251 and subsequent lactonisation attempts

Reagents and conditions: a) TFA, CH_2Cl_2, 0 °C to rt, 86%; b) I_2, KI, $NaHCO_3$, H_2O/THF.

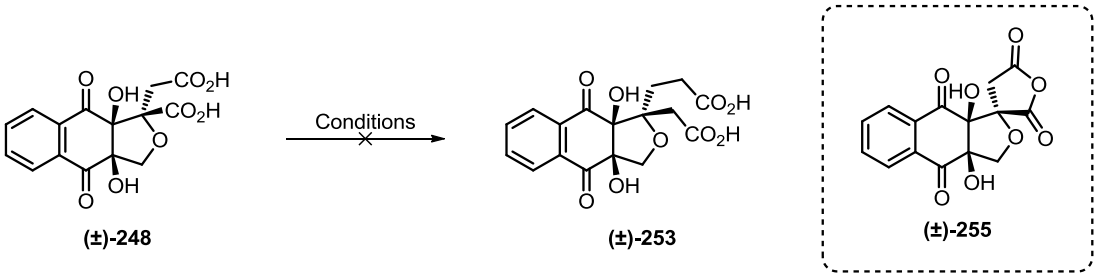
It was envisaged to modify the chain length of the tertiary carboxylic acid in order to facilitate the lactonisation (Scheme 76). Indeed, the addition of an extra carbon *via* an Arndt-Eistert homologation[97] could transform the tertiary carboxylic acid in **(±)-248** into a primary carboxylic acid which will be *syn* to both diols and therefore the lactonisation could occur. It is germane to add that the chain length extension should occur as well on the other carboxylic acid. Further manipulations could transform the $–CH_2CH_2CO_2H$ moiety into a tertiary carboxylic acid.



Scheme 76 – Arndt – Eistert homologation on (±)-248 and further transformations

The use of oxalyl chloride at 0 °C to convert acid **(±)-248** into the corresponding acid chloride proved to be difficult (Scheme 77). The crude mixture was nonetheless subjected to reaction with diazomethane, however, only a complex mixture was observed. In a similar manner, the formation of acid chloride with Ghosez reagent or thionyl chloride was complicated. Nonetheless, the crude mixture was taken forward with the addition of CH_2N_2, but only a complex mixture was obtained. In all cases, silver(I) oxide was added to the crude mixture but no Wolff rearrangement occurred and no expected product **(±)-253** was identifiable. The reaction was repeated again using Ghosez reagent and the reaction was checked by IR after addition of diazomethane. As suspected, no trace of the corresponding α-diazoketone could be observed (no peak from $–CO-CH=N^+=N^-$ around 3100-2090 cm^{-1}). This result could be explained by the formation of anhydride **(±)-255** (although not isolated),

which can be formed by intramolecular trapping of one acid chloride formed by the other carboxylic acid moiety.



Scheme 77 – Attempts to form 253 *via* an Arndt – Eistert homologation

Reagents and conditions: a) i) Ghosez reagent or $SOCl_2$ or $(COCl)_2$, CH_2Cl_2, 0 °C; ii) CH_2N_2, Et_2O; iii) Ag_2O.

2.8 Conclusion

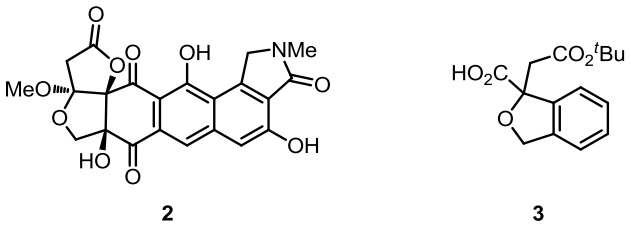
Starting from commercially available and inexpensive 1-naphthol **218**, naphthoquinone **203** was successfully synthesized in nine steps with an overall yield of 14%. Unfortunately, the *syn* dihydroxylation failed to give the desired diastereoisomer and the diastereoselectivity could not be reversed or improved. Moreover, alternative methods to favor the formation of the A ring were not successful. As a result, the synthesis towards a new model system with less complexity was investigated. Nevertheless, whilst all these results are not encouraging, they will still be of great help when the synthesis of the actual target structure will be examined.

3. Synthesis of model carboxylic acid (3)

3.1 Introduction

As the synthesis of model **4** was not successful, the synthesis of a simple model system was investigated. Of particular importance was the presence of the tertiary carboxylic acid and primary

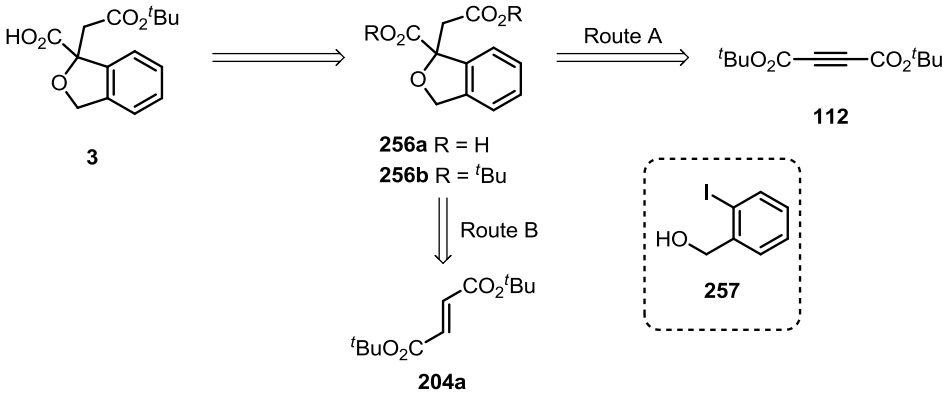
ester attached to the dihydroisobenzofuran functionality. As a result, it was envisaged that acid **3** could act as a suitable model for the electrodecarboxylation experiments (Figure 8).



2 **3**

Figure 8 – Lactonamycinone 2 and model carboxylic acid 3

Retrosynthetically, it was envisaged that carboxylic acid **3** could be obtained from di-acid **256a** after selective esterification or from di-ester **256b** by selective mono-saponification (Scheme 78). **256a** and **256b** could be obtained from 2-iodobenzyl alcohol **257** and di-*tert*-butyl acetylene dicarboxylate **112** *via* a radical cyclization[84] (Route A) or from **257** and di-*tert*-butyl fumarate **204a** *via* a tandem Heck coupling/Michael addition sequence.[63] (Route B) Although this latter sequence was not successful towards the synthesis of tricycle **233a**, it was envisaged that iodide **257** will be more reactive.



3

256a R = H
256b R = ^{t}Bu

112

257

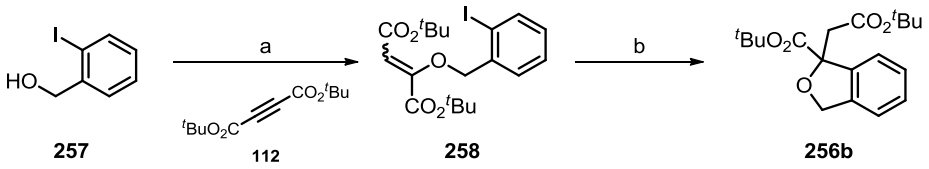
204a

Scheme 78 – Retrosynthetic analysis of model 3

3.2 Synthesis of di-ester 256b

Based on the results obtained towards the synthesis of model **4**, it was thought that di-ester **256b** could be synthesized *via* different pathways. The first route started with the Michael addition of 2-iodobenzyl alcohol **257** onto the triple bond of di-*tert*-butyl acetylene dicarboxylate **112** to afford **258**

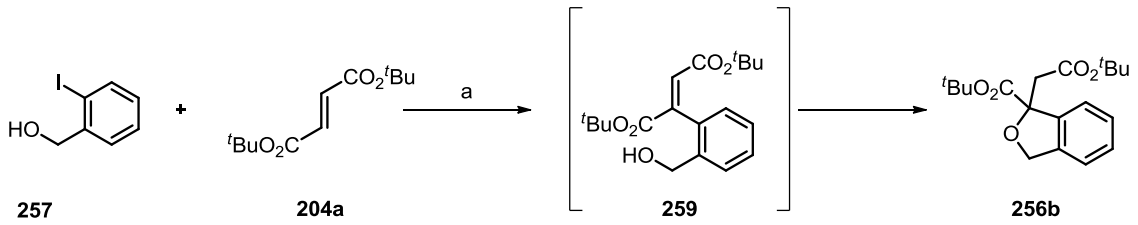
in high yield (Scheme 79).[31] Upon treatment with Bu_3SnH and AIBN in refluxing toluene, **258** was converted into bicycle **256b** under standard radical cyclisation conditions.[84]



Scheme 79 – First synthesis of di-ester 256b

Reagents and conditions: a) DMAP, CH_2Cl_2, 0 °C to rt, 12 h, 99%; b) Bu_3SnH, AIBN, PhH, reflux, 2 days, 48%.

Alternatively, it was envisaged that bicycle **256b** could be obtained from 2-iodobenzyl alcohol **257** and di-*tert*-butyl fumarate **204a** *via* a tandem Heck coupling/Michael addition sequence.[63] Pleasingly, the reaction between **204a** and 2-iodobenzyl alcohol **257** proceeded smoothly to give in one step bicycle **256b** in 69% yield (Scheme 80). This tandem sequence started with the Heck coupling giving rise to intermediate **259** that was converted to **256b** *via* an intramolecular Michael addition. Based on the latter results, large quantities of bicycle **256b** were synthesized using this tandem Heck coupling/Michael addition sequence.[i]



Scheme 80 – Second synthesis of di-ester 256b

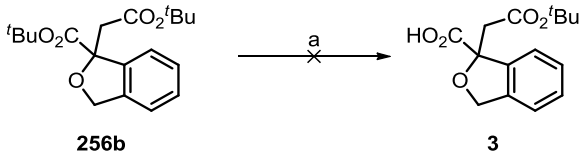
Reagents and conditions: a) $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, 85 °C, 12 h, 69%.

3.3 Diverse route towards model 3

Based on a precedent result within the Barrett group,[31] it was naively hoped that the tertiary *tert*-butyl ester in **256b** could undergo a selective saponification. Unfortunately, as explained in the

[i] In total, 14.4 g of bicycle **256b** were synthesized.

communication, the proximity of a ketone was compulsory for the selective saponification and as a result, upon treatment with one equivalent of potassium hydroxide in dioxane only a complex mixture was afforded (Scheme 81).

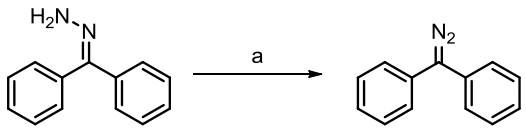


256b **3**

Scheme 81 – Attempt for the selective saponification

Reagents and conditions: a) KOH in H_2O, dioxane, 0 °C.

Alternatively, as depicted in Scheme 78, it was envisaged that model **3** could be obtained from di-acid **256a** after selective esterification. Indeed, it was thought that the use of a bulky reagent could introduce selectivity and that the less hindered carboxylic acid could be selectively esterified. To this aim, bulky diphenyldiazomethane **261** was chosen. Recently, Brewer and co-workers reported a new procedure to synthesize diazo compounds which was based on the dehydrogenation of hydrazones with "activated" DMSO.[98] A solution of benzophenone hydrazone **260** and triethylamine was treated with chlorodimethylsulfonium chloride (prepared *in situ* by addition of oxalyl chloride to DMSO) and pure diphenyldiazomethane **261** was obtained as deep red crystals after a single filtration (Scheme 82).



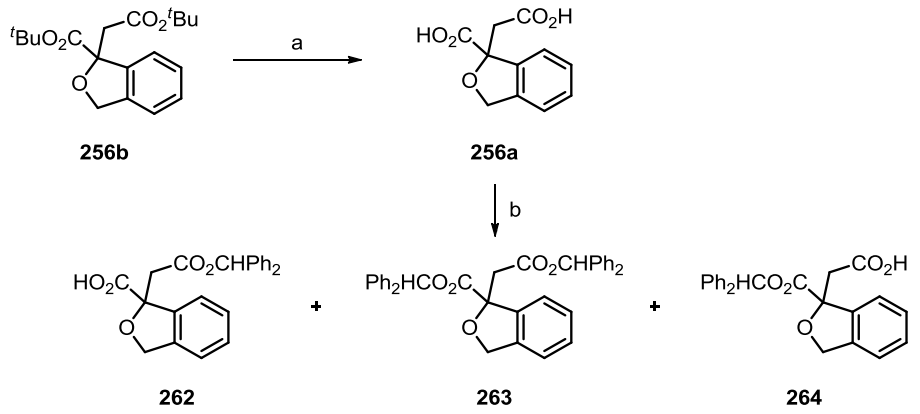
260 **261**

Scheme 82 – Synthesis of diphenyldiazomethane 261

Reagents and conditions: a) i) $(COCl)_2$, DMSO, –55 °C, 20 min; ii) **260**, Et_3N, THF, –78 °C, 1 h, quantitative.

Di-ester **256b** was treated with trifluoroacetic acid to afford di-acid **256a** in quantitative yield (Scheme 83). Unfortunately, treatment of di-acid **256a** with one equivalent of diphenyldiazomethane **261** in either acetonitrile (Table 9, entry a), acetone (Table 9, entry b) or benzene (Table 9, entry c) never proceeded cleanly and a complex mixture was obtained.[99]

Analysis of the crude ^{1}H-NMR revealed the presence of four products: diester **263**, primary ester **262**, tertiary ester **264** and unreactive starting material **256a**. Di-ester **263** could be easily separated by silica gel column chromatography but **262** and **264** could not be separated and were obtained in all attempts in a 5:1 ratio, respectively. As expected, the esterification with diphenyldiazomethane **261** showed some selectivity and the less hindered acid was preferentially esterified. It was thought that decreasing the temperature would increase the selectivity and thus simplify the purification so the reaction was attempted at −78 °C and a solution of diphenyldiazomethane **261** was slowly added. Unfortunately, no improvement was observed and **262** and **264** were obtained in the same 5:1 ratio.



Scheme 83 – Synthesis of di-acid 256a and selective esterification attempts

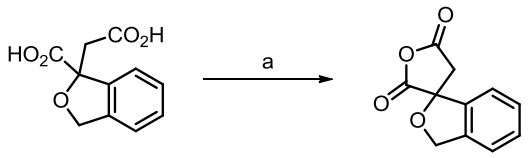
Reagents and conditions: a) TFA, CH_2Cl_2, 0 °C to rt, quantitative; b) **256a** (1.0 eq.), **261** (1.0 eq.), solvent (Table 9), temperature (Table 9).

Entry	Solvent	Temperature	Ratio	
			262	264
a	Acetonitrile	rt	5	1
b	Acetone	rt	5	1
c	Benzene	rt	5	1
d	Acetone	−78 °C	5	1

Table 9 – Optimization for the formation of ester 262

3.4 Completion of the synthesis of model 3 *via* an anhydride formation

As the previous attempts to differentiate both acids in **256a** proved to be unsuccessful, a new strategy was investigated. This strategy was based on the formation of an anhydride which could be selectively opened (Scheme 84). Unfortunately, upon treatment with neat acetic anhydride at reflux,[100] only decomposition occurred (Table 10, entry a). The reaction was repeated with milder conditions (Ac_2O and Et_3N at 60 °C),[101] however, di-acid 256a decomposed (Table 10, entry b). It was thought that di-acid **239a** was too sensitive and new conditions where no heating was necessary was investigated. To our delight, treatment of **256a** with trifluoroacetic anhydride at 0 °C proceeded cleanly and anhydride **265** was obtained in good yield.[102]



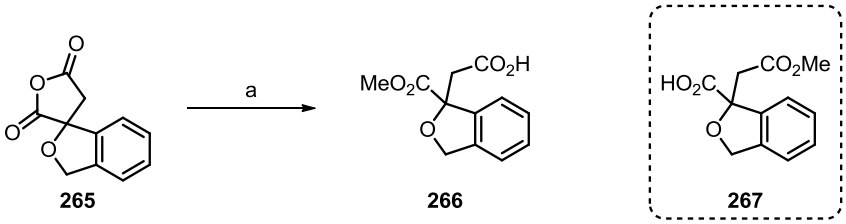
256a **265**

Scheme 84 – Conversion of di-acid 256a into anhydride 265

Entry	Reagent	Solvent	Temperature	Yield
a	Ac_2O	None	Reflux	Decomposition
b	Ac_2O	Et_3N	60 °C	Decomposition
c	TFAA	CH_2Cl_2	0 °C to rt	87%

Table 10 – Optimization for the formation of anhydride 265

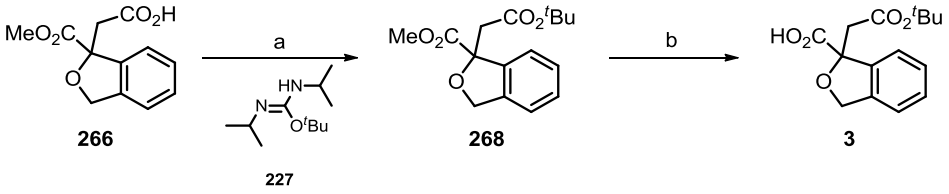
It was naively thought that upon treatment with sodium methoxide in methanol, the anhydride would be attacked on the less hindered side therefore giving rise to **267**. Unfortunately, upon treatment with sodium methoxide in methanol, the attack occurred on the other side of the anhydride to form preferentially the other isomer **266**, the structure of which was confirmed by NMR analysis (Scheme 85). This result can be explained by the fact that the carbonyl group near the oxygen atom is more reactive to the nucleophilic attack of methanol than the other.[103] In this particular case, the electronic factor predominates the steric factor and therefore tertiary ester **266** is formed preferentially.



Scheme 85 – Opening of anhydride 265 with MeOH

Reagents and conditions: a) MeOH, MeONa, reflux, 12 h, 71%.

Although the opening of the anhydride occurred with the opposite selectivity, it was envisaged that model system **3** could be synthesized in a two step procedure: first, an esterification of the primary carboxylic acid followed by a selective saponification of the methyl ester. To this aim, acid **266** was converted into the corresponding *tert*-butyl ester **268**[104] using already synthesized *tert*-butyl derivative **227**[76] (Scheme 86). Finally, the methyl ester moiety was selectively saponified using Me_3SnOH[105] to give model system **3**.

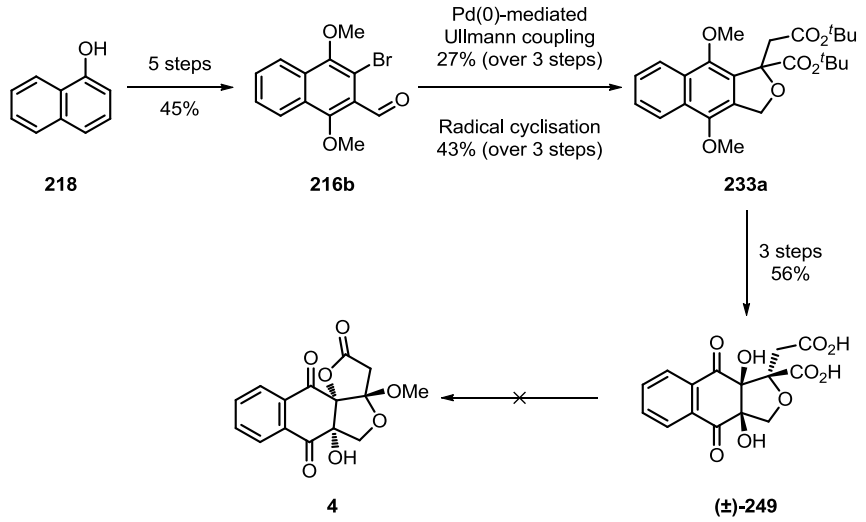


Scheme 86 – Synthesis of model carboxylic acid 3

Reagents and conditions: a) **227**, CH_2Cl_2, reflux, 2 h, 51%; b) Me_3SnOH, 1,2-dichloroethane, reflux in sealed tube, 12 h, 94%.

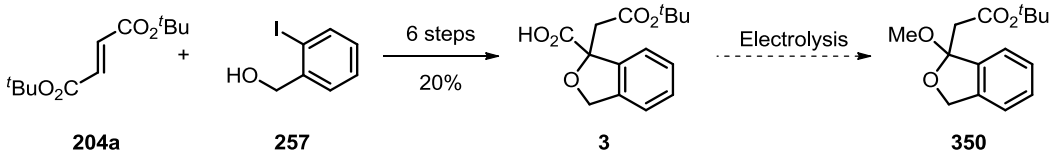
3.5 Conclusion

The synthesis towards ABCD rings model system **4** was revisited (Scheme 87). Bromo-aldehyde **216b** was synthesized in five steps from 1-naphthol **218** in 45% yield. Starting from **216b**, tricycle **233a** was successfully obtained *via* a modified Pd(0)-Ullmann coupling or *via* a radical cyclization. Finally, CAN oxidation followed by dihydroxylation and *tert*-butyl esters cleavage afforded diol **(±)-249**. Unfortunately, all attempts to invert the stereochemistry of the dihydroxylation or to form the A-ring failed.



Scheme 87 – Towards the synthesis of ABCD tetracycle model system 4

Despite the problems encountered during the synthesis, carboxylic model system **3** was successfully synthesized in six steps with an overall yield of 20%. The key steps of the synthesis are a one-pot tandem Heck coupling/Michael addition sequence and a differentiation between two carboxylic acids *via* an anhydride formation. With this model in hand, several electrodecarboxylation reactions would be attempted in order to optimize the conditions to introduce the angular methoxy group *via* an electrodecarboxylation.



Scheme 88 – Synthesis of carboxylic model system 3

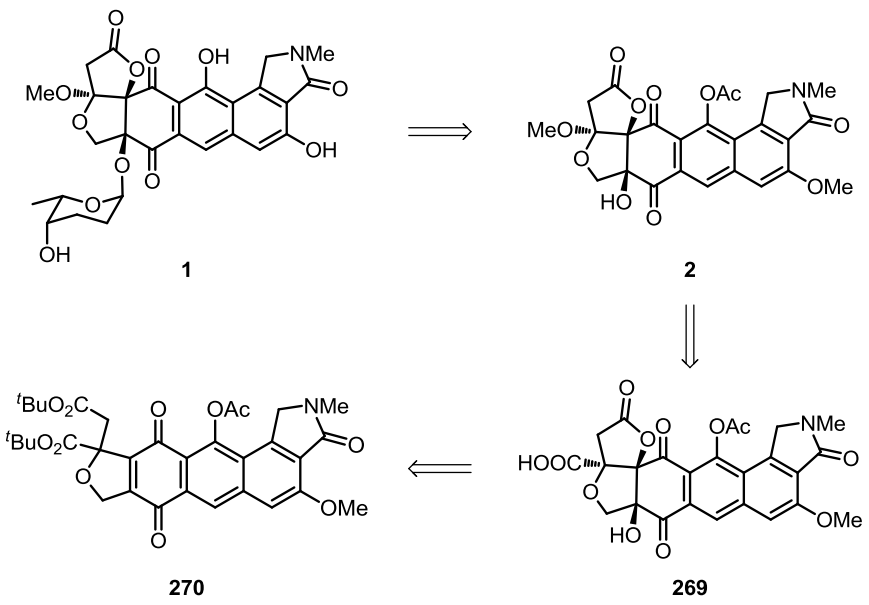
Chapter IV Results and Discussion

Towards the Total Synthesis of Lactonamycin

1. First strategy

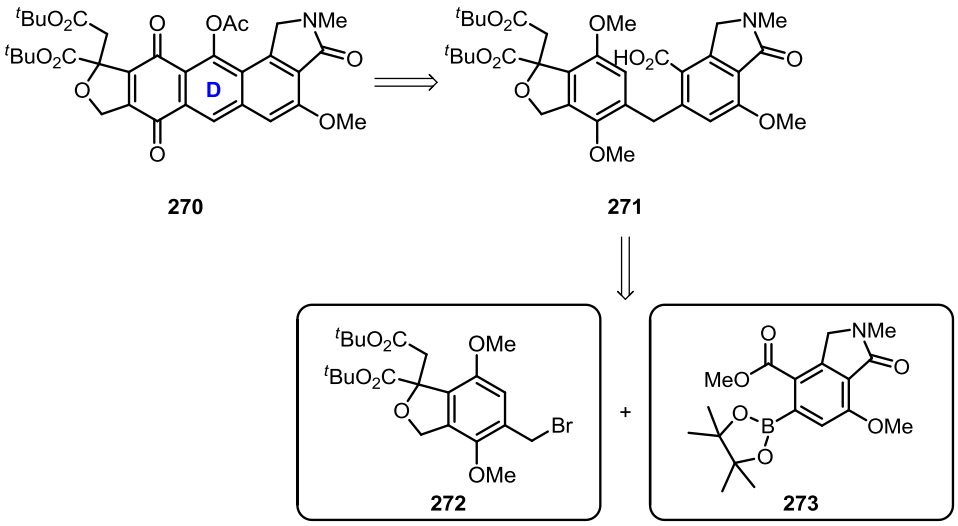
1.1 Introduction

Barrett and co-workers have been working on the synthesis of lactonamycin (**1**) over the last few years. Based on the results of previous model studies,[31,32a,32b] a new retrosynthetic approach was investigated which is depicted in Scheme 89 and Scheme 90. This strategy was based on a late glycosidation step of aglycone using palladium chemistry[106] and cleavage of the remaining protecting groups. As previous studies within the group[31] and by others[22,24,26] showed that the tertiary methoxy group in **2** was difficult to introduce, it was envisaged that it could be installed *via* an electrodecarboxylation reaction from carboxylic acid **269** which could be obtained from pentacycle **270** after dihydroxylation, *tert*-butyl esters cleavage and subsequent lactonisation to form the A-ring.



Scheme 89 – Current retrosynthetic approach towards lactonamycin (1)

The fused D-ring in **270** could be installed *via* a Friedel-Crafts acylation from carboxylic acid **271** followed by a selective oxidation (Scheme 90). Finally, a Suzuki coupling between bromide **272** and triflate **273** could furnish acid **271**.

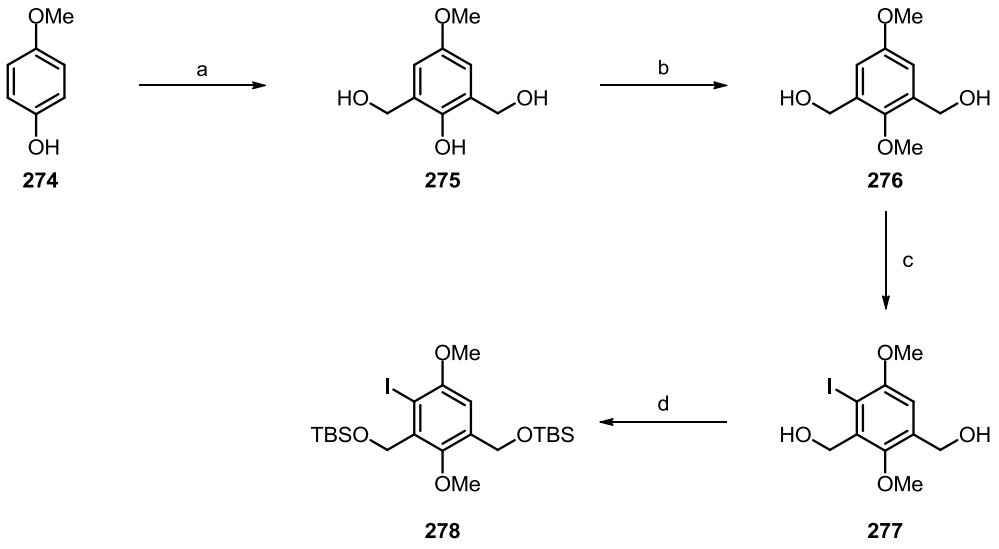


Scheme 90 – Retrosynthetic approach towards lactonamycin 1

1.2 Synthesis of coupling partner 272

Following the route developed within the group by Dr. Michaelis, significant quantities of the BC-ring bromide **272** were successfully prepared.[ii,80] The synthesis began with a double hydroxymethylation of **274** in the presence of calcium oxide (Scheme 91).[107] Phenol **275** was selectively methylated to give diol **276** in moderate yield and Ag(I)-assisted iodination yielded iodide **277**.[64] Finally, both alcohols were protected as their corresponding TBS-ethers and **278** was isolated in good yield.

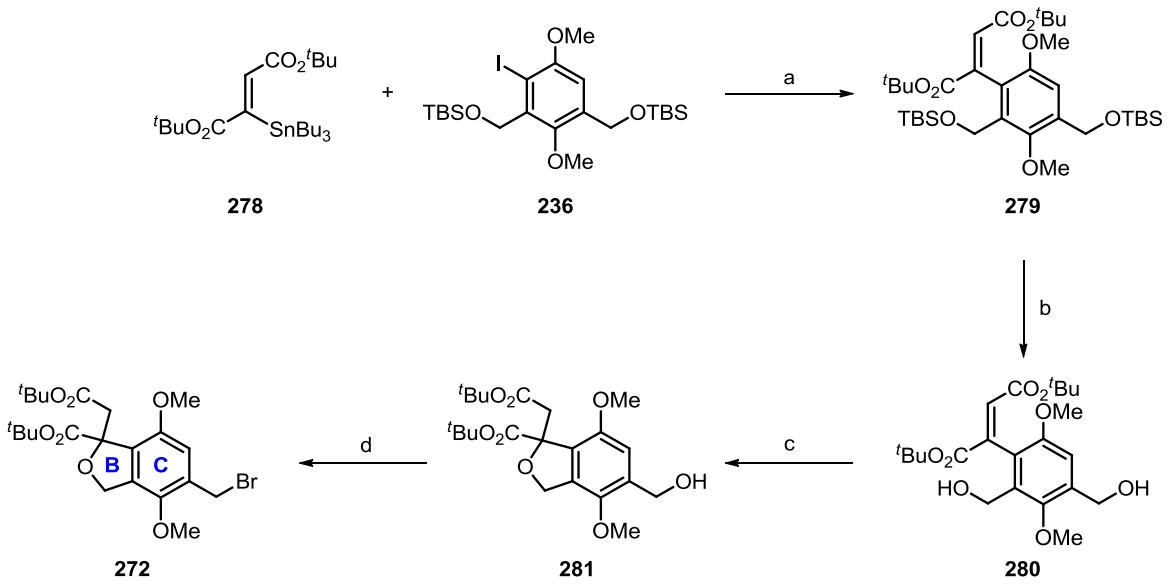
[ii] In total, 2.52 g of BC-ring bromide **272** were synthesized.



Scheme 91 – Synthesis of iodide 278

Reagents and conditions: a) H_2CO, CaO, H_2O, rt, 5 d, 64%; b) Me_2SO_4, K_2CO_3, Me_2CO, reflux, 12 h, 53%; c) $Ag(O_2CCF_3)$, I_2, $CHCl_3$, 0 °C, 1 h, 76%; d) TBSCl, imidazole, CH_2Cl_2, 0 °C, 2 h, 85%.

Pleasingly, treatment of iodide **278** with a slight excess of stannane **236** (prepared as described in Scheme 62) and a catalytic amount $Pd(PPh_3)_4$ and CuI afforded alkene **279** in good yield (Scheme 92). A two step procedure was used to form the B-ring: both TBS-ethers were first cleaved using HCl at 0 °C to from diol **280** which was converted into benzofuran derivative **281** upon treatment with sodium hydride in excellent yield. It is germane to note that the addition of HCl had to be slow and the reaction had to be check thoroughly in order to prevent the formation of polar side-products (presumably from the cleavage of the *tert*-butyl esters after prolonged reaction time). Finally, alcohol **281** was converted into the corresponding bromide **272** upon treatment with CBr_4 and PPh_3.[108] Starting from inexpensive starting material, BC-ring bromide **272** was successfully synthesized in eight steps with an overall yield of 12%.

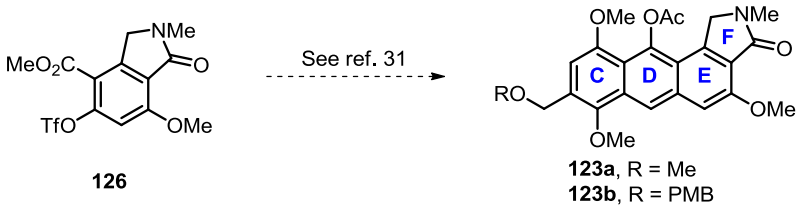


Scheme 92 – Synthesis of BC-ring bromide 272

Reagents and conditions: a) CuI, $Pd(PPh_3)_4$, 120 °C, 2 d , 74%; b) conc. HCl, THF, 0 °C, 1 h, 84%; c) NaH, THF, 0 °C, 4 h, 94%; d) CBr_4, PPh_3, DMF, rt, 1 h, 97%.

1.3 Synthesis of coupling partner 273

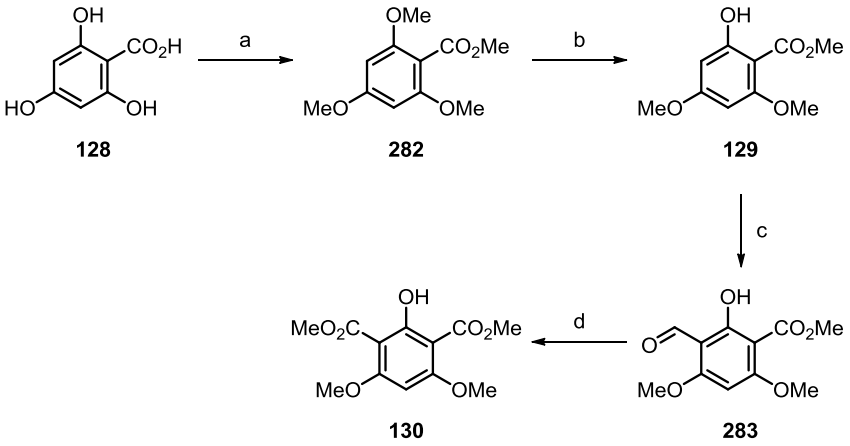
The synthesis of EF-ring triflate had previously been conducted within the Barrett group in order to develop chemistry for the construction of the CDEF ring system of lactonamycin (**1**) (Scheme 93).[31] It was envisaged that EF-ring boronate could be synthesized from triflate **126** *via* a Miyaura borylation.



Scheme 93 – Synthesis of CEDF ring system from triflate 126

Following Wehlan's procedure,[31] significant quantities of the EF-ring triflate were successfully prepared (Scheme 94). The scale-up started with the global protection of commercially available trihydroxy acid **128** under standard conditions (Me_2SO_4, K_2CO_3 in acetone). Selective deprotection of

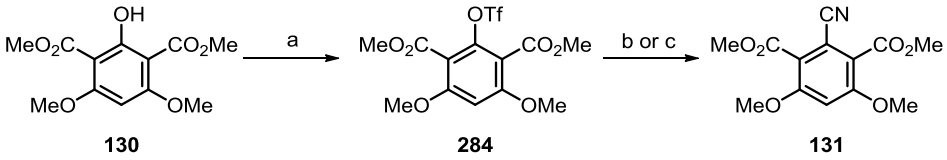
the *ortho*-methylether of **282** successfully afforded the desired phenol **129** in 83% yield.[109] Subsequent Vilsmeier-Haack formylation yielded aldehyde **283**, which was converted into symmetrical ester **130** in a two-step oxidation/esterification sequence. The aldehyde was first treated with sodium chlorite as the oxidizing agent in the presence of sulfamic acid and 2-methylbutene as a chlorine scavenger to afford the corresponding carboxylic acid, which was esterified using potassium bicarbonate and dimethylsulfate to give ester **130** in 84% over two steps.



Scheme 94 – Synthesis of phenol 130

Reagents and conditions: a) Me_2SO_4, K_2CO_3, Me_2CO, 0 °C to rt, 12 h, 82%; b) BCl_3, CH_2Cl_2, –78 °C to rt, 12 h, 83%; c) $POCl_3$, DMF, MeCN, 0 °C to rt, 12 h, 72%; d) i) $NaClO_2$, NH_2SO_3H, 2-methyl-2-butene, THF/H_2O/DMSO (12:10:1), 0 °C to rt, 1 h; ii) Me_2SO_4, $KHCO_3$, DMF, rt, 2 h, 84% over two steps.

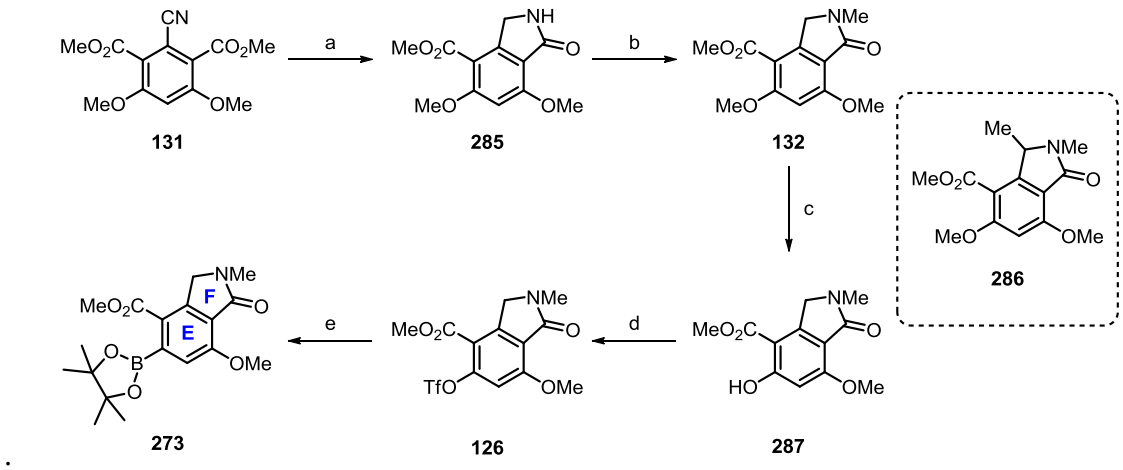
The synthesis continued with the condensation of phenol **130** with triflic anhydride followed by a palladium-catalyzed cross-coupling reaction with zinc cyanide to give nitrile **131** in excellent yield (Scheme 95).[110] Despite the high yield of this coupling, the reaction was not easy to carry out in a practical way as zinc cyanide was added portionwise over six hours and six equivalents of cyanide were necessary to observe complete conversion after overnight heating. Based on a procedure used for the coupling of aryl chlorides and zinc cyanide,[111] a more convenient alternative was used where only 1.2 equivalents of cyanide were necessary alongside the addition of a catalytic amount of zinc powder. All the reagents were mixed directly in the flask and full conversion was observed after two hours by ^{1}H-NMR. With this method, nitrile **131** was obtained in 87% yield.



Scheme 95 – Synthesis of nitrile 131

Reagents and conditions: a) Tf_2O, pyridine, 0 °C to rt, 2 h, 95%; b) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 60 °C, 12 h, 96%; b) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, Zn, DMF, 120 °C, 2 h, 87%.

Hydrogenation of nitrile **131** using Raney nickel,[112] gave the corresponding lactam **285** which was methylated in degassed DMF to give tertiary amide **132** (Scheme 96). It is worth noting that this reaction also needed care in execution in order to prevent the formation of methyl-isoindolinone derivative **286**, the formation of which can be explained during prolonged reaction times in the presence of iodomethane and sodium hydride. A second selective deprotection of the *ortho*-methylether of **132** using boron trichloride at −78 °C afforded **287**.[113] Triflation of the resulting phenol with *N*,*N*-ditriflylaniline and Et_3N gave triflate **126** which was successfully converted by a Miyaura borylation into the corresponding boronic ester **273**.[114] It is germane to mention that the success of this reaction was largely dependent on the concentration of the reaction mixture (0.5 M). In contrast, reaction at lower dilution was accompanied by the formation of the corresponding reduced product. Starting from inexpensive starting material, EF-ring boronate ester **273** was successfully synthesized in eleven steps with an overall yield of 23%.

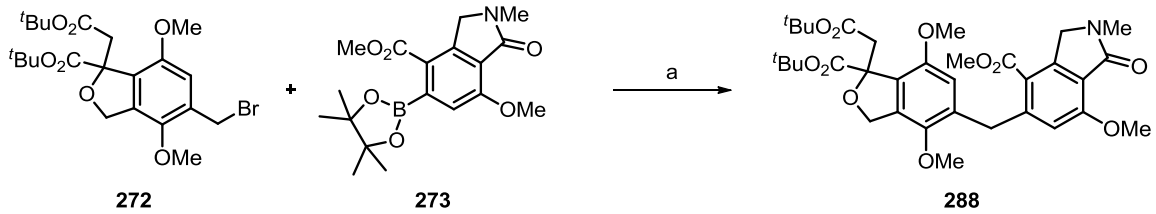


Scheme 96 – Completion of the synthesis towards EF-ring boronate 273

Reagents and conditions: a) Raney-Ni, DMF, 70 psi, rt, 94%; b) NaH, MeI, DMF, 0 °C, 2 h, 88%; c) BCl_3, CH_2Cl_2, −78 °C, 3 h, 92%; d) $PhNTf_2$, Et_3N, CH_2Cl_2, reflux, 48 h, 92%; e) Bis(pinacolato)diboron, $Pd(dppf)Cl_2$, NaOAc, PhH, 80 °C, 13 h, 86%.

1.4 Suzuki coupling and subsequent transformations

The key Suzuki coupling was investigated within the group by Dr. Michaelis and Dr. Gebhardt and coupling product **288** was obtained in 76% yield under classical reflux (Scheme 97).[80,115] This reaction was never attempted using microwave irradiation and more investigations were necessary to try to improve the yield of this reaction.



Scheme 97 – Synthesis of coupling product 288

Reagents and conditions: a) $PdCl_2(dppf)$, K_3PO_4, DME, 85 °C, 12 h, 76%.

Previous results within the group revealed that coupling product **288** was isolated alongside two main side products derived from bromide **272** and identified as alcohol **281** and dimer **289** (Figure 9).[80,107] As a result, it was thought that bromide **272** could be added in larger excess in order to favor the complete completion of boronic ester **273**. In addition, the synthesis of bromide **272** was much quicker and large quantities could be readily synthesized.

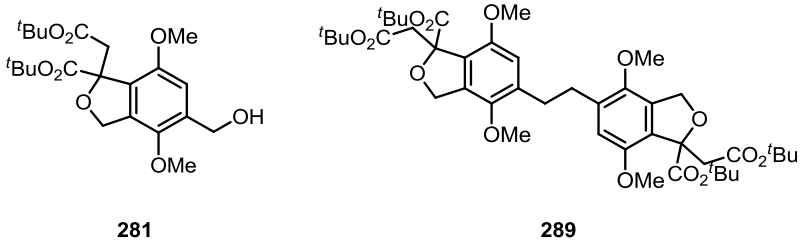
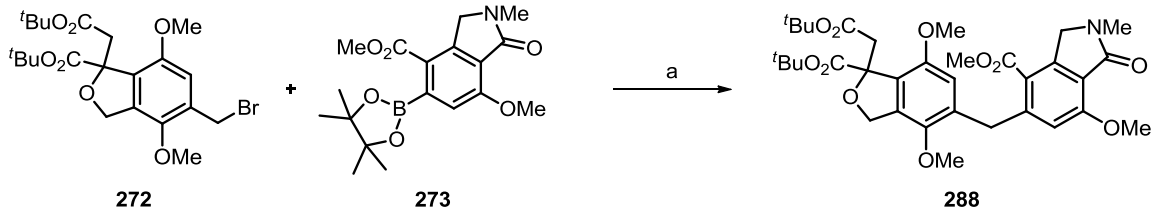


Figure 9 – Side products formed in the Suzuki coupling

The Suzuki coupling was attempted using the conditions optimized by Dr. Michaelis,[80] with two equivalents of bromide and the reaction was performed in a microwave (Scheme 98). Surprisingly, no reaction was observed and bromide **272** decomposed readily under these conditions (Table 11, entry a). The reaction was repeated with cesium carbonate, however, no reaction occurred and bromide **272**

decomposed (Table 11, entry b). It was thought that the base was not soluble enough in DME and as the reaction time was quicker in the microwave no reaction could occur. As a result, water was added as a co-solvent. Gratifyingly, upon treatment under the same conditions in a mixture DME/H_2O (4:1), the coupling product was obtained in a moderate 45% yield (Table 11, entry c). The amount of bromide was reduced to 1.1 equivalents and the reaction was run again with potassium phosphate and the expected product **288** was obtained in a comparable yield (Table 11, entry d). Accordingly, the conditions developed by Michaelis were used for the large scale synthesis of coupling product **288**.



272 **273** **288**

Scheme 98 – Synthesis of coupling product 288

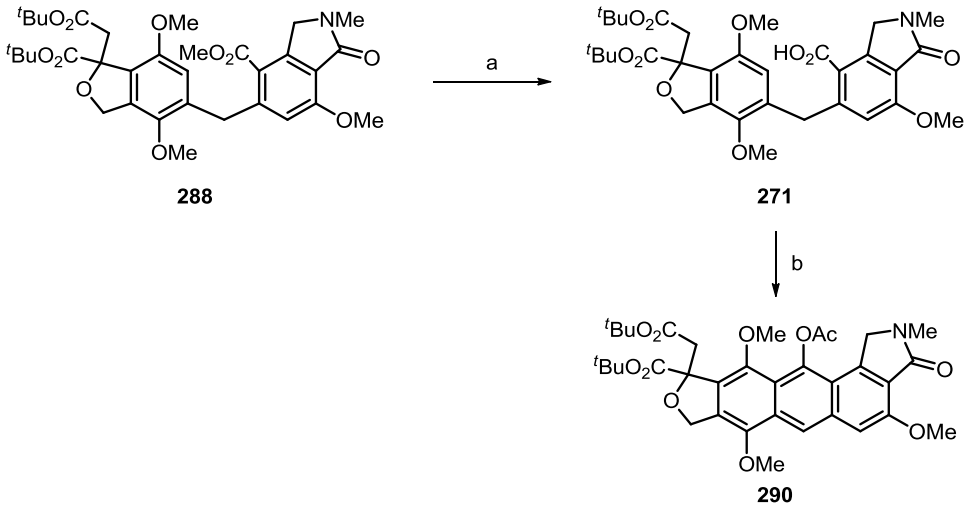
Reagents and conditions: a) $PdCl_2$(dppf), Base (3.0 eq, see Table 11), Solvent (see Table 11), microwave 80 °C, 2 x 5 min.

Entry	272 (eq.)	273 (eq.)	Base	Solvent	Results
a	2.0	1.0	K_3PO_4	DME	No reaction
b	2.0	1.0	Cs_2CO_3	DME	No reaction
c	2.0	1.0	Cs_2CO_3	DME/H_2O (4:1)	45% of **288**
d	1.1	1.0	K_3PO_4	DME/H_2O (3:1)	55% of **288**

Table 11 – Optimization for the formation of 288

The next two steps towards pentacycle **290** were conducted by Dr. Michaelis and Dr. Gebhardt. The synthesis continued with the selective saponification of the methyl ester in **288**. Treatment with ten equivalents of LiOH successfully afforded **271** in good yield (Scheme 99). Based on previous studies,[31] the Friedel-Crafts acylation was planned to be performed in a three-step procedure. First, the carboxylic acid **271** would be converted into the corresponding acid chloride, the acylation would take place and finally the resulting phenol would be protected for stability purpose. Treatment of carboxylic acid **271** with Ghosez's reagent[116] successfully gave the corresponding acid chloride which was treated with $ZnCl_2$. Finally, treatment with a mixture of Ac_2O and pyridine successfully afforded

in good yield pentacycle **290**, the structure of which was confirmed by X-ray crystallography (Figure 10).



Scheme 99 – Synthesis of pentacycle 290

Reagents and conditions: a) LiOH, MeOH/H_2O (1:1), 48 h; b) i) $Me_2C(Cl)NMe_2$, CH_2Cl_2, 0 °C; ii), $ZnCl_2$, 0 °C; iii) Ac_2O, pyridine, DMAP, 12 h, 75% over two steps.

