Helsinki University of Technology
Department of Chemical Technology
Laboratory of Organic Chemistry

CNEORINS, CYCLOPROPANES AND PROPELLANES:

SYNTHESIS OF WINDMILL MOLECULES

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Abstract

Propellanes are molecules in which a tricyclic system is conjoined by a carbon–carbon single bond. They have been studied both theoretically and synthetically. Propellane structures are present in many different classes of natural products. Total syntheses of these natural products are reviewed.

Cneorin C has been isolated from the xerophytic shrub *Cneorum pulverulentum*, which is native to the Canary Islands. It is a natural product containing a [4.3.1]propellane ring system as the northern part of the molecule and a 5,5-spiroketal unit and a butenolide moiety as the southern part. Despite the intriguing structure, the molecule has not attracted synthetic attention except from our group. The northern DEFG ring system of cneorin C is an ideal candidate for the copper-catalyzed intramolecular cyclopropanation of a diazomalonate. The synthesis of the DEFG ring system of cneorin C is described. The key steps include: 1) an enzymatic kinetic resolution providing the first stereogenic center of the molecule in an enantioselective fashion, 2) intramolecular cyclopropanation of a diazomalonate providing the EFG ring fragment and 3) an anionic cyclization of a sulfone yielding the [4.3.1]propellane ring system.

Acknowledgements

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Espoo, April 2005 *Ainoliisa Pihko*

Abbreviations and definitions

*	denotes formal total synthesis
acac	acetylacetonato
AIBN	azobis(isobutyronitrile)
alloc	allyloxycarbonyl
app	apparent
BINOL	1,1'-bi-2-naphthol
Boc	*t*-butoxycarbonyl
br	broad
CAL-A	*Candida antarctica* lipase A
CAL-B	*Candida antarctica* lipase B
calcd	calculated
CAN	cerium(IV) ammonium nitrate
m-CPBA	*m*-chloroperbenzoic acid
CSA	camphorsulfonic acid
d	day
D–A	Diels–Alder reaction
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL-H	diisobutyl aluminum hydride
DIPE	diisopropyl ether
DIPT	diisopropyl tartrate
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPE	1,2-bis(diphenylphosphino)ethane

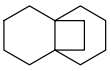
h	hour
HMDS	bis(trimethylsilyl)amine
HMPA	hexamethylphosphoramide
IBX	*o*-iodoxybenzoic acid
IMDA	intramolecular Diels–Alder reaction
imid.	imidazole
LDA	lithium diisopropylamide
lipase PS	lipase from *Pseudomonas cepacia*
Ms	methanesulfonyl
MS	molecular sieves
MOM	methoxymethyl
MTBE	methyl *t*-butyl ether
MTPA	α-methoxy-α-(trifluoromethylphenyl)acetic acid
MVK	methyl vinyl ketone
MW	microwave
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
Ns	*p*-nitrophenylsulfonyl
obs	obscure
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivalate
PMB	*p*-methoxybenzyl
PPA	polyphosphoric acid
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
rac	racemic
RR	rearrangement
rt	room temperature
sat. aq.	saturated aqueous
sm	starting material
TASF	tris(dimethylamino)sulfur (trimethylsilyl)difluoride
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TBS	*t*-butyldimethylsilyl
TEOC	trimethylsilylethoxycarbonyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
thexyl	1,1,2-trimethylpropyl
THF	tetrahydrofuran
TMS	trimethylsilyl

TPAP	tetra-*n*-propylammonium perruthenate
tol	toluene
trisyl	triisopropylbenzenesulfonyl
Ts	*p*-toluenesulfonyl
p-TsOH	*p*-toluenesulfonic acid

Contents

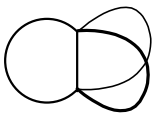
1. Propellanes and their synthesis

The first propellanes were synthesized in the 1930's during investigations into the Diels–Alder reaction.[1-6] However, the first 'propellane by design' was synthesized much later, in 1965.[7,8] Their nomenclature was introduced shortly thereafter. In 1966, Bloomfield and Irelan reported a synthesis of [4.4.2]propellane (**1**) and used the term propellerane in this context,[9] but the editors did not accept this nomenclature[10] and the compound was reported as 9,10-dihydro-9,10-ethanonaphthalene. In the same year, Ginsburg and co-workers introduced the name propellane in a paper that reported the syntheses of a variety of different propellanes without editorial dissent.[11]

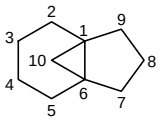


1

Webster's Unabridged Dictionary defines a propeller as 'a device having a revolving hub with radiating blades'[12] and, indeed, the structure of the molecules is in accordance with the name (see Figures 1 and 2). The name propellane refers to a tricyclic system conjoined by a carbon–carbon single bond. The nomenclature, suggested by Ginsburg and co-workers, follows and simplifies the one used for tricycloalkanes (Figure 1).[11]



General structure of propellanes



Numbering of [4.3.1]propellane

[1.1.1]propellane (**2**)

Figure 1. Propellanes.

Photo: Markku Ahonen

Figure 2. Windmills in January in Oritkari, Oulu, Finland.

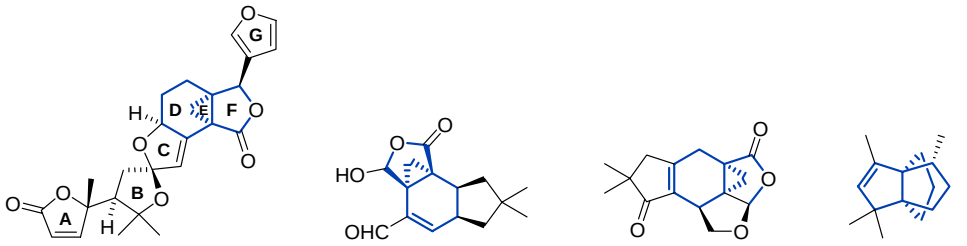
The first synthesis of a small-ring propellane, [3.2.1]propellane, was published in 1968.[13] Theoretically the most interesting propellane is [1.1.1]propellane (**2**) (Figure 1). The reports of the first modeling studies concluded that **2** should be more stable than the corresponding diradical that lacks the conjoining bond.[14,15] However, the researchers were uncertain that **2** could ever exist. A decade later, Wiberg and Walter reported the synthesis and isolation of a surprisingly stable molecule, [1.1.1]propellane.[16] The nature of the central bond of the molecule has been the subject of many studies. The theoretical and experimental results of many different research groups agree on the special nature of the bond.[17-19] Some groups have questioned the existence of the central bond,[14,15,17,20,21] but Wiberg, Bader and Lau argue cogently that the bond definitely exists between the bridgehead carbons with a bond order of 0.73.[22,23,a]

Ginsburg[28-30] and Wiberg[19,31,32] have reviewed the syntheses and the theoretical studies of propellanes extensively, Wiberg concentrating on the small-ring propellanes and Ginsburg on the medium sized rings. In his book titled 'Propellanes', Ginsburg even describes the syntheses and structures of natural products possessing the propellane structure.[33]

Indeed, propellane structures are present in many different classes of natural products (Figure 3). Whereas theoretical studies have focused on small-ring propellanes containing

[a] The controversy regarding the central bond revolves around differing explanations of similar experimental facts and theoretical results of the nature of the bonding interaction. In addition to Wiberg's results, other theories have also been suggested.[18,24-27]

more than one 3- or 4-membered ring, in known natural products only one of the rings is small, the rest being 5 to 8-membered. The literature selected for this review describes the total syntheses of propellane containing natural products. Particular emphasis is on propellanes having a 3-membered ring in the ring system, because the interest of the author is cneorin C (**3**) (see Chapter 8 and Figure 3). The descriptions of the syntheses focus on the methods used for construction of the propellane ring systems of the molecules.



3: Cneorin C **4**: Marasmic acid **5**: Sterepolide **6**: Modhephene

Figure 3. Natural products which contain a propellane ring system.

By far, one of the most popular avenues to synthesize any ring system has been the venerable Diels–Alder reaction.[34] This has also been the case with propellane ring structures. If the ~20 syntheses of modhephene, a [3.3.3]propellane, are disregarded because the molecule consists of 5-membered rings (see Figure 3), half of the syntheses analyzed here have utilized the Diels–Alder reaction as one of the key ring-forming transformations. The following chapters describe the syntheses of natural products, which contain a propellane ring system.

2. [*n.n*.1]Propellanes

There are quite a few natural products with the [*n.n*.1]propellane structure. However, only eight of them have been synthesized. Two of these contain a cyclopropane ring and in six of them the smallest ring is an epoxide. From a synthetic point of view this is a crucial difference since constructing a cyclopropane ring is still considered a challenge while many excellent methods exist for the formation of epoxides. The ring system of propellanes poses its own challenge for three-membered ring formation.

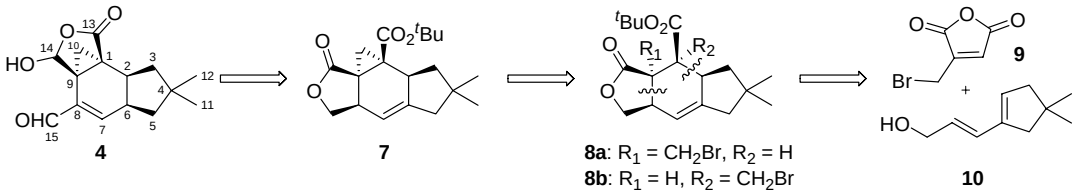
2.1 Cyclopropanes: marasmic acid, sterepolide

Of all natural products described in Chapter 2, marasmic acid (**4**) and sterepolide (**5**) most closely resemble the target molecule of this thesis, cneorin C (**3**) (see Figure 3). Parts of these molecules, highlighted in Figure 3, can all be described as [4.3.1]propellanes in which the smallest ring is a cyclopropane. The synthetic strategies that have been used to date for marasmic acid and sterepolide do not utilize a cyclopropanation reaction to install the challenging cyclopropane ring, instead most of them have adapted variants of the method developed by Woodward which accesses the cyclopropane ring by a Diels–Alder–enolate alkylation sequence (*vide infra*).

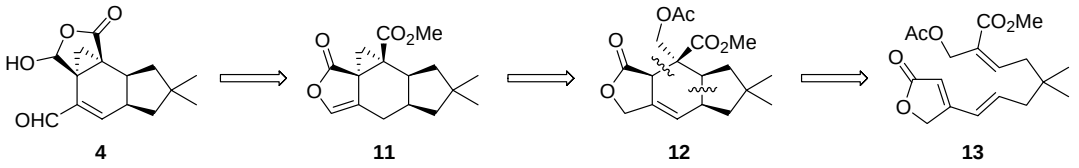
2.1.1 Marasmic acid

Marasmic acid (**4**) is an antibacterial agent isolated for the first time by Kavanagh *et al.* from the *Bacidiomycetes*.[35,36] To date, three different syntheses have been reported for this molecule. Retrosynthetic analysis of the syntheses (Scheme 1) reveals that two of the groups, Woodward[37-39] and Boeckman,[40] have employed the Diels–Alder reaction as the key ring-forming step. While both of these used a similar enolate alkylation strategy to form the cyclopropane ring, the third synthesis by Tobe *et al.* used a 1-oxaspirohexane rearrangement to make the carbon framework of the molecule.[41]

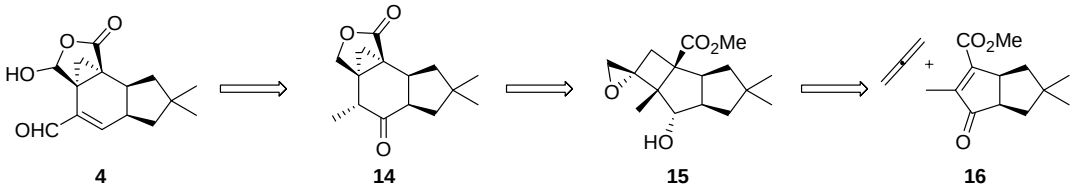
(±)-Marasmic acid/Woodward 1976



(±)-Marasmic acid/Boeckman 1980



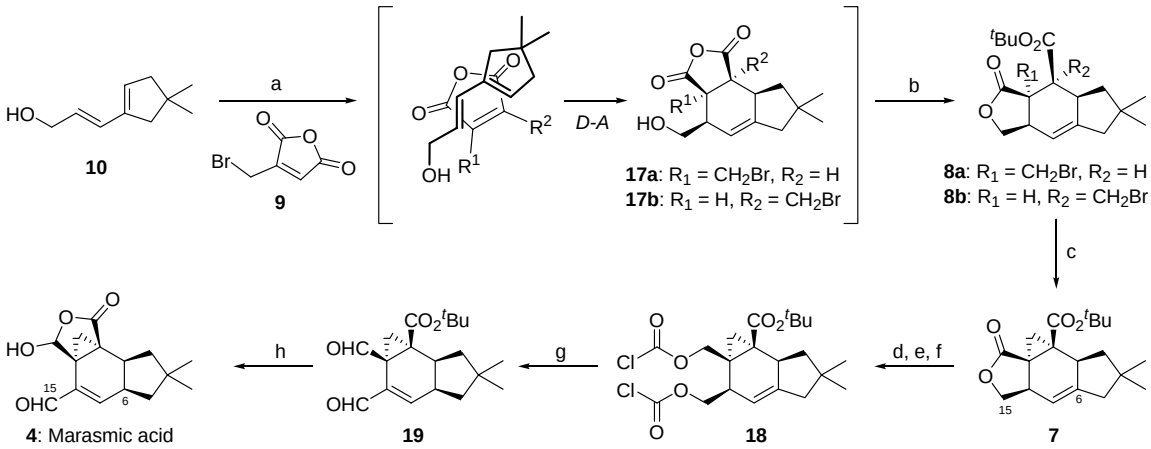
(±)-Marasmic acid/Tobe* 1990



Scheme 1. Retrosynthetic analysis of marasmic acid.

The Woodward group's synthesis of (±)-marasmic acid (Scheme 2)[37-39] commences with a completely *endo*-selective Diels–Alder reaction of diene **10** and 2-(bromomethyl)maleic anhydride (**9**), yielding a mixture of *tert*-butyl esters **8a** and **8b** after treatment of the cycloaddition product with isobutylene under acidic conditions. Subjection of the esters to potassium *tert*-butoxide afforded a single cyclopropane **7** in 44% yield over the three steps. Having obtained the carbon framework of the molecule with the correct stereochemistry, the oxidation states of carbons C_6 and C_{15} had to be adjusted. To that end, lactone **7** was subjected to a sequence of reductions and chloroformate formation with quinoline and phosgene to give dichloroformate **18**. The dichloroformate **18** was then oxidized[42] to dialdehyde **19**, which gave (±)-marasmic acid (**4**) after de-esterification.

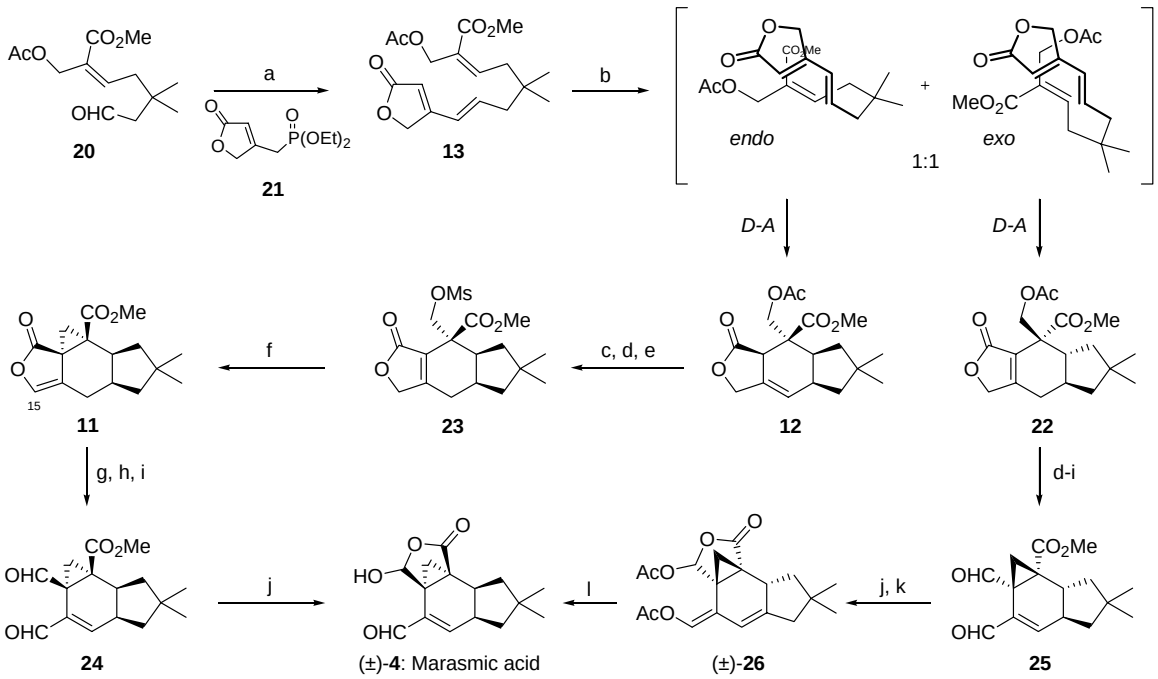
(±)-Marasmic acid/Woodward 1976



Scheme 2. a) **9**, CH_2Cl_2, rt, 36 h, **17a**:**17b** 1:1; b) isobutylene, *p*-TsOH, CH_2Cl_2, rt, 4 d; c) *t*-BuOK, *t*-BuOH, PhH, rt, 10 min, 44% over 3 steps; d) DIBAL-H, tol, –78 °C, 4 h; e) $NaBH_4$, MeOH, rt, 15 min, 65% over 2 steps; f) phosgene, quinoline, Et_2O, 0 °C → rt, 30 min, 91%; g) DMSO, 15 °C, 25 min, then Et_3N, 15 °C, 20 min, 25%; h) TFA, PhH, rt, 30 min, 50%.

Boeckman and co-workers chose to make the carbon skeleton of marasmic acid via an intramolecular Diels–Alder reaction (Scheme 3).[40] While Woodward's strategy provided essentially one diastereomer after the cyclopropane ring formation, Boeckman's group was unable to avoid a 1:1 mixture of two diastereomers **12** and **22** resulting from *endo* and *exo* transition states, respectively. They were able to transform both diastereomers to marasmic acid, however, thus enhancing the productivity of the synthesis. After isomerization of the double bond of **12** to give an α,β-unsaturated lactone (see **23**), the acetate was transformed into a mesylate to set the stage for the cyclopropane ring formation. Exposure of mesylate **23** to DBU in refluxing THF provided cyclopropane **11** in excellent yield. Next, a sequence of phenyl selenide formation, DIBAL-H reduction and *m*-CPBA oxidation yielded methyl marasmate (**24**). Finally, **24** was treated with BBr_3 to give (±)-marasmic acid (**4**).

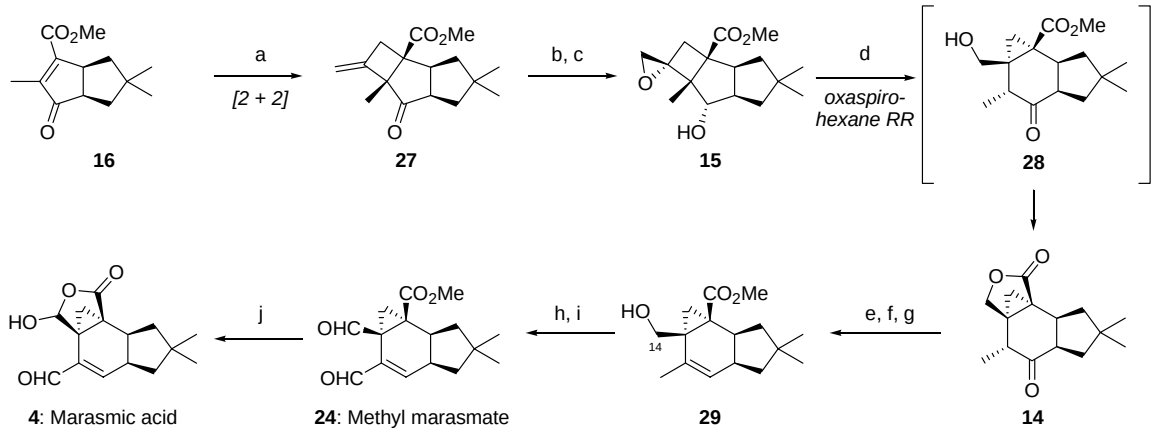
(±)-Marasmic acid/Boeckman 1980



Scheme 3. a) NaH, **21**, DMF, –5 → 0 °C, 30 min; b) tol, 200 °C, 30 min, 92%, **12**:**22** 1:1; c) *t*-BuOK, Et_2O, 0 °C, 30 min, quant.; d) cat. *p*-TsOH, MeOH, 65 °C, 12 h, quant.; e) MsCl, Et_3N, CH_2Cl_2, –5 °C, 30 min; f) DBU, THF, 65 °C, 8 h, >90% over 2 steps; g) PhSeBr, MeOH, rt, 2 h, 92%; h) DIBAL-H, tol:THF 1:1, –78 °C, 12 h; i) *m*-CPBA, CH_2Cl_2, –78 °C → rt, 4.5 h, 77% over 2 steps; j) BBr_3, CH_2Cl_2, –20 → 0 °C, 4.5 h, 50%, [k)[36] *p*-TsOH, isopropenyl acetate, reflux, 5 h; l)[36] AcOH, HCl, H_2O, "cold", 24 h, reactions not performed].

Tobe and co-workers have reported a 1-oxaspirohexane rearrangement as an entry to the norcarane skeleton present in the marasmane-type natural products (Scheme 4).[43] To utilize this rearrangement in the synthesis of marasmic acid,[41] an entry to cyclobutyl epoxide **15** was required. Thus, enone **16** was irradiated in the presence of allene to yield the head-to-head photoadduct **27** as the major product. Sodium borohydride reduction of the remaining ketone and *m*-CPBA epoxidation of the exocyclic double bond provided the rearrangement precursor **15** in a highly stereoselective manner. Exposure of **15** to concentrated sulfuric acid in methylene chloride for 1 hour gave cyclopropanolactone **14** in 80% yield, less than 5% of the β-Me isomer of **14** was observed. Next, ketone **14** was reduced and eliminated and the lactone ring was opened to enable the oxidation at C_{14}. Allylic oxidation[44] of **29** followed by Swern oxidation gave methyl marasmate (**24**) thus completing a formal total synthesis (denoted with an asterisk in Scheme 4) of (±)-marasmic acid (**4**).

(±)-Marasmic acid/Tobe* 1990

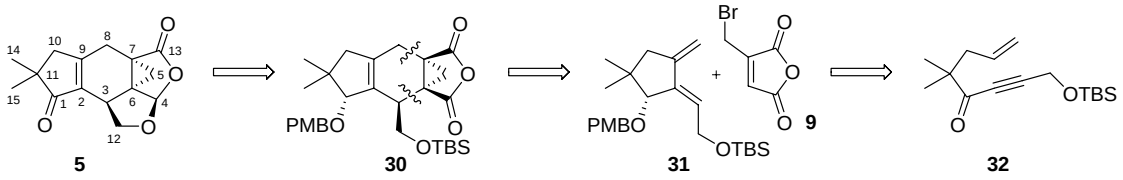


Scheme 4. a) *h*ν, allene, CH_2Cl_2, –78 °C, 3 h, 73%, 91% selectivity; b) $NaBH_4$, MeOH, rt, 4 h, 98%; c) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C, 89%; d) H_2SO_4, CH_2Cl_2, 80%; e) $NaBH_4$, THF:MeOH 1:2, rt, overnight, 9:1 selectivity; f) MsCl, pyr, DMF, 80 °C, 1 h, 87% over 2 steps; g) NaOH, H_2O, MeOH, reflux, overnight, 92%; h) TBHP, SeO_2, CH_2Cl_2, rt, overnight; i) $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C, 10 min, then Et_3N, 15 min → rt, 19% over 2 steps; [j)[40] BBr_3, CH_2Cl_2, –20 → 0 °C, 4.5 h, reaction not performed, formal total synthesis].

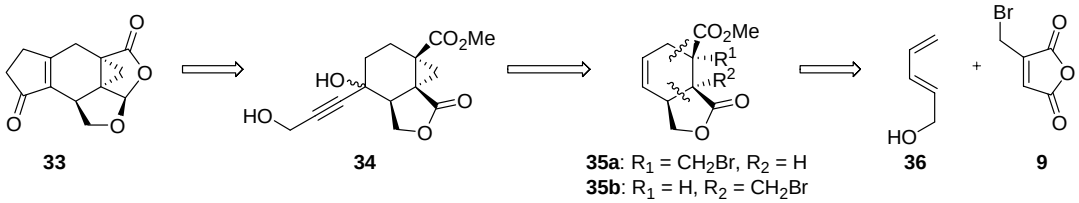
2.1.2 Sterepolide

Two different syntheses have been reported for the pentacyclic framework of sterepolide (**5**), a metabolite of the fungus *Stereum purpureum* (Scheme 5).[45] Trost and co-workers have reported a racemic[46] and an asymmetric[47] synthesis relying on a palladium-catalyzed cyclization and a Diels–Alder–cyclopropane formation sequence very similar to the one Woodward and co-workers used in their synthesis of marasmic acid (*vide supra*). Arai *et al.* have synthesized nor-sterepolide (**33**), which lacks the gem-dimethyl groups of sterepolide, utilizing a Diels–Alder–cyclopropane formation sequence and a Nazarov cyclization to form the ring system.[48]

(-)-Sterepolide/Trost 1985/1989



(±)-Nor-sterepolide/Arai 1985



Scheme 5. Retrosynthetic analysis of sterepolide.

In 1985, Trost and Chung published a racemic synthesis of sterepolide.[46] In 1989, they published a refined, enantioselective route to the molecule and assigned its absolute stereochemistry (Scheme 6).[47] Thus, reduction of the acetylenic ketone **32** with $LiAlH_4$/Darvon alcohol complex gave the protected alcohol **38** in >98% ee after PMB-protection. The stage was now set for the palladium catalyzed cyclization. In the presence of palladium acetate and ligand **39**, the Diels–Alder precursor **31** formed smoothly in 81% yield. Heating diene **31** and 2-(bromomethyl)maleic anhydride (**9**) in benzene followed by base treatment yielded cyclopropanoanhydride **30** as a single diastereomer. Removal of the silyl protecting group then opened the anhydride and consequently closed the 5-membered lactone ring. Reduction then closed the second lactone ring and deprotection followed by oxidation completed the total synthesis of (–)-sterepolide (**5**) and established its absolute stereochemistry as shown. On the basis of this stereochemical assignment, Trost has proposed that sterepolide and marasmic acid are biosynthetically derived from the same enantiomeric folding of farnesyl pyrophosphate (Figure 4).[36,45] Interestingly, the final step of the synthesis also destroys the stereocenter at C_1 that has been employed as a stereochemical control element throughout the synthesis.

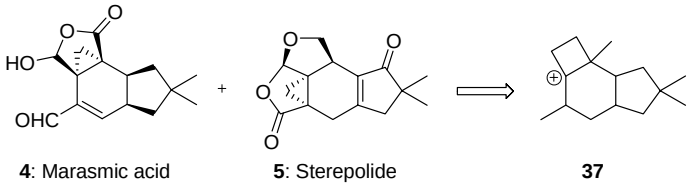
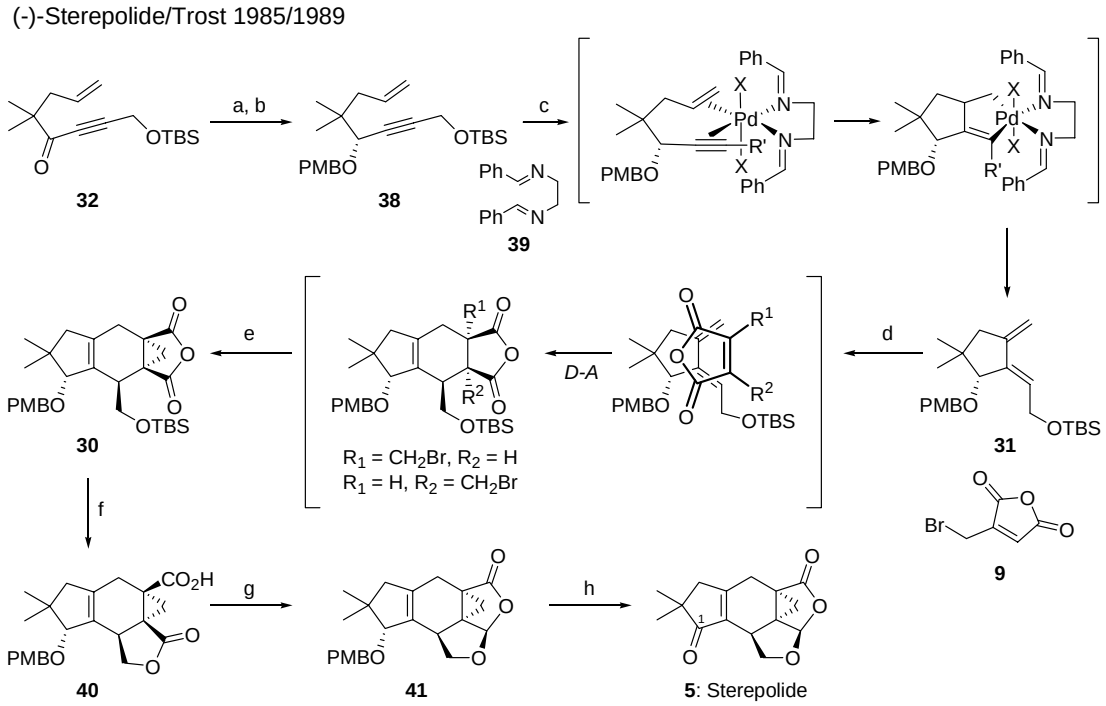
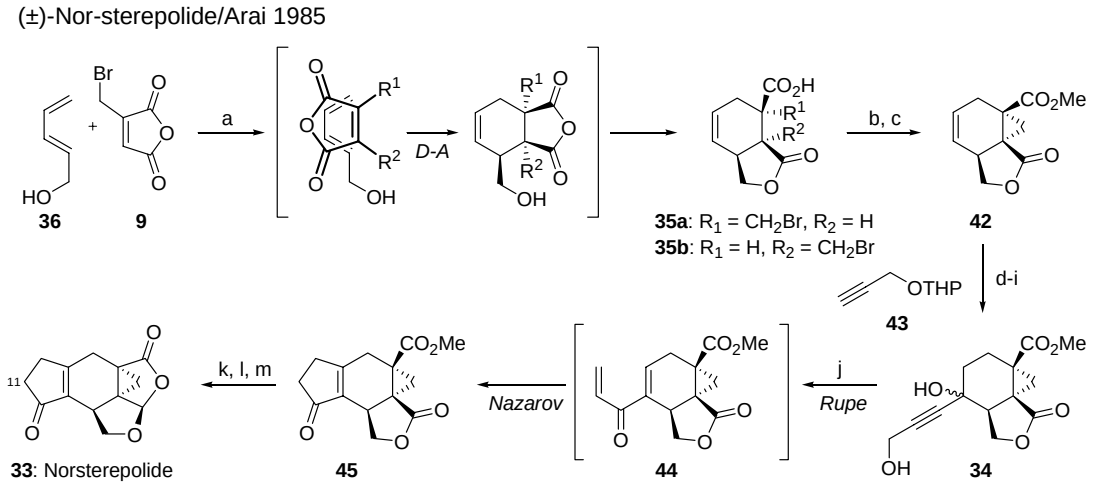


Figure 4. Biogenetic origin of marasmic acid and sterepolide.



Scheme 6. a) $LiAlH_4$/Darvon alcohol complex, Et_2O, –100 °C, quant., >98% ee; b) NaH, PMBBr, cat. Bu_4NI, THF, rt, 82%; c) 5% $Pd(OAc)_2$, 10% **39**, PhH, 70 °C, 81%; d) **9**, PhH, 80 °C; e) DBU, PhH, rt, 81% over 2 steps; f) TBAF, THF, rt; g) disiamylborane, Et_2O, 0 °C → rt, 75%; h) DDQ, CH_2Cl_2, H_2O, then PDC, 3Å MS, CH_2Cl_2, 83%.

Arai and co-workers' synthesis of nor-sterepolide (**33**) also commences with a Diels–Alder reaction of 2-(bromomethyl)maleic anhydride (**9**) and diene **36** (Scheme 7). The cycloaddition produced the *endo*-products **35a** and **35b** in a ratio of 4.5:1, which was inconsequential since after esterification the compound was treated with potassium *tert*-butoxide to close the cyclopropane ring in 90% yield. Next, the acetylenic side chain was introduced to prepare for the crucial Nazarov cyclization. Epoxidation, opening of the epoxide with hydrogen bromide, Jones oxidation and treatment with zinc to remove the bromide gave a ketone ready to be alkylated with **43**. Alkylation of the ketone with the lithium acetylide of **43** followed by deprotection of THP in acidic conditions produced diol **34**. Subjection of **34** to phosphorus pentoxide and methanesulfonic acid yielded the cyclopentenone **45** via a Rupe rearrangement followed by a Nazarov-type conrotatory electrocyclization.[49] The final lactone ring was closed by protecting the enone as a ketal, reducing the lactone and treating the resulting hemiacetal with acid to close the lactone and release the enone to give (±)-nor-sterepolide (**33**). Attempts were made to introduce the gem-dimethyl groups at C_{11}, but they proved unsuccessful.



Scheme 7. a) PhH, rt, 72 h, 72%, **35a**:**35b** 4.5:1; b) CH_2N_2, MeOH, Et_2O, quant.; c) *t*-BuOK, *t*-BuOH, PhH, rt, 1 h, 90%; d) *m*-CPBA, cat. bis(3-*t*-Bu-4-hydroxy-5-methylphenyl) sulfide, $NaHCO_3$, $CHCl_3$, reflux, 6 h, α: 58%, β: 16%; e) 48% HBr, $CHCl_3$, 0 °C → rt, 1 h, α-OH & β-Br: 80%, α-Br & β-OH: 70%; f) Jones reagent, acetone, rt, 6 h; g) Zn, AcOH, rt, 15 h; h) **43**, BuLi, –70 → –30 °C, 1 h, then sm, –78 °C, 1 h; i) *p*-TsOH, MeOH, rt, 48 h; 47% over 2 steps; j) P_2O_5, MsOH, rt, 2.5 h, 34%; k) ethylene glycol, PPTS, PhH, reflux, 5 h, 93%; l) DIBAL-H, THF, –90 °C, 30 min, 84%; m) *p*-TsOH, PhH, 55 °C, 7 h, 85%.

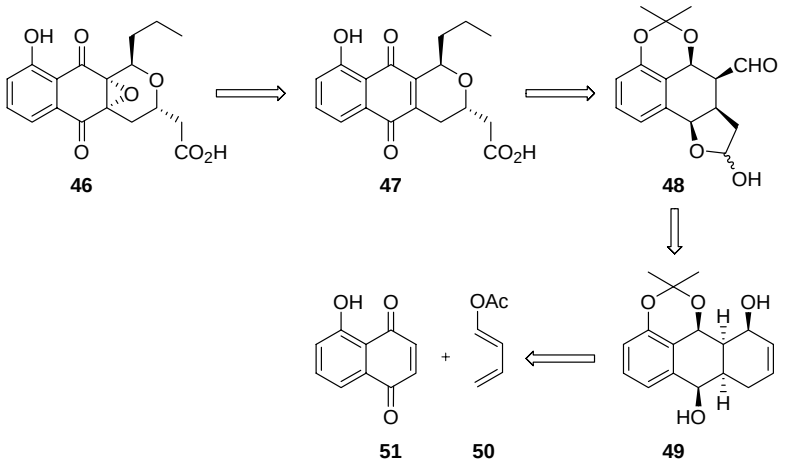
2.2 Epoxides: frenolicin B, dynemicin A, fusicogigantone A, SF 2315B, diepoxin σ, arthrinone

This rather heterogeneous group of molecules is unified by the fact that all of them have an epoxide ring fused to two other rings in their ring system. Most of them, namely frenolicin B, dynemicin A, SF 2315B, and diepoxin σ, are [4.4.1]propellanes, whereas fusicogigantone A is a [6.3.1]propellane and arthrinone a [4.3.1]propellane. The Diels–Alder reaction is a frequent feature of these syntheses; seven of the ten routes described herein utilize the cycloaddition to form the carbon backbone of the molecule. Once the rings are in place, the epoxidations generally proceed stereoselectively and give good yields of the products.

2.2.1 Frenolicin B

Frenolicin B (**46**), a pyranonaphthoquinone antibiotic isolated from *Streptomyces fradiae* in 1960,[50,51] has been synthesized[52] only once, although six syntheses for deoxyfrenolicin (**47**) have been reported. Since those syntheses, by Naruta and co-workers,[53] Semmelhack *et al.*,[54-56] Uno,[57] Kraus *et al.*,[58] Moore and co-workers,[59,60] Brimble and Lynds,[61] as well as Xu *et al.*,[62] lack the formation of the epoxide, which makes the molecule a propellane, they will not be treated here. Scheme 8 shows Ichihara's retrosynthetic approach to frenolicin (**46**). The key steps include a Lewis acid catalyzed Diels–Alder cyclization and an alkylation followed by cyclization of the pyran ring.

(±)-Frenolicin/Ichihara 1980



Scheme 8. Retrosynthetic analysis of frenolicin B.

Ichihara's synthesis of racemic frenolicin starts with a highly selective boron trifluoride catalyzed Diels–Alder reaction of juglone (**51**) and acetoxybutadiene (**50**), which gives the tricyclic acetate **52** in excellent yield (Scheme 9).[63] Selective reduction, ketal formation and reduction of the remaining ketone and acetate provided the allylic alcohol **49**. Lemieux-Johnson oxidation of the double bond in **49** afforded an equilibrated mixture of aldehyde **48** and hemiacetal **53**. This mixture was then treated with *n*-propyl magnesium bromide to give hemiacetal **54** stereoselectively in a chelation-controlled addition. Next, a Horner-Wadsworth-Emmons reaction added the needed two-carbon side chain, and a sequence of PCC- and DDQ-oxidations followed by basic hydrolysis provided naphthoquinone **47**. Subjection of **47** to *tert*-butyl hydroperoxide in the presence of Triton B gave a 1:1 mixture of two unseparable epoxide diastereomers, which was methylated, separated and hydrolyzed to give (±)-frenolicin (**46**). The lack of selectivity in the epoxidation step can be explained by the fact that the two bulky substituents can reside either pseudo-equatorial/pseudo-axially or pseudo-axial/pseudo-equatorially (Figure 5).

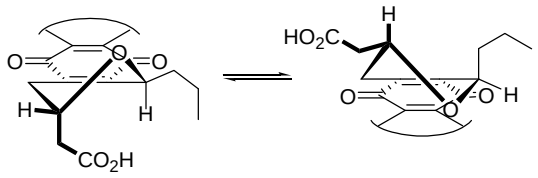
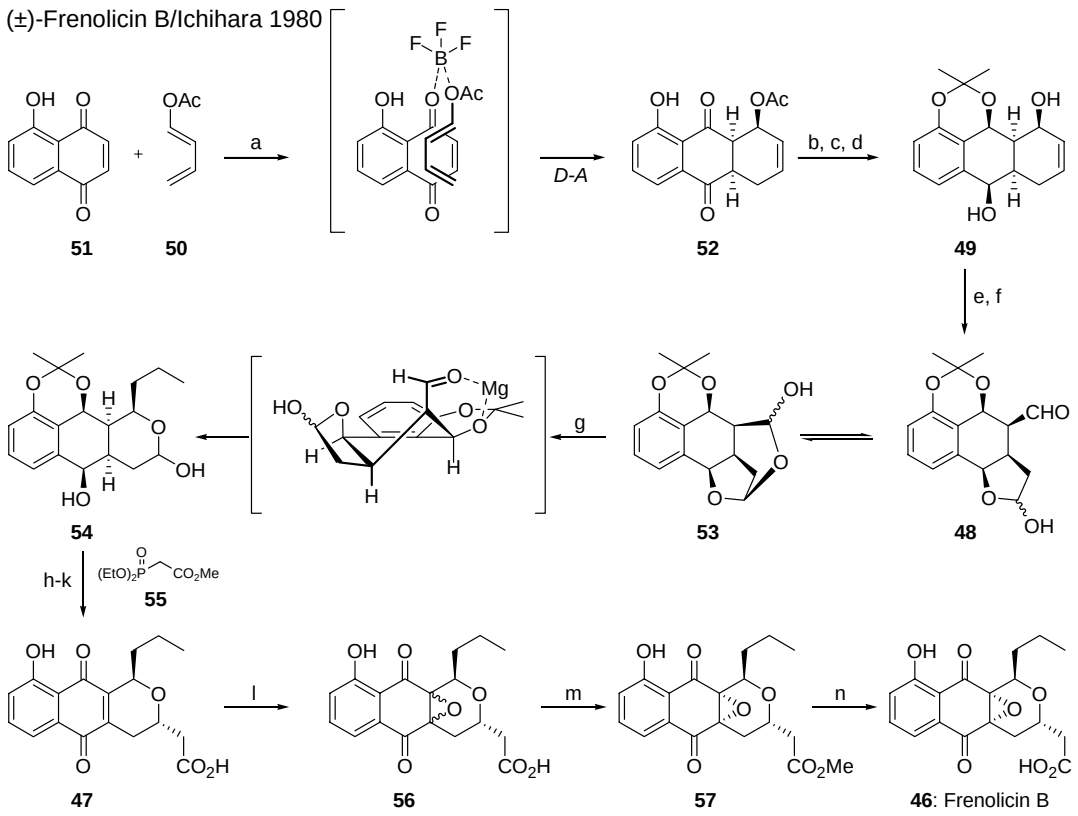


Figure 5. Conformations of alkene 47.

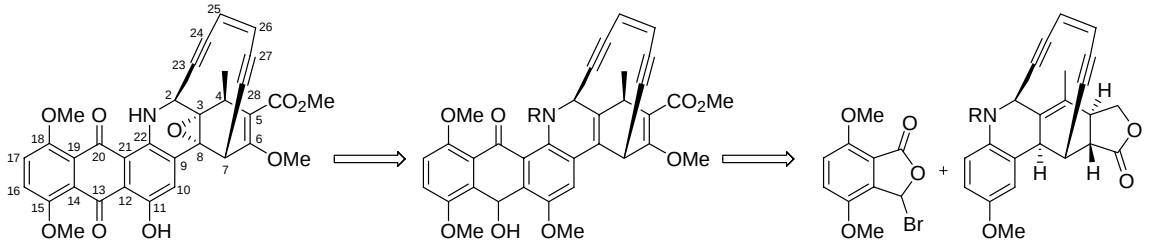


Scheme 9. a) BF_3, PhH or $CHCl_3$, 55 °C, 97%; b) $NaBH_4$, THF, 5 °C, quant.; c) 2,2-dimethoxypropane, acetone, $BF_3{\cdot}OEt_2$, 70%; d) $LiAlH_4$, Et_2O, 97%; e) OsO_4, $NaIO_4$, *t*-BuOH, H_2O; f) NaOAc, DABCO, 99% over 2 steps, g) *n*-PrMgBr, Et_2O, 66%; h) **55**, *n*-BuLi, DMSO, rt, 2 h, 61%; i) PCC, CH_2Cl_2, rt, 98%; j) DDQ, TsOH, MeOH, reflux, 9 h, then dioxane, reflux, 12 h; k) KOH, MeOH, H_2O; l) TBHP, triton B, dioxane, EtOH, rt, α:β 1:1; m) CH_2N_2, then separation of diastereomers; n) KOH, MeOH, H_2O, rt.

2.2.2 Dynemicin A

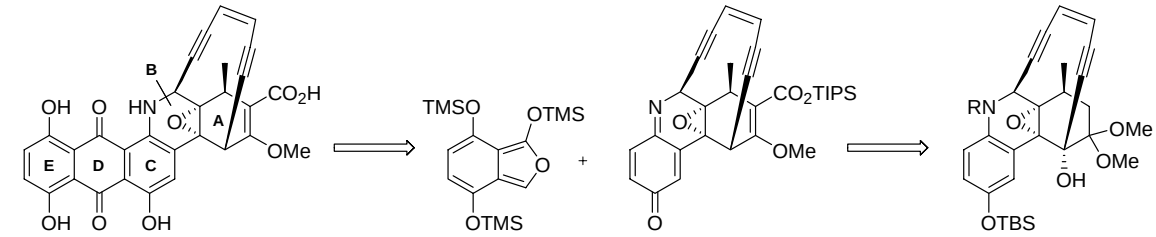
Dynemicin A (**62**), a potent antibacterial and anticancer agent isolated from *Micromonospora chersina*,[64,65] has attracted wide synthetic interest due to its biological activity and intriguing molecular structure. So far, two elegant total syntheses of dynemicin A and one of di-*O*-methyl dynemicin A methyl ester have appeared in the literature (Schemes 10 and 11). Also, five different synthetic approaches to model compounds of the dynemicin A ring framework have been published. The total syntheses by the groups of Schreiber,[66-69] Myers[70,71] and Danishefsky[72-77] will be treated here with more detail. The groups of Nicolaou,[78-81] Isobe,[82-84] Magnus[85], Maier[86] and Takahashi[87,88] have reported their efforts towards dynemicin A model compounds. Of these, the Nicolaou and Takahashi models include a [4.4.1]propellane ring system, so the retrosynthetic analyses of these syntheses are shown in Scheme 15. The syntheses of Isobe, Magnus and Maier did not result in the formation of the propellane skeleton and are thus outside the scope of this review. Maier has published a review that details the investigations of different dynemicin A analogs.[89]

(±)-Di-*O*-methyl dynemicin A methyl ester/Schreiber 1993



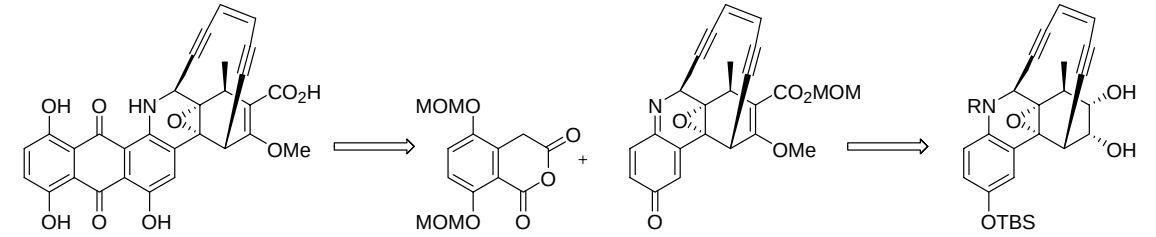
58 **59** **60** **61**

(+)-Dynemicin A/Myers 1995



62 **63** **64** **65**

(±)-Dynemicin A/Danishefsky 1995

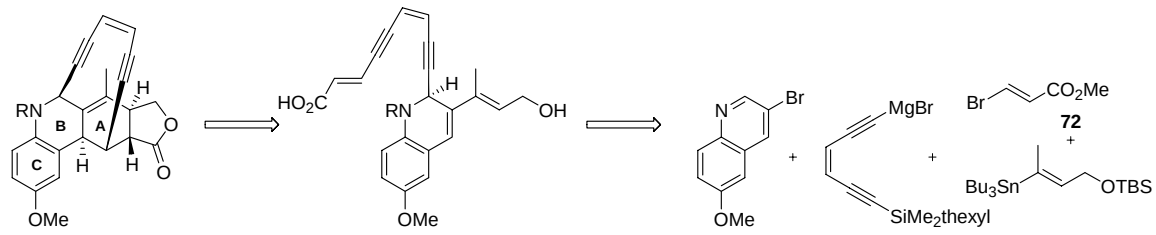


62 **66** **67** **68**

Scheme 10. Retrosynthetic analysis of dynemicin A.

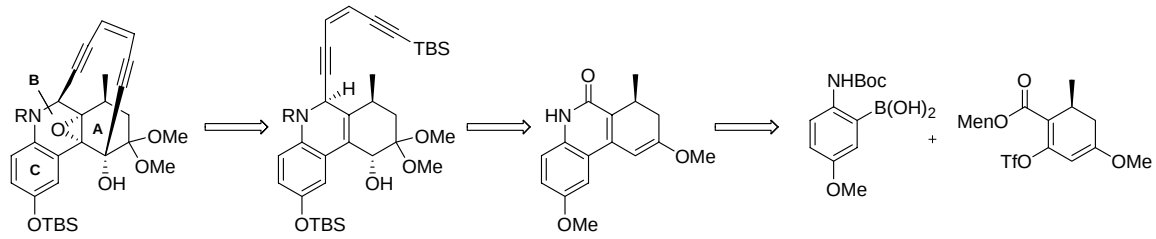
Retrosynthetic analyses of the dynemicin A syntheses are shown in Schemes 10 and 11. All of the groups have accessed the final compound via fairly similar ABC ring structures (**61**, **65** and **68**), although the Schreiber group installed the epoxide in the late stages of the synthesis. The Schreiber group also decided to use an intramolecular Diels–Alder reaction (IMDA) to form the A ring and close the enediyne bridge of the molecule, whereas the Danishefsky group utilized IMDA only to form the A ring. The Myers group joined the A and C rings with a Suzuki cross-coupling reaction and subsequently closed the B ring by lactam formation.

(±)-Di-*O*-methyl dynemicin A methyl ester/Schreiber 1993



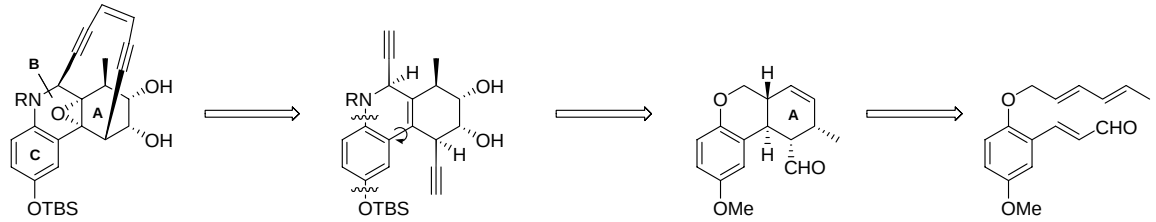
61 **69** **70** **71** **72** **73**

(+)-Dynemicin A/Myers 1995



65 **74** **75** **76** **77**

(±)-Dynemicin A/Danishefsky 1995

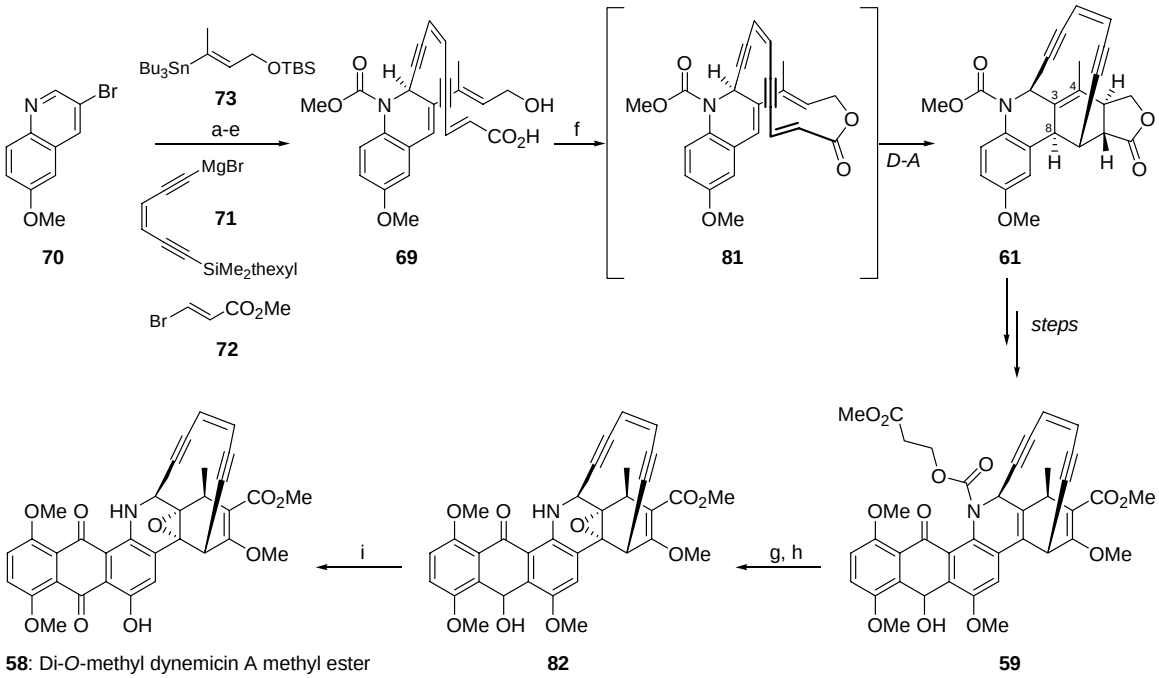


68 **78** **79** **80**

Scheme 11. Retrosynthetic analysis of advanced intermediates of dynemicin A.

The synthesis of di-*O*-methyl dynemicin A methyl ester by Schreiber and co-workers begins with the assembly of the intramolecular Diels–Alder substrate (Scheme 12).[66,68,69] Stille coupling of **70** with vinyl stannane **73** followed by a 1,2-addition of acetylide **71** to the resulting pyridinium salt provided a diyne. Silyl deprotection gave an acetylide that was then coupled with vinyl bromide **72**. After ester hydrolysis the IMDA-substrate **69** was exposed to Yamaguchi macrolactonization conditions, effecting the macrocyclization and subsequently the intramolecular Diels–Alder reaction to give lactone **61** in 50% yield. Next, the stereochemistry at C_4 and the oxidation state of carbons C_3 and C_8 were adjusted followed by functional group manipulation and construction of the anthraquinone fragment with a Diels–Alder reaction (see Scheme 10). Exposure of **59** to *m*-CPBA in pH 7 phosphate buffer gave epoxide **82** stereoselectively after deprotection of the carbamate nitrogen with DBU. Finally, the secondary alcohol was oxidized with ceric ammonium nitrate to give (±)-di-*O*-methyl dynemicin A methyl ester (**58**).

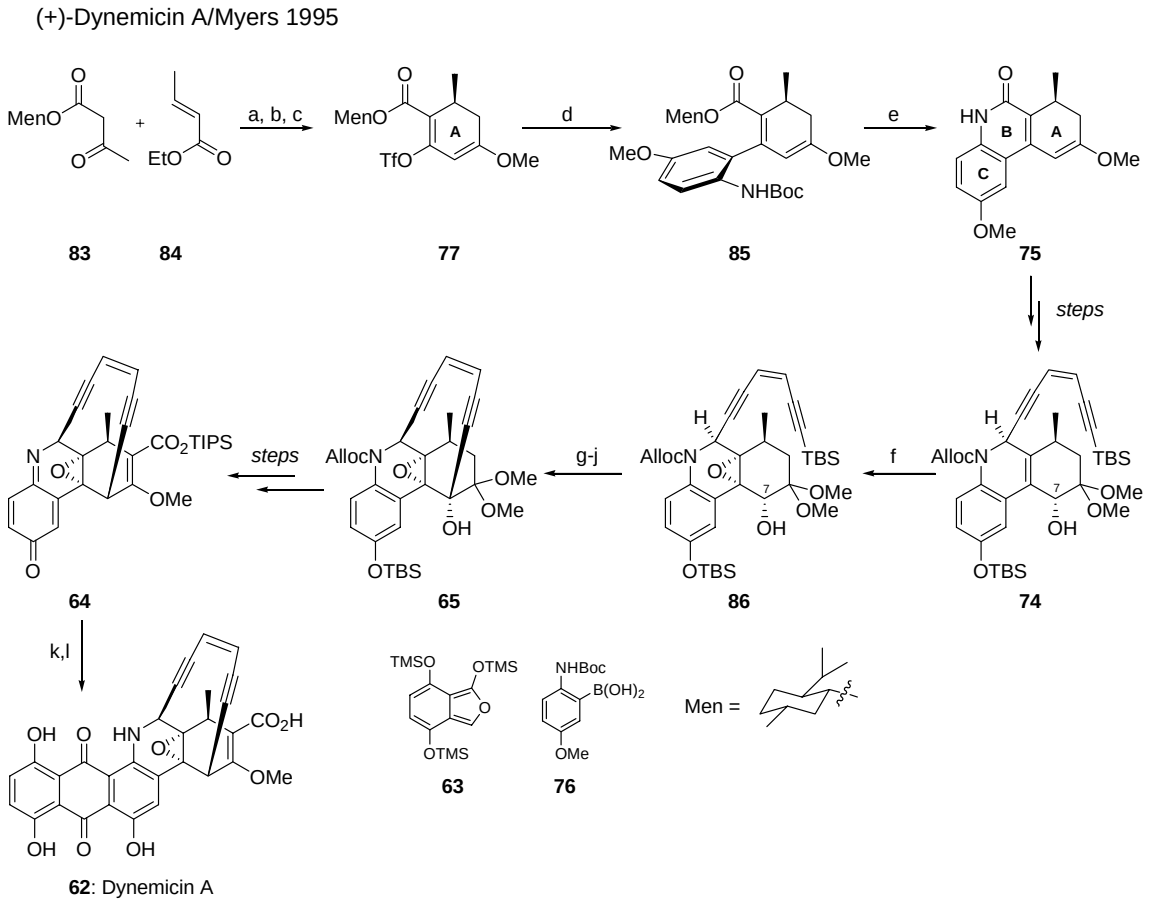
(±)-Di-*O*-methyl dynemicin A methyl ester/Schreiber 1993



Scheme 12. a) **73**, $Pd(PPh_3)_4$, 85%; b) **71**, $ClCO_2Me$, THF; c) TBAF, THF, 60% over 2 steps; d) **72**, $Pd(PPh_3)_4$, CuI, 20%; e) LiOH, H_2O, THF, 65%; f) Bromotrispyrrolidinophosphonium hexafluorophosphate (PyBroP), Et_3N, CH_2Cl_2, rt, 13 h, 51%; *steps*; g) *m*-CPBA, pH 7 buffer, CH_2Cl_2, rt, 2.5 h, 73%; h) 0.11 M DBU, MeOH, rt, 1 h; i) CAN, aq. MeCN, 0 °C, 45 min.

The total synthesis of dynemicin A by Myers and co-workers starts with the construction of the A ring (Scheme 13).[70,71] Condensation of menthyl acetoacetate (**83**) and *trans*-ethyl crotonate (**84**) provided a 36% yield of the correct β-methyl diastereomer after recrystallization. Stirring the 1,3-diketone in methanolic camphorsulfonic acid led to the formation of an enol ether, which was then subjected to sodium hydride and triflic anhydride to yield the coupling precursor **77**. The Suzuki cross-coupling of enol triflate **77** with aryl boronic acid **76** in the presence of tetrakis(triphenylphosphine)palladium and sodium carbonate afforded the AC ring structure **85** in 90% yield. Next, heating the carbamate **85** in 4-chlorophenol cleaved the nitrogen-protecting group and closed the B ring of the molecule. After a series of functional group manipulations as well as incorporation of the enediyne side chain, allylic alcohol **74** was ready to be epoxidized. Initially, the Myers group tried to close the enediyne bridge with various electrophiles at C_7 before the epoxidation without succeeding. In the event, buffered *m*-CPBA effected the epoxidation in 88% yield. Then, removal of the silyl groups, re-protection of the phenol and oxidation at C_7 provided the cyclization precursor. Indeed, deprotonation of the acetylene caused the enediyne bridge to attack the ketone at C_7 and gave alcohol **65** in excellent yield. After adjusting the oxidation states of various carbons, the stage was set for the final Diels–Alder reaction to complete the anthraquinone part of the molecule. The Diels–Alder reaction between the quinone imine **64** and isobenzofuran **63** proceeded

in 5 minutes to give the di-TMS-ether, which was immediately oxidized with manganese dioxide to provide (+)-dynemicin A (**62**) in 40% yield over two steps.

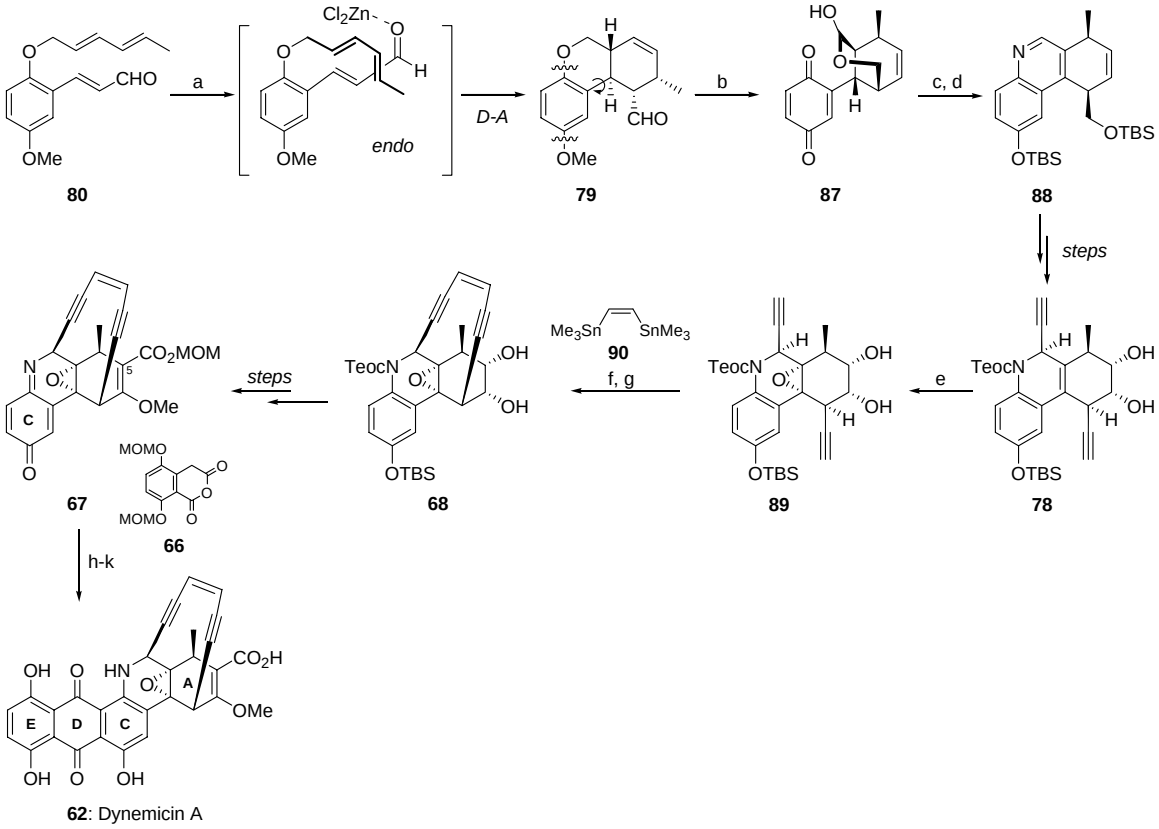


Scheme 13. a) *t*-BuOK, *t*-BuOH, reflux, 3.5 h, 36% after recryst., 1:1 diastereoselectivity; b) CSA, MeOH, rt, 12 h, 71%, 4:1 regioselectivity; c) NaH, Et_2O, rt, 5 h, then Tf_2O, –78 → 0 °C, 30 min, 95%; d) **76**, $Pd(PPh_3)_4$, $NaCO_3$, *p*-dioxane, reflux, 45 min, 90%; e) 4-ClPhOH, 180 °C, 30 min, 84%; *steps*; f) *m*-CPBA, pH 7 buffer, CH_2Cl_2, 0 °C, 19 h, 88%; g) TBAF, THF, 0 °C, 15 min, quant.; h) TBSCl, imid., DMF, rt, 1 h, 96%; i) $(COCl)_2$, DMSO, CH_2Cl_2, –40 °C, 10 h, then Et_3N, –78 → 0°C, 30 min, 92%; j) KHMDS, $CeCl_3$, THF, –78 °C, 5 min, 94%; steps; k) **63**, THF, –20 → 55 °C, 5 min; l) MnO_2, $3HF{\cdot}Et_3N$, THF, rt, 9 min, 40% over 2 steps.

Danishefsky and co-workers also decided to begin the construction of dynemicin A ring system with an intramolecular Diels–Alder reaction (Scheme 14).[72-77] A zinc chloride catalyzed IMDA led selectively to the *endo* adduct **79** in 60% yield. Exposure of adduct **79** to ceric ammonium nitrate gave rise to quinone lactol **87** via oxidation of the aromatic ring and lactol formation between the unveiled alcohol and the aldehyde. Ammonium acetate followed by silylation then afforded **88** with both of its stereocenters arising from the Diels–Alder step. After installation of the acetylenic functions, olefin **78** was ready for the epoxidation step. Thus, epoxidation of olefin **78** with *m*-CPBA proceeded smoothly to give epoxide **89** in 87% yield. Next, the diacetylene **89** was transformed into a diiodide which could then be treated with vinyl bis(stannane) (**90**) and $Pd(PPh_3)_4$ to

close the enediyne bridge giving **68** in 81% yield. The enediyne bridge could not be closed without the presence of the epoxide (for instance compound **78**); a similar observation was also made by the Myers group (Scheme 13 and discussion thereof). Then, after adjusting the oxidation state of the C ring and adding a carboxyl group at C_5, quinone imine **67** was ready to react with the anion of anhydride **66** to form the remaining rings of dynemicin A. The adduct was immediately oxidized with $PhI(OCOCF_3)_2$. Exposure of the product to air and daylight also oxidized ring D and the final step was to remove the MOM-protecting groups. This was accomplished with magnesium bromide to provide (±)-dynemicin A (**62**) in 15% yield over the last four steps.

(±)-Dynemicin A/Danishefsky 1995



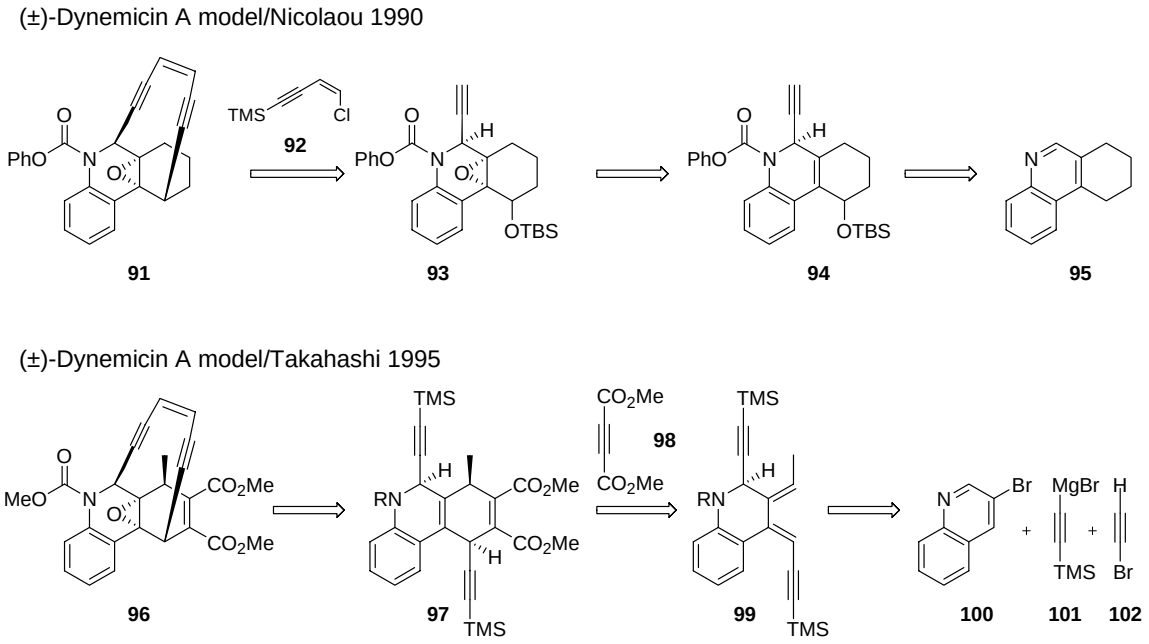
80 **79** **87** **88** **78** **89** **68** **67** **66**

62: Dynemicin A

Scheme 14. a) $ZnCl_2$, CH_2Cl_2, rt, 3 d, 60%, *endo*:*exo* 20:1, b) CAN, MeCN, H_2O, 0 °C, 30 min, 90%; c) NH_4OAc, AcOH, 100 °C, 1 h, 89%; d) TBSCl, imid., CH_2Cl_2, 0 °C, 2 h, 98%; *steps*; e) *m*-CPBA, CH_2Cl_2, rt, 8.5 h, 87%; f) cat. $AgNO_3$, NIS, THF, rt, 3.5 h, 91%; g) **90**, $Pd(PPh_3)_4$, DMF, 75 °C, 1.2 h, 81%; *steps*; h) LiHMDS, **66**, THF, 0 °C, 35 min, then **67**, 0 °C, 35 min; i) $PhI(OCOCF_3)_2$, THF, 0 °C, 5 min; j) air, daylight, THF, high concentration, 20 h; k) $MgBr_2$, Et_2O, 0 °C → rt, 12 h, 15% over 4 steps.

The synthesis of dynemicin A model compounds by Nicolaou and co-workers[78-81] is based on functionalizing quinoline derivative **91** (Scheme 15).[90,91] Takahashi and co-workers decided to form the A ring of their model compound **96** with a Diels–Alder

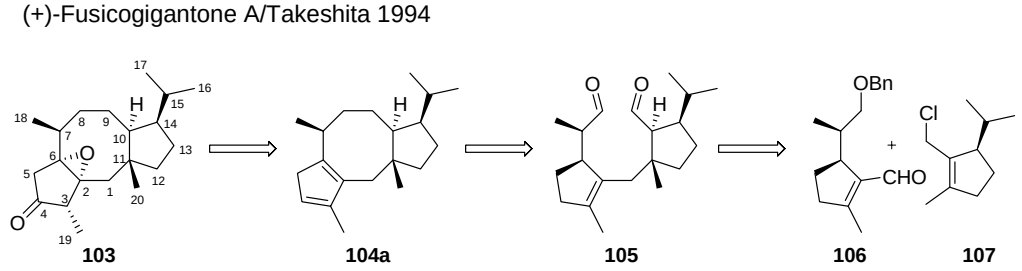
reaction (Scheme 15).[87,88] The diene part **99** is derived from a [2,3]-Wittig rearrangement. The enediyne bridge was closed with a palladium catalyzed coupling.



Scheme 15. Retrosynthetic analyses of dynemicin A model compounds.

2.2.3 Fusicogigantone A

Fusicogigantone A (**103**) and fusicogigantepoxide (**112**) were isolated from *Pleurozia gigantea* collected from East Malaysia in 1990.[92] The only reported synthetic route to the fusicogigantones is from the group of Takeshita, the retrosynthetic analysis of which is shown in Scheme 16. The key ring forming steps are a singlet oxygen oxidation and a titanium-mediated McMurry ring-closure of a dialdehyde.[93,94]

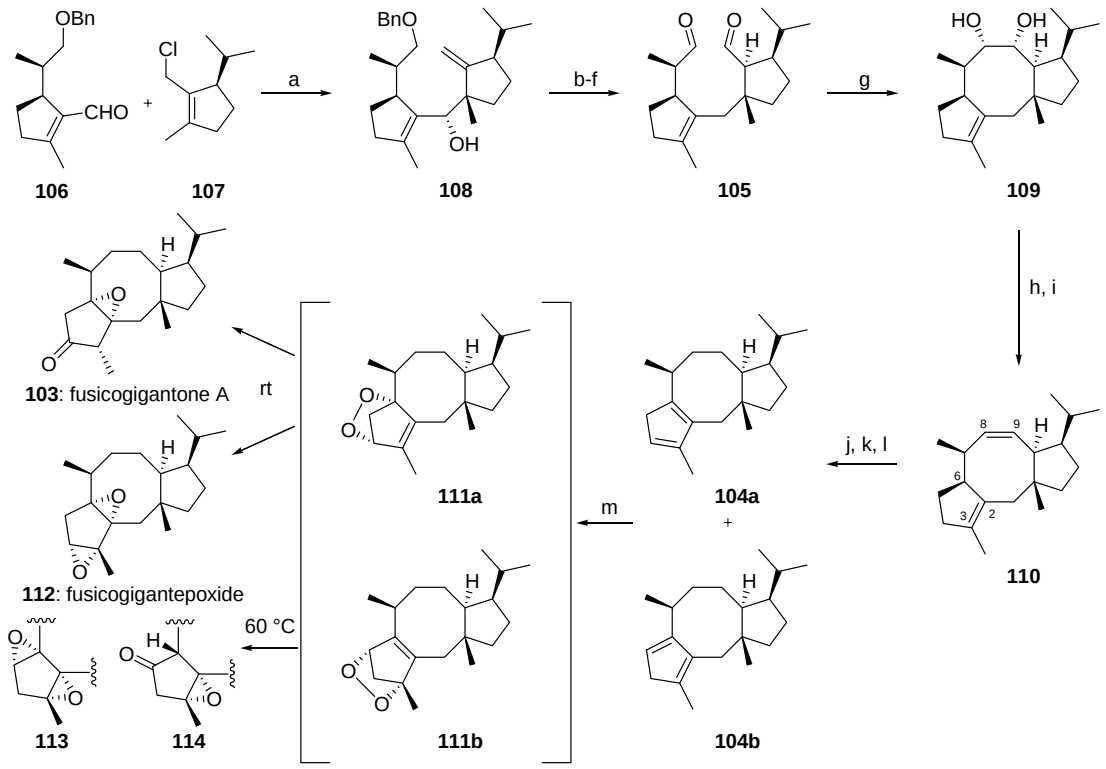


Scheme 16. Retrosynthetic analysis of fusicogigantone A.

Optically active enal **106** and allyl chloride **107** were mixed with chromium dichloride to obtain alcohol **108** in good yield (Scheme 17). Next, the double bond in **108** was hydroborated, the benzyl group removed, the free secondary alcohol eliminated and the resulting double bond reduced with lithium and ethylamine. After a Swern oxidation of

the diol, the resulting dialdehyde **105** was treated with titanium tetrachloride in the presence of zinc to obtain the cyclized α-*cis*-diol **109** in 38% yield together with the β-*cis*-diol in 7% yield. The diol was removed by orthoformate formation and subsequent reductive elimination.[95,96] The $C_{8\text{-}9}$ double bond in **110** was hydrogenated to give a mixture of $C_{2\text{-}6}$ and $C_{2\text{-}3}$ double bond containing compounds. This mixture was treated with singlet oxygen generated by means of Rose Bengal photosensitization, followed by reduction with triphenylphosphine and dehydration with silica gel to obtain a 2:3 mixture of **104a** and **104b**. Oxidation of this mixture with singlet oxygen generated with tetraphenylporphyrin at –78 °C gave a mixture of **111a** and **111b** (observed by NMR), which were only stable below 0 °C. This mixture was left to stand at room temperature for 10 h, and **111a** gradually turned into (+)-fusicogigantone A (**103**) and (+)-fusicogigantepoxide (**112**). Heating the mixture to 60 °C for 1 h gave two more products, (+)-fusicogigantone B (**114**) and **113**, from the more stable endoperoxide **111b**. The products were separated by column chromatography. The authors report that the attack of $^1O_2$ had occurred exclusively from the α-side of the dienes in **104a** and **104b**.

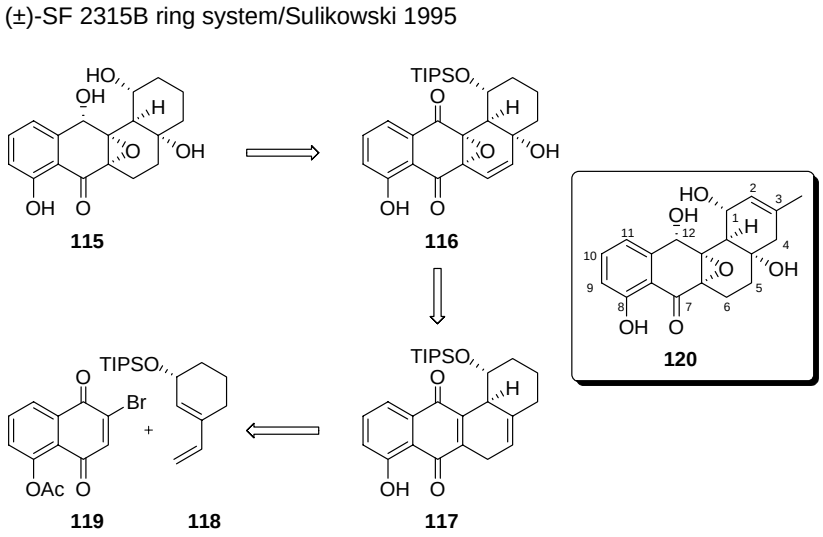
(+)-Fusicogigantone A & (+)-fusicogigantepoxide/Takeshita 1994



Scheme 17. a) $CrCl_2$, $LiAlH_4$, DMF:THF 2:1, *i*-PrOH, 90%; b) $Me_2CHCMe_2BH_2$, H_2O_2, ^-OH, 88%; c) H_2, Pd/C, 82%; d) HCl, THF, 99%, e) Li, $EtNH_2$, 68%; f) $(COCl)_2$, DMSO, Et_3N, 74%; g) $TiCl_4$, Zn, PhH:THF 5:1, α-*cis* 38%, β-*cis* 7%; h) $CH(OMe)_3$, PPTS, CH_2Cl_2, 93%; i) Δ, Ac_2O, tol, 82%; j) H_2, Pd/C, EtOAc, 99%; k) $^1O_2$; l) PPh_3, silica, 90%, **104a**:**104b** 2:3; m) $^1O_2$, tol, –78 °C → rt/60 °C, **103** 23%, **112** 12%, **113** 8%, **114** 8%.

2.2.4 SF 2315B

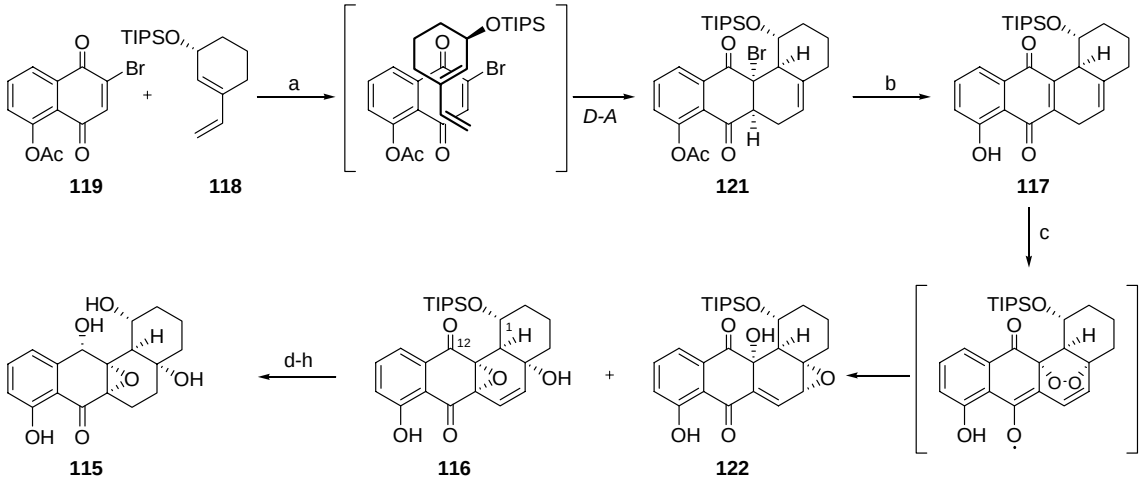
Sulikowski and co-workers have reported a synthetic route[97,98] to the ring system of SF 2315B (**120**), an angucyclinone antibiotic isolated from a soil microorganism of the *Actinomycete* strain *Excellospora viridilutea*.[99,100] A retrosynthetic analysis of their synthesis is shown in Scheme 18. The key transformations in the synthesis are a highly selective Diels–Alder reaction to set up the carbon framework and an oxygenation to provide the correct oxidation pattern.



Scheme 18. Retrosynthetic analysis of SF 2315B ring system.

Sulikowski's synthesis of epoxy quinol **115** started with a highly regioselective Diels–Alder cycloaddition between 2-bromo-acetoxyjuglone (**119**) and diene **118** (Scheme 19). The reaction produced cycloadduct **121**, which was then dehydrobrominated with lithium hydroxide to give quinone **117**. Exposure of **117** to molecular oxygen and tetrabutylammonium fluoride provided epoxyalcohols **116** and **122**, which were separated by column chromatography. Then, a sequence of hydrogenation, acetylation of the phenol, TIPS deprotection, C_1-hydroxyl directed reduction of the C_{12}-ketone and acetyl removal gave epoxy quinol **115**, which bears the complete array of stereogenic centers present in SF 2315B (**120**).

(±)-SF 2315B ring system/Sulikowski 1995

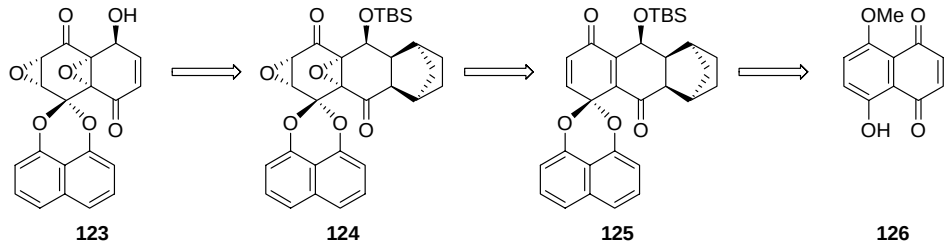


Scheme 19. a) tol, reflux, 71%; b) LiOH, THF:MeOH 1:1, 0 °C, 30 min, 70%; c) TBAF, O_2, THF, –78 °C → rt, **116** 33%, **122** 16%, **117** 20%; d) H_2, PtO_2, EtOAc, 0 °C, 30 min, 76%; e) Ac_2O, DMAP, pyr, CH_2Cl_2, rt, 30 min, 96%; f) HF·pyr, MeCN, 0 °C → rt, 2 h, quant.; g) $Me_4NB(OAc)_3$, AcOH, MeCN:THF 1:1, –10 °C, 53% (+ 38% of recovered sm); h) Bu_4NOH, THF, 0 °C, 80%.

2.2.5 Diepoxin σ

Diepoxin σ (**123**) was isolated from fermentation broths of a nonsporulating fungus, LL-07F275, collected in Panama from a tree trunk in 1993.[101] To date, one total synthesis of the molecule has appeared in the literature by Wipf and Jung (Scheme 20).[102-104] The key steps in their synthesis include an Ullmann coupling followed by an oxidative spirocyclization to introduce the naphthalene ketal and a stereoselective epoxidation. Another notable feature is the use of a Diels–Alder–retro-Diels–Alder strategy to introduce chirality to the molecule as well as to protect the highly reactive naphthoquinone ring system.

(+)-Diepoxin σ/Wipf 1999/2000

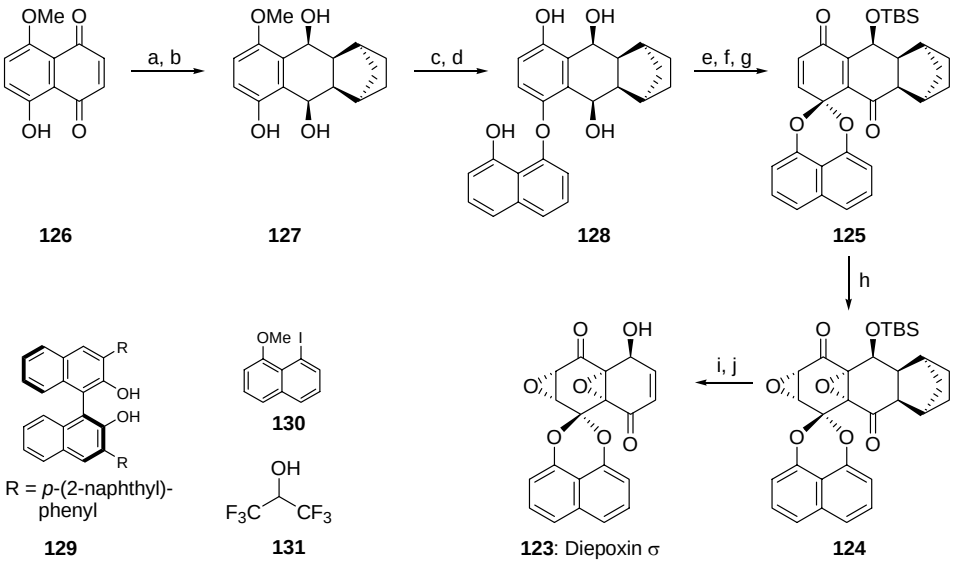


Scheme 20. Retrosynthetic analysis of diepoxin σ.

The first task in the diepoxin σ synthesis by Wipf and Jung (Scheme 21) was the protection of the reactive double bond in **126** as a Diels–Alder adduct with cyclopentadiene.[102-104] In their preliminary work, Wipf and Jung developed a racemic

synthesis of the molecule after which they successfully performed the cycloaddition in an enantioselective manner. In the strictest sense, the synthesis is thus a formal total synthesis of (+)-diepoxin σ, but because the same group performed the racemic synthesis, this is trivial. The Diels–Alder reaction of **126** and cyclopentadiene in the presence of borane and ligand **129** proceeded well to give 94% ee and 72% yield of the cycloadduct. Sodium borohydride reduction then gave the required precursor for the Ullmann ether coupling, which provided **128** after demethylation. The spiroketal ring was then closed with an oxidative cyclization in the presence of $PhI(OAc)_2$ in hexafluoro-2-propanol (**131**) followed by TBS protection of the less hindered secondary alcohol and PDC oxidation of the remaining alcohol to yield dienone **125**. Next, epoxidation of the two double bonds proceeded smoothly to give *syn*-diepoxide **124** in 88% yield as a single diastereomer. Now the only remaining task was to cleave the protecting groups. Surprisingly, the enone double bond was unmasked with a retro-Diels–Alder reaction at 250 °C in boiling phenyl ether without significant decomposition of the product. Then, treatment of the product with hydrogen fluoride gave (±)-diepoxin σ (**123**) in 73% yield over 2 steps.

(+)-Diepoxin σ/Wipf 1999/2000



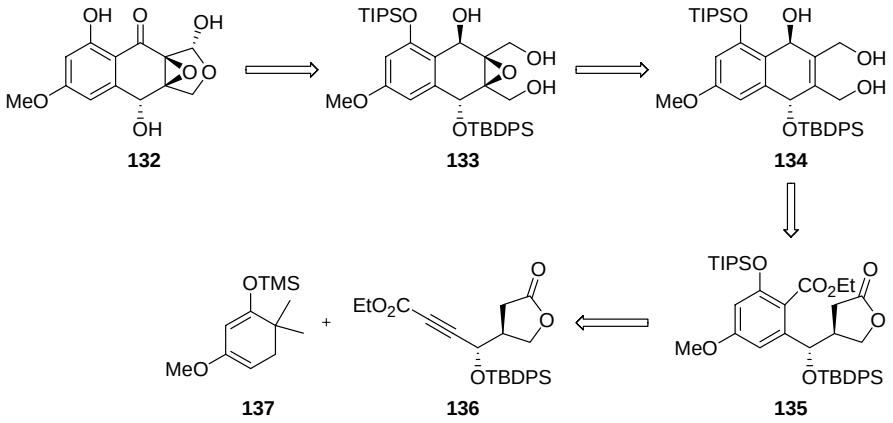
Scheme 21. a) **129**, BH_3·THF, AcOH, THF, rt, 1 h, then cyclopentadiene, –78 °C, 2 h, 72%, 94% ee; b) $NaBH_4$, THF, MeOH, –78 → 0°C, 3 h, 88%; c) **130**, Cu_2O, pyr, reflux, 20 h, 70%; d) Ph_2PH, *n*-BuLi, THF, rt, 7 d, 95%; e) $PhI(OAc)_2$, 4Å MS, **131**, rt, 1 h, 61%; f) TBSOTf, lutidine, CH_2Cl_2, –78 °C, 1 h, 91%; g) PDC, DMF, rt, 24 h, 72%; h) H_2O_2, K_2CO_3, THF, H_2O, 0 °C, 9 h, 88%; i) PhOPh, reflux, 1 h; j) HF, MeCN, H_2O, 0 °C → rt, 20 h, 73% over 2 steps.

2.2.6 Arthrinone

Arthrinone (**132**) is an antifungal metabolite, which was isolated from *Arthrinium* sp. FA 1744 in 1994.[105] Its only total synthesis was reported in 2000 by Uchiyama and co-

workers (Scheme 22).[106] The key ring forming steps in the synthesis include a Diels–Alder–cycloreversion reaction of a diene and an acetylene to form a highly substituted aromatic ring, as well as a Dieckmann condensation.