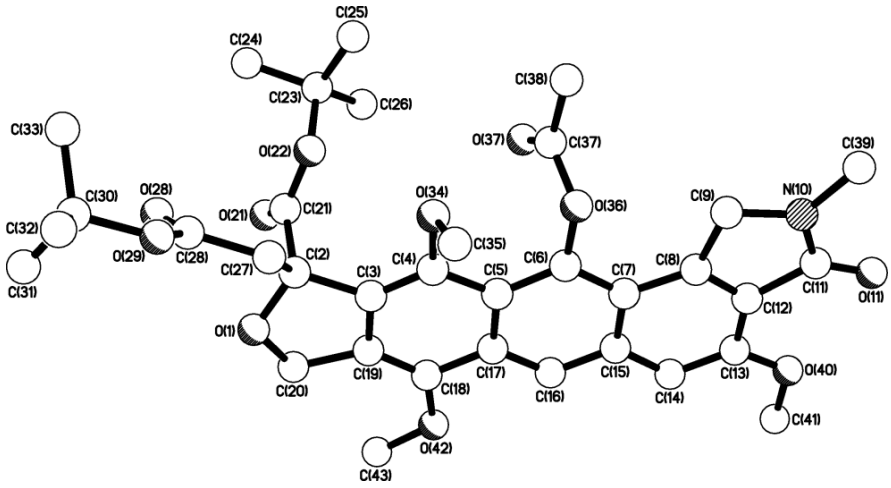
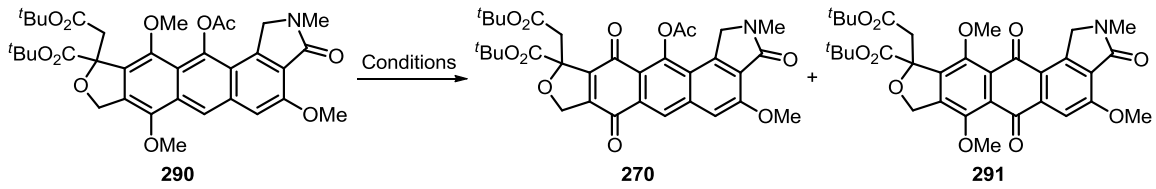


Figure 10 – X-ray structure of pentacycle 290

The synthesis continued with the oxidative demethylation to afford quinone derivative **270** (Scheme 100). Previous reported attempts for the oxidation on various model systems revealed that CAN was an excellent oxidation reagent.[31] In addition, Behar described that the success of the CAN oxidation required the presence of the electron-withdrawing acetate protecting group on the center ring phenol; otherwise, oxidation preferentially occurred at the central ring of the anthracene system.[117] Pentacycle

290 was treated with an excess of CAN at 0 °C for one hour and the reaction was warmed to room temperature for twelve hours. Surprisingly, an inseparable mixture of quinones **270** and **291** was obtained in a 1:5 ratio, respectively (Table 12, entry a). The ratio could be reduced to 1:1.7 when the reaction was conducted only at 0 °C but the undesirable quinone **291** was still obtained as the major product (Table 12, entry b). As a result, the reaction was attempted with a variety of oxidative agents. Treatment with PIFA gave a complex mixture and quinones **270** and **291** could be isolated in a 1:10 ratio (Table 12, entry c) whereas treatment with DDQ or Ag_2O gave no conversion after twelve hours (Table 12, entries d and e).[118] Pleasingly, treatment with an excess of AgO with HNO_3 at room temperature favored the formation of the desired quinone **270** and quinones **270** and **291** were obtained in a 2.7:1 ratio, respectively (Table 12, entry f).[119] Upon treatment under the same conditions at −10 °C, the ratio was further increased to 5:1 in favor for **270** (Table 12, entry g). Finally, the reaction was conducted at −45 °C and only traces of quinone **291** were detected and quinone **270** could be obtained pure in 43% yield (Table 12, entry h).

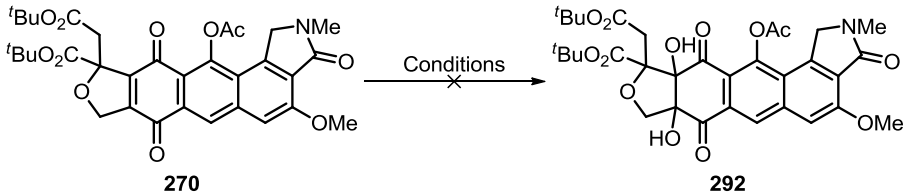


Scheme 100 – Oxidation of pentacycle 290

Entry	Oxidant (eq.)	Temperature	Ratio	
			270	291
a	CAN (3.0)	0 °C to rt	1	5
b	CAN (3.0)	0 °C	1	1.7
c	PIFA (1.1)	0 °C to rt	1	10
d	DDQ (2.5)	rt	No reaction	
e	Ag_2O (3.0)	−20 °C	No reaction	
f	AgO (5.0), 4 N HNO_3	rt	2.7	1
g	AgO (5.0), 4 N HNO_3	−20 °C	5	1
h	AgO (5.0), 4 N HNO_3	−45 °C	43%	traces

Table 12 – Optimization for the formation of quinone 270

With quinone **270** in hand, the dihydroxylation was investigated by Dr. Michaelis and Dr. Gebhardt (Scheme 101 and Table 13). Following the Danishefsky precedent,[24] quinone **270** was treated with a mixture of OsO_4 (catalytic or stoichiometric amount) and NMO. Unfortunately, quinone **270** decomposed (Table 13, entries a and b).[24] Upon treatment under Sharpless conditions, no reaction took place and starting material **270** was recovered (Table 13, entry c).[120] The dihydroxylation was repeated with ruthenium tetraoxide (prepared *in situ* from ruthenium(III) chloride and sodium periodate), however, no reaction was observed (Table 13, entry d).[92]



270 **292**

Scheme 101 – Dihydroxylation attempts on 292

Entry	Conditions (eq.)	Solvent	Results
a	OsO_4 (5 mol%), NMO (1.5)	acetone/H_2O (9:1)	Decomposition
b	OsO_4 (1.0)	acetone/H_2O (9:1)	Decomposition
c	$K_3Fe(CN)_6$ (3.0), K_2CO_3 (3.0), $K_2OsO_2(OH)_4$ (5 mol%), $(DHQD)_2PHAL$ (0.1), $MeSO_2NH_2$ (2.0)	*tert*-BuOH/H_2O (1:1)	No reaction
d	$RuCl_3$ (0.5 mol%), $NaIO_4$ (0.5), H_2SO_4 (0.2)	EtOAc/MeCN/H_2O (6:6:1)	No reaction

Table 13 – Dihydroxylation attempts on quinone 292

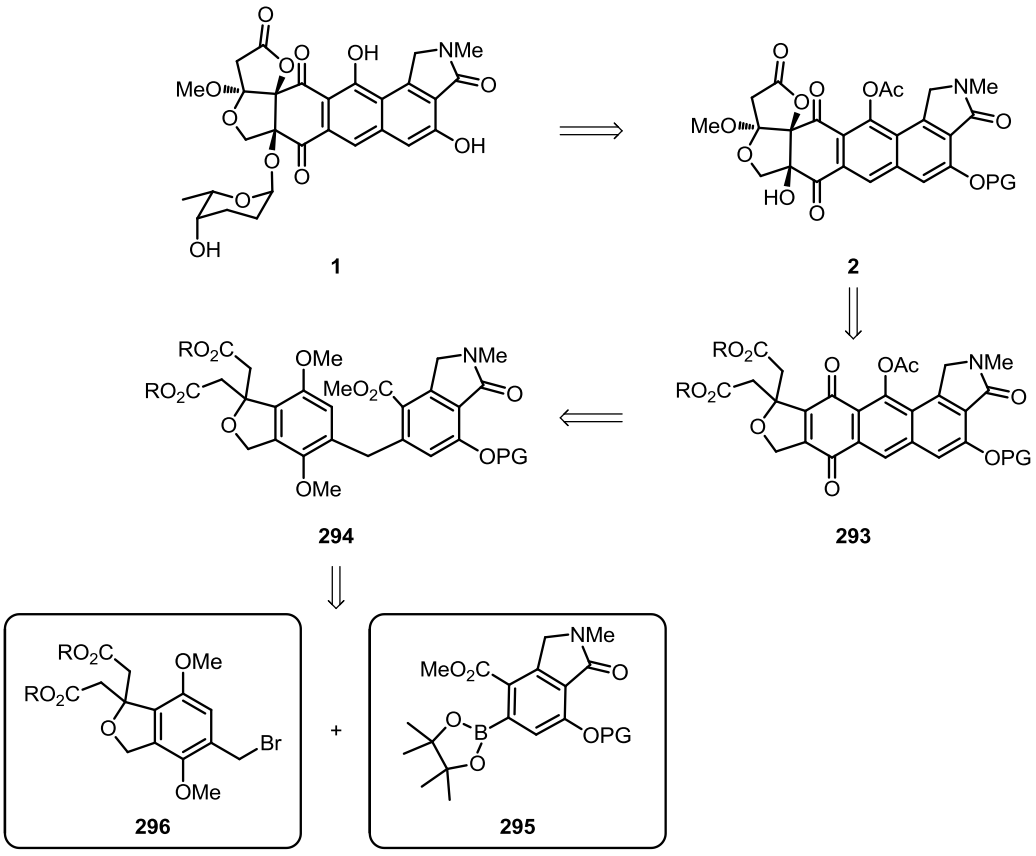
1.5 Conclusion

In summary, it was shown that pentacycle **270** can be assembled from boronic ester **273** and benzyl bromide **272** in good yield from readily synthesized components. So far, the dihydroxylation failed to be successful despite similarities with model studies. It was suggested that the dihydroxylation was not successful mainly due to the steric hindrance generated by both *tert*-butyl esters. In a new strategy, we sought to diminish the steric hindrance with a few modifications.

2. Second strategy

2.1 Introduction

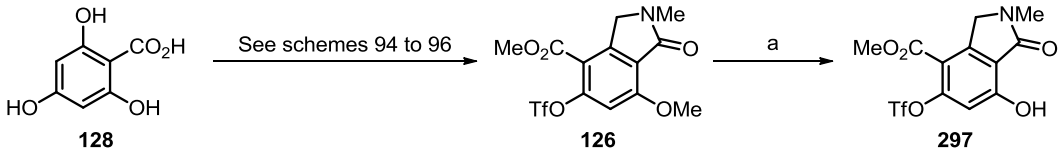
In addition to the steric hindrance from both *tert*-butyl esters, it was feared that the methyl ether *ortho* to the amide moiety would be difficult to cleave at a late stage of the synthesis.[80] As a result, this possible issue will also be addressed in the new strategy which is depicted in Scheme 102. It was still envisaged that lactonamycin **1** could be obtained from the aglycone core **2** after introduction of the sugar moiety and cleavage of the remaining protecting groups. **2** could be synthesized from pentacycle **293** after dihydroxylation, lactonisation and introduction of the angular methoxy group. Pentacycle **293** could be obtained from **294** after selective saponification, Friedel-Crafts acylation and subsequent oxidation of the C-ring. Finally, Suzuki coupling between benzyl bromide **296** and boronic ester **295** could furnish **294**.



Scheme 102 – New strategy towards the synthesis of lactonamycin 1

2.2 Synthesis of boronic ester 304

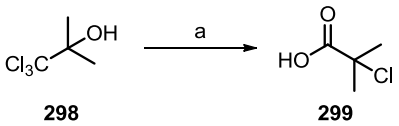
The synthesis towards boronic ester **295** was similar to the previous synthesis of **273**. Starting from trihydroxy acid **128**, triflate **126** was successfully synthesized using the same methodology as shown in Scheme 94 to Scheme 96). Pleasingly, upon treatment with BBr_3, the methyl ether was successfully cleaved and phenol **297** was obtained in good yield (Scheme 103).[121]



Scheme 103 – Synthesis of triflate 297

Reagents and conditions: a) BBr_3, CH_2Cl_2, −78 °C to rt, 12 h, 88%.

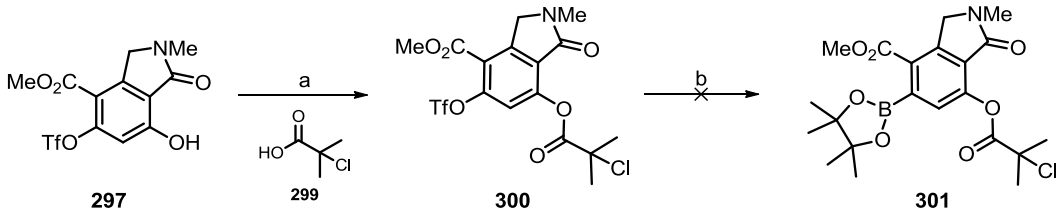
At this point of the synthesis, it was anticipated that the resulting phenol could be protected as a 2-chloro-2-methylpropanoic ester and acid **299** was synthesized in one step starting from 1,1,1-trichloro-2-methylpropan-2-ol **298** in good yield (Scheme 104).[122]



Scheme 104 – Synthesis of acid 299

Reagents and conditions: a) H_2SO_4, rt, 12 h, 88%.

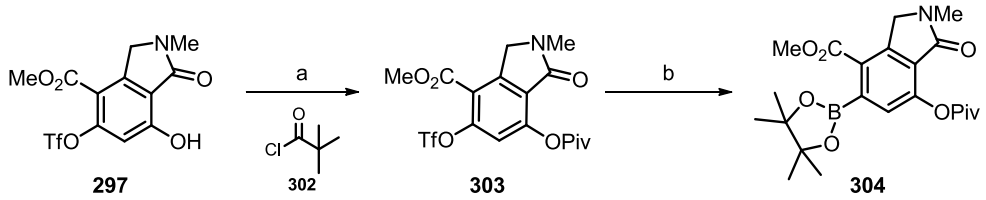
The coupling of phenol **297** with acid **299** in the presence of EDCI and DMAP successfully afforded the corresponding ester **300** (Scheme 105).[123] Unfortunately, the formation of the corresponding boronic ester was problematic and no formation of the expected product **301** was observed probably due to the instability of the ester moiety. As a result, phenol **297** was protected as a pivaloic ester.



Scheme 105 – Towards the synthesis of boronic ester 301

Reagents and conditions: a) **299**, EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 2 h, 67%; b) Bis(pinacolato) diboron, Pd(dppf)Cl_2, NaOAc, PhH, 80°C.

Treatment of phenol **297** with trimethylacetyl chloride **302** in the presence of pyridine successfully afforded ester **303** (Scheme 106). Finally, triflate **303** was converted into the corresponding boronic ester under classical Miyaura conditions.[114] Starting from trihydroxy acid **128**, boronic ester **304** was synthesized in thirteen steps with an overall yield of 12%.



Scheme 106 – Synthesis of boronic ester 304

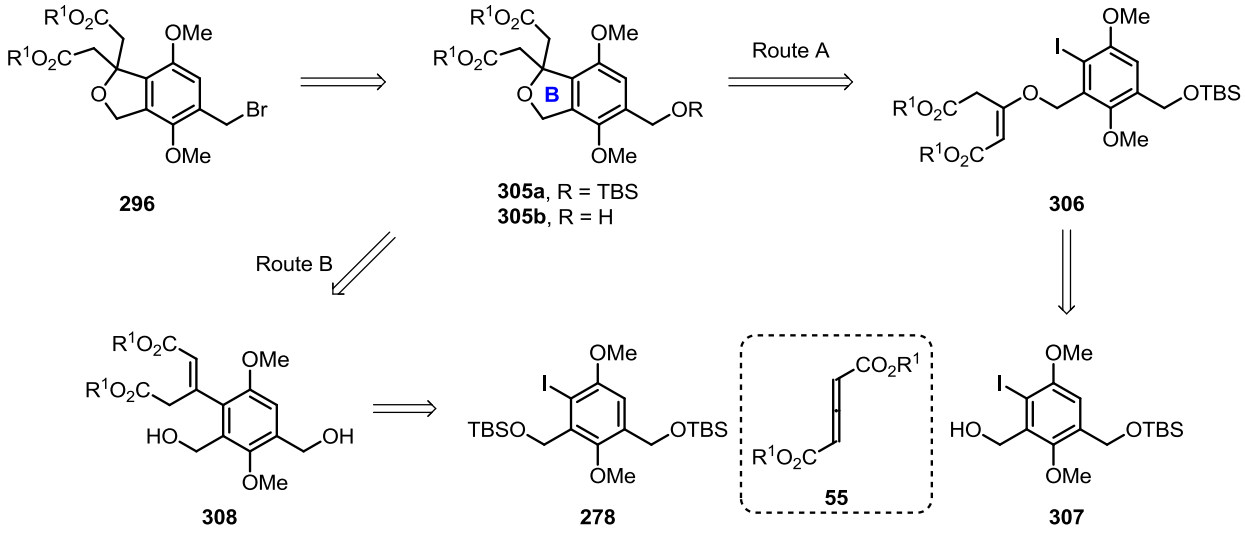
Reagents and conditions: a) **302**, pyridine, CH_2Cl_2, 0 °C to rt, 12 h, 65% b) Bis(pinacolato)diboron, Pd(dppf)Cl_2, NaOAc, PhH, 80 °C, 12 h, 70%.

2.3 Synthesis of benzyl bromide 296

2.3.1 The allene approach

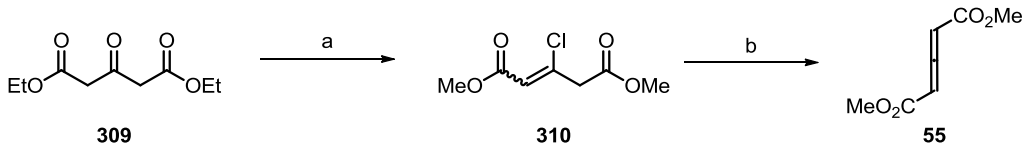
We sought to take advantage of the developed route towards bromide **272** and following certain modifications, it was thought that benzyl bromide **296** could be synthesized from alcohol **305b** or from TBS-protected alcohol **305a**. The B-ring could be formed *via* a radical cyclization from intermediate **306** which could be synthesized from iodide **307** and allene **55** *via* a Michael addition (Scheme 107,

Route A). Alternatively, the B-ring could be constructed from known iodide **278** *via* a palladium coupling with allene **55** followed by a Michael addition from precursor **308** (Scheme 107, Route B).



Scheme 107 – Proposed retrosynthesis of bromide 296 starting from allene 55

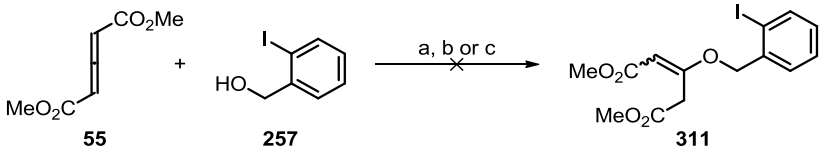
Diethyl acetone-1,3-dicarboxylate **309** was reacted with phosphorous pentachloride followed treatment with sulphuric acid in methanol to give vinyl chloride **310**.[124] Treatment of **310** with triethylamine successfully gave the desired allene **55** in moderate yield (Scheme 108).



Scheme 108 – Synthesis of allene 55

Reagents and conditions: a) i) PCl_5, rt, 30 min; ii) H_2SO_4, MeOH, reflux, 12 h 38%; b) Et_3N, THF, 0 °C, 12 h, 55%.

It has been reported in the literature that 1,3-dicarboalkoxyallene react readily with a wide range of nucleophiles to give the corresponding addition products.[125] In order to test the reaction, 2-iodobenzylalcohol **257** was used to model the alcohol **307** (Scheme 109). Allene **55** was added to a mixture of 2-iodobenzyl alcohol **257** and DMAP at 0 °C, however, no reaction occurred and allene **55** decomposed readily under these conditions. The reaction was repeated with sodium hydride and potassium *tert*-butoxide as bases, but no expected product **311** was formed and allene **55** decomposed.



Scheme 109 – Michael addition attempts on allene 55

Reagents and conditions: a) DMAP, THF, 0 °C to rt; b) NaH, THF, 0 °C to rt; c) *tert*-BuOK, THF, 0 °C to rt.

As the Michael addition to allene **55** was not successful, it was envisaged that the formation of the C-O and C-C bonds could be reversed and **312** or **313** could be obtained *via* a palladium-catalyzed reaction (Route B). Indeed, it is known in the literature that allenes react readily with aryl iodide *via* palladium-catalyzed coupling reactions[126] and in most of the catalytic reactions, the aryl group is transferred to the central carbon of allenes.[127] Unfortunately, upon treatment with palladium acetate, tri(*o*-tolyl)phosphine and silver orthophosphate, no reaction occurred and allene **55** decomposed (Table 14, entry a). The reaction was repeated with a combination of catalysts, phosphine ligands, bases and solvents but in all cases, allene **55** decomposed and alcohol **257** was recovered (Table 14, entries b to e).

Scheme 110 – Palladium-catalyzed heteroannulation on 257 with allene 55

Reagents and conditions: a) Catalyst (see Table 14), phosphine ligand (see Table 14), base (see Table 14), solvent (Table 14), 80 °C.

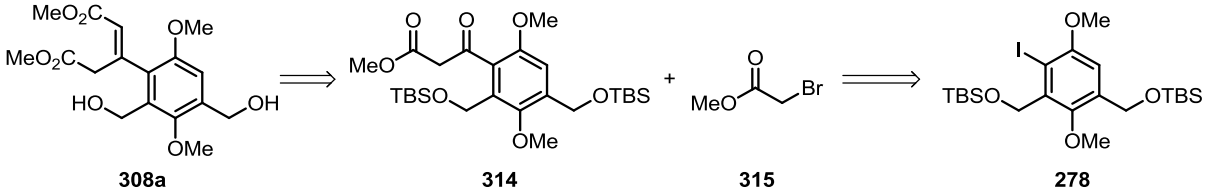
Entry	Catalyst (mol%)	Phosphine ligand (mol%)	Base (eq.)	Solvent	Results
a	$Pd(OAc)_2$ (5)	P(*o*-tol)$_3$ (10)	Ag_3PO_4 (0.4)	DMF	No reaction
b	$Pd(OAc)_2$ (5)	P(*o*-tol)$_3$ (10)	K_2CO_3 (2)	MeCN	No reaction
c	$Pd(OAc)_2$ (5)	PPh_3 (10)	K_2CO_3 (2)	MeCN	No reaction

d	$Pd(PPh_3)_4$ (5)	None	K_2CO_3 (2)	MeCN	No reaction
e	$Pd(PPh_3)_4$ (5)	None	Et_3N (2)	MeCN	No reaction

Table 14 – Palladium coupling attempts between iodide 257 and allene 55

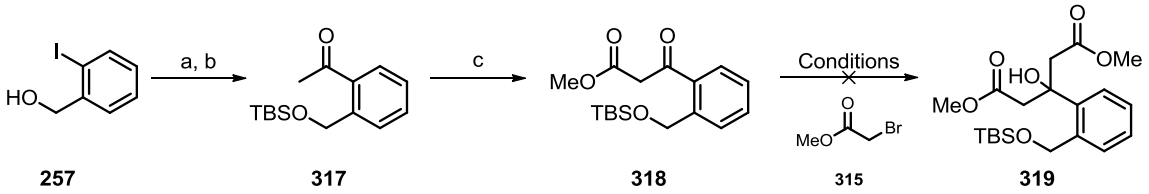
2.3.2 The Reformatsky approach

As the previous methodology was not successful, it was envisaged that key diol **308a** could be synthesized using a Reformatsky reaction as the key step (Scheme 111). Retrosynthetically, diol **308a** could be obtained from keto-ester **314** after treatment with methyl 2-bromoacetate **315** followed by elimination and TBS-deprotection. Finally, keto-ester **314** could be synthesized from already synthesized iodide **278**.



Scheme 111 – Synthesis of diol 308a *via* a Reformatsky reaction

In order to investigate the Reformatsky reaction, protected 2-iobobenzyl alcohol was used to model iodide **257**. The synthesis began with the protection of 2-iodobenzyl alcohol **257** as its TBS-ether to form **316** under classical conditions followed by treatment with *n*-BuLi and methyl acetate to form the corresponding ketone **317** (Scheme 112).[128] Ketone **317** was treated with sodium bis(trimethylsilyl)amide and dimethyl carbonate to give keto ester derivative **318** albeit in a low 34% yield. The zinc enolate, prepared from methyl 2-bromoacetate **315**, activated zinc[129] and catalytic amount of iodine was reacted with keto ester derivative **318**, however, no reaction occurred (Table 15, entry a). The reaction was repeated with samarium(II) iodide,[130] but **318** could be recovered (Table 15, entry b). Methyl 2-bromoacetate **315** was reacted instead with manganese and Cp_2TiCl,[131] but no improvement was observed (Table 15, entry c). As a result, this strategy was abandoned.



Scheme 112 – Synthesis of keto-ester 318 and Reformatsky attempts

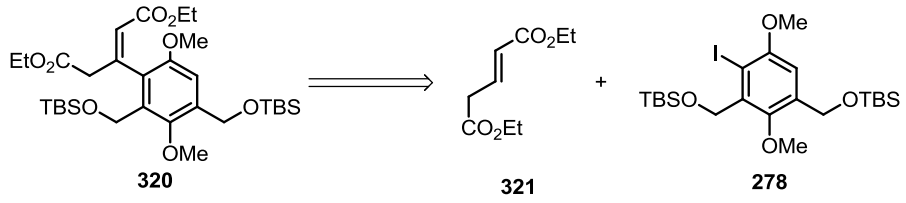
Reagents and conditions: a) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 12 h, 95%; b) *n*-BuLi, TMEDA, AcOMe, −78 °C, 3 h, 61%; c) NaHMDS, MeO(CO)OMe, THF, −78 °C, 1 h, 34%.

Entry	Conditions (eq.)	Results
a	Activated zinc (7.5), I_2 (cat.), **315** (1.57)	No reaction
b	SmI_2 (5.0), **315** (1.2)	No reaction
c	Cp_2TiCl_2 (2.2), Mn (4.0), **315** (1.0)	No reaction

Table 15 – Reformatsky attempts on 318

2.3.3 The Heck approach

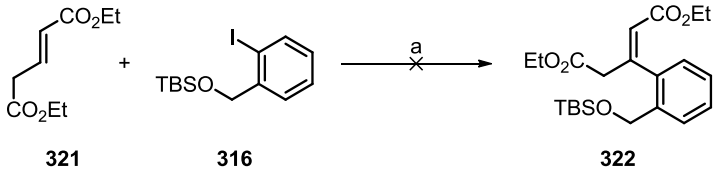
A new strategy for the synthesis of alkene **320** was needed and it was envisaged that alkene **320** could be obtained from known iodide **278** and diethyl glutaconate **321** *via* a Heck coupling (Scheme 113).



Scheme 113 – Retrosynthetic approach towards alkene 320 *via* a Heck coupling

TBS-protected alcohol **316** was used to model iodide **278**. Based on the work developed by Trigle,[132] iodide **316** was treated with glutaconate **321** in equimolar proportions in anhydrous DMF in the presence of palladium(II) acetate, triphenylphosphine and sodium acetate at 135-140 °C, however, no reaction occurred and glutaconate **321** decomposed (Table 16, entry a). As a result, the reaction was

repeated under milder conditions using the conditions developed for the synthesis of model carboxylic acid **3** ($Pd(OAc)_2$, P(*o*-tol)$_3$ in Et_3N at 80 °C) but no improvement was observed (Table 16, entry b).[63a] The conditions detailed by Fu[133] were also attempted but no reaction occurred (Table 16, entry c). The reaction was attempted with $Pd(PPh_3)_4$ and Et_3N in acetonitrile, but no reaction occurred (Table 16, entry d).



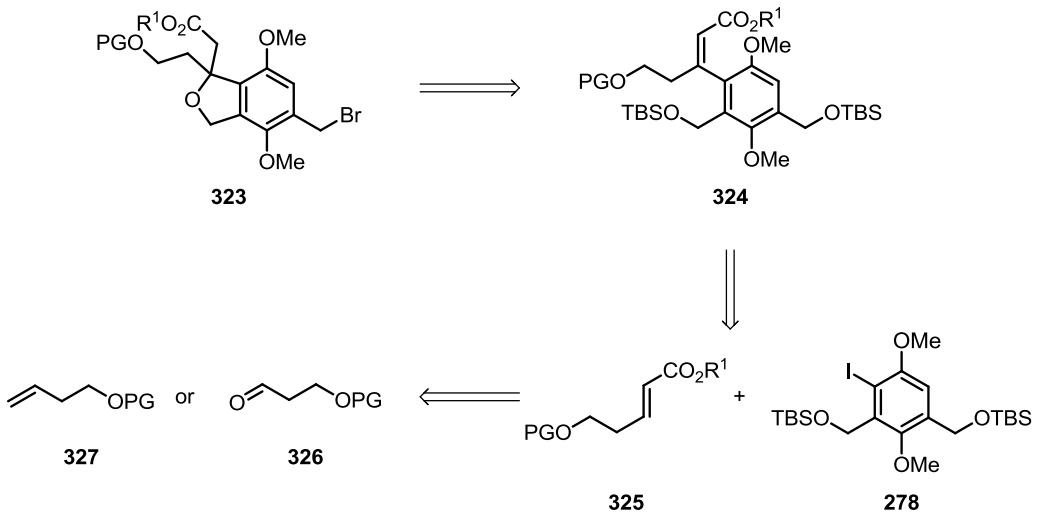
Scheme 114 – Heck coupling attempts between iodide 316 and glutaconate 321

Reagents and conditions: a) Catalyst (see Table 16), Phosphine ligand (see Table 16), base (see Table 16), Solvent (see Table 16), Temperature (see Table 16).

Entry	Catalyst	Phosphine	Base	Solvent	Temperature	Results
a	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	135 °C	No reaction
b	$Pd(OAc)_2$	P(*o*-tol)$_3$	Et_3N	None	80 °C	No reaction
c	$Pd_2(dba)_3$	P(*tert*-Bu)$_3$	Cy_2NMe	Dioxane	rt	No reaction
d	$Pd(PPh_3)_4$	None	Et_3N	MeCN	80 °C	No reaction

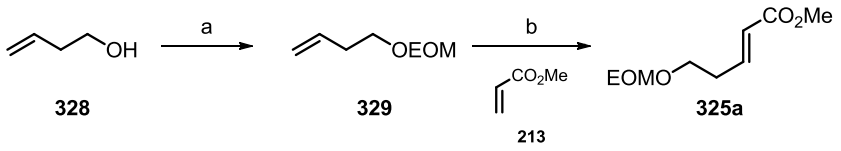
Table 16 – Heck coupling attempts between iodide 316 and glutaconate 321

As a second alternative, it was envisaged that bromide **323** could be synthesized from alkene **324** after alcohol deprotection, subsequent Michael addition followed by conversion of the remaining alcohol into the corresponding bromide (Scheme 115). Heck coupling between alkene **325** and known iodide **278** could furnish alkene **324**. Finally, alkene **325** could be obtained either from protected but-3-en-1-ol **327** after metathesis with methyl acrylate **213** or from protected alcohol **326** after Wittig olefination.



Scheme 115 – Retrosynthetic approach towards bromide 323 *via* a Heck coupling

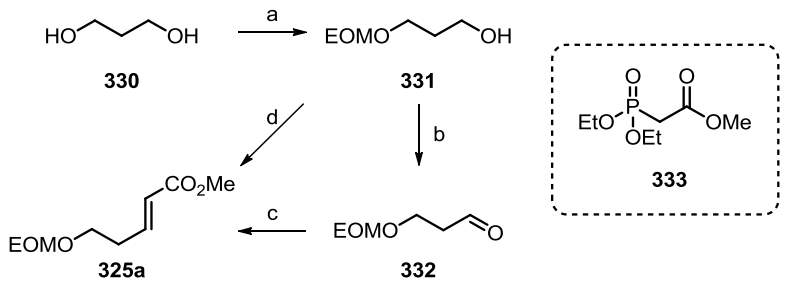
The synthesis of alkene **325a** began with the protection of but-3-en-1-ol **328** with chloromethyl ethyl ether and Hünig's base to form **329**[134] which was treated with Grubbs II catalyst and excess of methyl acrylate **213** to from alkene **325a** in good yield (Scheme 116).[135]



Scheme 116 – Synthesis of alkene 325a

Reagents and conditions: a) EOMCl, Hünig's base, CH_2Cl_2, 0 °C to rt, 2 h, 84%; b) Grubbs II catalyst, **312**, CH_2Cl_2, reflux, 12 h, 72%.

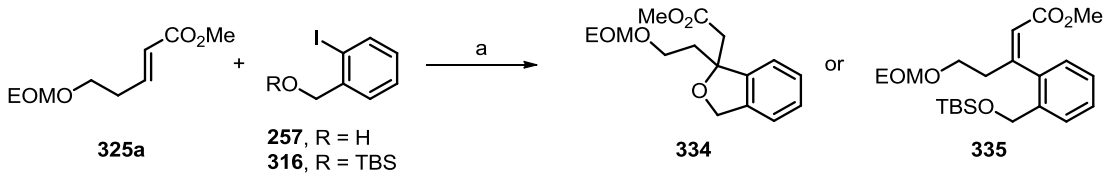
Alternatively, propane-1,3-diol **330** was mono protected with chloromethyl ethyl ether and sodium hydride and alcohol **331** was isolated in good yield (Scheme 117).[136] Alcohol **331** was successfully oxidized into the corresponding aldehyde **332** *via* a Swern oxidation. However, the aldehyde proved to be unstable and decomposed when treated with methyl 2-(diethoxyphosphoryl)acetate **333** to give alkene **325a** in a low 35% yield.[137] As a result, it was envisaged that alkene **325a** could be synthesized from alcohol **331** in a single step *via* a one-pot DMP oxidation-Wittig reaction developed within the group.[138] Dess-Martin periodinane was added to a mixture of alcohol **331**, ester ylide **333**, and benzoic acid, and pleasingly, alkene **325a** was obtained in 57%.



Scheme 117 – Alternative synthesis of alkene 325a

Reagents and conditions: a) NaH, EOMCl, THF, 0 °C to rt, 12 h, 66%; b) i) $(COCl)_2$, DMSO, 10 min; ii) **331**, 15 min; iii) Et_3N, CH_2Cl_2, –78 °C to 0 °C, 30 min, 89%; c) i) NaH, **333**, 30 min; ii) **332**, THF, 0 °C, 2 h, 35%; d) i) $PhCO_2H$, **333**; ii) DMP, CH_2Cl_2/DMSO, rt, 30 min, 57% .

With alkene **325a** in hand, several Heck coupling were attempted with alcohol **257** or TBS-protected alcohol **316** (Scheme 118). Based on the previous results obtained during the synthesis of model carboxylic acid **3**, alcohol **257** and alkene **235a** were treated with palladium acetate, tri(*o*-tolyl)phosphine and triethylamine as base, however, the expected product **334** was only obtained in a poor 19% yield (Table 17, entry a).[63a] The reaction was repeated with palladium acetate, tri(*o*-tolyl)phosphine and *N*-methyldicyclohexylamine, however, no reaction occurred and alkene **325a** decomposed (Table 17, entry b). The conditions optimised by Fu[133] were tested but no reaction occurred (Table 17, entry c). Finally, the coupling was attempted using a different palladium source ($Pd_2(dba)_3$) but no conversion was observed (Table 17, entry d). The Heck coupling was also attempted with TBS-protected alcohol **316**. Unfortunately, upon treatment with palladium acetate, tri(*o*-tolyl)phosphine and triethylamine as base, the corresponding coupling product **335** was obtained in a low 25% yield (Table 17, entry e).[63a]



Scheme 118 – Attempts to couple alkene 325a and iodide 257 or 316 *via* a Heck coupling

Reagents and conditions: a) Catalyst (see Table 17), Phosphine ligand (see Table 17), base (see Table 17), solvent (see Table 17), 80 °C, 12 h.

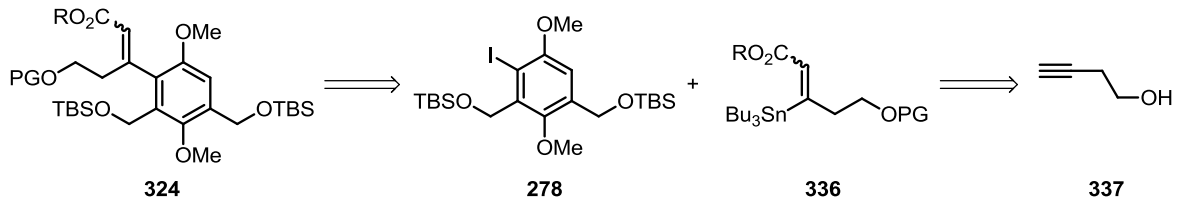
Entry	Starting material	Catalyst (mol%)	Phosphine ligand (mol%)	Base (eq.)	Solvent	Results
a	**257**	$Pd(OAc)_2$ (1)	P(*o*-tol)$_3$ (2)	Et_3N (2.15)	None	**334** 19%
b	**257**	$Pd(OAc)_2$ (5)	P(*o*-tol)$_3$ (10)	$NMe(Cy)_2$ (1.1)	MeCN	No reaction
c	**257**	$Pd_2(dba)_3$ (5)	P(*tert*-Bu)$_3$ (10)	Cy_2NMe	Dioxane	No reaction
d	**257**	$Pd_2(dba)_3$ (5)	P(*o*-tol)$_3$ (20)	Et_3N (4.1)	MeCN	No reaction
e	**316**	$Pd(OAc)_2$ (1)	P(*o*-tol)$_3$ (2)	Et_3N (2.15)	None	**335** 25%

Table 17 – Palladium coupling attempts between alkene 325a and iodides 257 and 316

Overall, due to the low yields obtained in the Heck coupling and the problems associated with the stability of aldehyde **316**, this route was not a reliable method for obtaining large quantities of benzyl bromide **305**. As a result, the Heck approach was abandoned.

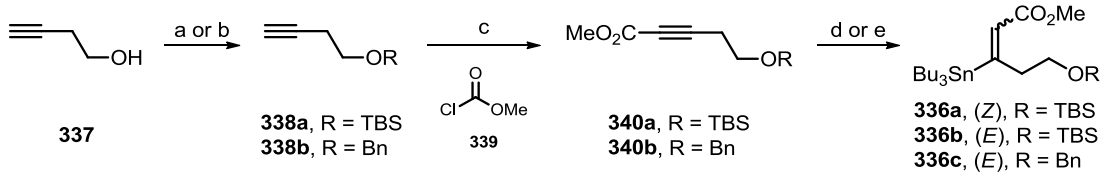
2.3.4 The Stille approach

As a last effort, it was envisaged that alkene **324** could be obtained from known iodide **278** and stannane **336** (Scheme 119). Stannane **336** could be synthesized from 3-butyn-1-ol **337** after protection of the alcohol, acylation and subsequent Piers hydrostannation.



Scheme 119 – Retrosynthetic approach towards alkene 324 *via* a Stille coupling

3-Butyn-1-ol **337** was converted to ester **340a** in two steps by first protecting the primary hydroxyl group as a TBS-ether (Scheme 120). The resulting TBS-ether **338a** was subjected to *n*-BuLi followed by methyl chloroformate **339** to yield ester **340a** in excellent yield.[139a] In a similar manner, 3-butyn-1-ol **337** was converted to ester **340b** in moderate yield over two steps.[139c] Following the conditions developed by Piers *et al.*,[140] **340a** was treated with lithium(phenylthio)(tributylstannyl)cuprate (prepared *in situ* from lithium diisopropylamide, tributyltin hydride and copper(I) thiophenolate[141]) to give the (*Z*)-vinylstannane **336a** in a moderate 55% yield. When alkynes **340a** and **340b** were subjected to the same conditions in the presence of methanol, the (*E*)-isomers **336b** and **336c** were afforded in 80% and 77% yields, respectively.

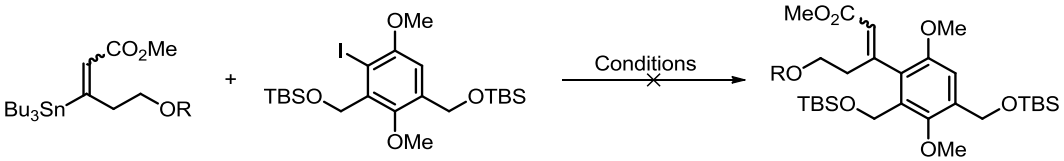


Scheme 120 – Synthesis of stannanes 336a-c

Reagents and conditions: a) TBSCl, DIPEA, CH_2Cl_2, 0 °C to rt, 12 h, 99%; b) BnBr, NaH, THF, 0 °C to rt, 12 h, 70%; c) i) *n*-BuLi, THF, –78 °C, 1 h; ii) **339**, 1 h, 86% for **340a**, 70% for **340b**; d) i) DIPA, *n*-BuLi, THF, 0 °C, 1 h; ii) Bu_3SnH, 0 °C, 1 h; iii) PhSCu, –20 °C, 1 h; iv) **340a**, –78 °C, 1 h, 55% for **336a**; e) i) DIPA, *n*-BuLi, THF, 0 °C, 1 h; ii) Bu_3SnH, 0 °C, 1 h; iii) PhSCu, –20 °C, 1 h; iv) **340a** or **340b**, MeOH, –78 °C, 1 h, 80% for **336b**, 77% for **336c**.

Stannanes **336a** and **336b** and iodide **261** were treated with tetrakis(triphenylphosphine)palladium and copper(I) iodide in refluxing toluene (Scheme 121), however, no reaction occurred and stannanes **336a** and **336b** decomposed (Table 18, entry a). It was feared that stannanes **336a** and **336b** was too sensitive to undergo coupling at high temperature, as a result, the reaction was repeated under the same conditions at 45 °C. Unfortunately, no reaction was observed (Table 18, entry b). Although the beneficial effect of Cu(I)[142] and fluoride ion[143] for the Stille coupling had been demonstrated separately, Baldwin and co-workers reported first the simultaneous use of CuI and CsF to promote the Stille coupling by facilitating a preliminary transmetallation reaction from the organostannane to generate a more reactive organocopper intermediate and by easing the purification with the formation of the insoluble Bu_3SnF.[144] Based on their results, iodide **278** and alkenes **336a** and **336b** were reacted with a catalytic amount of copper(I) iodide and cesium fluoride in DMF at 45 °C. Unfortunately, stannanes **336a** and **336b** decomposed (Table 18, entry c). In this particular case, it was suggested that the coupling failed due to the incompatibility of the fluoride additive with the silyl protecting group in

stannanes **336a** and **336b**. Accordingly, the reaction was attempted with stannane **336c**, but no improvement was observed (Table 18, entry c). In 2008, Fürstner *et al.* showed that a combination of copper thiophene-2-carboxylate (CuTC) and phosphinate salt $[Ph_2PO_2][NBu_4]$ allowed a series of exigent Stille reactions to be performed with high yields and as the protocol was fluoride free, a variety of *O*-silyl and C-silyl groups remained intact.[145] Stannanes **336a** and **336b** were treated with freshly prepared copper thiophene-2-carboxylate[146] and $[Ph_2PO_2][NBu_4]$,[147] however, no reaction was observed (Table 18, entry d). As a last effort, stannanes **336a** and 336**b** and iodide **278** were treated with palladium(II) acetate and tri(*o*-tolyl)phosphine, but no conversion was observed (Table 18, entry e).



336a, (*Z*), R = TBS
336b, (*E*), R = TBS
336c, (*E*), R = Bn

278

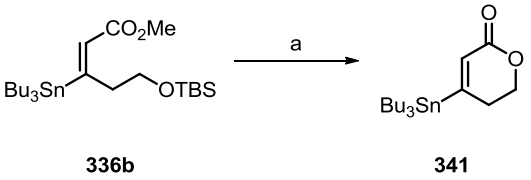
324a, (*Z*), R = TBS
324b, (*E*), R = TBS
324b, (*E*), R = Bn

Scheme 121 – Attempts to synthesis 334a-c *via* a Stille coupling

Entry	R-Sn	Catalyst (mol%)	Copper source	Additive (eq.)	Solvent	T (° C)	Results
a	**336a-b**	$Pd(PPh_3)_4$ (5)	CuI (0.25 eq.)	None	PhMe	120	No reaction
b	**336a-b**	$Pd(PPh_3)_4$ (5)	CuI (0.25 eq.)	None	PhMe	45	No reaction
c	**336a-c**	$Pd(PPh_3)_4$ (5)	CuI (20 mol%)	CsF (2.0)	DMF	45	No reaction
d	**336a-b**	$Pd(PPh_3)_4$ (5)	CuTc (0.8 eq.)	$[Ph_2PO_2]$ $[ClO_4]$ (1.4)	DMF	rt	No reaction
e	**336a-b**	$Pd(OAc)_2$ (5)/ $P(o\text{-tol})_3$ (10)	CuI (20% mol)	CsF (2.0)	DMF	45	No reaction

Table 18 – Stille coupling attempts between stannanes 336a-c and iodide 278

As an alternative, stannane **336b** was treated with camphorsulfonic acid; the TBS-ether was successfully deprotected and the resulting alcohol spontaneously condensed on the methyl ester moiety to form stannane **341** in good yield (Scheme 122).

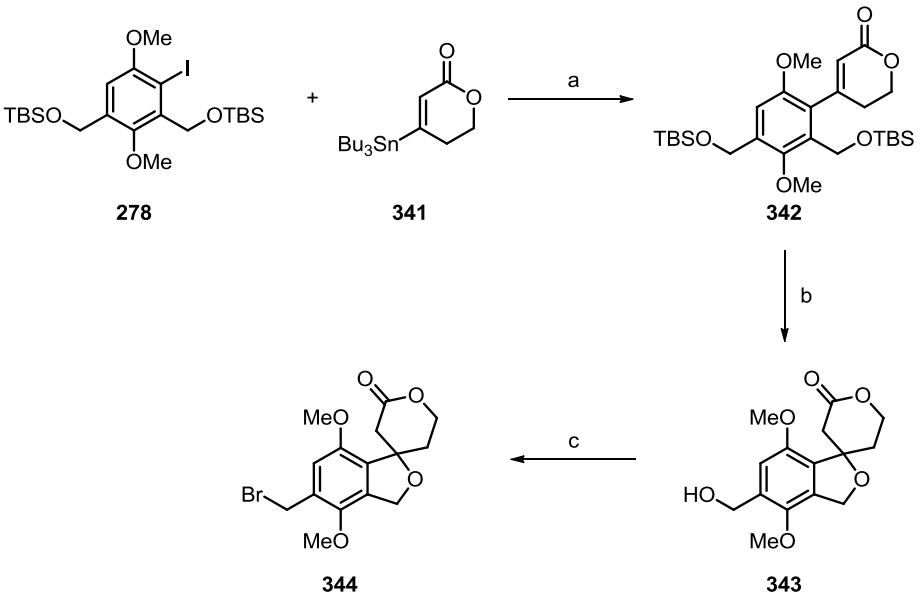


336b **341**

Scheme 122 – Synthesis of stannane 341

Reagents and conditions: a) CSA, MeOH, 0 °C, 1 h, 76%.

To our delight, treatment of iodide **278** and stannane **341** with tetrakis(triphenylphosphine)palladium and copper(I) iodide gave alkene **342** in good yield (Scheme 123). Upon treatment with concentrated HCl at 0 °C, both TBS-ethers were cleaved and spiro-isobenzofuran derivative **343** was obtained after Michael addition. Finally, the remaining alcohol was converted into the corresponding bromide **344** using PPh_3 and CBr_4.[108]

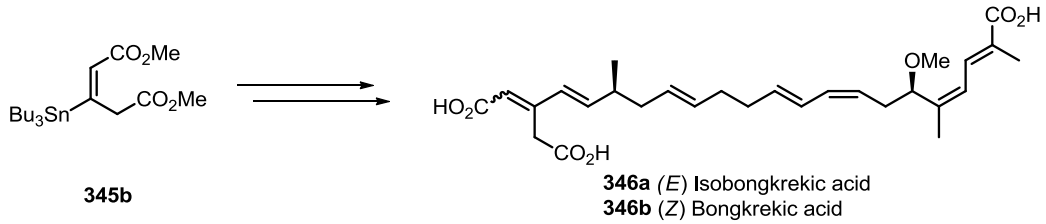


278 **341** **342** **344** **343**

Scheme 123 – Synthesis of bromide 344

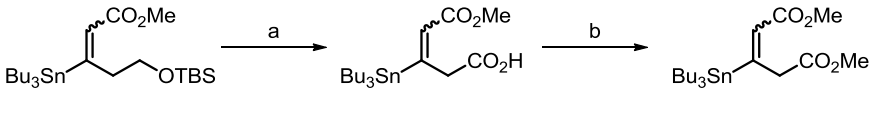
Reagents and conditions: a) $Pd(PPh_3)_4$, CuI, PhMe, reflux, 12 h, 72%; b) conc. HCl, THF, 0 °C, 1 h, 66%; c) PPh_3, CBr_4, DMF, 2 h, rt, 71%.

At this time, our attention was drawn to a strategy developed by Ley and co-workers who reported the synthesis of stannane **345b** on route to the synthesis of iso- and bongkrekic acids **346a** and **346b** (Scheme 124).[148] It was envisaged that stannane **345b** could be a precursor for the synthesis of alkene **308**.



Scheme 124 – Ley's synthesis of iso- and bongkrekic acids 346a and 346b starting from stannane 345b

Silyl ethers **336a** and **336b** were treated with freshly prepared Jones reagent (H_2CrO_4) to simultaneously deprotect and oxidize *in situ* the intermediate alcohol to the carboxylic acids **347a** and **347b** (Scheme 125). Stannanes **345a** and **345b** were finally obtained after esterification using trimethylsilyldiazomethane.[148] Unfortunately, this sequence yielded stannanes **345a** and **345b** in a significantly lower yield (44% and 22% over 2 steps, respectively) than the 68% previously reported by Ley and co-workers and all attempts to improve the yield of the sequence (cleavage of the TBS-ether with CSA and purification, addition of the Jones reagent at 0 °C or use of periodic acid[149] instead of sulfuric acid) proved to be unsuccessful.



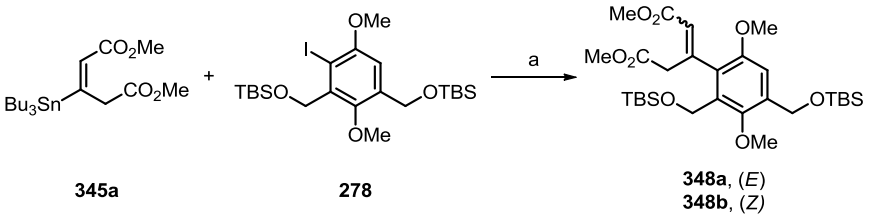
336a, (*Z*)
336b, (*E*)
347a, (*Z*)
347b, (*E*)
345a, (*Z*)
345b, (*E*)

Scheme 125 – Synthesis of stannanes 345a and 345b

Reagents and conditions: a) CrO_3, H_2SO_4, $H_2O/(CH_3)_2CO$, 0 °C, 10 min; b) $TMSCHN_2$, MeOH, CH_2Cl_2, 0 °C, 40 min, 44% for **345a** (over 2 steps), 22% for **345b** (over 2 steps).

Treatment with tetrakis(triphenylphosphine)palladium and copper(I) iodide allowed the coupling to proceed in an encouraging 83% yield. However, the reaction delivered a 1:2 mixture of isomers **348a** and **348b** which could be separated by conventional column chromatography and assigned after

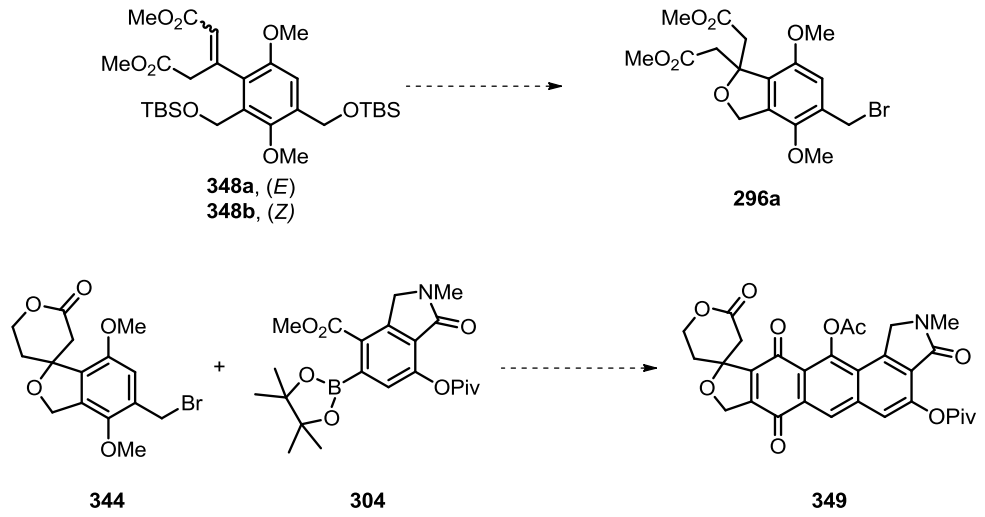
extensive NMR analysis (Scheme 126). In this particular case, this lack of selectivity was inconsequential as the geometry of the double bond in question will ultimately be lost after the Michael addition.



Scheme 126 – Stille coupling between iodide 278 and stannane 345a

Reagents and conditions: a) $Pd(PPh_3)_4$, CuI, PhMe, reflux, 12 h, 25% for **348a**, 58% for **348b**.

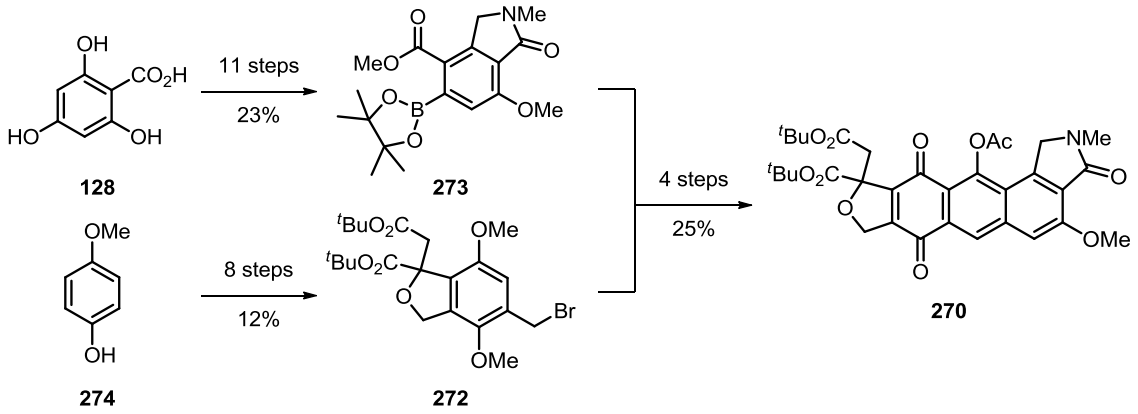
Further transformations of alkenes **348a** and **348b** into bromide **296a** and further elaborations of benzyl bromide **344** and boronic ester **304** to a more advanced intermediate such as **349** could not be performed because of a lack of time and material but will be undertaken in the continuation of the project (Scheme 127).



Scheme 127 – Towards the synthesis of bromide 296a and advanced intermediate 349

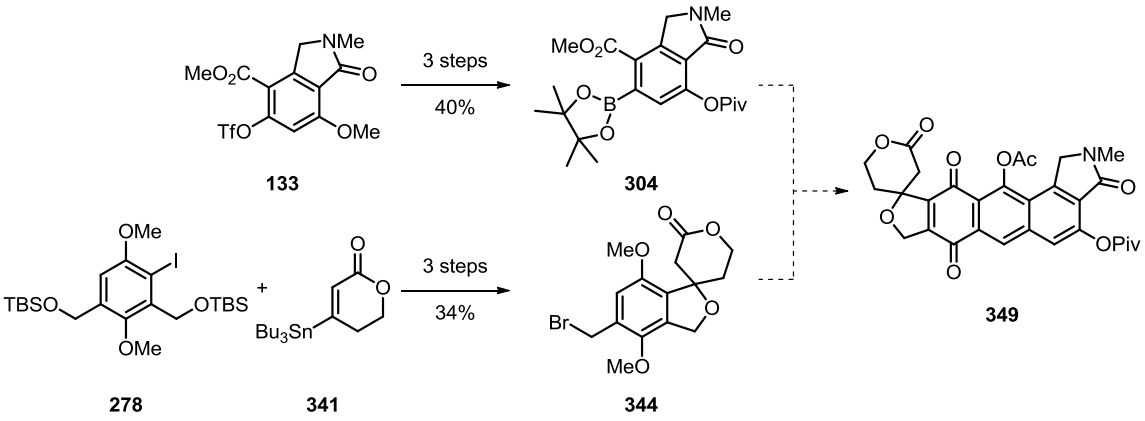
3. Conclusion and future work

As part of studies towards the total synthesis of lactonamycin (**1**), this thesis has described the synthesis of pentacycle **270** containing the novel naphtha[*e*]isoindole ring system of lactonamycin (**1**). Pentacycle **270** was obtained in four steps from benzyl bromide **272** and boronic ester **273** which were synthesized in eight and eleven steps in 12% and 23% yield, respectively starting from commercially available starting materials. Unfortunately so far, all dihydroxylation attempts failed on quinone **270** and the synthesis of the highly-oxygenated fused perhydrofuran-furanone, in the western half of lactonamycin (**1**), was so far not possible.



Scheme 128 – Synthesis of pentacycle 270

As a result of the issues encountered during the dihydroxylation of quinone **270**, two new coupling partners were successfully synthesized (Scheme 129). Boronic ester **304** was obtained from known triflate **133** and bromide **344** was formed from known iodide **278** and stannane **341**. Two advanced intermediates **348a** and **348b** were also synthesized from iodide **278** and stannane **345a**. Further elaborations from benzyl bromide **344** and boronic ester **304**, to a more advanced intermediate such as **349** could not be performed but will be undertaken in the continuation of this project.



Scheme 129 – Synthesis of boronic ester 304 and benzyl bromide 344 towards pentacycle 349

Chapter V Results and Discussion

Towards the Synthesis of EF-Ring Boronate using Resorcylate Chemistry

1. Introduction

A distinguishing feature of numerous bioactive natural products is the 6-alkyl-2,4-dihydroxybenzoic acid or β-resorcylate unit **351**.[150] Several examples of these resorcylic acid lactones (RALs) are shown below (Figure 11).

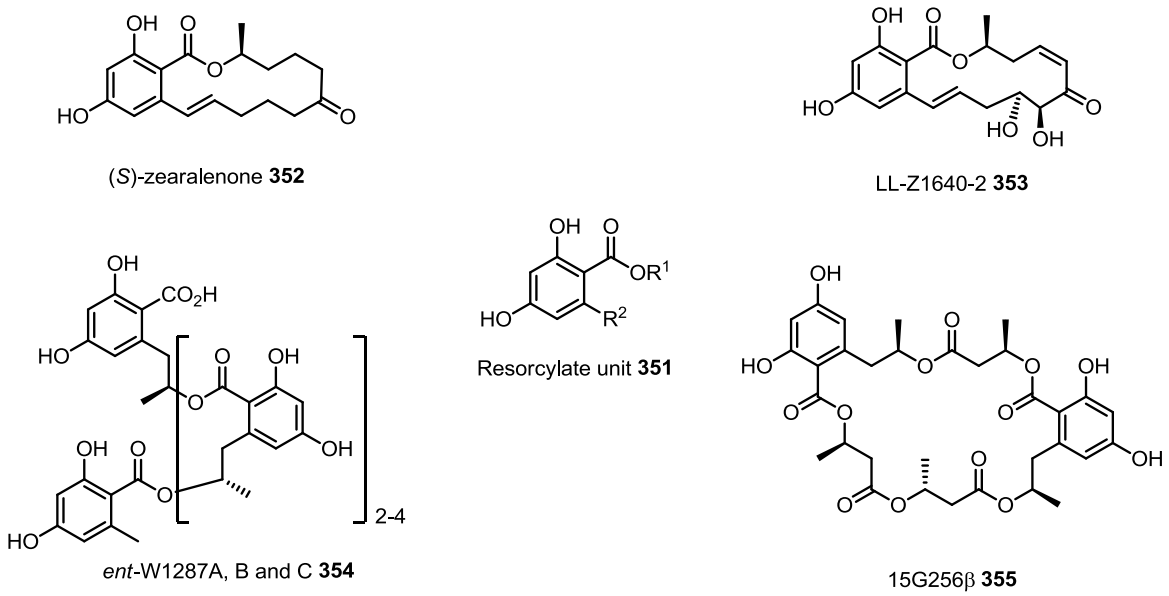
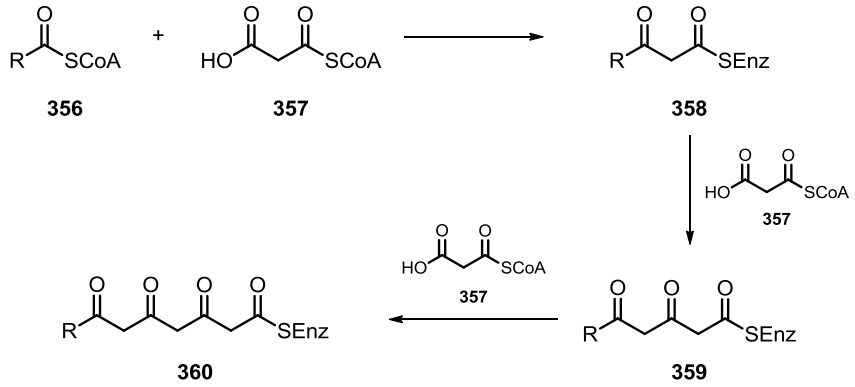


Figure 11 – Examples of related resorcylic acid lactones

1.1 Biosynthesis of simple resorcylates

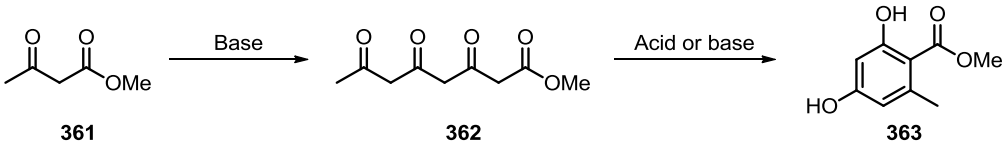
Many of the aromatic compounds found in nature are formed from acetates *via* poly-β-carbonyl intermediates. After Collie first grasped the pathway by which polyketides are formed,[151] interest was renewed in 1948 when Robinson[152] revived Collie's idea and Birch formulated a synthetic pathway

(Scheme 130).[153] Condensation of acetyl coenzyme A **356** with malonyl coenzyme A **357** followed by decarboxylation gives the β-keto thioester **358**, which in turn can undergo a further Claisen-type condensation with malonyl coenzyme A **357** to form a more complex polyketide **360**.



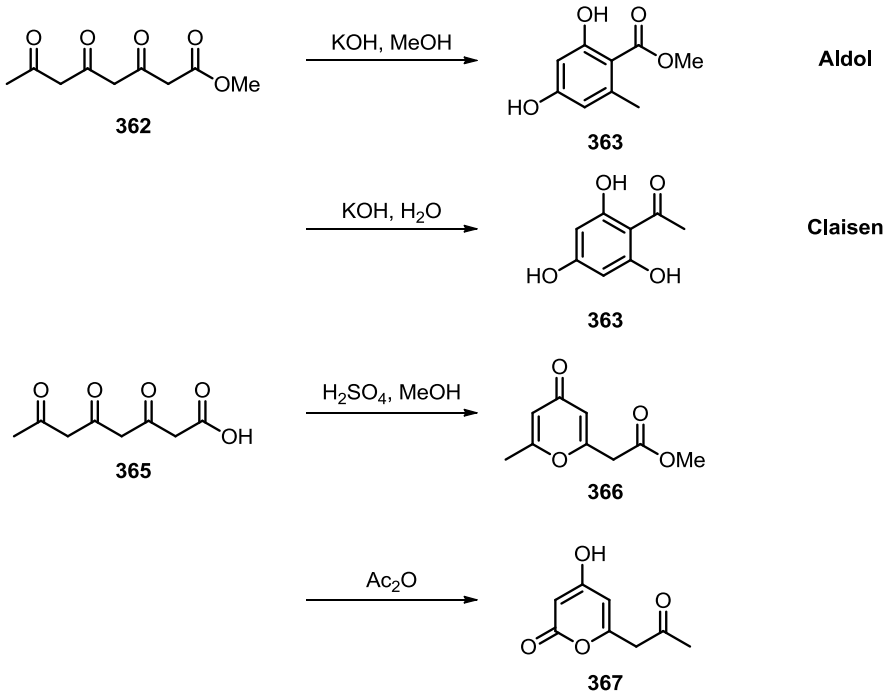
Scheme 130 – Polyketide biosynthesis pathway

Based on this hypothesis, Harris reported the biomimetic synthesis of simple resorcylates.[154] He demonstrated the self condensation of methyl acetoacetate **360** to give triketo-methyl ester **362** followed by aromatization under pH conditions of 4 and 12 (Scheme 131).



Scheme 131 – Formation of resorcylate 363 from methyl acetoacetate 361

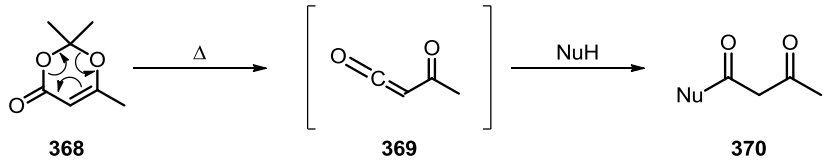
He further demonstrated that triketo ester **362** or triketo acid **365** can undergo a variety of intramolecular condensations to give aromatic and heteroaromatic systems (Scheme 132).[154] Carbocyclic systems can be formed by aldol or Claisen (Dieckman) cyclizations to give **363** and **364**, respectively. Other rings closures can afford 4-pyrones **366** and 4-hydroxy-2-pyrones **367**.



Scheme 132 – Intramolecular condensations to form aromatic and heteroaromatic systems

1.2 Acetylketene

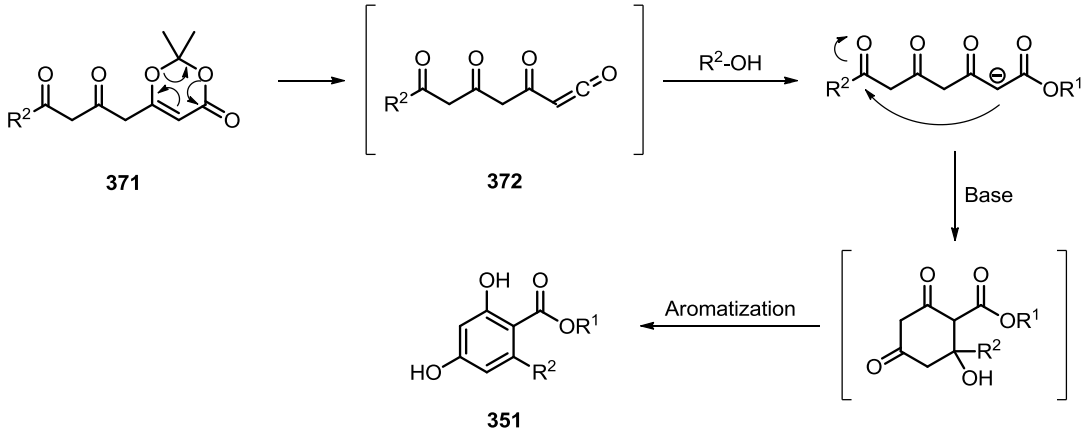
In 1984, Hyatt *et al.* showed that 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**368**) can undergo a retro Diels-Alder reaction to give acetylketene **369** which can be trapped with a nucleophile to form β-keto esters, β-keto amides or β-keto thio esters **370** (Scheme 133).[155]



Scheme 133 – Thermolysis and nucleophilic ketene trapping of 368

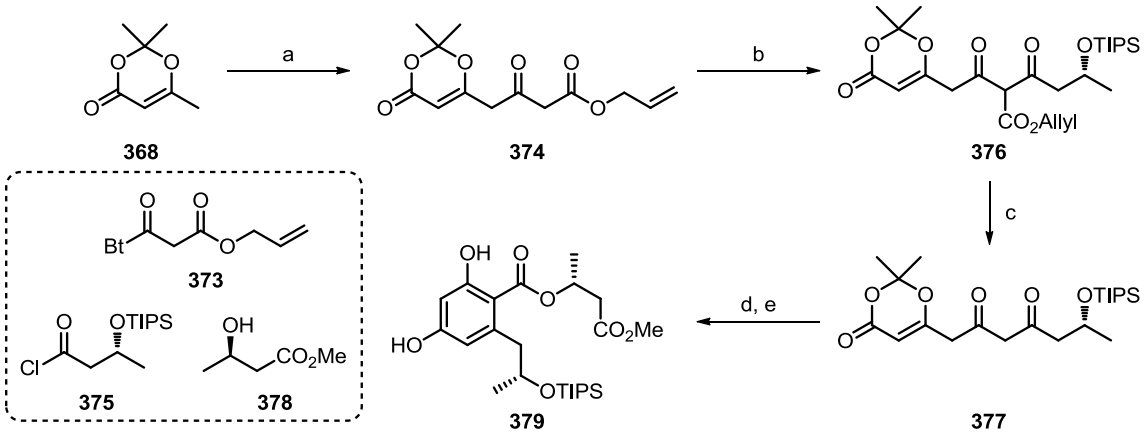
1.3 Previous work within the Barrett group

Inspired by the proposed polyketide biosynthesis of resorcylate natural products and the biomimetic syntheses of simple resorcylates by Harris and others, Barrett and co-workers sought to establish a strategy for the synthesis of resorcylate units utilizing tandem late stage aromatization, from 2,4,6-triketo-ester precursors, and macrocyclization. As a result, diketo dioxinones **371** have been used as precursors towards the total synthesis of resorcylate natural products such as 15G256β,[156] (*S*)-zearalenone[157] and aigialomycin D.[158]



Scheme 134 – Synthesis of resorcylate units 351 utilizing tandem late stage aromatization

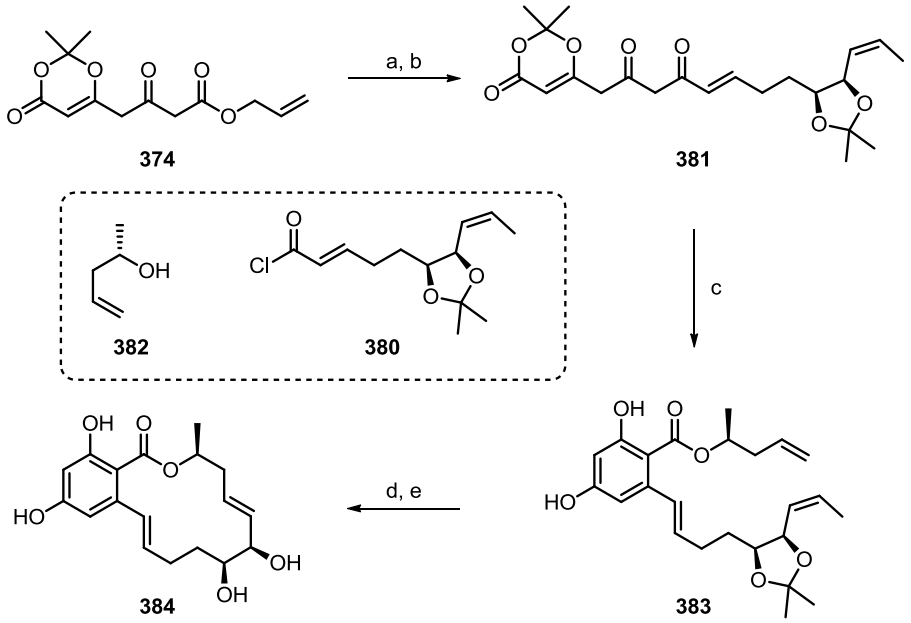
A synthesis of diketo dioxinone, such as **374**, has been developed on route towards the natural product 15G256β (**355**) (Scheme 135).[156] Alkylation of dioxinone **368** with benzotriazole derivative **373** synthesized from the corresponding acid, gave allylester-keto dioxinone **374**. The magnesium enolate of **374** was acylated with acid chloride **375** to provide **376** and subsequent palladium-catalyzed deallylation-decarboxylation gave the key diketo-ester **377**. Thermal decomposition of dioxinone **377** in the presence of alcohol **378** followed by aromatization by sequential treatment with base and acid provided the 15G256 monomer unit **379**.



Scheme 135 – Synthesis of 15G256 monomer unit (379)

Reagents and conditions: a) i) $LiN(SiMe_3)_2$, THF, –78 °C, 15 h; ii) **373**, rt, 16 h, 63%; b) i) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C, 20 min; ii) **375**, 0 °C, 45 min, 83%; c) morpholine, $Pd(PPh_3)_4$, THF, 0 °C to rt, 89%; d) **378**, PhMe, 110 °C; e) i) K_2CO_3, ^{i}PrOH, CH_2Cl_2; ii) HCl, MeOH, 75% (over 3 steps).

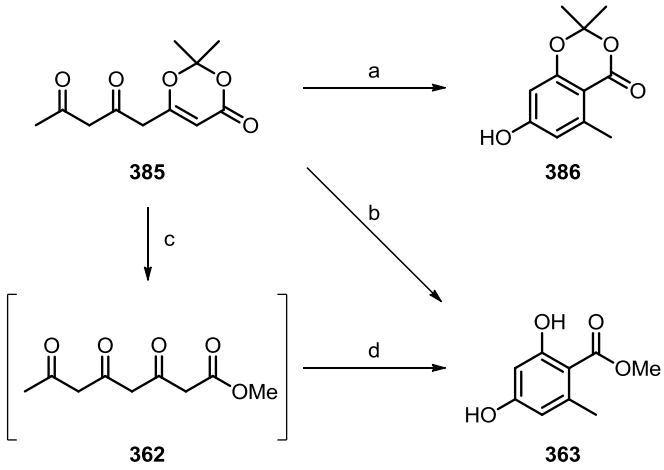
In a similar manner, this methodology was used for the synthesis of aigialomycin D (**384**) (Scheme 136).[158] Claisen condensation between the Mg-enolate of **374** and crude acid chloride **380**, followed by palladium-catalyzed deallylation-decarboxylation gave the desired diketo dioxinone **381**. Upon heating, **381** underwent a retro Diels-Alder reaction, the resultant ketene was trapped with alcohol **382**, and directly aromatized by treatment with cesium acetate followed by acetic acid to form resorcylate **383**. Ring closing metathesis and subsequent acetonide deprotection gave aigialomycin D (**384**).



Scheme 136 – Synthesis of aigialomycin D (384)

Reagents and conditions: a) i) $MgCl_2$, pyridine, THF, 0 °C; ii) **380**, 0 °C, 81%; b) morpholine, $Pd(PPh_3)_4$, THF, 0 °C to rt; c) PhMe, **382**, CsOAc, AcOH, 44% (over 2 steps); d) Grubbs-Hoveyda II, PhMe, 100 °C, 83%; e) HCl, MeOH, 95%.

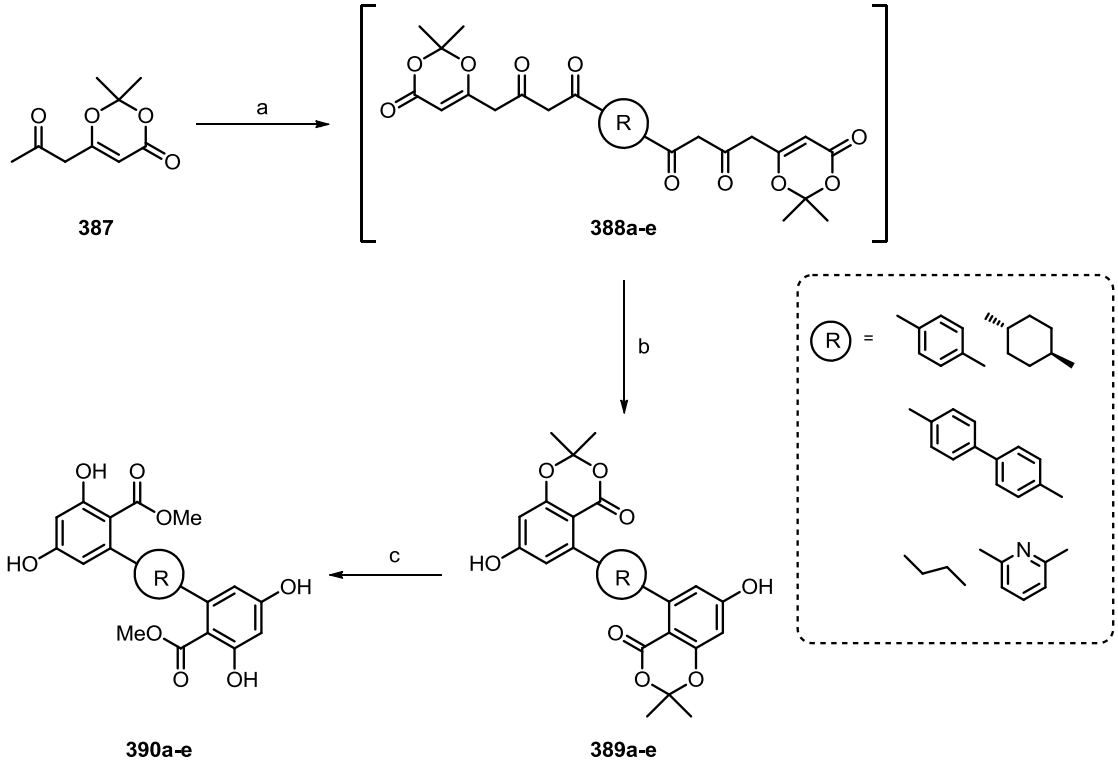
In addition to this one-pot ketene generation−trapping−aromatization sequence, Barrett and co-workers have demonstrated that diketo dioxinones can be cyclized by base-mediated cycloaromatization to give isopropylidene protected resorcylates.[159] This methodology was illustrated with simple diketo dioxinone **385**, which could undergo cyclization using a variety of bases such as triethylamine, 1,4-diazabicyclo[2.2.2]octane, or *N*,*N*-4-dimethylaminopyridine to give **386** (Scheme 137). Alternatively, thermolysis in toluene containing methanol and aromatization with cesium carbonate, followed by acidification, gave the resorcylate **363** (87%).[159]



Scheme 137 – Different cyclization reactions of diketo-1,3-dioxinone 385

Reagents and conditions: a) Et_3N, CH_2Cl_2, 96%; b) MeOH, MS 4Å, CH_2Cl_2, sealed tube, 100 °C, 85%; c) MeOH, PhMe, 100 °C, d) i) Cs_2CO_3, MeOH; ii) HCl, 87%.

This methodology was successfully applied to the synthesis of novel resorcylate oligomers (Scheme 138).[160] Treatment of **387** with LDA followed by transmetallation with diethyl zinc and reaction with a variety of double Weinreb amides gave the corresponding diketo dioxinones **388a–e**. Compounds **388a–e** were directly subjected to double cyclization using triethylamine and the corresponding crude adducts **389a-e** were directly methanolyzed in the presence of cesium carbonate to provide the double resorcylates **390a–e** in 36–44% yield over the three steps.



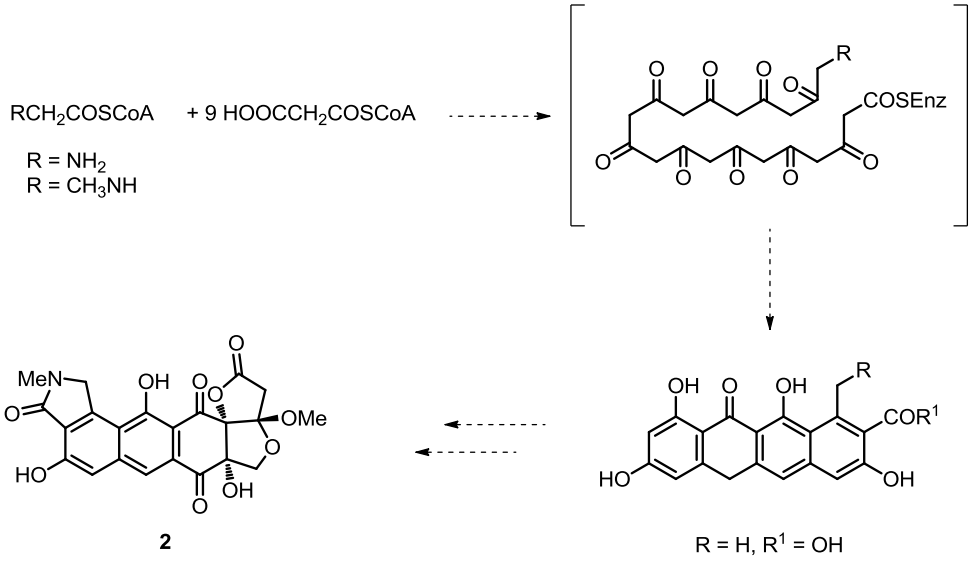
Scheme 138 – Synthesis of novel resorcylate oligomers 390a–e

Reagents and conditions: a) i) LDA, THF, −78 °C; ii) Et_2Zn; iii) diamide, –20 to –5 °C; b) Et_3N, CH_2Cl_2, 30 °C; c) Cs_2CO_3, MeOH, 60 – 65 °C, 36 – 44% (over 3 steps).

2. Towards the synthesis of EF-ring boronic ester

2.1 Introduction

In 2008, Parry and co-workers investigated the biosynthetic pathway of lactonamycinone (**1**) and suggested a hypothetical pathway (Scheme 139).[161] They postulated that lactonamycinone (**2**) could be biosynthesized in a manner where glycine or a glycine derivative served as a starter unit extended by nine acetate units to form a polyketide which after several transformations gives lactonamycinone (**2**).



Scheme 139 – Hypothetical biosynthetic pathway for lactonamycinone (2)

Enlighted by this hypothetical biosynthetic pathway and following on the promising results within the Barrett group,[156-160] this approach was considered to be attractive for the synthesis of the EF-ring boronic ester (**273**).

2.2 Retrosynthetic approach

We sought to take advantage of the developed route using allylester-keto dioxinone. Following certain modifications and without removal of the ester moiety should lead us to boronic ester **391** (Figure 12).

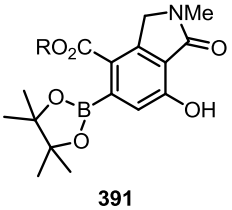


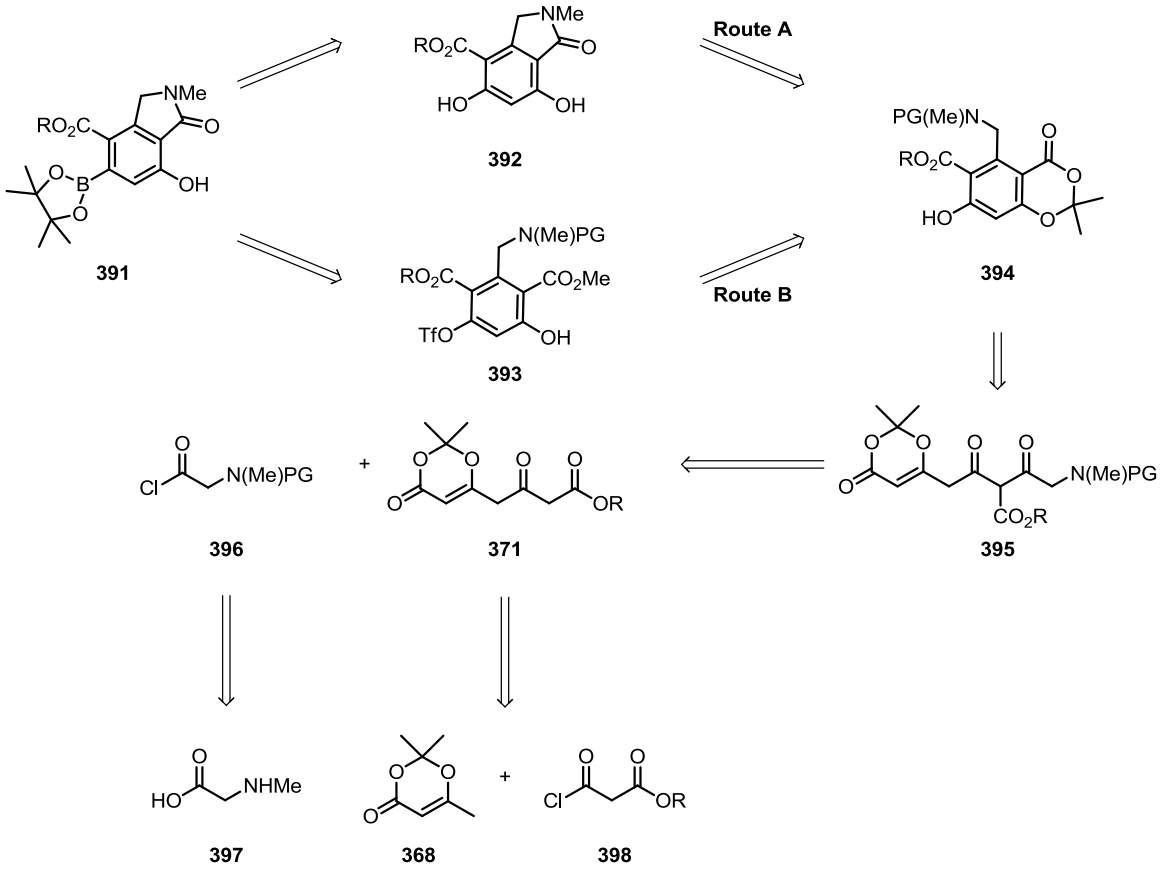
Figure 12 – Structure of boronic ester 391

The synthesis of **391** could be approached in two ways (Routes A and B). The EF-ring boronic ester **391** should be available from **392** following triflation and Miyaura borylation of the phenol *ortho* to

the ester moiety (Scheme 140, route A). **392** could be synthesized from **394** after opening of the dioxinone, amine deprotection and subsequent lactamization.

Alternatively, EF-ring boronic ester **391** could be synthesized from **393** after amine deprotection and subsequent lactamization, followed by Miyaura borylation (route B). Triflate **393** could be obtained after triflation and opening of the dioxinone of **394**.

Isopropylidene protected resorcylate **394** could be constructed from diketo-ester dioxinone **395**, which may be prepared by *C*-acylation between keto-ester dioxinone **371** and acid chloride **396**, derived from sarcosine **397**. Keto-ester dioxinone **371** could be synthesized by *C*-acylation between the lithium enolate of dioxinone **368** and acid chloride **398** or any synthetic equivalent.

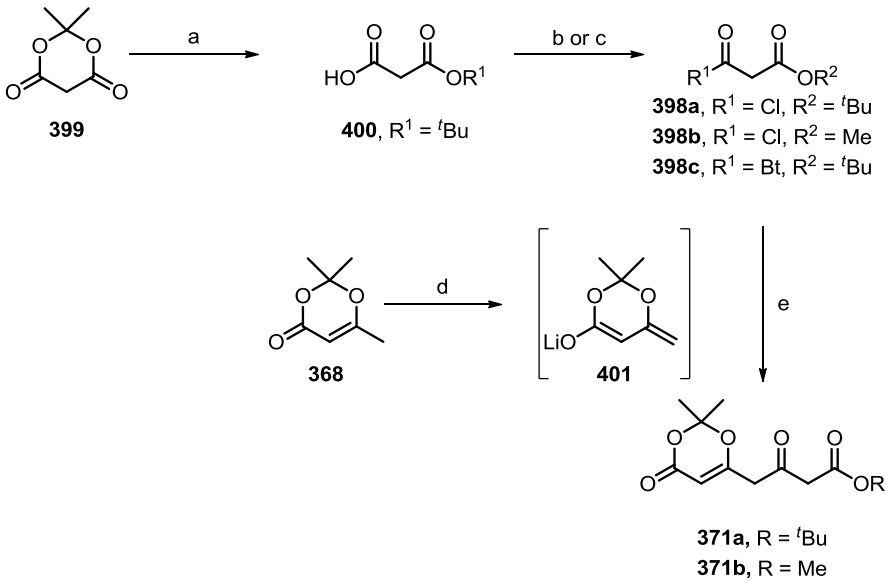


Scheme 140 – Retrosynthesis strategy

2.3 Synthesis of keto-ester dioxinone 371a and 371b

The synthesis began from Meldrüm's acid **399** which was ring opened with *tert*-butanol to furnish carboxylic acid **400** in 52% yield (Scheme 141).[162] Upon treatment with a mixture of thionyl chloride and benzotriazole, carboxylic acid **400** was successfully converted into benzotriazole derivative **398c**.[163] Carboxylic acid **400** was also converted into the corresponding acid chloride **398a** upon treatment with oxalyl chloride. Methyl 3-chloro-3-oxopropionate **398b** was purchased from sigma-aldrich and used as received.

With **398a**, **398b** and **398c** in hand, several conditions were tested for the acylation of dioxinone **368** (Scheme 141 and Table 19). The lithium enolate **401** was reacted with benzotriazole derivative **398c**, however, the expected product **371a** was only isolated in 12% yield (Table 19, entry a). Based on a precedent within the group which had shown that benzotriazole derivatives reacted in higher yield under high dilution,[164] the reaction was attempted at a concentration of 0.08 M, however, the yield only increased slightly to 20% (Table 19, entry b). The enolate **401** was instead reacted with crude acid chloride **397a** and gratifyingly afforded **371a** in a good yield of 76% (Table 19, entry c). In a similar manner, methylester-keto dioxinone **371b** was synthesized albeit in a lower yield possibly due to the instability of the acid chloride **397b**.



Scheme 141 – Synthesis of keto-ester dioxinone 371a and 371b

Reagents and conditions: a) *tert*-BuOH, 100 °C, 12 h, 50%; b) $SOCl_2$, benzotriazole, CH_2Cl_2, rt, 12 h, 81%; c) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 2 h; d) i) HMDS (see Table 19), *n*-BuLi (see Table 19),

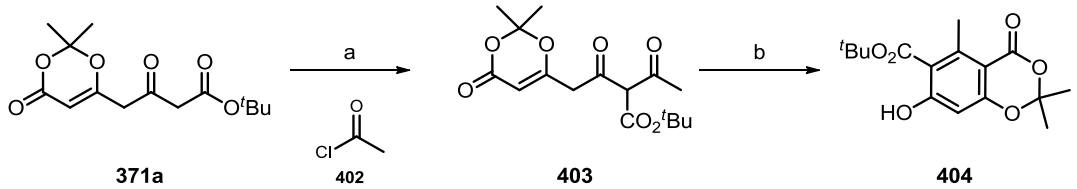
THF [see Table 19], –78 °C, 30 min; ii) **368** (see Table 19) –78 °C, 1 h; e) **400**, **397a** and **397b** (1.0 eq.), –78 °C, 2.5h

Entry	HMDS (eq.)	*n*-BuLi (eq.)	THF [conc]	368 (eq.)	Electrophile	Yields
a	3.6	3.6	0.5 M	3.0	**400**	12% of **371a**
b	4.6	5.0	0.08 M	3.8	**400**	20% of **371a**
c	3.6	3.6	0.5 M	3.0	**397a**	76% of **371a**
d	3.6	3.6	0.5 M	3.0	**397b**	35% of **371b**

Table 19 – Optimization for the formation of keto-ester dioxinone 371a and 371b

2.4 Model system synthesis

Acetyl chloride **402** was used to model the acid chloride and was subjected to the methodology developed and optimized within the Barrett group.[156,158] Acetyl chloride **402** was added to the magnesium enolate of **371a** and gave diketo-ester dioxinone **403** in good yield (Scheme 142). Cyclization using an excess of triethylamine[159,160] provided isopropylidene protected resorcylate **404** in moderate yield. It is worth noting that in order to obtain a more rapid conversion, the base-mediated cycloaromatization had to be heated to 30 °C, due to the possible steric hindrance cause by the *tert*-butyl ester moiety.



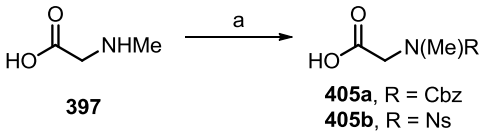
371a **402** **403** **404**

Scheme 142 – Synthesis of model system 404

Reagents and conditions: a) i) $MgCl_2$, pyridine, CH_2Cl_2, 5 min, 0 °C; ii) **371a**, 30 min, 0 °C; iii) **402**, 30 min, 0 °C, 77 %; b) Et_3N, CH_2Cl_2, 30 °C, 12 h, 53%.

2.5 Synthesis of *N*-protected sarcosine

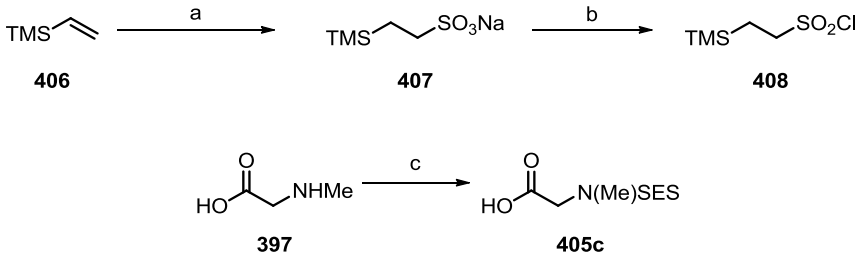
As model studies were successful, the strategy was employed using protected-sarcosine derivatives. Protected acids **405a** and **405b** were easily obtained by reaction of sarcosine **397** with benzyl chloroformate (CbzCl) or 4-nitrobenzenesulfonyl chloride (NsCl) to form **405a** and **405b**, respectively (Scheme 143).[165]



Scheme 143 – Synthesis of Cbz and Ns–protected sarcosine

Reagents and conditions: a) Na_2CO_3, RCl, H_2O/THF (3:1), 0 °C to rt, 12 h, R = Cbz, 95%; R = Ns, 91%.

It was thought that 2-(trimethylsilyl)ethanesulfonamide could also be a suitable *N*-protecting group. It was synthesized in two steps starting from vinyltrimethylsilane **406**.[166] Free radical addition of sodium bisulfite to the vinyl group, catalyzed by *tert*-butylperbenzoate, successfully afforded sulfonate salt **407** which was directly converted to **408** with triphenylphospine and sulfuryl chloride (Scheme 144).[167a] Sarcosine **397** was treated with trimethylsilyl chloride in refluxing dichloromethane prior to the addition of triethylamine and SESCl to give **405c** as an off-white solid in 71% yield.[168]



Scheme 144 – Synthesis of SESCl 408 and formation of SES-protected sarcosine 405c

Reagents and conditions: a) $PhCO_3{}^tBu$ (2 mol%), $NaHSO_3$, MeOH/H_2O (1:1), 50 °C, 3 d, 66%; b) PPh_3, SO_2Cl_2, CH_2Cl_2, rt, 16 h, 81%; c) i) TMSCl, CH_2Cl_2, reflux, 2 h; ii) Et_3N, SESCl, CH_2Cl_2, rt, 12 h, 71%.

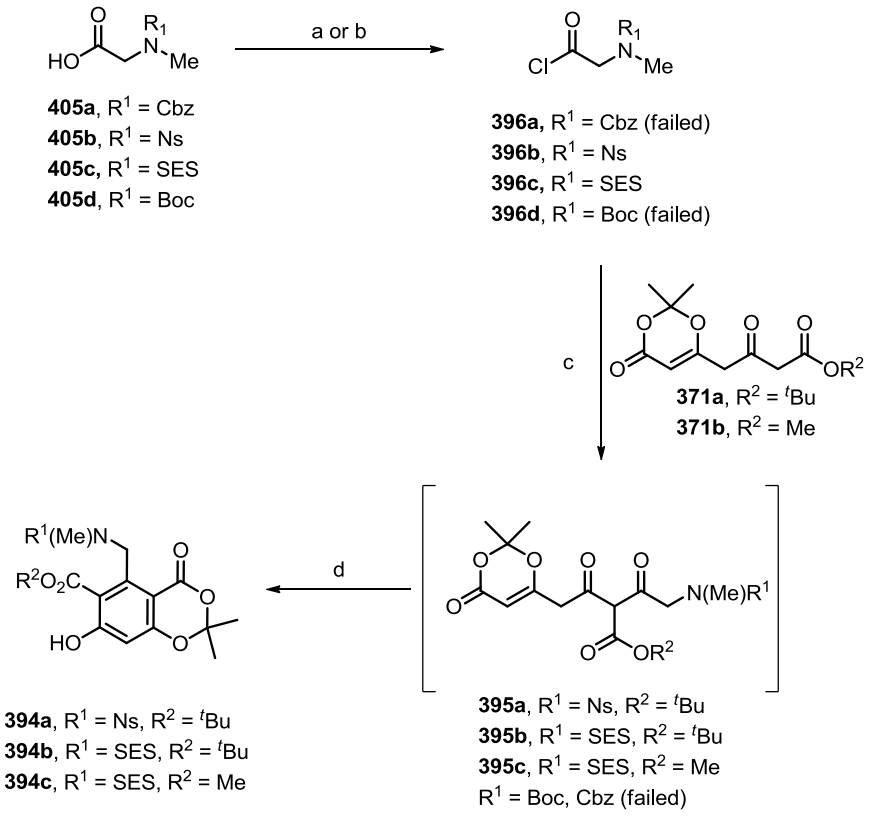
2.6 *C*-acylation and aromatization studies

The key step to this proposed synthesis was the *C*-acylation of keto-ester dioxinone **371a** and **371b** with amino acid chloride as it has not been previously attempted successfully (Scheme 145). The reaction was first attempted with commercially available *N*-Boc-protected sarcosine **405d**. The use of oxalyl chloride at 0 °C to convert acid **405d** into acid chloride **396d** proved to be difficult, even in the presence of pyridine to quench the HCl formed *in situ*. The crude mixture of **405d** was nonetheless subjected to reaction with the Mg-enolate of **371a**, however, no reaction was observed.

In a similar manner, the formation of the acid chloride **396a** derived from Cbz-protected sarcosine **405a** was problematic. The crude mixture was taken forward in the *C*-acylation step, but only unreacted starting material **371a** was recovered.