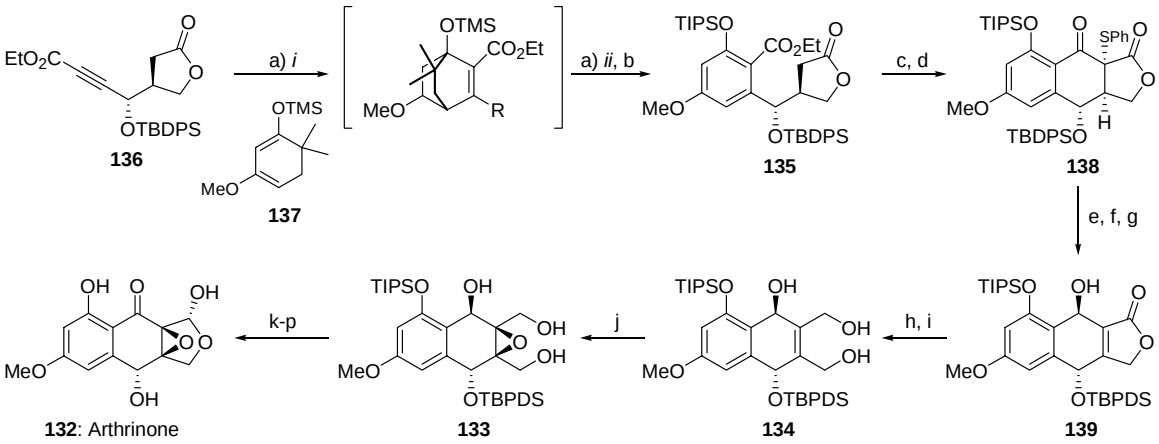
(±)-Arthrinone/Uchiyama 2000



Scheme 22. Retrosynthetic analysis of arthrinone.

The synthesis of arthrinone by Uchiyama *et al.* is illustrated in Scheme 23.[106] The Diels–Alder reaction between acetylene **136** and diene **137** proceeded smoothly and gave ester **135** in 81% yield after cycloreversion and TIPS-protection. With all requisite carbon atoms in place, NaHMDS effected a Dieckmann condensation to close the required cyclohexane ring. Because the cyclization product was not stable, it was immediately converted to phenyl sulfone **138** to create unsaturation for the subsequent epoxidation. After reduction of the ketone in **138**, the sulfone was oxidized to two epimeric sulfoxides and eliminated to give the α,β-unsaturated lactone **139**. Attempts to insert the epoxide at this point in the synthesis only resulted in aromatization of the cyclohexene ring. Thus, the lactone was reduced to diol **134** and the epoxidation took place to give epoxide **133** in 72% yield as a single diastereomer. The excellent selectivity obtained can be attributed to the directing effect of the allylic hydroxyl group. The tetrahydrofuran ring was then reconstructed using the following sequence: the less hindered primary alcohol was protected with a TBS group and the other with a TBDPS group, the TIPS and TBS groups were removed, the benzylic alcohol was oxidized with MnO_2 and the free primary alcohol with TPAP and finally the two TBPDS groups were removed to give (±)-arthrinone (**132**).

(±)-Arthrinone/Uchiyama 2000

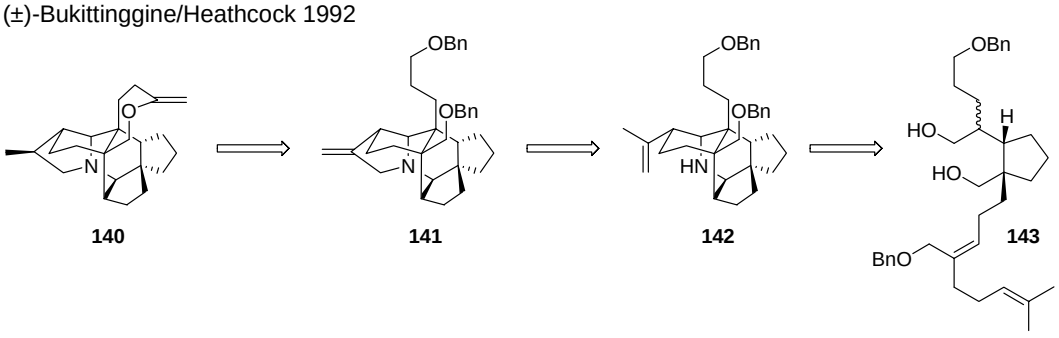


Scheme 23. a) *i*. **137**, 160 °C, *ii*. THF, 5% HCl, rt, 81%; b) TIPSCl, imid., DMF, rt, quant.; c) NaHMDS, THF, –78 °C; d) NaH, THF, 0 °C, then PhSCl, 87% over 2 steps; e) $Zn(BH_4)_2$, CH_2Cl_2, 0 °C, 83%; f) *m*-CPBA, CH_2Cl_2, 0 °C, 90%, 9:1 selectivity; g) $P(OMe)_3$, tol, reflux, 89% from major sulfone, 76% from minor; h) DIBAL-H, CH_2Cl_2, –78 °C; i) $NaBH_4$, MeOH, 0 °C, 77% over 2 steps; j) *m*-CPBA, CH_2Cl_2, pH 7.9 phosphate buffer, 0 °C → rt, 72%; k) TBSOTf, pyr, THF, –60 °C, 78%; l) TBDPSCl, imid., DMF, rt, 91%; m) 5% NaOH in EtOH, THF, rt, 61%; n) MnO_2, acetone, rt, 91%; o) cat. TPAP, NMO, 4Å MS, CH_2Cl_2, rt; p) TBAF, AcOH, THF, rt, 73% over 2 steps.

3. Other propellanes with all-carbon quaternary stereocenters

3.1 Bukittinggine

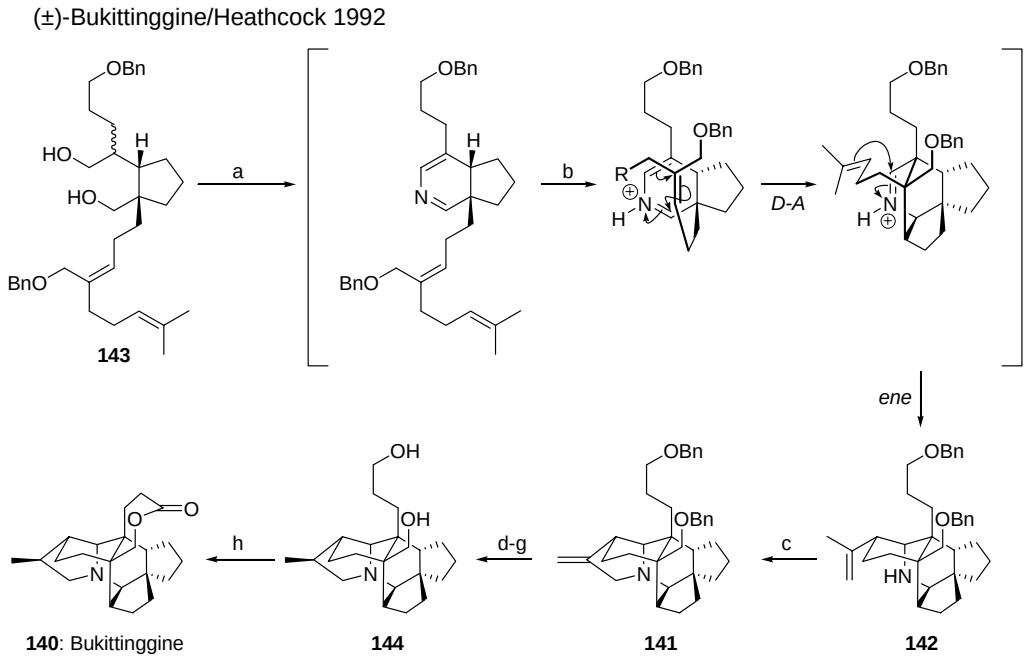
Bukittinggine (**140**) was isolated in 1990 from the leaves and branches of *Sapium baccatum* near the town of Bukittinggi in West Sumatra, Indonesia.[107] The Heathcock group synthesized this unique heptacyclic alkaloid in 1992.[108] The main transformation in their synthesis, a tetracyclization reaction developed in the group, suggests diol **143** as a starting material (Scheme 24).



Scheme 24. Retrosynthetic analysis of bukittinggine.

The tetracyclization process is effected by a Swern oxidation of diol **143** followed by gaseous ammonia (Scheme 25). Exposure of the product to acetic acid then triggers an inverse-electron-demand Diels–Alder reaction followed by an ene reaction to give the pentacycle **142**. There has been some discussion as to whether the mechanism is stepwise or concerted,[109] but the Heathcock group has reported experimental evidence which indicates that the cyclization proceeds through a concerted but asynchronous Diels–Alder reaction.[110,111] Next, the pentacyclic amine **142** was treated with palladium triflate to cyclize the sixth ring of the molecule. The following sequence reduced the exocyclic double bond in **141** stereoselectively (>15:1): hydroboration and oxidation of the double bond, tosylation of the formed primary alcohol followed by reduction with lithium triethoxyborohydride. Removal of the benzyl protecting groups then gave diol **144**, which

was ready for the final cyclization. Finally, oxidation of the diol with Fetizon's reagent provided (±)-bukittinggine (**140**) as the sole product.



Scheme 25. a) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 15 min, then Et_3N, –78 → 0 °C, 1 h, then NH_3 (g), 0 °C → rt, 45 min; b) NH_4OAc, AcOH, 30 min, rt, then 75 °C, 2 h, 76% from **143**; c) $(CF_3CO_2)_2Pd$, PPh_3, *p*-benzoquinone, MeCN, 24 h, rt, 70%; d) BH_3·THF, THF, 0 °C → rt, 2 h, then $NaBO_3$·$4H_2O$, H_2O, 3 h, rt; e) *p*-TsCl, DMAP, pyr, $CHCl_3$, 0 °C → rt, 46 h; f) $LiEt_3BH$, THF, 0 °C → rt, 4 h, then $NaBO_3$·$4H_2O$, H_2O, 0 °C → rt, 2.5 h; g) Na, NH_3, THF, –78 °C, 20 min; h) Ag_2CO_3 on Celite ®, PhH, reflux, 5 h; 52% over 5 steps.

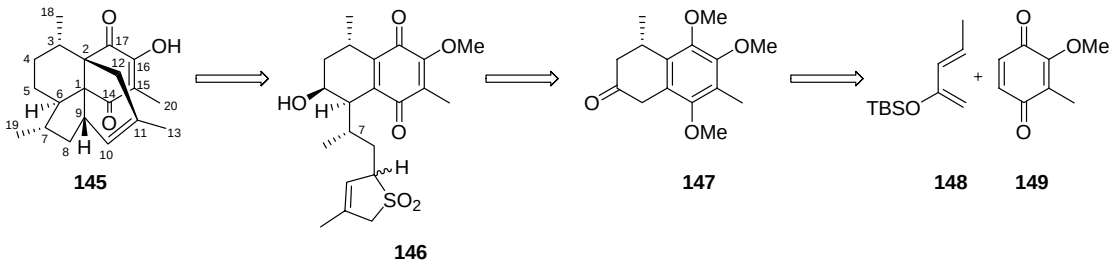
3.2 Colombiasin A

Colombiasin A (**145**), a diterpene isolated from the gorgonian octacoral *Pseudopterogorgia elisabethae*,[112] has attracted the interest of the synthetic community with its novel and challenging molecular framework. To date, three total syntheses, from the Nicolaou,[113,114] Rychnovsky,[115] and Harrowven[116,117] groups, have been published (Scheme 26). In addition, an approach to this complex ring system has appeared in the literature (Scheme 30).[118]

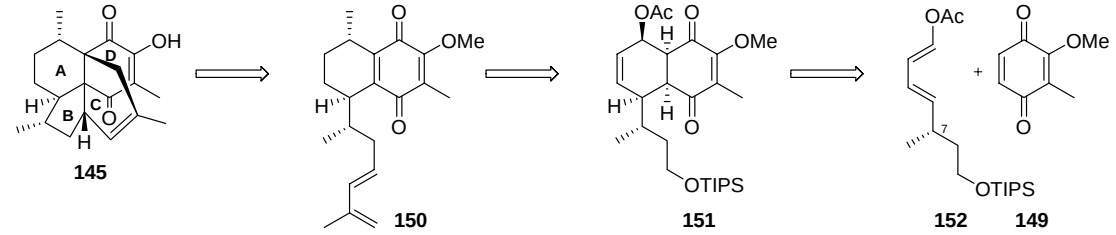
Unsurprisingly, all of the total syntheses rely heavily on the Diels–Alder reaction in the final stages of the synthesis (Scheme 26). The main difference in the first two synthetic routes, by Nicolaou *et al.* and Rychnovsky *et al.* is the point at which the side chain, which later forms the B and C rings, is installed. In the Nicolaou group strategy it is attached after the initial Diels–Alder reaction, whereas the Rychnovsky group decided to include part of the side chain, including the crucial C_7 methyl group, in their first Diels–Alder substrate. The Harrowven group relied on a Moore rearrangement to construct the

A and D rings of colombiasin A in their recent synthesis. In this route, the methyl group stems from a hydroboration, where a separable 5:2 mixture of diastereomers is obtained.

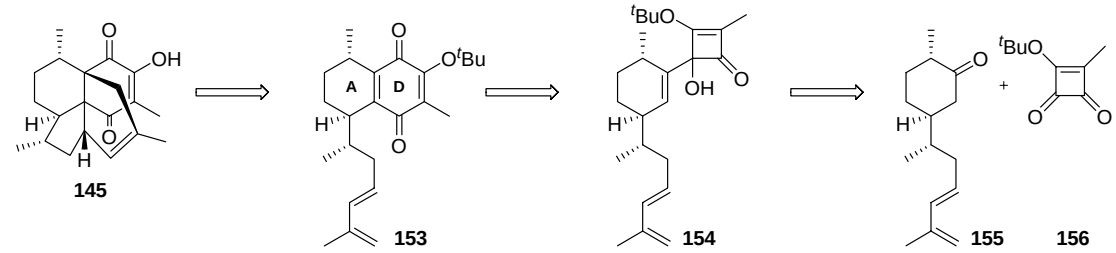
(-)-Colombiasin A, Nicolaou 2001



(-)-Colombiasin A, Rychnovsky 2003



(-)-Colombiasin A, Harrowven 2005

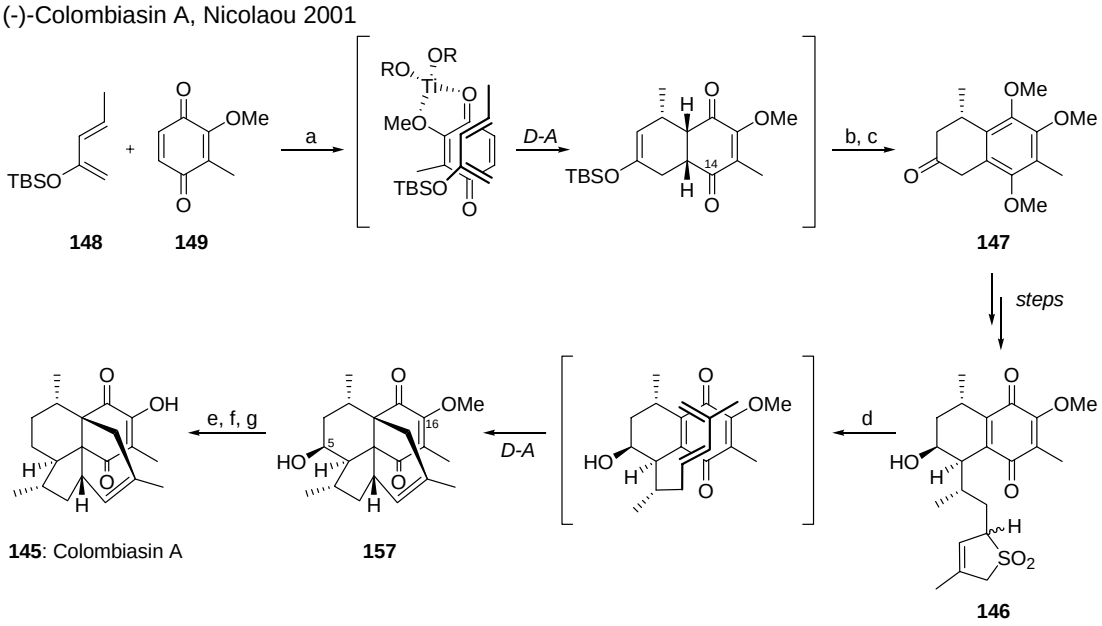


Scheme 26. Retrosynthetic analysis of colombiasin A.

The Nicolaou group synthesis commences with a catalytic asymmetric Diels–Alder reaction (Scheme 27).[113,114] The reaction between diene **148** and quinone **149** in the presence of [(*S*)-BINOL–$TiCl_2$] provided the Diels–Alder adduct **147** after aromatization, methylation and desilylation in 94% ee and 85:15 regioselectivity. The main regioisomer was thought to arise from a bidentate coordination of titanium as shown in Scheme 27. The minor regioisomer would then originate from monodentate coordination of titanium to the more electron rich vinylogous ester carbonyl oxygen at C_{14} (colombiasin A numbering).[a] After further elaboration and attachment of the side chain, the sulfone-protected diene **146** was ready for the critical IMDA reaction. The reaction was

[a] Note that there is an error in the original paper[114] in Scheme 9; the transition states $\mathbf{TS_a}$ and $\mathbf{TS_b}$ provide the enantiomers of compounds **8** and **8**'. (Personal communication with Prof. G. Vassilikogiannakis.)

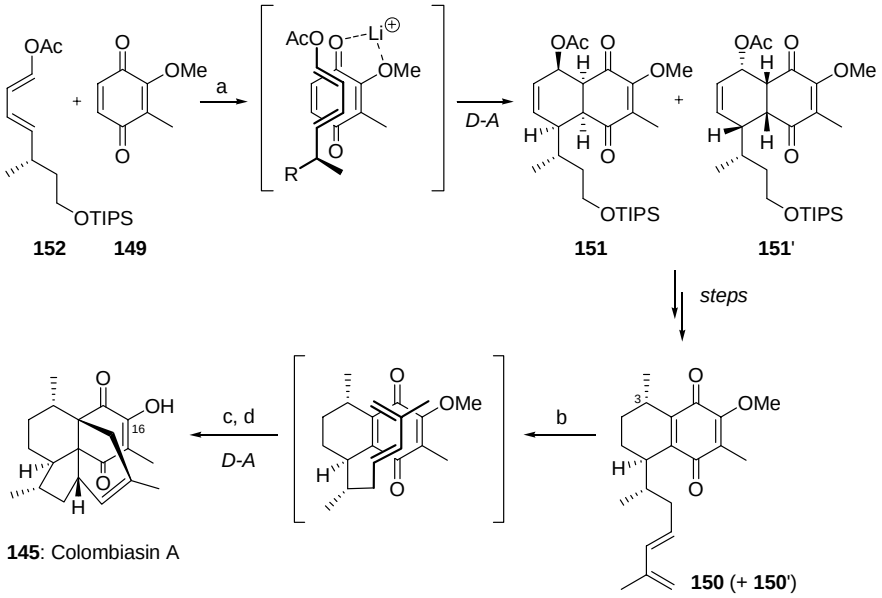
performed at 180 °C in toluene in a sealed tube and provided tetracycle **157** in 89% yield as a single product. Deoxygenation at C_5 and demethylation at C_{16} then gave (–)-colombiasin A (**145**).



Scheme 27. a) [(*S*)-BINOL–$TiCl_2$], tol, –60 → –10 °C, 7 h, 85:15 regiochemistry, 94% ee; b) K_2CO_3, MeI, acetone, reflux, 48 h; c) TFA, CH_2Cl_2, rt, 2 h, 70% over 3 steps, 94% ee; *steps*; d) tol (sealed tube), 180 °C, 20 min, 89%, 100% selectivity; e) NaH, THF:CS_2:MeI 4:1:1, 50 °C, 3 h, 95%; f) AIBN, Bu_3SnH, tol, 110 °C, 30 min, 77%; g) BBr_3, *cis*-cyclooctene, CH_2Cl_2, –78 °C, 43% based on 70% conversion.

The Rychnovsky group used a Lewis acid catalyzed Diels–Alder reaction between diene **152** and quinone **149** to start the synthesis of the colombiasin A ring system (Scheme 28).[115] The reaction gave a 1.7:1 mixture of **151** and **151'** that could only be separated in the last step of the synthesis despite attempts to do so earlier. The use of chiral Lewis acids to catalyze the reaction was not successful. After installing the C_3-methyl and the diene required for the IMDA, compound **150** was ready for cyclization. The final cyclization of diene **150** (and **150**') was performed in a similar fashion to that used in the Nicolaou synthesis, followed by deprotection of the C_{16}-methoxy group and separation of the diastereomers providing (–)-colombiasin A (**145**).

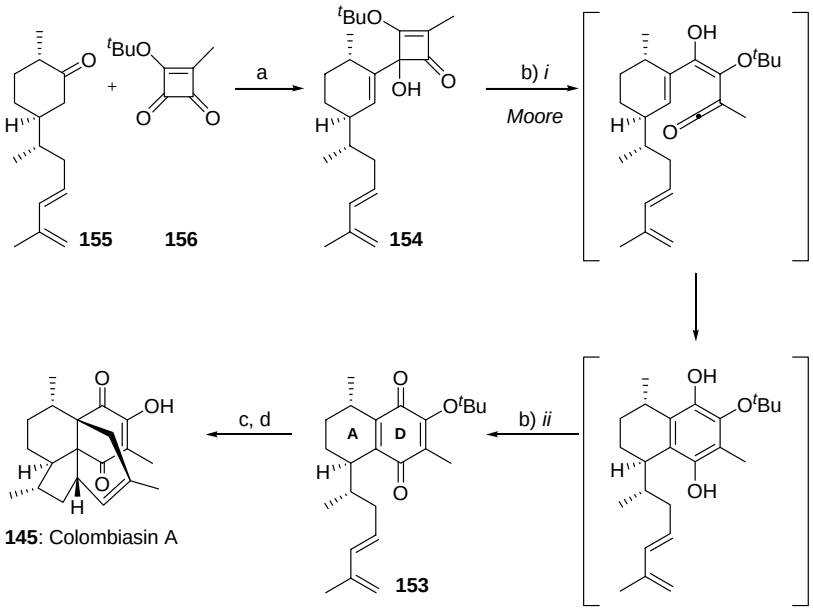
(-)-Colombiasin A, Rychnovsky 2003



Scheme 28. a) 5 M $LiClO_4$, Et_2O, rt, 24 h, 75%, **151**:**151'** 1.7:1; *steps*; b) tol, 180 °C, 83%; c) $AlCl_3$, $PhNMe_2$, CH_2Cl_2, 0 °C → rt, 73%; d) separation of diastereomers.

In the Harrowven group's synthesis of colombiasin A (Scheme 29),[116] the crucial intermediate **154** for the Moore reaction[119-121] was obtained from a Shapiro coupling between ketone **155** and diketone **156**. After some experimentation it was found that an *in situ* formation of a trisylhydrazone from ketone **155**, which could then be treated with *n*-butyllithium and diketone **156**, was the best way to obtain the Moore substrate **154**. Heating **154** to 110 °C in a microwave effected the formation of the Diels–Alder substrate **153**. As the penultimate step, an intramolecular Diels–Alder reaction provided the tetracycle in a similar fashion to the Nicolaou (Scheme 27) and Rychnovsky (Scheme 28) syntheses. Finally, trifluoroborane-etherate deprotected the alcohol to give (–)-colombiasin A (**145**).

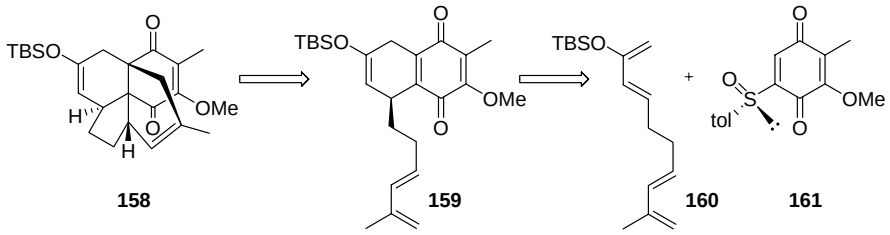
(-)-Colombiasin A, Harrowven 2005



Scheme 29. a) Trisylhydrazine, **155**, THF, rt, 2 h, then *n*-BuLi, –78 °C, then **156**, –20 °C, 36%; b) *i*. MW, THF, 110 °C, then *ii*. air, rt, 80%; c) tol, 150 °C, 61%; d) $BF_3 \cdot OEt_2$, 0 °C, 78%.

The research group of Flynn[118] has also published their efforts towards colombiasin A (Scheme 30). They used an enantioselective double Diels–Alder approach to construct the tetracyclic framework of colombiasin A. Their strategy is similar to Rychnovsky's (Scheme 28), but differs in execution of the actual route. As a source of chirality they use sulfoxide **161**, which, after the first enantioselective Diels–Alder reaction, eliminates to give the substrate for the second intramolecular Diels–Alder reaction.

(±)-Colombiasin A model/Flynn 2003



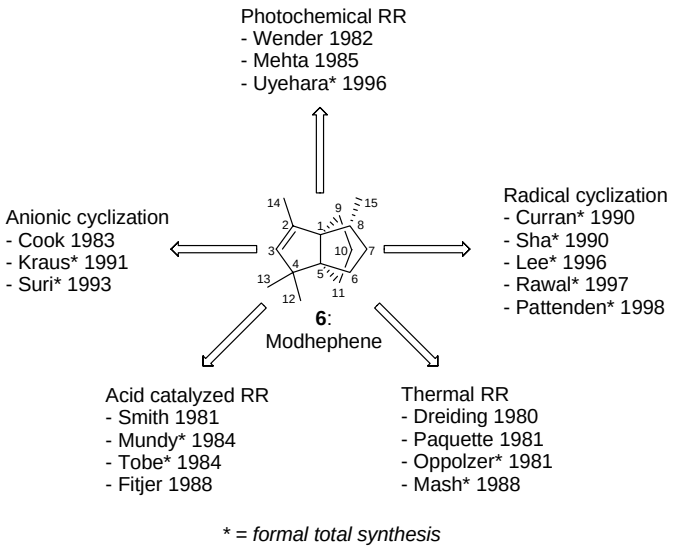
Scheme 30. Retrosynthetic analysis of a colombiasin A model study.

3.3 Modhephene

Modhephene (**6**) was the first isolated natural product shown to possess the [3.3.3]propellane skeleton. It was isolated for the first time in 1978 from *Isocoma wrightii* by Zalkov *et al.*[122,123] and has inspired a total of 19 syntheses of which 13 are formal. The different approaches can be classified into five different key reaction types,

namely acid catalyzed rearrangements, thermal rearrangements, photochemical rearrangements, anionic cyclizations and radical cyclizations (Scheme 31). Because of the number of syntheses published, only the key ring forming steps of each synthesis will be shown. The syntheses of modhephene until 1996 have appeared as a subsection in a review on polyquinane natural products.[124] There have also been two accounts of approaches towards modhephene.[125,126]

The stereoselective installation of the C_8-methyl group has been one of the greatest challenges in the synthesis of modhephene, further complicated by difficulties in separation of diastereomers.



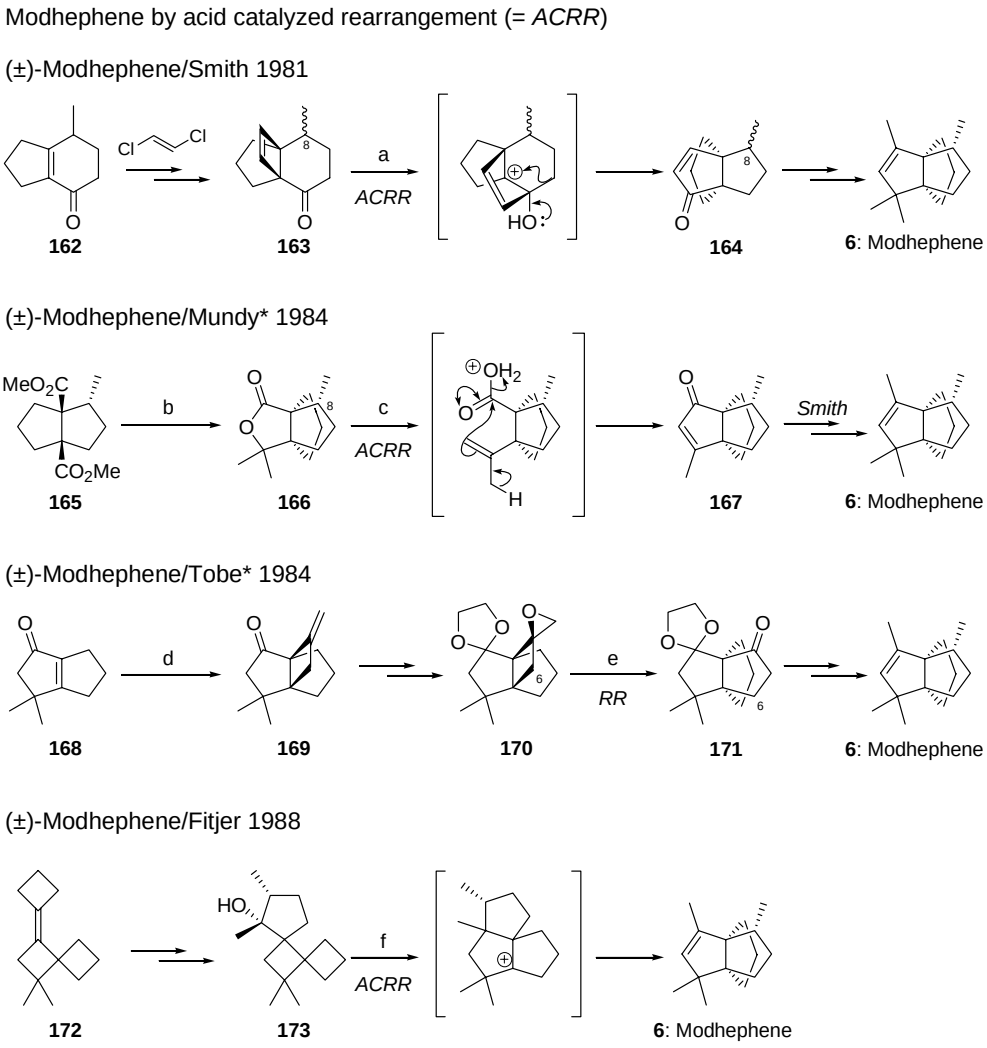
Scheme 31. Classification of different approaches towards modhephene by key reaction.

3.3.1 Acid catalyzed rearrangement

Smith and Jerris published one of the first total syntheses of modhephene (**6**) (Scheme 32) in 1981 (others followed shortly after; a total of three different total syntheses were published in 1981 and one in 1980).[127,128] They utilized Cargill's work on acid catalyzed rearrangements of β,γ-unsaturated ketones[129] to perform the key ring forming step, namely **163** → **164**. Ketone **163** was synthesized from enone **162** via a [2+2] photochemical cyclization, which, unfortunately, gave only ca. 1.3:1 ratio of the C_8-methyl group with the major diastereomer being the desired one.

In 1984, Wilkening and Mundy published a formal total synthesis of modhephene (**6**)[130] relying on a phosphorus pentoxide–methanesulfonic acid catalyzed rearrangement (**166** → **167**).[131] Catalytic hydrogenation was used to obtain the correct stereochemistry at C_8 selectively. They also published a total synthesis of modhephene[132], but later the Curran group (see Scheme 36) found that there was a discrepancy with the assignment of a common intermediate (see ref. 47 in the paper).[133] Since Wilkening and Mundy only had

mass spectral data of modhephene, this casts doubt over the identity of the products in the total synthesis.[a]



Scheme 32. a) *p*-TsOH, PhH, reflux, 4 h, 64%, α-Me:β-Me 57:43. b) MeLi, THF, rt, overnight, 80%; c) MsOH, P_2O_5, 85 °C, 44 h, 22%. d) allene, CH_2Cl_2, –78 °C, 94%, 4.5:1 selectivity; e) LiBr, HMPA, PhH, 60 °C, 86%, 10:1 selectivity. f) *p*-TsOH, PhH, 70 °C, 20 min, 34%.

The key step in the formal synthesis by the Tobe group[135] is not an acid catalyzed rearrangement, but a very efficient lithium bromide–HMPA catalyzed[136] epoxide–carbonyl rearrangement[137-140] of epoxide **170**. Since the rearrangement is chelation

[a] The Curran group also reports[133] (see ref. 70 in the paper) that there has been a misassignment of spectra of the two diastereomers of ketone **164** (Scheme 32) in the Smith paper.[128] Wilkening and Mundy used a sample provided by Smith to prove the identity of **164** and thus the product of their catalytic hydrogenation. Kraus and Shi[134] claim that the misassignment derives from the mix-up in Smith's data, but in fact the Mundy assignment was based on comparison with an authentic sample of **164** from Prof. Smith. It remains unclear whether Prof. Smith has sent the wrong diastereomer of **164** to Wilkening and Mundy or if there is a genuine error with the chemistry.

controlled, the less substituted carbon (C_6) migrates with good selectivity. The precursor to epoxide **170**, olefin **169**, is made from the readily available enone **168**. It is interesting to note the similarity of the strategy to the Tobe group synthesis of marasmic acid (**4**) in Scheme 4.

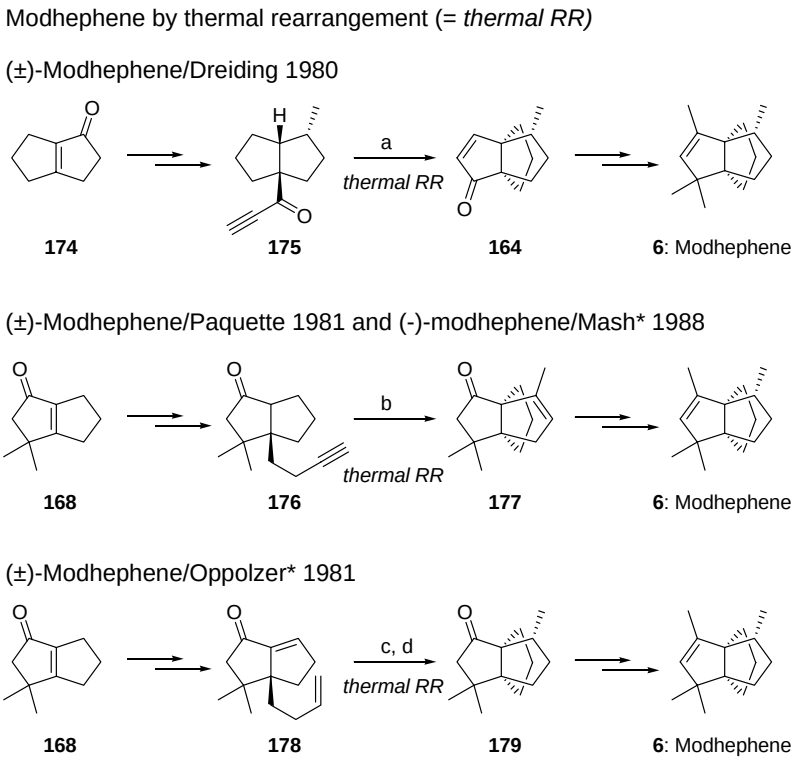
Fitjer *et al.* have published a short and original synthesis of modhephene via an acid catalyzed cascade rearrangement of alcohol **173**.[141-143] The group has also studied the absolute configuration and optical rotation of modhephene by resolving an intermediate and preparing both (–)- and (+)-modhephene separately.[144]

3.3.2 Thermal rearrangement

Thermal rearrangement has been the strategy of choice for four different groups who synthesized modhephene (Scheme 33). Karpf and Dreiding utilized an α-alkynone cyclization of alkyne **175** to construct the [3.3.3]propellane ring framework.[145,146] While the reaction gives a good yield, it also gives two other products in a 2:1:1 ratio that can be separated later. They arrive at the same intermediate as Smith and Jerris (**164**, see Scheme 32), but since the publications were received within eight days by the editorial staff of the journals, the syntheses can be considered independent.

Schostarez and Paquette used an intramolecular ene reaction of acetylene **176** to form the modhephene ring system in good yield in their short synthesis of modhephene.[147,148] Seven years later, Mash *et al.* published the first total synthesis of (–)-modhephene,[149-151] where a chiral auxiliary based strategy was used to synthesize enantiomerically enriched acetylene **176** (78% ee). From intermediate **176** onwards, they follow the footsteps of Schostarez and Paquette.

The Oppolzer group has published two different routes to **177** (see Scheme 32), a common intermediate to the Dreiding and Smith syntheses.[152,153] Of these, the latter is significantly shorter. The key transformation in their synthesis was the ene reaction of **178**, which produced propellane **179** selectively.



Scheme 33. a) 620 °C, 14 Torr, 1 h, 95%, 2:1:1 mixture of products. b) decalin, 360 °C, 4 h, 85%. c) tol, 250 °C, 16 h, 76%; d) H_2, Pd/C, EtOH, rt, 12 h, 98%.

3.3.3 Photochemical rearrangement

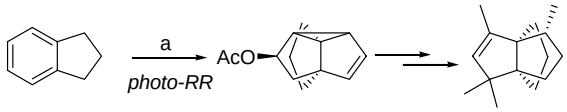
A photochemical rearrangement has been the basis of three different syntheses of modhephene (Scheme 34). In the first of them, by Wender and Dreyer, indan (**180**) and vinyl acetate were irradiated with Vycor-filtered light to produce a complex mixture from which acetate **181** was isolated in 21% yield.[154] This arene-olefin meta cycloaddition established the [3.3.3]propellane structure and the remaining steps were used to incorporate the required methyl groups into the molecule.

In their synthesis of modhephene,[155-157] Mehta and Subrahmanyam relied on a Diels–Alder reaction (**182** → **183**) followed by an oxa-di-π-methane rearrangement (**183** → **184**).

The Uyehara group also chose an oxa-di-π-methane rearrangement to construct the ring system of modhephene.[158,159] Irradiation of bicycle **185** for 1.5 hours provided tricyclic ketone **186** in 91% yield. To form the third 5-membered ring, ketone **186** was elaborated to bromide **187**, which cyclized to give propellane **188** in the presence of tributyltin hydride and AIBN.

Modhephene by photochemical rearrangement (= *photo-RR*)

(±)-Modhephene/Wender 1982

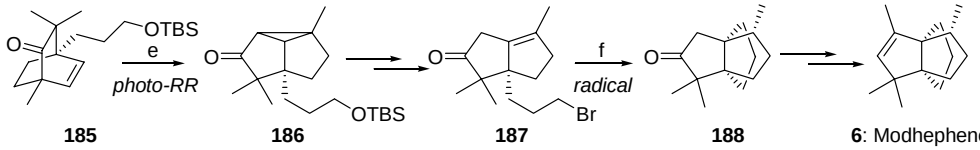


180 **181** **6**: Modhephene

(±)-Modhephene/Mehta 1985

182 **183** **184** **6**: Modhephene

(±)-Modhephene/Uyehara* 1996



185 **186** **187** **188** **6**: Modhephene

Scheme 34. a) *h*ν, Vycor, vinyl acetate, cyclohexane, 35 h, 21%. b) 1-chloroacrylonitrile, tol, 80 °C, 16 h, 43%, 4:1 regioselectivity; c) $Na_2S{\cdot}10H_2O$, EtOH, 60 °C, 6 h, 58%; d) *h*ν, acetone, 45 min, 47%, 15:1 selectivity. e) *h*ν, acetone, rt, 1.5 h, 91%; f) Bu_3SnH, AIBN, PhH, reflux, 2 h, 42%.

3.3.4 Anionic cyclization

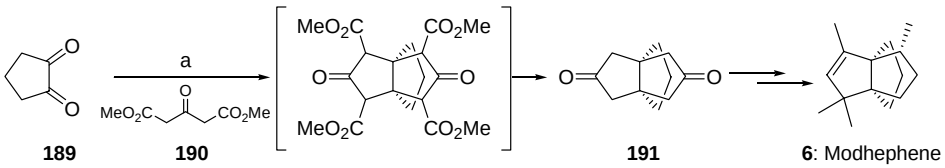
An anionic cyclization has been employed by three research groups during their synthesis of modhephene (Scheme 35). Cook and co-workers[160] decided to use the Weiss reaction,[161,162] *i.e.* the reaction between dimethyl-3-ketoglutarate (**190**) and diketone **189**, to construct the [3.3.3]propellane system.

Kraus and Shi have published a formal total synthesis of modhephene utilizing a rearrangement of bridgehead bromide **192** with the anion of dimethyl methyl phosphonate followed by a potassium hydride mediated cyclization of the resulting phosphonate **193**.[134,163]

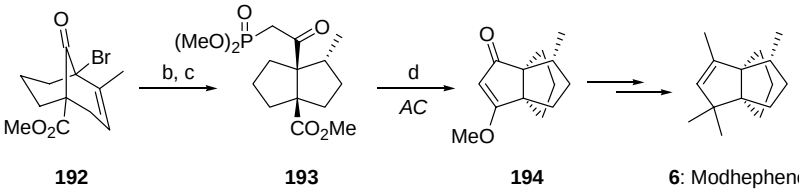
Suri's original but lengthy approach towards modhephene involved an intramolecular enolate alkylation of bromide **196** to provide the [3.3.3]propellane ring system.[164]

Modhephene by anionic cyclization (= *AC*)

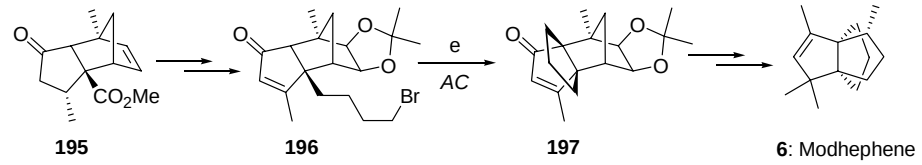
(±)-Modhephene/Cook 1983



(±)-Modhephene/Kraus* 1991



(±)-Modhephene/Suri* 1993



Scheme 35. a) **190**, pH 5 aqueous buffer, rt, several days, then H_3O^+, heat. b) $(MeO)_2P(O)Me$, *n*-BuLi, –78 °C, 15 min, then **192**, –78 °C → rt, 1 h, 49%; c) $[Ir(COD)(PCy_3)(py)]PF_6$, H_2, CH_2Cl_2, rt, 15 h; d) KH, 18-crown-6, PhH, reflux, 6 h, 33% over 2 steps. e) LDA, HMPA, THF, –70 °C, 79%.

3.3.5 Radical reaction

Radical cyclizations have been the most popular way to make the [3.3.3]propellane ring system in modhephene. It has been the key reaction in six different total syntheses. In addition to the syntheses shown in Scheme 36, the Uyehara group has also utilized it to build the third unsubstituted ring of modhephene (see Scheme 34, **187** → **188**). The Curran group has published two different radical based syntheses of modhephene. The first was a formal total synthesis with sequential radical cyclizations[133] and the second used a tandem transannular radical cyclization.[165] Because their first route was significantly shorter and more effective (11 steps and 16% overall yield vs. 21 steps and 6% overall yield), it will be discussed here. Their strategy hinged on closing two of the three 5-membered rings with a radical reaction. Vinyl stannane **198** cyclized smoothly to give the *trans* ester **199**, which was further elaborated to give vinyl iodide **200**, which in turn provided enone **164** in 88% yield.

In their formal total synthesis of modhephene, Sha *et al.* also used an intramolecular radical cyclization.[166] Their substrate, iodoolefin **201** afforded 4:1 selectivity of the desired α-C_8 diastereomer when exposed to the standard tributyltin hydride/AIBN conditions.

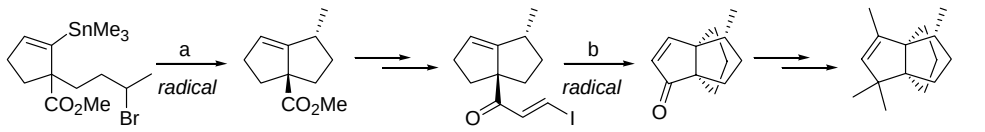
Lee *et al.* have published a short and successful tandem radical cyclization approach towards modhephene.[167] Cyclization of *N*-aziridinyl imine **204** provided >90% selectivity for the desired exocyclic olefin **205**. Recently, they published another tandem radical cyclization route to modhephene.[168]

Dvorak and Rawal synthesized their intramolecular radical cyclization substrate in an interesting manner.[169] They used a Diels–Alder reaction followed by a Paterno-Büchi reaction to access oxetane **206**. The hidden diquinane unit present in **206** was revealed by a direct fragmentation of **206** followed by oxidation of the remaining alcohol and selenation to give enone **207**. Then, exposure of **207** to tributyltin hydride and AIBN provided propellane **167** in 6:1 selectivity as the major product.