As a result, the *C*-acylation was investigated with Ns-protected sarcosine **405b**. Treatment of **405b** with oxalyl chloride at 0 °C successfully gave the corresponding acid chloride **396b** which was subjected crude to reaction with the Mg-enolate of **371a** to give diketo-ester dioxinone **395a**.[156,158] **395a** proved to be slightly unstable and therefore was directly treated with triethylamine at 30 °C and isopropylidene protected resorcylate **394a** was obtained in 48% yield over two steps (Table 20, entry a).[160]

The *C*-acylation reaction was repeated with SES-protected sarcosine **405c**. Upon treatment with oxalyl chloride, **405c** was successfully converted into the corresponding acid chloride **396c**, which was added crude to the Mg-enolate of **371a** and **371b** to form diketo-ester dioxinone **395b** and **395c**, respectively.[156,158] Crude **395b** and **395c** were directly treated with triethylamine at 30 °C and isopropylidene protected resorcylates **394b** and **394c** were obtained in 49% and 30% yields over two steps, respectively (Table 20, entries b and c).[160]



Scheme 145 – *C*-acylation and aromatization starting from keto-ester dioxinone 371a and 371b

Reagents and conditions: a) For **405a** and **405d**: pyridine, $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 2 h; b) For **405b** and **405c**: $(COCl)_2$, DMF, CH_2Cl_2 or THF, 0 °C to rt, 2 h; c) i) $MgCl_2$, pyridine, CH_2Cl_2, 5 min, 0 °C; ii) **371a** or **371b**, 30 min, 0 °C; iii) Acid chloride (see Table 20), 2.5 h, 0 °C; d) Et_3N, CH_2Cl_2, 30 °C, 12 h,.

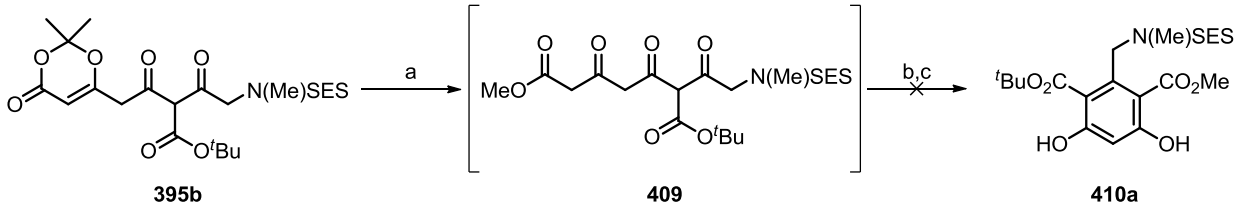
Entry	R^1	R^2	Acid chloride (eq.)	Yield (over 2 steps)
a	Ns	^{t}Bu	**396b** (2.0)	**394a** (48%)
b	SES	^{t}Bu	**396c** (1.3)	**394b** (49%)
c	SES	Me	**396c** (2.0)	**394c** (30%)

Table 20 – Optimization for the formation of isopropylidene protected resorcylates 394a-c

Starting from purified diketo-ester dioxinone **395b**, the triethylamine-cyclization reaction was further studied. As detected by TLC, keto-ester dioxinone **371a** was formed alongside the expected isopropylidene protected resorcylate **394b**, thus lowering the overall yield of the reaction and

providing difficulties during the purification. The formation of **371a** could be explained by a retro-Claisen reaction which can occur during the cyclization.[169] The cyclization was repeated with Hünig's base but proved to be slower than with Et_3N and needed two days to go to completion. Unfortunately, isopropylidene protected resorcylate **394b** was isolated in a low 27% yield.

Keto-ester dioxinone has been successfully converted into the corresponding resorcylate *via* a ketene intermediate.[156-158] This methodology could be applied here and could minimize the side retro-Claisen reaction. Purified diketo-ester dioxinone **395b** was heated to reflux in the presence of methanol to give polyketide **409**, which was directly treated with a mixture of cesium carbonate in methanol and the crude mixture was subjected to aromatization using 1 N HCl in methanol. Unfortunately, only some unknown by-products were formed (Scheme 146).



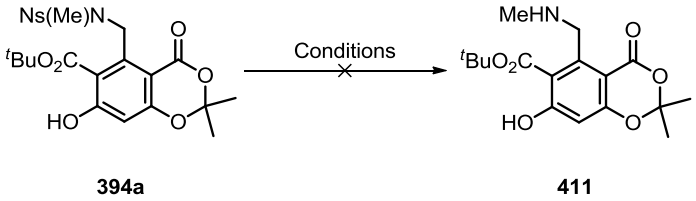
395b **409** **410a**

Scheme 146 – Attempt to synthesis of aromatic product 410a using *via* ketene intermediate

Reagents and conditions: a) MeOH, PhMe, 110 °C, 45 min; b) Cs_2CO_3, MeOH, 2 d, 30 °C; c) 1 N HCl in MeOH, rt, 12 h.

2.7 Synthesis of isoindolinones 392a and 392b

With isopropylidene protected resorcylate **394a** in hand, the nosyl deprotection was addressed (Scheme 147 and Table 21). Surprisingly, upon treatment with potassium carbonate and thiophenol (Fukuyama's conditions)[170] at room temperature, no reaction was observed. As a result, the temperature was raised to 60 °C but after 2 h, no expected product could be isolated (Table 21, entry b). The addition of DMSO as a co-solvent did not improve the reaction outcome (Table 21, entry c). **394a** was instead treated with a combination of 3-mercaptopropanoic acid and lithium hydroxide, however no reaction was observed (Table 21, entry d).[171] As a last effort, **394a** was reacted with mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene but only starting material **394a** was recovered (Table 21, entry e).[172]



394a 411

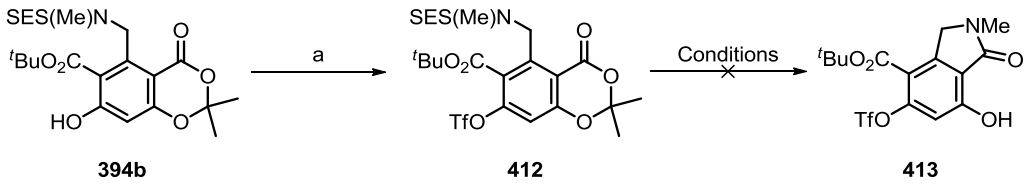
Scheme 147 – Nosyl Deprotection

Entry	Thiols (eq.)	Base (eq.)	Solvent	T (° C)	Results
a	PhSH (1.3)	K_2CO_3 (3.0)	MeCN	rt	No reaction
b	PhSH (1.3)	K_2CO_3 (3.0)	MeCN	60	Decomposition
c	PhSH (3.0)	K_2CO_3 (3.0)	MeCN/DMSO (29:1)	rt	No reaction
d	$HS(CH_2)_2CO_2H$ (2.0)	LiOH (4.0)	MeCN/DMSO (29:1)	rt	No reaction
e	$HSCH_2CH_2OH$ (10.0)	DBU (5.0)	DMF	rt	No reaction

Table 21 – Attempts to deprotect the nosyl

As the nosyl deprotection failed to be successful, the synthesis of EF-ring boronic ester starting from Ns-protected sarcosine **405c** was stopped at this point and the synthesis was pursued using resorcylates **394b** and **394c**.

Following Route B, phenol **394b** was converted to the corresponding triflate and **412** was isolated in 77% yield (Scheme 148). Based on literature precedents,[170] an excess of fluoride source is usually needed but because of the presence of the triflate, it was feared that this reaction might be problematic. Unfortunately, upon treatment with either cesium fluoride or tetrabutylammonium fluoride, only cleavage of the triflate was observed to give alcohol **394b** (Table 22, entries a and b).



394b 412 413

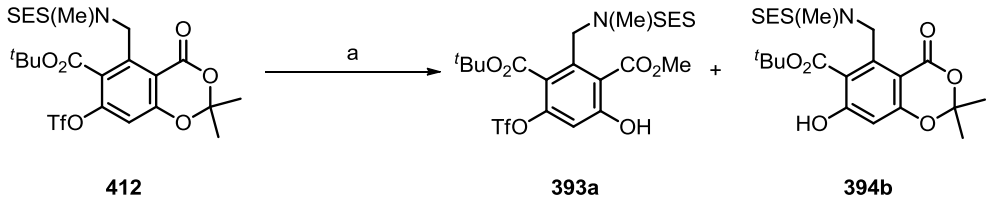
Scheme 148 – Synthesis of triflate 412 and further manipulations

Reagents and conditions: a) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 2 h, 77%.

Entry	Fluoride source (eq.)	Solvent	Temperature	Time	Results
a	CsF (1.0)	MeCN	80 °C	12 h	**394b**
b	TBAF (1.0)	THF	reflux	12 h	**394b**

Table 22 – Attempts to cleave the SES protecting group

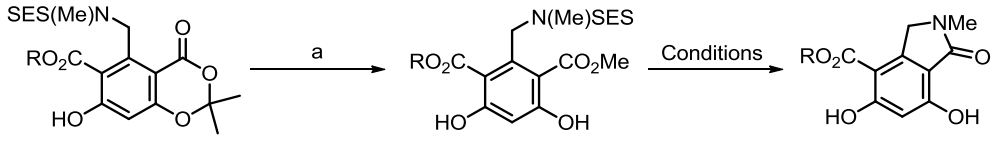
It was known within the Barrett group that the opening of the isopropylidene moiety is difficult with an amine but is rather smooth with an alcohol.[173] Unfortunately, treatment of triflate **412** under these conditions afforded an inseparable 1:1 mixture of product **393a** and phenol **394b** (Scheme 149).



Scheme 149 – Opening of dioxinone 412 with MeOH and Cs_2CO_3

Reagents and conditions: a) Cs_2CO_3, MeOH, 60 °C, 12 h.

As the deprotection of the SES seemed to be problematic in the presence of the triflate, route A was further investigated. Treatment of **394b** and **394c** with cesium carbonate in methanol proceeded smoothly and afforded **414a** and **414b** in good yield (Scheme 150).[160] Upon treatment with an excess of cesium fluoride, no SES-deprotection was observed after 12 h at 80 °C and starting material **414a** was recovered (Table 23, entry a).[167c] Treatment with tetrabutylammonium fluoride in refluxing THF successfully cleaved the SES to give **392a** or **392b**.[171] Unfortunately, the remaining TBAF salts were difficult to wash away and many acid/base extractions were necessary thus lowering the yield (Table 23, entry b). Based on the work developed by Parlow *et al.*[174] and improved by Kishi and co-workers[175] addition of a sulfonic acid resin (DOWEX 50WX8-400) and calcium carbonate successfully sequestered tetrabutylammonium fluoride and **392a** and **392b** were isolated in 63% and 75% yield, respectively after a single filtration. In order to decrease the reaction time, ten equivalents of tetrabutylammonium fluoride were used and the reaction went to completion after six hours and isoindolinones **392a** and **392b** were isolated in similar yields (Table 23, entry d).



394b, R = ^{t}Bu
394c, R = Me

414a, R = ^{t}Bu
414b, R = Me

392a, R = ^{t}Bu
392b, R = Me

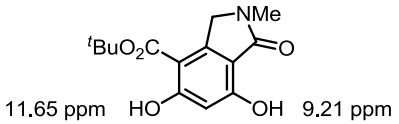
Scheme 150 – Opening of dioxinone and synthesis of isoindolinone

Reagents and conditions: a) Cs_2CO_3 (2.0 eq.), MeOH, 60 °C, 16 h, **414a** (77%), **414b** (60%).

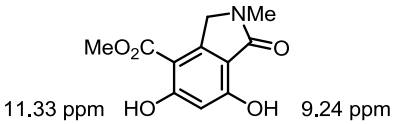
Entry	Fluoride source (eq.)	Solvent	Temperature	Time	Work-up	Yields 392a	392b
a	CsF (10.0)	MeCN	80 °C	12 h	Solid filtered	No reaction	
b	TBAF (2.0)	THF	reflux	36 h	Aqueous work-up	37%	29%
c	TBAF (2.0)	THF	reflux	36 h	Resin	75%	63%
d	TBAF (10.0)	THF	reflux	6 h	Resin	78%	65%

Table 23 – Optimization for the formation of 392a and 392b

As suggested by ^{1}H NMR analysis of **392a** or **392b**, hydrogen bonding was observed between both phenols and the *ortho*-ester or the *ortho*-amide, respectively (Scheme 151). The phenol *ortho* to the ester is the most acidic so it should be the most reactive towards deprotonation with a base. As a result, it was tempting to think that treatment of **392a** or **392b** with one equivalent of base and one equivalent of triflation reagent should give the expected product **391a** or **391b**.



392a



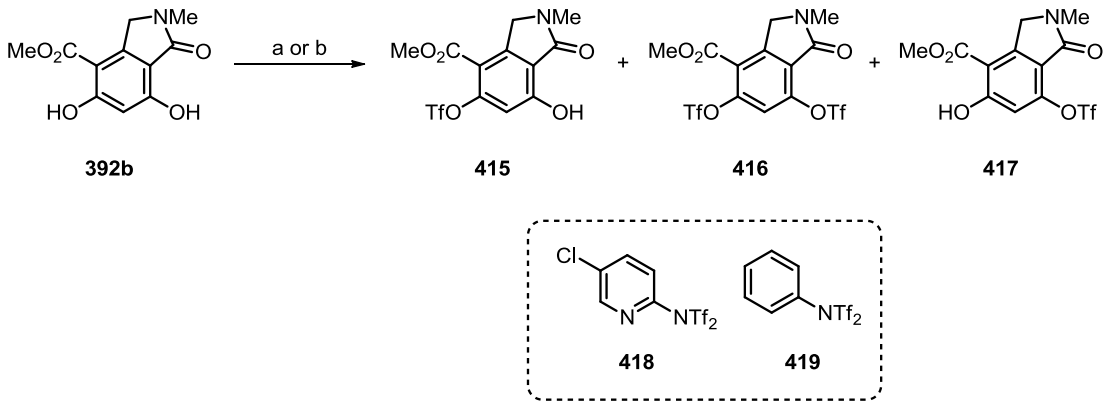
392b

Scheme 151 – Chemical shift for both phenols in 392a and 392b

Resorcylate was first treated with one equivalent of trifluoromethane sulfonic anhydride but the reaction was not successful and no expected triflate could be observed by ^{1}H-NMR. It was reported before that triflation using trifluoromethanesulfonicanhydride can be complicated by benzylic oxidation to provide phthalimide derivative.[31]

Resorcylate **392b** was treated with 0.95 equivalents of *N*-Phenylbis(trifluoromethane sulfonimide) **419** and 0.95 equivalents of Et_3N and the reaction was stirred at 30 °C for 12 h. Unfortunately, the reaction turned out to be rather messy and only a complex mixture of unreactive starting material **392b**, bis-triflated product **416** and mono-triflated product **417** was observed (Table 24, entry a). Upon treatment of **392b** with an excess of **419** and Et_3N, bis-triflated product **416** could obtained as the major product in a moderate 47% yield (Table 24, entry b). It is worth noting that in these two attempts no formation of the desired triflate **415** was observed by ^{1}H-NMR.

It was thought that Et_3N was too basic and too nucleophilic for this transformation. As a result, a variety of milder bases such as pyridine, collidine or 2,6-lutidine were tested in addition alongside a different triflation reagent (Comin's reagent **418**[176]). Unfortunately, treatment of **392b** with all the bases mentioned before and **418** afforded a complex and inseparable mixture of starting material **392b**, bis-triflated product **416** and mono-triflated product **417** in different ratios depending on the base used (Table 24, entries c to g). Here again, no formation of the expected triflate **415** was observed by ^{1}H–NMR.



Scheme 152 – Investigation towards the mono-triflation of 392b

Reagents and conditions: a) **418** (see Table 24), Et_3N (see Table 24), CH_2Cl_2, 30 °C, 12 h; b) i) **419** (1.0 eq, see Table 24), base (1.0 eq., see Table 24), CH_2Cl_2, 0 °C, 2 h; ii) same base (1.0 eq., see Table 24), 0 °C, 2 h (see Table 24).

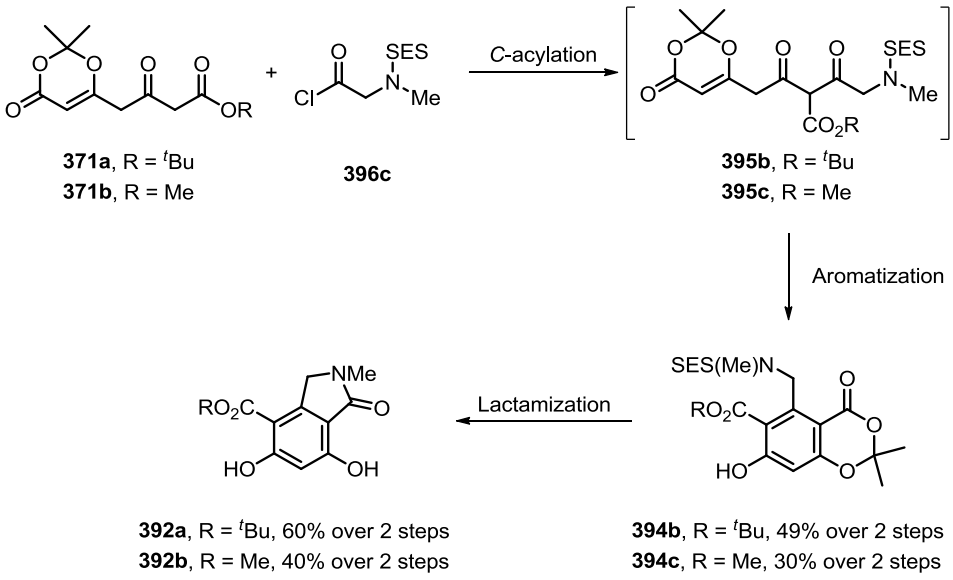
Entry	Conditions	Triflation reagent (eq.)	Base (eq.)	Ratio			
				392b	**416**	**417**	**415**
a	a	**419** (0.95)	Et_3N (0.95)	1	4	3	0
b		**419** (2.0)	Et_3N (2.0.)	0	47%	0	0
c	b	**418**	DMAP (0.02)	2	1	1	0
d		**418**	pyridine	4	1	1	0
e		**418**	collidine	2	2	1	0
f		**418**	2,6-lutidine	2	2	1	0
g		**418**	Et_3N	2	3	1	0

Table 24 – Attempts to synthesize mono-triflate 415

Unfortunately, due to a lack of time and material, the investigation towards the EF-ring boronic ester could not be pursued.

3. Conclusion and future work

This efficient and reproducible multi-step synthesis gave novel isoindolinones **392a** and **392b** in moderate yield over 5 steps (Scheme 153). This methodology could be further applied for the synthesis of analogues starting from a different amino-acids or keto-ester dioxinone derivatives.



371a, R = ^{t}Bu
371b, R = Me

396c

395b, R = ^{t}Bu
395c, R = Me

394b, R = ^{t}Bu, 49% over 2 steps
394c, R = Me, 30% over 2 steps

392a, R = ^{t}Bu, 60% over 2 steps
392b, R = Me, 40% over 2 steps

Scheme 153 – Synthesis of isoindolinones 392a and 392b

Unfortunately, the synthesis of EF-ring boronic ester **391** has not been possible so far. As difficulties encountered during the mono-triflation seemed to be difficult to overcome, the use of different nitrogen protecting groups may be necessary in order to follow Route B.

Experimental

General Experimental Procedure

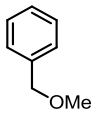
All reactions were carried out in flame-dried or oven-dried glassware in an atmosphere of dry nitrogen or argon unless otherwise stated. Prolonged periods of vessel cooling were attained by the use of CryoCool apparatus. All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The following reaction solvents were distilled under nitrogen: Et_2O and THF from sodium benzophenone ketyl; PhMe from sodium; CH_2Cl_2 and Et_3N from CaH_2. MeOH was dried by refluxing over magnesium turnings and iodine, followed by distillation from CaH_2. H_2O refers to distilled H_2O. Flash column chromatography was performed using silica gel unless otherwise stated. Thin layer chromatography (TLC) was performed on pre-coated aluminium backed plates, visualization was accomplished by either UV light (254 nm) or by staining with acidic vanillin.

Melting points were obtained using a melting point apparatus and are uncorrected. Infrared spectra are given with adsorptions (λmax) reported in wave numbers (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) were recorded at 400 MHz or at 500 MHz with chemical shifts (δ) quoted in parts per million (ppm) and referenced to the residual solvent peak (7.26 ppm for $CDCl_3$). Coupling constants (*J*) are recorded in Hertz (Hz). Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 75, 100 or at 125 MHz with chemical shifts (δ) quoted in ppm and referenced to the residual solvent peak (77.0 ppm for $CDCl_3$). Low and high resolution mass spectra (EI, CI, ESI) were recorded by Imperial College Mass Spectrometry Service. Microanalyses were determined by the University of North London Analytical Service. X-ray diffraction data were recorded by the Imperial College Department of Chemistry X-ray diffraction service.

Electrodecarboxylation Reactions on Simple Substrates and Model Studies

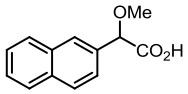
Electrodecarboxylation on simple substrates

(Methoxymethyl)benzene (196):[177]



Phenyl acetic acid **195** (0.2 g, 1.47 mmol, 1.0 eq.) was dissolved in MeOH (5 mL) and MeONa (5.4 M in MeOH, 2 mL) followed by NH_4Cl (779 mg, 14.7 mmol, 10.0 eq.) were added. Two graphite electrodes were placed in the reaction mixture and constant current electrolysis was applied. The charge was passed until complete consumption of the substrate was observed. The reaction was quenched with Dowex 50WX2-100 and passed through a glass filter. The solvent was evaporated under reduced pressure to give (methoxymethyl)benzene **196** (0.15 g, 84%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.33 (m, 5H, Ar-*H*), 4.45 (s, 2H, C*H*$_2$OMe), 3.38 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 128.3, 127.6, 127.5, 74.6, 58.0. Data in accordance with the literature.

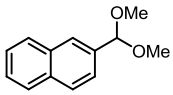
2-Methoxy-2-(naphthalen-2-yl)acetic acid (198):[61]



2-Naphthaldehyde **197** (3.0 g, 19.0 mmol, 1.0 eq.) was dissolved in MeOH (10 mL) and $CHBr_3$ (2.01 mL, 23.0 mmol, 1.5 eq.) was added. The resulting mixture was cooled to 0 °C and KOH (5.9 g, 105.0 mmol, 5.5 eq.) in MeOH (20 mL) was added dropwise over 1 h. The mixture was allowed to warm to room temperature and stirred for 12 h. H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The aqueous layer was acidified to pH 1 with 12 M HCl and was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was concentrated under reduced pressure. The crude material was purified by recrystallization (benzene) to give acid **198** (2.8 g, 68%) as a white solid. ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 7.91 (s, 1H, Ar-*H*), 7.86 – 7.82 (m, 3H, Ar-*H*), 7.54 (dd, *J* = 8.5, 1.4 Hz, 1H, Ar-*H*), 7.48 – 7.46 (m, 2H, Ar-*H*), 4.96 (s, 1H, C*H*OMe), 3.41 (s, 3H, OMe); ^{13}C NMR (100 MHz, methanol-*d*$_4$) δ 174.3, 135.5, 134.9, 134.6, 129.4, 129.1, 128.8, 128.0, 127.5, 127.4, 125.6, 83.6, 57.5; Mp 91 – 93 °C (lit.[178] 98 °C); IR (film) 3453, 1725, 1633, 1602, 1509, 1463, 1509, 1193, 1101, 993, 817, 750 cm^{-1}; MS (ESI) *m/z* 215 [M –

H]$^-$; HRMS (ESI) calc for $C_{13}H_{11}O_3$ [M – H]$^-$ 215.0708. Found: 215.0715; Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.12; H, 5.59. Found: C, 72.23; H, 5.59. Data in accordance with the literature.

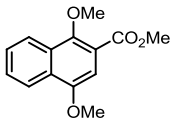
2-(Dimethoxymethyl)naphthalene (199):[179]



Acid **198** (0.2 g, 0.9 mmol, 1.0 eq.) was dissolved in MeOH and MeONa (5.4 M in MeOH, 3 mL) was added. Two graphite electrodes were placed in the reaction mixture and constant current electrolysis was applied. The charge was passed until complete consumption of the substrate was observed. The reaction was quenched with Dowex 50WX2-100 and passed through a glass filter. The solvent was evaporated under reduced pressure to give naphthalene derivative **199** (0.14 g, 75%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 4H, Ar-*H*), 7.56 – 7.48 (m, 3H, Ar-*H*), 5.56 (s, 1H, C*H*OMe), 3.37 (s, 6H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.5, 133.4, 128.3, 128.1, 127.7, 126.2, 126.2 (2C), 124.4, 103.2, 52.8 (2C); MS (ESI) *m/z* 202 [M]$^+$; HRMS (ESI) calc for $C_{13}H_{14}O_2$ [M]$^+$ 202.0994. Found: 202.0986. Data in accordance with the literature.

Towards a new synthesis of ABCD ring system of lactonamycin (1)

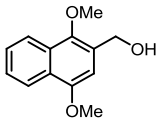
Methyl 1,4-dimethoxy-2-naphthoate (208):[62]



Potassium carbonate (15 g, 0.11 mol, 7.5 eq.) and methyl iodide (9.2 mL, 0.147 mol, 15.0 eq.) were added to a solution of 1,4-dihydroxy-2-naphthoic acid **207** (2.00 g, 9.8 mmol, 1.0 eq.) in acetone (60 mL) at room temperature. The mixture was heated to reflux for 4 h. H_2O (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were washed with additional H_2O (2 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1) to give methyl ester **208** (2.32 g, 96%) as a white solid. R*f* 0.62 (hexanes/EtOAc 1:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.26 – 8.21 (m, 2H, Ar-*H*), 7.60 – 7.57 (m, 2H, Ar-*H*), 7.16 (s, 1H, Ar-*H*), 4.02 (s, 3H, OMe), 4.01 (s, 3H, OMe), 3.99 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 152.0, 151.3, 129.2, 128.7, 127.7,

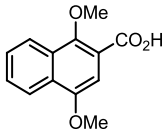
127.0, 123.4, 122.3, 118.6, 103.5, 63.3, 55.7, 52.3; Mp 49 – 51 °C (lit.[62] 48 – 50 °C); IR (film) 2998, 2949, 1725, 1595, 1460, 1220, 1087 cm^{-1}; MS (ESI) *m/z* 247 $[M + H]^+$; HRMS (ESI) calc for $C_{14}H_{15}O_4$ $[M + H]^+$ 247.0970. Found: 247.0975; Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.26; H, 5.80. Data in accordance with the literature.

1,4-Dimethoxy-2-hydroxymethylnaphthalene (206):[62]



A solution of lithium aluminum hydride (2.4 M in THF, 9.81 mL, 23.0 mmol, 1.0 eq.) in Et_2O (24 mL) was heated to reflux. A solution of methyl ester **208** (5.80 g, 23.0 mmol, 1.0 eq.) in Et_2O (24 mL) and THF (6 mL) was added dropwise over 35 min. The resulting mixture was heated to reflux for 3 h and cooled to 0 °C. Methanol (8 mL) was added dropwise and the resulting clear yellow solution was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm up to room temperature and saturated aqueous NH_4Cl (16 mL) and 10% HCl (4 mL) were added. The aqueous layer was extracted with Et_2O (6 × 20 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 (2 × 20 mL) and H_2O (2 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give alcohol **206** (4.83 g, 94%) as a white solid which was used without any further purification. R*f* 0.31 (hexanes/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.03 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.56 – 7.46 (m, 2H, Ar-*H*), 6.82 (s, 1H, Ar-*H*), 4.89 (s, 2H, C*H*$_2$OH), 3.99 (s, 3H, OMe), 3.92 (s, 3H, OMe), 1.95 (bs, 1H, O-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 146.9, 128.5, 128.4, 126.7, 126.2, 125.5, 122.3, 121.7, 103.7, 62.6, 61.0, 55.6; Mp 69 – 70 °C (lit.[62] 69 – 70 °C); IR (film) 3417, 3070, 2839, 1596, 1461, 1369, 1267, 1094 cm^{-1}; MS (CI) *m/z* 218 $[M]^+$; HRMS (CI) calc for $C_{13}H_{14}O_3$ $[M]^+$ 218.0943. Found: 218.0943; Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.50. Data in accordance with the literature.

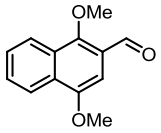
1,4-Dimethoxy-2-naphthoic acid (212):[68]



Methyl ester **208** (2.32 g, 9.42 mmol, 1.0 eq.) was dissolved in MeOH (10 mL) and 10% aqueous NaOH (10 mL) was added. The resulting mixture was heated to reflux for 3 h. The reaction mixture

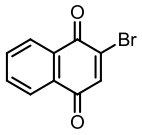
was allowed to cool to room temperature and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the organic layer was discarded. The aqueous layer was acidified with 1 N HCl and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give acid **212** (2.1 g, 95%) as a light brown solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 11.3 (bs, 1H, CO_2H), 8.26 – 8.21 (m, 2H, Ar-*H*), 7.67 – 7.65 (m, 2H, Ar-*H*), 7.25 (s, 1H, Ar-*H*), 4.05 (s, 3H, OMe), 4.03 (s, 3H, OMe); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.9, 153.4, 153.2, 130.7, 130.5, 129.7, 129.1, 125.1, 124.1, 121.0, 105.6, 67.8, 57.2; Mp 68 – 69 ºC (lit.[68] 68.3 – 69.2 °C); IR (film) 3252, 1747, 1623, 1508, 1473, 1111 cm^{-1}; MS (EI) *m/z* 231 $[M - H]^-$; HRMS (EI) calc for $C_{13}H_{11}O_4$ $[M - H]^-$ 231.0650. Found: 231.0657; Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.25; H, 5.19. Data in accordance with the literature.

1,4-Dimethoxy-2-naphthaldehyde (215):[70]



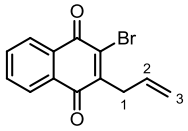
A solution of 1,4-dimethoxynaphthalene **214** (428 mg, 2.27 mmol, 1.0 eq.) in $CHCl_3$ (9 mL) was added to a mixture of phosphoryl chloride (2.14 mL, 23.4 mmol, 10.3 eq.) and *N*,*N*-dimethylformamide (1.79 mL, 23.2 mmol, 10.2 eq.). The resulting mixture was heated to reflux for 2 h. The reaction was quenched by addition of ice water and the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1, 3:1) to give aldehyde **215** as an orange solid (262 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H, C*H*O), 8.30 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 8.28 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.67 – 7.60 (m, 2H, Ar-*H*), 7.13 (s, 1H, Ar-*H*), 4.10 (s, 3H, OMe), 4.03 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 168.5, 157.1, 152.3, 130.3, 128.9, 127.3, 124.7, 123.0, 122.9, 98.3, 65.8, 55.8; Mp 119 – 120 °C (lit.[70] 119.5 – 120 °C); IR (film) 1675, 1598, 1385, 1375, 1130, 1100 cm^{-1}. Data in accordance with the literature.

2-Bromonaphthalene-1,4-dione (219):[71]



NBS (59.3 g, 332 mmol, 4.0 eq.) was dissolved in AcOH (600 mL) and H_2O (1200 mL), and the resulting mixture was heated to 45 °C. 1-Naphthol **218** (12.0 g, 83 mmol, 1.0 eq.) in AcOH (400 mL) was added dropwise and the reaction mixture was stirred at the aforementioned temperature for 1 h. The reaction mixture was allowed to cool to room temperature and H_2O (800 mL) was added. The aqueous layer was extracted with $CHCl_3$ (4 × 400 mL) and the combined organic layers were successively washed with saturated aqueous $NaHCO_3$ (400 mL), H_2O (2 × 200 mL) and brine (200 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by recrystallization (EtOH) to give 2-bromo naphthoquinone **219** (17.9 g, 91%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.17 (m, 1H), 8.11 – 8.08 (m, 1H), 7.81 – 7.75 (m, 2H), 7.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 177.8, 140.3, 140.1, 134.4, 134.1, 131.7, 130.9, 127.8, 126.9; Mp 132 – 133 ºC (lit.[71] 131 – 132 °C); IR (film) 3044, 2923, 1676, 1658, 1571, 1292, 1246, 1168 cm^{-1}; MS (EI) *m/z* 235 [M[^{79}Br]]$^+$, 237 [M[^{81}Br]]$^+$; HRMS (EI) calc for $C_{10}H_5{}^{79}BrO_2$ [M]$^+$ 235.9466. Found: 235.9473; Anal. Calcd. for $C_{10}H_5BrO_2$: C, 50.67; H, 2.13. Found: C, 50.29; H, 2.05. Data in accordance with the literature.

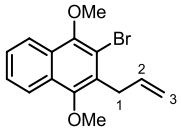
2-Allyl-3-bromonaphthalene-1,4-dione (220):[72b]



2-Bromonaphthalene-1,4-dione **219** (4.0 g, 16.87 mmol, 1.0 eq.) was dissolved in degassed acetonitrile (130 mL). But-3-enoic acid (2.15 mL, 25.3 mmol, 1.5 eq.) and $AgNO_3$ (1.43 g, 8.4 mmol, 0.5 eq.) were added and the resulting mixture was heated to 65 ºC. Ammonium persulfate (7.32 g, 32.06 mmol, 1.90 eq.) in degassed H_2O (60 mL) was added dropwise and the resulting mixture was stirred for 2 h. The reaction mixture was allowed to cool to room temperature and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give bromo-naphthoquinone **220** (3.43 g, 73%) as a yellowish solid. R*f* 0.72 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 6.5,

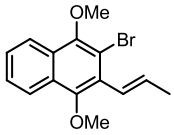
2.5 Hz, 1H, Ar-*H*), 8.11 (dd, *J* = 6.3, 2.6 Hz, 1H, Ar-*H*), 7.77 – 7.71 (m, 2H, Ar-*H*), 5.85 (ddt, *J* = 16.7, 9.9, 6.5 Hz, 1H, H2), 5.25 (dd, *J* = 17.1, 1.2 Hz, 1H, H3 *trans*), 5.13 (dd, *J* = 9.6. 1.2 Hz, 1H, H3 *cis*), 3.62 (dt, *J* = 6.5, 1.2 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 177.8, 149.0, 139.4, 134.2, 133.9, 131.5, 131.1, 131.4, 127.5, 127.2, 118.3, 35.4; Mp 78 – 79 ºC (lit.[72b] 70 – 71 °C); IR (film) 1663, 1593, 1424, 1275, 1163, 922, 721 cm^{-1}; MS (EI) *m/z* 276 [M[^{79}Br]]$^+$, 278 [M[^{81}Br]]$^+$; HRMS (EI) calc for $C_{13}H_9{}^{79}BrO_2$, $C_{13}H_9{}^{81}BrO_2$ [M]$^+$ 275.9787, 277.9775. Found: 275.9886, 277.9772; Anal. Calcd. for $C_{13}H_9BrO_2$: C, 56.34; H, 3.27. Found: C, 56.36; H, 3.29. Data in accordance with the literature.

2-Allyl-3-bromo-1,4-dimethoxynaphthalene (221):[72b]



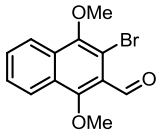
To a mixture of quinone **220** (6.93 g, 25.0 mmol, 1.0 eq.) and TBAI (0.73 g, 2.0 mmol, 0.08 eq.) in THF (350 mL) was added a solution of $Na_2S_2O_4$ (26.1 g, 150.0 mmol, 6.0 eq.) in H_2O (140 mL) with vigorous stirring. After 30 min, KOH (32.2 g, 575.0 mmol, 23.0 eq.) in H_2O (140 mL) was added dropwise and the resulting mixture was stirred for 1 h. Me_2SO_4 (47.3 mL, 500.0 mmol, 20.0 eq.) was added and the mixture was stirred further for 4 h. The reaction was quenched with 1.5 M aqueous NH_3 (175 mL) and H_2O (250 mL). The aqueous layer was extracted with EtOAc (3 × 150 mL) and the combined organic layers were washed with 2 M HCl (200 mL) and H_2O (3 × 100 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give methyl-protected quinone **221** (7.22 g, 93%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.0, 2.3 Hz, 1H, Ar-*H*), 8.06 (dd, *J* = 7.0, 2.3 Hz, 1H, Ar-*H*), 7.57 – 7.50 (m, 2H, Ar-*H*), 6.07 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H, H2), 5.09 (dd, *J* = 10.2, 1.4 Hz, 1H, H3 *cis*), 5.03 (dd, *J* = 17.1, 1.6 Hz, 1H, H3 *trans*), 3.98 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.79 (dt, *J* = 5.8, 1.4 Hz, 2H, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 150.1, 135.7, 128.8, 128.0, 127.9, 126.6, 126.5, 122.6, 122.5, 116.7, 115.8, 62.7, 61.3, 34.3; Mp 57 ºC (lit.[72b] 56 – 57 °C); IR (film) 1695, 1569, 1454, 1358, 1528, 1079, 1007, 912, 774 cm^{-1}; MS (EI) *m/z* 306 [M[^{79}Br]]$^+$, 308 [M[^{81}Br]]$^+$; HRMS (EI) calc for $C_{15}H_{15}{}^{79}BrO_2$, $C_{15}H_{15}{}^{81}BrO_2$ [M]$^+$ 306.0255, 308.0238. Found: 306.0262, 308.0238; Anal. Calcd. for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found: C, 58.71; H, 5.01. Data in accordance with the literature.

(*E*)-2-Bromo-1,4-dimethoxy-3-(prop-1-enyl)naphthalene (222):



Methyl-protected quinone **221** (1.50 g, 4.88 mmol, 1.0 eq.) was dissolved in THF (115 mL) and cooled to 0 ºC. *tert*-BuOK (1 M in THF, 9.76 mL, 9.76 mmol, 2.0 eq.) was added and the resulting mixture was stirred for 2 h at 0 ºC. The reaction was quenched with H_2O (70 mL) and extracted with EtOAc (3 × 70 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give double bond migrated naphthoquinone **222** (1.50 g, 99%) which was used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.1, 2.1 Hz, 1H, Ar-*H*), 8.06 (dd, *J* = 6.8, 1.9 Hz, 1H, Ar-*H*), 7.55 – 7.48 (m, 2H, Ar-*H*), 6.59 (dd, *J* = 15.9, 1.6 Hz, 1H, C*H*=CHCH$_3$), 6.49 (dq, *J* = 15.8, 6.2 Hz, 1H, CH=C*H*CH$_3$), 3.97 (s, 3H, OMe), 3.80 (s, 3H, OMe), 2.01 (dd, *J* = 6.7, 1.2 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 149.8, 133.4, 128.4, 127.7, 127.4, 126.7, 126.6, 125.7, 122.9, 122.3, 115.7, 61.3, 30.6, 19.5; Mp 71 – 73 ºC; IR (film) 3070, 2931, 2845, 1560, 1453, 1357, 1260, 1080, 965, 770 cm^{-1}; MS (EI) *m/z* 306 [M[^{79}Br]]$^+$, 308 [M[^{81}Br]]$^+$; HRMS (EI) calc for $C_{15}H_{15}{}^{79}BrO_2$, $C_{15}H_{15}{}^{81}BrO_2$ [M]$^+$ 306.0255, 308.0243. Found: 306.0262, 308.0243; Anal. Calcd. for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found: C, 58.60; H, 5.00.

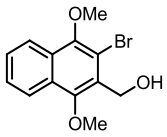
3-Bromo-1,4-dimethoxy-2-naphthaldehyde (216b):[180]



To a solution of double bond migrated naphthoquinone **222** (1.30 g, 4.23 mmol, 1.0 eq.) in THF (30 mL) and H_2O (15 mL) was added OsO_4 (10 mg, 0.04 mmol, 0.01 eq.) and $NaIO_4$ (2.2 g, 10.16 mmol, 2.40 eq.) at room temperature. The reaction mixture was heated to 70 ºC and stirred for 12 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (65 mL) and stirred vigorously for 30 min. The aqueous layer was extracted with EtOAc (3 × 120 mL) and the combined organic layers were washed with brine (40 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 7:1, 4:1) to give bromo-aldehyde naphthoquinone **216b** (0.912 g, 73%) as a yellow solid. R*f* 0.54 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H, C*H*O), 8.25 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 8.14 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 7.70 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, Ar-*H*), 7.63 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, Ar-*H*), 4.07 (s, 3H, OMe), 4.00 (s, 3H, OMe); ^{13}C NMR (100

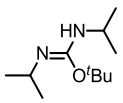
MHz, $CDCl_3$) δ 190.7, 157.2, 150.5, 131.5, 130.0, 128.3, 127.5, 124.2, 123.4, 122.7, 111.8, 65.0, 61.5; Mp 110 – 111 ºC (lit.[180] 110 °C); IR (film) 2935, 1742, 1693, 1447, 1351, 1080, 998, 931, 768 cm-1; MS (EI) *m/z* 293 $[M[^{79}Br]]^+$, 295 $[M[^{81}Br]]^+$; HRMS (EI) calc for $C_{13}H_{11}{}^{79}BrO_3$, $C_{13}H_{11}{}^{81}BrO_3$ $[M]^+$ 293.9892, 295.9871. Found: 293.9885, 295.9864; Anal. Calcd. for $C_{13}H_{11}BrO_3$: C, 52.91; H, 3.76. Found: C, 53.00; H, 3.71. Data in accordance with the literature.

(3-Bromo-1,4-dimethoxynaphthalen-2-yl)methanol (205b):[62]



Bromo-aldehyde naphthoquinone **216b** (795 mg, 2.69 mmol, 1.0 eq.) was dissolved in MeOH (33 mL) and the reaction mixture was cooled to 0 ºC. $NaBH_4$ (153 mg, 4.04 mmol, 1.5 eq.) was added in portions and the resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with Saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford alcohol **205b** (760 mg, 95%) as a white solid which was used without further purification. R*f* 0.31 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.09 (m, 2H, Ar-*H*), 7.58 – 7.56 (m, 2H, Ar-*H*), 5.03 (s, 2H, C*H*$_2$), 4.02 (s, 3H, OMe), 3.98 (s, 3H, OMe), 2.39 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 150.2, 129.0, 128.9, 128.0, 127.4, 126.9, 123.0, 122.5, 115.2, 63.9, 61.5, 60.1; Mp 115 – 117 ºC (lit.[62] 115 – 117 °C); IR (film) 3433, 2935, 2843, 1571, 1453, 1358, 1621, 1083, 1000, 775, 758 cm^{-1}; MS (EI) *m/z* 296 $[M[^{79}Br]]^+$, 298 $[M[^{81}Br]]^+$; HRMS (EI) calc for $C_{13}H_{13}{}^{79}BrO_3$, $C_{13}H_{13}{}^{81}BrO_3$ $[M]^+$ 296.0043, 298.0024. Found: 296.0048, 298.0029; Anal. Calcd. for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41. Found: C, 52.52; H, 4.38. Data in accordance with the literature.

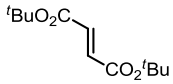
***tert*-Butyl *N,N*'-diisopropylcarbamimidate (227):**[76b]



A mixture of 1,3-diisopropylcarbodiimide **226** (60 mL, 387 mmol, 1.0 eq.), *tert*-butanol (42 mL, 449 mmol, 1.16 eq) and CuCl (400 mg) was stirred for 5 d at room temperature. Excess *tert*-butanol was concentrated under reduced pressure and *N,N'*-diisopropyl-*O*-*tert*-butylisourea **227** was distilled under reduced pressure to give a colorless liquid (66.2 g, 85 %, mixture of *cis* and *trans* isomers).^{1}H NMR

(400 MHz, $CDCl_3$) δ 3.73 (br sept, J = 6.4, 6.0 Hz, 0.45H, N=C*H*$(CH_3)_2$), 3.65 (sept, J = 6.4, 6.0 Hz, 0.55H, N=C*H*$(CH_3)_2$), 3.22 (br sept, J = 6.1 Hz, 0.45H, NH-C*H*$(CH_3)_2$), 3.13 (sept, J = 6.1 Hz, 0.55H, N=C*H*$(CH_3)_2$), 1.46 (s, 4H, C(C*H*$_3)_3$), 1.37 (s, 5H, C(C*H*$_3)_3$), 1.07 (d, J = 6.4 Hz, 6.5H, CH(C*H*$_3)_2$), 1.03 (d, J = 6.4 Hz, 5.5H, CH(C*H*$_3)_2$). Data in accordance with the literature.

Di-*tert*-butyl fumarate (204a):[73]



Method A.[73] *tert*-Butyl acrylate **223** (800 mg, 6.2 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (20 mL) and Grubbs II catalyst (33 mg, 0.03 mmol, 0.5 mol%) was added. The reaction mixture was heated to reflux for 12 h. As TLC showed unreactive starting material, additional Grubbs II catalyst (16 mg, 0.015 mmol, 0.25 mol%) was added and the reaction mixture was heated to reflux for further 12 h. The reaction mixture was filtered through silica, charcoal and sand and washed with CH_2Cl_2/MeOH (10:1). The solvents were concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (hexanes/EtOAc 60:1, 30:1) to give fumarate **204a** as a white solid (631 mg, 88%).

Method B.[76a] A mixture of fumaric acid **224** (200 mg, 1.72 mmol, 1.0 eq.) and *tert*-butyl *N*,*N*'-diisopropylcarbamimidate **227** (2.06 g, 10.33 mmol, 6.0 eq.) in CH_2Cl_2 (3 mL) was heated to reflux for 2 h. The solvent was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 20:1, 10:1, 5:1) to give fumarate **204a** (258 mg, 66 %) as a white solid.

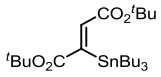
Method C. <u>*Caution:*</u> *Suitable safety protections were taken and all manipulations were conducted behind safety shields.* Fumaric acid **224** (32.0 g, 275 mmol, 1.0 eq.) was suspended in Et_2O (60 mL) in a pressure bottle and conc. H_2SO_4 (3 mL) followed by isobutylene **225** (~47 g, 825 mmol, 3.0 eq.), which was liquefied by passage in a large test tube immersed in a Dry Ice-acetone bath, were added. The pressure bottle was sealed and the reaction mixture was stirred for 24 h. The reaction mixture was poured into H_2O (140 mL) containing NaOH (40 g) and ice (140 g). The resulting mixture was stirred carefully and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 75 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give fumarate **204a** as a white solid (2.5 g, 4%).

Method D.[78] Dimethylaniline (9.4 mL, 74.3 mmol, 2.0 eq.) in Et_2O (26 mL) was added to *tert*-BuOH (11.0 mL, 118.9 mmol, 3.2 eq.) and the mixture was stirred at room temperature for 15 min. Fumaryl

chloride **229** (4 mL, 37.2 mmol, 1.0 eq.) was added *via* a dropping funnel in Et_2O (4 mL) and the mixture was heated to reflux for 2.5 h. The reaction was quenched with 6 N H_2SO_4 (20 mL). The aqueous layer was washed with Et_2O (3 × 25 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 (25 mL), brine (25 mL) and dried over $MgSO_4$. The resulting organic layer was concentrated under reduced pressure and the crude material was purified by recrystallization (acetone) to give fumarate **204a** (3.26 g, 38 %) as a white solid.

Method E.[78] To *tert*-BuOH (12.4 mL, 130 mmol, 3.5 eq.) was added *tert*-BuOK (1 M in THF, 74 mL, 74.3 mmol, 2.0 eq.) over 35 min at 0 °C and the resulting solution was stirred for 30 min at the aforementioned temperature. The resulting solution was added to a solution of fumaryl chloride **229** (4 mL, 37.7 mmol, 1.0 eq.) in Et_2O (13 mL) *via* a dropping funnel at room temperature over 30 min. After stirring for 2 h, the reaction was quenched by addition of H_2O (15 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 mL), brine (25 mL) and dried over $MgSO_4$. The resulting organic layer was concentrated under reduced pressure and the crude material was purified by recrystallization (hexanes) to give fumarate **204a** (4.77 g, 57 %) as a white solid. R*f* 0.44 (hexanes/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 2H, C=C*H*), 1.52 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (2C), 134.6 (2C), 81.6 (2C), 27.9 (6C); IR (film) 2981, 2937, 1703, 1672, 1460, 1390, 1367, 1306, 1253, 1137, 973 cm^{-1}; Mp 68 – 70 °C (lit.[78] 71 – 71.5 °C); MS (ESI) *m/z* 246 $[M + NH_4]^+$; HRMS (ESI) calc for $C_{12}H_{24}NO_4$ $[M + NH_4]^+$ 246.1705. Found: 246.1706; Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.18; H, 8.80. Data in accordance with the literature.

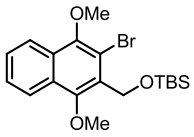
Di-*tert*-butyl 2-(tributylstannyl)fumarate (236):[79]



Di-*tert*-butylacetylene dicarboxylate **112** (10 g, 44.2 mmol, 1.0 eq.) was dissolved in benzene (170 mL). Tributyltin hydride (13.07 mL, 48.6 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. The solvent was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 200:1, 100:1, 50:1, 25:1) to give stannane **236** (22.8 g, 99%) as a colorless oil. R*f* 0.46 (hexanes/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 1.51 – 1.44 (m, 6H), 1.49 (s, 9H), 1.47 (s, 9H), 1.34 – 1.25 (m, 6H), 1.03 – 0.99 (m, 6H), 0.87 (t, *J* = 7.4 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 166.6, 161.5, 135.0, 81.3, 81.0, 28.9 (3C), 28.2 (3C), 27.9 (3C), 27.3 (3C), 13.7 (3C), 12.0 (3C); IR (film) 2956, 2923, 2871, 2854, 1704, 1458, 1368, 1322, 1247, 1154 cm^{-1}; MS (CI) *m/z* 519 $[M + H]^+$, 536 [M +

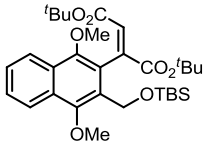
$NH_4]^+$; HRMS (CI) calc for $C_{24}H_{50}NO_4Sn$ $[M + NH_4]^+$ 536.2762. Found: 536.2781; Anal. calcd. for $C_{24}H_{46}O_4Sn$: C, 55.72; H, 8.96. Found: C, 55.63; H, 8.86. Data in accordance with the literature.

((3-Bromo-1,4-dimethoxynaphthalen-2-yl)methoxy)(*tert*-butyl)dimethylsilane (235):



Alcohol **205b** (200 mg, 0.67 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (3 mL) and the reaction mixture was cooled to 0 ºC. TBSCl (126 mg, 0.84 mmol, 1.25 eq.) and imidazole (68 mg, 1.0 mmol, 1.5 eq.) were added and the resulting mixture was stirred for 12 h at room temperature. H_2O (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give TBS-protected alcohol **235** (269 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13– 8.08 (m, 2H, Ar-*H*), 7.56 – 7.52 (m, 2H, Ar-*H*), 5.02 (s, 2H, CH_2), 4.02 (s, 3H, OMe), 3.99 (s, 3H, OMe), 0.95 (s, 9H, Si-C(CH_3)$_3$), 0.21 (s, 6H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 150.1, 129.1, 128.9, 128.0, 127.1, 126.6, 122.9, 122.5, 116.5, 64.0, 61.3, 60.2, 25.9 (3C), 18.5, -5.20 (2C); MS (CI) *m/z* 428 $[M[^{79}Br]]^+$, 430 $[M[^{81}Br]]^+$; HRMS (CI) calc for $C_{19}H_{31}{}^{79}BrO_3Si$ $[M + NH_4]^+$ 428.1250. Found: 428.1257; Anal. Calcd. for $C_{19}H_{27}BrO_3Si$: C, 55.47; H, 6.61. Found: C, 55.52; H, 6.59.

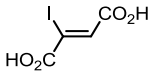
Di-*tert*-butyl 2-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,4-dimethoxynaphthalen-2-yl)fumarate (234a):



Bromide **235** (242 mg, 0.59 mmol, 1.0 equiv), stannane **236** (366 mg, 0.71 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (34 mg, 0.03 mmol, 5 mol%) and CuI (28 mg, 0.15 mmol, 0.25 equiv) were dissolved in toluene (2 mL) and the reaction mixture was refluxed for 12 h. The solvent was evaporated under reduced pressure and the crude material was purified by silica gel column chromatography to give alkene **234a** (148 mg, 45%) as an yellow oil. R*f* 0.81 (Hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.08 (m, 2H, Ar-*H*), 7.56 – 7.50 (m, 2H, Ar-*H*), 7.01 (s, 1H, C=C*H*), 4.79 (d, *J* = 10.8

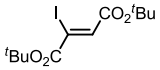
Hz, 1H, CH_2OTBS), 4.69 (d, J = 11.2 Hz, 1H, CH_2OTBS), 4.02 (s, 3H, OMe), 3.98 (s, 3H, OMe), 1.46 (s, 9H, C(CH_3)$_3$), 1.43 (s, 9H, C(CH_3)$_3$), 0.94 (s, 9H, Si-C(CH_3)$_3$), 0.09 (s, 6H, SiMe_2).

2-Iodofumaric acid (241):[82]



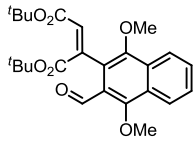
Acetylenedicarboxylic acid **240** (10 g, 87.7 mmol, 1.0 eq.) was added portionwise to HI (57% in H_2O, 12 mL, 91.2 mmol, 1.04 eq.) at 0 °C. The resulting mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was diluted with Et_2O (50 mL) and the organic layers were washed with saturated aqueous $Na_2S_2O_3$ (50 mL), H_2O (50 mL) and dried over $MgSO_4$. The resulting organic layer was concentrated under reduced pressure to give acid **241** (16.6 g, 78%) as a bright yellow solid which was used without any further purification. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.06 (s, 1H, C=CH); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.7, 165.6, 139.9, 104.1; Mp 192 – 194 °C (lit.[82] 194 – 195 °C); IR (film) 2977, 2792, 1684, 1605, 1385, 1252, 1199, 933, 886, 657 cm^{-1}; MS (EI) *m/z* 482 [2M – H]$^-$; HRMS (EI) calc for $C_8H_5I_2O_8$ [2M – H]$^-$ 482.8080. Found: 482.8074; Anal. Calcd. for $C_4H_3IO_4$: C, 19.85; H, 1.25. Found: C, 19.90; H, 1.19. Data in accordance with the literature.

Di-*tert*-butyl 2-iodomaleate (239):



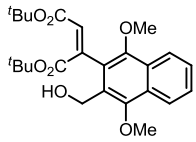
To a suspension of acid **241** (2.0 g, 8.26 mmol, 1.0 eq.) in CH_2Cl_2 (35 mL) was added *tert*-butyl *N*,*N*'-diisopropylcarbamimidate **227** (10 g, 49.6 mmol, 6.0 eq.) over 1 h *via* a syringe pump. The resulting mixture was stirred for 12 h and the resulting precipitate was filtered. The filtrate was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1) to afford *tert*-butyl ester **239** (2.47g, 85%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H, C=CH), 1.53 (s, 9H, C(CH_3)$_3$), 1.51 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 161.7, 137.9, 103.8, 84.0, 82.8, 28.0 (3C), 27.7 (3C); IR (film) 2980, 1712, 1368, 1250, 1140, 1000, 841 cm^{-1}; MS (EI) *m/z* 372 [M + NH_4]$^+$; HRMS (EI) calc for $C_{12}H_{23}NIO_4$ [M + NH_4]$^+$ 372.0666. Found: 372.0661; Anal. Calcd. for $C_{12}H_{19}IO_4$: C, 40.69; H, 5.41. Found: C, 40.58; H, 5.37.

Di-*tert*-butyl 2-(3-formyl-1,4-dimethoxynaphthalen-2-yl)maleate (238):



Iodide **239** (2.49 g, 7.05 mmol, 3.0 eq.), bromide **216b** (654 mg, 2.35 mmol, 1.0 eq.), Cu (1.49 g, 23.5 mmol, 10.0 eq.), CuI (179 mg, 0.94 mmol, 0.4 eq.) and $Pd_2(dba)_3$ (215 mg, 0.23 mmol, 0.1 eq.) were dissolved in DMSO (5 mL) and the resulting mixture was stirred at 65 °C for 12 h. The reaction mixture was diluted with Et_2O (10 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1) to give alkene **238** (570 mg, 58%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H, C*H*O), 8.24 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.12 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.68 (dd, *J* = 8.4, 6.8 Hz, 1H, Ar-*H*), 7.61 (dd, *J* = 8.4, 6.8 Hz, 1H, Ar-*H*), 6.98 (s, 1H, C=C*H*), 4.10 (s, 3H, OMe), 3.75 (s, 3H, OMe), 1.46 (s, 9H, C(CH_3)$_3$), 1.06 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 165.1, 164.8, 159.6, 149.9, 140.2, 131.9 (2C), 129.8, 129.5, 128.4, 127.2, 124.3, 123.3, 123.2, 81.7, 80.6, 65.6, 61.5, 27.8 (3C), 27.5 (3C); IR (film) 2979, 1714, 1686, 1457, 1373, 1353, 1253, 1154, 1068 cm^{-1}; MS (EI) *m/z* 465 $[M + Na]^+$; HRMS (EI) calc for $C_{25}H_{30}O_7Na$ $[M + Na]^+$ 465.1882. Found: 465.1889; Anal. Calcd. for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found: C, 67.92 H, 6.77.

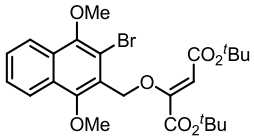
Di-*tert*-butyl 2-(3-(hydroxymethyl)-1,4-dimethoxynaphthalen-2-yl)maleate (237):



Aldehyde **238** (1.12 g, 2.53 mmol, 1.0 eq.) was dissolved in MeOH (23 mL) and the mixture was cooled to 0 °C. $NaBH_4$ (95 mg, 2.53 mmol, 1.0 eq.) was added and the reaction was stirred for 2 h. H_2O (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$. The resulting organic layer was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give alcohol **237** (998 mg, 88%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.14 (m, 1H, Ar-*H*), 8.07 – 8.05 (m, 1H, Ar-*H*), 7.56 – 7.50 (m, 2H, Ar-*H*), 7.09 (s, 1H, C=C*H*), 4.73 (d, *J* = 11.6 Hz, 1H, CH_2OH), 4.63 (d, *J* = 11.3 Hz, 1H, CH_2OH), 4.06 (s, 3H, OMe), 3.79 (s, 3H, OMe), 1.46 (s, 9H, C(CH_3)$_3$), 1.39 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.1, 151.1, 149.1, 140.1, 132.2, 128.9, 128.4, 128.2, 126.4 (2 C), 125.3,

122.8, 122.7, 82.7, 82.2, 63.7, 61.8, 58.2, 27.8 (3 C), 27.6 (3 C); IR (film) 2972, 2931, 1720, 1455, 1358, 1274, 1154, 1069, 1033 cm^{-1}; MS (EI) *m/z* 467 $[M + Na]^+$; HRMS (EI) calc for $C_{25}H_{32}O_7Na$ $[M + Na]^+$ 467.2028. Found: 467.2019.

Di-*tert*-butyl-2-((3-bromo-1,4-dimethoxynaphthalen-2-yl)methoxy)fumarate (243):



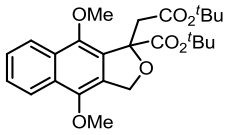
Alcohol **205b** (0.76 g, 2.57 mmol, 1.0 eq.) and alkyne **112** (0.756 g, 3.34 mmol, 1.3 eq.) were dissolved in CH_2Cl_2 (20 mL) and the reaction mixture was cooled to 0 ºC. DMAP (31 mg, 0.26 mmol, 0.1 eq.) was added and the resulting mixture was stirred for 1 h at 0 ºC and for 12 h at room temperature. The reaction mixture was poured into saturated aqueous NH_4Cl (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give *O*-alkylated product **243** (1.19 g, 88%) as a white solid. R*f* 0.51 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.08 (m, 2H, Ar-*H*), 7.57 – 7.55 (m, 2H, Ar-*H*), 6.07 (s, 1H, C=C*H*), 5.51 (s, 2H, CH_2), 4.02 (s, 3H, OMe), 3.97 (s, 3H, OMe), 1.48 (s, 9H, C(CH_3)$_3$), 1.35 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 162.2, 154.4, 153.3, 150.0, 129.5, 127.8, 127.6, 126.7, 125.3, 123.2, 122.5, 116.3, 109.2, 82.7, 80.8, 69.9, 64.2, 61.3, 27.9 (3C), 27.8 (3C); Mp 83 – 85 °C; IR (film) 2977, 2935, 1722, 1631, 1572, 1455, 1393, 1361, 1281, 1256, 1152, 1086, 1008, 847, 759 cm^{-1}; MS (EI) *m/z* 522 $[M[^{79}Br]]^+$, 524 $[M[^{81}Br]]^+$; HRMS (EI) calc for $C_{25}H_{31}{}^{79}BrO_7$, $C_{25}H_{31}{}^{81}BrO_7$ $[M]^+$ 522.1253, 524.1231. Found: 522.1252, 524.1231; Anal. Calcd. for $C_{25}H_{31}BrO_7$: C, 57.37; H, 5.97. Found: C, 57.42; H, 5.97.

Tributylgermanium hydride (246):[89]

Germanium tetrachloride **245** (5.0 g, 23.3 mmol) was loaded into a 0 °C-precooled three necked flask containing Et_2O (143 mL) and Cp_2TiCl_2 (460 mg, 1.86 mmol, 0.08 eq.). To the resulting mixture was added *n*-BuMgCl (2 M in Et_2O, 58 mL, 116 mmol, 5.0 eq.) over a period of 1 h with stirring. The reaction mixture was slowly allowed to warm to room temperature and was heated to reflux for 12 h. The mixture was hydrolyzed by carefully adding 2 M HCl (58 mL) at 0 °C over a period of 1 h. The organic layer was separated while the aqueous layer was extracted with Et_2O (3 × 28 mL) and the washings were collected along with the organic layer. The organic layer was dried over $MgSO_4$ and

the solvent was concentrated under reduced pressure. The crude material was filtered to remove a small amount of an orange–red solid, presumably a Cp_2Ti-based complex (not characterized). GC analysis of the crude showed mainly two peaks due to Bu_3GeH **246** and Bu_4Ge 2**47**, respectively. These two products were separated by careful distillation under reduced pressure to give Bu_3GeH **246** (2.50 g, 44%) at 85 °C/7 – 8 mbar as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (septet, *J* = 3.0 Hz, 1H), 1.41 – 1.30 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 9H), 0.82 – 0.78 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (3C), 26.1 (3C), 13.8 (3C), 11.8 (3C). Data in accordance with the literature.

***tert*-Butyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-4,9-dimethoxy-1,3-dihydronaphtho[2,3-*c*]furan-1-carboxylate (233a):**



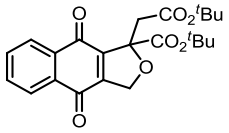
Method A. Alcohol **237** (307 mg, 0.69 mmol, 1.0 eq.) was dissolved in THF (70 mL) and the reaction mixture was cooled to 0 °C. NaH (60% dispersion in paraffin oil, 55 mg, 1.35 mmol, 2.0 eq.) was added dropwise and the resulting mixture was stirred for 2 h at 0 °C. The reaction was quenched by addition of H_2O (2.5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to afford tricycle **233a** (132 mg, 43%) as a white solid.

Method B. Alcohol **237** (200 mg, 0.45 mmol, 1.0 eq.) was dissolved in THF (3 mL) and the reaction mixture was cooled to 0 °C. *tert*-BuOK (1 M in THF, 134 μL, 0.13 mmol, 0.3 eq.) was added dropwise and the resulting mixture was stirred for 2 h at 0 °C. The reaction was quenched by addition of H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with brine (5 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give tricycle **233a** (107 mg, 53%) as a white solid.

Method C. Bromide **243** (2.5 g, 4.78 mmol, 1.0 eq.) was dissolved in degassed benzene (100 mL). $GeBu_3H$ (1.37 mL, 5.26 mmol, 1.1 eq.) and ACCN (117 mg, 0.47 mmol, 0.1 eq.) were added and the reaction mixture was heated to reflux for 12 h. As TLC showed incomplete reaction, additional $GeBu_3H$ (1.37 mL, 5.26 mmol, 1.1 eq.) and ACCN (117 mg, 0.47 mmol, 0.1 eq.) were added and the reaction mixture was heated to reflux for 12 h. The solvent was concentrated under reduced pressure

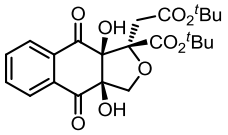
and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to afford tricycle **233a** (1.09 g, 52%) as a white solid. R*f* 0.42 (hexanes/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.14 (m, 1H, Ar-*H*), 8.06 – 8.02 (m, 1H, Ar-*H*), 7.53 – 7.49 (m, 2H, Ar-*H*), 5.55 (d, *J* = 12 Hz, 1H, C*H*$_2$), 5.39 (d, *J* = 12.4 Hz, 1H, C*H*$_2$), 3.96 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.67 (d, *J* = 16 Hz, 1H, C*H*$_2$CO$_2$^{t}Bu), 3.12 (d, *J* = 16 Hz, 1H, C*H*$_2$CO$_2$^{t}Bu), 1.42 (s, 9H, C(C*H*$_3$)$_3$), 1.29 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.2, 146.5, 145.5, 129.9, 129.5, 129.0, 126.4, 126.1, 125.8, 122.4 (2C), 88.1, 81.9, 80.4, 71.8, 62.6, 60.3, 41.5, 27.9 (3C), 27.8 (3C); Mp 77 – 79 °C; IR (film) 2977, 2935, 2869, 1731, 1604, 1459, 1355, 1276, 1256, 1157, 1052, 844, 771 cm^{-1}; MS (EI) *m/z* 444 [M]$^{+}$; HRMS (EI) calc for $C_{25}H_{32}O_7$ [M]$^{+}$ 444.2148. Found: 444.2147; Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.62; H, 7.29.

***tert*-Butyl 1-(2-*tert*-butoxy-2-oxoethyl)-4,9-dioxo-1,3,4,9-tetrahydronaphtho[2,3-*c*]furan-1-carboxylate (203):**[31]



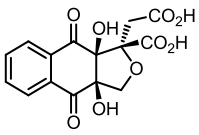
Tricycle **233a** (166 mg, 0.37 mmol, 1.0 eq.) was dissolved in MeCN (12 mL) and the reaction mixture was cooled to 0 °C. CAN (819 mg, 1.49 mmol, 4.0 eq.) in H_2O (6 mL) was added dropwise and the resulting mixture was stirred for 15 min at 0 °C and for 15 min at room temperature. H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give naphthoquinone **203** (112 mg, 73%) as a yellow solid. R*f* 0.45 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.10 (m, 2H, Ar-*H*), 7.77 – 7.75 (m, 2H, Ar-*H*), 5.19 (d, *J* = 15.6, Hz, 1H, C*H*$_2$O), 5.13 (d, *J* = 15.6 Hz, 1H, C*H*$_2$O), 3.29 (d, *J* = 15.6 Hz, 1H, C*H*$_2$CO$_2$^{t}Bu), 3.20 (d, *J* = 15.6 Hz, 1H, C*H*$_2$CO$_2$^{t}Bu), 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.31 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7, 180.5, 168.5, 167.9, 147.4 (2C), 134.1, 133.9, 132.9, 132.8, 126.6, 126.4, 91.4, 83.2, 81.0, 73.3, 40.7, 27.8 (3C), 27.7 (3C); Mp 100 – 102 °C (lit.[31] 111 °C); IR (film) 2977, 2935, 1722, 1631, 1572, 1455, 1393, 1361, 1281, 1256, 1152, 1086, 1008, 847, 759 cm^{-1}; MS (EI) *m/z* 437 [M + Na]$^{+}$; HRMS (EI) calc for $C_{23}H_{26}O_7Na$ [M + Na]$^{+}$ 437.1576. Found: 437.1586; Anal. Calcd. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.67; H, 6.27. Data in accordance with the literature.

(1S,3aR,9aR)-*tert*-Butyl 1-(2-*tert*-butoxy-2-oxoethyl)-3a,9a-dihydroxy-4,9-dioxo-1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-carboxylate ((±)-248):



Naphthoquinone **203** (238 mg, 0.57 mmol, 1.0 eq.) and $NaIO_4$ (184 mg, 0.86 mmol, 1.5 eq.) were dissolved in MeCN (1.7 mL) and EtOAc (1.7 mL) and the solution was cooled to 0 °C. 1 M H_2SO_4 (115 μL, 0.115 mmol, 0.2 eq.) was added followed by addition of a 0.1 M aqueous solution of $RuCl_3$ (28 μL, 2.8 μmol, 0.5 mol%) and the resulting mixture was stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (3 mL). The aqueous layer was extracted with EtOAc (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1, 1:1) and recrystallization (hexanes/EtOAc 2:1) to give pure diol **(±)-248** as a white solid (198 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 6.8, 2.0 Hz, 1H, Ar-*H*), 8.18 (dd, J = 6.8, 2.0 Hz, 1H, Ar-*H*), 7.94 – 7.87 (m, 2H, Ar-*H*), 4.80 (s, 1H, OH), 4.77 (d, J = 8.8 Hz, 1H, CH_2O), 4.17 (d, J = 8.8 Hz, 1H, CH_2O), 3.48 (s, 1H, OH), 2.69 (d, J = 16.0 Hz, 1H, CH_2CO$_2^t$Bu), 1.93 (d, J = 16.0 Hz, 1H, CH_2CO$_2^t$Bu), 1.54 (s, 9H, C(CH_3)$_3$), 1.32 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 191.1, 167.4, 167.3, 136.2, 135.5, 133.9, 133.7, 128.6, 127.3, 89.1, 84.3, 83.0, 82.3, 81.7, 73.1, 41.9, 28.0 (3C), 27.9 (3C); Mp 161 – 163 ºC; IR (film) 3450, 2975, 2933, 1739, 1702, 1592, 1369, 1267, 1145, 1076, 782, 624 cm^{-1}; MS (EI) *m/z* 471 [M + Na]$^+$; HRMS (EI) calc for $C_{23}H_{28}O_9Na$ [M + Na]$^+$ 471.1636. Found: 471.1631; Anal. Calcd. for $C_{23}H_{28}O_9$: C, 61.60; H, 6.29. Found: C, 61.58; H, 6.36.

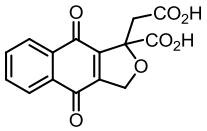
(1S,3aR,9aR)-1-(Carboxymethyl)-3a,9a-dihydroxy-4,9-dioxo-1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-carboxylic acid ((±)-249):



Di-ester **(±)-248** (20 mg, 44 μmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1.0 mL) and the resulting solution was cooled to 0 °C. TFA (0.1 mL) was added dropwise and the reaction was stirred for 1 h at 0 °C and for 2 h at room temperature. As the TLC showed unreactive starting material, additional TFA (0.1 mL) was added and the reaction mixture was stirred further for 1 h. The reaction mixture was

concentrated under reduced pressure to give di-acid **(±)-249** (14.9 mg, 99%) as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.24 – 8.21 (m, 2H, Ar-*H*), 7.99 – 7.93 (m, 2H, Ar-*H*), 4.69 (d, *J* = 6.4 Hz, 1H, C*H*$_2$), 4.11 (d, *J* = 6.4 Hz, 1H, C*H*$_2$), 2.70 (d, *J* = 12.4 Hz, 1H, C*H*$_2$CO$_2$H), 1.93 (d, *J* = 12.8 Hz, 1H, C*H*$_2$CO$_2$H); ^{13}C NMR (100 MHz, acetone-d_6) δ 183.2, 182.4, 171.7, 171.2, 146.9, 145.7, 136.2, 136.1, 134.7, 128.7, 128.1, 127.9, 92.1, 74.8, 40.5; Mp 159 ºC; IR (film) 3442, 2924, 1733, 1488, 1419, 1261, 1233, 1062, 1035 cm^{-1}; MS (EI) *m/z* 335 [M – H]$^-$; HRMS (EI) calc for $C_{15}H_{11}O_8$ [M – H]$^-$ 335.0396. Found: 335.0390.

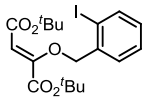
1-(Carboxymethyl)-4,9-dioxo-1,3,4,9-tetrahydronaphtho[2,3-*c*]furan-1-carboxylic acid (251):[31]



Di-ester **203** (500 mg, 1.2 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (5.0 mL) and the resulting solution was cooled to 0 °C. TFA (2 mL) was added dropwise and the reaction mixture was stirred for 1 h at 0 °C and for 2 h at room temperature. As the TLC showed unreactive starting material, additional TFA (1 mL) was added and the reaction mixture was stirred further for 1 h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by recrystallization (H_2O/Acetone 1:1) to afford di-acid **251** (313 mg, 86%) as an off-white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.12 – 8.09 (m, 2H, Ar-*H*), 7.94 – 7.89 (m, 2H, Ar-*H*), 5.19 (d, *J* = 15.2, Hz, 1H, C*H*$_2$O), 5.14 (d, *J* = 15.2, Hz, 1H, C*H*$_2$O), 3.38 (d, *J* = 16.4, 1H, C*H*$_2$CO$_2$H), 3.31 (d, *J* = 16.4, 1H, C*H*$_2$CO$_2$H); ^{13}C NMR (100 MHz, acetone-d_6) δ 183.2, 182.4, 171.7, 171.2, 146.9, 145.7, 136.2, 136.1, 134.7 (2C), 128.7, 127.9, 92.1, 74.8, 40.5; Mp 159 °C (lit.[31] 157 °C); IR (film) 3297, 1707, 1666, 1590, 1285, 1170, 1019, 697 cm^{-1}; Anal. Calcd. for $C_{15}H_{10}O_7$: C, 59.61; H, 3.33. Found: C, 59.571; H, 3.30. Data in accordance with the literature.

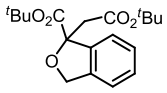
Synthesis of model carboxylic acid (3)

Di-*tert*-butyl 2-(2-iodobenzyloxy)fumarate (258):



2-Iodobenzyl alcohol **257** (2.0 g, 8.5 mmol, 1.0 eq.) and alkyne **112** (2.5 g, 11.1 mmol, 1.3 eq.) were dissolved in CH_2Cl_2 (50 mL) and the resulting mixture was cooled to 0 °C. DMAP (103 mg, 0.85 mmol, 0.1 eq.) was added and the reaction mixture was stirred for 2 h at 0 °C and for 12 h at room temperature. The reaction was quenched with H_2O (60 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL) and the combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give *O*-alkylated product **258** as a colorless oil (3.9 g, 99%). R*f* 0.72 (hexanes/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.70 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.37 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.99 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.13 (s, 1H, C=C*H*), 5.08 (s, 2H, CH_2O), 1.49 (s, 9H, C(CH_3)$_3$), 1.47 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 161.9, 153.8, 139.2, 138.8, 129.3, 128.6, 128.3, 110.9, 96.2, 83.1, 81.2, 78.4, 28.1 (3C), 27.9 (3C); IR (film) 2978, 2932, 1719, 1636, 1456, 1392, 1368, 1349, 1279, 1255, 1152, 1011, 846, 749 cm^{-1}; MS (CI) *m/z* 461 $[M + H]^+$, 478 $[M + NH_4]^+$; HRMS (CI) calc for $C_{19}H_{26}O_5I$ $[M + H]^+$ 461.0825. Found: 461.0829; Anal. Calcd. for $C_{19}H_{25}O_5I$: C, 49.58; H, 5.47. Found: C, 49.67; H, 5.51.

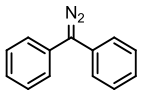
***tert*-Butyl 1-(2-*tert*-butoxy-2-oxoethyl)-1,3-dihydroisobenzofuran-1-carboxylate (256b):**



Method A. Benzene (22 mL) was degassed using a stream of N_2 for 15 min. Aryl iodide **258** (100 mg, 0.22 mmol, 1.0 eq.), Bu_3SnH (64 μL, 0.24 mmol, 1.1 eq.) and AIBN (3.57 mg, 0.02 mmol, 0.1 eq.) were added and the resulting mixture was heated to reflux for 12 h. As TLC showed unreactive starting material, additional Bu_3SnH (64 μL, 0.24 mmol, 1.1 eq.) and AIBN (3.57 mg, 0.02 mmol, 0.1 eq.) were added and the resulting mixture was heated to reflux for 12 h. The solvent was concentrated under reduced pressure and the crude mixture was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give benzofuran derivative **256b** as a colorless oil (34.7 mg, 48%).

Method B. 2-Iodobenzyl alcohol **257** (1.71 g, 7.3 mmol, 1.0 eq.), fumarate **204a** (2.0 g, 8.7 mmol, 1.2 eq.), $Pd(OAc)_2$ (16 mg, 0.07 mmol, 0.01 eq.), P(*o*-tol)$_3$ (44 mg, 0.14 mmol, 0.02 eq.) and Et_3N (1.27 mL, 9.1 mmol, 1.25 eq.) were mixed together and the resulting mixture was heated to 85 °C for 12 h. As TLC showed unreactive starting material, additional $Pd(OAc)_2$ (16 mg, 0.07 mmol, 0.01 eq.), P(*o*-tol)$_3$ (44 mg, 0.14 mmol, 0.02 eq.) were added and the reaction mixture was heated to 85 °C for another 12 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (hexanes/EtOAc 20:1, 15:1, 10:1) to give benzofuran derivative **256b** as a colorless oil (1.69 g, 69%). R*f* 0.51 (hexanes/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 4H, Ar-*H*), 5.35 (d, *J* = 12 Hz, 1H, C*H*$_2$O), 5.17 (d, *J* = 12 Hz, 1H, C*H*$_2$O), 3.27 (d, *J* = 16 Hz, 1H, C*H*$_2$CO$_2$^{t}Bu), 2.80 (d, *J* = 16 Hz, 1H, C*H*$_2$CO$_2$^{t}Bu), 1.42 (s, 9H, C(C*H*$_3$)$_3$), 1.39 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.7, 139.5, 139.4, 128.6, 127.4, 121.8, 121.0, 88.3, 81.7, 80.8, 73.7, 44.2, 27.9 (3C), 27.8 (3C); IR (film) 2978, 2932, 2868, 1732, 1476, 1459, 1368, 1252, 1154, 1063, 845, 741 cm^{-1}; MS (CI) *m/z* 335 $[M + H]^+$, 352 $[M + NH_4]^+$; HRMS (CI) calc for $C_{19}H_{27}O_5$ $[M + H]^+$ 335.1858. Found: 335.1857; Anal. Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.26; H, 7.84.

Diphenyldiazomethane (261):[98]

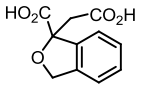


<u>Caution:</u> Diazo compounds are known to be explosive and ground glass is thought to catalyse the explosive decomposition of diazomethane. Although I had no explosions while working with diphenyldiazomethane, suitable safety protections were taken and all manipulations were conducted behind safety shields.

Oxalyl chloride (0.93 mL, 10.70 mmol, 1.05 eq.) was added dropwise to a stirred solution of DMSO (0.80 mL, 11.21 mmol, 1.10 eq.) in THF (100 mL) at −55 °C. The reaction was maintained at −55 °C until gas evolution ceased (~20 min) at which point the reaction was cooled further to −78 °C. A solution of benzophenone hydrazone **260** (2.0 g, 10.19 mmol, 1.0 eq.) and Et_3N (3.01 mL, 21.40 mmol, 2.1 eq.) in THF (10 mL) were added dropwise to provide a deep red solution containing a white precipitate. The reaction mixture was maintained at −78 °C with stirring for 1 h and was filtered under reduced pressure under a nitrogen atmosphere into a round bottom flask. The solvent was concentrated under reduced pressure to give nearly pure diphenyldiazomethane **261** (1.95 g, 99%) as a thick red oil which solidified on cooling. Trace impurities could be removed by low temperature recrystallization

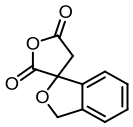
(Pentane) to provide deep red crystals. Mp 29 – 30 °C (lit.[98] 29 – 30 °C). Data in accordance with the literature.

1-(Carboxymethyl)-1,3-dihydroisobenzofuran-1-carboxylic acid (256a):



Di-ester **256b** (398 mg, 1.19 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (2.0 mL) and the solution was cooled to 0 °C. TFA (1.34 mL) was added dropwise and the reaction was stirred for 1 h at 0 °C and for 2 h at room temperature. As the TLC showed unreactive starting material, additional TFA (1.33 mL) was added and the reaction was stirred for further 1 h. The reaction mixture was concentrated under reduced pressure to give di-acid **256a** as a brown solid (255 mg, 99%) which was used without any further purification. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.49 - 7.39 (m, 4H, Ar-*H*), 5.34 (d, *J* = 12.4 Hz, 1H, C*H*$_2$O), 5.23 (d, *J* = 12.4 Hz, 1H, C*H*$_2$O), 3.50 (d, *J* = 16.4 Hz, 1H, C*H*$_2$CO$_2$H), 2.87 (d, *J* = 16.4 Hz, 1H, C*H*$_2$CO$_2$H); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.1, 170.4, 140.2, 139.8, 129.5, 128.4, 122.7, 121.8, 88.5, 73.7, 41.2; IR (film) 2983, 2879, 1722, 1459, 1396, 1342, 1205, 1180, 1062, 1002, 738 cm^{-1}; MS (ESI) *m/z* 221 [M – H]$^-$; HRMS (ESI) calc for $C_{11}H_9O_5$ [M – H]$^-$ 221.0450. Found: 221.0446.

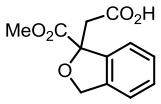
2*H*,3'*H*-Spiro[furan-3,1'-isobenzofuran]-2,5(4*H*)-dione (265):



Di-acid **256a** (250 mg, 1.12 mmol, 1.0 eq.) was suspended in CH_2Cl_2 (5 mL) and cooled to 0 °C. TFAA (312 μL, 2.50 mL, 2.0 eq.) was added and the reaction mixture was stirred for 2 h. The solvent was concentrated under reduced pressure and the residue was taken up in $CHCl_3$ (10 mL), washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give anhydride **265** as brown solid (200 mg, 87%) which was used without any further purification. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.59 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.51 – 7. 42 (m, 3H, Ar-*H*), 5.31 (d, *J* = 12.4 Hz, 1H, *CH*$_2$O), 5.27 (d, *J* = 12.4 Hz, 1H, *CH*$_2$O), 3.68 (d, *J* = 18.8 Hz, 1H, *CH*$_2$CO), 3.51 (d, *J* = 19.2 Hz, 1H, *CH*$_2$CO); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.9, 169.7, 142.0,

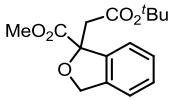
138.2, 131.5, 130.2, 123.5, 123.2, 90.4, 75.7, 42.8; MS (EI) *m/z* 222 $[M + NH_4]^+$; HRMS (EI) calc for $C_{11}H_{12}NO_4$ $[M + NH_4]^+$ 222.0766. Found: 222.0763.

2-(1-(Methoxycarbonyl)-1,3-dihydroisobenzofuran-1-yl)acetic acid (266):



A mixture of anhydride **265** (200 mg, 0.9 mmol, 1.0 eq.) and MeONa (79 mg, 1.45 mmol, 1.5 eq.) in MeOH (10 mL) was heated to reflux for 12 h. H_2O (5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give methyl ester **266** (163 mg, 71%) as a brown solid which was used without any further purification. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.41 – 7.32 (m, 4H, Ar-*H*), 5.22 (d, *J* = 12,4 Hz, 1H, CH_2O), 5.15 (d, *J* = 12.4 Hz, 1H, CH_2O), 3.65 (s, 3H, OMe), 3.48 (d, *J* = 16.4 Hz, 1H, CH_2CO$_2$H), 2.81 (d, *J* = 16.4 Hz, 1H, CH_2CO$_2$H); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.8, 171.6, 141.6, 141.4, 130.7, 129.6, 123.9, 123.2, 89.9, 75.0, 53.4, 44.5; IR (film) 3493, 2954, 2933, 1731, 1459, 1436, 1203, 1091, 1062, 781 cm^{-1}; MS (CI) *m/z* 254 $[M + NH_4]^+$; HRMS (CI) calc for $C_{16}H_{16}NO_5$ $[M + NH_4]^+$ 254.1028. Found: 254.1032; Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.05; H, 5.16.

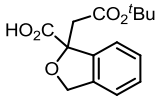
Methyl-1-(2-*tert*-butoxy-2-oxoethyl)-1,3-dihydroisobenzofuran-1-carboxylate (268):



A mixture of methyl ester **266** (151 mg, 0.63 mmol, 1.0 eq.) and *tert*-butyl *N*,*N*'-diisopropylcarbamimidate **227** (400 mg, 1.59 mmol, 2.5 eq.) in CH_2Cl_2 (3 mL) was heated to reflux for 2 h. The solvent was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 20:1, 10:1, 5:1) to give *tert*-butyl ester **268** (95 mg, 51 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 3H, Ar-*H*), 7.24 – 7.22 (m, 1H, Ar-*H*), 5.34 (d, *J* = 9.6 Hz, 1H, CH_2O), 5.21 (d, *J* = 10.0 Hz, 1H, CH_2O), 3.74 (s, 3H, OMe), 3.39 (d, *J* = 12.4 Hz, 1H, CH_2CO$_2$H), 2.78 (d, *J* = 12.8 Hz, 1H, CH_2CO$_2$H), 1.40 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 168.6, 139.1 (2C), 128.9, 127.7, 122.1, 121.1, 88.3, 81.2, 73.7, 52.6, 44.8, 27.9 (3C); IR (film) 2977, 1731, 1459, 1367, 1159, 1062, 742, 622 cm^{-1}; MS (CI) *m/z* 310 [M +

$NH_4]^+$; HRMS (CI) calc for $C_{16}H_{24}NO_5$ [M + $NH_4]^+$ 310.1654. Found: 310.1659; Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.80; H, 6.81.

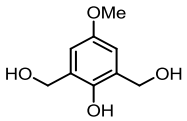
1-(2-*tert*-Butoxy-2-oxoethyl)-1,3-dihydroisobenzofuran-1-carboxylic acid (3):



Me_3SnOH (560 mg, 3.1 mmol, 3.0 eq.) was added to *tert*-butyl ester **268** (277 mg, 0.94 mmol, 1.0 eq.) in $ClCH_2CH_2Cl$ (20 mL) and the resulting mixture was heated at 85 °C in a sealed tube for 12 h. The solvent was concentrated under reduced pressure and the crude product was dissolved in EtOAc (20 mL) and washed with 1 N HCl (2 × 20 mL) and brine (20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CH_2Cl_2/MeOH 15:1) to give acid **3** (246 mg, 94 %) as a colorless oil. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.40 (d, J = 7.2 Hz, 1H, Ar-*H*), 7.35 – 7.27 (m, 2H, Ar-*H*), 7.20 (d, J = 6.8 Hz, 1H, Ar-*H*), 5.32 (d, J = 12.4 Hz, 1H, CH_2O), 5.20 (d, J = 12.4 Hz, 1H, CH_2O), 3.37 (d, J = 16.4 Hz, 1H, CH_2CO$_2$H), 2.75 (d, J = 16 Hz, 1H, CH_2CO$_2$H), 1.37 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, acetone-d_6) δ 174.4, 169.9, 141.4, 141.0, 130.6, 129.5, 124.1, 123.0, 90.1, 81.9, 75.0, 46.1, 29.1 (3C); MS (ESI) *m/z* 277 [M – H]$^-$; HRMS (ESI) calc for $C_{15}H_{17}O_5$ [M – H]$^-$ 277.1076. Found: 277.1075.

Towards the Total Synthesis of Lactonamycin (1)

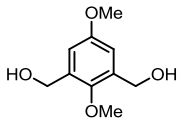
(2-Hydroxy-5-methoxy-1,3-phenylene)dimethanol (275):[107a]



Grounded *p*-Methoxyphenol **274** (31 g, 0.25 mol, 1.0 eq.) was suspended in H_2O (200 mL) and degassed by passing through a stream of N_2 for 30 min. Formaldehyde (37% in H_2O, 45 mL, 0.60 mol, 2.4 eq.) and CaO (7.01 g, 0.125 mol, 0.5 eq.) were added at room temperature and the mixture was stirred for 5 d with exclusion from light. Glacial acetic acid (20 mL) was added and the mixture was heated until the most of the solid was dissolved. Charcoal (10 g) was added and the solution was

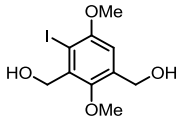
filtered while it was hot. The filtrate was cooled to room temperature and placed in a freezer at –30 °C for 12 h. The resulting mixture was allowed to warm to room temperature and filtered to give a white solid. The solid was subsequently washed with cold H_2O and under reduced pressure to give phenol **275** (29.6 g, 64%) as a white solid. R*f* 0.32 (hexanes/EtOAc 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 2H, Ar-*H*), 4.78 (s, 4H, C*H*$_2$O), 3.75 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 145.6, 136.2 (2C), 111.6 (2C), 63.6 (2 C), 55.8; Mp 126 – 127 ºC (lit.[107a] 124 – 125 °C); IR (film) 2938, 1731, 1611, 1483, 1314, 860, 789 cm^{-1}; MS (ES) *m/z* 184 $[M]^+$; HRMS (ES) calc for $C_9H_{12}O_4$ $[M]^+$ 184.0732. Found: 184.0736; Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.63; H, 6.52. Data in accordance with the literature.

(2,5-Dimethoxy-1,3-phenylene)dimethanol (276):[181]



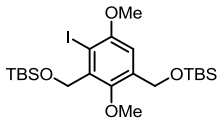
Phenol **275** (27.6 g, 0.150 mol, 1.0 eq.) was dissolved in acetone (800 mL). K_2CO_3 (24.9 g, 0.180 mol, 1.2 eq.) and dimethylsulfate (15.6 mL, 0.165 mol, 1.1 eq.) were added at room temperature and the reaction was heated to reflux for 12 h. The reaction mixture was allowed to cool to room temperature and was quenched by addition of a mixture of MeOH (75 mL) and saturated NH_3-solution (30 mL). The insoluble solid was filtered off, washed with EtOAc (50 mL) and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (500 mL) at 60 °C and allowed to cool to room temperature. Saturated aqueous $NaHCO_3$ (150 mL) and H_2O (75 mL) was added and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The yellow residue was purified by recrystallization (EtOAc/Et_2O 2:1) to give methoxyether **276** (15.7 g, 53%) as a white solid. R*f* 0.40 (EtOAc/hexanes 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 2H, Ar-*H*), 4.70 (s, 4H, C*H*$_2$O), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 149.4, 134.9 (2C), 113.5 (2C), 62.2, 60.9 (2C), 55.6; Mp 106 – 108 ºC (lit.[181] 106 – 108 °C); IR (film) 3261, 3165, 2923, 2834, 2359, 1607, 1473, 1362, 1317, 1234, 1208, 1146, 1052, 997, 949, 850 cm^{-1}; MS (ES) *m/z* 198 $[M]^+$; HRMS (ES) calc for $C_{10}H_{14}O_4$ $[M]^+$ 198.0892. Found: 198. 0894; Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.57; H, 7.00. Data in accordance with the literature.

(4-Iodo-2,5-dimethoxy-1,3-phenylene)dimethanol (277):



Methoxyexther **276** (7.0 g, 35 mmol, 1.0 eq.) was dissolved in $CHCl_3$ (100 mL) and the resulting mixture was cooled to 0 °C. $Ag(O_2CCF_3)$ (11.7 g, 52.9 mmol, 1.5 eq.) was added followed by immediate dropwise addition of iodine (9.4 g, 37 mmol, 1.05 eq.) in $CHCl_3$ (200 mL). The reaction mixture was stirred for 1 h at 0 °C. As TLC showed incomplete conversion, additional $Ag(O_2CCF_3)$ (1.9 g, 8.75 mmol, 0.25 eq.) and a solution of iodine (2.2 g, 8.75 mmol, 0.25 eq.) in $CHCl_3$ (100 mL) were added and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was filtered through cotton and SiO_2 and washed with CH_2Cl_2/MeOH (25:1). The crude product was purified by recrystallization (Pentane/EtOAc 1:1) to give aryl iodide **277** (8.7 g, 76%) as a white solid. R*f* 0.41 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H, Ar-*H*), 4.87 (s, 2H, C*H*$_2$O), 4.74 (s, 2H, C*H*$_2$O), 3.88 (s, 3H, OMe), 3.84 (s, 3H, OMe); ^{13}C NMR (100 MHz , $CDCl_3$) δ 154.9, 150.4, 137.7, 135.1, 110.4, 91.7, 64.1, 63.3, 60.7, 56.9; Mp 126 – 127 ºC; IR (film) 3338, 2849, 1582, 1424, 1395, 1314, 1227, 1080, 1007 cm^{-1}; MS (CI) : *m/z* 342 $[M + NH_4]^+$; HRMS (CI) calc for $C_{10}H_{17}NIO_4$ $[M + NH_4]^+$ 342.0202. Found: 342.0199; Anal. Calcd. For $C_{10}H_{13}IO_4$: C, 37.06; H, 4.04. Found: C, 36.94; H, 4.07.

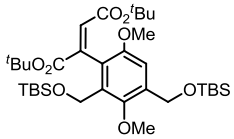
(4-Iodo-2,5-dimethoxy-1,3-phenylene)bis(methylene)bis(oxy)bis(*tert*-butyldimethylsilane) (278):



Iodide **277** (4.3 g, 13.1 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (60 mL) and the resulting mixture was cooled to 0 °C. Imidazole (2.7 g, 39.4 mmol, 3.0 eq.) and TBSCl (4.9 g, 32.8 mmol, 2.5 eq.) were added in portions and the resulting mixture was stirred at 0 °C for 2 h. H_2O (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 200:1, 100:1, 50:1) to give TBS-protected alcohol **278** (6.2 g, 85%) as a white solid. R*f* 0.69 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H, Ar-*H*), 4.84 (s, 2H, C*H*$_2$O), 4.77 (s, 2H, C*H*$_2$O), 3.86 (s, 3H, OMe), 3.78 (s, 3H, OMe), 0.95 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.93 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.19 (s, 6H, Si*Me*$_2$), 0.12 (s, 6H, Si*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 149.6, 137.0, 135.6, 109.4, 91.7, 64.1, 63.0, 59.8, 56.7,

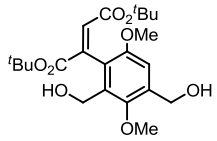
26.0 (3C), 25.8 (3C), 18.5, 18.3, -5.1 (2C), -5.3 (2C); Mp 38 – 40 °C; IR (film) 2953, 2930, 2885, 2856, 1583, 1460, 1424, 1368, 1255, 1109, 1075, 1007, 837, 776 cm^{-1}; MS (CI) *m/z* 570 $[M + NH_4]^+$; HRMS (CI) calc for $C_{22}H_{44}NIO_4Si_2$ $[M + NH_4]^+$ 570.1932. Found: 570.1942; Anal. Calcd. for $C_{22}H_{41}IO_4Si_2$: C, 47.81; H, 7.48. Found: C, 47.85; H, 7.53.

Di-*tert*-butyl-2-(2,4-bis((*tert*-butyldimethylsilyloxy)methyl)-3,6-dimethoxyphenyl)fumarate (279):



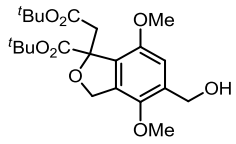
Iodide **278** (6.0 g, 10.9 mmol, 1.0 eq.) was dissolved in toluene (50 mL) and stannane **236** (6.8 g, 13.1 mmol, 1.2 eq.) was added *via* syringe. CuI (0.52 g, 2.7 mmol, 0.25 eq.) and $Pd(PPh_3)_4$ (0.63 g, 0.55 mmol, 5 mol%) were added. The reaction mixture was heated to 120 °C for 12 h. As crude ^1H NMR showed incomplete conversion, additional stannane **236** (1.13 g, 2.2 mmol, 0.2 eq.), CuI (0.52 g, 2.7 mmol, 0.25 eq.) and $Pd(PPh_3)_4$ (0.63 g, 0.55 mmol, 5 mol%) were added and the reaction mixture was stirred for 12 h at 120 °C. The solvent was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (hexanes/EtOAc 50:1, 25:1, 10:1) and (hexanes/EtOAc 100:1, 50:1, 25:1) to give alkene **279** (5.32 g, 74%) as a yellow oil. R*f* 0.69 (hexanes/EtOAc 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H, Ar-*H*), 6.90 (s, 1H, C=C*H*), 4.83 (d, *J* = 13.6 Hz, 1H, CH_2O), 4.78 (d, *J* = 13.6 Hz, 1H, CH_2O), 4.57 (d, *J* = 10.8 Hz, 1H, CH_2O), 4.47 (d, *J* = 10.8 Hz, 1H, CH_2O), 3.75 (s, 3H, OMe), 3.74 (s, 3H, OMe), 1.44 (s, 9H, C(CH_3)$_3$), 1.17 (s, 9H, C(CH_3)$_3$), 0.95 (s, 9H, Si-C(CH_3)$_3$), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.11 (s, 6H, SiMe_2), 0.05 (s, 6H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 164.8, 152.9, 149.0, 140.5, 134.6, 131.7, 131.1, 124.8, 109.2, 81.4, 80.7, 62.7, 60.0, 57.6, 55.8, 27.9 (3C), 27.6 (3C), 26.1 (3C), 25.9 (3C), 18.6, 18.4, -5.3 (2C), -5.5 (2C); IR (film) 2954, 2931, 2887, 2857, 1711, 1462, 1368, 1252, 1155, 837, 777 cm^{-1}; MS (CI) *m/z* 653 $[M + H]^+$; HRMS (CI) calc for $C_{34}H_{61}O_8Si_2$ $[M + H]^+$ 653.3905. Found: 653.3921; Anal. Calcd. for $C_{34}H_{60}O_8Si_2$: C, 62.54; H, 9.26. Found: C, 62.47; H, 9.18.