The latest synthesis of modhephene was published by De Boeck and Pattenden.[170,171] Their approach called for the construction of an 8-membered ring that was then cyclized by virtue of an α-ketenyl radical intermediate to propellane **209**.

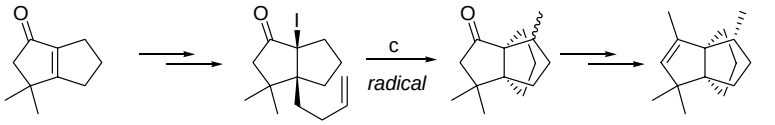
Modhephene by radical reaction

(±)-Modhephene/Curran* 1990



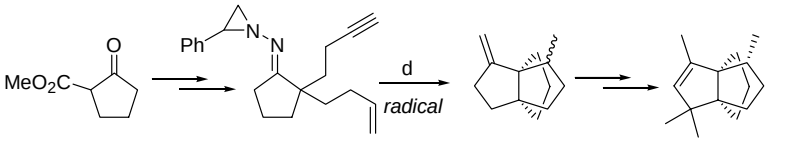
198 **199** **200** **164** **6**: Modhephene

(±)-Modhephene/Sha* 1990



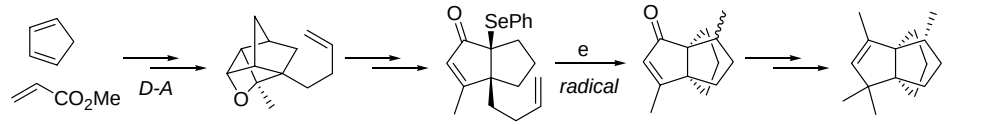
168 **201** **202** **6**: Modhephene

(±)-Modhephene/Lee* 1996



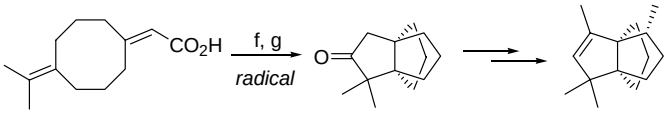
203 **204** **205** **6**: Modhephene

(±)-Modhephene/Rawal* 1997



206 **207** **167** **6**: Modhephene

(±)-Modhephene/Pattenden* 1998



208 **209** **6**: Modhephene

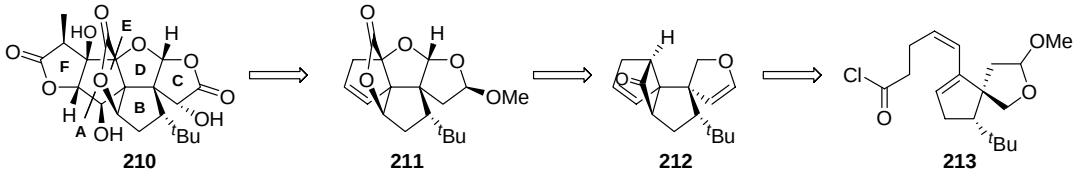
Scheme 36. a) Bu_3SnH, AIBN, PhH, reflux, 10 h, 90%; b) Bu_3SnH, AIBN, DPPE, PhH, reflux, 7 h, 88%. c) Bu_3SnH, AIBN, PhH, 85%, α:β 4:1. d) Bu_3SnH, AIBN, PhH, 8 h, then SiO_2, 74%, α:β >9:1. e) Bu_3SnH, AIBN, PhH, –78 °C, α:β 6:1. f) 2-(*o*-IC_6H_4)CH_2CH_2SH, DCC, DMAP, CH_2Cl_2, 85%; g) Bu_3SnH, AIBN, PhH, reflux, 59%.

4. Propellanes with lactones

4.1 Ginkgolide B

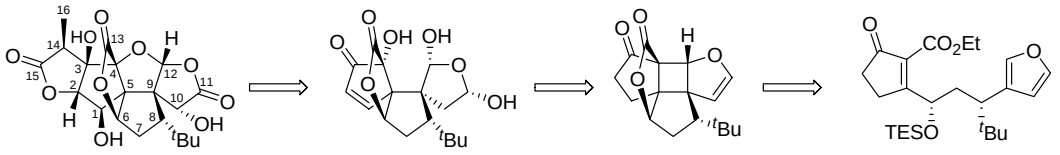
Ginkgolide B (**210**) is a complex polyoxygenated and polycyclic natural product isolated from the extracts of *Ginkgo biloba*.[172-174] It is the most active platelet activating factor (PAF) antagonist isolated from ginkgo extracts. This synthetically challenging molecule has been the target of two different total syntheses, by the groups of Corey[175,176] and Crimmins (Scheme 37).[177-179] The key ring forming transformation in the Corey group synthesis is an internal ketene-olefin cycloaddition whereas the Crimmins group relied on a [2+2] photocycloaddition.

(-)-Ginkgolide B/Corey 1988



210 **211** **212** **213**

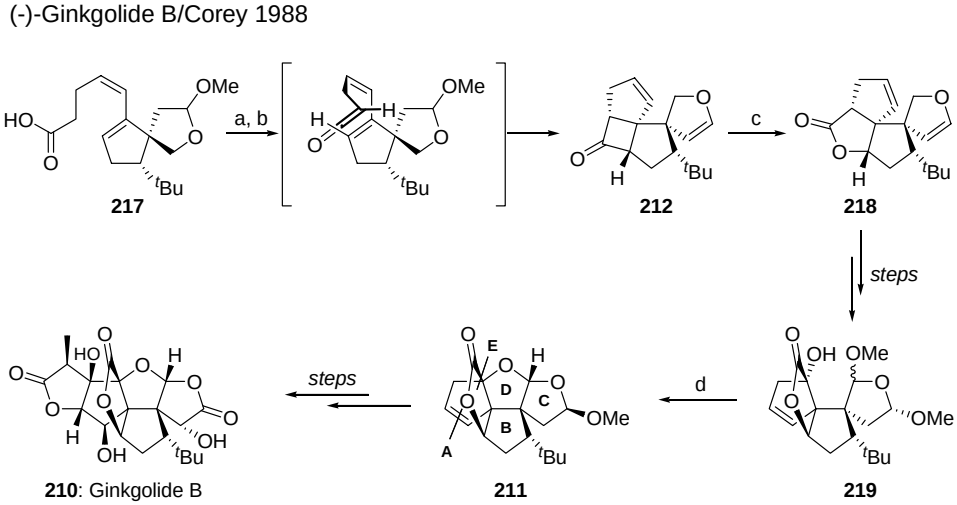
(±)-Ginkgolide B/Crimmins 1999



210 **214** **215** **216**

Scheme 37. Retrosynthetic analysis of ginkgolide B.

The first ring forming step in the Corey group synthesis of ginkgolide B[175,176,a] was the internal ketene–olefin cycloaddition (Scheme 38).[181,182] Treatment of acid **217** with oxalyl chloride gave the corresponding acid chloride (**213**, see Scheme 37), which was then eliminated with tributylamine to form the ketene. The ketene immediately underwent cycloaddition followed by elimination of the anomeric methoxy group to give tetracyclic ketone **212**. Baeyer–Villiger oxidation by triphenylmethyl hydroperoxide then produced lactone **218**, which was further elaborated to more highly oxidized lactone **219**. Treatment of **219** with acid then provided the ABCDE ring fragment of ginkgolide B (**211**), that also contains a [3.3.3]propellane structure. Ten further steps afforded (–)-ginkgolide B (**210**).

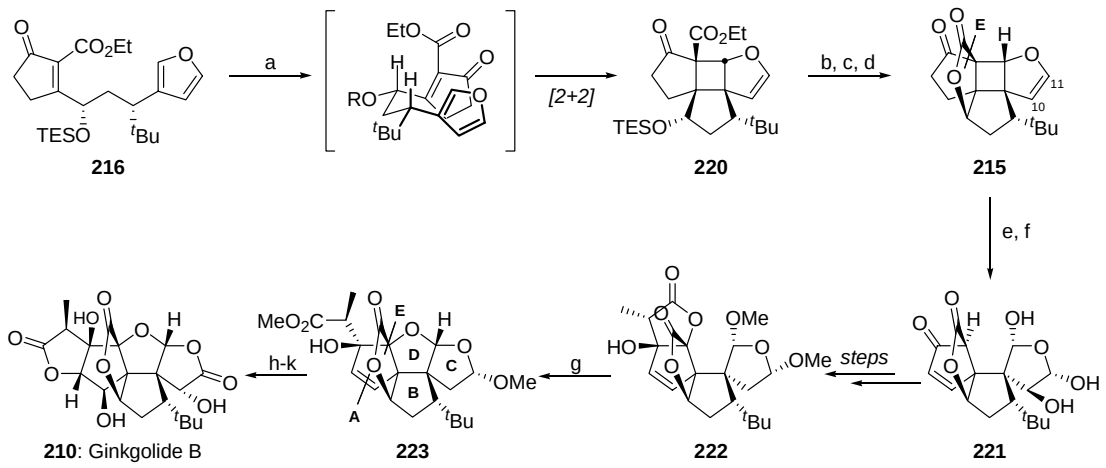


Scheme 38. a) $(COCl)_2$, PhH, rt, 2 h, then b) *n*-Bu_3N, tol, reflux, 3 h, 71-89% over 2 steps; c) Ph_3COOH, 8:1 acetone:1 N NaOH, –30 °C, 2 h, 86%; *steps*; d) CSA, CH_2Cl_2, rt, 24 h (75% over 2 steps).

The first key ring forming transformation in the Crimmins group's synthesis of ginkgolide B (Scheme 39)[177-179] was a [2+2] photocycloaddition of enoate **216**, which proceeded with remarkable efficiency and stereoselectivity to give a single cycloadduct **220** in quantitative yield. The E-ring of ginkgolide B was then closed via a sequence of silyl deprotection, mesylation and acid catalyzed cyclization. Next, the cyclobutane ring was opened with a retroaldol fragmentation via a one-pot selenylation–elimination sequence followed by epoxidation of the C_{10}-C_{11} double bond to furnish the dialdehyde hydrate **221**. Several steps later, the dilactone **222** was ready for the closure of ring D. Treatment of dilactone **222** with camphorsulfonic acid gave the ABCDE ring fragment **223**. Four more steps were required to deliver (±)-ginkgolide B (**210**).

[a] The Corey group syntheses of ginkgolide A, B and bilobalide have been thoroughly analyzed in Prof. Corey's Robert Robinson lecture.[180]

(±)-Ginkgolide B/Crimmins 1999



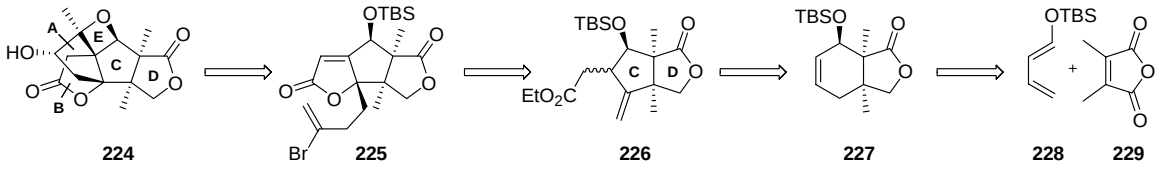
Scheme 39. a) *h*ν, >350 nm, hexanes, rt, 17 h, quant.; b) 5% HF, MeCN, 0 °C → rt, 1 h; c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min; d) 4Å MS, EtOH, reflux, 26 h, then H_2O, reflux, 8 h, then PPTS, PhH, reflux, 16 h, 63% from **220**; e) PhSeCl, HCl, EtOAc, rt, 1 h, then $NaIO_4$, H_2O, THF, 2 h, rt; 78%; f) DMDO, acetone, H_2O, 8 h, rt, then *p*-TsOH, rt, 15 h, 94%; *steps*; g) CSA, MeOH, reflux, 18 h, 88%; h) PPTS, pyr, PhCl, reflux, 4 h, 85%; i) $VO(acac)_2$, TBHP, 4Å MS, CH_2Cl_2, rt, 4 d, then *p*-TsOH, rt, 2 h, 81%; j) DMDO, acetone, H_2O, rt, 20 h; k) Br_2, NaOAc, H_2O, AcOH, rt, 20 h, 52% over 2 steps.

4.2 Merrilactone A

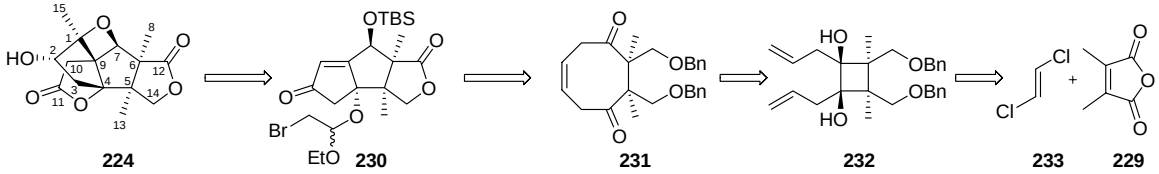
The pentacyclic sesquiterpene dilactone merrilactone A (**224**), isolated from *Illicim merrilianum* in 2000,[183] has already been the target of two formal total syntheses, by the Danishefsky group in 2002[184,a] and by the Inoue group a year later (Scheme 40).[186] The Danishefsky group had envisaged a radical cyclization to form the A ring and an "allyl-lactonization" to form the B ring. The CD ring fragment **226** could be formed with a ring cleavage–reclosure sequence of the Diels–Alder adduct **227**. The Inoue group strategy called for desymmetrization of *meso*-diketone **231** through an intramolecular aldol reaction. Mehta and Singh recently published their approach to the ABCD ring system of merrilactone A.[187]

[a] The Danishefsky group has recently published an enantioselective approach to intermediate **236** (scheme 41).[185]

(±)-Merrilactone A/ Danishefsky 2002



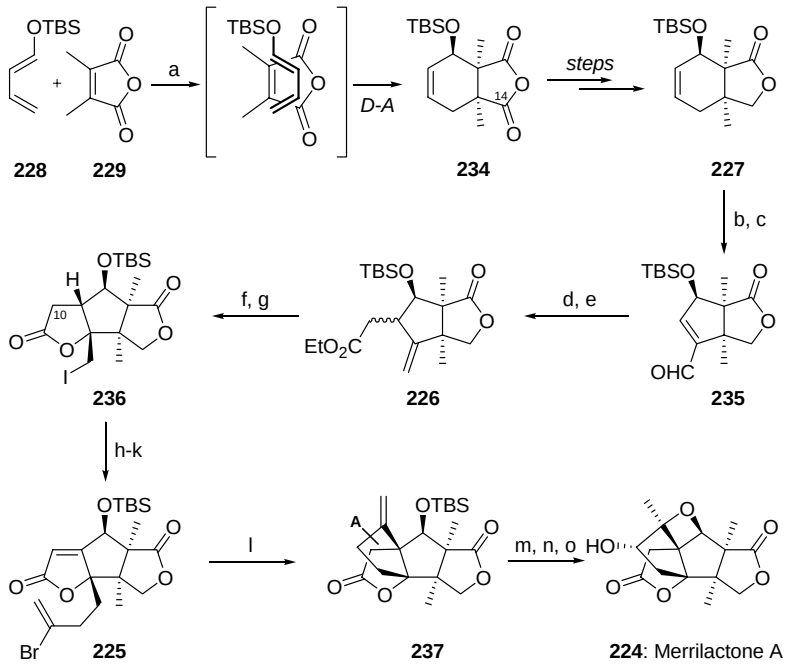
(±)-Merrilactone A/ Inoue 2003



Scheme 40. Retrosynthetic analysis of merrilactone A.

The merrilactone A synthesis by Birman and Danishefsky commences with a Diels–Alder reaction of diene **228** and dimethylmaleic anhydride (**229**) (Scheme 41).[184] After reducing the C_{14}-carbonyl (merrilactone A numbering) regioselectively, ozonolysis effected the opening of the 6-membered ring. This was followed by an aldol condensation to close the 5-membered ring to give enal **235**. Reduction of the aldehyde paved the way for the Johnson ortho ester variant of the Claisen rearrangement, which provided a 1:1.8 mixture of esters (**226**), which was subsequently hydrolyzed. Iodolactonization and chromatographic separation then gave the pure minor iodide **236**, which was allylated to prepare for the A ring cyclization. Selenylation at C_{10}, bromoselenylation of the terminal vinyl group and oxidative deselenylation afforded the cyclization precursor **225**. Exposure of vinyl bromide **225** to tributyltin hydride and AIBN then effected the formation of the [3.3.3]propellane **237**. Isomerization of the exocyclic double bond, epoxidation and acid catalyzed homo-Payne rearrangement according to the procedure of Fukuyama and co-workers[188] produced (±)-merrilactone A (**224**) in 71% yield over two steps.

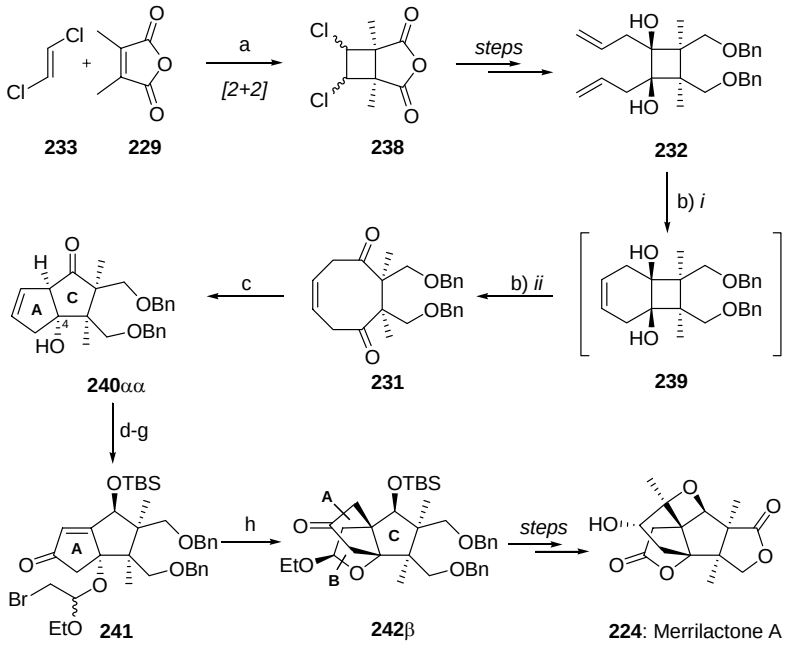
(±)-Merrilactone A/ Danishefsky 2002



Scheme 41. a) symm-collidine, Methylene Blue, mesitylene, 165 °C, 2.5 d, 74%; *steps*; b) O_3, CH_2Cl_2, MeOH, –78 °C, then PPh_3, → rt; c) $Bn_2NH{\cdot}TFA$, PhH, 63 °C, 9 h, 94% over 2 steps; d) $NaBH_4$, CH_2Cl_2, MeOH, –78 °C → rt, quant.; e) $MeC(OEt)_3$, PivOH, mesitylene, 135 °C, 24 h, 92%, α:β 1:1.8; f) LiOH, MeOH, H_2O, rt 12 h, g) I_2, $NaCHO_3$, THF, rt, 12 h, then separation, 59% over 2 steps; h) $allylSnBu_3$, AIBN, PhH, 85 °C, 4.5 h, 75%; i) LHMDS, TMSCl, THF, –78 °C, 30 min, then PhSeCl, → rt, 1.5 h; j) PhSeBr, MeCN, rt, 30 min; k) O_3, CH_2Cl_2, –78 °C, then 1-hexene, then NEt_2, PhH, reflux, 30 min, 77% over 3 steps; l) Bu_3SnH, AIBN, PhH, 85 °C, 1.5 h, 90%; m) $TsOH{\cdot}H_2O$, PhH, reflux, 3 h, 90%; n) *m*-CPBA, CH_2Cl_2, rt, 2 d, α:β 3.5:1, o)[188] $TsOH{\cdot}H_2O$, CH_2Cl_2, rt, 1 d, 71% over 2 steps.

The first step in the Inoue group's synthesis towards merrilactone A was a [2+2] photocycloaddition between 1,2-dichloroethene (**233**) and dimethylmaleic anhydride (**229**) (Scheme 42).[186] The side chains of the symmetrical diol **232** were installed so that ring closing metathesis could be performed. This was followed by opening of the 4-membered ring to give diketone **231**. Exposure of **231** to LHMDS provided the AC ring fragment **240**αα together with the A ring diastereomer **240**ββ in a 3.1:1 ratio, respectively. A two-carbon side chain was attached to the C_4-hydroxyl of ring A (merrilactone A numbering) to allow the B ring cyclization to be performed. With the enoate **241** in hand, cyclization with tributyltin hydride and triethyl borane gave the ABC ring fragment **242** of merrilactone A. Another 13 steps were required to finish the synthesis of (±)-merrilactone A (**224**).

(±)-Merrilactone A/ Inoue 2003



Scheme 42. a) *h*ν, benzophenone, acetone, rt, 3 h; *steps*; b) *i*. $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 14 h, then *ii*. $Pb(OAc)_4$, rt, 95%; c) LHMDS, THF, –78 °C, 1 h, 64% **240**αα, 22% **240**ββ; d) *m*-CPBA, CH_2Cl_2, rt, 4 h, 81%; e) DBU, CH_2Cl_2, –30 °C, 1 h, 81%, f) IBX, DMSO, rt, 30 min, 94%, g) Br_2, ethyl vinyl ether, CH_2Cl_2, –78 °C, 15 min, then sm, *N*,*N*-dimethylaniline, → rt, 1 d, 62%, 4:1 selectivity; h) Bu_3SnH, BEt_3/O_2, tol, rt, 30 min, 57% **242**β, 16% **242**α.

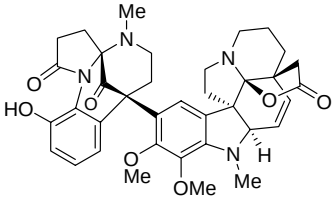
5. Indole alkaloids

Indole alkaloids are a large group of nitrogen containing natural products. The scope of this review covers the syntheses of four of them, namely 1-acetylaspidoalbidine, aspidophytine, kopsanone and lapidilectine B, because these natural products can also be classified as propellanes. They have been further divided into two groups on the basis of similarities in their structures (Schemes 43 and 48).

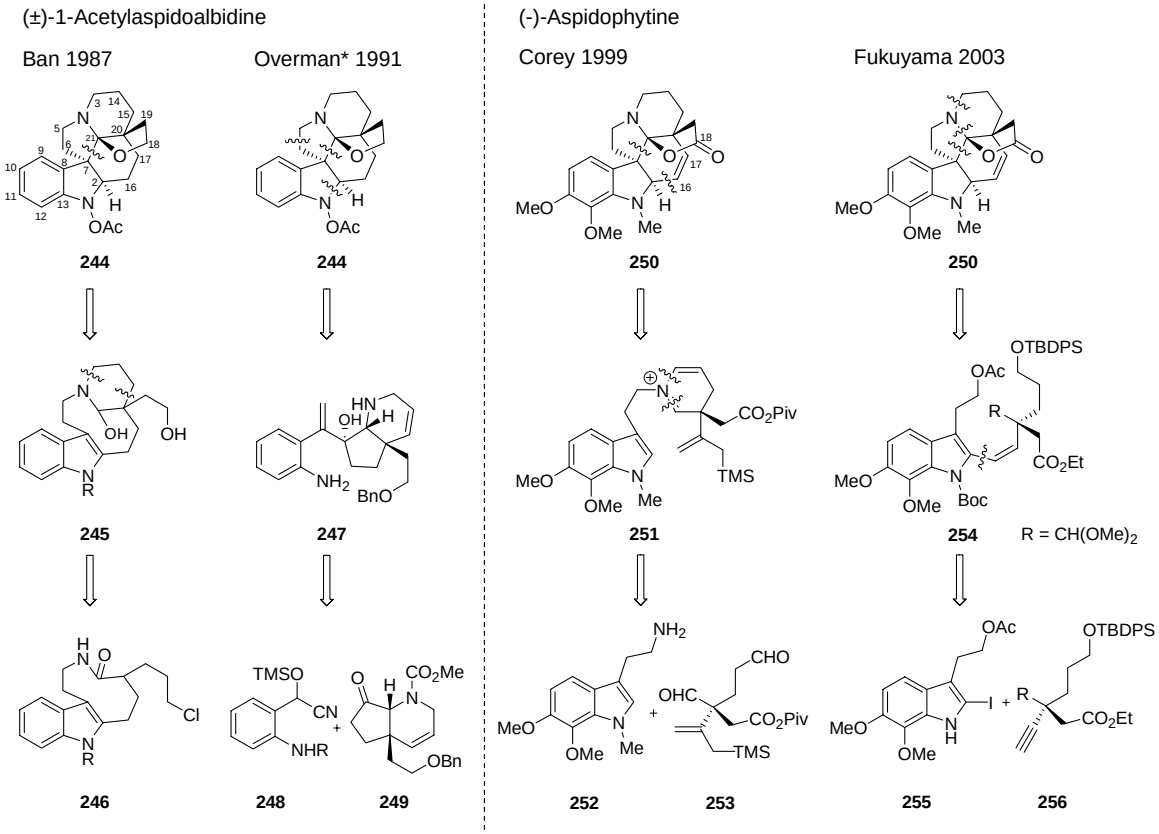
5.1 1-Acetylaspidoalbidine and aspidophytine

1-Acetylaspidoalbidine (**244**) was isolated in 1963 from *Vallesia dichotoma* RUIZ ET PAV[189] and the structure was proposed originally by Walser and Djerassi in 1964.[190] Several syntheses of the molecule have been reported in the literature, by the groups of Ban[191-193] and Overman (Scheme 43).[194] The Ban group has considerable experience in this area and confirmed the structure of 1-acetylaspidoalbidine by total synthesis in 1975.[193] The route described herein is the latest of their total syntheses of this compound. The Overman group's synthesis is based on a tandem aza-Cope–Mannich process with the disconnections shown in Scheme 43.

The structure of aspidophytine (**250**) differs from 1-acetylaspidoalbidine (**244**) only in the degree of unsaturation at the C_{16}-C_{17} bond and at C_{18} and in the substitution of the aromatic ring. Aspidophytine is actually a degradation product of haplophytine (**243**), which was isolated from *Haplophyton cimicidum* in Mexico.[195,196] Aspidophytine has inspired two total syntheses to date by the Corey[197] and Fukuyama[198,199] groups. The retrosynthetic analyses of these syntheses (Scheme 43) show the same basic disconnections, but the order of realization is different.

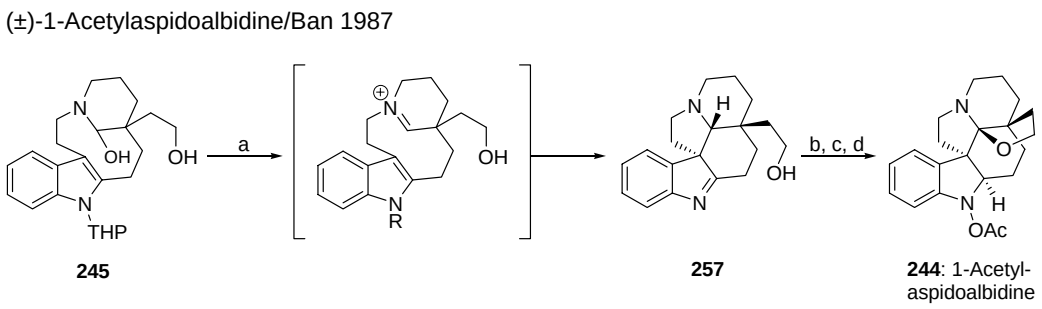


243: Haplophytine



Scheme 43. Retrosynthetic analyses of 1-acetoxyaspidoalbidine and aspidophytine.

The key step in the 1-acetylaspidoalbidine synthesis by the Ban group is the acid catalyzed transannular cyclization of diol **245** to the pentacyclic alcohol **257**, only three steps from the natural product itself (Scheme 44).[191-193] As the ultimate step, mercury(II)acetate effects the final cyclization to give the [4.4.3]propellane structure.[200]

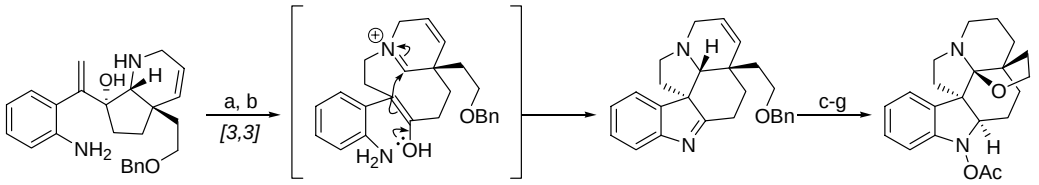


Scheme 44. a) 10% HCl, THF, 0 °C, 30 min, 70%; b) $LiAlH_4$; c) acetylation; d) $Hg(OAc)_2$, 5% AcOH, 65-70 °C, 7 h, 64%.

The key ring forming transformation in the formal total synthesis of 1-acetylaspidoalbidine by the Overman group[194] is the aza-Cope rearrangement–Mannich cyclization sequence that was developed in the group (Scheme 45).[109] The treatment of aminoalcohol **247** with paraformaldehyde effects an imine formation, which is followed

by an aza-Cope [3,3]-sigmatropic rearrangement–Mannich cyclization under acidic conditions to provide pentacycle **258**. The five following steps then conclude the synthesis of (±)-1-acetylaspidoalbidine (**244**).

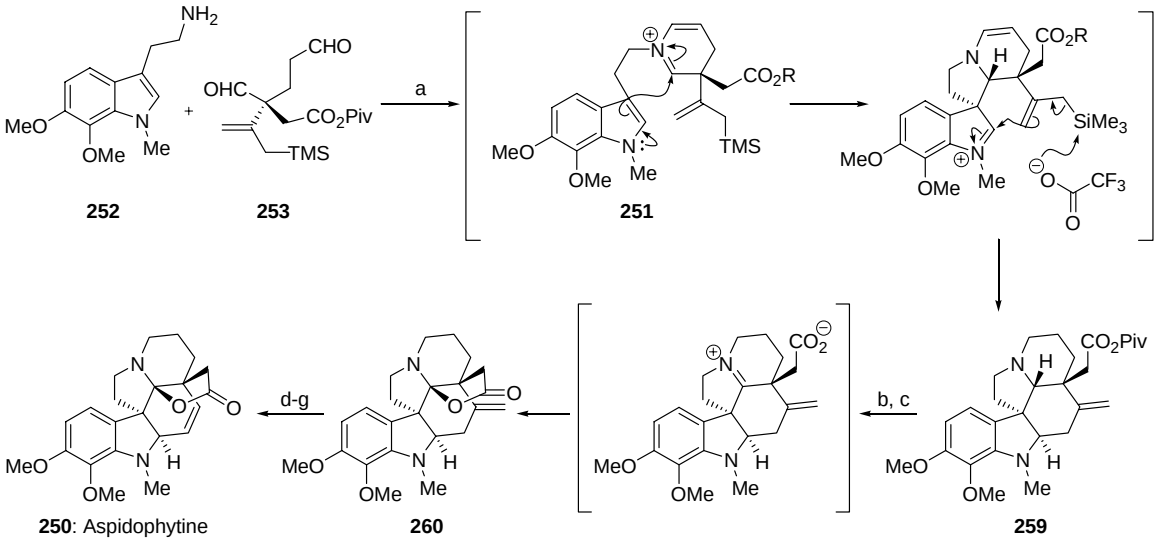
(±)-1-Acetylaspidoalbidine/Overman* 1991



Scheme 45. a) $(CH_2O)_n$, Na_2SO_4, tol, rt, 24 h, quant.; b) CSA, Na_2SO_4, PhH, reflux, 2.5 h; c) $LiAlH_4$, THF, 0 °C, 2 h, 67% over 2 steps; d) Na, NH_3, THF, –70 °C, quant.; e) Pd/C, HCO_2NH_4, EtOH, reflux, 1 h, 98%; f) Ac_2O; [g)[193] $Hg(OAc)_2$, 5% AcOH, 65-70 °C, 7 h, 64%, reaction not performed, formal total synthesis].

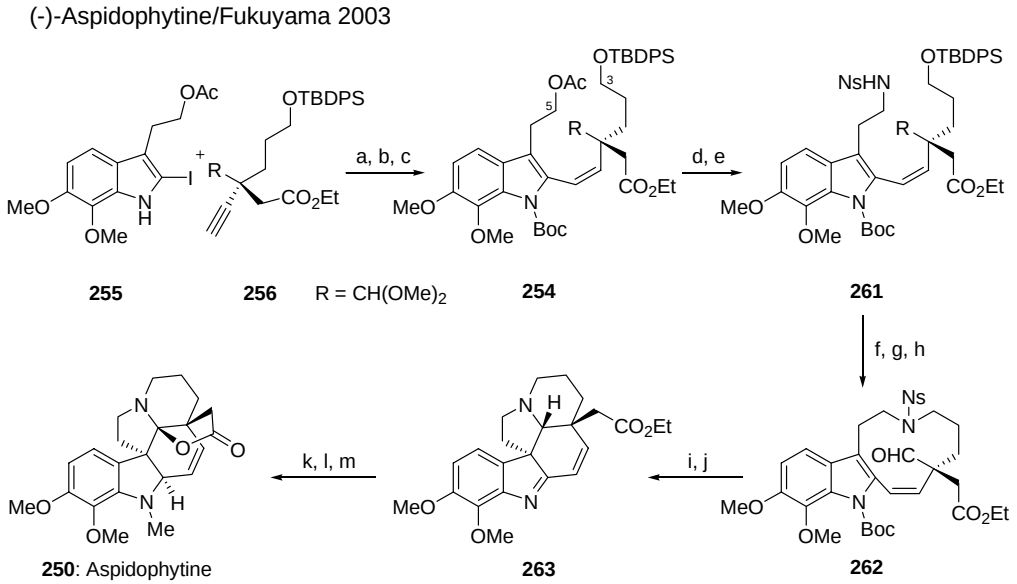
The Corey group devised the concise and convergent synthesis of aspidophytine **250** shown in Scheme 46.[197] The key transformation was an acid catalyzed cascade cyclization of the tryptamine derivative **252** and dialdehyde **253,** which forms the pentacyclic core of the molecule. Then, after having hydrolyzed the pivalate of **259**, potassium ferricyanide effected an oxidative lactonization to the [4.4.3]propellane **260**. An oxidative cleavage of the exocyclic double bond in **260** followed by enol triflate formation and treatment with tributyltin hydride provided (–)-aspidophytine (**250**).

(-)-Aspidophytine/Corey 1999



Scheme 46. a) MeCN, rt, 5 min, then TFAA, 0 °C, 2 h, then $NaBH_3CN$, 0 °C → rt, 30 min, 66%; b) NaOH, EtOH, 75 °C, 20 h, 88%; c) $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH:H_2O 1:2, rt, (fast), 92%, d) OsO_4, DMAP, *t*-BuOH:H_2O 1:2, rt, 5-10 min, then Na_2SO_3; e) $Pb(OAc)_4$, AcOH, CH_2Cl_2, –20 °C, 5-10 min, 71% over 2 steps; f) KHMDS, THF, –78 °C, 30 min, then $PhNTf_2$, 54%; g) $Pd(PPh_3)_4$, Bu_3SnH, THF, rt, 1 h, 86%.

A Sonogashira coupling between iodoindole **255** and acetylene **256** is the first step towards forming the propellane ring system of aspidophytine in the Fukuyama group's synthesis (Scheme 47).[198,199] The coupled product was Boc-protected and the triple bond was reduced selectively to olefin **254**. Changing the C_5 substituent to a nosylate-activated nitrogen enabled the formation of the 11-membered ring (**262**) once the C_3-alcohol was deprotected. Removing the nosylate and exposure of the product to trifluoroacetic acid furnished the pentacycle **263** in 56% yield over two steps. Conversion of the imine of **263** to the corresponding *N*-methylindole derivative followed by lactone formation to close the last remaining ring provided (–)-aspidophytine (**250**).



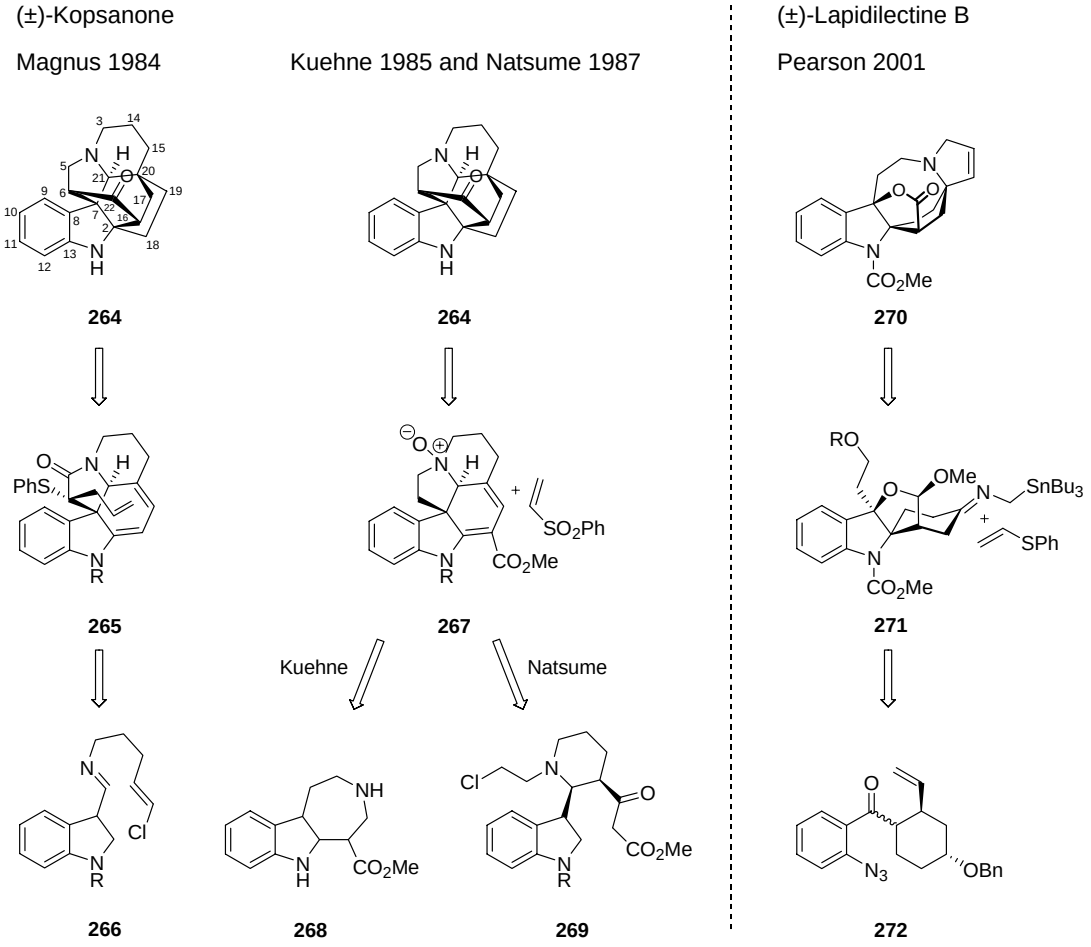
Scheme 47. a) $Pd(PPh_3)_4$, CuI, EtN_3, 70 °C, 2 h, 78%; b) Boc_2O, DMAP, CH_3CN, rt, 15 min, 94%; c) Pd/C, H_2, EtOH, rt, 3.5 h, 97%; d) K_2CO_3, H_2O, MeOH, rt, 1 h, 96%; e) *o*-$NsNH_2$, PPh_3, PhH, DEAD, rt, 5 min, 93%; f) TBAF, THF, rt, 1 h, 93%; g) PPh_3, DEAD, PhH, rt, 5 min, 92%; h) TMSBr, CH_2Cl_2, 70 °C, 15 min, then pH 7.0 buffer, 92%; i) PhSH, Cs_2CO_3, MeCN, 55 °C, 20 min; j) TFA, Me_2S, CH_2Cl_2, rt, 5 min, then pH 7.8 buffer, EtOAc, 5 °C, 30 min, 56% over 2 steps; k) HCHO, pH 7.0 buffer, MeOH, H_2O, $NaBH_3CN$, –70 °C, 30 min, → rt, 2 h, 67%; l) NaOH, EtOH, 70 °C, 2.5 h, then HCl, 5 °C, 52 %; m) $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH:H_2O 1:2, 5 °C → rt, 10 min, 56%.

5.2 Kopsanone and lapidilectine B

The kopsane alkaloids have been known since 1890,[201] but their structures remained unknown until the 1960's. Two total syntheses and one formal total synthesis have been published for kopsanone (**264**), a member of this group (Scheme 48). The syntheses of the Natsume[202,203] and Kuehne[204] groups use the same methods to install the [4.3.3]propellane ring system so only the earlier synthesis from the Kuehne group is discussed here in detail (see Scheme 48). The Kerr group has also published an approach towards kopsane alkaloids.[205] A key step in the first published synthesis of kopsanone by Magnus *et al.* is the intramolecular Diels–Alder reaction of **265**.[206,207] The Kuehne group

synthesis is based on a Diels–Alder reaction between diene **267** and phenyl vinyl sulfone.[204]

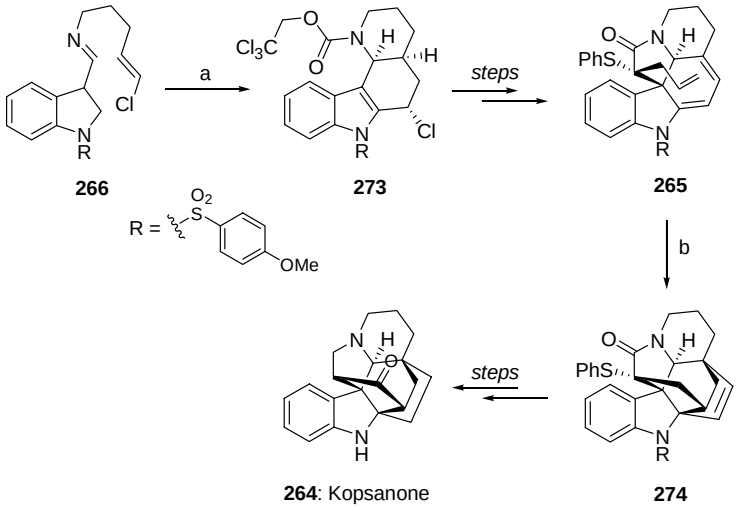
Lapidilectine B (**270**) was isolated from *Kopsia lapidilecta* in 1992[208] and was synthesized by the group of Pearson (Scheme 48).[209,210] The main features of the synthesis of this polycyclic indole alkaloid include a Smalley azido–enolate cyclization to form the indoxy core of the molecule.



Scheme 48. Retrosynthetic analyses of kopsanone and lapidilectine B.

The synthesis of the propellane moiety of kopsanone by Magnus *et al.* began with the treatment of vinyl chloride **266** with trichloroethyl chloroformate and gave tetracycle **273** in 50% yield (Scheme 49).[206,207] After installing the diene portion and the allylic side chain, the stage was set for the intramolecular Diels–Alder reaction of **265**, which provided the [4.3.3]propellane **274** in 81% yield. Six more steps were required to finish the first total synthesis of (±)-kopsanone (**264**).

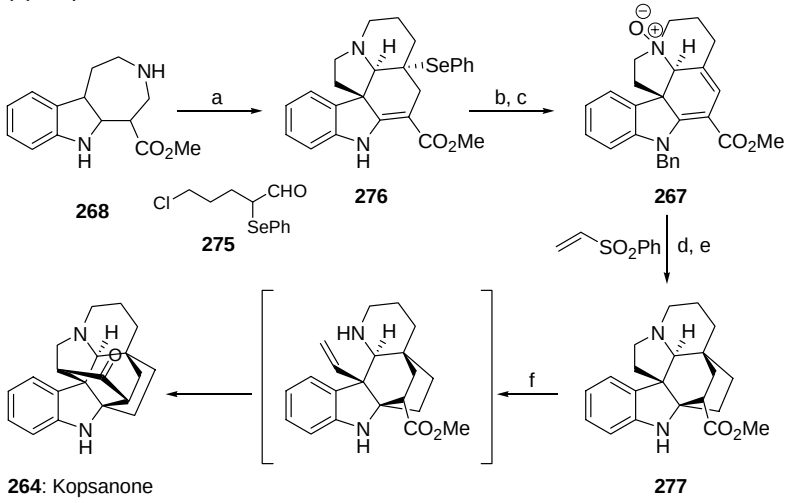
(±)-Kopsanone/Magnus 1984



Scheme 49. a) Cl_3CCH_2OCOCl, *i*-Pr_2NEt, PhCl, 0 → 120 °C, 40 min, then 120 °C, 8 h, 50%; *steps*; b) 95-100 °C, PhH, 4 h, 81%.

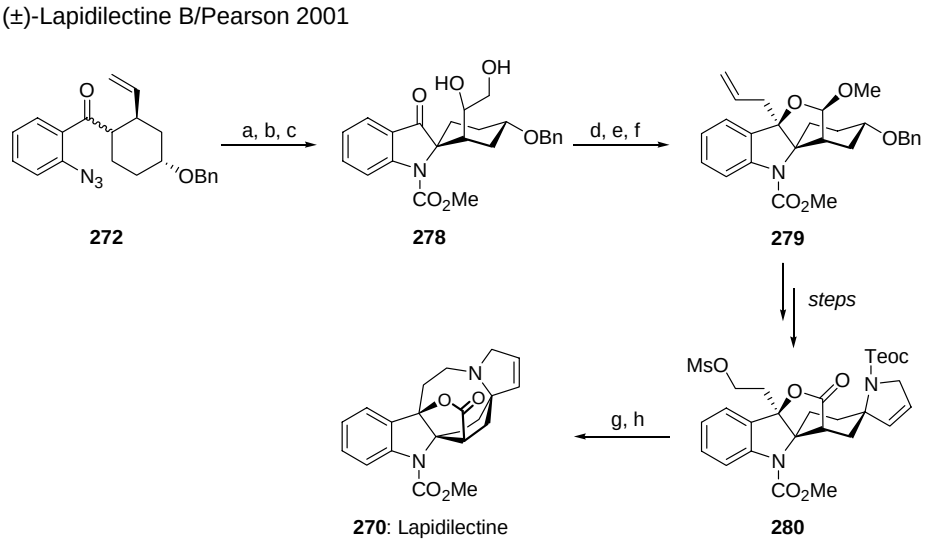
In the Kuehne group synthesis of kopsanone (Scheme 50),[204] the key pentacyclic intermediate **276** came from an adaptation of a biomimetic secodine cyclization that they had investigated extensively.[211] Benzylation of the indole nitrogen and oxidative elimination of the selenyl group afforded *N*-oxide **267**, which was ready for the Diels–Alder cyclization. Heating of diene **267** with phenyl vinyl sulfone effected the formation of hexacycle **277** after reduction of the double bond and the sulfone with Raney nickel. Finally, heating of ester **277** to 210 °C for 36 h provided (±)-kopsanone (**264**).

(±)-Kopsanone/Kuehne 1985



Scheme 50. a) **275**, H_3BO_3, CH_2Cl_2, reflux, 12 h, 33%; b) BnBr, NaH, DMF, rt, 30 min, 86%; c) *m*-CPBA, CH_2Cl_2, –78 °C, 79%; d) phenyl vinyl sulfone, PhH, 100 °C, 16 h, 57%; e) Raney-Ni, EtOH, reflux, 3 h, 67%; f) MeOH, 210 °C, 36 h, 88%.

Treatment of azide **272** with potassium hydroxide is the first ring-forming step in the lapidilectine B synthesis by Pearson *et al.* (Scheme 51).[209,210] The Smalley cyclization provided an indole derivative that was then protected at the nitrogen and dihydroxylated to give diol **278** in 6:1 selectivity. Allylation of the ketone followed by oxidative cleavage of the diol and treatment with camphorsulfonic acid furnished methyl acetal **279**. After closing the pyrroline ring with a cycloaddition (see Scheme 48), mesylate **280** was ready for the final 8-membered ring closure. Removing the Teoc-group from the pyrroline nitrogen and treatment of the remaining salt with diisopropylethylamine provided (±)-lapidilectine B (**270**).



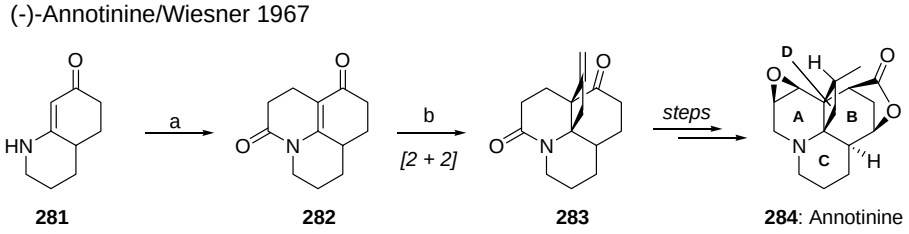
Scheme 51. a) KOH, *i*-PrOH, 15 °C, 1 h, (68% over 2 steps), 2.2:1 selectivity; b) *t*-BuLi, $ClCO_2Me$, THF, –10 °C, 30 min, 89%; c) OsO_4, NMO, acetone, rt, overnight, 82%, 6:1 selectivity; d) allylMgBr, THF, –40 °C → rt, overnight, 90%; e) $NaIO_4$, pH 7 buffer, THF, 0 °C → rt, overnight; f) CSA, MeOH, 1 h, rt, 59% over 2 steps; *steps*; g) TFA, CH_2Cl_2, rt, 30 min; h) *i*-Pr_2NEt, MeCN, rt, 2 h, then 60 °C, 10 h, 76% over 2 steps.

6. Other alkaloids

Other than the indole alkaloids covered in Chapter 5, only the syntheses of four alkaloids with the propellane ring structure have appeared in the literature. Two of these, namely cepharamine and metaphanine, share a common ring structure called the hasubanan skeleton and will be discussed together in Section 6.2. Three research groups have reported on their synthetic efforts towards the hasubanan skeleton and these will also be briefly discussed in the same section.

6.1 Annotinine

The same research group that reported the total synthesis of the *Lycopodium* alkaloid annotinine (**284**) in 1967[212-215] deduced the structure of the molecule during the years 1956-1957 (Scheme 52).[216] Their synthesis starts with a condensation of acrylic acid and vinylogous amide **281** to provide the [2+2] photochemical cycloaddition substrate **282**. The cycloaddition of **282** with allene proceeded smoothly to give the ABCD ring system of annotinine (**283**). Several more steps, including an optical resolution, were required to finish the synthesis of (–)-annotinine (**284**).

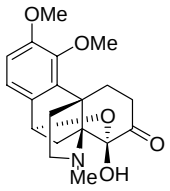


Scheme 52. a) acrylic acid, 135 °C, 2 h, 63%; b) allene, *h*ν, -70 °C, 20 h, 54%.

6.2 Cepharamine and the hasubanan skeleton

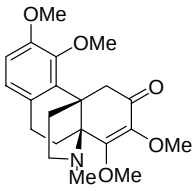
Three total syntheses of cepharamine (**290**) have been published (Scheme 53), an alkaloid isolated from *Stephania cepharantha* Hayata in 1966.[217] The Ibuka group published the

first total synthesis in 1969,[218][Inubushi, 1971 #163] then the Tahk group published in 1970[219] and Schultz in 1998.[220] Ibuka *et al.* has also published a synthesis of methaphanine (**285**)[221,222] and hasubanonine (**286**)[223,224] but since these syntheses use the same methodology to form the [4.3.3]propellane ring system as in their synthesis of cepharamine, they will not be discussed here in more detail.



285: Methaphanine

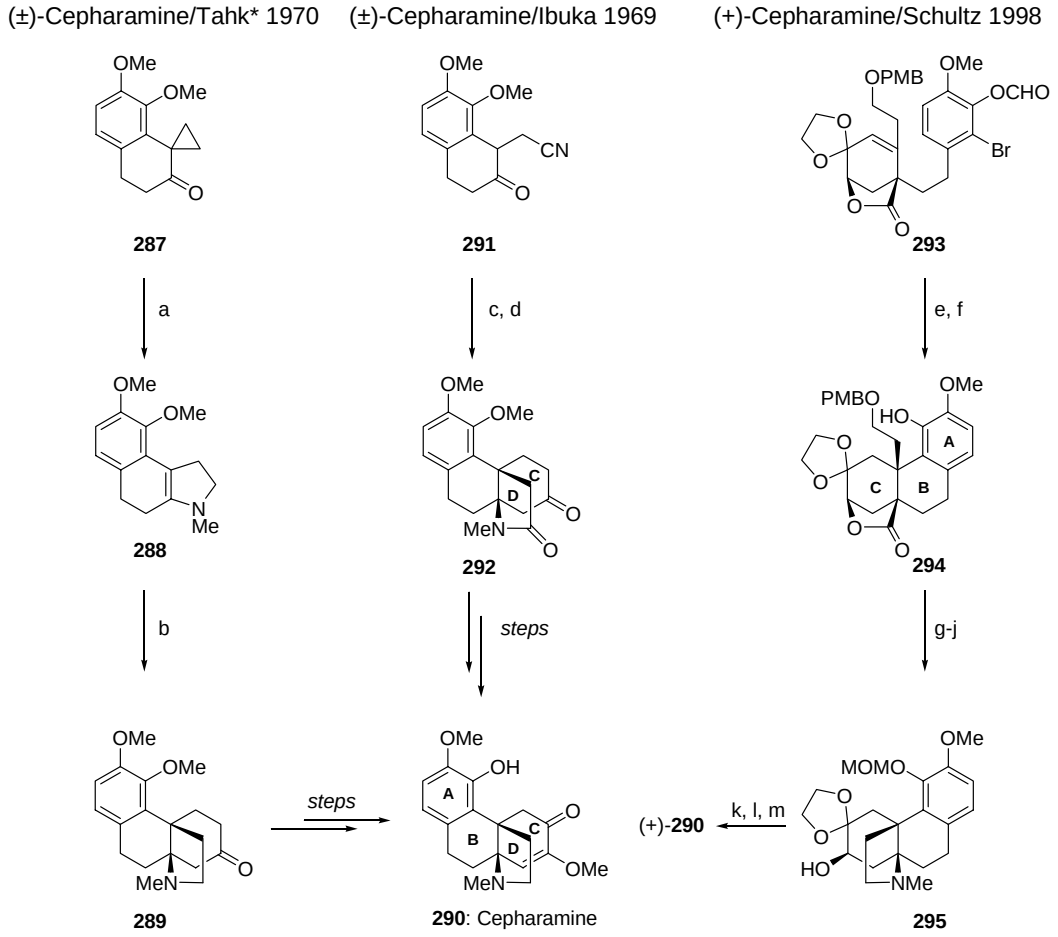
In the Ibuka group synthesis of cepharamine (**290**) (Scheme 53),[218,225] the key ring forming step was the formation of the CD ring system. Exposure of nitrile **291** to methyl vinyl ketone (MVK) followed by treatment with sodium ethoxide provided ketoamide **292** in 50% yield.



286: Hasubanonine

In the formal total synthesis of cepharamine by the Tahk group (Scheme 53),[219] the CD ring system was formed by treatment of cyclopropyl ketone **287** with methylamine to afford the ring expansion product **288**. Annulation with methyl vinyl ketone then completed the ring system of cepharamine (**289**).

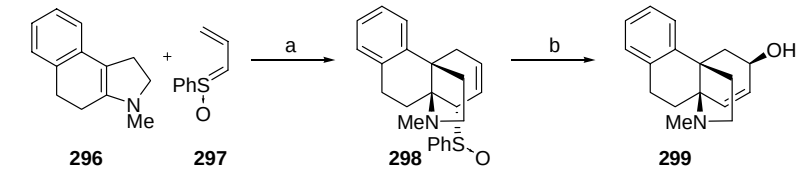
The Schultz group strategy for the synthesis of cepharamine differs significantly from the previous syntheses (Scheme 53).[220] The key step in their synthesis was a radical cyclization of **293** followed by hydrolysis of the formate ester to give the ABC ring fragment **294**. After a MOM-protection and a Hofmann-type rearrangement to transform the 5-membered lactone to a 6-membered lactam ring, treatment with lithium aluminium hydride provided alcohol **295**. This alcohol was then transformed into (+)-cepharamine ((+)-**290**), the unnatural enantiomer of the molecule, in three steps.



Scheme 53. a) $MeNH_2$, CaO, PhH, 100-110 °C, 7 d, 69%; b) MVK, rt, 1 h, then AcOH, 40 → –78 °C, evacuated to 125 mmHg, → 70 °C, 5 h, 20 %. c) MVK, NaOH, MeOH, reflux, 45 min; d) Na, EtOH, reflux, 4 h, 50% over 2 steps. e) Bu_3SnH, AIBN, PhH, 80 °C, 10 h; f) K_2CO_3, MeOH, THF, H_2O, rt, overnight, 56% over 2 steps; g) NaH, MOMCl, THF, reflux, 15 h, 99%; h) $NaNH_2$, NH_3, THF, –30 °C → rt, 2 h; i) NaOMe, Br_2, MeOH, THF, –78 °C, 1 h, → reflux, 1 h, 93% over 2 steps; j) $LiAlH_4$, THF, reflux, 22 h, 99%; k) $(COCl)_2$, DMSO, CH_2Cl_2, –78 → 10°C, 1 h, then Et_3N, –10 °C → rt, 30 min, 85%; l) KH, 18-crown-6, DMF, 0 °C → rt, 30 min, then MeI, rt, 15 h, 65%; m) *p*-TsOH, acetone, H_2O, 60 °C, 39 h, 97%.

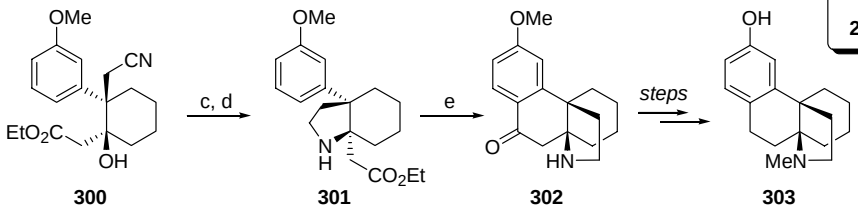
The synthetic efforts towards the hasubanan skeleton are summarized in Scheme 54. The key transformation in the Evans group approach is a Diels–Alder reaction between tetrahydrobenzindole **296** and sulfoxide **297** to give tetracycle **298**.[226-228] Bruderer *et al.* used a dehydration to achieve the closure of the 5-membered pyrroline ring (**300** → **301**). An acid catalyzed cyclization then furnished tetracycle **302**.[229] The latest synthesis of the hasubanan skeleton by the Mulzer group features an intramolecular 1,3-dipolar cycloaddition of **304** followed by a subsequent elimination of N_2 to give aminoenone **306**.[230]

(±)-Hasubanan skeleton/Evans 1972

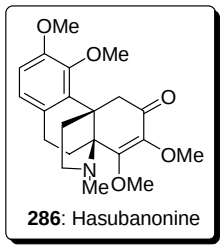


296 **297** **298** **299**

(±)-Hasubanan skeleton/Bruderer *et al.* 1977

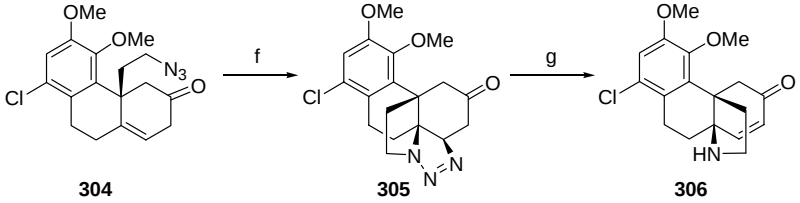


300 **301** **302** **303**



286: Hasubanonine

(±)-Hasubanan skeleton/Mulzer 1998



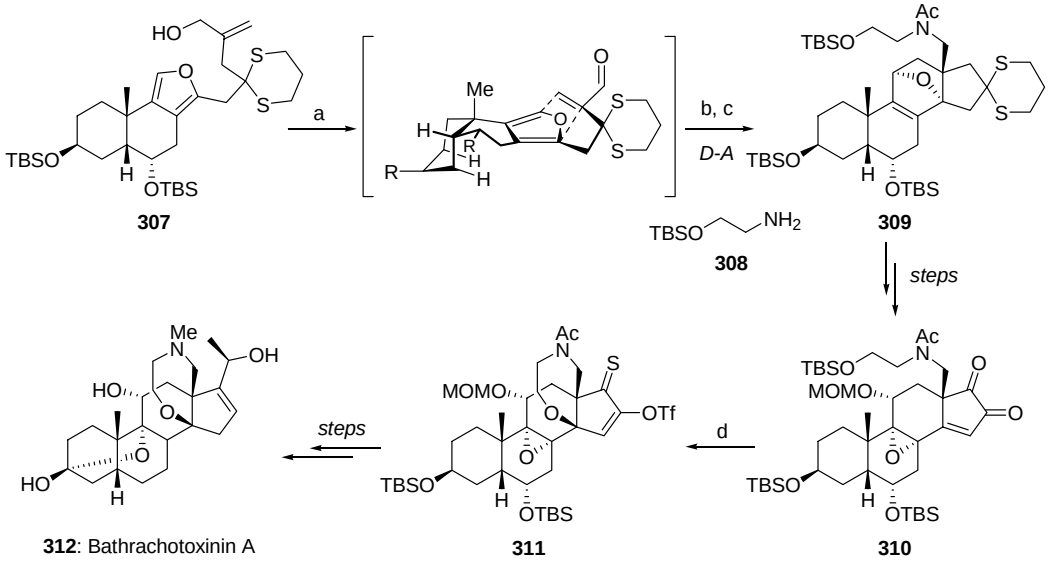
304 **305** **306**

Scheme 54. a) MeCN, 70 °C, 24 h; b) $Na_2S{\cdot}9H_2O$, MeOH, 65 °C, 8 h. c) $POCl_3$, pyr, reflux, 5 h; d) NH_3, Raney-Ni, H_2, EtOH, 80 °C, 38% over 2 steps; e) HCl, H_2O, reflux, 1 h, 83%. f) PhH, reflux, 1 h, 76%; g) pyr, reflux, 5 h, 73%.

6.3 Bathrachotoxinin A

Bathrachotoxinin A (**312**) is a unique steroidal alkaloid that possesses several interesting structural features. It has been synthesized partially from steroid precursors by Wehrli and co-workers.[231,232] A total synthesis was published by the Kishi group in 1998 (Scheme 55).[233] The synthesis features an *exo*-selective intramolecular Diels–Alder reaction (step a) and an oxy-Michael addition (step d).

(±)-Batrachotoxinin A/Kishi 1998



Scheme 55. a) Mn_2O, CH_2Cl_2, rt, 1 h; then filtration; then CH_2Cl_2, rt, 12 h; b) **308**, AcOH, 4Å MS, PhH, rt, 3 h; then $NaCNBH_3$, MeOH, 0 °C, 15 min; c) Ac_2O, pyr, rt, overnight, 76% over 3 steps, >25:1 selectivity; *steps*; d) TASF, THF:DMF 10:1, 0 °C → rt, 1 h; then $PhNTf_2$, Et_3N, 30 min, rt, 95%.

7. Summary

The syntheses of propellane containing natural products have been reviewed with the emphasis being on natural products which contain a three-membered ring as part of the propellane structure. Propellanes are a well-established structural motif that can be found in diverse natural products. This makes their total synthesis a challenging task because no generally applicable method can be utilized in the syntheses. However, the Diels–Alder reaction arises as one of the more commonly applied ring forming reactions among these syntheses.[34]

For the cyclopropane ring containing natural products described here, only two different methods for the formation of the cyclopropane ring have been applied. Potential new avenues for synthesizing [*n*.*n*.1]propellane containing natural products could involve both inter- and intramolecular cyclopropanation reactions.

8. Synthesis of DEFG ring system of cneorin C

8.1 Introduction: cneorins

Cneorin C (**3**) (Figure 6) was originally isolated from the xerophytic shrub *Cneorum pulverulentum*, native to the Canary Islands, in the late 1970's.[234] This shrub hosts a variety of bitter principles called cneorins, all of which contain the [4.3.1]propellane ring system. These oxidized pentanortriterpenes (C_{25} compounds) also have other interesting structural features in common, such as a 5,5-spiroketal unit and a butenolide moiety. Biogenetically these compounds are thought to be related to the limonoid triterpenes.[235] Due to a lack of material from natural sources, these compounds have not received proper pharmacological screening. In addition to *Cneorum pulverulentum*, the Cneoraceae plant family consists of two other species, *Cneorum tricoccon*, which is native to coastal areas of the western Mediterranean, and *Cneorum trimerum*, which belongs to the flora of Cuba. The tricoccins (Figure 6) were isolated from the former, but the latter has not been adequately studied due to a lack of access to the required plant materials. Recently, some close structural relatives of the cneorins, the cedkathryns (**316**), were isolated from *Cedrelopsis gracilis* from Madagascar (Figure 6).[236] In addition, some compounds that could result from rearrangements of the cneorins or the tricoccins, for example cedmilinol (**317**), have been isolated from *Cedrelopsis grevei*.[237]

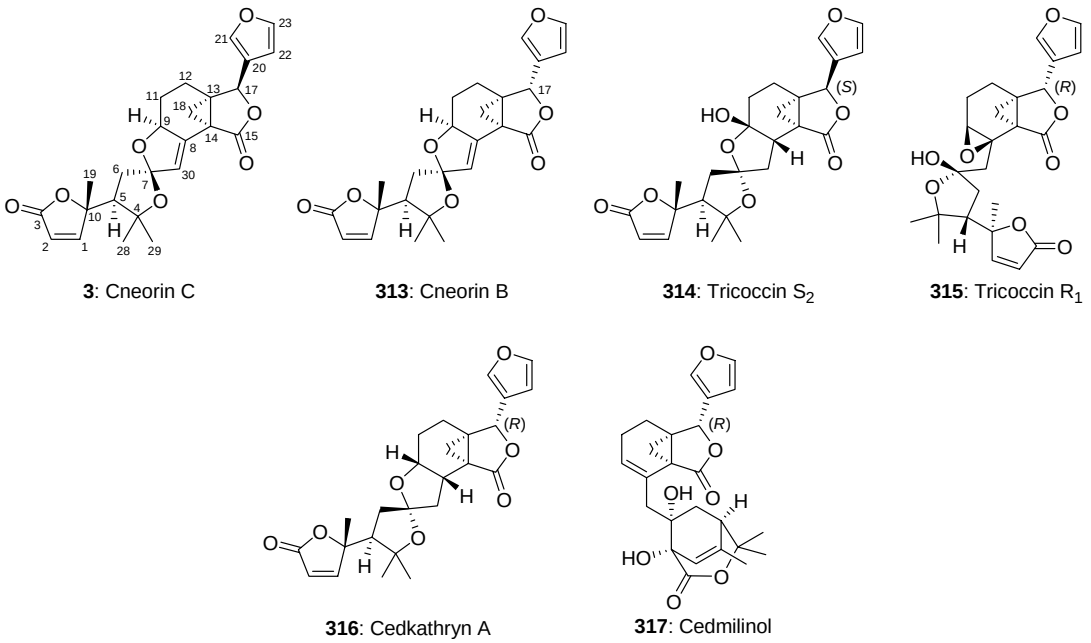
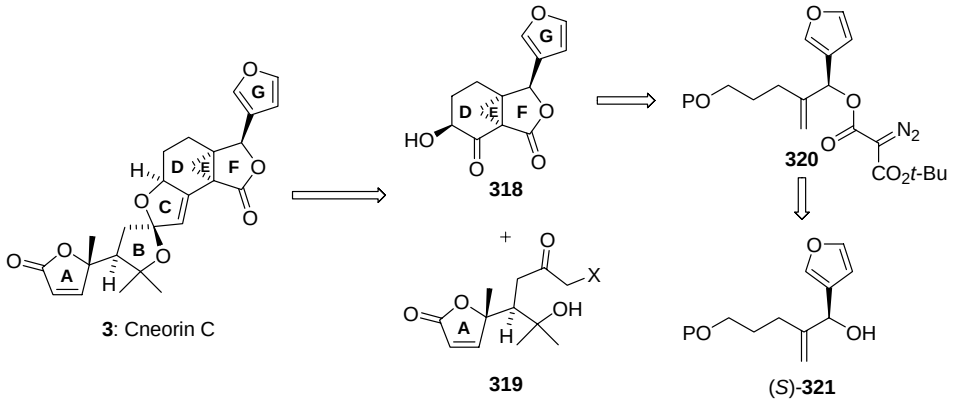


Figure 6. Selected structures of natural products related to cneorin C.

Despite cneorin C's intriguing structure, the molecule has not attracted synthetic attention except from our group.[238] Retrosynthetically (Scheme 56), the structure of the molecule can be divided into two advanced substructures, namely hydroxyketone **318**, which consists of the DEFG rings of the molecule, and the A ring butenolide fragment **319**. It was envisaged that when fragments **318** and **319** were joined, the rings B and C would also simultaneously close. The Koskinen group has long been interested in copper-catalyzed intramolecular cyclopropanations of diazomalonates.[239-243] As evident from the retrosynthetic analysis shown in Scheme 56, the DEFG ring system of cneorin C (**318**) is an ideal candidate for the intramolecular cyclopropanation of diazomalonate **320**, which can be conveniently prepared from the furyl substituted allylic alcohol (*S*)-**321**.



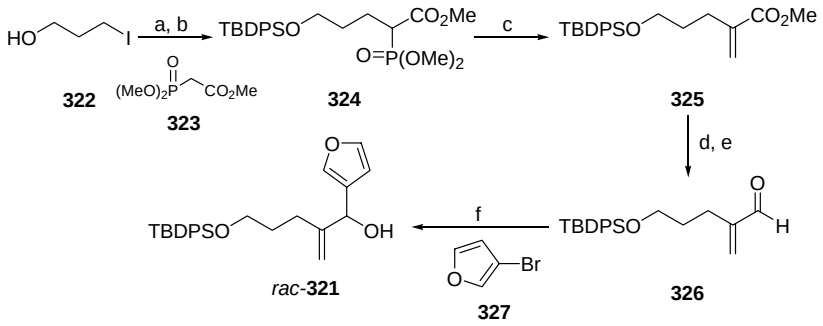
Scheme 56. Retrosynthetic analysis of cneorin C.

Thus, the synthesis of the DEFG ring system of cneorin C can be divided into three smaller subgoals: (1) securing access to the allylic alcohol (*S*)-**321** efficiently and enantioselectively, (2) performing the cyclopropanation reaction to yield the EFG ring fragment and (3) closing the D ring to obtain the [4.3.1]propellane structure.

8.2 Synthesis of DEFG ring fragment: the early steps

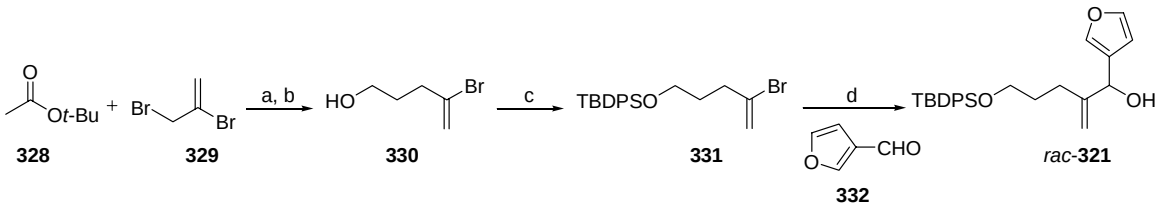
As the first task, I undertook the preparation of allylic alcohol **321** in racemic form. Two different synthetic routes were devised to gain access to allylic alcohol **321**, both of which involved coupling of an aldehyde (either **326** or **332**) with a bromide (either **327** or **331**) (Schemes 57 and 58).

Enal **326** was prepared from 3-iodopropanol (**322**) via a Horner-Wadsworth-Emmons reaction of phosphonate **324** with paraformaldehyde (Scheme 57).[244,245] The enal **326** was then alkylated with 3-furyl lithium yielding the racemic furyl substituted allyl alcohol *rac*-**321**.



Scheme 57. a) TBDPSCl, imid., CH_2Cl_2, rt, 15 min, 88%; b)[244] NaH, trimethyl phosphonoacetate (**323**), DMSO, rt, 70 min, then sm, 3 h, 71%; c)[245] paraformaldehyde, K_2CO_3, THF, reflux, 6 h, 71%; d) DIBAL-H, THF, –78 °C, 30 min, 99%; e) MnO_2, CH_2Cl_2, rt, 27 h, 94%; f) 3-bromofuran (**327**), *t*-BuLi, THF, –78 °C, 40 min, then **326**, 2 h, 87%.

An alternative preparation of the racemic alcohol *rac*-**321** was developed as follows: vinyl bromide **331** (Scheme 58) was prepared according to the literature[246] from *t*-butyl acetate (**328**) and 2,3-dibromopropene (**329**). The vinyl bromide **331** was then converted to the corresponding vinyl lithium species by halogen metal exchange with *t*-BuLi and treated with 3-furaldehyde (**332**) as the electrophile to furnish the racemic furyl substituted allyl alcohol *rac*-**321**. This route was found to be the more efficient way to obtain alcohol *rac*-**321** (overall yield 47% for Scheme 58 vs. 36% for Scheme 57).



Scheme 58. a)[246] LDA, **328**, THF, –78 °C, 1 h, then **329**, –78 °C → rt, 2.5 h, 82%; b)[246] $LiAlH_4$, THF, 0 °C → rt, 2 h, 95%; c) TBDPSCl, imid., CH_2Cl_2, rt, 50 min, 90%; d) **331**, *t*-BuLi, THF, –78 °C, 30 min, then 3-furaldehyde (**332**), –78 °C → rt, 2 h, 70%.

8.3 Enantioselective synthesis of furyl substituted allyl alcohol 321

The preparation of enantiopure compounds is of crucial importance in modern organic synthesis, and chiral allylic alcohols provide a useful template for a variety of stereoselective transformations of olefins. The stereogenic center of the allylic alcohol can be used to direct a variety of synthetic transformations, for example epoxidations[247,248] and dihydroxylations.[249] In a recent example, Evans' synthesis of pectenotoxins-4 and -8 utilizes a hydroxyl directed epoxidation twice in a highly diastereoselective manner.[250,251] This section describes our journey towards the preparation of enantiopure allylic alcohol (*S*)-**321**.[238]

8.3.1 Enantioselective alkylation

The first attempt to obtain (*S*)-**321** utilized a catalytic enantioselective alkylation.[252,253] It was envisaged that a vinyl bromide could be converted to a vinyl zinc species and added to an aldehyde in the presence of a chiral ligand in an enantioselective manner (Figure 7). Two different routes were attempted: (1) alkylation of 3-furaldehyde (**332**) with the vinyl bromide **331** (Scheme 58) and (2) alkylation of enal **326** with 3-furylbromide (**327**) (Scheme 57). In the first case with vinyl bromide **331** and 3-furaldehyde, the vinyl zinc species was never formed and only unreacted vinyl bromide was recovered. In the second case with enal **326** and 3-furylbromide, the corresponding furyl zinc species was not reactive enough to add to the aldehyde, which was recovered.

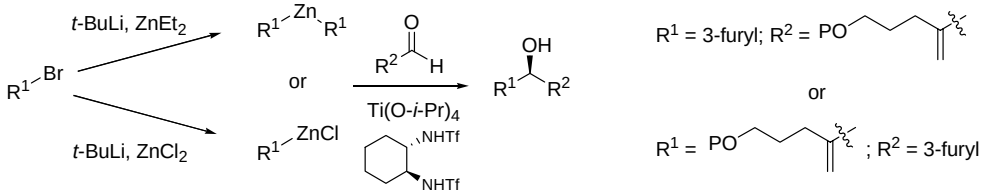


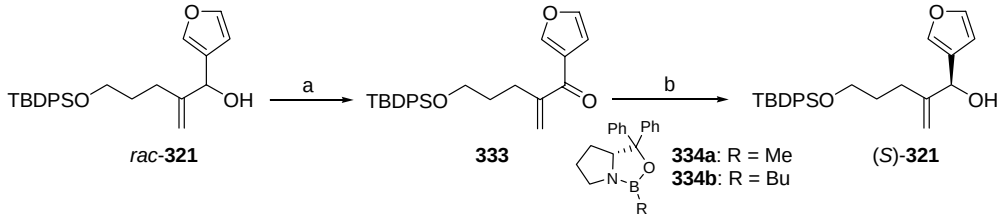
Figure 7. Two routes for enantioselective alkylation.

Also, the alkylation reactions with the lithiated species described in Schemes 57 and 58 were found to be relatively fast, so it was suspected that in a catalytic enantioselective

alkylation the uncatalyzed racemic background reaction would diminish the ee of the product.

8.3.2 CBS reduction

My second approach to the problem was to convert the furyl substituted allyl alcohol to the corresponding enone followed by an enantioselective reduction. Thus, the alcohol *rac*-**321** was oxidized to ketone **333** with MnO_2 (Scheme 59).[254] The Corey-Bakshi-Shibata (CBS) reduction[255] is a widely established catalytic asymmetric reduction method. In this case, reduction of ketone **333** with $BH_3 \cdot SMe_2$ in the presence of the chiral catalyst **334a-b**[256,257] gave the alcohol in 35% ee at its best (Scheme 59, table 1). BINAL reduction[258,259] as well as DIP-chloride reduction[260-263] were also tried, but only starting material was recovered.



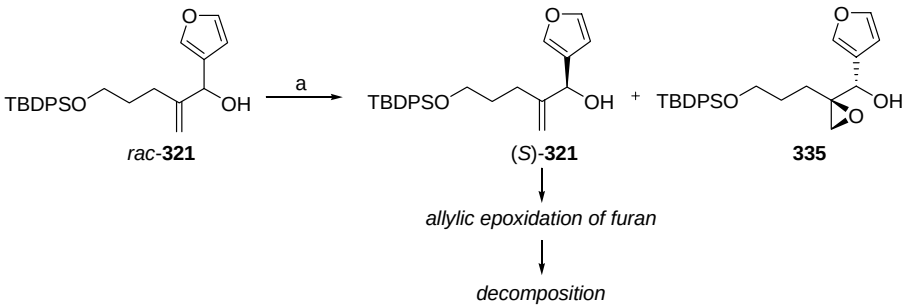
Scheme 59. a) MnO_2, CH_2Cl_2, rt, 27 h, 83%; b) catalyst **334a-b**, THF, –20 °C. See table 1 for details. Yields were not determined.

*Table 1. CBS-reduction of enone **333**.*

entry	reagents	% ee	time (h)
1	$BH_3 \cdot SMe_2$, **334a**	35	114
2	$BH_3 \cdot SMe_2$, **334b**	13	70
3	catecholborane, **334b**	22	67

8.3.3 Kinetic resolution by Sharpless asymmetric epoxidation

The third approach to (*S*)-**321** was kinetic resolution of the furyl substituted allyl alcohols *via* Sharpless asymmetric epoxidation (SAE).[264,265] Both diethyl and diisopropyl tartrates were tested, both giving 50% conversion to the alcohol (*S*)-**321** with 57 and 68% ee, respectively, after two days of reaction at –20 °C (Scheme 60, table 2). The enantiopurity of the corresponding epoxide **335** was very high with both tartrates. One reason to account for the ee difference of alcohol (*S*)-**321** with the two tartrates is that with a smaller tartrate the allylic double bond of the furan ring starts to epoxidize, thus causing the molecule to decompose faster.



Scheme 60. a) (+)-tartrate, Ti(O-*i*-Pr)$_4$, 3Å MS, CH_2Cl_2, –20 °C, 60 min, then TBHP, 2 d. See table 2 for details. Conversion 50% according to NMR.

Table 2. Kinetic resolution by Sharpless asymmetric epoxidation.

		(*S*)-**321**		**335**	
entry	tartrate	% ee	yield (%)[a]	% ee	yield (%)[a]
1	(+)-DET	57	38%	96	36%
2	(+)-DIPT	68	37%	94	39%

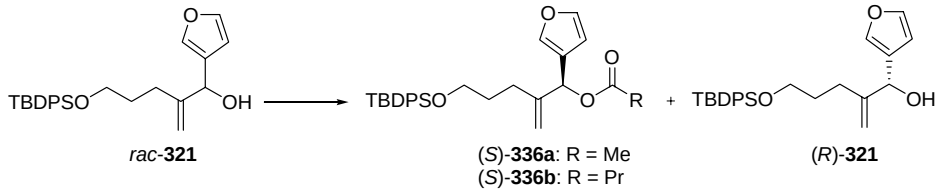
[a]Maximum theoretical yield 50%.

8.3.4 Enzymatic kinetic resolution

Hampered by these not very satisfying results I turned to our collaborators in the University of Turku, the research group of Prof. Liisa Kanerva. They have been actively studying enzymatic kinetic resolutions via acylations and deacylations for some time.[266-271] They undertook the task of producing enantiomerically pure (*S*)-**321** and the results are shown below.

The capacities of *Candida antarctica* lipase B (CAL-B) and the lipase from *Pseudomonas cepacia* (lipase PS) are well recognized for carrying out highly enantioselective acylations of racemic secondary alcohols.[272] Especially in the case of sterically hindered substrates, it is advisable to add the relatively rarely applied *Candida antarctica* lipase A (CAL-A) to the list of potential lipases.[266-271] Thus, the above lipases (CAL-A and lipase PS adsorbed on Celite ® in the presence of sucrose[273] and commercially available CAL-B and lipase PS-C II immobilized on ceramic) were screened for the enantioselective acylation of *rac*-**321** with 2,2,2-trifluoroethyl butanoate in methyl *t*-butyl ether (MTBE) at room temperature (Scheme 61, table 3). CAL-B (entry 10) and the lipase PS preparations (entries 11 and 12) performed poorly under the reaction conditions while CAL-A catalyzed a fast formation of (*S*)-butanoate **336b** (entry 7) in a highly enantioselective manner ($E > 300$). MTBE was chosen as the solvent due to its positive effects on reactivity (measured as a conversion reached after 1 h; entries 1-7) and its convenient boiling point (55.2 °C) for the gram-scale resolution of *rac*-**321**. After filtering off the enzyme, the (*S*)-butanoate **336b** (48% yield (maximum theoretical yield

50%), 96% ee) and (*R*)-alcohol **321** (41% yield, 95% ee) were isolated by column chromatography at 50% conversion. The butanoate was finally reduced with DIBAL-H at –78 °C in dichloromethane to furnish (*S*)-**321** in 98% yield and 96% ee.[263]



rac-**321** (*S*)-**336a**: R = Me (*S*)-**336b**: R = Pr (*R*)-**321**

Scheme 61. See table 3 for details. The reactions were conducted at room temperature.

Table 3. Lipase catalyzed asymmetric acylation

entry	lipase	acyl donor	solvent	time (h)	% conv.	(*S*)-**336** % ee	(*R*)-**321** % ee	*E*
1	CAL-A	$PrCO_2CH_2CF_3$	acetonitrile	1	44	99	79	>300
2	CAL-A	$PrCO_2CH_2CF_3$	*t*-amyl alcohol	1	17	>99	21	>300
3	CAL-A	$PrCO_2CH_2CH_3$	ethyl butanoate	1	16	>99	19	>300
4	CAL-A	$PrCO_2CH_2CF_3$	hexane	1	32	>99	47	>300
5	CAL-A	$PrCO_2CH_2CF_3$	toluene	1	32	>99	47	>300
6	CAL-A	$PrCO_2CH_2CF_3$	DIPE	1	47	97	85	>300
7	CAL-A	$PrCO_2CH_2CF_3$	MTBE	1	45	99	80	>300
8	CAL-A	$PrCO_2CH{=}CH_2$	MTBE	1	46	98	83	>300
9	CAL-A	$MeCO_2CH{=}CH_2$	MTBE	1	5	99	5	>300
10	CAL-B	$PrCO_2CH_2CF_3$	MTBE	24	0.3	99	*rac*	-
11	Lipase PS CII	$PrCO_2CH_2CF_3$	MTBE	24	2	38	0.7	2
12	Lipase PS	$PrCO_2CH_2CF_3$	MTBE	24	1	66	0.4	5

In the above acylation of *rac*-**321** in the presence of celite bound CAL-A, commercial vinyl butanoate (entry 8) or acetate (entry 9) can replace 2,2,2-trifluoroethyl butanoate as an acyl donor. The reaction with vinyl acetate was slow (5% conversion in 1 h, entry 9) compared to that with the butanoates, taking 27 h to reach 50% conversion. It is important to recognize that the butanoate (*S*)-**336b** (or the corresponding acetate) is an activated ester and is easily hydrolyzed through enzymatic ester hydrolysis by the water present in the medium and in the enzyme preparation. Such a reaction (if it takes place) lowers the ee value of the alcohol enantiomer (*R*)-**321** and the yield of the ester product (*S*)-**336b**. In order to furnish a fast enzymatic reaction on a preparative scale, the butanoate ester rather than the acetate has been used as an acyl donor in dried organic solvents. On the other hand, sucrose in the CAL-A preparation apparently binds the water necessary for enzymatic activity in the seemingly dry enzyme preparation.

This method provides us with both enantiomers of allylic alcohol **321** efficiently and selectively. As can be seen from Figure 8, some of the natural products isolated from the plants of the genus *Cneorum* or its relatives also possess the (*R*) configuration at C_{17}, so all types of these natural products could be accessed via this route.

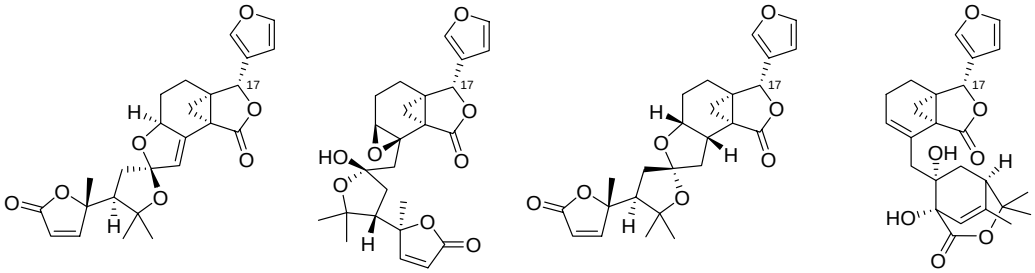


Figure 8. Natural products with (*R*) configuration at C_{17}.

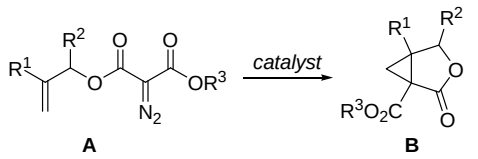
The inversion of (*R*)-**321** was attempted with the Mitsunobu reaction[274] and by transforming the alcohol to a tosylate and treating it with potassium nitrite,[275,276] but they proved unsuccessful.

The enzymatic reactions were monitored by chiral HPLC. The absolute configurations of the reduction and epoxidation products ((*S*)-**321** and **335**) and resolution products ((*R*)-**321** and (*S*)-**336**) are based on Mosher ester analysis[277-279] of (*S*)-**321** (see the experimental section for details) and then on comparison with the corresponding peaks in the chromatogram.

Having established a suitable enzymatic preparation and optimizing the reaction conditions, Liisa Kanerva then kindly supplied me with sufficient enzyme material to produce the allylic alcohol (*S*)-**321** used in this project.

8.4 Intramolecular cyclopropanation of diazomalonates

With the enantiopure allylic alcohol (*S*)-**321** in hand, I proceeded to the next task on the way to the DEFG ring system of cneorin C, the intramolecular cyclopropanation reaction. The advantages of this reaction include atom economy — except for the catalyst, no other reagents are needed — and the absence of regiochemical issues, which are problematic in intermolecular cyclopropanations. The intramolecular cyclopropanation of diazomalonates (Scheme 62) has been a longstanding interest in the Koskinen group.[239-242] An excellent review of transition metal catalyzed intramolecular cyclopropanation reactions can be found in the PhD thesis of Hassila.[241-243] The thesis also includes a study of the scope and the kinetics of the cyclopropanation reaction of diazomalonates as well as a proposed transition state model for the reaction. Some mechanistic studies of the intermolecular copper(I)-catalyzed cyclopropanations have also been published.[280-282]



Scheme 62. Intramolecular cyclopropanation of a diazomalonate.

The intramolecular cyclopropanation of diazomalonates of type **A** in Scheme 62 — a 1,1-disubstituted olefin — is unprecedented in the literature. There are earlier examples of both 1,2-disubstituted and even 1,2,2–trisubstituted olefins being cyclopropanated with copper catalysts.[240] The beauty of the reaction lies in the reagents, or rather in the lack of them. Both the nucleophile and the electrophile are within the molecule. Thus, the only reagent needed is the catalyst.