Di-*tert*-butyl 2-(2,4-bis(hydroxymethyl)-3,6-dimethoxyphenyl)fumarate (280):



Alkene **279** (1.0 g, 1.53 mmol, 1.0 eq.) was dissolved in THF (7.5 mL) and the reaction mixture was cooled to 0 °C. Conc. HCl (1.21 mL) was added *via* syringe and the reaction mixture was stirred at 0 °C for 1 h. H_2O (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CH_2Cl_2/MeOH 200:1, 100:1, 50:1) to give alcohol **280** (544 mg, 84%) as a colorless oil. R*f* 0.34 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1H, Ar-*H*), 6.92 (s, 1H, C=C*H*), 4.77 (s, 2H, CH_2O), 4.53 (d, *J* = 11.6 Hz, 1H, CH_2O), 4.42 (d, *J* = 11.2 Hz, 1H, CH_2O), 3.89 (s, 3H, OMe), 3.75 (s, 3 H, OMe), 1.46 (s, 9H, C(CH_3)$_3$), 1.25 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.2, 152.6, 150.2, 139.7, 134.8, 133.3, 131.8, 124.4, 110.3, 82.5, 82.0, 63.1, 61.1, 58.1, 55.9, 27.8 (3C), 27.7 (3C); IR (film) 3442, 2977, 2937, 1708, 1641, 1602, 1461, 1369, 1251, 1153, 1070, 1010, 850, 769 cm^{-1}; MS (CI) *m/z* 447 [M + Na]$^+$; HRMS (CI) calc for $C_{22}H_{32}O_8Na$ [M + Na]$^+$ 447.1995. Found: 447.2000; Anal. Calcd. for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60. Found: C, 62.22; H, 7.56.

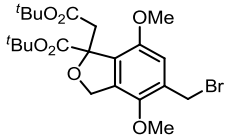
***tert*-Butyl-1-(2-*tert*-butoxy-2-oxoethyl)-5-(hydroxymethyl)-4,7-dimethoxy-1,3-dihydroisobenzofuran-1-carboxylate (281):**



Alcohol **280** (491 mg, 1.16 mmol, 1.0 eq.) was dissolved in THF (115 mL) and the reaction mixture was cooled to 0 °C. NaH (55 mg, 2.3 mmol, 2.0 eq.) was added and the reaction was stirred at 0 °C for 1 h. Additional NaH (27.5 mg, 1.16 mmol, 1.0 eq.) was added every hour for 2 h and the reaction mixture was allowed to stir at 0 °C. The reaction was quenched by addition of H_2O (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CH_2Cl_2/MeOH 200:1, 100:1, 50:1, 25:1) to give benzofuran derivative **281** (463 mg, 94%) as a yellow solid. R*f* 0.46 (hexanes/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H, Ar-*H*), 5.39 (d, *J* = 11.6 Hz, 1H, CH_2O), 5.25 (d, *J* = 12.0 Hz, 1H, CH_2O), 4.68

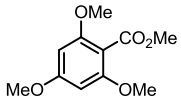
(s, 2H, CH_2OH), 3.80 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.47 (d, J = 16 Hz, 1H, CH_2C$O_2{}^t$Bu), 2.94 (d, J = 16 Hz, 1H, CH_2C$O_2{}^t$Bu), 1.38 (s, 9H, C(CH_3)$_3$), 1.33 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.3, 150.2, 145.4, 134.0, 132.3, 128.1, 110.7, 88.6, 81.3, 80.2, 72.4, 61.1, 60.0, 55.6, 41.1, 27.9 (3C), 27.7 (3C); Mp 74 – 76 °C; IR (film) 3442, 2977, 2929, 1735, 1637, 1486, 1465, 1367, 1249, 1160, 1049, 846 cm^{-1}; MS (CI) *m/z* 447 [M + Na]$^+$; HRMS (CI) calc for $C_{22}H_{32}O_8$Na [M + Na]$^+$ 447.1995. Found: 447.2003; Anal. Calcd. for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60. Found: C, 62.26; H, 7.75.

***tert*-Butyl-5-(bromomethyl)-1-(2-*tert*-butoxy-2-oxoethyl)-4,7-dimethoxy-1,3-dihydroisobenzofuran-1-carboxylate (272):**



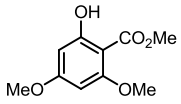
Alcohol **281** (1.49 g, 3.53 mmol, 1.0 eq.) was dissolved in DMF (17 mL) at room temperature. PPh_3 (1.84 mg, 7.06 mmol, 2.0 eq.) and CBr_4 (2.33 g, 7.06 mmol, 2.0 eq.) were added and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was filtered through silica (hexanes/EtOAc 10:1, 5:1) and the crude product was purified by silica gel column chromatography (hexanes/EtOAc 20: 1, 10:1, 5:1) to give bromide **272** (1.67 g, 97%) as a white solid. R*f* 0.85 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H, Ar-*H*), 5.38 (d, J = 12 Hz, 1H, CH_2O), 5.24 (d, J = 12 Hz, 1H, CH_2O), 4.56 (d, J = 10 Hz, 1H, CH_2Br), 4.51 (d, J = 9.6 Hz, 1H, CH_2Br), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.40 (d, J = 16 Hz, 1H, CH_2C$O_2{}^t$Bu), 2.98 (d, J = 15.6 Hz, 1H, CH_2C$O_2{}^t$Bu), 1.39 (s, 9H, C(CH_3)$_3$), 1.31 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.2, 150.2, 146.0, 133.0, 131.2, 129.7, 112.3, 88.8, 81.5, 80.3, 72.5, 60.1, 55.7, 41.1, 28.2, 27.9 (3C), 27.8 (3C); Mp 98 – 102 °C; IR (film) 2977, 2939, 2868, 2383, 1734, 1491, 1416, 1367, 1249, 1160, 1056, 847, 757 cm^{-1}; MS (EI) *m/z* 509 [M[^{79}Br] + Na]$^+$, 511 [M[^{81}Br] + Na]$^+$; HRMS (EI) calc for $C_{22}H_{31}{}^{79}BrO_7Na$, $C_{22}H_{31}{}^{81}BrO_7Na$ [M + Na]$^+$ 509.1151, 511.1142. Found: 509.1151, 511.1142; Anal. Calcd. for $C_{22}H_{31}BrO_7$: C, 54.22; H, 6.41. Found: C, 54.29; H, 6.46.

Methyl 2,4,6-trimethoxybenzoate (282):[31]



To a solution of 2,4,6-trihydroxybenzoic acid **128** (80 g, 0.42 mol, 1.0 eq.) in acetone (1.25 L) was added potassium carbonate (350 g, 2.53 mol, 6.0 eq.) and the suspension was cooled to 0 °C. Dimethylsulfate (241 mL, 2.53 mol, 6.0 eq.) was added and the reaction mixture was stirred for 2 h. The ice bath was removed and the reaction mixture was mechanically stirred for 21 h at room temperature. The reaction was quenched by carefully addition of a mixture of MeOH (75 mL) and saturated NH_3-solution (25 mL). After 1 h stirring, the insoluble solid was filtered off into saturated NH_3/saturated NH_4Cl (250 mL, 1:4) under stirring. After 30 min of stirring, the solution was filtered off again and the solution was concentrated under reduced pressure. The residue aqueous layer was extracted with Et_2O (1 × 400 mL, 3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The dark brown residue was dried for 12 h under reduced pressure to give a brown solid, which was purified by recrystallization (*c*-hexane/EtOAc 150 mL, 6:1) to give ester **282** (79.0 g, 82%) as a white solid. R*f* 0.47 (EtOAc/hexanes 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.79 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 162.5, 158.6 (2C), 90.5 (3C), 55.9 (2C), 55.4, 52.9. Data in accordance with the literature.

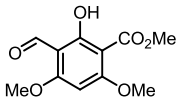
Methyl 4,6-dimethoxy-2-hydroxy-benzoate (129):[31]



Ester **282** (41 g, 180 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (800 mL) and cooled to −78 °C. BCl_3 (1.0 M in CH_2Cl_2, 217 mL, 217 mmol, 1.2 eq.) was added slowly maintaining the internal temperature below −73 °C. After 1 h, the cooling was removed and the solution was further stirred for 12 h at room temperature. Since TLC analysis showed some unreacted starting material, the reaction mixture was recooled to −78 °C again and additional BCl_3 (1.0 M in CH_2Cl_2, 72 mL, 72 mmol, 0.4 eq.) was added. The reaction mixture was stirred for 1 h at −78 °C and for 12 h at room temperature. The reaction was quenched with 10% HCl (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (300 mL) and brine (300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by recrystallization (*c*-hexane/EtOAc 20:1) to give a first

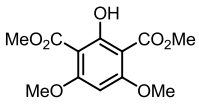
batch of phenol **129** (21.8 g, 57%) and a second batch of phenol **129** (9.9 g, 26%) as a white solid. R*f* 0.63 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.06 (s, 1H), 6.13 (d, J = 2.2 Hz, 1H), 5.98 (d, J = 2.2 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 166.0, 165.4, 162.2, 96.6, 93.4, 91.6, 56.1, 55.5, 52.4; MS (CI) *m/z* 213 $[M + H]^+$; HRMS (CI) calc for $C_{10}H_{13}O_5$ $[M + H]^+$ 213.0762. Found: 213.0763. Data in accordance with the literature.

Methyl 2,4-dimethoxy-5-formyl-6-hydroxy-benzoate (283):[31]



$POCl_3$ (24.5 mL, 0.27 mol, 2.0 eq.) was added to DMF (52 mL, 0.67 mol, 5.0 eq.) at 0 °C. The resulting mixture was stirred for 1 h and MeCN (80 mL) was added. Phenol **129** (28.3 g, 0.13 mmol, 1.0 eq.) was added in portions and the reaction mixture was stirred for 15 min. The cooling bath was removed and the clear yellow-orange solution was stirred for 12 h at room temperature. The reaction mixture was cooled to 0 °C and the reaction was quenched by slow addition of cold H_2O (185 mL). The mixture was brought to pH 5-6 by addition of 5 M NaOH (250 mL) and the aqueous layer was extracted with EtOAc (1 × 200 mL, 3 × 150 mL). The combined organic layers were washed with brine (2 × 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by recrystallization (EtOAc) to give a first batch of aldehyde **283** (18.95 g, 78 mmol, 59%) as a white solid. The mother liquid was concentrated under reduced pressure and purified by silica gel column chromatography (CH_2Cl_2/MeOH 100:1) to give aldehyde **283** (3.02 g, 9%) and starting material **129** (3.66 g, 11%). R*f* 0.15 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.74 (s, 1H), 10.11 (s, 1H), 5.94 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0 (2C), 165.3, 162.9, 105.5 (2C), 104.4, 85.9, 56.3, 56.0, 52.4; IR (film) 3438, 1725, 1632, 1476, 1277, 1217, 1126, 1107 cm^{-1}; MS (CI) *m/z* 241 $[M + H]^+$; HRMS (CI) calc for $C_{11}H_{13}O_6$ $[M + H]^+$ 241.0703. Found: 241.0712. Data in accordance with the literature.

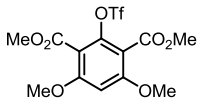
1,3-Dimethyl 4,6-dimethoxy-2-hydroxydibenzoate (130):[31]



Aldehyde **283** (9.00 g, 37.5 mmol, 1.0 eq.) was dissolved in THF (280 mL), H_2O (220 mL) and DMSO (22 mL) and cooled to 15 °C. 2-Methyl-2-butene (80 mL, 0.75 mol, 20.0 eq.) and

amidosulfonic acid (12.4 g, 127 mmol, 3.4 eq.) were added successively. After dissolution of the acid, $NaClO_2$ (80%, 13.5 g, 0.12 mmol, 3.2 eq.) in H_2O (36 mL) was rapidly (< 5 min) added *via* a dropping funnel maintaining the internal temperature below 30 °C. After 30 min of stirring, the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (150 mL). The aqueous layer was extracted with EtOAc (1 × 500 mL, 5 × 100 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in DMF (100 mL) at room temperature. $KHCO_3$ (4.51 g, 45.0 mmol, 1.2 eq.) and dimethyl sulfate (3.9 mL, 41 mmol, 1.1 eq.) were added successively and the mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of saturated NH_3/saturated NH_4Cl (25 mL, 1:4) and the resulting mixture was stirred for 30 min. H_2O (350 mL) was added and the insoluble solid was filtered off and washed with additional H_2O (150 mL). After drying by suction, EtOAc (60 mL) was added to the solid and the suspension was stirred at 50 °C for 10 min (rotavapor). Pentane (60 mL) was added and the mixture was filtered after cooling. The solid was washed first with EtOAc/Pentane (~100 mL, 1:1) and finally with pentane to give a first batch of di-ester **130** (8.3 g, 82%). The mother liquid was concentrated under reduced pressure and purified by recrystallization as described above to give a further batch of di-ester **109** (0.25 g, 2%). R*f* 0.39 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.31 (s, 1H), 5.95 (s, 1H), 3.88 (s, 6H), 3.85 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (2C), 163.0 (2C), 162.3, 100.7, 86.9 (2C), 56.0 (2C), 52.3 (2C); IR (film) 3417, 2999, 2940, 1718, 1621, 1570, 1439, 1417, 1302, 1274, 1109 cm^{-1}; MS (CI) *m/z* 271 $[M + H]^+$; HRMS (CI) calc for $C_{12}H_{15}O_7$ $[M + H]^+$ 271.0819. Found: 271.0818. Data in accordance with the literature.

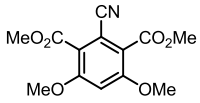
1,3-Dimethyl 4,6-dimethoxy-2-trifluormethylsulfonyldibenzoate (284):[31]



To a solution of phenol **130** (6.4 g, 27.6 mmol, 1.0 eq.) in CH_2Cl_2 (200 mL) at 0 °C were added pyridine (2.9 mL, 35.4 mmol, 1.5 eq.) and Tf_2O (5.2 mL, 30.7 mmol, 1.3 eq.) successively. After 2 h at 0 °C, H_2O (200 mL) was added to the orange reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (4 × 150 mL) and the combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by recrystallization (*c*-hexane/EtOAc 2:1) to give a first batch of triflate **284** (7.75 g, 81%) as colorless crystals. Rotary evaporation and recrystallization gave a second batch of triflate **284** (1.24 g, 14%). R*f* 0.27 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 3.91 (s, 6H), 3.88 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (2C), 160.6 (2C), 144.6, 118.3 (q, *J* = 318.1Hz), 110.3, 95.2 (2C),

56.6 (2C), 52.7 (2C); Mp (EtOAc) 87 – 90 °C (lit.[31] 87 – 90 °C); IR (film) 3010, 2962, 1743, 1727, 1568, 1567, 1400, 1241 cm^{-1}; MS (CI) *m/z* 420 $[M + NH_4]^+$; HRMS (CI) calc for $C_{13}H_{17}F_3O_9SN$ $[M + NH_4]^+$ 420.0576. Found: 420.0572. Data in accordance with the literature.

1,3-Dimethyl 2-cyano-4,6-dimethoxy-dibenzoate (131):[31]

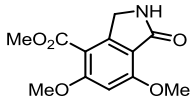


Method A. Triflate **284** (14.5 g, 36.0 mmol, 1.0 eq.) was degassed in DMF (120 mL) for 2 h by bubbling N_2 through the reaction mixture. Dppf (4.0 g, 7.2 mmol, 0.2 eq.) and Pd_2dba_3 (1.7 g, 1.8 mmol, 0.05 eq.) were added and the resulting mixture was heated to 60 °C. At 60 °C, $Zn(CN)_2$ (12.7 g, 108 mmol, 3.0 eq.) was added in portions over 6 h. After the addition was complete, Pd_2dba_3 (0.68 g, 0.6 mmol, 0.02 eq.) was added again and the mixture was stirred for 12 h at 60 °C. The reaction mixture was allowed to cool down to room temperature and quenched with saturated NH_3/saturated NH_4Cl (600 mL, 1:9), H_2O (400 mL) and EtOAc (1.5 L). The cloudy dark heterogeneous mixture was heated to 30 – 40 °C and turned into two clear phases after 20 min of stirring. The aqueous layer was extracted with EtOAc (3 × 200 mL) and the combined organic layers were washed with H_2O (2 × 150 mL) and brine (200 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The dark residue was taken up in CH_2Cl_2 (100 mL) and heated gently at 40 °C. After cooling to room temperature, the solid was filtered and washed with pentane. To the pale yellow solid were added EtOAc (60 mL) and the suspension was heated at 50 °C. After cooling to room temperature, the solid was filtered and pentane/EtOAc (1:1) was used to transfer all material from the flask into the sinter. The shining white solid was gently washed twice with EtOAc and pentane and dried under reduced pressure. Nitrile **131 (**5.77 g, 57%) was obtained as a shining white microcrystalline solid. The filtrate was combined and concentrated under reduced pressure. Silica gel column chromatography of the brown residue gave another batch of nitrile **110** as a white to light brown solid (3.87 g, 39%).

Method B. Triflate **284** (22.5 g, 55.9 mmol, 1.0 eq.) was dissolved in DMF (120 mL). $Zn(CN)_2$ (3.9 g, 33.5 mmol, 0.6 eq.), Zn (438 mg, 6.7 mmol, 12 mol%), dppf (1.2 g, 2.2 mmol, 4 mol%) and $Pd_2(dba)_3$ (1.0 g, 1.1 mmol, 2 mol%) were added and the resulting mixture was stirred at 120 °C for 2 h. The reaction mixture was allowed to cool down to room temperature and quenched with saturated NH_3/saturated NH_4Cl (450 mL, 1:9), H_2O (300 mL) and EtOAc (1 L). The cloudy dark heterogeneous mixture was heated to 30 – 40 °C and turned into two clear phases after 20 min of stirring. The aqueous layer was extracted with EtOAc (3 × 150 mL) and the combined organic layers were washed

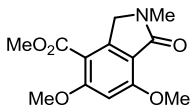
with H_2O (2 × 100 mL) and brine (150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was triturated with EtOAc, filtered, wash with EtOAc and dried to give nitrile **131** as a white powder (13.6, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (s, 1H), 3.96 (s, 6H), 3.94 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (2C), 160.2 (2C), 118.7, 114.6, 112.8 (2C), 99.5, 56.6 (2C), 53.0 (2C); Mp (Pentane) 169 – 172 °C (lit.[31] 169 – 172 °C); IR (film) 2987, 2954, 2233, 1720, 1576, 1455, 1426, 1328, 1316, 1116, 1066 cm^{-1}; MS (CI) *m/z* 297 [M + NH_4]$^+$; HRMS (CI) calc for $C_{13}H_{17}N_2O_6$ [M + NH_4]$^+$ 297.1084. Found: 297.1087; Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69; N, 5.02. Found: C, 55.89; H, 4.75; N, 5.01. Data in accordance with the literature.

Methyl 5,7-dimethoxy-1-oxoisoindoline-4-carboxylate (285):[31]



Nitrile **131** (3.00 g, 10.7 mmol, 1.0 eq.) was dissolved in DMF (200 mL) in an autoclave and a Raney Nickel suspension (20 mL, 50% in H_2O) was added. The resulting mixture was stirred for 3 d under H_2 atmosphere at 5 bar pressure. The mixture was filtered over a small pad of Celite and washed several times with hot DMF (~100 °C). The solvent was concentrated under reduced pressure and the residue was triturated using EtOAc/MeOH (25 mL, 15:1) at 50 °C. The solid was filtered, washed with EtOAc and dried to give isoindole **285** as a white solid (2.54 g, 94%). R*f* 0.39 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (bs, 1H), 6.47 (s, 1H), 4.59 (s, 2H), 4.04 (s, 3H), 4.00 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 164.8, 161.4 (2C), 151.2, 107.6, 98.4, 94.9, 57.5, 56.7, 47.0, 21.7; Mp (Pentane) 228 – 235 °C (lit.[31] 228 – 235 °C); IR (film) 3354, 1699, 1661, 1596, 1402, 1258 cm^{-1}; MS (CI, NH_3) *m/z* 252 [M + H]$^+$; HRMS (CI) calc for $C_{12}H_{14}NO_5$ [M + H]$^+$ 252.0872. Found: 252.0872. Data in accordance with the literature.

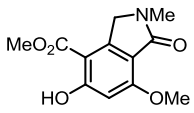
Methyl 5,7-dimethoxy-2-methyl-1-oxoisoindoline-4-carboxylate (132):[31]



Lactam **285** (9.00 g, 35.9 mmol, 1.0 eq.) was suspended in DMF (300 mL). The mixture was degassed by bubbling N_2 through the reaction mixture for 3 h. The mixture was cooled to 0 °C and NaH (60 % dispersion in mineral oil, 1.58 g, 39.5 mmol, 1.1 eq.) was added in portions over 15 min. The resulting

mixture was stirred at 0 °C for 15 min and MeI (4.1 mL, 64.6 mmol, 1.8 eq) was added to the suspension. After stirring for 15 min at 0 °C, the reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Half saturated aqueous NH_4Cl solution (200 mL) and EtOAc (300 mL) were added and the aqueous layer was extracted with $CHCl_3$ (2 × 150 mL) and $CHCl_3/^iPrOH$ (4 × 100 mL, 5:1). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue solid was taken up in $Na_2S_2O_3$ solution (2 M, 140 mL) and $CHCl_3/^iPrOH$ (400 mL, 5:1), and stirred for 30 min. The phases were separated and the aqueous layer was extracted with $CHCl_3/^iPrOH$ (4 × 100 mL, 5:1). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. EtOAc (25 mL) and MeOH (5 drops) were added to the light yellow residue and the resulting mixture was heated at 50 °C. After cooling to room temperature, the solid was filtered, washed with EtOAc and pentane and dried under reduced pressure to give lactam **132** as a white solid (8.36 g, 88%). R*f* 0.48 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (s, 1H), 4.47 (s, 2H), 4.01 (s, 3H), 3.97 (s, 3H), 3.88 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.3, 164.2, 160.9, 148.4, 113.8, 107.2, 95.0, 56.6, 56.1, 53.2, 51.7, 29.0; Mp (Pentane) 196 – 201 °C (lit.[31] 196 – 201 °C); IR (film) 1713, 1672, 1596, 1467, 1431, 1336, 1271, 1219 cm^{-1}; MS (CI, NH_3) *m/*z 266 $[M + H]^+$; HRMS (CI) calc for $C_{13}H_{16}NO_5$ $[M + H]^+$ 266.1033. Found: 266.1028; Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.73; H, 5.80; N, 5.26. Data in accordance with the literature.

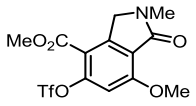
Methyl 5-hydroxy-7-methoxy-2-methyl-1-oxoisoindoline-4-carboxylate (287):[31]



Lactam **132** (9.00 g, 33.9 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (400 mL) and cooled to –78 °C. BCl_3 (1 M in CH_2Cl_2, 75 mL, 75.0 mmol, 2.2 eq.) was added over 1 h. After 3 h stirring at –78 °C, 10% aqueous HCl (130 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was transferred into a 3 L flask containing 10% aqueous HCl (1.2 L) and CH_2Cl_2 (400 mL) and stirred for 2 h. The aqueous layer was extracted with $CHCl_3$ (3 × 250 mL) and $CHCl_3/^iPrOH$ (2 × 250 mL, 5:1). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure. EtOAc (25 mL) and MeOH (5 drops) were added and the resulting mixture was heated at 50 °C. After cooling to room temperature, the solid was filtered, washed with EtOAc and pentane and dried under reduced pressure to give phenol **287** as a white solid (7.82 g, 92%). R*f* 0.44 (CH_2Cl_2/MeOH 15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (s, 1H), 6.47 (s, 1H), 4.47 (s, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz,

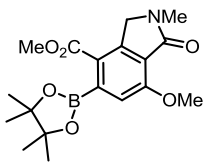
$CDCl_3$) δ 170.0, 167.2, 166.4, 162.4, 147.4, 114.0, 100.9, 99.3, 56.2, 53.4, 52.3, 29.0; Mp (Pentane) 198 – 203 °C (lit.[31] 198 – 203 °C); IR (film) 1713, 1672, 1596, 1467, 1431, 1336, 1271, 1219 cm^{-1}; MS (CI, NH_3) *m/z* 252 $[M + H]^+$; HRMS (CI) calc for $C_{12}H_{14}NO_5$ $[M + H]^+$ 252.0872. Found: 252.0871. Data in accordance with the literature.

Methyl 7-methoxy-2-methyl-1-oxo-5-(((trifluoromethyl)sulfonyl)oxy)isoindoline-4-carboxylate (126):[31]



Phenol **287 (**8.30 g, 33.0 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (100 mL) with stirring. Et_3N (6.95 mL, 50.0 mmol, 1.5 eq.) and $PhNTf_2$ (14.2 g, 39.7 mmol, 1.2 eq.) were added and the resulting mixture was heated to 40 °C and stirred for 48 h. The reaction was allowed to cool to room temperature and H_2O (80 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by recrystallization (EtOAc/MeOH 30:1) to give triflate **126** (12.3 g, 92%) as a white solid. R*f* 0.49 (CH_2Cl_2/MeOH 15:1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.65 (s, 2H), 4.02 (s, 3H), 3.97 (s, 3H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 163.1, 160.5, 151.6, 148.6, 121.1, 120.8, 114.2 (q, *J* = 362.9 Hz), 105.9, 56.8, 53.2, 52.4, 29.2; Mp (Et_2O) 152 – 157 °C (lit.[31] 152 – 157 °C); IR (film) 3061, 2960, 1727, 1694, 1632, 1423, 1287, 1206, 1137 cm^{-1}; MS (CI, NH_3) *m/z* 384 $[M + H]^+$; HRMS (CI) calc for $C_{13}H_{13}F_3NO_7S$ $[M + H]^+$ 384.0365. Found: 384.0367; Anal. Calcd for $C_{13}H_{12}F_3NO_7S$: C, 40.74; H, 3.16; N, 3.65. Found: C, 40.79; H, 3.14; N, 3.57. Data in accordance with the literature.

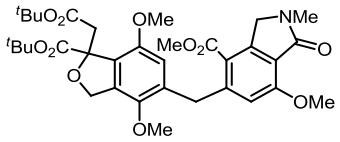
Methyl 7-methoxy-2-methyl-1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindoline-4-carboxylate (273):



Triflate **133** (6.40 g, 16.7 mmol, 1.0 eq.) bis(pinacolato)diboron (6.36 g, 25.0 mmol, 1.5 eq.), $Pd(dppf)Cl_2$ (341 mg, 418 μmol, 2.5 mol%) and NaOAc (4.11 g, 50.1 mmol, 3.0 eq.) were added to freshly degassed benzene (50 mL) and the reaction mixture was stirred in a rubber septum sealed flask

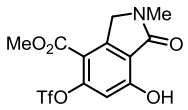
for 13 h at 80 °C. After cooling to room temperature, the reaction mixture was filtered over silica (CH_2Cl_2/MeOH 10:1) and the solvent was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH 20:1, 10:1) to give boronic ester **273** (4.93 g, 86%) as an off-white solid. R*f* 0.47 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 4.53 (s, 2H), 4.02 (s, 3H), 3.93 (s, 3H), 3.15 (s, 3H), 1.44 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.3, 159.7, 145.1 (2C), 121.1, 119.7, 113.9, 84.2 (2C), 55.9, 52.7, 52.0, 28.9, 24.7 (4C); Mp 166 – 170 °C; IR (film) 2985, 1681, 1580, 1442, 1361, 1300, 1247, 1143, 1051, 845 cm^{-1}; MS (ES) *m/z* 362 $[M + H]^+$; HRMS (ES) calc for $C_{18}H_{25}BNO_6$ $[M + H]^+$ 362.1758. Found: 362.1775.

Methyl 5-((1-(2-(*tert*-butoxy)-2-oxoethyl)-1-(*tert*-butoxycarbonyl)-4,7-dimethoxy-1,3-dihydroisobenzofuran-5-yl)methyl)-7-methoxy-2-methyl-1-oxoisoindoline-4-carboxylate (288):



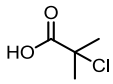
Bromide **272** (31 mg, 63.6 μmol, 1.1 eq.) and boronic ester **273** (20 mg, 57.8 μmol, 1.0 eq.) were dissolved in a DME (0.3 mL) and H_2O (0.1 mL). K_3PO_4 (37 mg, 173 μmol, 3.0 eq.) and $PdCl_2$(dppf) (1.9 mg, 1.5 μmol, 2.5 mol%) were added and the resulting mixture was put in a microwave (80 °C, 2 × 5 min). The crude mixture was filtered through SiO_2 and washed with EtOAc/MeOH (10:1). The solvents were evaporated under reduced pressure and the crude was purified by silica gel column chromatography (EtOAc/MeOH 100:1, 50:1, 10:1) to give **288** (20 mg, 55%) as a pale brown solid. R*f* 0.36 (EtOAc/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H, Ar-*H*), 6.41 (s, 1H, Ar-*H*), 5.37 (d, *J* = 12.0 Hz, 1H, C*H*$_2$O), 5.21 (d, *J* = 12.0 Hz, 1H, C*H*$_2$O), 4.51 (s, 2H, C*H*$_2$NMe), 4.39 (s, 2H, Ar-C*H*$_2$-Ar), 3.85 (s, 3H, CO_2*Me*), 3.82 (s, 3H, OMe), 3.64 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.41 (d, *J* = 15.9 Hz, 1H, C*H*$_2$$CO_2$^{t}Bu), 3.10 (s, 3H, N*Me*), 2.91 (d, *J* = 15.9 Hz, 1H, C*H*$_2$$CO_2$^{t}Bu), 1.34 (s, 9H, C(C*H*$_3$)$_3$), 1.27 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.2 (2C), 166.3, 158.7, 150.1, 148.6, 146.5, 145.6, 133.7, 132.5, 126.9, 119.0, 117.2, 113.4, 111.9, 88.5, 81.1, 80.0, 72.4, 59.7, 55.9, 55.5, 53.3, 51.5, 40.9, 34.4, 28.9, 27.7 (3C), 27.6 (3C); Mp 78 – 80 °C; IR (film) 2925, 1686, 1596, 1487, 1366, 1249, 1154, 1054, 845 cm^{-1}; MS (ES) *m/z* 641 $[M]^+$, 642 $[M + H]^+$; HRMS (ES) calc for $C_{34}H_{44}NO_{11}$ $[M + H]^+$ 642.2914. Found: 642.2913; Anal. Calcd. for $C_{34}H_{43}NO_{11}$: C, 63.64; H, 6.75; N, 2.18. Found: C, 63.63; H, 6.73; N, 2.19.

Methyl 7-hydroxy-2-methyl-1-oxo-5-(((trifluoromethyl)sulfonyl)oxy)isoindoline-4-carboxylate (297):



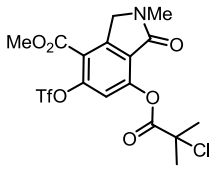
Triflate **133** (2.96 g, 7.72 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (120 mL) and the reaction mixture was cooled to −78 °C. BBr_3 (1 M in CH_2Cl_2, 16.9 mL, 16.98 mmol, 2.2 eq.) was added and the resulting mixture was stirred for 1 h at −78 °C, allowed to warm up to room temperature and stirred at this temperature for 12 h. H_2O/MeOH (120 mL, 1:1) was added and the volatiles were concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give phenol **297** (2.50 g, 88%) as an off-white solid. R*f* 0.47 (CH_2Cl_2/MeOH 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (bs, 1H, OH), 6.81 (s, 1H, Ar-*H*), 4.71 (s, 2H, C*H*$_2$NMe), 3.95 (s, 3H, CO_2*Me*), 3.19 (s, 3H, N*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 163.0, 159.3, 151.9, 146.5, 118.6 (q, *J* = 318.8Hz), 117.7, 111.8, 110.3, 54.7, 52.3, 28.9; Mp 110 – 114 °C; IR (film) 1724, 1671, 1426, 1280, 1209 cm^{-1}; MS (ES) *m/z* 370 $[M + H]^+$; HRMS (ESI) calc for $C_{12}H_{11}F_3NO_7S$ $[M + H]^+$ 370.0195. Found: 370.0208; Anal. Calcd. for $C_{12}H_{11}F_3NO_7S$: C, 39.03; H, 2.73; N, 3.79; S, 8.68. Found: C, 39.12; H, 2.62; N, 3.82; S, 8.77.

2-Chloro-2-methylpropanoic acid (299):[182]



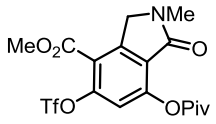
1,1,1-Trichloro-2-methylpropan-2-ol **298** (20 g, 107.3 mmol, 1.0 eq.) was added portionwise to conc. H_2SO_4 (20 mL) at room temperature over 15 min and the reaction mixture was stirred for 12 h. The reaction was quenched by pouring over ice (60 g). The resulting mixture was stirred for 1 h and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give acid **299** (11.5 g, 88%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (bs, 1H), 1.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 64.1, 29.5 (2C); Mp 27 °C (lit.[182] 20 – 30 °C); IR (film) 2989, 2670, 1712, 1460, 1282, 1179, 1120 cm^{-1}; MS (ES) *m/z* 121 $[M - H]^-$; HRMS (ES) calc for $C_4H_6ClO_2$ $[M - H]^-$ 121.0054. Found: 121.0056. Data in accordance with the literature.

Methyl 7-((2-chloro-2-methylpropanoyl)oxy)-2-methyl-1-oxo-5-(((trifluoromethyl)sulfonyl)oxy) isoindoline-4-carboxylate (300):



Phenol **297** (250 mg, 0.67 mmol, 1.0 eq.), acid **299** (182 mg, 1.48 mmol, 2.2 eq.) and DMAP (16 mg, 0.13 mmol, 0.2 eq.) were dissolved in CH_2Cl_2 (2.5 mL) and the resulting mixture was cooled to 0 °C. EDCI (286 mg, 1.48 mmol, 2.2 eq.) was added and the resulting mixture was stirred for 2 h. The reaction was quenched with 1 N HCl and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O (3 × 5 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2/MeOH 200:1, 100:1) to give ester **300** (280 mg, 88%) as an orange oil. R*f* 0.75 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H, Ar-*H*), 4.71 (s, 2H, C*H*$_2$NMe), 4.01 (s, 3H, CO_2*Me*), 3.16 (s, 3H, N*Me*), 2.01 (s, 6H, C(C*H*$_3$)$_2$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.9, 163.6, 162.7, 150.4, 150.3, 147.5, 125.5, 118.6 (q, *J* = 255.3 Hz), 117.9, 117.4, 64.2, 53.2, 52.8, 29.6 (2C), 29.3; Mp 82 °C; IR (film) 1776, 1731, 1704, 1430, 1241, 1099, 818 cm^{-1}; MS (ES) *m/z* 474 $[M + H]^+$; HRMS (ESI) calc for $C_{16}H_{16}ClF_3NO_8S$ $[M + H]^+$ 474.0248. Found: 474.0277; Anal. Calcd. for $C_{16}H_{15}ClF_3NO_8S$: C, 40.56; H, 3.19; N, 2.96; S, 6.77. Found: C, 40.59; H, 3.02; N, 2.84; S, 6.82.

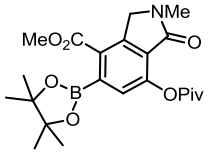
Methyl 2-methyl-1-oxo-7-(pivaloyloxy)-5-(((trifluoromethyl)sulfonyl)oxy)isoindoline-4-carboxy late (303):



Phenol **297** (250 mg, 0.67 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (3.5 mL) and the reaction mixture was cooled to 0 °C. Pyridine (60 μL, 0.74 mmol, 1.1 eq.) was added and the resulting mixture was stirred for 5 min before trimethylacetyl chloride **302** (108 μL, 0.88 mmol, 1.3 eq.) was added. The reaction mixture was stirred for 15 min at 0 °C and for 12 h at room temperature. The reaction was quenched by addition of 1 N HCl (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CH_2Cl_2/MeOH 50:1, 25:1, 10:1) to

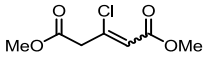
give protected phenol **303** (200 mg, 65%) as a white solid. R*f* 0.64 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H, Ar-*H*), 4.68 (s, 2H, C*H*$_2$NMe), 3.99 (s, 3H, CO_2*Me*), 3.16 (s, 3H, N*Me*), 1.44 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.7, 163.8, 162.8, 151.3, 150.2, 147.4, 125.7, 118.6 (q, *J* = 255.1 Hz), 117.6, 117.2, 53.1, 52.7, 39.3, 29.3, 27.1 (3C); Mp 96 °C; IR (film) 2965, 1711, 1672, 1589, 1421, 1275, 1201, 1136, 983 cm^{-1}; MS (ES) *m/z* 454 [M + H]$^+$; HRMS (ESI) calc for $C_{17}H_{19}F_3NO_8S$ [M + H]$^+$ 454.0771. Found: 454.0783; Anal. Calcd. for $C_{17}H_{18}F_3NO_8S$: C, 45.03; H, 4.00; N, 3.09; S, 7.07. Found: C, 45.12; H, 3.95; N, 3.01; S, 6.89.

Methyl 2-methyl-1-oxo-7-(pivaloyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindoline-4-carboxylate (304):



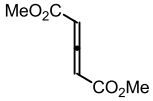
Triflate **303** (500 mg, 1.11 mmol, 1.0 eq.) was dissolved in toluene (11 mL) and the mixture was degassed using N_2 for 15 min. Bis(pinacolato)diboron (426 mg, 1.67 mmol, 1.5 eq.), Pd(dppf)Cl_2 (23 mg, 0.03 μmol, 2.5 mol%) and NaOAc (275 mg, 3.35 mmol, 3.0 eq.) were added and the reaction mixture was stirred in a rubber septum sealed flask for 12 h at 80 °C. The reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (5 mL) and filtered over Celite. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (hexanes/EtOAc 5:1, 3:1) to get boronic ester **304** (312 mg, 70%) as a white solid. R*f* 0.47 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H, Ar-*H*), 4.57 (s, 2H, C*H*$_2$NMe), 3.95 (s, 3H, CO_2*Me*), 3.14 (s, 3H, OMe), 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.42 (s, 12H, C(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 166.8, 165.2, 150.6, 144.1 (2C), 126.1, 126.0, 125.5, 84.5 (2C), 52.9, 52.4, 39.1, 29.2, 27.2 (3C), 24.9 (4C); Mp 238 °C; IR (film) 2988, 2932, 1759, 1715, 1693, 1444, 1351, 1302, 1104, 846 cm^{-1}; MS (ES) *m/z* 432 [M + H]$^+$; HRMS (ES) calc for $C_{22}H_{31}BNO_7$ [M + H]$^+$ 432.2194. Found: 432.2194; Anal. Calcd for $C_{22}H_{30}BNO_7$: C, 61.27; H, 7.01; N, 3.25. Found: C, 61.22; H, 6.98; N, 3.17.

Dimethyl 3-chloropent-2-enedioate (310):[124]



Diethylacetone-1,3-dicarboxylate **309** (20 mL, 110.1 mmol, 1.0 eq.) was charged in a flask and a steady flow of N_2 was passed through the reaction vessel. PCl_5 (23.8 g, 115.6 mmol, 1.05 eq.) was added in thirteen approximately equal portions to the neat diester **309** at 3-min intervals with vigorous stirring. After the addition was complete, the reaction mixture was warmed to 40 °C for 30 min. The red solution was cooled at 0 °C and poured onto *ca.* 50 mL of ice in an Erlenmeyer flask immersed in an ice bath. A mixture of H_2O (10 mL) and CH_2Cl_2 (10 mL) was used to rinse traces of the product from the reaction vessel and the resulting mixture was stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$. The resulting organic layer was concentrated under reduced pressure to give a red oil which was placed in a round bottom flask containing sulphuric acid (6 mL) in anhydrous MeOH (140 mL) and the solution was heated to reflux for 12 h. Excess MeOH was distilled under reduced pressure and the residual yellow solution was cooled to room temperature and poured into H_2O (35 mL). Brine was added to saturation and the aqueous layer was extracted with Et_2O (8 × 30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was distilled under reduced pressure to give vinyl chloride **310** (8 mL, 38%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (s, 1H, C*H*CO_2Me), 4.11 (s, 2H, C*H*$_2$), 3.74 (s, 3H, CO_2*Me*), 3.72 (s, 3H, CO_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 164.6, 147.1, 121.6, 52.5, 52.0, 41.3; IR (film) 2955, 1743, 1716, 1435, 1318, 1157, 1007, 866 cm^{-1}; Bp 50 – 60 °C at 0.02 mmHg; MS (CI) *m/z* 210 $[M + NH_4]^+$; HRMS (CI) calc for $C_7H_{14}NO_4Cl$ $[M + NH_4]^+$ 210.0533. Found: 210.0530. Data in accordance with the literature.

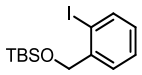
Dimethyl 2,3-pentadienedioate (55):



Vinyl chloride **310** (3.6 g, 18.8 mmol, 1.0 eq.) was dissolved in THF (15 mL) and the resulting solution was cooled to 0 °C. Et_3N (3.9 mL, 28.22 mmol, 1.5 eq.) was added dropwise over 10 min and the mixture was stirred at 0 °C for 12 h. The precipitate formed was removed by filtration and washed with Et_2O (3 × 15 mL). The combined filtrates were washed with 0.1 N HCl (3 × 10 mL) and brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was distilled under reduced pressure to give allene **55** (1.6 g, 55%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05

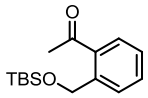
(s, 2H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.7, 163.7 (2C), 92.2 (2C), 52.6 (2C); IR (film) 3026, 2956, 1964, 1715, 1436, 1243, 1144, 1021, 815 cm^{-1}; Bp 58 °C at 0.02 mmHg. Data in accordance with the literature.

tert-Butyl(2-iodobenzyloxy)dimethylsilane (316):[183]



2-Iodobenzyl alcohol **257** (5.0 g, 21.3 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (90 mL) and the resulting solution was cooled to 0 °C. Imidazole (2.2 g, 32.0 mmol, 1.5 eq.) and TBSCl (3.9 g, 25.6 mmol, 1.2 eq.) were added and the resulting mixture was stirred for 15 min at 0 °C. The reaction was allowed to warm up to room temperature and further stirred for 2 h. H_2O (90 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1) to give TBS-protected alcohol **316** (7.07 g, 95%) as a colorless oil. R*f* 0.84 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.8, 0.9 Hz, 1H, Ar-*H*), 7.51 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar-*H*), 7.36 (dt, *J* = 7.7, 0.9 Hz, 1H, Ar-*H*), 6.96 (dt, *J* = 7.7, 1.8 Hz, 1H, Ar-*H*), 4.62 (s, 2H, CH_2OTBS), 0.97 (s, 9H, Si-C(CH_3)$_3$), 0.14 (s, 6H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 138.6, 128.5, 128.1, 127.4, 95.7, 69.4, 25.9 (3C), 18.4, -5.3 (2C); IR (film) 2928, 1471, 1253, 1115, 1089, 833, 743 cm^{-1}; MS (CI) *m/z* 366 $[M + NH_4]^+$; HRMS (CI) calc for $C_{13}H_{25}NIOSi$ $[M + NH_4]^+$ 366.0750. Found: 366.0750; Anal. Calcd. for $C_{13}H_{21}IOSi$: C, 44.83; H, 6.08. Found: C, 44.78; H, 6.02. Data in accordance with the literature.

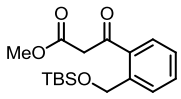
1-(2-(((_tert_-Butyldimethylsilyl)oxy)methyl)phenyl)ethanone (317):



TBS-protected alcohol **316** (5.83 g, 16.7 mmol, 1.0 eq.) and TMEDA (6.76 mL, 45.1 mmol, 2.6 eq.) were dissolved in Et_2O (28 mL) and the mixture was cooled to −78 °C. *n*-BuLi (1.5 M in hexanes, 30 mL, 45.6 mmol, 2.72 eq.) was added dropwise and the mixture was stirred for 30 min at −78 °C and was allowed to warm up to room temperature over 3 h. The reaction mixture was recooled to −78 °C and AcOMe (3.6 mL, 45.6 mmol, 2.72 eq.) in THF (14 mL) was added. The resulting mixture was stirred for 30 min at −78 °C and was allowed to warm up to room temperature. The reaction was

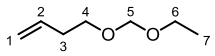
quenched with 1 N HCl (25 mL) and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 25:1, 10:1, 5:1) to give benzoate **317** (2.70 g, 61 %) as a colorless oil. R*f* 0.75 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.41 – 7.33 (m, 2H, Ar-*H*), 7.32 – 7.29 (m, 1H, Ar-*H*), 5.16 (s, 2H, C*H*$_2$OTBS), 2.10 (s, 3H, CO*Me*), 0.89 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.37 (s, 6H, Si*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 141.2, 136.8, 136.4, 129.5, 129.2, 127.1, 67.2, 26.7 (3C), 21.0, 17.6, -3.4 (2C); IR (film) 2960, 1737, 1475, 1223, 1024, 835, 821, 809, 755 cm^{-1}; MS (CI) *m/z* 265 [M + H]$^+$; HRMS (CI) calc for $C_{15}H_{25}O_2Si$ [M + H]$^+$ 265.1624. Found: 265.1620; Anal. Calcd. for $C_{15}H_{24}O_2Si$: C,68.13; H, 9.15. Found: C, 68.06 H, 9.15.

Methyl 3-(2-((*tert*-butyldimethylsilyloxy)methyl)phenyl)-3-oxopropanoate (318):



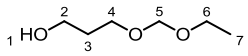
Benzoate **317** (500 mg, 1.89 mmol, 1.0 eq.) was dissolved in THF (25 mL) and the mixture was cooled to −78 °C. NaHMDS (5.67 mL, 5.67 mmol, 3.0 eq.) was added dropwise and the resulting mixture was stirred for 30 min at −78 °C. The reaction was allowed to warm up to 0 °C and stirred further for 1 h. Dimethyl carbonate (478 μL, 5.6 mmol, 3.0 eq.) was added dropwise and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 50:1, 30:1, 10:1) to give keto ester **318** (206 mg, 34 %) as a colorless oil. R*f* 0.73 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.1 Hz, 1H, Ar-*H*), 7.40 – 7.36 (m, 2H, Ar-*H*), 7.34 – 7.29 (m, 1H, Ar-*H*), 5.24 (s, 2H, C*H*$_2$OTBS), 3.74 (s, 3H, OMe), 3.43 (s, 2H, C*H*$_2$CO$_2$Me), 0.88 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.36 (s, 6H, Si*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 140.5, 136.8, 136.4, 129.5, 129.3, 127.3, 68.1, 52.5, 41.4, 26.7, 17.6 (3C), -3.4 (2C), carbonyl peak missing ; IR (film) 2924, 1735, 1436, 1332, 1259, 1144, 1019, 835, 772 cm^{-1}; MS (ES) *m/z* 345 [M + Na]$^+$; HRMS (ES) calc for $C_{17}H_{26}O_4NaSi$ [M + Na]$^+$ 345.1498. Found: 345.1481; Anal. Calcd. for $C_{17}H_{26}O_4Si$: C,63.22; H, 8.13. Found: C, 63.34 H, 8.09.

4-(Ethoxymethoxy)but-1-ene (329):



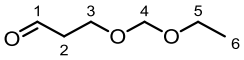
But-3-en-1-ol **328** (5 mL, 58.1 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (90 mL) and the solution was cooled to 0 °C. Hünig's base (15.2 mL, 116.3 mmol, 2.0 eq.) and EOMCl (8 mL, 116.3 mmol, 2.0 eq.) were added and the resulting mixture was stirred for 30 min at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred further for 2 h. H_2O (90 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was distilled under reduced pressure to afford EOM-protected alcohol **329** (6.4 g, 84%) as a colorless oil. R*f* 0.79 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (tdd, *J* = 17.0, 10.3, 6.7 Hz, 1H, H2), 5.10 (dd, *J* = 17.2, 1.4 Hz, 1H, H1 *trans*), 5.02 (dd, *J* = 10.3, 0.8 Hz, 1H, H1 *cis*), 4.66 (s, 2H, H5), 3.61 – 3.55 (m, 4H, H4 and H6), 2.33 (td, *J* = 6.8, 1.4 Hz, 2H, H3), 1.20 (t, *J* = 7.1 Hz, 3H, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 116.4, 95.0, 66.9, 63.1, 34.2, 15.1; IR (film) 2977, 1735, 1098, 1113, 1036, 1015,991, 914, 847 cm^{-1}; MS (CI) *m/z* 148 $[M + NH_4]^+$; HRMS (CI) calc for $C_7H_{18}NO_2$ $[M + NH_4]^+$ 148.1331. Found: 148.1338.