The catalyst complexes (Figure 9) and reaction conditions used in this study were chosen in accordance with Hassila's results. His best results were obtained with catalyst complex **337c**,[283] which requires careful exclusion of moisture during its preparation due to the inherent oxidation potency of copper(I)triflate. However, as Doyle *et al.* report, the air stability and ease of handling of $Cu(MeCN)_4PF_6$[284] compared to CuOTf makes the former superior to the latter.[285] Complex **337b**[286] was thought to reduce the Lewis acidity of copper thus making it less reactive and more selective towards the targeted double bond.

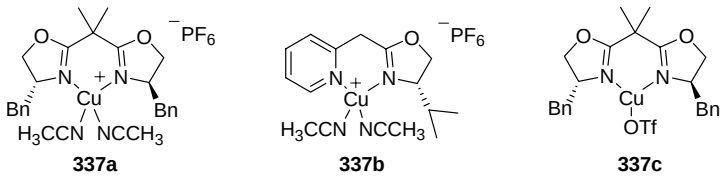
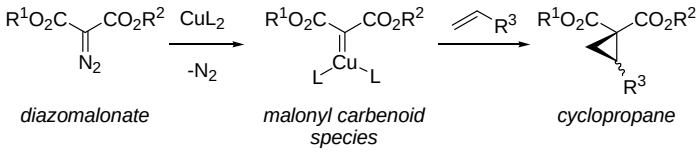


Figure 9. Catalysts employed in the intramolecular cyclopropanation.

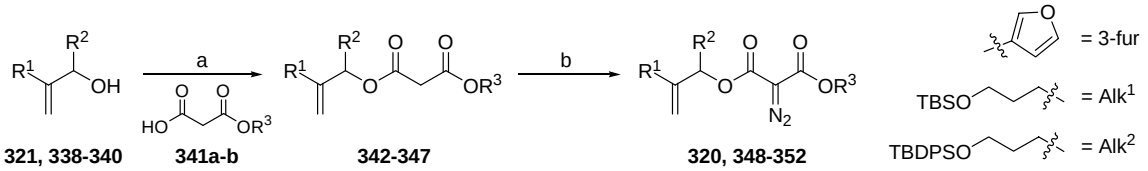
During the cyclopropanation reaction, I wanted to keep the temperature as low as possible to avoid side reactions, such as cyclopropanation of the furan ring. However, elevated temperatures are required for the formation of the carbenoid species (Scheme 63), which is essential for the cyclopropanation to take place. Effervescence of the reaction mixture served as a clear indicator of the formation of the carbenoid species. Typically, heating of the reaction mixture increased until effervescence occurred, after which the reaction temperature was maintained. This practice led to some variability in the reaction temperatures but ensured that all reactions were conducted under the mildest possible conditions.



Scheme 63. General mechanism of the cyclopropanation of a diazomalonate.

8.4.1 Preparation of diazomalonates

The diazomalonates needed for the cyclopropanation reaction were synthesized as follows (Scheme 64 and table 4). The alcohols (**321**, **338-340**) were treated with the monoester of malonic acid (**341a-b**) in the presence of dicyclohexylcarbodiimide and *N*,*N*-dimethylaminopyridine[287] that provided the corresponding malonates (**342-347**). These malonates were then reacted with tosyl azide[288] according to the published procedure[289] to furnish the cyclopropanation precursors (**320**, **348-352**).



Scheme 64. a) DCC, DMAP, CH_2Cl_2, 0 °C → rt, 1-2 h; b) TsN_3, K_2CO_3, MeCN, rt, 2 h. For substrates and yields, see table 4.

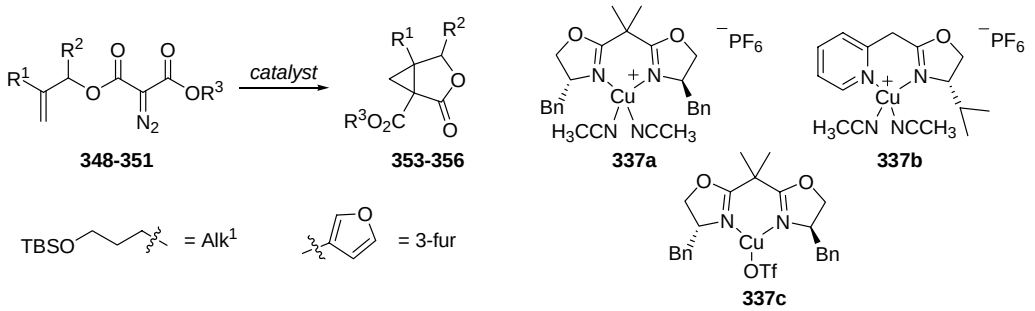
Table 4. Substrates and yields for preparation of the diazomalonates.

entry	alcohol	R^1	R^2	malonic acid	R^3	malonate	yield step a	diazo-malonate	yield step b
1	**338**	Me	Ph	**341a**	Et	**342**	63 %	**348**	quant.[a]
2	**339**	Me	3-fur	**341a**	Et	**343**	67 %	**349**	71 %
3	**340**	Alk^1	3-fur	**341a**	Et	**344**	81 %	**350**	92 %
4	**340**	Alk^1	3-fur	**341b**	*t*-Bu	**345**	88 %	**351**	93 %
5	**321**	Alk^2	3-fur	**341a**	Et	**346**	97 %	**352**	quant.[a]
6	**321**	Alk^2	3-fur	**341b**	*t*-Bu	**347**	98 %[a]	**320**	98 %

[a]Crude yield.

8.4.2 Model studies

Initially, some model studies were performed on a substrate without the furyl substituent, then on model systems containing the furyl substituent (see Scheme 65 and table 5). Phenyl substituted diazomalonate **348** was tried first (entry 1) and the reaction indeed produced the desired cyclopropanolactone **353** in 67% yield. It was soon discovered, though, that it was not the perfect substrate to model the reaction of a 3-furyl substituted diazomalonate, because the reaction with **349** gave only a 28% yield of the product **354** at its best (entry 3). It was also discovered that the source of copper(I) plays an important role in this reaction. With the furyl substituted compounds, catalyst **337c** caused extensive decomposition and only traces of products could be observed (see Scheme 66 and table 6). With the substrates containing the alkyl chain (**350** and **351**), the *t*-butyl ester was found to be more stable than the ethyl ester (entries 4-6). However, the TBS protecting group was considered too labile for further studies.



Scheme 65. See details in table 5. Solvent 1,2-dichloroethane.

Table 5. Results of model studies of the intramolecular cyclopropanation reaction.

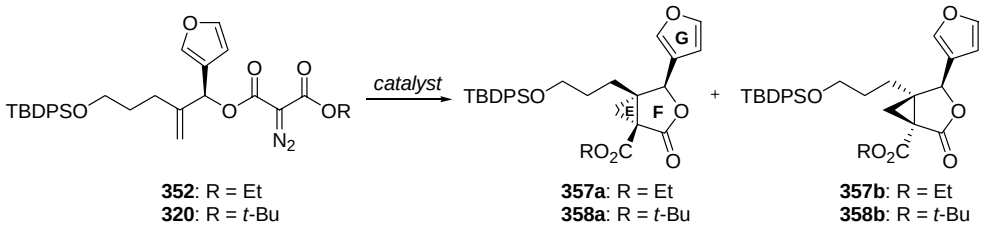
entry	substr.	R^1	R^2	R^3	catalyst	mol%	temp.	time (h)	prod.	ratio	yield
1	**348**	Me	Ph	Et	**337c**[a]	5	60 °C	2	**353**	1:1	67%
2	**349**	Me	3-fur	Et	**337b**	10	60 °C	1	**354**	1:1	18%
3	**349**	Me	3-fur	Et	**337a**	5	57 °C	1.5	**354**	1:1.2	28%
4	**350**	Alk^1	3-fur	Et	**337b**	3+3[b]	65 °C	22	**355**	1:1	n.d.[c]
5	**351**	Alk^1	3-fur	*t*-Bu	**337b**	3.8	53 °C	24	**356**	1:1	n.d.[c]
6	**351**	Alk^1	3-fur	*t*-Bu	**337a**	3	60 °C	21	**356**	1:1	23%

[a]The catalyst was not premixed. See the experimental section for the procedure. [b]The catalyst was added in two batches. See the experimental section. [c]n.d. = not determined

The ability of the furan ring to participate in carbenoid insertion reactions is well known[290,291] and, indeed, the model studies confirmed this. Nonetheless it was also anticipated that a stepwise construction of the furan ring at a later stage would ultimately lead to a much longer, less convergent synthesis with no added benefit in terms of yield or efficiency. Thus, I felt that the decision to push forward with the actual substrate was justified.

8.4.3 The actual substrates

Two different diazomalonates were evaluated for the intramolecular cyclopropanation reaction *en route* to cneorin C, namely ethyl ester **352** and *t*-butyl ester **320** (Scheme 66 and table 6). As expected from the literature,[290,291] rhodium acetate caused decomposition of **352** in two hours (entry 1). Similar to the results in the model study, the *t*-butyl ester was found to be more stable and better yielding than the ethyl ester. The best catalytic complex for producing the cyclopropanolactone **358a** with the correct stereochemical features needed for the total synthesis of the natural isomer of cneorin C was found to be complex **337a** (entry 6). The E, F and G rings of cneorin C were now in place!



Scheme 66. See details in table 6. Solvent 1,2-dichloroethane.

*Table 6. Results of the intramolecular cyclopropanation with the substrates **352** and **320**.*

entry	substr.	R	catalyst	mol%	temp.	time (h)	prod.	ratio[a]	yield
1	**352**	Et	$(Rh(OAc)_2)_2$	5	60 °C	2	decomposition		
2	**352**	Et	**337a**	3	63 °C	21	decomposition		
3	**352**	Et	**337b**	3	60 °C	20	**357**	1:1	21%
4	**352**	Et	**337c**	2.3	80 °C	2.5	decomposition		
5	**320**	*t*-Bu	**337b**	3	80 °C	2	**358**	1:1	26%
6	**320**	*t*-Bu	**337a**	3+2[b]	55 °C	24	**358**	1:1	30%

[a]The ratio of the diastereomers was obtained from crude NMR data. [b]The catalyst was added in two batches. See the experimental section.

Interestingly, the ethyl ester **352** decomposed completely under the reaction conditions with catalyst complex **337a** (entry 2), which was best for the *t*-butyl ester **320** (entry 6), but reacted relatively well with catalyst **337b** (entry 3).

The lack of selectivity in the reaction can be explained by the models shown in Figure 10. There is precedent from the Koskinen laboratories that an R^2-substituent (the furan ring in case of **320** – see Scheme 66) can induce diastereoselectivity in the cyclopropanation reaction,[292] but apparently the fairly large R^1-substituent (the alkyl chain) made the induction more difficult in this case.

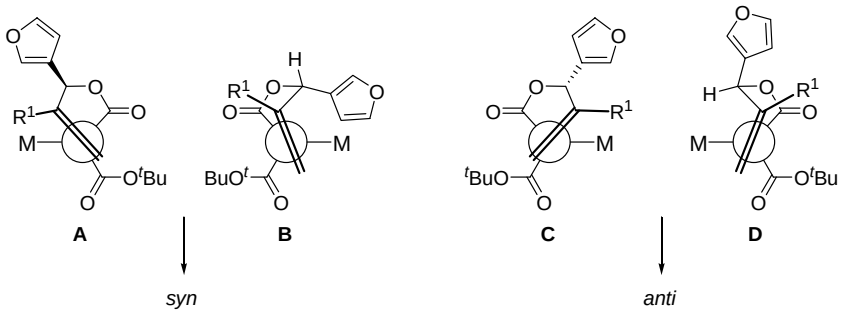
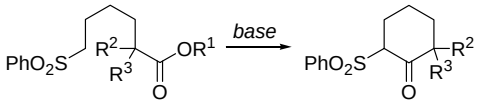


Figure 10. Models of the cyclopropanation reaction of 320.

I was delighted to find that, despite the complex mixture the reaction provided, the diastereomeric *t*-butyl esters **358a** and **358b** could be separated by simple flash chromatographic purification.

8.5 Synthesis of DEFG ring fragment: closing the rings

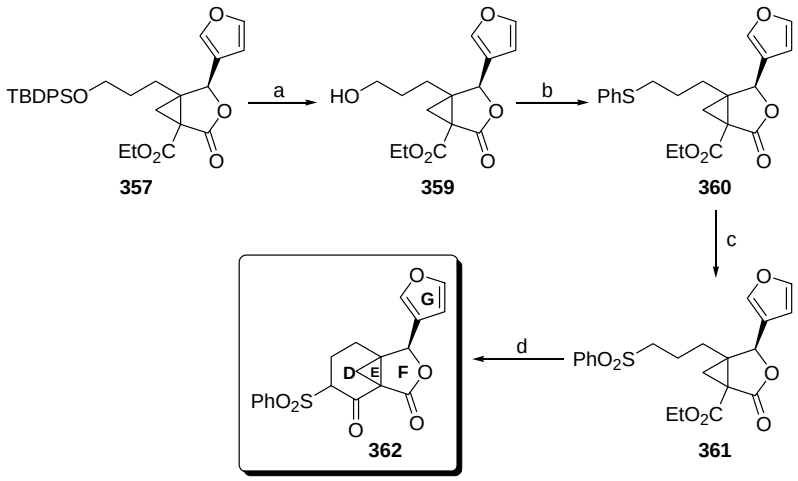
Cyclization of an anionic sulfone to an ester was chosen as the strategy to close the final D ring of the molecule (Scheme 67). All that remained to be effected before the cyclization was the transformation of the protected hydroxyl moiety in the cyclopropanolactone to a sulfone.



Scheme 67. Anionic cyclization of a sulfone.

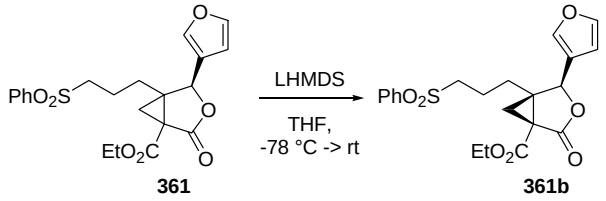
8.5.1 The ethyl ester

Before the insertion of the sulfone and cyclization were attempted with the diastereomerically pure *t*-butyl ester material, the feasibility of the reaction sequence to produce the DEFG ring fragment of cneorin C was tested with the ethyl ester **357** (Scheme 68). Because the diastereomers produced by the cyclopropanation reaction could not be separated efficiently at any point, the whole sequence was conducted with a mixture of diastereomers. Tetrabutylammonium fluoride effected removal of the TBDPS protecting group in the presence of acetic acid in 73% yield.[293] The free alcohol **359** was then transformed into sulfide **360** under the Hata conditions[294,295] and the sulfide was oxidized with *m*-CPBA to sulfone **361** in excellent yield. Now the stage was set for the crucial cyclization. To our delight, exposure of sulfone **361** to *n*-butyllithium effected closure of the D ring in a small-scale experiment as proven by mass spectral data. As could be imagined, the product was a complex mixture of diastereomers, so the focus then turned to the *t*-butyl ester series in the hopes that the reaction sequence, when performed on a single diastereomer, would give clearer results and allow the route be developed further.



Scheme 68. a) TBAF, AcOH, THF, 0 °C → rt, 4.5 h, 73%; b) $(SPh)_2$, Bu_3P, pyr, 0 °C → rt, 1 h 15 min, 80%; c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 50 min, 95%; d) *n*-BuLi, THF, –78 °C, 3.5 h, yield not determined.

An interesting observation from the studies with the ethyl ester **361** was that the use of LHMDS to promote cyclization[296] resulted in the formation of pure *syn*-sulfone **361b** (Scheme 69). There is currently no explanation for this observation.



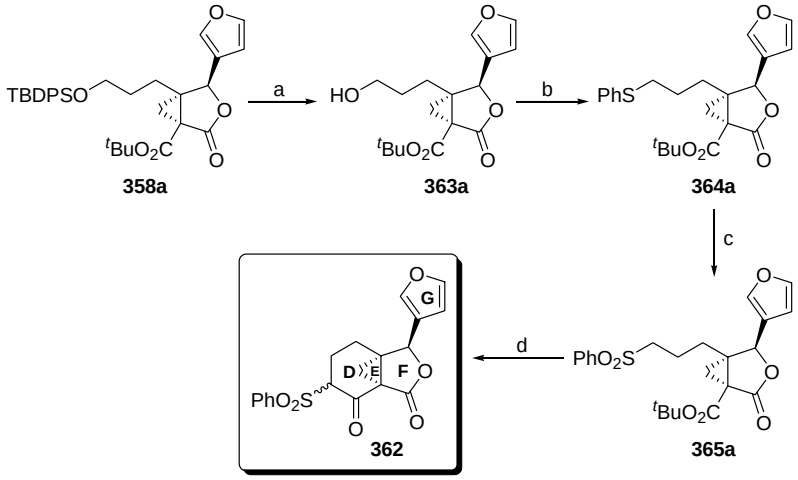
Scheme 69.

8.5.2 The t-butyl ester

Although the two diastereomeric cyclopropanolactones **358a** and **358b** could be separated, the nature of the diastereomers was unclear until the sulfone **365** was obtained (see Scheme 70). Thus, in the first instance, the route was conducted with the more hydrophobic product. It was only the 2D NOESY data obtained from sulfone **365** that revealed that this diastereomer was the *syn*-sulfone **365b**.

The TBDPS protected cyclopropanolactone **358a** was deprotected with tetrabutylammonium fluoride to yield alcohol **363a** in modest yield (Scheme 70). Compared to the ethyl ester (Scheme 68), the use of acetic acid was found to be of little consequence to the yield of the reaction, so its use was abandoned. Sulfide formation and oxidation were performed as established with the ethyl ester derivatives and afforded sulfone **365a**. This time, the conditions for the cyclization reaction were somewhat optimized. It was discovered that conducting the reaction at –100 °C in THF freshly distilled from lithium aluminum hydride was essential in order to obtain reproducible

results. Indeed, despite the hindered nature of the *t*-butyl ester as an electrophile, the [4.3.1]propellane **362** was obtained in 55% yield as a 1:0.8 mixture of two diastereomers at the sulfur bearing carbon. The DEFG ring fragment of cneorin C had now been synthesized for the first time!



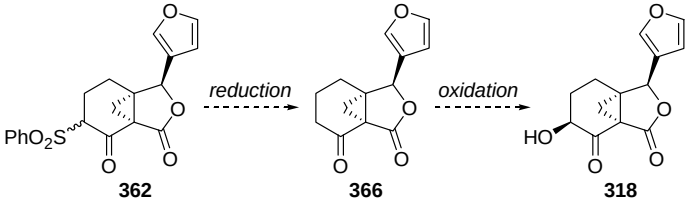
Scheme 70. a) TBAF, THF, 0 °C → rt, 2 h, 57%; b) $(SPh)_2$, Bu_3P, pyr, 0 °C → rt, 1.5 h, 75%; c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 1 h, 88%; d) *n*-BuLi, THF, –100 °C, 30 min, 55%.

The yields in this series were consistently lower than in the ethyl ester series. It is suspected that impurities left in the diastereomeric mixture of the ethyl esters may have resulted in falsely high yields of the ethyl esters.

Later, the *syn*-sulfone **365b** was also subjected to the final cyclization conditions in the hope that this could provide more material for the following steps. However, this reaction failed to give any identifiable products and resulted in decomposition of the starting sulfone instead.

8.6 Synthesis of DEFG ring fragment: the quest to remove the sulfone

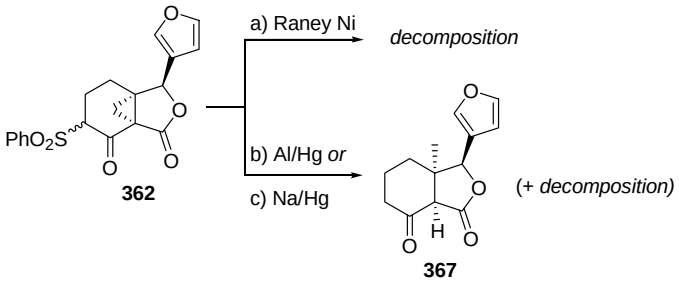
All that remained at this point of the synthesis was to remove the sulfone reductively and oxidize the α-position of the ketone (Scheme 71).



Scheme 71. Remaining transformations.

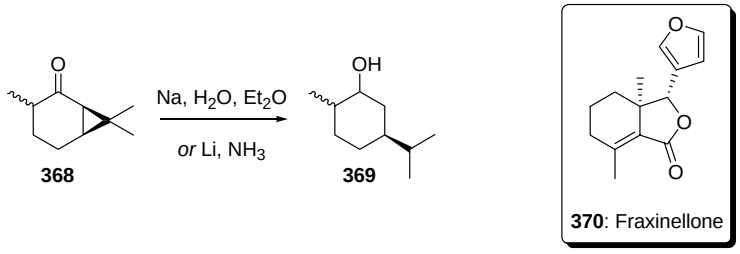
However, when the reductive removal of the sulfone was attempted, very disappointing results were obtained (Scheme 72). Raney nickel caused slow decomposition of the

starting sulfone **362** and the single electron reductants, aluminum amalgam[297] and sodium amalgam[298], effected a reductive opening of the cyclopropyl ring and ketone **367** was obtained in addition to decomposed starting material.



Scheme 72. a) Raney Ni, EtOH, THF, rt, 18 h; b) Al-foil immersed in $HgCl_2$,[297] THF:H_2O 9:1, 0 °C → rt (slowly), 4 h, 45%; c) Na-Hg, Na_2HPO_4, THF, MeOH, –15 °C → rt (slowly), 4 h, yield not determined.

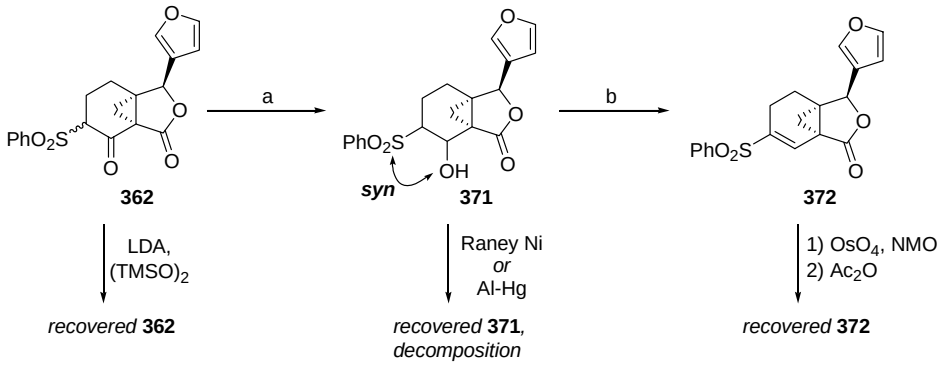
The reductive opening of cyclopropyl ring systems is known in the literature.[299] The reduction of carone (**368**) by sodium in moist ether (Scheme 73) was first reported by Baeyer in 1895,[300] although the correct structures were not known at that time. Later, Norin[301] and Dauben and Deviny[302] investigated the same transformation using lithium in liquid ammonia.



Scheme 73. Reductive opening of a conjugated cyclopropyl ketone.

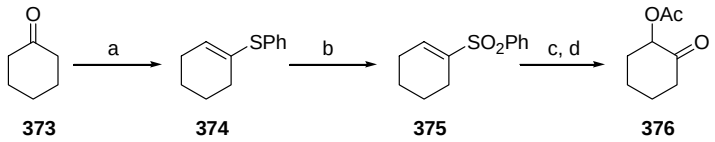
Disappointing though this was for the synthesis of cneorin C, it does present a possible avenue for the synthesis of other interesting natural products! For example, fraxinellone (**370**) has a similar structure to ketone **367** (see Schemes 73 and 72).[303]

Because the ketone functionality in **362** was apparently activating the cyclopropyl ring too much, the ketone was reduced stereoselectively to provide a 1:1 mixture of α- and β-*syn*-hydroxysulfones **371**. However, reduction of the hydroxysulfones **371** with either Raney nickel or aluminum amalgam resulted in recovery of part of the starting material accompanied with decomposition. An attempt to form an enolate from ketosulfone **362** and then use bis(trimethylsilyl) peroxide[304] as an electrophile failed as well. Elimination of the hydroxyl group in **372** could be effected in fairly rigorous conditions using KHMDS and mesyl chloride.



Scheme 74. a) $NaBH_4$, EtOH:CH_2Cl_2 1:1, rt, 90%; b) KHMDS, MsCl, THF, –10 → 0 °C, 1.5 h, 32% based on recovered **372**.

It was thought that a dihydroxylation of the double bond in vinyl sulfone **372** would consequently cause the removal of the sulfone and introduce an oxygen moiety to the sulfur bearing carbon. A model compound (**376**, Scheme 75) was chosen to determine the feasibility of the transformation. First, cyclohexanone (**373**) was condensed with thiophenol according to a literature procedure[305] and the vinyl sulfide **374** was then oxidized with oxone[306] to the corresponding vinyl sulfone **375**. This was then subjected to the dihydroxylation conditions refined recently by Sharpless and co-workers to better suit electron-deficient olefins.[307] The reaction did indeed give a hydroxyketone that was immediately acetylated to prevent it from decomposing. Encouraged by this result the same protocol was attempted with vinyl sulfone **372** (Scheme 74), but only starting material was recovered.



Scheme 75. a)[305] P_2O_5, CH_2Cl_2, rt, 17 h, 40%; b)[306] oxone, H_2O:MeOH 1:1, 0 °C → rt, 3 h, 72%; c) OsO_4, NMO, citric acid, H_2O:*t*-BuOH 1:1, rt, 3 h; d) Ac_2O, DMAP, CH_2Cl_2, rt, 1 h, 26% over 2 steps.

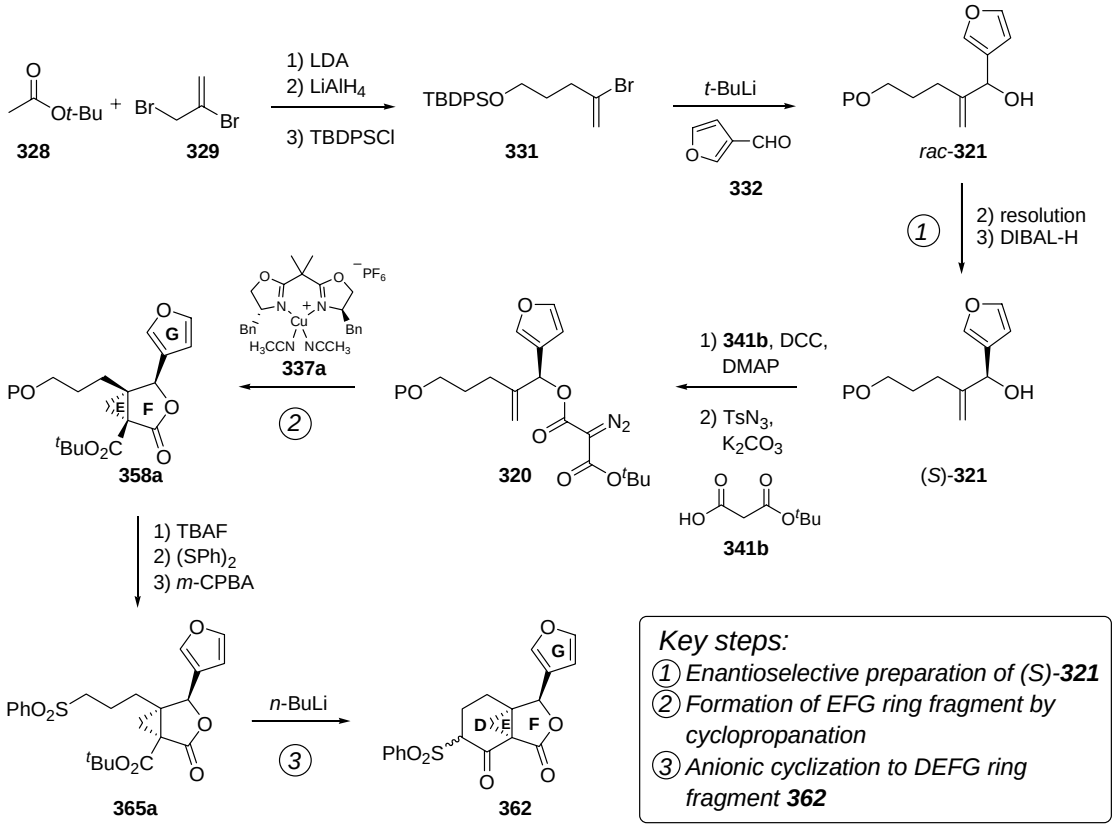
8.7 Conclusions

In this work, the synthetic efforts towards the DEFG ring system of cneorin C have been reported. Three goals were set in the beginning of this work and they were: (1) to secure access to the allylic alcohol (*S*)-**321** efficiently and enantioselectively, (2) to perform the cyclopropanation reaction to yield the EFG ring fragment, and (3) to close the D ring to obtain the [4.3.1]propellane structure. The goals were met as follows (Scheme 76):

(1) The enzymatic kinetic resolution provided both enantiomers of the key allylic alcohol **321** with excellent enantioselectivity. Thus, access to both of the C_{17} epimers of the natural product was secured.

(2) Despite the difficulties encountered in the cyclopropanation reaction, it provided the cyclized EFG ring fragment diastereomerically pure after separation.

(3) The DEFG ring fragment **362** of cneorin C was synthesized for the first time in 13 steps from commercially available starting materials. This is the first time that a cyclopropane containing [*n.n.*1]propellane structure of a natural product has been prepared by means of a cyclopropanation reaction.



Scheme 76. Synthesis of DEFG ring fragment of cneorin C.

Projects in total synthesis rarely reach completion and several interesting directions for the future have been uncovered during my research. Firstly, the removal of the sulfone from ketosulfone **362** or its derivatives must be addressed and secondly ketone **367** opens an exciting route into other types of natural products, for example fraxinellone (**370**).

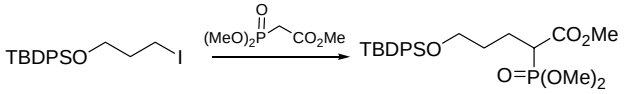
9. Experimental section

9.1 General experimental

Tetrahydrofuran was distilled from Na/benzophenone. Dichloromethane was pre-dried with $CaCl_2$ and distilled from CaH_2. All other solvents were distilled from CaH_2. Unless otherwise noted, all experiments were performed under Ar-atmosphere using flame-dried glassware. Silica gel (230-400 mesh) for column chromatography as well as the corresponding TLC plates were purchased from Merck. Na_2SO_4 was used as a drying agent for organic extracts. ^1H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ on a spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C. Chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.26 ppm in ^1H NMR spectra and 77.0 ppm in ^{13}C NMR spectra). In NMR spectra of mixtures of diastereomers, 'a+b' equals 'a and b', 'a/b' equals 'a or b'. Enantiomeric excesses were determined by HPLC analysis using Chiralcel OD columns 0.46 × 5 cm and 0.46 × 25 cm. CAL-A (*Candida antarctica* lipase A, Chirazyme L5, lyo.) and CAL–B (*Candida antarctica* lipase B, Chirazyme L2) were purchased from Roche and lipase PS and lipase PS-C II (*Pseudomonas cepacia*) from Amano Pharmaceuticals. Before use, CAL-A and lipase PS were adsorbed on Celite ® (17 g) by dissolving the enzyme (5 g) and sucrose (3 g) in Tris-HCl buffer (250 mL, 20 mM, pH = 7.9) as described previously, the final preparation containing 20% (w/w) of the lipase.[273] 2,2,2-Trifluoroethyl butanoate was prepared from the acid chloride and 2,2,2-trifluoroethanol. Equation $E=\ln[(1-ee_S)/(1+ee_S/ee_P)]/\ln[(1+ee_S)/(1+ee_S/ee_P)]$ with $c=ee_S/(ee_S+ee_P)$ gave the E (enantiomeric ratio)[308] values and conversion.

9.2 Synthesis of alcohol (*S*)-321

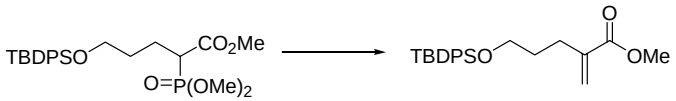
9.2.1 5-(tert-Butyldiphenylsilanyloxy)-2-(dimethoxyphosphoryl)pentanoic acid methyl ester (324)[244]



377 **324**

To a stirred suspension of NaH (60% suspension in mineral oil, 1.37 g, 34.2 mmol, 360 mol%) in DMSO (25 mL) at rt was added trimethyl phosphonoacetate (4.10 mL, 28.5 mmol, 300 mol%) dropwise over 30 min. After 70 min, *tert*-butyl-(3-iodopropoxy)-diphenylsilane (**377**) (4.03 g, 9.5 mmol, 100 mol%) in DMSO (15 mL) was added. After 2 h 40 min, HCl (0.1 M, 15 mL) was added and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 0-2% MeOH in CH_2Cl_2) provided phosphonate **324** as a colorless oil (3.20 g, 71%). TLC R_f = 0.37 (silica, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.63 (m, 4H), 7.47-7.35 (m, 6H), 3.80 (d, *J* = 8.1 Hz, 3H), 3.77 (d, *J* = 7.6 Hz, 3H), 3.70 (s, 3H), 3.66 (t, *J* = 6.1 Hz, 2H), 3.05 (ddd, *J* = 22.8, 10.6, 4.5 Hz, 1H), 2.14-1.93 (m, 2H), 1.71-1.49 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 135.5, 133.7, 129.6, 127.6, 63.0, 53.3 (d, *J* = 15.1 Hz), 53.2 (d, *J* = 15.1 Hz), 52.5, 44.8 (d, *J* = 131 Hz), 31.0 (d, *J* = 14.3 Hz), 26.8, 23.6 (d, *J* = 4.8 Hz), 19.1; IR (film) ν_{max} 1738 cm^{-1}; HRMS (ESI+) *m/z* 501.1844 (MNa^+, calcd for $C_{24}H_{35}O_6NaSiP$ 501.1838).

9.2.2 5-(tert-Butyldiphenylsilanyloxy)-2-methylenepentanoic acid methyl ester (325)[245]

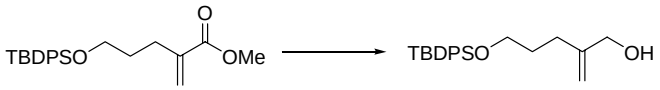


324 **325**

To a stirred solution of phosphonate **324** (3.20 g, 6.7 mmol, 100 mol%) in THF (10 mL) at rt were added paraformaldehyde (0.40 g, 13.4 mmol, 200 mol%) and K_2CO_3 (1.86 g, 13.4 mmol, 200 mol%). After 6 h at reflux, the reaction mixture was cooled down, water (10 mL) was added and the aqueous layer was extracted with hexane (3 × 20 mL). The combined organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5% EtOAc in hexanes) provided methyl ester **325** as a colorless oil (1.80 g, 71%). TLC R_f = 0.68 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.65 (m, 4H), 7.47-7.35 (m, 6H), 6.14 (s, 1H), 5.52 (s, 1H), 3.75 (s, 3H), 3.70 (t, *J* = 6.3 Hz, 2H), 2.43 (t, *J* = 7.6 Hz, 2H), 1.77-1.71 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 140.3, 135.6, 134.0, 129.5, 127.6, 124.9, 63.1,

51.7, 31.2, 28.3, 26.8, 19.2; IR (film) ν_{max} 1720, 1627 cm^{-1}; HRMS (ESI+) *m/z* 405.1888 (MNa^+, calcd for $C_{23}H_{30}O_3NaSi$ 405.1862).

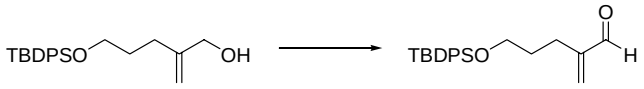
9.2.3 5-(tert-Butyldiphenylsilanyloxy)-2-methylenepentan-1-ol (378)[309]



325 **378**

To a stirred solution of methyl ester **325** (1.19 g, 3.1 mmol, 100 mol%) in THF (16 mL) at –78 °C was added DIBAL-H (1 M in toluene, 9.3 mL, 9.3 mmol, 300 mol%) dropwise. After 30 min, MeOH (3.1 mL) was added, the solution was allowed to warm to 0 °C and HCl (1 M, 30 mL) was added. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine, dried, filtered and concentrated. Alcohol **378** was isolated as a yellowish oil (1.10 g, 99%). TLC R_f = 0.59 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.65 (m, 4H), 7.47-7.35 (m, 6H), 5.02 (br s, 1H), 4.86 (br s, 1H), 4.06 (s, 2H), 3.69 (t, *J* = 6.2 Hz, 2H), 2.16 (t, *J* = 7.8 Hz, 2H), 1.78-1.68 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 135.6, 134.0, 129.6, 127.6, 109.3, 66.0, 63.4, 30.7, 29.2, 26.9, 19.2.

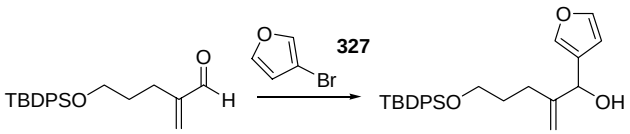
9.2.4 5-(tert-Butyldiphenylsilanyloxy)-2-methylenepentanal (326)[309]



378 **326**

To a stirred solution of alcohol **378** (0.53 g, 1.5 mmol, 100 mol%) in CH_2Cl_2 (15 mL) was added MnO_2[254] (0.65 g, 7.5 mmol, 500 mol%). After 17 h, more MnO_2 (0.13 g, 1.5 mmol, 100 mol%) was added. After 21 h, the mixture was filtered through a pad of Celite ® and concentrated. Enal **326** was isolated as a colorless oil (0.50 g, 94%). TLC R_f = 0.57 (silica, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.70-7.65 (m, 4H), 7.47-7.35 (m, 6H), 6.21 (br s, 1H), 5.97 (br s, 1H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.36 (t, *J* = 7.8 Hz, 2H), 1.70-1.67 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 149.9, 135.6, 134.0, 133.9, 129.6, 127.6, 63.1, 30.5, 26.8, 24.3, 19.2.

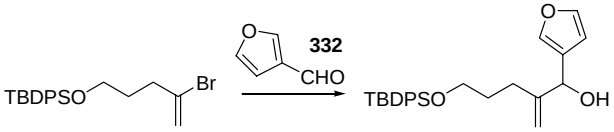
9.2.5 5-(tert-Butyldiphenylsilanyloxy)-1-furan-3-yl-2-methylenepentan-1-ol (rac-321) from enal 326



326 *rac*-**321**

To a stirred solution of 3-bromofuran (**327**) (0.51 mL, 5.7 mmol, 200 mol%) in THF (12 mL) at –78 °C was added *t*-BuLi (7.6 mL, 9.9 mmol, 350 mol%) dropwise. After 40 min, aldehyde **326** (1.00 g, 2.8 mmol, 100 mol%) in THF (3 mL) was added. After 2 h 10 min, sat. aq. NH_4Cl (10 mL) was added, the mixture was allowed to warm to rt and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 7.5-15% EtOAc in hexanes) provided alcohol *rac*-**321** as a colorless oil (1.04 g, 87%). TLC R_f = 0.38 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.62 (m, 4H), 7.46-7.33 (m, 8H), 6.33-6.30 (m, 1H), 5.22 (br s, 1H), 5.11 (br d, *J* = 3.8 Hz, 1H), 4.94 (br s, 1H), 3.66 (t, *J* = 6.2 Hz, 2H), 2.10-1.98 (m, 2H), 1.96 (d, *J* = 3.8 Hz, 1H), 1.77-1.65 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 143.2, 139.9, 135.6, 133.9, 129.6, 127.6, 127.2, 110.1, 109.0, 70.4, 63.5, 30.9, 28.0, 26.8, 19.2; IR (film) ν_{max} 3401, 1648, 1590, 1502 cm^{-1}; HRMS (ESI+) *m/z* 443.2034 (MNa^+, calcd for $C_{26}H_{32}O_3NaSi$ 443.2011).

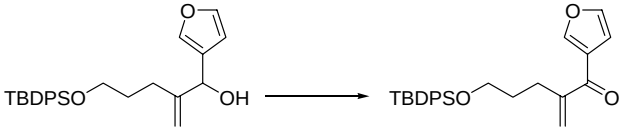
9.2.6 Alcohol rac-321 from vinyl bromide 331



331 *rac*-**312**

To a stirred solution of vinyl bromide **331**[309] (4.00 g, 9.9 mmol, 100 mol%) in THF (50 mL) at –78 °C was added *t*-BuLi (17.7 mL, 24.8 mmol, 250 mol%) dropwise over 10 min. After 30 min, 3-furylaldehyde (**332**) (1.24 mL, 14.9 mmol, 150 mol%) was added dropwise. After stirring at –78 °C for 2 h the reaction mixture was allowed to warm to rt. Sat. aq. NH_4Cl (10 mL) was then added and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5-15% EtOAc in hexanes) provided alcohol *rac*-**321** as a colorless oil (2.91 g, 70%).

9.2.7 5-(tert-Butyldiphenylsilanyloxy)-1-furan-3-yl-2-methylenepentan-1-one (333)

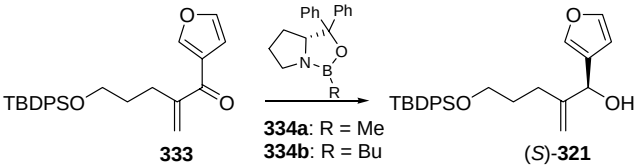


rac-**321** **333**

To a stirred solution of alcohol *rac*-**321** (0.25 g, 0.59 mmol, 100 mol%) in CH_2Cl_2 (6.0 mL) was added MnO_2[254] (0.26 g, 3.0 mmol, 500 mol%). After 4 h, more CH_2Cl_2 (6.0 mL) and MnO_2 (0.26 g, 3.0 mmol, 500 mol%) were added. After 22 h, a third portion of MnO_2 (0.26 g, 3.0 mmol, 500 mol%) was added. After 27 h, the reaction mixture was filtered

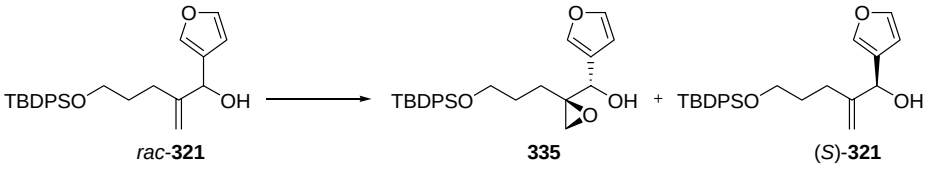
through a pad of Celite ® and concentrated. Flash column chromatography (silica, 5-15% EtOAc in hexanes) provided ketone **333** as a colorless oil (0.15 g, 83% based on recovered starting material (0.071 g)). TLC R_f = 0.5 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (m, 1H), 7.71-7.65 (m, 4H), 7.47-7.35 (m, 7H), 6.81-6.77 (m, 1H), 5.76 (br s, 1H), 5.67 (br d, J = 0.92 Hz, 1H), 3.69 (t, J = 6.3 Hz, 2H), 2.55 (br t, J = 7.5 Hz, 2H), 1.80-1.71 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 149.4, 147.8, 143.9, 135.5, 133.9, 129.5, 127.6, 126.5, 122.9, 109.9, 63.1, 30.8, 28.5, 26.8, 19.2; IR (film) ν_{max} 1646 cm^{-1}; HRMS (ESI+) *m/z* 441.1884 (MNa^+, calcd for $C_{26}H_{30}O_3NaSi$ 441.1862).

9.2.8 General procedure for the CBS-reduction



To a stirred solution of ketone **333** (55 μmol, 100 mol%) in THF (0.5 mL) at rt was added the catalyst **334a-b** (1 M in toluene, 11.0 μmol, 20 mol%). The solution was cooled to –20 °C and $BH_3{\cdot}SMe_2$ (33 μmol, 60 mol%) or catecholborane (165 μmol, 300 mol%) was added. After the time shown in table 1 (see Section 8.3.2) at –20 °C, methanol (0.5 mL) and sat. aq. $NaHCO_3$ (1 mL) were added. The phases were separated, the aqueous phase was extracted with EtOAc (3 × 5 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5-7.5% EtOAc in hexanes) provided alcohol (*S*)-**321** as a colorless oil. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD): 1% *i*-PrOH in hexanes, 0.4 mL/min, t_S = 69 min, t_R = 73 min.

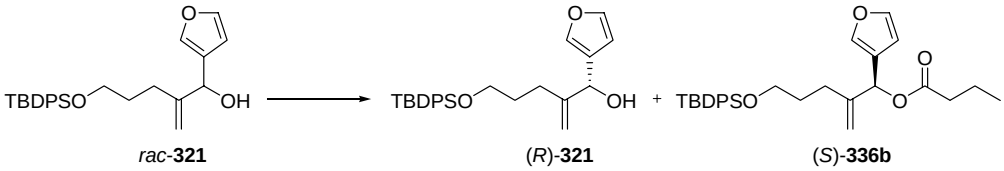
9.2.9 Resolution of rac-321 by Sharpless asymmetric epoxidation



To a stirred mixture of powdered and activated 3Å molecular sieves (0.30 g, 30 wt%), alcohol *rac*-**321** (1.00 g, 2.4 mmol, 100 mol%) and (+)-DIPT (76 μl, 0.36 mmol, 15 mol%) in CH_2Cl_2 (10 mL) at –20 °C was added Ti(O-*i*-Pr)$_4$ (71 μl, 0.24 mmol, 10 mol%). After 80 min, TBHP[265] (5 M in isooctane, 0.29 mL, 1.4 mmol) was added. After 47 h at –20 °C, water (1.36 mL) was added. After another 30 min, 30% NaOH in brine (0.35 mL) was added. After stirring for 30 min, the mixture was filtered through a cotton plug, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL)

The organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5-50% EtOAc in hexanes) provided alcohol (*S*)-**321** as a colorless oil (0.37 g, 37%, 68% ee) and epoxide **335** as a colorless oil (0.41 g, 39%, 94% ee) The ee of **335** was determined by chiral HPLC (Chiralcel OD): 0.5% *i*-PrOH in hexanes, 1.0 mL/min, t_{RR}(major) = 53 min, t_{SS}(minor) = 62 min. **Epoxide 335:** TLC R_f = 0.15 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ +20.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.61 (m, 4H), 7.47-7.34 (m, 8H), 6.41-6.38 (m, 1H), 4.76 (br s, 1H), 3.70-3.58 (m, 2H), 3.04 (d, *J* = 4.7 Hz, 1H), 2.68 (d, *J* = 4.7 Hz, 1H), 2.43 (app. d, *J* = 1.5 Hz, 1H), 1.85-1.76 (m, 1H), 1.73-1.49 (m, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 140.6, 135.5, 133.8, 129.6, 127.6, 124.3, 109.0, 65.8, 63.5, 61.5, 48.5, 27.3, 27.0, 26.8, 19.2; IR (film) ν_{max} 3468 cm^{-1}; HRMS (ESI+) *m/z* 459.1961 (MNa^+, calcd for $C_{26}H_{32}O_4NaSi$ 459.1968).

9.2.10 Resolution of rac-321 by lipase-catalyzed acylation



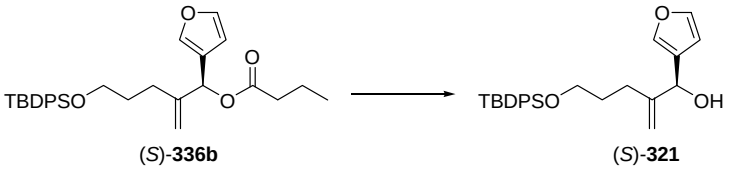
rac-**321** (*R*)-**321** (*S*)-**336b**

The reactions were typically performed as small-scale experiments at room temperature (22-24 °C) where the acyl donor (0.1 M) was added into the solution (0.05 M) of *rac*-**321** in an organic solvent and one of the enzyme preparations (25 mg/ml) was added in order to start the reaction. The progress of enzymatic reactions and the ee values of the unreacted (*R*)-**321** and the formed (*S*)-**336** were followed by taking samples (0.1 mL) at intervals and analyzing them by HPLC on Chiracel OD-column (220 nm) eluting with isopropanol in hexanes (0.3% for the alcohol (t_R = 96 min, t_S = 104 min); 0.1% for the acetate (t_S = 33 min, t_R = 37 min) and butanoate (t_S = 28 min, t_R = 33 min)) or analyzing them by NMR.

In a gram-scale experiment, 2,2,2-trifluoroethyl butanoate (0.36 mL, 2.4 mmol, 200 mol%) and CAL-A preparation (0.59 g, 25 mg/ml) were added to a solution of *rac*-**321** (0.50 g, 1.2 mmol, 100 mol%) in MTBE (24 mL). After 5 h, the enzyme was filtered off at 50% conversion. Purification by column chromatography (silica, 5-10% EtOAc in hexanes) yielded (*S*)-**336b** as a colorless oil (0.28 g, 48%, 96% ee) and (*R*)-**321** as a colorless oil (0.21 g, 41%, 95% ee, $[\alpha]^{20}_D$ +5.1 (*c* 1.0, $CHCl_3$)). **Butanoate (*S*)-336b:** TLC R_f = 0.50 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ –26.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.62 (m, 4H), 7.45-7.33 (m, 8H), 6.33-6.31 (m, 1H), 6.20 (br s, 1H), 5.17 (br s, 1H), 4.97 (br s, 1H), 3.66 (t, *J* = 6.2 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.20-2.03 (m, 2H), 1.77-1.60 (m, 4H), 1.04 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 146.6, 143.2, 140.8, 135.5, 133.9, 129.5, 127.6, 123.8, 111.1, 109.4, 70.5, 63.3, 36.4, 30.6, 28.5, 26.8, 19.2, 18.4, 13.6; IR (film) ν_{max} 1738, 1652,

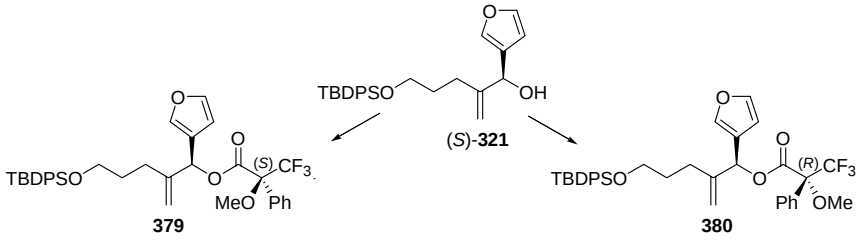
1590, 1503 cm^{-1}; HRMS (ESI+) *m/z* 513.2456 (MNa^+, calcd for $C_{30}H_{38}O_4NaSi$ 513.2437).

9.2.11 Hydrolysis of butanoate (S)-336b



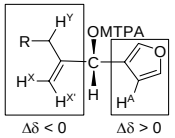
To a stirred solution of (*S*)-**336b** (72 mg, 0.15 mmol) in CH_2Cl_2 (0.8 mL) at –78 °C was added DIBAL-H (1 M in CH_2Cl_2, 0.30 mL, 0.30 mmol) dropwise. After 30 min, HCl (1 M, 1 mL) was added and the solution was allowed to warm to rt. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Furyl substituted allyl alcohol (*S*)-**321** was isolated as a colorless oil (61 mg, 98%, 96% ee). $[\alpha]^{20}_D$ –6.2 (*c* 1.0, $CHCl_3$).

9.3 Analysis of stereochemistry of (*S*)-321 by the Mosher ester method



For determination of stereochemistry, alcohol (*S*)-**321** was converted to (*S*)- and (*R*)-MTPA esters according to the procedure of Kobayashi et al.[279] The NMR signals were assigned with reference to two dimensional correlation spectra (HMQC and HMBC). The chemical shift differences (Δδ) between (*R*) and (*S*) isomers were calculated (table 7) and the results were compared against the Mosher configuration model.[278] The stereochemistry of the alcohol was assigned to be (*S*).

Table 7. Mosher ester analysis



	δ(*S*)	δ(*R*)	Δδ[a]		δ(*S*)	δ(*R*)	Δδ[a]
H^X	5.09	5.25	-0.16	H^A	6.33	6.21	0.12
$H^{X'}$	4.96	5.04	-0.08				
H^Y	2.02	2.11	-0.09				

[a] $\Delta\delta = \delta(S) - \delta(R)$

9.3.1 3,3,3-Trifluoro-(2S)-methoxy-2-phenylpropionic acid 5-(tert-butyl-diphenylsilanyloxy)-(1S)-furan-3-yl-2-methylenepentyl ester (379)

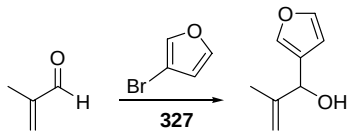
To a stirred solution of alcohol (*S*)-**321** (16 mg, 38 μmol, 100 mol%) in CH_2Cl_2 (0.1 mL) were added (*S*)-MTPA (18 mg, 76 μmol, 200 mol%), DMAP (2.3 mg, 19.0 μmol, 50 mol%) and DCC (16 mg, 76 μmol, 200 mol%). After 3 h, the mixture was filtered, washed with HCl (0.5 M, 2 × 1 mL), sat. aq. $NaHCO_3$ (2 × 1 mL) and brine, dried, filtered and concentrated. Flash column chromatography (silica, 0-2% EtOAc in hexanes) provided the (*S*)-MTPA ester **379** as a colorless oil (17 mg, 70%). TLC R_f = 0.50 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ –32.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.61 (m, 4H), 7.47-7.29 (m, 13H), 6.40 (br s, 1H), 6.33 (br d, *J* = 1.6 Hz, 1H), 5.09 (br s, 1H), 4.96 (br s, 1H), 3.59 (dt, *J* = 6.2, 2.0 Hz, 2H), 3.50 (s, 3H), 2.02 (dd, *J* = 8.4, 7.1 Hz, 2H), 1.70-1.60 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 145.1, 143.5, 141.5, 135.5, 133.9, 132.3, 129.6, 129.5, 128.3, 127.6, 127.3, 126.7 (q, *J* = 395 Hz), 122.6, 112.3, 109.4, 84.4 (q, *J* = 28 Hz), 72.8, 63.2, 55.4, 30.4, 28.4, 26.8, 19.2; IR (film) ν_{max} 1749, 1716, 1655, 1590, 1504 cm^{-1}; HRMS (ESI+) *m/z* 659.2408 (MNa^+, calcd for $C_{36}H_{39}O_5F_3NaSi$ 659.2417).

9.3.2 3,3,3-Trifluoro-(2R)-methoxy-2-phenylpropionic acid 5-(tert-butyl-diphenylsilanyloxy)-(1S)-furan-3-yl-2-methylenepentyl ester (380)

Prepared as **379**. $[\alpha]^{20}_D$ +6.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.61 (m, 4H), 7.48-7.30 (m, 13H), 6.40 (br s, 1H), 6.21 (br d, *J* = 0.9 Hz, 1H), 5.25 (br s, 1H), 5.04 (br s, 1H), 3.63 (t, *J* = 6.2 Hz, 2H), 3.50 (s, 3H), 2.11 (dd, *J* = 9.1, 6.6 Hz, 2H), 1.75-1.66 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 145.3, 143.3, 141.1, 135.5, 133.9, 132.2, 129.6, 129.5, 128.3, 127.6, 127.4, 126.7 (q, *J* = 391 Hz), 122.6, 112.9, 109.2, 84.6 (q, *J* = 27 Hz), 73.4, 63.2, 55.4, 30.5, 28.3, 26.8, 19.2; IR (film) ν_{max} 1749, 1652, 1501 cm^{-1}; HRMS (ESI+) *m/z* 659.2393 (MNa^+, calcd for $C_{36}H_{39}O_5F_3NaSi$ 659.2417).

9.4 Model compounds for the intramolecular cyclopropanation

9.4.1 1-Furan-3-yl-2-methylprop-2-en-1-ol (339)

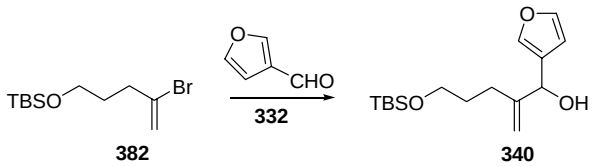


381 **339**

To a stirred solution of 3-bromofuran (**327**) (0.90 mL, 10.0 mmol, 200 mol%) in THF (10 mL) at –78 °C was added *t*-BuLi (12.4 mL, 20.0 mmol, 400 mol%) dropwise. After 15 min, 2-methyl propenal (**381**) (0.41 mL, 5.0 mmol, 100 mol%) was added dropwise. After 1 h 15 min, sat. aq. NH_4Cl (5 mL) was added and the biphasic solution was allowed

to warm to rt. The phases were separated, the aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Crude alcohol **339** (0.90 g) was used without further purification for the next reaction. TLC R_f = 0.3 (silica, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.40 (m, 1H), 7.38 (br t, *J* = 1.7 Hz, 1H), 6.34 (br dd, *J* = 0.6, 1.7 Hz, 1H), 5.17-5.14 (m, 1H), 5.12 (br s, 1H), 4.96-4.93 (m, 1H), 1.70 (s, 3H).

9.4.2 5-(tert-Butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentan-1-ol (340)



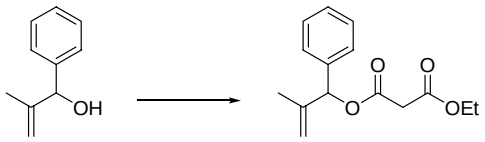
382 **340**

To a stirred solution of vinyl bromide **382**[310] (0.21 g, 0.76 mmol, 100 mol%) in THF (4.0 mL) at –78 °C was added *t*-BuLi (1.35 mL, 1.9 mmol, 250 mol%) dropwise. After 20 min, 3-furaldehyde (**332**) (95 μl, 1.1 mmol, 150 mol%) was added. After 40 min, the solution was allowed to warm to rt and concentrated. The residue was dissolved in EtOAc (10 mL) and washed with sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL), washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5-15% EtOAc in hexanes) provided furyl alcohol **340** as a colorless oil (0.137 g, 61%). TLC R_f = 0.3 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (m, 1H), 7.37 (br t, *J* = 1.7 Hz, 1H), 6.32 (br dd, *J* = 0.7, 1.7 Hz, 1H), 5.22 (br s, 1H), 5.15 (br d, *J* = 3.7 Hz, 1H), 4.97 (br d, *J* = 0.7 Hz, 1H), 3.62 (t, *J* = 6.2 Hz, 2H), 2.22 (d, *J* = 3.7 Hz, 1H), 2.16-1.96 (m, 2H), 1.77-1.62 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 143.2, 139.8, 127.4, 110.4, 109.0, 70.7, 62.7, 31.1, 28.0, 25.9, 18.3, –5.3; IR (film) ν_{max} 3401, 1650, 1503 cm^{-1}; HRMS (ESI+) *m/z* 319.1683 (MNa^+, calcd for $C_{16}H_{28}O_3NaSi$ 319.1705).

9.4.3 General procedure for preparation of malonates[287]

To a stirred solution of the alcohol (100 mol%), mono-ethyl malonate (**341a**)[311] or mono-*t*-butyl malonate (**341b**)[240,311,312] (110 mol%) and DMAP (10 mol%) in CH_2Cl_2 (0.5 M) at 0 °C was added DCC (120 mol%). After 1-2 h at rt, the mixture was filtered, washed twice with HCl (0.5 M) and sat. aq. $NaHCO_3$ and once with brine, dried, filtered and concentrated.

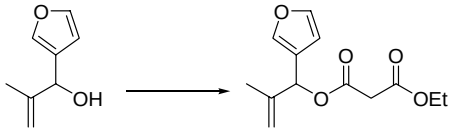
9.4.4 Ethyl-2-methyl-1-phenylallyl malonate (342)



338 **342**

Prepared according to the general procedure for preparation of malonates (Section 9.4.3) with alcohol **338** (1.00 g, 6.8 mmol, 100 mol%), mono-ethyl malonate (**341a**) (1.04 mL, 8.8 mmol, 130 mol%), DMAP (82 mg, 0.68 mmol, 10 mol%), CH_2Cl_2 (35 mL) and DCC (1.81 g, 8.8 mmol, 130 mol%). Flash column chromatography (silica, 2.5-10% EtOAc in hexanes) provided malonate **342** as a yellowish oil (1.12 g, 63%). TLC R_f = 0.38 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 6.22 (br s, 1H), 5.14 (br d, *J* = 0.8 Hz, 1H), 5.01 (br d, *J* = 0.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.44 (s, 2H), 1.65 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.4, 142.5, 137.8, 128.4, 128.2, 127.0, 113.1, 79.5, 61.5, 41.9, 18.7, 14.0; IR (film) ν_{max} 1752, 1736, 1654 cm^{-1}; HRMS (ESI+) *m/z* 285.1118 (MNa^+, calcd for $C_{15}H_{18}O_4Na$ 285.1103).

9.4.5 Ethyl-1-furan-3-yl-2-methylallyl malonate (343)



339 **343**

Prepared according to the general procedure for preparation of malonates (Section 9.4.3) with alcohol **339** (crude, 0.69 g, 5.0 mmol, 100 mol%), mono-ethyl malonate (**341a**) (0.77 mL, 6.5 mmol, 130 mol%), DMAP (61 mg, 0.50 mmol, 10 mol%), CH_2Cl_2 (25 mL) and DCC (1.34 g, 6.5 mmol, 130 mol%). Flash column chromatography (silica, 2.5-7.5 % EtOAc in hexanes) provided the malonate **343** as a colorless oil (0.84 g, 67%). TLC R_f = 0.4 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.41 (m, 1H), 7.37 (br t, *J* = 1.7 Hz, 1H), 6.33 (br dd, *J* = 0.6, 1.7 Hz, 1H), 6.20 (br s, 1H), 5.13 (br d, *J* = 0.8 Hz, 1H), 5.00 (br d, *J* = 0.8 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.41 (s, 2H), 1.72 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.4, 143.3, 141.8, 140.8, 123.0, 113.2, 109.3, 72.7, 61.6, 41.8, 18.7, 14.0; IR (film) ν_{max} 1734, 1655 cm^{-1}; HRMS (ESI+) *m/z* 275.0901 (MNa^+, calcd for $C_{13}H_{16}O_5Na$ 275.0895).

9.4.6 Ethyl-5-(tert-butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentyl malonate (344)

Prepared according to the general procedure for preparation of malonates (Section 9.4.3) with alcohol **340** (58 mg, 0.20 mmol, 100 mol%), mono-ethyl malonate (**341a**) (25 μl, 0.22 mmol, 110 mol%), DMAP (2.4 mg, 20 μmol, 10 mol%), CH_2Cl_2 (0.4 mL) and DCC (61 mg, 0.30 mmol, 150 mol%). Flash column chromatography (silica, 2.5-7.5% EtOAc in hexanes) provided malonate **344** as a yellowish oil (65 mg, 81%). TLC R_f = 0.48 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 1H), 7.36 (br t, *J* = 1.7 Hz, 1H), 6.33 (br s, 1H), 6.22 (br s, 1H), 5.20 (s, 1H), 5.02 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 3.39 (s, 2H), 2.14-1.98 (m, 2H), 1.71-1.62 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.4, 145.9, 143.3, 141.1, 123.2, 111.7, 109.5, 72.0, 62.5, 61.5, 41.8, 30.8, 28.5, 25.9, 18.3, 14.0, –5.3; IR (film) ν_{max} 1752, 1735, 1650, 1503 cm^{-1}; HRMS (ESI+) *m/z* 433.2036 (MNa^+, calcd for $C_{21}H_{34}O_6NaSi$ 433.2022).

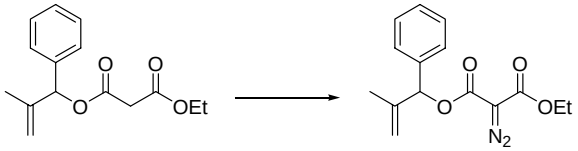
9.4.7 tert-Butyl-5-(tert-butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentyl malonate (345)

Prepared according to the general procedure for preparation of malonates (Section 9.4.3) with alcohol **340** (71 mg, 0.24 mmol, 100 mol%), mono-*t*-butyl malonate (**341b**) (26 μl, 0.29 mmol, 120 mol%), DMAP (2.9 mg, 24 μmol, 10 mol%), CH_2Cl_2 (0.5 mL) and DCC (74 mg, 0.36 mmol, 150 mol%). Flash column chromatography (silica, 2.5-10% EtOAc in hexanes) provided malonate **345** as a yellowish oil (92 mg, 88%). TLC R_f = 0.6 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 7.36 (br t, *J* = 1.7 Hz, 1H), 6.33 (br s, 1H), 6.21 (br s, 1H), 5.21 (s, 1H), 5.02 (s, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.31 (s, 2H), 2.12-1.98 (m, 2H), 1.69-1.61 (m, 2H), 1.43 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.4, 145.9, 143.2, 141.1, 123.3, 111.5, 109.5, 82.1, 71.7, 62.5, 43.2, 30.8, 28.5, 27.9, 25.9, 18.3, –5.3; IR (film) ν_{max} 1749, 1732, 1651, 1503 cm^{-1}; HRMS (ESI+) *m/z* 461.2360 (MNa^+, calcd for $C_{23}H_{38}O_6NaSi$ 461.2335).

9.4.8 General procedure for preparation of diazomalonates[289]

To a stirred solution of the malonate (100 mol%) in MeCN (0.5 M) was added powdered and dried K_2CO_3 (105 mol%) followed by TsN_3 (105 mol%)[288] in MeCN. After 2 h, the solvent was evaporated. The residue was dissolved in Et_2O and the resulting solution washed twice with K_2CO_3 (10% aq. soln.), dried, filtered and concentrated. The residue was dissolved in Et_2O and hexanes were added to precipitate $TsNH_2$. The mixture was filtered through a pad of silica (10% Et_2O in hexanes flush) and concentrated. Generally the products were used without further purification for the cyclopropanation reaction.

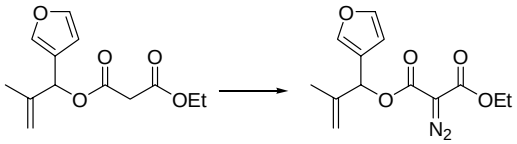
9.4.9 Ethyl-2-methyl-1-phenylallyl diazomalonate (348).



342 **348**

Prepared according to the general procedure for preparation of diazomalonates (Section 9.4.8) with malonate **342** (1.00 g, 3.8 mmol, 100 mol%), MeCN (7.6 mL), TsN_3 (0.79 g, 4.0 mmol, 105 mol%) and K_2CO_3 (0.55 g, 4.0 mmol, 105 mol%). The reaction provided diazomalonate **348** as a yellow oil (1.2 g), which was sufficiently pure for the next reaction. TLC R_f = 0.38 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 6.31 (br s, 1H), 5.19 (br d, J = 0.8 Hz, 1H), 5.01 (br d, J = 0.8 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.65 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.2, 142.5, 137.9, 128.4, 128.1, 126.9, 113.0, 79.5, 61.6, 18.5, 14.3; IR (film) ν_{max} 2142, 1761, 1735, 1693, 1653 cm^{-1}; HRMS (ESI+) *m/z* 311.1003 (MNa^+, calcd for $C_{15}H_{16}N_2O_4Na$ 311.1008).

9.4.10 Ethyl-1-furan-3-yl-2-methylallyl diazomalonate (349)

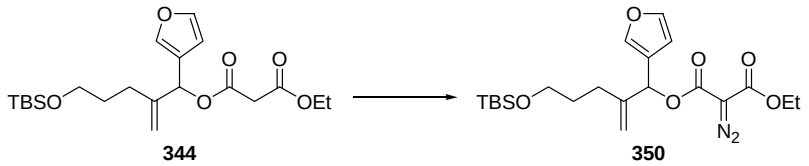


343 **349**

Prepared according to the general procedure for preparation of diazomalonates (Section 9.4.8) with malonate **343** (0.82 g, 3.2 mmol, 100 mol%), MeCN (6.5 mL), TsN_3 (0.67 g, 3.4 mmol, 105 mol%) and K_2CO_3 (0.47 g, 3.4 mmol, 105 mol%). The reaction provided diazomalonate **349** as a yellow oil (0.64 g, 71%). TLC R_f = 0.4 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 1H), 7.37 (br t, J = 1.7 Hz, 1H), 6.35 (br dd, J = 1.7, 0.7 Hz, 1H), 6.28 (br s, 1H), 5.16 (br d, J = 0.8 Hz, 1H), 5.01 (br d, J = 0.8 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.72 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 160.8, 160.3, 143.3, 141.9, 141.0, 123.1, 113.1, 109.2, 72.6, 61.7, 18.6, 14.3; IR (film) ν_{max} 2142, 1759, 1732, 1690, 1655, 1504 cm^{-1}; HRMS (ESI+) *m/z* 301.0817 (MNa^+, calcd for $C_{13}H_{14}N_2O_5Na$ 301.0800).

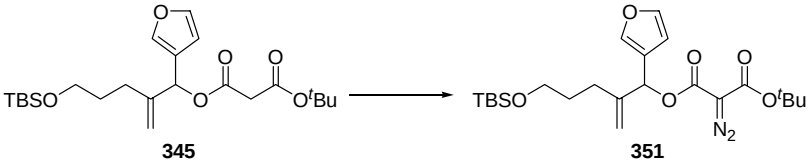
9.4.11 Ethyl-5-(tert-butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentyl diazomalonate (350)



344 **350**

Prepared according to the general procedure for preparation of diazomalonates (Section 9.4.8) with malonate **344** (60 mg, 0.15 mmol, 100 mol%), MeCN (0.3 mL), TsN_3 (30 mg, 0.15 mmol, 105 mol%) and K_2CO_3 (21 mg, 0.15 mmol, 105 mol%). The reaction provided diazomalonate **350** as a yellow oil (59 mg, 92%). TLC R_f = 0.48 (silica, 20% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (m, 1H), 7.37 (br t, *J* = 1.6 Hz, 1H), 6.36-6.34 (m, 1H), 6.30 (br s, 1H), 5.24 (s, 1H), 5.03 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.58 (t, *J* = 6.3 Hz, 2H), 2.15-1.98 (m, 2H), 1.70-1.61 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.2, 145.9, 143.3, 141.2, 123.2, 111.6, 109.4, 71.9, 62.4, 61.7, 30.8, 28.5, 25.9, 18.2, 14.3, –5.4; IR (film) ν_{max} 2141, 1762, 1735, 1693, 1651, 1503 cm^{-1}; HRMS (ESI+) *m/z* 459.1930 (MNa^+, calcd for $C_{21}H_{32}N_2O_6NaSi$ 459.1927).

9.4.12 tert-Butyl-5-(tert-butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentyl diazomalonate (351)



345 **351**

Prepared according to the general procedure for preparation of diazomalonates (Section 9.4.8) with malonate **345** (80 mg, 0.18 mmol, 100 mol%), MeCN (0.4 mL), TsN_3 (38 mg, 0.19 mmol, 105 mol%) and K_2CO_3 (27 mg, 0.19 mmol, 105 mol%). The reaction provided diazomalonate **351** as a yellow oil (79 mg, 93%). TLC R_f = 0.6 (silica, 20% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.42 (m, 1H), 7.36 (br t, *J* = 1.6 Hz, 1H), 6.36-6.33 (m, 1H), 6.31 (br s, 1H), 5.22 (s, 1H), 5.03 (s, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 2.14-1.98 (m, 2H), 1.70-1.60 (m, 2H), 1.51 (s, 9H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 159.7, 146.0, 143.3, 141.2, 123.3, 111.6, 109.4, 83.1, 71.5, 62.4, 30.8, 28.5, 28.2, 25.9, 18.3, –5.4; IR (film) ν_{max} 2137, 1759, 1731, 1688, 1503 cm^{-1}; HRMS (ESI+) *m/z* 487.2224 (MNa^+, calcd for $C_{23}H_{36}N_2O_6NaSi$ 487.2240).

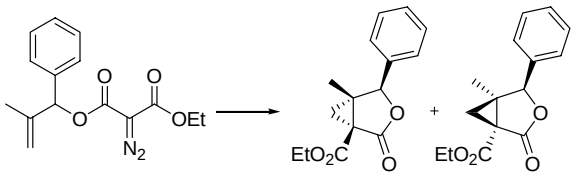
9.4.13 General procedure for preparing the catalytic complexes for cyclopropanation[240,243]

To a stirred solution of the ligand (100 mol%) in CH_2Cl_2 (0.1 M) was added the copper complex (100 mol%). The solution was stirred overnight and evaporated to dryness under a gentle flow of argon.

9.4.14 General procedure for cyclopropanation of diazomalonates[240,241,243]

To a stirred solution of the diazomalonate (100 mol%) in 1,2-dichloroethane (DCE, 0.1 M) was added the catalyst (3-10 mol%). The solution was heated up to the temperature at which the mixture started to effervesce and turned brown in color. After all diazocompound had been consumed as judged by TLC, the solution was cooled to rt and concentrated. The residue was dissolved in MTBE, stirred with activated carbon for 5 min, filtered through a pad of Celite ® and concentrated.

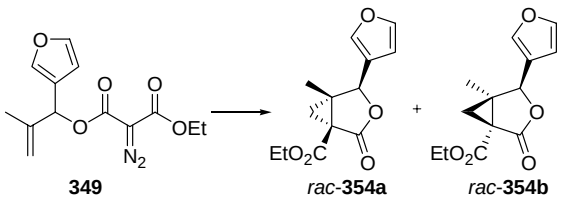
9.4.15 5-Methyl-2-oxo-4-phenyl-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (353)



348 *rac*-**353a** *rac*-**353b**

To a solution of ligand part of **337c** (1.9 mg, 5.2 μmol, 5 mol%) and $(CuOTf)_2 \cdot C_6H_6$ (2.6 mg, 5.2 μmol, 5 mol%) in DCE (0.5 mL) after 10 min of stirring was added diazomalonate **348** (30 mg, 0.10 mmol, 100 mol%) in DCE (0.5 mL). The solution was heated to 60 °C for 2 h, cooled to rt and concentrated. The residue was dissolved in MTBE, stirred with activated carbon for 5 min, filtered through a pad of Celite ® and concentrated. Flash column chromatography provided cyclopropanolactone *rac*-**353** as a yellow oil (18 mg, 67%, a:b 1:1 mixture of diastereomers). TLC R_f = 0.18 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.24 (m, 10H, a+b), 5.41 (s, 1H, b), 5.26 (s, 1H, a), 4.35-4.25 (m, 4H, a+b), 1.98 (d, J = 4.8 Hz, 1H, a), 1.80 (d, J = 5.3 Hz, 1H, b), 1.56 (d, J = 4.8Hz, 1H, a), 1.52 (d, J = 5.3 Hz, 1H, b), 1.52 (s, 3H, b), 1.33 (t, J = 7.2 Hz, 3H, a/b), 1.32 (t, J = 7.2 Hz, 3H, a/b), 0.98 (s, 3H, a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (a), 170.7 (b), 165.7 (a/b), 165.6 (a/b), 136.7 (a), 135.3 (b), 128.8 (a+b), 128.7 (a+b), 126.5 (a), 125.4 (b), 83.8 (a), 82.5 (b), 62.00 (a/b), 61.96 (a/b), 39.6 (b), 39.3 (a), 35.9 (b), 35.0 (a), 25.0 (a), 22.4 (b), 14.3 (a/b), 14.2 (a/b), 14.1 (a/b), 13.7 (a); IR (film) ν_{max} 1786, 1727 cm^{-1}; HRMS (ESI+) *m/z* 283.0933 (MNa^+, calcd for $C_{15}H_{16}O_4Na$ 283.0946).

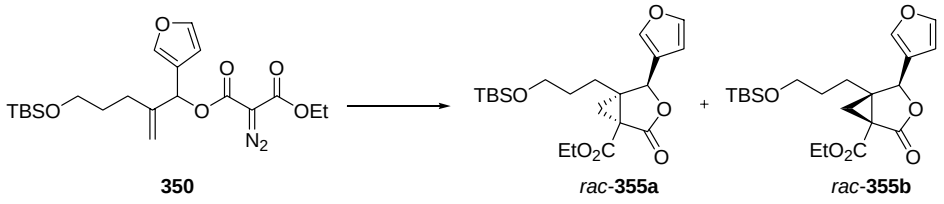
9.4.16 4-Furan-3-yl-5-methyl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (354)



349 *rac*-**354a** *rac*-**354b**

Prepared according to the general procedure for cyclopropanation of diazomalonates (Section 9.4.14) with diazomalonate **349** (32 mg, 0.12 mmol, 100 mol%), catalytic complex **337a** (3.8 mg, 5.8 μmol, 5 mol%) and DCE (1.15 mL). The reaction time was 1.5 h at 57 °C. Flash column chromatography (silica, 5-10 % EtOAc in hexanes) provided cyclopropanolactone *rac*-**354** as a yellow oil (8 mg, 28%, a:b 1:1.2 mixture of diastereomers). TLC R_f = 0.2 (silica, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (br s, 1H, a/b), 7.49-7.47 (m, 1H, a/b), 7.47-7.44 (m, 2H, a+b), 6.41-6.39 (m, 1H, a), 6.38-6.36 (m, 1H, b), 5.32 (br s, 1H, a), 5.30 (br s, 1H, b), 4.33-4.27 (m, 4H, a+b), 1.98 (d, *J* = 4.9 Hz, 1H, b), 1.91 (d, *J* = 5.1 Hz, 1H, a), 1.53 (d, *J* = 4.9 Hz, 1H, b), 1.52 (d, *J* = 5.1 Hz, 1H, a), 1.49 (s, 3H, a), 1.33 (t, *J* = 7.2 Hz, 6H, a+b), 1.16 (s, 3H, b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (a/b), 170.9 (a/b), 165.64 (a/b), 165.57 (a/b), 144.4 (a/b), 144.0 (a/b), 141.0 (a/b), 140.2 (a/b), 122.3 (a/b), 120.4 (a/b), 108.4 (a), 107.9 (b), 77.2 (a+b), 62.0 (a+b), 39.0 (a), 38.4 (b), 35.6 (a), 34.8 (b), 25.1 (b), 23.2 (a), 14.3 (a/b), 14.2 (a/b), 14.0 (a), 13.5 (b); IR (film) ν_{max} 1780, 1726 cm^{-1}; HRMS (ESI+) *m/z* 273.0737 (MNa^+, calcd for $C_{13}H_{14}O_5Na$ 273.0739).

9.4.17 5-[3-(tert-Butyldimethylsilanyloxy)propyl]-4-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (355)

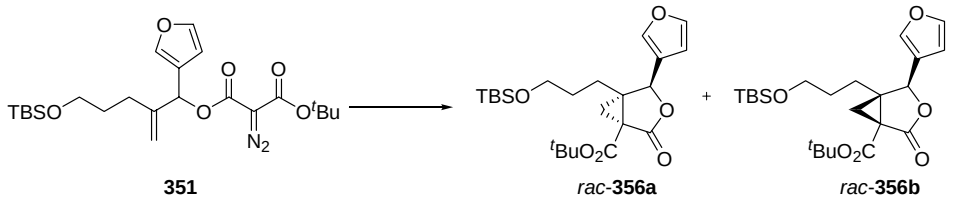


350 *rac*-**355a** *rac*-**355b**

Prepared according to the general procedure for cyclopropanation of diazomalonates (Section 9.4.14) with diazomalonate **350** (30 mg, 69 μmol, 100 mol%), catalytic complex **337b** (1.0 mg, 2.1 μmol, 3 mol%) and DCE (0.7 mL). The reaction time was 22 h at 65 °C. Flash column chromatography provided <5 mg of cyclopropanolactones *rac*-**355a** and *rac*-**355b**. (1:1 mixture of diastereomers). *rac*-**355a**: TLC R_f = 0.23 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 1H), 7.45 (br t, *J* = 1.5 Hz, 1H), 6.43 (m, 1H), 5.34 (s, 1H), 4.39-4.25 (m, 2H), 3.54-3.47 (m, 2H), 1.97 (d, *J* = 4.9 Hz, 1H), 1.74-1.61 (m, 1H), 1.59-1.50 (m, 2H), 1.49 (dd, *J* = 4.9, 1.6 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.32-1.27 (m, 1H), 0.84 (s, 9H), –0.015 (s, 6H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 178.0, 165.6, 144.4, 141.3, 121.9, 108.0, 76.0, 62.2, 62.1, 41.8, 35.5, 30.2, 25.8, 24.1, 23.5, 18.2, 14.3, –5.4; IR (film) ν_{max} 1785, 1733, 1505 cm^{-1}; HRMS (ESI+) *m/z* 431.1866 (MNa^+, calcd for $C_{21}H_{32}O_6NaSi$ 431.1866). *rac*-**355b**: TLC R_f = 0.28 (silica, 20% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 0.8, 0.7 Hz, 1H), 7.44 (br t, *J* = 1.7 Hz, 1H), 6.41 (br dd, *J* = 1.7, 0.8 Hz, 1H), 5.49 (br s, 1H), 4.38-4.21 (m, 2H), 3.83-3.50 (m, 2H), 2.06-1.98 (m, 1H), 1.96 (d, *J* = 5.1 Hz, 1H), 1.78-1.63 (m, 2H), 1.57 (d, *J* = 5.1 Hz, 1H), 1.51-1.42 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.025 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.7, 144.0, 140.5, 120.8, 108.6, 74.7, 62.3, 62.1, 43.0, 35.4, 29.6, 25.9, 25.0, 23.3, 18.3, 14.2, –5.4; IR (film) ν_{max} 1789, 1729, 1505 cm^{-1}; HRMS (ESI+) *m/z* 431.1862 (MNa^+, calcd for $C_{21}H_{32}O_6NaSi$ 431.1866).

9.4.18 5-[3-(tert-Butyldimethylsilanyloxy)propyl]-4-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid tert-butyl ester (356)



351 *rac*-**356a** *rac*-**356b**

Prepared according to the general procedure for cyclopropanation of diazomalonates (Section 9.4.14) with diazomalonate **351** (28 mg, 60 μmol, 100 mol%), catalytic complex **337a** (1.2 mg, 1.8 μmol, 3 mol%) and DCE (0.6 mL). The reaction time was 21 h at 60 °C. Flash column chromatography (silica, 2.5-10% EtOAx in hex) provided cyclopropanolactones *rac*-**356a** and *rac*-**356b** (6 mg, 23%, 1:1 mixture of diastereomers). *rac*-**356a**: TLC R_f = 0.35 (silica, 20% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.50 (m, 1H), 7.45 (br t, *J* = 1.5 Hz, 1H), 6.44-6.42 (m, 1H), 5.31 (s, 1H), 3.50 (td, *J* = 6.0, 1.8 Hz, 2H), 1.85 (d, *J* = 4.9 Hz, 1H), 1.72-1.63 (m, 1H), 1.56-1.49 (m, 1H), 1.52 (s, 9H), 1.40 (dd, *J* = 4.9, 1.5 Hz, 1H), 1.30-1.20 (m, 2H), 0.84 (s, 9H), –0.021 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 164.5, 144.3, 141.3, 122.1, 108.0, 82.9, 75.9, 62.2, 41.0, 36.5, 30.1, 28.1, 25.8, 24.2, 22.7, 18.2, –5.4; IR (film) ν_{max} 1784, 1728 cm^{-1}; HRMS (ESI+) *m/z* 459.2179 (MNa^+, calcd for $C_{23}H_{36}O_6NaSi$ 459.2179). *rac*-**356b**: TLC R_f = 0.43 (silica, 20% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (br s, 1H), 7.44 (br t, *J* = 1.7 Hz, 1H), 6.40 (br s, 1H), 5.47 (s, 1H), 3.64-3.52 (m, 2H), 2.05-1.96 (m, 1H), 1.87 (d, *J* = 5.1 Hz, 1H), 1.74-1.62 (m, 2H), 1.54-1.46 (m, 2H), 1.51 (s, 9H), 0.88 (s, 9H), 0.024 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 164.6, 143.9, 140.4, 120.9, 108.7, 82.9, 74.6, 62.4, 42.2, 36.1, 29.7, 28.0, 25.9, 25.1, 22.9, 18.3, –5.4; IR (film) ν_{max} 1789, 1726, 1504 cm^{-1}; HRMS (ESI+) *m/z* 459.2179 (MNa^+, calcd for $C_{23}H_{36}O_6NaSi$ 459.2179).

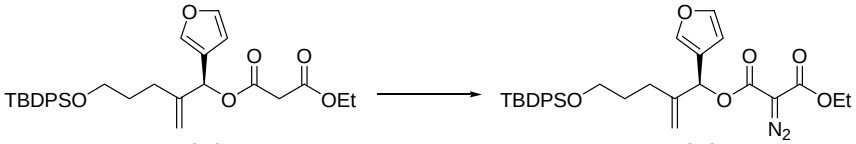
9.5 The route with TBDPS-protection and ethyl ester

9.5.1 Ethyl-5-(tert-butyldiphenylsilanyloxy)-(1S)-furan-3-yl-2-methylenepentyl malonate (346)

(*S*)-**321** **346**

Prepared according to the general procedure for preparation of malonates (Section 9.4.3) with alcohol (*S*)-**321** (0.86 g, 2.1 mmol, 100 mol%), mono-ethyl malonate (**341a**) (0.24 mL, 2.1 mmol, 100 mol%), DMAP (25 mg, 0.21 mmol, 10 mol%), CH_2Cl_2 (4.1 mL) and DCC (0.55 g, 2.7 mmol, 130 mol%). Dry-column flash chromatography[313] (silica, 0-20% EtOAc in hexanes) provided malonate **346** as a yellowish oil (1.06 g, 97%). TLC R_f = 0.43 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ –7.9 (*c* 1.0, $CHCl_3$; 59% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.62 (m, 4H), 7.45-7.35 (m, 8H), 6.33 (br dd, *J* = 1.8, 0.6 Hz, 1H), 6.22 (br s, 1H), 5.21 (br s, 1H), 5.00 (br s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.40 (s, 2H), 2.20-2.03 (m, 2H), 1.77-1.65 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.4, 145.8, 143.3, 141.0, 135.5, 133.9, 129.5, 127.6, 123.1, 111.6, 109.4, 71.9, 63.2, 61.5, 41.8, 30.5, 28.4, 26.8, 19.2, 14.0; IR (film) ν_{max} 1735 cm^{-1}; HRMS (ESI+) *m/z* 557.2337 (MNa^+, calcd for $C_{31}H_{38}O_6NaSi$ 557.2335).

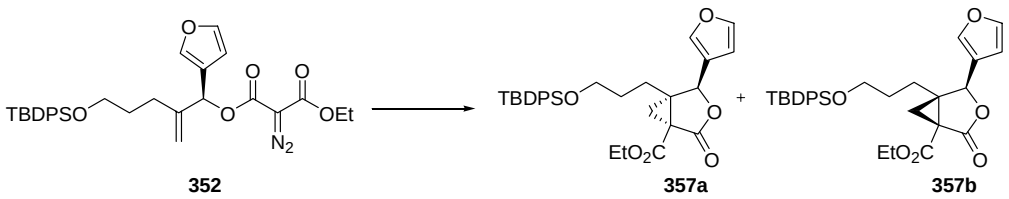
9.5.2 Ethyl-5-(tert-butyldiphenylsilanyloxy)-(1S)-furan-3-yl-2-methylenepentyl diazomalonate (352)



346 **352**

Prepared according to the general procedure for preparation of diazomalonates (Section 9.4.8) with malonate **346** (1.06 g, 2.0 mmol, 100 mol%), MeCN (4.0 mL), TsN_3 (0.41 g, 2.1 mmol, 105 mol%) and K_2CO_3 (0.29 g, 2.1 mmol, 105 mol%). Reaction provided diazomalonate **352** as a yellow oil (1.10 g, quant.). TLC R_f = 0.43 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ –15.9 (*c* 1.0, $CHCl_3$; 59% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.61 (m, 4H), 7.45-7.33 (m, 8H), 6.34 (br dd, *J* = 1.8, 0.6 Hz, 1H), 6.30 (br s, 1H), 5.23 (br s, 1H), 5.01 (br s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.64 (t, *J* = 6.2 Hz, 2H), 2.19-2.04 (m, 2H), 1.76-1.65 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.2, 145.8, 143.3, 141.2, 135.5, 133.9, 129.5, 127.6, 123.1, 111.7, 109.3, 71.8, 63.2, 61.7, 30.5, 28.5, 26.8 19.2, 14.3; IR (film) ν_{max} 2141, 1759, 1734, 1691, 1589, 1503 cm^{-1}; HRMS (ESI+) *m/z* 583.2226 (MNa^+, calcd for $C_{31}H_{36}N_2O_6NaSi$ 583.2240).