3-(Ethoxymethoxy)propan-1-ol (331):



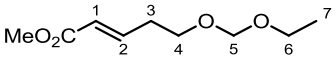
Propane-1,3-diol **330** (20 mL, 277 mmol, 6.0 eq.) was dissolved in THF (500 mL) and the mixture was cooled to 0 °C. NaH (60% dispersion in mineral oil, 3.2 g, 46 mmol, 1.0 eq.) was added and the resulting mixture was stirred at 0 °C for 30 min. The reaction was allowed to warm up to room temperature and stirred for 12 h. EOMCl (4.3 mL, 46 mmol, 1.0 eq.) was added and the reaction mixture was stirred further for 12 h. The reaction mixture was cooled to 0 °C and H_2O (100 mL) was carefully added. The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 50:1, 1:1) to give EOM-protected alcohol **331** (4.1 g, 66 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 2H, H5), 3.77 (td, *J* = 5.8, 1.5 Hz, 2H, H2), 3.71 (td, *J* = 6.0, 1.2 Hz, 2H, H4), 3.59 (qd, *J* = 10.2, 0.8 Hz, 2H, H6), 2.15 (br, 1H, H1), 1.84 (q, *J* = 5.6 Hz, 2H, H3), 1.22 (td, *J* = 7.1, 0.7 Hz, 3H, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.2, 66.4, 63.3, 61.5, 32.1, 15.1; IR (film) 3416, 2931, 2877, 1388, 1113, 1037 cm^{-1}; MS (CI) *m/z* 135 $[M + H]^+$; HRMS (CI) calc for $C_6H_{15}O_3$ $[M + H]^+$ 135.1026. Found: 135.1021; Anal. Calcd. for $C_6H_{14}O_3$: C,53.71; H, 10.52. Found: C, 53.65 H, 10.49.

3-(Ethoxymethoxy)propanal (332):



$(COCl)_2$ (320 μL, 3.72 mmol, 2.0 eq.) was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to −78 °C. DMSO (529 μL, 7.45 mmol, 4.0 eq.) was added and the resulting mixture was stirred for 10 min. EOM-protected alcohol **331** (250 mg, 1.86 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) was added and the reaction mixture was stirred for 15 min. Et_3N (1.1 mL, 7.45 mmol, 4.0 eq.) was subsequently added, the reaction was stirred for 30 min. The reaction mixture was allowed to warmed up to 0 °C and stirred for 30 min. H_2O (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with 1 N HCl (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give aldehyde **332** (220 mg, 89%) as a colorless oil which was used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, J = 1.7 Hz, 1H, H1), 4.67 (s, 2H, H4), 3.88 (t, J = 6.0 Hz, 2H, H3), 3.58 (q, J = 7.0 Hz, 2H, H5), 2.68 (td, J = 5.9, 1.7 Hz, 2H, H2), 1.21 (t, J = 7.1 Hz, 3H, H6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 95.1, 63.3, 61.3, 43.7, 15.1; IR (film) 2883, 1725, 1392, 1115, 1044 cm^{-1}; MS (CI) *m/z* 150 $[M + NH_4]^+$; HRMS (CI) calc for $C_6H_{16}NO_3$ $[M + NH_4]^+$ 150.1130. Found: 150.1136.

(*E*)-Methyl 5-(ethoxymethoxy)pent-2-enoate (325a):



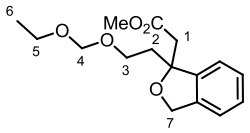
Metathesis: Grubbs II catalyst (275 mg, 0.32 mmol, 2.5 mol%) was added to a solution of EOM-protected alcohol **329** (1.7 g, 13.0 mmol, 1.0 eq.) and methyl acrylate **213** (11.7 mL, 130.0 mmol, 10.0 eq.) in CH_2Cl_2 (68 mL). The reaction mixture was heated to reflux for 12 h. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give methyl ester **325a** (1.75 g, 72 %) as a colorless oil.

Wittig: NaH (60% dispersion in mineral oil, 2.42 g, 60.6 mmol, 2.0 eq.) was suspended in THF (150 mL) and the resulting mixture was cooled to 0 °C. Methyl 2-(diethoxyphosphoryl)acetate **333** (11.1 mL, 60.6 mmol, 2.0 eq.) was added in THF (25 mL) and the reaction mixture was stirred for 30 min at 0 °C. The reaction was allowed to warm up to room temperature and stirred further for 30 min. The reaction mixture was recooled to 0 °C and aldehyde **332** (4.0 g, 30.3 mmol, 1.0 eq.) in THF (25 mL) was added and the mixture was stirred further for 2 h. H_2O (100 mL) was carefully added and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was

purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give methyl ester **325a** (1.98 g, 35 %) as a colorless oil.

One-pot DMP oxidation-Wittig reaction: EOM-protected alcohol **331** (356 mg, 2.65 mmol, 1.0 eq.), $PhCO_2H$ (434 mg, 10.6 mmol, 4.0 eq.) and methyl 2-(diethoxyphosphoryl)acetate **333** (3.55 g, 10.6 mmol, 4.0 eq.) were dissolved in CH_2Cl_2 (20 mL) and DMSO (3.5 mL). Dess-Martin periodinane (2.70 g, 6.36 mmol, 2.4 eq.) was added and the resulting mixture was stirred for 30 min at room temperature. Saturated aqueous $NaHCO_3$ (10 mL), Et_2O (10 mL) and $NaHCO_3$ were added and the resulting mixture was stirred for 10 min. The solid was filtered off and the organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give methyl ester **325a** (285 mg, 57%) as a colorless oil. R*f* 0.39 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (td, *J* = 15.8, 6.9 Hz, 1H, H2), 5.91 (dt, *J* = 15.7, 1.5 Hz, 1H, H1), 4.67 (s, 2H, H5), 3.73 (s, 3H, CO_2*Me*), 3.66 (t, 6.4 Hz, 2H, H4), 3.59 (q, *J* = 7.1 Hz, 2H, H6), 2.49 (dq, *J* = 6.6, 1.5 Hz, 2H, H3), 1.2 (t, *J* = 7.1 Hz, 3H, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 145.9, 122.5, 95.1, 65.7, 63.3, 51.4, 32.6, 15.1; IR (film) 2879, 1722, 1660, 1436, 1316, 1270, 1221, 1171, 1097, 1032, 840 cm^{-1}; MS (NH_3) *m/z* 206 [M + NH_4]$^+$; HRMS (NH_3) calc for $C_{17}H_{26}NO_4$ [M + NH_4]$^+$ 206.1392. Found: 206.1392; Anal. Calcd. for $C_9H_{16}O_4$: C,57.4; H, 8.57. Found: C, 57.36 H, 8.48.

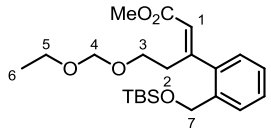
Methyl 2-(1-((ethoxymethoxy)methyl)-1,3-dihydroisobenzofuran-1-yl)acetate (334):



2-Iodobenzyl alcohol **257** (262 mg, 1.11 mmol, 1.0 eq.) and alkene **325a** (250 mg, 1.34 mmol, 1.2 eq.) were dissolved in Et_3N (390 μL). P(*o*-tol)$_3$ (6.8 mg, 0.02 mmol, 0.02 eq.) and $Pd(OAc)_2$ (2.5 mg, 0.01 mmol, 0.01 eq.) were added and the resulting mixture was stirred at 80 °C for 3 h. The reaction was allowed to cool down to room temperature, filtered through Celite and washed with EtOAc (5 mL). The volatiles were concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 50:1, 25:1) to give dihydroisobenzofuran **334** (63 mg, 19%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 5.5, 3.1Hz, 2H, Ar-*H*), 7.19 (dd, *J* = 5.3, 3.4 Hz, 2H, Ar-*H*), 5.12 (d, *J* = 12.3 Hz, 1H, H7), 5.06 (d, *J* = 12.3 Hz, 1H, H7), 4.55 (d, *J* = 6.7 Hz, 1H, H4), 4.51 (d, *J* = 6.6 Hz, 1H, H4), 3.63 – 3.57 (m, 1H, H3), 3.56 (s, 3H, CO_2*Me*), 3.52 – 3.43 (m, 2H, H5), 3.35 – 3.29 (m, 1H, H3) , 2.87 (d, *J* = 14.6 Hz, 1H, H1), 2.81 (d, *J* = 14.6 Hz, 1H, H1), 2.40 – 2.33 (m, 1H, H2), 2.26 – 2.19 (m, 1H, H2), 1.14 (t, *J* = 6.8 Hz, 3H, H6); ^{13}C NMR (100 MHz,

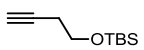
$CDCl_3$) δ 170.4, 142.0, 139.1, 127.9, 127.4, 121.5, 120.9, 95.0, 87.4, 72.4, 63.7, 63.0, 51.5, 45.5, 39.7, 15.1; IR (film) 2925, 1737, 1437, 1360, 1168, 1112, 1032, 845, 761 cm^{-1}.

(*E*)-Methyl-3-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)-5-(ethoxymethoxy)pent-2-enoate (335):



Iodobenzene derivative **316** (389 mg, 1.11 mmol, 1.0 eq.) and alkene **325a** (250 mg, 1.34 mmol, 1.2 eq.) were dissolved in Et_3N (195 μL). P(*o*-tol)$_3$ (6.8 mg, 0.02 mmol, 0.02 eq.) and $Pd(OAc)_2$ (2.5 mg, 0.01 mmol, 0.01 eq.) were added and the resulting mixture was stirred at 80 °C for 3 h. The reaction was allowed to cool down to room temperature, filtered through Celite and washed with EtOAc (5 mL). The volatiles were concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 50:1, 25:1) to give alkene **335** (115 mg, 25%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.8, 0.6 Hz, 1H, Ar-*H*), 7.33 (td, *J* = 7.5, 1.3Hz, 1H, Ar-*H*), 7.24 (dt, *J* = 7.6, 1.2 Hz, 1H, Ar-*H*), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1H, Ar-*H*), 5.85 (s, 1H, H1), 4.64 (s, 2H, H7), 4.56 (s, 2H, H4), 3.75 (s, 3H, CO_2Me), 3.55 (t, *J* = 6.9 Hz, 2H, H3), 3.49 (q, *J* = 7.0 Hz, 2H, H5), 3.29 (t, *J* = 6.9 Hz, 2H, H2), 1.14 (t, *J* = 7.2 Hz, 3H, H6), 0.92 (s, 9H, Si-C(CH_3)$_3$), 0.08 (s, 6H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 157.6, 140.1, 137.7, 127.9, 127.7, 127.5, 126.8, 120.9, 94.8, 65.4, 63.1, 62.6, 51.1, 33.6, 25.9 (3C), 18.3, 15.0, -5.3 (2C); IR (film) 2952, 2928, 2857, 1720, 1637, 1255, 1168, 1117, 1070, 839 cm^{-1}; MS (ES) *m/z* 431 $[M + Na]^+$; HRMS (ES) calc for $C_{22}H_{36}O_5SiNa$ $[M + Na]^+$ 431.2215. Found: 431.2230.

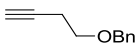
(But-3-ynyloxy)(*tert*-butyl)dimethylsilane (338a):[139b]



To a solution of 3-butyn-1-ol **337** (5 mL, 66.0 mmol, 1.0 eq.) in CH_2Cl_2 (130 mL) was added at 0 °C TBSCl (14.9 g, 99.1 mmol, 1.5 eq.) and DIPEA (17.3 mL, 99.1 mmol, 1.5 eq.). The resulting mixture was stirred at 0 °C for 1 h, allowed to warm up to room temperature and further stirred for 12 h. The reaction was quenched with H_2O (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give TBS-protected alcohol **338a** (12 g, 99%) as a colorless oil which was used without any further purification. R*f* 0.73 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz,

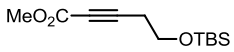
$CDCl_3$) δ 3.74 (t, J = 7.1 Hz, 2H, CH_2OTBS), 2.40 (td, J = 7.2, 2.8 Hz, 2H, HC≡CCH_2), 1.96 (t, J = 2.6 Hz, 1H, HC≡C), 0.90 (s, 9H, Si-C(CH_3)$_3$), 0.07 (s, 6H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.5, 69.3, 61.7, 25.9 (3C), 22.8, 18.3, -5.3 (2C); IR (film) 3317, 2930, 2954, 1472, 1254, 1102, 833, 774 cm^{-1}. Data in accordance with the literature.

((But-3-ynyloxy)methyl)benzene (338b):[139c]



To a solution of 3-butyn-1-ol **337** (2 mL, 26.4 mmol, 1.0 eq.) in THF (45 mL) was added at 0 °C NaH (60% dispersion in paraffin oil, 1.1 g, 26.7 mmol, 1.01 eq.), benzyl bromide (3.2 mL, 26.4 mmol, 1.0 eq.) and TBAI (100 mg, 0.26 mmol, 0.01 eq.) and the resulting mixture was stirred for 12 h. The reaction was quenched with aqueous saturated NH_4Cl (20 mL) and the aqueous layer was extracted with Et_2O (2 × 45 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 20:1, 10:1, 5:1) to give benzyl-protected alcohol **338b** (2.98 g, 70%) as a colorless oil. Rf 0.65 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.35 (m, 4H, Ar-H), 7.29 (dd, J = 9.1, 4.4 Hz, 1H, Ar-H), 4.57 (s, 2H, OCH_2Ph), 3.61 (t, J = 6.9 Hz, 2H, CH_2OBn), 2.51 (td, J = 6.9, 2.7 Hz, 2H, HC≡CCH_2), 2.01 (t, J = 2.6 Hz, 1H, HC≡C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 128.4 (2C), 127.6 (3C), 81.2, 72.9, 69.3, 68.1, 19.8; IR (film) 3294, 2863, 1496, 1454, 1362, 1203, 1098, 735, 696 cm^{-1}; MS (EI) m/z 159 [M – H]$^+$; HRMS (EI) calc for $C_{11}H_{11}O$ [M – H]$^+$ 159.0807. Found: 159.0810. Data in accordance with the literature.

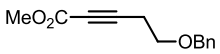
Methyl 5-(*tert*-butyldimethylsilyloxy)pent-2-ynoate (340a):[148]



TBS-protected alcohol **338a** (3.87 g, 20.9 mmol, 1.0 eq.) was dissolved in THF (38 mL) and the reaction mixture was cooled to −78 °C. n-BuLi (1.6 M in hexanes, 13.7 mL, 22.0 mmol, 1.05 eq.) was added dropwise and the reaction mixture was stirred for 1 h at −78 °C. Methylchloroformate **339** (2.3 mL, 30.4 mmol, 1.45 eq.) was added dropwise and the reaction mixture was stirred further for 1 h at −78 °C. The reaction was allowed to warm up to room temperature and was quenched with aqueous saturated NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 7:3) to

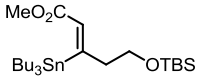
give methyl ester **340a** (4.35 g, 86%) as a pale yellow oil. R*f* 0.69 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (t, *J* = 6.9 Hz, 2H, C*H*$_2$OTBS), 3.75 (s, 3H, CO_2*Me*), 2.53 (t, *J* = 6.9 Hz, 2H, $MeO_2C{\equiv}CCH_2$), 0.88 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.06 (s. 6H, Si*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 86.8, 73.7, 60.6, 52.5, 25.8 (3C), 23.0, 18.2, -5.34 (2C); IR (film) 2958, 2934, 2246, 1717, 1435, 1248, 1107, 912, 835, 775 cm^{-1}; MS (CI) *m/z* 260 $[M + NH_4]^+$; HRMS (CI) calc for $C_{12}H_{26}NO_3Si$ $[M + NH_4]^+$ 260.1685. Found: 260.1682; Anal. Calcd. for $C_{12}H_{22}O_3Si$: C,59.46; H, 9.15. Found: C, 59.45 H, 9.10. Data in accordance with the literature.

Methyl 5-(benzyloxy)pent-2-ynoate (340b):[139c]



Benzyl-protected alcohol **338b** (5.0 g, 31.2 mmol, 1.0 eq.) was dissolved in THF (50 mL) and the reaction mixture was cooled to −78 °C. *n*-BuLi (1.6 M in hexanes, 24.4 mL, 39.0 mmol, 1.25 eq.) was added dropwise and the reaction mixture was stirred for 1 h at −78 °C. Methylchloroformate **339** (3.50 mL, 45.3 mmol, 1.45 eq.) was added dropwise and the reaction mixture was stirred further for 1 h at −78 °C. The reaction was allowed to warm up to room temperature and was quenched with aqueous saturated NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (2 × 75 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 50:1, 20:1, 10:1) to afford methyl ester **340b** (4.79 g, 70%) as a colorless oil. R*f* 0.62 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H, Ar-*H*), 4.55 (s, 2H, OC*H*$_2$Ph), 3.76 (s, 3H, CO_2*Me*), 3.64 (t, *J* = 6.8 Hz, 2H, C*H*$_2$OBn), 2.64 (t, *J* = 6.8 Hz, 2H, $MeO_2C{\equiv}CCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 137.6, 128.4, 127.8 (2C), 127.7 (2C), 86.4, 73.6, 73.0, 66.9, 52.6, 20.1; IR (film) 3034, 2871, 2244, 1708, 1434, 1250, 1100, 1079, 750, 697 cm^{-1}; MS (CI) *m/z* 236 $[M + NH_4]^+$; HRMS (CI) calc for $C_{13}H_{18}NO_3$ $[M + NH_4]^+$ 236.1297. Found: 236.1287; Anal. Calcd. for $C_{13}H_{14}O_3$: C,71.54; H, 6.47. Found: C, 71.62 H, 6.41. Data in accordance with the literature.

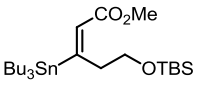
(*Z*)-Methyl 5-(*tert*-butyldimethylsilyloxy)-3-(tributylstannyl)pent-2-enoate (336a):[140]



To a solution of *N*,*N*-diisopropylamine (1.3 mL, 9.49 mmol, 2.3 eq.) in THF (44 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 5.2 mL, 8.26 mmol, 2.0 equiv) was added and the resulting mixture

was stirred for 1 h at 0 °C. Bu_3SnH (2.2 mL, 8.26 mmol, 2.0 eq.) was added and the reaction mixture was stirred further for 1 h at 0 °C. The solution was cooled to −20 °C and PhSCu (1.43 g, 8.26 mmol, 2.0 eq.) was added in one portion. The reaction mixture was stirred at −20 °C for 1 h and recooled to −78 °C at which alkyne **340a** (1.0 g, 4.13 mmol, 1.0 eq.) in THF (5 mL) was added dropwise. The reaction was stirred further for 1 h at −78 °C, allowed to warm up to room temperature and quenched with MeOH (1 mL). The reaction mixture was diluted with H_2O (50 mL) and filtered through Celite. The aqueous layer was extracted with Et_2O (2 × 50 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 100:1) to give stannane **336a** (1.22 g, 55%) as a yellow oil. R*f* 0.78 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (t, *J* = 1.2 Hz, 1H, C=C*H*), 3.71 (s, 3H, CO_2*Me*), 3.62 (t, *J* = 7.1 Hz, 2H, CH_2OTBS), 2.62 (td, *J* = 7.2, 1.2 Hz, 2H, CH_2C=C), 1.49 – 1.42 (m, 6H), 1.34 – 1.24 (m, 6H), 0.98 – 0.84 (m, 6H), 0.87 (t, *J* = 7.3 Hz, 9H), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.05 (s, 6H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 168.1, 129.9, 62.2, 51.4, 43.2, 29.2 (3C), 27.4 (3C), 25.9 (3C), 18.3, 13.7 (3C), 11.0 (3C), -5.3 (2C); IR (film) 2954, 2932, 2857, 1709, 1214, 1194, 1182, 1089, 907, 835, 731 cm^{-1}; MS (ES) *m/z* 531 [M[^{116}Sn] + H]$^+$; HRMS (ES) calc for $C_{24}H_{50}O_3{}^{116}SnSi$ [M[^{116}Sn] + H]$^+$ 531.2615. Found: 531.2625. Data in accordance with the literature.

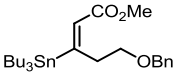
(*E*)-Methyl 5-(*tert*-butyldimethylsilyloxy)-3-(tributylstannyl)pent-2-enoate (336b):[140]



To a solution of *N*,*N*-diisopropylamine (5 mL, 35.6 mmol, 2.3 eq.) in THF (165 mL) was added at 0 °C *n*-BuLi (1.6 M in hexanes, 19.3 mL, 30.9 mmol, 2.0 eq.) and the resulting mixture was stirred at 0 °C for 1 h. Bu_3SnH (8.3 mL, 30.9 mmol, 2.0 eq.) was added and the reaction was stirred further for 1 h at 0 °C. The solution was cooled to −20 °C and PhSCu (5.3 g, 30.9 mmol, 2.0 eq.) was added in one portion. The reaction mixture was stirred at −20 °C for 1 h and recooled to −78 °C at which alkyne **340a** (3.75 g, 15.5 mmol, 1.0 eq.) in THF (20 mL) and MeOH (1 mL, 26.2 mmol, 1.69 eq.) was added dropwise. The reaction was stirred further for 1 h at −78 °C, allowed to warm up to room temperature and quenched with MeOH (4 mL). The reaction mixture was diluted with H_2O (100 mL) and filtered through Celite. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 100:1) to give stannane **336b** (6.6 g, 80%) as a yellow oil. R*f* 0.76 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (t, *J* = 1.2 Hz, 1H, C=C*H*), 3.69 (s, 3H, OMe), 3.66 (t, *J* = 7.2 Hz, 2H, CH_2OTBS), 3.10 (td, *J* = 7.3, 1.0 Hz, 2H,

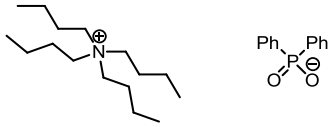
C*H*$_2$C=C), 1.52 – 1.45 (m, 6H), 1.35 – 1.26 (m, 6H), 0.98 – 0.94 (m, 6H), 0.90 (t, *J* = 7.3 Hz, 9H), 0.88 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.06 (s, 6H, Si*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 164.3, 129.2, 62.6, 50.8, 38.7, 28.9 (3C), 27.4 (3C), 26.0 (3C), 18.4, 13.6 (3C), 10.0 (3C), -5.2 (2C); IR (film) 2928, 2857, 1719, 1464, 1254, 1190, 1087, 833, 775 cm^{-1}; MS (ES) *m/z* 531 [M[^{116}Sn] + H]$^+$; HRMS (ES) calc for $C_{24}H_{50}O_3{}^{116}SnSi$ [M[^{116}Sn]+H]$^+$ 531.2615. Found: 531.2625. Data in accordance with the literature.

(*E*)-Methyl 5-(benzyloxy)-3-(tributylstannyl)pent-2-enoate (336c):



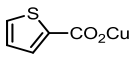
To a solution of *N*,*N*-diisopropylamine (1.5 mL, 10.5 mmol, 2.3 eq.) in THF (44 mL) was added at 0°C *n*-BuLi (1.6 M in hexanes, 5.73 mL, 9.2 mmol, 2.0 eq.) and the resulting mixture was stirred further for 1 h at 0 °C. Bu_3SnH (2.45 mL, 9.2 mmol, 2.0 eq.) was added and the reaction was stirred for 1 h at 0 °C. The solution was cooled to –20 °C and PhSCu (1.58 g, 9.2 mmol, 2.0 eq.) was added in one portion. The reaction mixture was stirred at –20 °C for 1 h and recooled to –78 °C at which alkyne **340b** (1.0 g, 4.58 mmol, 1.0 eq.) in THF (5 mL) and MeOH (314 μL, 7.75 mmol, 1.69 eq.) was added dropwise. The reaction was stirred further for 1 h at –78 °C, allowed to warm up to room temperature and quenched with MeOH (1 mL). The reaction mixture was diluted with H_2O (50 mL) and filtered through Celite. The aqueous layer was extracted with Et_2O (2 × 50 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 100:1) to give stannane **336c** (1.80 g, 77%) as a colorless oil. R*f* 0.63 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.32 (m, 4H, Ar-*H*), 7.28 (dd, *J* = 4.8, 3.9 Hz, 1H, Ar-*H*), 6.02 (t, *J* = 1.1 Hz, 1H, C=C*H*), 4.50 (s, 2H, O*CH*$_2$Ph), 3.68 (s, 3H, CO_2*Me*), 3.54 (t, *J* = 6.8 Hz, 2H, C*H*$_2$OBn), 3.21 (td, *J* = 6.8, 1.1 Hz, 2H, C*H*$_2$C=C), 1.49 – 1.41 (m, 6H), 1.33 – 1.24 (m, 6H), 0.93 – 0.90 (m, 6H), 0.87 (t, *J* = 7.2 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 164.4, 138.4, 128.9, 128.3 (2C), 127.7 (2C), 127.5, 72.8, 69.6, 50.8, 35.4, 28.9 (3C), 27.3 (3C), 13.6 (3C), 10.1 (3C); IR (film) 2954, 2922, 2857, 1716, 1455, 1190, 1165, 1089, 867, 734 cm^{-1}; MS (ES) *m/z* 507 [M[^{116}Sn] + H]$^+$; HRMS (ES) calc for $C_{25}H_{45}O_3{}^{116}SnSi$ [M[^{116}Sn] + H]$^+$ 507.2239. Found: 507.2230.

Tetrabutylammonium diphenylphosphinate:[147]



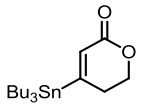
Diphenylphosphinic acid (4.0 g, 18.33 mmol, 1.0 eq.) was dissolved in MeOH (20 mL). Tetrabutylammonium hydroxide (1 M in MeOH, 18.33 mL, 18.33 mmol, 1.0 eq.) was added and the resulting mixture was shaken briefly. The resulting cloudy solution was filtered through Celite and the solvent was concentrated under reduced pressure. The pale yellow oil obtained was dried for 12 h under vacuum to give a semi-solid which was purified by recrystallization (Et_2O/hexanes 1:1) to give tetrabutylammonium diphenylphosphinate (8.17 g, 97%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 4H), 7.25 – 7.22 (m, 6H), 3.28 (t, J = 8.4 Hz, 8H), 1.60 – 1.52 (m, 8H), 1.33 (sex, J = 7.2 Hz, 8H), 0.92 (t, J = 7.3 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7 (3C), 131.6 (3C), 128.5 (2C), 127.3 (2C), 127.2 (2C), 58.8 (4C), 24.1 (4C), 19.6 (4C), 13.6 (4C); IR (film) 2956, 1474, 1212, 1119, 1042, 698 cm^{-1}; Anal. Calcd. for $C_{28}H_{46}NO_2P$: C,73.17; H, 10.09; N, 3.05. Found: C,73.62; H, 10.12; N, 3.14. Data in accordance with the literature.

Copper(I) thiophenecarboxylate (CuTC):[146]



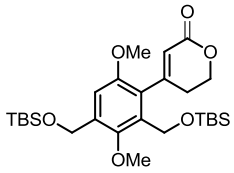
Thiophene-2-carboxylic acid (10 g, 78.0 mmol, 4.0 eq.) was dissolved in toluene (30 mL) and Cu_2O (2.79 g, 19.50 mmol, 1.0 eq.) was added. The resulting solution was heated to reflux under Dean-Stark conditions for 12 h with azeotropic removal of H_2O. The yellow/brown suspension was cooled to 60 °C and the solid was filtered, washed with MeOH (30 mL) and Et_2O until the eluant became colourless and finally with hexanes. The product was dried for 12 h under vacuum to give copper(I) thiophenecarboxylate (5.0 g, 67%) as a brown powder. IR (film) 3096, 1600, 1424, 1389 cm^{-1}; Anal. Calcd. for $C_5H_3CuO_2S$: C,31.49; H, 1.59; S, 16.82. Found: C,31.52; H, 1.50; S, 16.71.

4-(Tributylstannyl)-5,6-dihydro-2*H*-pyran-2-one (341):



To a solution of stannane **336b** (500 mg, 0.93 mmol, 1.0 eq.) in MeOH (4.6 mL) at to 0 °C was added CSA (109 mg, 0.46 mmol, 0.5 eq.) and the resulting mixture was stirred for 1 h at 0 °C. The volatiles were evaporated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 5:1, 4:1) to give lactone **341** (275 mg, 76%) as a colorless oil. R*f* 0.47 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (t, *J* = 1.8 Hz, 1H, C=C*H*), 4.36 (t, *J* = 6.1 Hz, 2H, CH_2CH_2O), 2.52 (td, *J* = 6.1, 1.8 Hz, 2H, CH_2C=C), 1.53 – 1.46 (m, 6H), 1.36 – 1.27 (m, 6H), 1.04 – 0.99 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 161.5, 129.7, 66.6, 30.7, 28.9 (3C), 27.2 (3C), 13.6 (3C), 9.4 (3C); IR (film) 2960, 2930, 1728, 1711, 1279, 1214, 1083, 909, 872 cm^{-1}; MS (ES) *m/z* 385 [M[^{116}Sn] + H]$^{+}$; HRMS (ES) calc for $C_{17}H_{33}O_2{}^{116}$Sn [M[^{116}Sn] + H]$^{+}$ 385.1499. Found: 385.1498.

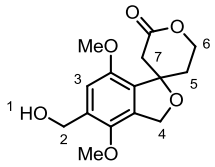
4-(2,4-Bis((*tert*-butyldimethylsilyloxy)methyl)-3,6-dimethoxyphenyl)-5,6-dihydro-2*H*-pyran-2-one (342):



Iodide **278** (5.3 g, 9.53 mmol, 1.0 eq.) and stannane **341** (4.4 g, 11.44 mmol, 1.2 eq.) were dissolved in toluene (38 mL) and $Pd(PPh_3)_4$ (1.1 g, 0.95 mmol, 10 mol%) and CuI (455 mg, 2.3 mmol, 0.25 eq.) were added. The resulting mixture was heated to reflux for 12 h. The solvent was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 50:1, 25:1) to give alkene **342** (3.79 g, 72%) as a yellow solid. R*f* 0.59 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H, Ar-*H*), 5.97 (s, 1H, C=C*H*), 4.81 (s, 2H, CH_2OTBS), 4.59 (s, 2H, CH_2OTBS), 4.51 (t, *J* = 6.1 Hz, 2H, CH_2O), 3.79 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2.68 (t, *J* = 5.2 Hz, 2H, CH_2C=C), 0.97 (s, 9H, Si-C(CH_3)$_3$), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.14 (s, 6H, SiMe_2), 0.09 (s, 6H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 156.2, 152.3, 149.1, 135.8, 131.1, 127.9, 119.4, 109.6, 66.6, 62.9, 59.9, 56.9, 55.8, 29.5, 25.94 (6C), 18.3, 18.2, -5.3 (2C), -5.5 (2C); Mp 106 – 108 °C; IR (film) 2953, 2856, 1728, 1462, 12314, 1088 cm^{-1}; MS (ES) *m/z* 523 [M +

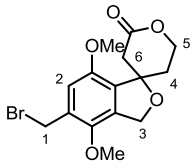
H]$^+$; HRMS (ES) calc for $C_{27}H_{47}O_6Si$ [M + H]$^+$ 523.2907. Found: 523.2911; Anal. Calcd. for $C_{27}H_{46}O_6Si_2$: C, 62.03; H, 8.87. Found: C, 61.96; H, 8.93.

5-(Hydroxymethyl)-4,7-dimethoxy-5',6'-dihydro-3*H*-spiro[isobenzofuran-1,4'-pyran]-2'(3'*H*)-one (343):



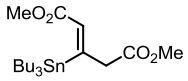
TBS-protected alcohol **342** (64 mg, 0.12 mmol, 1.0 eq.) was dissolved in THF (614 μL) and the solution was cooled to 0 °C. Conc. HCl (39 μL) was added and the resulting mixture was stirred for 1 h. Additional conc. HCl (39 μL) was added and the reaction was further stirred for 1 h. The reaction was quenched with H_2O (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 2:1, 1:1) to give alcohol **343** (23.7 mg, 66%) as a colorless oil. R*f* 0.40 (hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H, H3), 5.18 (d, *J* = 12.5 Hz, 1H, H4), 5.14 (d, *J* = 12.5 Hz, 1H, H4), 4.70 (s, 2H, H2), 4.60 (td, *J* = 10.8, 3.7 Hz, 1H, H6), 4.44 (td, *J* = 11.2, 4.7 Hz, 1H, H6), 3.82 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.17 (d, *J* = 17.2 Hz, 1H, H7), 2.72 (dd, *J* = 17.2, 1.7 Hz, 1H, H7), 2.53 (ddd, *J* = 14.8, 10.4, 5.2 Hz, 1H, H5), 2.27 (br. s, 1H, H1), 1.95 (dtd, *J* = 14.5, 4.0, 1.8 Hz, 1H, H5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 149.4, 145.5, 134.1, 130.8, 130.6, 110.8, 84.6, 69.8, 65.9, 60.9, 60.1, 55.6, 40.5, 32.9; Mp 104 - 106°C; IR (film) 3442, 2924, 1733, 1488, 1419, 1261, 1233, 1062, 1035 cm^{-1}; MS (ES) *m/z* 295 [M + H]$^+$; HRMS (ES) calc for $C_{15}H_{19}O_6$ [M + H]$^+$ 295.1189. Found: 295.1182; Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.05; H, 6.03.

5-(Bromomethyl)-4,7-dimethoxy-5',6'-dihydro-3*H*-spiro[isobenzofuran-1,4'-pyran]-2'(3'*H*)-one (344):



Alcohol **343** (1.0 g, 3.5 mmol, 1.0 eq.) was dissolved in DMF (17 mL). PPh_3 (1.8 g, 6.9 mmol, 2.0 eq.) and CBr_4 (2.3 g, 6.9 mmol, 2.0 eq.) were added and the reaction mixture was stirred for 2 h at room temperature. H_2O (28 mL) was added followed by hexanes/EtOAc (28 mL, 1:1). The aqueous layer was extracted with hexanes/EtOAc (5 × 20 mL, 1:1). The combined organic layers were washed with H_2O (3 × 20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 1:1, 1:2, 1:3, 1:9) to give bromide **344** (875 mg, 71%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H, H2), 5.18 (d, *J* = 12.8 Hz, 1H, H3), 5.14 (d, *J* = 12.8 Hz, 1H, H3), 4.61 (td, *J* = 11.2, 3.6 Hz, 1H, H5), 4.57 (d, *J* = 9.6 Hz, 1H, H1), 4.53 (d, *J* = 9.6 Hz, 1H, H1), 4.45 (dt, *J* = 11.2, 4.8 Hz, 1H, H5), 3.84 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.17 (d, *J* = 17.2 Hz, 1H, H6), 2.74 (dd, *J* = 17.3, 1.8 Hz, 1H, H6), 2.57 – 2.49 (m, 1H, H4), 1.96 (dtd, *J* = 14.4, 4.0, 1.9 Hz, 1H, H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 149.4, 149.1, 132.2, 131.6, 131.2, 112.4, 84.8, 69.8, 65.9, 60.1, 55.6, 40.4, 32.9, 27.9; Mp 100 °C; IR (film) 2932, 1739, 1493, 1415, 1323, 1262, 1081, 1053, 978 cm^{-1}; MS (ES) *m/z* 357 $[M[^{79}Br] + H]^+$; HRMS (ES) calc for $C_{15}H_{18}{}^{79}BrO_5$ $[M + H]^+$ 357.0331. Found: 357.0338; Anal. Calcd. for $C_{15}H_{17}BrO_5$: C,50.44; H, 4.80. Found: C,50.58; H, 4.77.

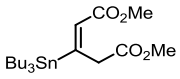
(*Z*)-Dimethyl 3-(tributylstannyl)pent-2-enedioate (345a):[148]



To a solution of stannane **336a** (500 mg, 0.94 mmol, 1.0 eq.) in acetone (2.6 mL) at 0 °C was slowly added a freshly made solution of Jones reagent (0.28 g of CrO_3 in 630 μL of H_2O and 260 μL of concentrated H_2SO_4, 2.8 mmol, 3.0 eq.). The reaction was stirred for 10 min at 0 °C and was quenched with H_2O (3 mL). The aqueous layer was extracted with Et_2O (2 × 6 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the corresponding acid **347a** which was used in the next step without further purification.

The crude acid **347a** (410 mg, 0.94 mmol, 1.0 eq.) was dissolved in MeOH (375 μL) and CH_2Cl_2 (1.5 mL) and the solution was cooled to 0 °C. $TMSCHN_2$ (2 M in Et_2O, 565 μL, 1.1 mmol, 1.2 eq.) was added and the reaction mixture was stirred for 40 min at 0 °C. The volatiles were concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 25:1, 10:1) to give stannane **345a** (184 mg, 44% over 2 steps) as yellow oil. R*f* 0.65 (hexanes/Et_2O 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (t, *J* = 1.3 Hz, 1H, C=C*H*), 3.73 (s, 3H, CO_2*Me*), 3.68 (s, 3H, CO_2*Me*), 3.42 (d, *J* = 1.1 Hz, 2H, C*H*$_2$$CO_2$Me), 1.50 – 1.43 (m, 6H), 1.34 – 1.25 (m, 6H), 0.99 – 0.94 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 167.7, 166.4, 131.6, 51.9, 51.6, 44.8, 29.1 (3C), 27.4 (3C), 13.7 (3C), 11.3 (3C); IR (film) 2955, 2929, 2860, 1737, 1715, 1462, 1435, 1324, 1216, 1167 cm^{-1}; MS (ES) *m/z* 449 [M[^{120}Sn] + H]$^+$; HRMS (ES) calc for $C_{19}H_{37}O_4{}^{120}SnSi$ [M[^{120}Sn] + H]$^+$ 449.1729. Found: 449.1714. Data in accordance with the literature.

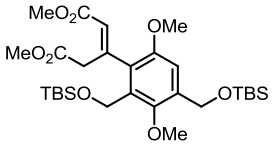
(*E*)-Dimethyl 3-(tributylstannyl)pent-2-enedioate (345b):

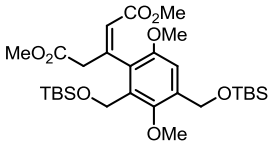


To a solution of stannane **336b** (200 mg, 0.37 mmol, 1.0 eq.) in acetone (1.0 mL) at 0 °C was slowly added a freshly made solution of Jones reagent (0.112 g of CrO_3 in 252 μL of H_2O and 100 μL of concentrated H_2SO_4, 1.12 mmol, 3.0 eq.). The reaction mixture was stirred for 10 min at 0 °C and was quenched with H_2O (1.5 mL). The aqueous layer was extracted with Et_2O (2 × 3 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the corresponding acid **347b** which was used without any further purification.

The crude acid **347b** (186 mg, 0.37 mmol, 1.0 eq.) was dissolved in MeOH (147 μL) and CH_2Cl_2 (610 μL) and the solution was cooled to 0 °C. $TMSCHN_2$ (2 M in Et_2O, 225 μL, 0.45 mmol, 1.2 eq.) was added and the reaction mixture was stirred for 40 min at 0 °C. The volatiles were concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 25:1, 10:1) to give stannane **345b** (38 mg, 22% over 2 steps) as yellow oil. R*f* 0.67 (hexanes/Et_2O 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (t, *J* = 1.8 Hz, 1H, C=C*H*), 4.01 (d, *J* = 1.6 Hz, 2H, C*H*$_2$$CO_2$Me), 3.70 (s, 3H, CO_2*Me*), 3.69 (s, 3H, CO_2*Me*), 1.52 – 1.43 (m, 6H), 1.35 – 1.26 (m, 6H), 0.98 – 0.94 (m, 6H), 0.86 (t, *J* = 7.2 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 164.8, 164.5, 129.7, 51.8, 51.0, 39.0, 28.9 (3C), 27.3 (3C), 13.6 (3C), 10.6 (3C); IR (film) 2955, 2929, 2860, 1737, 1715, 1462, 1435, 1324, 1216, 1167 cm^{-1}; MS (ES) *m/z* 449 [M[^{120}Sn] + H]$^+$; HRMS (ES) calc for $C_{19}H_{37}O_4{}^{120}SnSi$ [M[^{120}Sn] + H]$^+$ 449.1729. Found: 449.1714.

(*E*)-Dimethyl 3-(2,4-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-3,6-dimethoxyphenyl)pent-2-enedioate (348a) and (*Z*)-Dimethyl 3-(2,4-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-3,6-dimethoxyphenyl)pent-2-enedioate (348b):

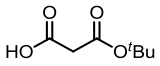




Iodide **278** (100 mg, 0.10 mmol, 1.0 eq.) and stannane **345a** (97 mg, 0.21 mmol, 1.2 eq.) were dissolved in toluene (725 μL) and $Pd(PPh_3)_4$ (21 mg, 0.025 mmol, 10 mol%) and CuI (8.6 mg, 0.04 mmol, 0.25 eq.) were added. The resulting mixture was heated to reflux for 12 h. The solvent was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (hexanes/EtOAc 20:1, 10:1) to give alkene **348a** (27 mg, 25%) as a yellow solid. Further elution (hexanes/EtOAc 10:1) gave alkene **348b** (61 mg, 58%) as a yellow oil. **348a**. R*f* 0.66 (Hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H, Ar-*H*), 6.25 (s, 1H, C=C*H*), 4.81 (s, 2H, CH_2OTBS), 4.59 (d, *J* = 16.8 Hz, 1H, CH_2OTBS), 4.35 (d, *J* = 16.8 Hz, 1H, CH_2OTBS), 3.80 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.74 – 3.71 (m, 2H, CH_2CO$_2$Me), 3.72 (s, 3H, CO$_2$*Me*), 3.61 (s, 3H, CO$_2$*Me*), 0.96 (s, 9H, Si-C(CH_3)$_3$), 0.90 (s, 9H, Si-C(CH_3)$_3$), 0.13 (s, 6H, SiMe_2), 0.11 ‘s, 6H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 166.5, 152.5, 149.9, 148.4, 135.3, 132.0, 131.0, 123.7, 109.4, 62.8, 59.9, 57.3, 55.6, 51.6, 51.0, 38.7, 25.9 (6C), 18.4, 18.2, -5.3 (2C), -5.6 (2C); HRMS (ES) calc for $C_{29}H_{50}O_8NaSi_2$ $[M + Na]^+$ 605.2930. Found: 605.2942. **348b**. R*f* 0.56 (Hexanes/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H, Ar-*H*), 6.21 (t, *J* = 1.3 Hz, 1H, C=C*H*), 4.84 (d, *J* = 13.9 Hz, 1H, CH_2OTBS), 4.78 (d, *J* = 13.9 Hz, 1H, CH_2OTBS), 4.66 (d, *J* = 10.2 Hz, 1H, CH_2OTBS), 4.41 (d, *J* = 10.2 Hz, CH_2OTBS), 3.75 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.71 (s, 3H, CO$_2$*Me*), 3.51 (s, 3H, CO$_2$*Me*), 3.47 (dd, *J* = 16.0, 1.0 Hz, 1H, CH_2CO$_2$Me), 3.39 (dd, *J* = 16.1, 1.5 Hz, CH_2CO$_2$Me), 0.96 (s, 9H, Si-C(CH_3)$_3$), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.13 (s, 6H, SiMe_2), 0.09 (s, 3H, SiMe_2), 0.08 (s, 3H, SiMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 165.4, 151.4, 149.2, 148.5, 134.5, 130.4, 128.6, 120.3, 109.5, 62.7, 59.9, 57.4, 55.8, 51.8, 51.0, 44.1, 26.0 (3C), 25.9 (3C), 18.3 (2C), -5.3 (2C), -5.5, -5.6; HRMS (ES) calc for $C_{29}H_{50}O_8NaSi_2$ $[M + Na]^+$ 605.2930. Found: 605.2942.

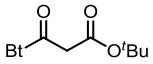
Towards the Synthesis of EF-Ring Boronate using Resorcylate Chemistry

3-(*tert*-Butoxy)-3-oxopropanoic acid (400):[162]



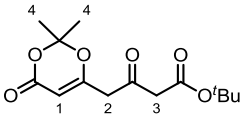
Meldrüm's acid **399** (10 g, 69.4 mmol, 1.0 eq.) and *tert*-BuOH (27 mL, 277.5 mmol, 4.0 eq.) were stirred at 100 °C for 12 h. The reaction mixture was allowed to cool down to room temperature and was slowly poured into an aqueous saturated solution of $NaHCO_3$ (400 mL). The resulting mixture was stirred for 1 h and washed with hexanes/Et_2O (3 × 300 mL, 1:1). The aqueous layer was acidified to pH 3-4 using 1 N HCl and extracted with EtOAc (3 × 300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give acid **400** (5.6 g, 50%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 2H, CH_2), 1.49 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 166.1, 82.7, 41.9, 27.7 (3C); IR (film) 2981, 1713, 1369, 1141, 836 cm^{-1}; MS (CI) *m/z* 178 $[M + NH_4]^+$; HRMS (CI) calc for $C_7H_{16}NO_4$ $[M+ NH_4]^+$ 178.1080. Found: 178.1079. Data in accordance with the literature.

***tert*-Butyl 3-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3-oxopropanoate (398c):**



To a solution of benzotriazole (7.0 g, 59.0 mmol, 3.15 eq.) in CH_2Cl_2 (120 mL) at room temperature was added $SOCl_2$ (1.36 mL, 18.7 mmol, 1.0 eq.) and the resulting mixture was stirred for 1 h. Carboxylic acid **400** (3.0 g, 18.7 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was quickly added and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was filtered and the volatiles were concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with pH 9 buffer (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure to give benzotriazole derivative **398c** (3.9 g, 81%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.07 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.64 – 7.60 (m, 1H, Ar-*H*), 7.50 – 7.46 (m, 1H, Ar-*H*), 4.30 (s, 2H, CH_2), 1.42 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 164.9, 146.1, 130.8, 130.5, 126.3, 120.1, 114.1, 82.9, 43.9, 27.7 (3C); IR (film) 2991, 1747, 1718, 1718, 1600, 1486, 1457, 1382, 1369, 1323, 1289, 1211, 1151 cm^{-1}; MS (ES) *m/z* 184 $[M]^+$; HRMS (ES) calc for $C_{13}H_{16}N_3O_3$ $[M + H]^+$ 262.1190. Found: 262.1192; Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.81; H, 5.73; N, 16.15.

***tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (371a):**[184]



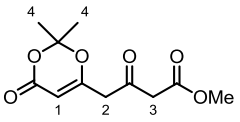
Method A. Carboxylic acid **400** (5.6 g, 35.1 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (16 mL) at 0 °C. Oxalyl chloride (4.0 mL, 46.7 mmol, 1.33 eq.) was added followed by DMF (5 drops) and the reaction mixture was stirred for 15 min at 0 °C. The reaction was allowed to warm up to room temperature and further stirred for 2 h. The volatiles were concentrated under reduced pressure to give the corresponding acid chloride **398a** as a yellow oil.

To a solution of HMDS (26.3 mL, 105.3 mmol, 3.6 eq.) in THF (206 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 50.5 mL, 126.4 mmol, 3.6 eq.) and the resulting mixture was stirred for 30 min. Dioxinone **368** (14.9 g, 105.3 mmol, 3.0 eq.) in THF (45 mL) was added dropwise to the stirring solution and the resulting mixture was allowed to stir further for 1 h at −78 °C. Acid chloride **398a** (6.2 g, 35.1 mmol, 1.0 eq.) in THF (20 mL) was added dropwise and the reaction mixture was further stirred for 3 h at −78 °C. The reaction was quenched at −78 °C by addition of aqueous saturated NH_4Cl (150 mL) and was allowed to warm up to room temperature. The aqueous layer was acidified to pH 3 with 1 N HCl and was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexanes/EtOAc, 100:1, 10:1, 5:1, 4:1, 3:2) to give keto-ester dioxinone **371a** (7.6 g, 76%) as an off-white solid.

Method B. To a solution of HMDS (5.42 mL, 25.8 mmol, 4.65 eq.) in THF (250 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 11.1 mL, 27.7 mmol, 5.0 eq.) and the resulting mixture was stirred for 30 min. Dioxinone **368** (3.0 g, 21.1 mmol, 3.8 eq.) in THF (10 mL) was added dropwise to the stirring solution and the resulting mixture was allowed to stir further for 1 h at −78 °C. Benzotriazole derivative **398c** (1.45 g, 5.5 mmol, 1.0 eq.) in THF (20 mL) was added dropwise and the resulting mixture was further stirred for 3 h at −78 °C and allowed to warm up to room temperature overnight. The reaction was quenched by addition of aqueous saturated NH_4Cl (30 mL) and was allowed to warm up to room temperature. The aqueous layer was acidified to pH 3 with 1 N HCl and was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexanes/EtOAc, 100:1, 10:1, 5:1, 4:1, 3:2) to give keto-ester dioxinone **371a** (204 mg, 20%) as an off-white solid. R*f* 0.48 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H, H1), 3.48 (s, 2H, H3), 3.42 (s, 2H, H2), 1.72 (s, 6H, H4), 1.48 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100

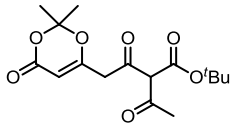
MHz, $CDCl_3$) δ 196.0, 165.5, 163.7, 160.5, 107.3, 97.0, 82.7, 50.4, 46.9, 27.9 (3C), 24.9 (2C); Mp 44 ºC; IR (film) 2988, 1732, 1715, 1635, 1392, 1370, 1315, 1267, 1252, 1206, 1165, 1130, 1055 cm^{-1}; MS (CI) *m/z* 285 $[M + H]^+$; HRMS (CI) calc for $C_{14}H_{21}O_6$ $[M + H]^+$ 285.1345. Found: 285.1338; Anal. Calcd. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.18; H, 7.10. Data in accordance with the literature.

Methyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (371b):



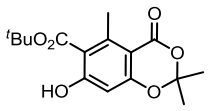
To a solution of HMDS (3.52 mL, 16.8 mmol, 3.6 eq.) in THF (28 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 6.75 mL, 16.8 mmol, 3.6 eq.) and the resulting mixture was stirred for 30 min. Dioxinone **368** (2.0 g, 14.0 mmol, 3.0 eq.) in THF (5 mL) was added dropwise to the stirring solution and the resulting mixture was allowed to stir further for 1 h at −78 °C. Methyl 3-chloro-3-oxopropanoate **398b** (502 μL, 4.68 mmol, 1.0 eq.) in THF (2 mL) was added dropwise and the reaction mixture was further stirred for 3 h at −78 °C. The reaction was quenched at −78 °C by addition of aqueous saturated NH_4Cl (20 mL) and was allowed to warm up to room temperature. The aqueous layer was acidified to pH 3 with 1 N HCl and was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexanes/EtOAc, 100:1, 10:1, 5:1, 4:1, 3:2) to give keto-ester dioxinone **371b** (395 mg, 35%) as a yellow oil. R*f* 0.36 (hexanes/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (s, 1H, H1), 3.76 (s, 3H, CO_2*Me*), 3.53 (s, 2H, H3), 3.49 (s, 2H, H2), 1.71 (s, 6H, H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 166.7, 163.4, 160.4, 107.4, 97.1, 52.6, 48.8, 46.9, 24.9 (2C); IR (film) 3001, 2956, 1724, 1637, 1438, 1391, 1332, 1273, 1204 cm^{-1}; MS (ES) *m/z* 243 $[M + H]^+$; HRMS (ES) calc for $C_{11}H_{15}O_6$ $[M + H]^+$ 243.0868. Found: 243.0869; Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.65; H, 5.75.

***tert*-Butyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (403):**



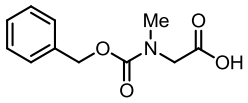
Magnesium chloride (67 mg, 0.70 mmol, 2.0 eq.) and pyridine (77 μL, 0.95 mmol, 2.7 eq.) were mixed in CH_2Cl_2 (3 mL) at 0 °C and stirred for 5 min. Keto-ester dioxinone **371a** (100 mg, 0.35 mmol, 1.0 eq.) was added and the resulting mixture was stirred at 0 °C for 30 min. Acetyl chloride **402** (33 μL, 0.45 mmol, 1.3 eq.) in CH_2Cl_2 (500 μL) was added dropwise and the reaction mixture was further stirred for 30 min at 0 °C. The reaction was quenched at 0 °C with aqueous saturated NH_4Cl (3 mL) and the mixture was allowed to warm up to room temperature. The aqueous layer was acidified to pH 3 using 1 N HCl and was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give diketo-ester dioxinone **403** (88 mg, 77%) as a yellow oil which was used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.68 (s, 2H), 2.38 (s, 3H), 1.70 (s, 6H), 1.54 (s, 9H).

***tert*-Butyl 7-hydroxy-2,2,5-trimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (404):**



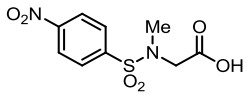
To a solution of diketo-ester dioxinone **403** (88 mg, 0.27 mmol, 1.0 eq.) in CH_2Cl_2 (2.3 mL) was added Et_3N (752 μL, 5.39 mmol, 20.0 eq.) and the resulting mixture was stirred at 30 °C for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (3 mL) and the aqueous layer was acidified to pH 1 using 1 N HCl and was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 7:3) to give the aromatic product **404** (45 mg, 53 %) as a white solid. R*f* 0.63 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (s, 1H, OH), 6.38 (s, 1H, Ar-*H*), 2.89 (s, 3H, Ar-*Me*), 1.69 (s, 6H, C(C*H*$_3$)$_2$), 1.63 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 167.1, 160.4, 159.9, 149.7, 112.3, 106.5, 104.8, 103.0, 84.8, 28.3 (3C), 25.7 (2C); Mp 72 – 74°C; IR (film) 2984, 1724, 1654, 1590, 1319, 1274, 1255, 1236, 1181, 1150, 1027 cm^{-1}; MS (ES) *m/z* 309 $[M + H]^+$; HRMS (ES) calc for $C_{16}H_{21}O_6$ $[M + H]^+$ 309.1335. Found: 309.1338; Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.18; H, 6.46.

2-(((Benzyloxy)carbonyl)(methyl)amino)acetic acid (405a):[165]



Sarcosine **397** (5.0 g, 56.1 mmol, 1.0 eq.) was dissolved in H_2O (150 mL) and the resulting mixture was cooled to 0 °C. Na_2CO_3 (17.8 g, 168.3 mmol, 3.0 eq.) was added followed by CbzCl (10 mL, 70.1 mmol, 1.25 eq.) in THF (50 mL). The resulting mixture was stirred for 30 min at 0 °C and was allowed to warm up to room temperature and further stirred for 12 h. The cloudy mixture was partitioned between Et_2O (50 mL) and H_2O (50 mL) and the organic layer was discarded. The aqueous layer was acidified to pH 1 using 1 N HCl and was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give Cbz-protected sarcosine **405a** (11.9 g, 95%) as a colorless oil which was used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (bs, 1H, CO_2H), 7.37 – 7.31 (m, 5H, Ar-*H*), 5.17 (s, 1.1H, rotamer 1, OCH_2Ar), 5.14 (s, 0.8H, rotamer 2, OCH_2Ar), 4.09 (s, 1.2H, rotamer 1, CH_2CO_2H), 4.04 (s, 0.8H, rotamer 2, CH_2CO_2H), 3.01 (s, 3H, N*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 174.5, 156.9, 156.1, 136.3, 128.5, 128.4, 128.1, 128.0, 127.8, 67.7, 67.6, 50.5, 50.2, 35.9, 35.4 (contains rotamers); IR (film) 3946, 1676, 1484, 1453, 1362, 1220, 1148 cm^{-1}; MS (CI) *m/z* 224 $[M + H]^+$; HRMS (CI) calc for $C_{11}H_{14}NO_4$ $[M + H]^+$ 224.0926. Found: 224.0923; Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.11; H, 5.96; N, 6.19. Data in accordance with the literature.

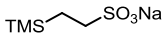
2-(*N*-methyl-4-nitrophenylsulfonamido)acetic acid (405b):



Sarcosine **397** (5.0 g, 56.1 mmol, 1.0 eq.) was dissolved in H_2O (150 mL) and the resulting mixture was cooled to 0 °C. Na_2CO_3 (17.8 g, 168.3 mmol, 3.0 eq.) was added followed by NsCl (15.5 g, 70.1 mmol, 1.25 eq.) in THF (50 mL). The resulting mixture was stirred for 30 min at 0 °C and was allowed to warm up to room temperature and further stirred for 12 h. The mixture was partitioned between Et_2O (50 mL) and H_2O (50 mL) and the organic layer was discarded. The aqueous layer was acidified to pH 1 using 1 N HCl and was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give Ns-protected sarcosine **405b** (13.9 g, 91%) as a white solid which was used without any further purification. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.41 (d, J = 9.0 Hz, 2H, Ar-*H*), 8.07 (d, J = 8.8 Hz, 2H, Ar-*H*), 4.07 (s, 2H, CH_2), 2.95 (s, 3H, N*Me*); ^{13}C NMR (100 MHz, Methanol-d_4) δ 171.6, 151.6, 145.7, 129.9 (2C), 125.3

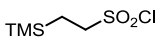
(2C), 51.6, 36.1; Mp 171 – 173 °C; IR (film) 1715, 1527, 13148, 1315, 1244, 1153, 1081 cm^{-1}; MS (CI) *m/z* 292 $[M + NH_4]^+$; HRMS (CI) calc for $C_9H_{14}N_3O_6S$ $[M + NH_4]^+$ 292.0604. Found: 292.0603; Anal. Calcd. for $C_9H_{10}N_2O_6S$: C, 39.42; H, 3.68; N, 10.21; S, 11.69. Found: C, 39.51; H, 3.74; N, 10.33; S, 11.55.

Sodium 2-(trimethylsilyl)ethanesulfonate (407):[166]



To a solution of vinyltrimethylsilane **406** (28.0 mL, 191 mmol, 1.0 eq.) and *tert*-butyl perbenzoate (0.70 mL, 3.6 mmol, 2 mol%) in MeOH (70 mL) was added a solution of $NaHSO_3$ (36.1 g, 347 mmol, 1.9 eq.) in H_2O (70 mL) and the resulting suspension was heated at 50 °C for 72 h. The suspension was concentrated under reduced pressure followed by azeotropic removal of the residual H_2O with MeOH (2 × 25 mL). MeOH (200 mL) was added to the resulting white solid and the suspension was stirred vigorously for 10 min. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The filter cake was resuspended in MeOH (200 mL) and stirred vigorously for 10 min, filtered into the vessel containing the original filtrate and further concentrated under reduced pressure. The preceding operations were repeated again on the filter cake and after the final concentration of the combined filtrates, the resulting white solid was dried (100 °C and 0.1 mmHg) for 12 h to give sodium β-trimethylsilylethanesulfonate **407** (25.0 g, 66%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 – 2.25 (m, 2H, CH_2SO$_3$Na), 0.82 – 0.77 (m, 2H, CH_2TMS), 0.03 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.4, 11.9, -1.8(3C); Mp > 310 °C. Data in accordance with the literature.

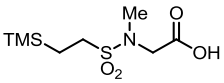
2-(Trimethylsilyl)ethanesulfonyl chloride (408):[167a]



To a solution of PPh_3 (11.5 g, 44.1 mmol, 2.0 eq.) in CH_2Cl_2 (18 mL) at 0 °C was slowly added SO_2Cl_2 (3.9 mL, 48.5 mmol, 2.2 eq.) and the resulting mixture was stirred for 5 min. The cooling bath was removed and sulfonate **407** was added portionwise over 15 min and the resulting mixture was further stirred for 12 h at room temperature. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to 5 mL under reduced pressure. EtOAc/hexanes (90 mL, 1:3) and Celite (3.6 g) were added and the resulting mixture was stirred for 15 min, filtered through a pad of Celite and concentrated under reduced pressure. The crude mixture was purified by silica gel column

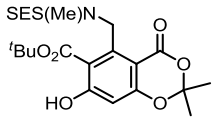
chromatography (hexanes) to give SESCl **408** (3.6 g, 81%) as a pale yellow oil. R*f* 0.65 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 – 3.58 (m, 2H, CH_2SO$_2$Cl), 1.33 – 1.29 (m, 2H, CH_2TMS), 0.11 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.4, 11.9, -2.0 (3C). Data in accordance with the literature.

2-(*N*-methyl-2-(trimethylsilyl)ethylsulfonamido)acetic acid (405c):



Sarcosine **397** (1.59 g, 17.8 mmol, 1.0 eq.) was suspended in CH_2Cl_2 (35 mL) and TMSCl (2.26 mL, 17.8 mmol, 1.0 eq.) was added .The resulting mixture was heated to reflux for 3 h and was allowed to cool to room temperature. Et_3N (4.97 mL, 35.6 mmol, 2.0 eq.) and SESCl (3.58 g, 17.8 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) were added and the reaction mixture was stirred for 12 h at room temperature. MeOH (50 mL) was added and the reaction mixture was concentrated under reduced pressure. H_2O (50 mL) was added and the pH was adjusted to 8 using saturated aqueous Na_2CO_3. The aqueous layer was extracted with Et_2O (2 × 25 mL) and the combined organic layers were discarded. The aqueous layer was acidified to pH 1 using 1 N HCl and was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give SES-protected sarcosine **405c** (3.20 g, 71%) as an off-white solid which was used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (bs, 1H, CO_2H), 4.14 (s, 2H, CH_2CO$_2$H), 3.04 – 2.99 (m, 2H, CH_2SO$_2$), 3.02 (s, 3H, N*Me*), 1.09 – 1.04 (m, 2H, CH_2TMS), 0.05 (s, 9H, Si(*CH*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 50.6, 48.7, 35.9, 10.1, -2.0 (3C); Mp 68 °C; IR (film) 2952, 2657, 1731, 1403, 1325, 1246, 1168, 1132, 1029, 830 cm^{-1}; MS (ES) *m/z* 252 [M – H]$^-$; HRMS (ES) calc for $C_8H_{18}NO_4SSi$ [M – H]$^-$ 252.0730. Found: 252.0726; Anal. Calcd. for $C_8H_{19}NO_4SSi$: C, 37.92; H, 7.56; N, 5.53; S,12.65. Found: C, 38.04; H, 7.63; N, 5.45; S,12.60.

***tert*-Butyl 7-hydroxy-2,2-dimethyl-5-((*N*-methyl-4-nitrophenylsulfonamido)methyl)-4-oxo-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (394a):**



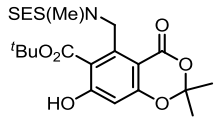
Ns-protected sarcosine **405b** (434 mg, 1.58 mmol, 1.0 equiv.) was dissolved in THF (3.5 mL) and the resulting solution was cooled to 0 °C. Oxalyl chloride (182 μL, 2.08 mmol, 1.3 equiv.) and DMF (5 drops) were added and the resulting mixture was stirred for 15 min at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 2 h. The volatiles were concentrated under reduced pressure to give the corresponding acid chloride **396b** which was used without any further purification.

Magnesium chloride (151 mg, 1.58 mmol, 2.0 eq.) and pyridine (172 μL, 2.13 mmol, 2.7 eq.) were mixed in CH_2Cl_2 (7 mL) at 0 °C and the resulting mixture was stirred for 5 min. Keto-ester dioxinone **371a** (225 mg, 0.79 mmol, 1.0 eq.) was added and the resulting mixture was stirred for 30 min at 0 °C. Acid chloride **396b** (463 mg, 1.58 mmol, 2.0 eq.) in CH_2Cl_2 (2 mL) was added dropwise and the resulting mixture was further stirred for 2.5 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (6 mL) at 0 °C and the mixture was allowed to warm up to room temperature. The aqueous layer was acidified to pH 3 using 1 N HCl and was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give diketo-ester dioxinone **395a** which was used without any further purification. R*f* 0.39 (hexanes/EtOAc 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.9 Hz, 2H), 5.34 (s, 1H), 4.60 (s, 2H), 3.73 (s, 2H), 2.95 (s, 3H), 1.70 (s, 6H), 1.56 (s, 9H).

To a solution of crude diketo-ester dioxinone **395a** (427 mg, 0.79 mmol, 1.0 eq.) in CH_2Cl_2 (8.5 mL) was added Et_3N (2.3 mL, 16.9 mmol, 20.0 eq.). The resulting mixture was stirred for 12 h at 30 °C and was allowed to cool down to room temperature. Saturated aqueous NH_4Cl (15 mL) was added and the aqueous layer was acidified with 1 N HCl and was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1) to give the aromatic product **394a** (198 mg, 48% over 2 steps) as a white solid. R*f* 0.48 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H, OH), 8.39 (d, J = 8.8 Hz, 2H, Ar-*H*), 7.99 (d, J = 8.8 Hz, 2H, Ar-*H*), 6.54 (s, 1H, Ar-*H*), 5.18 (s, 2H, ArCH_2N), 2.54 (s, 3H, N*Me*), 1.71 (s, 9H, C(CH_3)$_3$), 1.66 (s, 6H, C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 165.4, 159.9, 159.7, 150.2, 142.7, 141.8, 129.2 (2C), 124.2 (2C), 114.4, 107.2, 105.6, 105.4, 85.3, 46.8, 34.8 (3C), 28.1, 25.5 (2C); IR (film) 1686, 1611, 1529, 1353, 1271, 1165 cm^{-1}; MS (ES) *m/z* 523 [M + H]$^+$; HRMS (ES) calc for $C_{23}H_{27}N_2O_{10}S$ [M +

H]$^+$ 523.1367. Found: 523.1386; Anal. Calcd. for $C_{23}H_{26}N_2O_{10}S$: C, 52.87; H, 5.02; N, 5.36; S, 6.14. Found: C, 53.00; H, 4.93; N, 5.25; S, 6.30.

***tert*-Butyl 7-hydroxy-2,2-dimethyl-5-((*N*-methyl-2-(trimethylsilyl)ethylsulfonamido)methyl)-4-oxo-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (394b):**



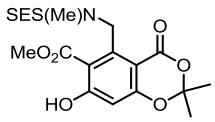
SES-protected sarcosine **405c** (500 mg, 1.97 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2 mL) and the resulting solution was cooled to 0 °C. Oxalyl chloride (206 μL, 2.36 mmol, 1.2 equiv.) and DMF (2 drops) were added and the resulting mixture was stirred for 15 min at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 2 h. The volatiles were concentrated under reduced pressure to give the corresponding acid chloride **396c** (505 mg, 95%) which was used without any further purification. ^{1}H NMR (400 MHz, acetone-d_6) δ 4.67 (s, 2H), 3.12 – 3.07 (m, 2H), 3.04 (s, 3H), 1.03 – 0.99 (m, 2H), 0.07 (s, 9H).

Magnesium chloride (273 mg, 2.87 mmol, 2.0 eq.) and pyridine (301 μL, 3.87 mmol, 2.7 eq.) were mixed in CH_2Cl_2 (20 mL) at 0 °C and the resulting mixture was stirred for 5 min. Keto-ester dioxinone **371a** (408 mg, 1.43 mmol, 1.0 eq.) was added and the resulting mixture was stirred for 30 min at 0 °C. Acid chloride **396c** (505 mg, 1.86 mmol, 1.3 eq.) in CH_2Cl_2 (3 mL) was added dropwise and the resulting mixture was further stirred for 2.5 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C and the mixture was allowed to warm up to room temperature. The aqueous layer was acidified to pH 3 using 1 N HCl and was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give diketo-ester dioxinone **395b** which was used without any further purification. R*f* 0.37 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 4.57 (s, 2H), 3.75 (s, 2H), 3.02 – 2.98 (m, 2H), 2.99 (s, 3H), 1.70 (s, 6H), 1.55 (s, 9H), 1.09 – 1.04 (m, 2H), 0.05 (s, 9H).

To a solution of crude diketo-ester dioxinone **395b** (745 mg, 1.43 mmol, 1.0 eq.) in CH_2Cl_2 (17 mL) was added Et_3N (4.0 mL, 28.7 mmol, 20.0 eq.). The resulting mixture was stirred for 12 h at 30 °C and was allowed to cool down to room temperature. Saturated aqueous NH_4Cl (20 mL) was added and the aqueous layer was acidified with 1 N HCl and was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 7:1, 5:1, 3:1) to give the aromatic product **394b** (345 mg, 49% over 2 steps) as a colorless oil. R*f* 0.52 (hexanes/EtOAc 1:1); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H, OH), 6.54 (s, 1H, Ar-*H*), 5.26 (s, 2H, ArCH_2N), 3.01 – 2.95 (m, 2H, CH_2SO_2), 2.65 (s, 3H, N*Me*), 1.72 (s, 6H, $C(CH_3)_2$), 1.68 (s, 9H, $C(CH_3)_3$), 1.06 – 1.02 (m, 2H, CH_2TMS), 0.06 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 165.7, 159.9, 159.7, 143.7, 114.4, 107.1, 105.3 (2C), 86.6, 46.5, 44.0, 34.5, 28.1 (3C), 25.6 (2C), 9.4, -1.9 (3C); IR (film) 2925, 1727, 1666, 1605, 1461, 1328, 1251, 1168 cm^{-1}; MS (ES) *m/z* 502 $[M + H]^+$; HRMS (ES) calc for $C_{22}H_{36}NO_8SSi$ $[M + H]^+$ 502.1938. Found: 502.1931.

Methyl 7-hydroxy-2,2-dimethyl-5-((*N*-methyl-2-(trimethylsilyl)ethylsulfonamido)methyl)-4-oxo-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (394c):



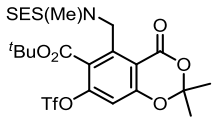
SES-protected sarcosine **405c** (827 mg, 3.26 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (3.5 mL) and the resulting solution was cooled to 0 °C. Oxalyl chloride (374 μL, 4.30 mmol, 1.3 equiv.) and DMF (3 drops) were added and the resulting mixture was stirred for 15 min at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 2 h. The volatiles were concentrated under reduced pressure to give the corresponding acid chloride **396c** which was used without any further purification.

Magnesium chloride (311 mg, 3.26 mmol, 2.0 eq.) and pyridine (355 μL, 4.40 mmol, 2.7 eq.) were mixed in CH_2Cl_2 (25 mL) at 0 °C and the resulting mixture was stirred for 5 min. Keto-ester dioxinone **371b** (395 mg, 1.63 mmol, 1.0 eq.) was added and the resulting mixture was stirred for 30 min at 0 °C. Acid chloride **396c** (880 mg, 3.26 mmol, 2.0 eq.) in CH_2Cl_2 (3 mL) was added dropwise and the resulting mixture was further stirred for 2.5 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) at 0 °C and the mixture was allowed to warm up to room temperature. The aqueous layer was acidified to pH 3 using 1 N HCl and was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give diketo-ester dioxinone **395c** which was used without any further purification. R*f* 0.35 (hexanes/EtOAc 1:1).

To a solution of crude diketo-ester dioxinone **395c** (778 mg, 1.63 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) was added Et_3N (4.5 mL, 28.7 mmol, 20.0 eq.). The resulting mixture was stirred for 12 h at 30 °C and was allowed to cool down to room temperature. Saturated aqueous NH_4Cl (20 mL) was added and the aqueous layer was acidified with 1 N HCl and was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material

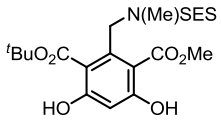
was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 5:1, 3:1) to give the aromatic product **394c** (223 mg, 30% over 2 steps) as an orange oil. R*f* 0.32 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H, OH), 6.57 (s, 1H, Ar-*H*), 5.37 (s, 2H, ArCH_2N), 4.03 (s, 3H, CO_2Me), 2.97 – 2.92 (m, 2H, CH_2SO_2), 2.62 (s, 3H, N*Me*), 1.73 (s, 6H, C(CH_3)$_2$), 1.09 – 1.04 (m, 2H, CH_2TMS), 0.07 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 166.4, 160.3, 159.9, 145.0, 111.9, 107.5, 105.5, 105.4, 53.5, 46.7, 44.2, 34.2, 25.7 (2C), 9.5, -1.9 (3C); IR (film) 2955, 1762, 1673, 1604, 1462, 1433, 1328, 1252, 1231, 1150 cm^{-1}; MS (ES) *m/z* 460 $[M + H]^+$; HRMS (ES) calc for $C_{19}H_{30}NO_8SSi$ $[M + H]^+$ 460.1447. Found: 460.1461.

***tert*-Butyl 2,2-dimethyl-5-((*N*-methyl-2-(trimethylsilyl)ethylsulfonamido)methyl)-4-oxo-7-(((trifluoromethyl)sulfonyl)oxy)-4*H*-benzo[*d*][1,3]dioxine-6-carboxylate (412):**



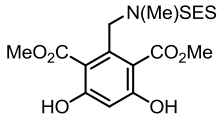
Phenol **394b** (240 mg, 0.47 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (478 μL) at 0 °C. Pyridine (58 μL, 0.72 mmol, 1.5 eq.) and Tf_2O (108 μL, 0.62 mmol, 1.3 eq.) were added and the reaction mixture was stirred for 2 h at 0 °C. The reaction was quenched with H_2O (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexanes/EtOAc 10:1, 7:1, 5:1) to give triflate **412** (232 mg, 77%) as a colorless oil. R*f* 0.59 (hexanes/EtOAc 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H, Ar-*H*), 4.99 (s, 2H, ArCH_2N), 3.01 – 2.97 (m, 2H, CH_2SO_2), 2.83 (s, 3H, N*Me*), 1.75 (s, 6H, C(CH_3)$_2$), 1.63 (s, 9H, C(CH_3)$_3$), 1.03 – 0.98 (m, 2H, CH_2TMS), 0.06 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 158.8, 157.8, 150.4, 142.6, 125.5, 113.0, 109.9, 106.6 (2C), 85.4, 47.2, 43.5, 37.3, 27.9 (3C), 25.4 (2C), 9.2, -1.9 (3C); IR (film) 2954, 1717, 1663, 1599, 1442, 1369, 1325, 1238, 1153, 1124, 1091 cm^{-1}; MS (ES) *m/z* 634 $[M + H]^+$; HRMS (ES) calc for $C_{23}H_{35}F_3NO_{10}S_2Si$ $[M + H]^+$ 634.1415. Found: 634.1424.

1-*tert*-Butyl 3-methyl 4,6-dihydroxy-2-((*N*-methyl-2-(trimethylsilyl)ethylsulfonamido)methyl) isophthalate (414a):



To a solution of phenol **394b** (62 mg, 0.12 mmol, 1.0 eq.) in MeOH (1.0 mL) in a sealed tube was added Cs_2CO_3 (81 mg, 0.25 mmol, 2.0 eq.) and the resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in EtOAc/1 N HCl (5 mL, 1:1). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 2:1, 1:1) to give methyl ester **414a** (46 mg, 77%) as a yellow foam. R*f* 0.45 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H, OH), 10.39 (s, 1H, OH), 6.53 (s, 1H, Ar-*H*), 5.04 (s, 2H, ArCH_2N), 3.97 (s, 3H, CO_2Me), 2.81 – 2.77 (m, 2H, CH_2SO_2), 2.52 (s, 3H, N*Me*), 1.64 (s, 9H, C(CH_3)$_3$), 1.03 – 0.98 (m, 2H, CH_2TMS), 0.05 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.8, 163.9 (2C), 142.1, 111.5, 108.9, 104.5, 85.2, 53.1, 49.6, 44.9, 34.4, 28.4 (3C), 9.6, -2.0 (3C); IR (film) 3344, 2954, 1717, 1663, 1599, 1442, 1369, 1325, 1238, 1091 cm^{-1}; MS (ES) *m/z* 476 [M + H]$^+$; HRMS (ES) calc for $C_{20}H_{34}NO_8SSi$ [M + H]$^+$ 476.1766. Found: 476.1774.

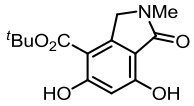
Dimethyl 4,6-dihydroxy-2-((*N*-methyl-2-(trimethylsilyl)ethylsulfonamido)methyl)isophthalate (414b):



To a solution of phenol **394c** (100 mg, 0.2 mmol, 1.0 eq.) in MeOH (1.6 mL) in a sealed tube was added Cs_2CO_3 (142 mg, 0.4 mmol, 2.0 eq.) and the resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in EtOAc/1 N HCl (5 mL, 1:1). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc 2:1, 1:1) to give methyl ester **414b** (57 mg, 60%) as an off-white solid. R*f* 0.42 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 2H, OH), 6.56 (s, 1H, Ar-*H*), 5.03 (s, 2H, ArCH_2N), 3.97 (s, 6H, CO_2Me), 2.83 – 2.78 (m, 2H, CH_2SO_2), 2.52 (s, 3H, N*Me*), 1.02 – 0.97 (m, 2H, CH_2TMS), 0.06 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100

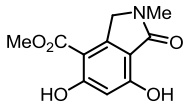
MHz, $CDCl_3$) δ 170.2 (2C), 164.3 (2C), 142.7, 109.5 (2C), 104.7, 53.0, 49.5, 45.2, 34.3 (2C), 9.6, -2.0 (3C); Mp (Et_2O) 76 – 78 °C; IR (film) 2954, 1727, 1665, 1598, 1433, 1322, 1226, 1168, 1149, 1122, 1018 cm^{-1}; MS (ES) *m/z* 434 $[M + H]^+$; HRMS (ES) calc for $C_{17}H_{28}NO_8SSi$ $[M + H]^+$ 434.1292. Found: 434.1305.

***tert*-Butyl 5,7-dihydroxy-2-methyl-1-oxoisoindoline-4-carboxylate (392a):**



To methyl ester **414a** (207 mg, 0.4 mmol, 1.0 eq) was added TBAF (1 M in THF, 4.36 mL, 4.3 mmol, 10.0 eq.) and the resulting mixture was heated to reflux for 12 h. $CaCO_3$ (722 mg), DOWEX 50WX8-400 (2.17 g) and MeOH (5 mL) were added and the mixture was further stirred for 12 h at room temperature. The reaction mixture was filtered over a pad of Celite and washed with MeOH (15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give isoindolinone **392a** (95 mg, 78%) as a white solid. R*f* 0.07 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H, OH), 9.20 (s, 1H, OH), 6.41 (s, 1H, Ar-*H*), 4.48 (s, 2H, ArCH_2N), 3.13 (s, 3H, N*Me*), 1.63 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.9, 167.7, 160.6, 145.0, 110.8 (2C), 102.8, 83.9, 54.7, 28.6, 28.4 (3C); Mp (Et_2O) 160 – 164 °C; IR (film) 3300, 2924, 2853, 1673, 1460, 1369, 1339, 1260, 1167, 1167 cm^{-1}; MS (ES) *m/z* 280 $[M + H]^+$; HRMS (ES) calc for $C_{14}H_{18}NO_5$ $[M + H]^+$ 280.1177. Found: 280.1185; Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.21; H, 6.13; N, 4.97.

Methyl 5,7-dihydroxy-2-methyl-1-oxoisoindoline-4-carboxylate (392b):



To methyl ester **414b** (64 mg, 0.15 mmol, 1.0 eq) was added TBAF (1 M in THF, 1.46 mL, 1.4 mmol, 10.0 eq.) and the resulting mixture was heated to reflux for 12 h. $CaCO_3$ (271 mg), DOWEX 50WX8-400 (814 mg) and MeOH (1.8 mL) were added and the mixture was further stirred for 12 h at room temperature. The reaction mixture was filtered over a pad of Celite and washed with MeOH (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give isoindolinone **392b** (23 mg, 65%) as a white solid. R*f* 0.07 (hexanes/EtOAc 1:1); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 11.33 (s, 1H, OH), 9.24 (s, 1H, OH), 6.42 (s, 1H, Ar-*H*), 4.50 (s, 2H, ArCH_2N), 3.97 (s, 3H, CO_2*Me*), 3.14 (s, 3H, N*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.3, 167.5, 161.0, 145.2, 111.1, 102.7, 101.4, 54.6, 52.3, 28.6; Mp (Et_2O) 160 – 162 °C; IR (film) 3315, 2951, 1663, 1620, 1439, 1242, 1189, 1053 cm^{-1}; MS (ES) *m/z* 238 $[M + H]^+$; HRMS (ES) calc for $C_{11}H_{12}NO_5$ $[M + H]^+$ 238.0704. Found: 238.0715; Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.69; H, 4.57; N, 5.82.

X-ray data

Crystal data and structure refinement for (±)-248

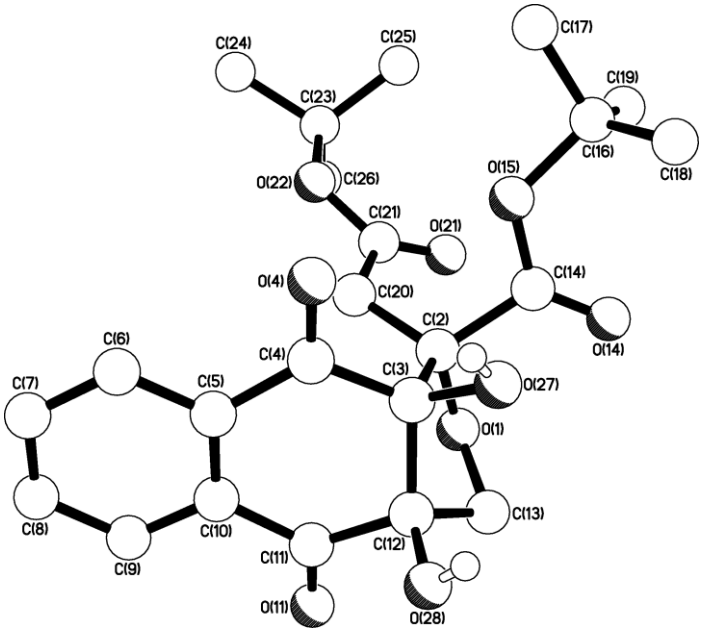


Table 1. Crystal data and structure refinement for AB0902.

Identification code	AB0902	
Empirical formula	C23 H28 O9	
Formula weight	448.45	
Temperature	293(2) K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Monoclinic, P2(1)	
Unit cell dimensions	a = 9.7615(3) Å	α = 90°
	b = 11.5743(3) Å	β = 111.407(3)°
	c = 10.9421(3) Å	γ = 90°

Volume, Z	1150.98(6) $Å^3$, 2
Density (calculated)	1.294 Mg/m^3
Absorption coefficient	0.838 mm^{-1}
F(000)	476
Crystal colour / morphology	Colourless tablets
Crystal size	0.25 x 0.17 x 0.06 mm^3
θ range for data collection	4.87 to 72.12°
Index ranges	-10<=h<=11, -13<=k<=13, -13<=l<=13
Reflns collected / unique	3623 / 2864 [R(int) = 0.0182]
Reflns observed [F>4σ(F)]	2404
Absorption correction	Analytical
Max. and min. transmission	0.955 and 0.874
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2864 / 3 / 298
Goodness-of-fit on F^2	1.051
Final R indices [F>4σ(F)]	R1 = 0.0442, wR2 = 0.1200
	R1+ = 0.0442, wR2+ = 0.1200
	R1- = 0.0444, wR2- = 0.1203
R indices (all data)	R1 = 0.0552, wR2 = 0.1276
Absolute structure parameter	x+ = 0.0(3), x- = 1.2(3)
	Absolute structure indeterminate
Extinction coefficient	0.0040(8)
Largest diff. peak, hole	0.386, -0.159 $eÅ^{-3}$

Mean and maximum shift/error 0.000 and 0.000

Table 2. Bond lengths [Å] and angles [°] for AB0902.

O(1)-C(2)	1.431(4)
O(1)-C(13)	1.441(4)
C(2)-C(20)	1.528(4)
C(2)-C(14)	1.553(5)
C(2)-C(3)	1.587(4)
C(3)-O(27)	1.422(4)
C(3)-C(4)	1.527(5)
C(3)-C(12)	1.551(4)
C(4)-O(4)	1.209(4)
C(4)-C(5)	1.491(5)
C(5)-C(10)	1.387(5)
C(5)-C(6)	1.389(5)
C(6)-C(7)	1.383(7)
C(7)-C(8)	1.358(8)
C(8)-C(9)	1.379(7)
C(9)-C(10)	1.384(5)
C(10)-C(11)	1.475(5)
C(11)-O(11)	1.216(4)
C(11)-C(12)	1.540(5)
C(12)-O(28)	1.399(4)

C(12)-C(13)	1.501(5)
C(14)-O(14)	1.179(4)
C(14)-O(15)	1.319(4)
O(15)-C(16)	1.504(4)
C(16)-C(18)	1.471(7)
C(16)-C(19)	1.483(7)
C(16)-C(17)	1.504(7)
C(20)-C(21)	1.503(4)
C(21)-O(21)	1.204(4)
C(21)-O(22)	1.326(4)
O(22)-C(23)	1.485(4)
C(23)-C(26)	1.476(7)
C(23)-C(25)	1.508(6)
C(23)-C(24)	1.515(6)

C(2)-O(1)-C(13)	107.7(2)
O(1)-C(2)-C(20)	108.6(3)
O(1)-C(2)-C(14)	106.7(3)
C(20)-C(2)-C(14)	112.4(2)
O(1)-C(2)-C(3)	104.7(2)
C(20)-C(2)-C(3)	113.2(3)
C(14)-C(2)-C(3)	110.7(3)
O(27)-C(3)-C(4)	109.7(3)
O(27)-C(3)-C(12)	106.9(2)

C(4)-C(3)-C(12)	114.6(3)
O(27)-C(3)-C(2)	108.9(2)
C(4)-C(3)-C(2)	114.1(2)
C(12)-C(3)-C(2)	102.0(2)
O(4)-C(4)-C(5)	122.2(3)
O(4)-C(4)-C(3)	118.8(3)
C(5)-C(4)-C(3)	118.9(3)
C(10)-C(5)-C(6)	119.8(4)
C(10)-C(5)-C(4)	121.5(3)
C(6)-C(5)-C(4)	118.7(3)
C(7)-C(6)-C(5)	119.8(5)
C(8)-C(7)-C(6)	120.3(4)
C(7)-C(8)-C(9)	120.6(4)
C(8)-C(9)-C(10)	120.2(5)
C(9)-C(10)-C(5)	119.4(4)
C(9)-C(10)-C(11)	119.3(4)
C(5)-C(10)-C(11)	121.4(3)
O(11)-C(11)-C(10)	121.2(3)
O(11)-C(11)-C(12)	119.5(3)
C(10)-C(11)-C(12)	119.3(3)
O(28)-C(12)-C(13)	116.5(3)
O(28)-C(12)-C(11)	104.8(2)
C(13)-C(12)-C(11)	109.3(3)
O(28)-C(12)-C(3)	113.5(3)

C(13)-C(12)-C(3)	100.7(2)
C(11)-C(12)-C(3)	112.4(3)
O(1)-C(13)-C(12)	101.8(3)
O(14)-C(14)-O(15)	128.2(3)
O(14)-C(14)-C(2)	123.0(3)
O(15)-C(14)-C(2)	108.7(3)
C(14)-O(15)-C(16)	119.6(3)
C(18)-C(16)-C(19)	116.0(5)
C(18)-C(16)-C(17)	108.8(5)
C(19)-C(16)-C(17)	110.0(4)
C(18)-C(16)-O(15)	109.7(3)
C(19)-C(16)-O(15)	110.3(4)
C(17)-C(16)-O(15)	101.1(4)
C(21)-C(20)-C(2)	115.6(3)
O(21)-C(21)-O(22)	125.7(3)
O(21)-C(21)-C(20)	124.9(3)
O(22)-C(21)-C(20)	109.4(3)
C(21)-O(22)-C(23)	123.1(3)
C(26)-C(23)-O(22)	110.5(3)
C(26)-C(23)-C(25)	111.6(5)
O(22)-C(23)-C(25)	109.6(4)
C(26)-C(23)-C(24)	112.2(5)
O(22)-C(23)-C(24)	102.1(4)
C(25)-C(23)-C(24)	110.5(4)

Crystal data and structure refinement for 290

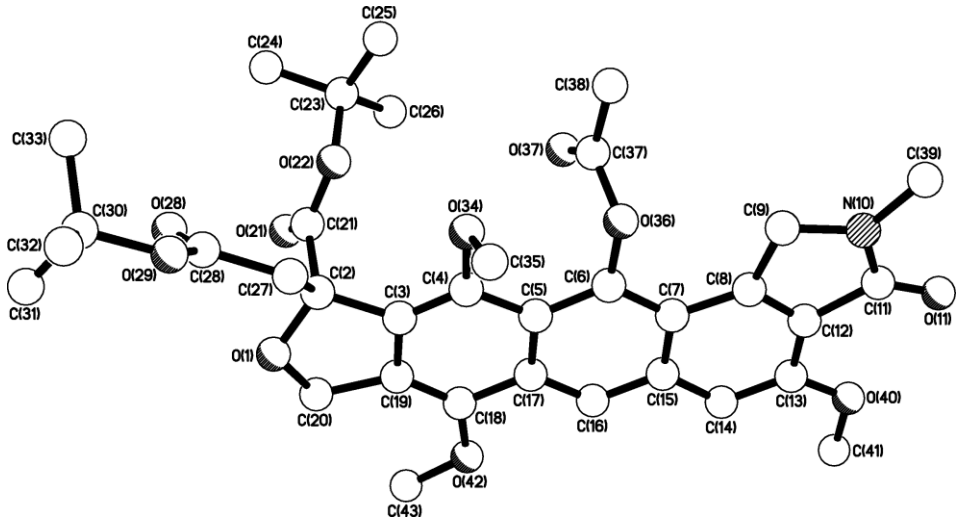


Table 1. Crystal data and structure refinement for AB0810b.

Identification code	AB0810b	
Formula	C35 H41 N O11, C H2 Cl2	
Formula weight	736.61	
Temperature	173 K	
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 18.1485(18) Å	$\alpha = 90°$
	b = 14.7283(7) Å	$\beta = 107.446(8)°$
	c = 14.2205(9) Å	$\gamma = 90°$
Volume, Z	3626.2(5) $Å^3$, 4	
Density (calculated)	1.349 Mg/m^3	
Absorption coefficient	0.240 mm^{-1}	

F(000)	1552
Crystal colour / morphology	Yellow tablets
Crystal size	0.23 x 0.21 x 0.05 mm^3
θ range for data collection	4.19 to 32.64°
Index ranges	-26<=h<=23, -21<=k<=20, -20<=l<=20
Reflns collected / unique	26843 / 11821 [R(int) = 0.0905]
Reflns observed [F>4σ(F)]	4578
Absorption correction	Analytical
Max. and min. transmission	0.988 and 0.956
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11821 / 25 / 467
Goodness-of-fit on F^2	1.023
Final R indices [F>4σ(F)]	R1 = 0.1084, wR2 = 0.2345
R indices (all data)	R1 = 0.2435, wR2 = 0.2984
Largest diff. peak, hole	0.597, -0.309 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for AB0810b.

O(1)-C(2)	1.426(4)
O(1)-C(20)	1.431(5)
C(2)-C(27)	1.501(5)
C(2)-C(3)	1.534(5)

C(2)-C(21)	1.545(5)
C(3)-C(4)	1.361(5)
C(3)-C(19)	1.427(5)
C(4)-O(34)	1.388(4)
C(4)-C(5)	1.430(5)
C(5)-C(6)	1.404(5)
C(5)-C(17)	1.449(5)
C(6)-O(36)	1.393(4)
C(6)-C(7)	1.402(5)
C(7)-C(15)	1.427(5)
C(7)-C(8)	1.439(5)
C(8)-C(12)	1.366(5)
C(8)-C(9)	1.503(5)
C(9)-N(10)	1.452(5)
N(10)-C(11)	1.349(6)
N(10)-C(39)	1.448(5)
C(11)-O(11)	1.228(5)
C(11)-C(12)	1.494(5)
C(12)-C(13)	1.421(6)
C(13)-O(40)	1.351(4)
C(13)-C(14)	1.366(5)
C(14)-C(15)	1.423(5)
C(15)-C(16)	1.389(4)
C(16)-C(17)	1.392(5)

C(17)-C(18)	1.436(5)
C(18)-C(19)	1.351(5)
C(18)-O(42)	1.376(4)
C(19)-C(20)	1.510(5)
C(21)-O(21)	1.196(4)
C(21)-O(22)	1.327(5)
O(22)-C(23)	1.487(5)
C(23)-C(24)	1.506(7)
C(23)-C(25)	1.506(7)
C(23)-C(26)	1.514(8)
C(27)-C(28)	1.524(5)
C(28)-O(28)	1.212(5)
C(28)-O(29)	1.325(5)
O(29)-C(30)	1.495(5)
C(30)-C(32)	1.518(7)
C(30)-C(31)	1.522(6)
C(30)-C(33)	1.538(7)
O(34)-C(35)	1.436(4)
O(36)-C(37)	1.380(4)
C(37)-O(37)	1.185(4)
C(37)-C(38)	1.478(6)
O(40)-C(41)	1.401(6)
O(42)-C(43)	1.414(4)

C(2)-O(1)-C(20)	110.2(3)
O(1)-C(2)-C(27)	107.3(3)
O(1)-C(2)-C(3)	103.8(3)
C(27)-C(2)-C(3)	117.7(3)
O(1)-C(2)-C(21)	109.0(3)
C(27)-C(2)-C(21)	113.4(3)
C(3)-C(2)-C(21)	104.9(3)
C(4)-C(3)-C(19)	123.0(3)
C(4)-C(3)-C(2)	129.5(3)
C(19)-C(3)-C(2)	107.3(3)
C(3)-C(4)-O(34)	120.0(3)
C(3)-C(4)-C(5)	119.2(3)
O(34)-C(4)-C(5)	120.8(3)
C(6)-C(5)-C(4)	125.5(3)
C(6)-C(5)-C(17)	116.3(3)
C(4)-C(5)-C(17)	118.2(3)
O(36)-C(6)-C(7)	115.4(3)
O(36)-C(6)-C(5)	121.1(3)
C(7)-C(6)-C(5)	123.4(3)
C(6)-C(7)-C(15)	118.6(3)
C(6)-C(7)-C(8)	125.3(3)
C(15)-C(7)-C(8)	116.1(3)
C(12)-C(8)-C(7)	120.5(3)
C(12)-C(8)-C(9)	109.4(3)

C(7)-C(8)-C(9)	130.0(3)
N(10)-C(9)-C(8)	102.1(3)
C(11)-N(10)-C(39)	122.4(4)
C(11)-N(10)-C(9)	114.0(3)
C(39)-N(10)-C(9)	123.6(4)
O(11)-C(11)-N(10)	126.2(4)
O(11)-C(11)-C(12)	128.2(5)
N(10)-C(11)-C(12)	105.5(3)
C(8)-C(12)-C(13)	123.0(3)
C(8)-C(12)-C(11)	108.9(4)
C(13)-C(12)-C(11)	128.1(4)
O(40)-C(13)-C(14)	126.2(4)
O(40)-C(13)-C(12)	116.2(3)
C(14)-C(13)-C(12)	117.7(4)
C(13)-C(14)-C(15)	121.2(4)
C(16)-C(15)-C(14)	119.5(3)
C(16)-C(15)-C(7)	119.1(3)
C(14)-C(15)-C(7)	121.4(3)
C(15)-C(16)-C(17)	122.1(3)
C(16)-C(17)-C(18)	120.3(3)
C(16)-C(17)-C(5)	120.2(3)
C(18)-C(17)-C(5)	119.5(3)
C(19)-C(18)-O(42)	127.7(3)
C(19)-C(18)-C(17)	120.6(3)

O(42)-C(18)-C(17)	111.7(3)
C(18)-C(19)-C(3)	119.4(3)
C(18)-C(19)-C(20)	133.1(3)
C(3)-C(19)-C(20)	107.5(3)
O(1)-C(20)-C(19)	105.5(3)
O(21)-C(21)-O(22)	126.5(4)
O(21)-C(21)-C(2)	123.8(4)
O(22)-C(21)-C(2)	109.5(3)
C(21)-O(22)-C(23)	120.6(3)
O(22)-C(23)-C(24)	108.9(4)
O(22)-C(23)-C(25)	101.2(3)
C(24)-C(23)-C(25)	111.8(5)
O(22)-C(23)-C(26)	109.1(4)
C(24)-C(23)-C(26)	114.4(4)
C(25)-C(23)-C(26)	110.6(5)
C(2)-C(27)-C(28)	112.3(3)
O(28)-C(28)-O(29)	126.0(4)
O(28)-C(28)-C(27)	123.0(4)
O(29)-C(28)-C(27)	111.0(3)
C(28)-O(29)-C(30)	121.4(3)
O(29)-C(30)-C(32)	102.4(4)
O(29)-C(30)-C(31)	109.4(4)
C(32)-C(30)-C(31)	111.2(4)
O(29)-C(30)-C(33)	109.6(3)

C(32)-C(30)-C(33)	111.6(4)
C(31)-C(30)-C(33)	112.2(4)
C(4)-O(34)-C(35)	112.3(3)
C(37)-O(36)-C(6)	116.8(3)
O(37)-C(37)-O(36)	122.3(3)
O(37)-C(37)-C(38)	126.8(4)
O(36)-C(37)-C(38)	110.8(3)
C(13)-O(40)-C(41)	115.8(3)
C(18)-O(42)-C(43)	120.6(3)

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