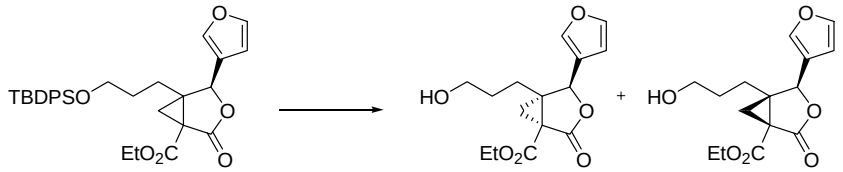
9.5.3 5-[3-(tert-Butyldiphenylsilanyloxy)propyl]-(4S)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (357)



352 **357a** **357b**

Prepared according to the general procedure for cyclopropanation of diazomalonates (Section 9.4.14) with diazomalonate **352** (0.50 g, 0.89 mmol, 100 mol%), catalytic complex **337b** (13 mg, 27 μmol, 3 mol%) and DCE (9.0 mL). The reaction time was 20 h at 60 °C. Flash column chromatography (silica, 5-20 % EtOAc in hexanes) provided cyclopropanolactone **357** as a greenish-yellow oil (98 mg, 21 %, 1:1 mixture of diastereomers). TLC R_f = 0.3 (silica, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.57 (m, 8H, a+b), 7.46-7.34 (m, 16H, a+b), 6.39-6.37 (m, 2H, a+b), 5.41 (s, 1H, b), 5.25 (s, 1H, a), 4.40-4.20 (m, 4H, a+b), 3.70-3.51 (m, 4H, a+b), 2.09-2.01 (m, 1H, a), 1.94 (d, *J* = 5.1 Hz, 1H, b), 1.93 (d, *J* = 4.9 Hz, 1H, a), 1.80-1.47 (m, 5H, 2a+2b+a/b), 1.55 (d, *J* = 5.1 Hz, 1H, b), 1.45 (dd, *J* = 4.9, 1.5 Hz, 1H, a), 1.40-1.25 (m, 2H, b+a/b), 1.33 (t, *J* = 7.0 Hz, 3H, a), 1.29 (t, *J* = 7.1 Hz, 3H, b), 1.04 (s, 9H, b), 1.00 (s, 9H, a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (a) 170.5 (b), 165.7 (b), 165.5 (a), 144.4 (a/b), 144.0 (a/b), 141.2 (a/b), 140.5 (a/b), 135.5 (a+b), 133.6 (a+b), 129.8 (a/b), 129.7 (a/b), 127.70 (a/b), 127.67 (a/b), 121.8 (a/b), 120.7 (a/b), 108.6 (a/b), 107.9 (a/b), 75.9 (a), 74.7 (b), 63.1 (a/b), 63.0 (a/b), 62.1 (a+b), 42.9 (a/b), 41.7 (a/b), 35.4 (a+b), 30.0 (a), 29.4 (b), 26.83 (b), 26.79 (a), 24.9 (a/b), 24.0 (a/b), 23.4 (a), 23.3 (b), 19.2 (a/b), 19.1 (a/b), 14.3 (a/b), 14.2 (a/b); IR (film) ν_{max} 1786, 1727, 1505 cm^{-1}; HRMS (ESI+) *m/z* 555.2184 (MNa^+, calcd for $C_{31}H_{36}O_6NaSi$ 555.2179).

9.5.4 (4S)-Furan-3-yl-5-(3-hydroxypropyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (359)

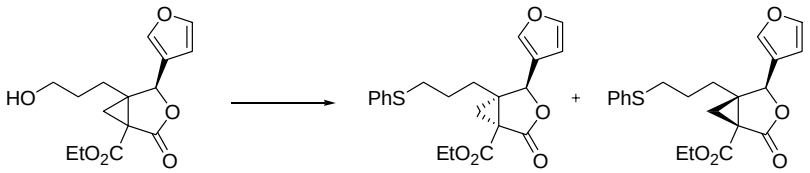


357 **359a** **359b**

To a stirred solution of cyclopropanolactone **357** (0.10 g, 0.20 mmol, 100 mol%) in THF (1.0 mL) at 0 °C were added AcOH (17 μl, 0.30 mmol, 150 mol%) and TBAF (1 M in THF, 0.30 mL, 0.30 mmol, 150 mol%). After 30 min, the brown solution was allowed to warm to rt. After 4 h, sat. aq. NH_4Cl (1 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 3 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica,

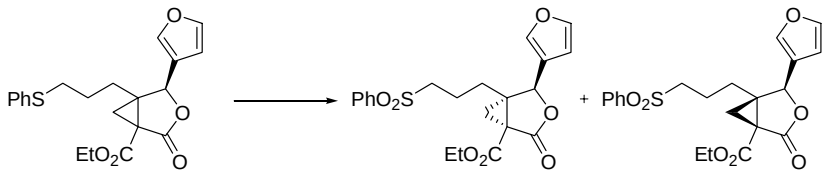
0-2% MeOH in CH_2Cl_2 with 0.5% Et_3N) provided cyclopropyl alcohol **359** as a brown oil (44 mg, 73%, 1:1 mixture of diastereomers). TLC R_f = 0.1 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, 1H, a), 7.51-7.49 (m, 1H, b), 7.48-7.46 (m, 1H, a), 7.46-7.43 (m, 1H, b), 6.44-6.39 (m, 2H, a+b), 5.50 (s, 1H, b), 5.36 (s, 1H, a), 4.37-4.25 (m, 4H, a+b), 3.61 (dd, *J* = 6.0, 5.7 Hz, 2H, a/b), 3.55 (dd, *J* = 6.2, 5.8 Hz, 2H, a/b), 2.13-2.00 (m, 2H, a+b), 1.98 (d, *J* = 4.9 Hz, 1H, a), 1.96 (d, *J* = 5.1 Hz, 1H, b), 1.85-1.53 (m, 4H, 2a+2b), 1.59 (d, *J* = 5.1 Hz, 1H, b), 1.51 (dd, *J* = 4.9, 1.2 Hz, 1H, a), 1.38-1.30 (m, 2H, a+b), 1.341 (t, *J* = 7.1 Hz, 3H, a/b), 1.335 (t, *J* = 7.0 Hz, 3H, a/b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (a/b), 170.4 (a/b), 165.9 (a/b), 165.6 (a/b), 144.5 (a), 144.0 (b), 141.3 (a), 140.6 (b), 121.8 (a/b), 120.7 (a/b), 108.6 (a/b), 107.9 (a/b), 75.9 (a), 74.6 (b), 62.2 (a+b), 61.99 (a/b), 61.96 (a/b), 42.9 (a/b), 41.7 (a/b), 35.4 (a+b), 29.9 (a/b), 29.2 (a/b), 24.8 (a/b), 23.9 (a/b), 23.5 (a), 23.4 (b), 14.3 (a/b), 14.2 (a/b); IR (film) ν_{max} 3534, 1781, 1725, 1506 cm^{-1}; HRMS (ESI+) *m/z* 317.0987 (MNa^+, calcd for $C_{15}H_{18}O_6Na$ 317.1001).

9.5.5 (4S)-Furan-3-yl-2-oxo-5-(3-phenylsulfanylpropyl)-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (360)



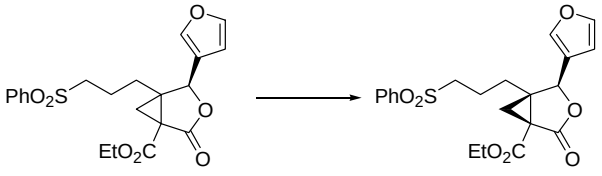
To a stirred solution of cyclopropyl alcohol **359** (57 mg, 0.19 mmol, 100 mol%) in pyridine (1.0 mL) was added $(SPh)_2$ (47 mg, 0.21 mmol, 110 mol%). The solution was cooled to 0 °C and freshly distilled Bu_3P (72 µl, 0.29 mmol, 150 mol%) was added. After 1 h 15 min at rt, the solution was diluted with Et_2O (5 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and brine, dried, filtered and concentrated. Flash column chromatography (silica, 10-20% EtOAc in hexanes) provided sulfide **360** as a colorless oil (60 mg, 80%, 1:1 mixture of diastereomers). TLC R_f = 0.75 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 1H, a), 7.44-7.40 (m, 2H, b), 7.37-7.35 (m, 1H, a), 7.32-7.16 (m, 10H, a+b), 6.37-6.34 (m, 2H, a+b), 5.37 (s, 1H, b), 5.26 (s, 1H, a), 4.36-4.27 (m, 2H, a), 4.26-4.17 (m, 2H, b), 2.94-2.69 (m, 4H, a+b), 2.11-2.01 (m, 1H, b), 1.94 (d, *J* = 5.1 Hz, 2H, a+b), 1.88-1.51 (m, 6H, a+b), 1.57 (d, *J* = 5.1 Hz, 1H, b), 1.47 (dd, *J* = 5.1, 1.2 Hz, 1H, a), 1.40-1.25 (m, 1H, a), 1.34 (t, *J* = 7.1 Hz, 3H, a), 1.29 (t, *J* = 7.1 Hz, 3H, b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (a), 170.1 (b), 165.6 (b), 165.5 (a), 144.5 (a), 144.0 (b), 141.3 (a), 140.5 (b), 135.6 (a), 135.5 (b), 129.6 (b), 129.5 (a), 129.0 (b), 128.9 (a), 126.3 (b), 126.2 (a), 121.6 (a), 120.5 (b), 108.5 (b), 107.8 (a), 75.6 (a), 74.5 (b), 62.2 (a), 62.1 (b), 42.6 (b), 41.5 (a), 35.2 (b), 35.1 (a), 33.4 (b), 33.2 (a), 27.2 (b), 26.52 (a), 26.50 (a), 25.8 (b), 23.4 (a), 23.2 (b), 14.2 (a), 14.1 (b); IR (film) ν_{max} 1784, 1727, 1584, 1505 cm^{-1}; HRMS (ESI+) *m/z* 409.1065 (MNa^+, calcd for $C_{21}H_{22}O_5NaS$ 409.1086).

9.5.6 5-(3-Benzenesulfonylpropyl)-(4S)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (361)



360 **361a** **361b**

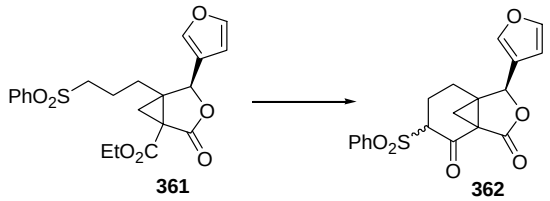
To a stirred mixture of sulfide **360** (37 mg, 96 μmol, 100 mol%) and $NaHCO_3$ (80 mg, 0.96 mmol, 1000 mol%) in CH_2Cl_2 (0.5 mL) at 0 °C was added *m*-CPBA (70%, 47 mg, 0.19 mmol, 200 mol%). After 50 min, sat. aq. $NaHCO_3$ (1 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 1 mL). The organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 0-1% MeOH in CH_2Cl_2) provided sulfone **361** as a colorless oil (38 mg, 95%, 1:1 mixture of diastereomers). TLC R_f = 0.35 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.82 (m, 4H, a+b), 7.72-7.64 (m, 2H, a+b), 7.62-7.54 (m, 4H, a+b), 7.47 (br s, 1H, b), 7.46-7.43 (m, 2H, a+b), 7.41 (br s, 1H, a), 6.41-6.37 (m, 1H, b), 6.34-6.30 (m, 1H, a), 5.41 (s, 1H, b), 5.29 (s, 1H, a), 4.36-4.14 (m, 4H, a+b), 3.07-2.97 (m, 1H, a), 3.02 (t, J = 7.4 Hz, 2H, b), 2.94-2.84 (m, 1H, a), 2.04 (ddd, J = 13.9, 11.7, 4.4 Hz, 1H, b), 1.99-1.87 (m, 1H, b), 1.92 (2 × overlapping d, J_a = 5.2, J_b = 5.3 Hz, 2H, a+b), 1.87-1.62 (m, 4H, 2a+2b), 1.61 (d, J = 5.3 Hz, 1H, b), 1.51 (dd, J = 5.1, 1.3 Hz, 1H, a), 1.36-1.23 (m, 2H, a) 1.32 (t, J = 7.1 Hz, 3H, a), 1.28 (t, J = 7.1 Hz, 3H, b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (a), 169.8 (b), 165.6 (b), 165.3 (a), 144.7 (a), 144.2 (b), 141.3 (a), 140.8 (b), 138.84 (b), 138.79 (a), 133.9 (a+b), 129.4 (a+b), 127.9 (a+b), 121.4 (a), 120.3 (b), 108.5 (b), 107.6 (a), 75.3 (a), 74.3 (b), 62.3 (a+b), 55.50 (b), 55.45 (a), 42.2 (b), 41.1 (a), 35.1 (b), 34.9 (a), 27.1 (b), 26.3 (a), 23.4 (a), 23.2 (b), 20.3 (a), 20.0 (b), 14.2 (a), 14.1 (b); IR (film) ν_{max} 1784, 1723, 1586, 1505 cm^{-1}; HRMS (ESI+) *m/z* 441.0967 (MNa+, calcd for $C_{21}H_{22}O_7NaS$ 441.0984).



361 **361b**

To a stirred solution of sulfone **361** (11 mg, 26 μmol, 100 mol%) in THF (0.9 mL) at –78 °C was added LHMDS (1 M in THF, 40 μl, 40 μmol, 150 mol%). After 1.5 and 3 h more LHMDS (2 × 20 μl, 20 μmol, 75 mol%) was added. After 4 h the solution was warmed to rt over 4 h and stirred overnight. Sat. aq. NH_4Cl (1 mL) was added, the biphasic mixture was concentrated and the aqueous phase was extracted with 25% EtOH in $CHCl_3$ (10 × 1 mL), dried, filtered and concentrated. Pure sulfone **361b** was obtained as a yellowish oil (5 mg). $[\alpha]^{20}_D$ –5.8 (*c* 0.24, $CHCl_3$; 47% ee).

9.5.7 Ketosulfone 362



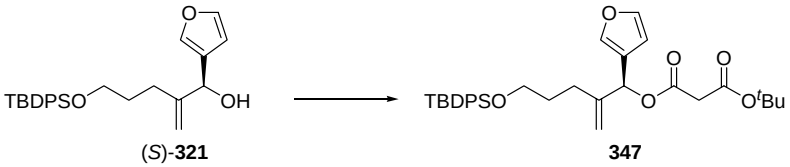
361 **362**

To a stirred solution of sulfone **361** (8.9 mg, 21 μmol, 100 mol%) in THF (0.5 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 17 μl, 43 μmol, 200 mol%) dropwise. After 2.5 h, more *n*-BuLi (8.5 μl, 21 μmol, 100 mol%) was added. After 3.5 h, sat. aq. NH_4Cl (1 mL) was added and the reaction was allowed to warm to rt. The aqueous phase was extracted with EtOAc (3 × 2 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. LRMS (EI) *m/z* 373 (M+1, calcd for $C_{19}H_{17}O_6S$ 373), 327 (M–CO_2H), 231 (M–SO_2Ph). *For more spectral data, see Section 9.6.7.*

9.6 The route with TBDPS protection and *t*-butyl ester

When data for both diastereomers are reported, there were no essential differences in the execution of the syntheses of the two diastereomers, so only one of them is covered.

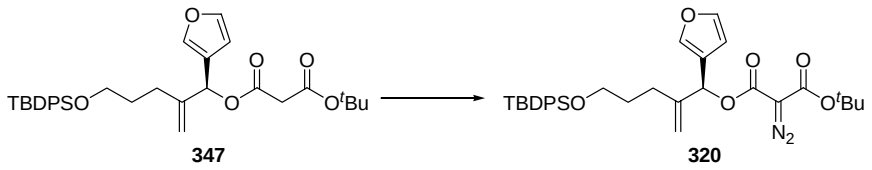
9.6.1 tert-Butyl-5-(tert-butyldiphenylsilanyloxy)-(1S)-furan-3-yl-2-methylenepentyl malonate (347)



(*S*)-**321** **347**

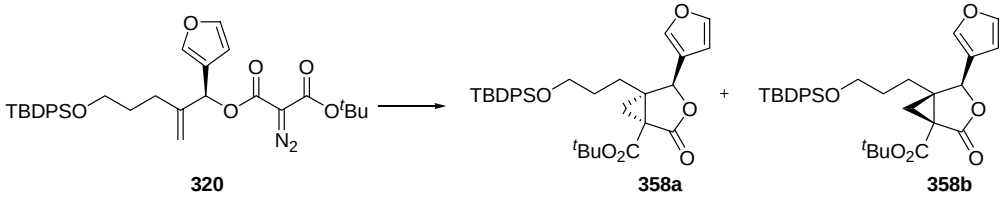
Prepared according to the general procedure for preparation of malonates (Section 9.4.3) with alcohol (*S*)-**321** (0.87 g, 2.1 mmol, 100 mol%), mono-*t*-butyl malonate (**341b**) (0.33 g, 2.1 mmol, 100 mol%), DMAP (25 mg, 0.21 mmol, 10 mol%), DCC (0.51 g, 2.5 mmol, 120 mol%) and CH_2Cl_2 (4.2 mL). The reaction provided malonate **347** as a yellow oil (1.14 g, 98%), which was sufficiently pure to be used in the next step. An analytical sample was purified by dry-column flash chromatography[313] (silica, 0-15% EtOAc in hexanes). TLC R_f = 0.40 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ –19 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.61 (m, 4H), 7.45-7.34 (m, 8H), 6.32 (br dd, *J* = 1.7, 0.6 Hz, 1H), 6.21 (br s, 1H), 5.21 (br s, 1H), 4.99 (br s, 1H), 3.64 (t, *J* = 6.3 Hz, 2H), 3.30 (s, 2H), 2.18-2.02 (m, 2H), 1.76-1.64 (m, 2H), 1.43 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.4, 145.8, 143.2, 141.0, 135.5, 133.9, 129.5, 127.6, 123.2, 111.5, 109.4, 82.0, 71.6, 63.2, 43.1, 30.5, 28.5, 27.8, 26.8, 19.1; IR (film) ν_{max} 1728, 1649, 1588 cm^{-1}; HRMS (ESI+) *m/z* 585.2625 (MNa^+, calcd for $C_{33}H_{42}O_5NaSi$ 585.2648).

9.6.2 tert-Butyl-5-(tert-butyldiphenylsilanyloxy)-(1S)-furan-3-yl-2-methylenepentyl diazomalonate (320)



Prepared according to the general procedure for preparation of diazomalonates (Section 9.4.8) with malonate **347** (2.06 g, 3.7 mmol, 100 mol%), MeCN (7.7 mL), K_2CO_3 (0.56 g, 4.1 mmol, 110 mol%) and TsN_3 (0.80 g, 4.1 mmol, 100 mol%). Dry column flash chromatography[313] (silica, 5-15% EtOAc in hexanes) provided diazomalonate **320** as a yellow oil (2.11 g, 98%). TLC R_f = 0.4 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ –22 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.61 (m, 4H), 7.45-7.33 (m, 8H), 6.33 (br dd, *J* = 1.8, 0.7 Hz, 1H), 6.30 (br s, 1H), 5.20 (br s, 1H), 4.99 (br s, 1H), 3.64 (t, *J* = 6.2 Hz, 2H), 2.18-2.02 (m, 2H), 1.74-1.64 (m, 2H), 1.51 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 159.6, 145.9, 143.2, 141.2, 135.5, 133.9, 129.5, 127.6, 123.2, 111.6, 109.4, 83.1, 71.4, 63.2, 30.6, 28.5, 28.2, 26.8, 19.1; IR (film) ν_{max} 2137, 1755, 1729, 1686, 1588 cm^{-1}; HRMS (ESI+) *m/z* 611.2548 (MNa^+, calcd for $C_{33}H_{40}N_2O_6NaSi$ 611.2553).

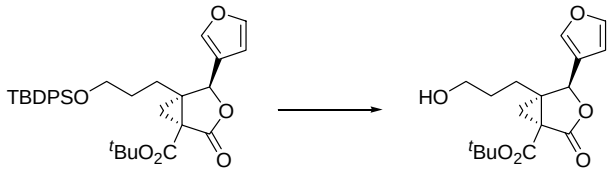
9.6.3 (5S)-[3-(tert-Butyldimethylsilanyloxy)propyl]-(4S)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-(1S)-carboxylic acid tert-butyl ester (358a) and (5R)-[3-(tert-Butyldimethylsilanyloxy)propyl]-(4S)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-(1R)-carboxylic acid tert-butyl ester (358b)



Prepared according to the general procedure for cyclopropanation of diazomalonates (Section 9.4.14) with diazomalonate **320** (1.15 g, 2.0 mmol, 100 mol%), catalytic complex **337a** (38 mg, 59 μmol, 3 mol%) and DCE (17 mL). Reaction time was 24 h at 55 °C. Flash column chromatography (silica, 5-15% EtOAc in hexanes) provided cyclopropanolactones **358a** and **358b** (184 and 149 mg, respectively, 30% in total) as a greenish-yellow oil. **358a**: TLC R_f = 0.36 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ +4.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 4H), 7.46-7.34 (m, 8H), 6.41 (br s, 1H), 5.24 (s, 1H), 3.61-3.49 (m, 2H), 1.83 (d, *J* = 4.9 Hz, 1H), 1.79-1.67 (m, 1H), 1.66-1.54 (m, 2H), 1.53 (s, 9H), 1.38 (d, *J* = 4.9 Hz, 1H), 1.35-1.24 (m, 1H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 164.5, 144.3, 141.2, 135.5, 133.6, 129.7, 127.6, 122.0, 107.9, 82.9, 75.8, 63.0, 40.8, 36.4, 29.9, 28.1, 26.7, 24.1, 22.6, 19.1; IR (film) ν_{max}

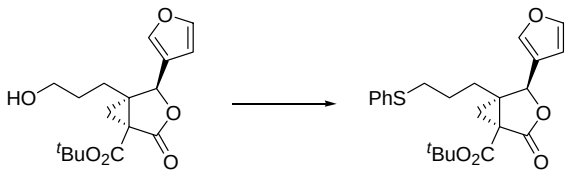
1784, 1727, 1506 cm^{-1}; HRMS (ESI+) *m/z* 583.2474 (MNa^+, calcd for $C_{33}H_{40}O_6NaSi$ 583.2492). **358b**: TLC R_f = 0.43 (silica, 20% EtOAc in hexanes); $[\alpha]^{20}_D$ –27 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.60 (m, 4H), 7.47-7.32 (m, 8H), 6.38 (br s, 1H), 5.41 (s, 1H), 3.72-3.55 (m, 2H), 2.06 (dd, *J* = 11.7, 10.4 Hz, 1H), 1.86 (d, *J* = 4.9 Hz, 1H), 1.77-1.67 (m, 2H), 1.55-1.45 (m, 2H), 1.49 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 164.6, 143.9, 140.4, 135.5, 133.6, 129.7, 127.7, 120.9, 108.6, 82.9, 74.5, 63.2, 42.5, 36.0, 29.5, 28.0, 26.8, 25.0, 22.8, 19.2; IR (film) ν_{max} 1787, 1721, 1500 cm^{-1}; HRMS (ESI+) *m/z* 583.2482 (MNa^+, calcd for $C_{33}H_{40}O_6NaSi$ 583.2493).

9.6.4 (4S)-Furan-3-yl-(5S)-(3-hydroxypropyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-(1S)-carboxylic acid tert-butyl ester (363a)



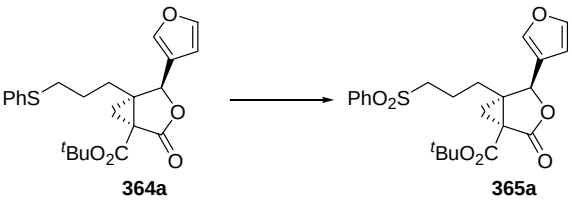
To a stirred solution of cyclopropanolactone **358a** (0.38 g, 0.67 mmol, 100 mol%) in THF (1.4 mL) at 0 °C was added TBAF (1 M in THF, 1.34 mL, 1.3 mmol, 200 mol%) dropwise. After 30 min at 0 °C, the brown solution was allowed to warm to rt and after 2 h, sat. aq. NH_4Cl (2 mL) was added. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 0-2% MeOH in CH_2Cl_2 with 2% Et_3N) provided alcohol **363a** as a brown oil (0.123 g, 57 %). **363a**: TLC R_f = 0.18 (silica, 50% EtOAc in hexanes); $[\alpha]^{20}_D$ +53 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.51 (m, 1H), 7.47 (br t, *J* = 1.7 Hz, 1H), 6.42 (br dd, *J* = 1.7, 0.7 Hz, 1H), 5.33 (s, 1H), 3.55 (br t, *J* = 5.9 Hz, 2H), 1.87 (d, *J* = 4.9 Hz, 1H), 1.72-1.55 (m, 3H), 1.53 (s, 9H), 1.43 (dd, *J* = 4.9, 1.5 Hz, 1H), 1.35-1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 164.5, 144.4, 141.3, 122.0, 107.9, 83.1, 75.8, 62.0, 40.9, 36.3, 29.9, 28.1, 23.8, 22.8; IR (film) ν_{max} 3523, 1778, 1725, 1507 cm^{-1}; HRMS (ESI+) *m/z* 345.1302 (MNa^+, calcd for $C_{17}H_{22}O_6Na$ 345.1314). **363b**: TLC R_f = 0.22 (silica, 50% EtOAc in hexanes); $[\alpha]^{20}_D$ –74 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 1H), 7.44 (t, *J* = 1.8 Hz, 1H), 6.41 (br dd, *J* = 1.8, 0.7 Hz, 1H), 5.48 (s, 1H), 3.70-3.57 (m, 2H), 2.04 (td, *J* = 11.2, 1.2 Hz, 1H), 1.88 (d, *J* = 5.1 Hz, 1H), 1.82-1.54 (m, 3H), 1.52 (s, 9H), 1.53-1.51 (obs m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 164.7, 144.0, 140.5, 120.8, 108.7, 83.1, 74.4, 62.1, 42.4, 36.0, 29.4, 28.0, 24.8, 23.0; IR (film) ν_{max} 3413, 1781, 1719, 1505 cm^{-1}; HRMS (ESI+) *m/z* 345.1306 (MNa^+, calcd for $C_{17}H_{22}O_6Na$ 345.1314).

9.6.5 (4S)-Furan-3-yl-2-oxo-(5S)-(3-phenylsulfanylpropyl)-3-oxabicyclo[3.1.0]hexane-(1S)-carboxylic acid tert-butyl ester (364a)



A stirred solution of alcohol **363a** (0.12 g, 0.38 mmol, 100 mol%) and $(SPh)_2$ (0.13 g, 0.45 mmol, 120 mol%) in pyridine (1.9 mL) at 0 °C was bubbled with argon for 10 min after which freshly distilled Bu_3P (0.19 mL, 0.76 mmol, 200 mol%) was added. After 15 min at 0 °C, the solution was allowed to warm to rt. After 1.5 h, Et_2O (10 mL) was added and the solution was washed with sat. aq. $NaHCO_3$ (5 mL) and brine, dried, filtered and concentrated. Flash column chromatography (silica, 10-15 % EtOAc in hexanes) provided sulfide **364a** as a colorless oil (0.118 g, 75%). **364a**: TLC R_f = 0.65 (silica, 50% EtOAc in hexanes); $[\alpha]^{20}_D$ +41 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (br t, *J* = 1.6 Hz, 1H), 7.36 (s, 1H), 7.33-7.17 (m, 5H), 6.39-6.35 (m, 1H), 5.23 (s, 1H), 2.88-2.71 (m, 2H), 1.84 (d, *J* = 5.0 Hz, 1H), 1.76-1.60 (m, 3H), 1.53 (s, 9H), 1.40 (dd, *J* = 5.0, 1.2 Hz, 1H), 1.37-1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 164.4, 144.4, 141.2, 135.7, 129.4, 128.9, 126.2, 121.8, 107.7, 83.1, 75.6, 40.7, 36.1, 33.2, 28.1, 26.54, 26.48, 22.7; IR (film) ν_{max} 1783, 1725, 1584, 1506 cm^{-1}; HRMS (ESI+) *m/z* 437.1396 (MNa^+, calcd for $C_{23}H_{26}O_5NaS$ 437.1399). **364b**: TLC R_f = 0.70 (silica, 50% EtOAc in hexanes); $[\alpha]^{20}_D$ –49 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (br t, *J* = 1.7 Hz, 1H), 7.42-7.40 (m, 1H), 7.33-7.25 (m, 4H), 7.23-7.16 (m, 1H), 6.35 (br dd, *J* = 1.7, 0.8 Hz, 1H), 5.36 (s, 1H), 2.96-2.78 (m, 2H), 2.07 (td, *J* = 11.9, 1.8 Hz, 1H), 1.86 (d, *J* = 5.1 Hz, 1H), 1.83-1.73 (m, 2H), 1.70-1.60 (m, 1H), 1.49 (s, 9H), 1.51-1.45 (obs m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 164.5, 143.9, 140.5, 135.6, 129.7, 129.0, 126.4, 108.6, 99.8, 83.1, 74.3, 42.1, 36.0, 33.7, 28.0, 27.4, 26.0, 22.7; IR (film) ν_{max} 1785, 1719, 1584, 1504 cm^{-1}; HRMS (ESI+) *m/z* 437.1388 (MNa^+, calcd for $C_{23}H_{26}O_5NaS$ 437.1399).

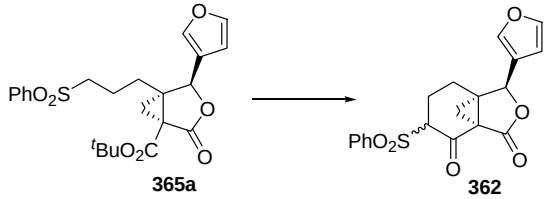
9.6.6 (5S)-(3-Benzenesulfonylpropyl)-(4S)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-(1S)-carboxylic acid tert-butyl ester (365a)



To a stirred solution of sulfide **364a** (82 mg, 0.20 mmol, 100 mol%) in CH_2Cl_2 (1.0 mL) at 0 °C was added $NaHCO_3$ (0.17 g, 2.0 mmol, 1000 mol%) and *m*-CPBA (70%, 0.11 g, 0.46 mmol, 230 mol%). After 60 min, sat. aq. $NaHCO_3$ (2 mL) was added and the

aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 33-50% EtOAc in hexanes) provided sulfone **365a** as a white foam (77 mg, 88%). **365a**: TLC R_f = 0.43 (silica, 50% EtOAc in hexanes); $[\alpha]^{20}_D$ +29 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2H), 7.71-7.69 (m, 1H), 7.61-7.54 (m, 2H), 7.45 (br t, *J* = 1.6 Hz, 1H), 7.39 (br s, 1H), 6.33 (br dd, *J* = 1.6, 0.7 Hz, 1H), 5.25 (s, 1H), 3.07-2.85 (m, 2H), 1.81 (d, *J* = 5.1 Hz, 1H), 1.83-1.62 (m, 3H), 1.49 (s, 9H), 1.42 (dd, *J* = 5.1, 1.3 Hz, 1H), 1.31-1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 164.2, 144.6, 141.2, 138.9, 133.9, 129.4, 127.9, 121.6, 107.6, 83.4, 75.3, 55.5, 40.3, 35.9, 28.1, 26.2, 22.6, 20.3; IR (film) ν_{max} 1781, 1724, 1586, 1506 cm^{-1}; HRMS (ESI+) *m/z* 469.1289 (MNa^+, calcd for $C_{23}H_{26}O_7NaS$ 469.1297). **365b**: TLC R_f = 0.53 (silica, 50% EtOAc in hexanes); $[\alpha]^{20}_D$ –54 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.83 (m, 2H), 7.70-7.64 (m, 1H), 7.62-7.53 (m, 2H), 7.48-7.42 (m, 2H), 6.41-6.37 (m, 1H), 5.40 (s, 1H), 3.02 (t, *J* = 7.7 Hz, 2H), 2.09-1.90 (m, 2H), 1.83 (d, *J* = 5.2 Hz, 1H), 1.85-1.63 (m, 2H), 1.52 (d, *J* = 5.2 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.5, 144.1, 140.7, 138.9, 133.9, 129.4, 127.9, 120.5, 108.6, 83.4, 74.1, 55.7, 41.7, 35.8, 27.9, 27.1, 22.7, 20.0; IR (film) ν_{max} 1784, 1718, 1586, 1505 cm^{-1}; HRMS (ESI+) *m/z* 469.1311 (MNa^+, calcd for $C_{23}H_{26}O_7NaS$ 469.1297).

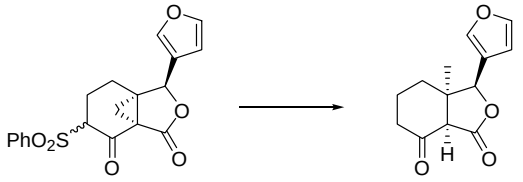
9.6.7 Ketosulfone 362



To a stirred solution of sulfone **365a** (77 mg, 0.17 mmol, 100 mol%) in THF (3.5 mL, freshly distilled from $LiAlH_4$) at –100 °C was added *n*-BuLi (0.16 mL, 0.35 mmol, 200 mol%) dropwise. After 15 min, more *n*-BuLi (15 μl, 34 μmol, 20 mol%) was added because some starting material was evident by TLC analysis. After 25 min, sat. aq. NH_4Cl (5 mL) was added and the mixture was allowed to warm to rt. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 40-60% EtOAc in hex) provided ketosulfone **362** as mixture of diastereomers (a:b = 1:0.8, 33 mg, 55%). TLC R_f = 0.1 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.83 (m, 2H, b), 7.82-7.77 (m, 2H, a), 7.72-7.66 (m, 2H, a+b), 7.60-7.54 (m, 5H, 3a+2b), 7.48 (br t, *J* = 1.7 Hz, 1H, a), 7.46-7.43 (m, 2H, b), 6.73 (br dd, *J* = 1.7, 0.7 Hz, 1H, a), 6.20 (br t, *J* = 1.4 Hz, 1H, b), 5.47 (s, 1H, a), 5.45 (s, 1H, b), 3.76 (dd, *J* = 10.0, 8.7 Hz, 1H, b), 3.59 (dd, *J* = 5.6, 1.9 Hz, 1H, a), 2.88-2.80 (m, 1H, a), 2.86 (d, *J* = 6.4 Hz, 1H, b), 2.48-2.30 (m, 3H, a+2b), 2.20 (dt *J* = 14.2, 4.1 Hz, 1H, b), 2.02-1.89 (m, 2H, a), 1.92 (d, *J* = 5.9 Hz, 1H, a), 1.81-1.71 (m, 1H, b), 1.81 (d, *J* = 6.4 Hz, 1H, b), 1.70 (d, *J* = 5.9 Hz, 1H, a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7 (a), 189.2 (b), 168.0 (a/b), 167.9 (a/b), 144.7

(b), 144.2 (a), 141.7 (a), 140.6 (b), 138.2 (a), 137.6 (b), 134.39 (a), 134.35 (b), 129.23 (a/b), 129.17 (2a/b), 129.1 (a/b), 121.5 (b), 120.7 (a), 109.2 (a), 107.8 (b), 77.2 (a), 75.7 (b), 68.5 (b), 67.2 (a), 40.3 (b), 35.6 (b), 35.0 (a), 34.8 (a), 23.6 (b), 23.2 (a), 20.0 (b), 19.9 (b), 19.3 (a), 18.3 (a); IR (film) ν_{max} 1780, 1704, 1583, 1503 cm^{-1}; HRMS (ESI+) *m/z* 395.0572 (MNa^+, calcd for $C_{19}H_{16}O_6NaS$ 395.0565).

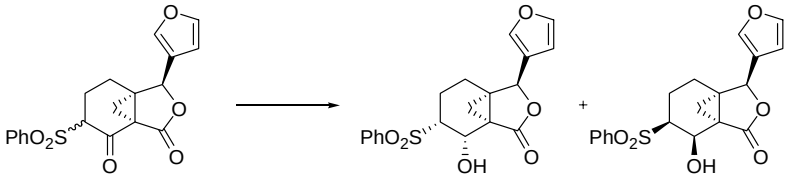
9.6.8 Methyl ketone 367



362 **367**

To a stirred solution of ketosulfone **362** (7.0 mg, 19 μmol, 100 mol%) in THF:H_2O (9:1, 1.0 mL) at 0 °C was added commercial aluminum foil (1.5 mg, 57 μmol, 300 mol%), which had been immersed in $HgCl_2$ (aq., 2%), washed with EtOH and Et_2O and cut into small pieces. After 1 h, more Al-foil (1.5 mg, 57 μmol, 300 mol%) was added and after 4 h, the mixture was filtered through a pad of Celite ®, dried, filtered and concentrated. Flash column chromatography (silica, 33-50% EtOAc in hex) provided methyl ketone **367** (2 mg, 45%). TLC R_f = 0.5 (silica, 50% EtOAc in hexanes); $[\alpha]^{20}_D$ –33 (*c* 0.23, $CHCl_3$; 46% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.48 (s, 1H), 6.40 (s, 1H), 5.08 (s, 1H), 3.30 (br s, 1H), 2.48-2.33 (m, 2H), 2.06-1.97 (m, 1H), 1.78-1.66 (m, 2H), 1.33-1.20 (obs m, 1H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 170.8, 143.8, 140.2, 118.3, 108.6, 82.9, 63.1, 49.6, 39.6, 28.3, 21.3, 20.6; IR (film) ν_{max} 1776, 1716, 1504 cm^{-1}; HRMS (ESI+) *m/z* 257.0779 (MNa^+, calcd for $C_{13}H_{14}O_4Na$ 257.0790).

9.6.9 Hydroxysulfone 371

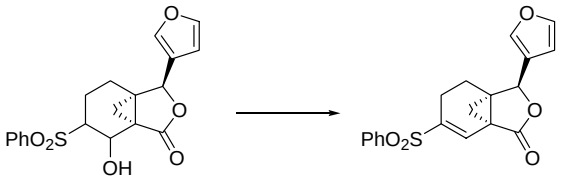


362 **371a** **371b**

To a stirred solution of ketosulfone **362** (17 mg, 46 μmol, 100 mol%) in CH_2Cl_2:EtOH (1:1, 0.2 mL) at 0 °C was added $NaBH_4$ (18 mg, 48 μmol, 105 mol%). After 50 min, sat. aq. NH_4Cl (1 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 33-50 % EtOAc in hexanes) provided hydroxysulfone **371** as a yellowish oil (a:b 1:0.6, 14 mg, 82%). TLC R_f = 0.2 (silica, 50% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.88 (m, 4H, a+b), 7.74-7.68 (m, 2H, a+b),

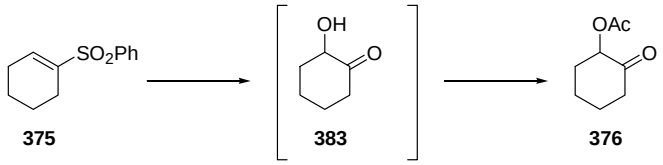
7.64-7.56 (m, 4H, a+b), 7.54-7.51 (m, 1H, b), 7.46 (br t, J = 1.6 Hz, 1H, a), 7.43 (br t, J = 1.5 Hz, 1H, b), 7.41-7.38 (m, 1H, a), 6.62 (br dd, J = 1.5, 0.6 Hz, 1H, b), 6.14 (br dd, J = 1.6, 0.8 Hz, 1H, a), 5.37 (s, 1H, a), 5.34 (s, 1H, b), 5.04 (br s, 1H, a), 4.95 (br s, 1H, b), 3.49 (d, J = 2.2 Hz, 1H, b), 3.22 (d, J = 2.4 Hz, 1H, a), 2.67 (dt, J = 12.7, 2.2 Hz, 1H, b), 2.52 (dt, J = 12.0, 2.7 Hz, 1H, a), 2.11-2.00 (m, 2H, a+b), 1.99-1.84 (m, 2H, a+b), 1.87 (d, J = 5.6 Hz, 1H, a), 1.81-1.73 (m, 1H, b), 1.72-1.54 (m, 3H, 2a+b), 1.26 (d, J = 5.6 Hz, 1H, a), 1.23 (d, J = 5.8 Hz, 1H, b), 0.94 (d, J = 5.8 Hz, 1H, b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9 (a/b), 174.2 (a/b), 144.7 (a), 144.6 (b), 141.6 (b), 140.3 (a), 137.5 (a), 137.5 (b), 134.4 (a), 134.3 (b), 129.5 (a), 129.4 (b), 129.0 (b), 128.8 (a), 122.3 (a), 122.1 (b), 108.0 (b), 107.7 (a), 78.3 (a), 78.0 (b), 65.3 (a), 62.2 (b), 60.2 (b), 59.7 (a), 33.7 (b), 33.5 (a), 32.9 (a), 28.3 (b), 22.8 (b), 22.7 (a), 22.2 (b), 18.6 (a), 15.0 (b), 13.5 (a); IR (film) ν_{max} 3497, 1760, 1599, 1505 cm^{-1}; HRMS (ESI+) *m/z* 397.0721 (MNa^+, calcd for $C_{19}H_{18}O_6NaS$ 397.0722).

9.6.10 Vinyl sulfone 372



To a stirred solution of hydroxysulfone **371** (8.0 mg, 21 μmol, 100 mol%) in THF (0.2 mL) at –10 °C were added KHMDS (0.3 M in toluene, 0.29 mL, 86 μmol, 400 mol%) and after 5 min, MsCl (6.6 μl, 86 μmol, 400 mol%). The solution was allowed to warm slowly to 0 °C and after 1.5 h, sat. aq. NH_4Cl (1 mL) was added. The aqueous phase was extracted with EtOAc (3 × 3 mL), washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 33-50% EtOAc in hexanes) provided hydroxysulfone **372** as a yellowish oil (1.6 mg, 32% based on recovered **371**) and hydroxysulfone **371** (2.7 mg). **372**: TLC R_f = 0.25 (silica, 50% EtOAc in hexanes); $[\alpha]^{20}_D$ +117 (*c* 0.1, $CHCl_3$; 42% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.80 (m, 2H), 7.66-7.60 (m, 2H), 7.56-7.5 (m, 2H), 7.43 (s, 2H), 6.16 (s, 1H), 5.51 (s, 1H), 2.53 (ddd, J = 17.4, 6.1, 1.2 Hz, 1H), 2.01 (dd, J = 13.0, 7.3 Hz, 1H), 1.90-1.78 (m, 1H), 1.73 (d, J = 5.0 Hz, 1H), 1.68 (d, J = 5.0 Hz, 1H), 1.40 (td, J = 13.0, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 144.5, 140.5, 138.9, 137.7, 133.6, 132.6, 129.3, 128.1, 121.8, 107.9, 77.7, 36.1, 27.5, 25.8, 19.8, 18.6; IR (film) ν_{max} 1773, 1629, 1504 cm^{-1}; HRMS (ESI+) *m/z* 379.0637 (MNa^+, calcd for $C_{19}H_{16}O_5NaS$ 379.0616).

9.6.11 2-Acetoxycyclohexenone (376)[314]



375 **383** **376**

To a stirred solution of vinyl sulfone **375**[305,306] (0.12 g, 0.52 mmol, 100 mol%) in H_2O:*t*-BuOH (1:1, 1.0 mL) were added citric acid (0.20 g, 1.0 mmol, 200 mol%), OsO_4 (0.20 mL, 16 μmol, 3 mol%, 2.5 wt% in 2-methyl-2-propanol) and NMO·H_2O (0.14 g, 1.1 mmol, 200 mol%). After 3 h, *t*-BuOH was evaporated and HCl (1 M, 3 mL) and EtOAc (10 mL) were added. The aqueous phase was extracted with EtOAc (2 × 5 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. To a solution of this crude product in CH_2Cl_2 (2.1 mL) were added Ac_2O (0.34 mL, 4.2 mmol, 1000 mol%) and DMAP (7.7 mg, 63 μmol, 15 mol%). After 1 h, H_2O (2 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5-25% EtOAc in hexanes) provided 2-acetoxycyclohexenone (**367**) as a colorless oil (17 mg, 26%). TLC R_f = 0.55 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19-5.10 (m, 1H), 2.54-2.46 (m, 1H), 2.38 (tdd, *J* = 13.5, 6.0, 1.1 Hz, 1H), 2.32-2.23 (m, 1H), 2.14 (s, 3H), 2.12-2.03 (m, 1H), 2.01-1.91 (m, 1H), 1.80-1.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 170.0, 76.5, 40.6, 33.0, 27.1, 23.7, 20.7.

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