THESIS ON NATURAL AND EXACT SCIENCES B158

Synthesis of Cyclopentane and Tetrahydrofuran Derivatives

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Declaration:
Hereby, I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology, has not been submitted for any other academic degree

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Tsüklopentaanide ja tetrahüdrofuraanide süntees

ALLAN NIIDU

TTÜ KIRJASTUS

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List of publications

I Niidu, A.; Paju, A.; Eek, M.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. Synthesis of chiral hydroxylated cyclopentanones and cyclopentanes. *Tetrahedron: Asymmetry* **2006**, *25*, 2678-2683.

II Niidu, A.; Paju, A.; Müürisepp, A.-M.; Kailas, T.; Pehk, T.; Lopp, M. Synthesis of chiral enantioenriched tetrahydrofuran derivatives. *ARKIVOC* **2009**, *(xiv)*, 39-52.

III Niidu, A.; Paju, A.; Müürisepp, A.-M.; Järving, I.; Kailas, T.; Pehk, T.; Lopp, M. Stereoselective synthesis of 1-methyl-1,2- and 1,3-cyclopentanediols *via* γ-lactones. *Chemistry of Heterocyclic Compounds* **2013**, *48*, 1751-1760.

Authors Contribution

The contribution by the author to the papers included in the theses is as follows:

I Participated in the planning of the experiments, carried out most of the experiments, and had a major role in the preparation of the manuscript.

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Abbreviations

(+)-DET	(+)-diethyltartrate
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
(S)-t-BuPhox	(*S*)-4-(*tert*-butyl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole
(*S,R*)-PPF-P(*t*-Bu)$_2$	(*S*)-1-[(R_P)-2-(diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
acac	acetylacetone
AcOH	acetic acid
AD-mix-α	$K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$
AD-mix-β	$K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$
AIBN	azobisisobutyronitrile
alk	alkyl
aq.	aqueous
BBN	9-borabicyclononane
BF_3*Et_2O	boron trifluoride diethyletherate
BINAP	(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	benzyl
BnBr	benzylbromide
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
COD	cyclooctadienyl
Cp	cyclopentadienyl
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEMS	diethoxymethylsilane
Dess-Martin	Dess-Martin periodinane
DIBALH	diisobutyl aluminum hydride

DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMM	dimethoxymethane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
dpe-phos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
dppe	1,2-bis(diphenylphosphino)ethane
ee	enantiomeric excess
Et	ethyl
Et_2O	diethyl ether
equiv.	equivalent
ESI	electrospray ionization
EtOAc	ethyl acetate
FT	Fourier transform
G-II	Grubb's second generation catalyst
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HSV	herpes simplex virus
i-Am	*iso*-amyl
i-PrOH	isopropyl alcohol
IBX	2-iodoxybenzoic acid
Im	imidazole
IR	infrared spectrometry
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m-CPBA	*meta*-chloroperbenzoic acid

Me	methyl
MeCN	acetonitrile
MeOH	methanol
[MOEMIM]Ms	1-methoxyethyl-3-methylimidazolium mesylate
MOMCl	methyloxymethyl chloride
MS	mass spectrometry
MsCl	methylsulfonyl chloride (mesyl chloride)
NBS	*N*-bromosuccine imide
NHC	*N*-heterocyclic carbene
NME	*N*-methylephedrine
NMO	*N*-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
OCP	*orto*-chlorophenyl
Oxone	potassium peroxymonosulfate
p-TsOH	*para*-toluenesulfonic acid
PBP	*para*-bromophenyl
PCC	pyridinium chlorochromate
PCP	*para*-chlorophenyl
PDC	pyridinium dichromate
PFP	*para*-fluorophenyl
Ph	phenyl
Ph-Box	(*S,S*)-2,2′-methylenebis(4-phenyl-2-oxazoline)
Piv	pivaloyl
PMB	*para*-methoxybenzyl
pmdb	*para*-methoxybenzylidene
pmdba	*para*-methoxybenzylideneacetone
PMP	*para*-methoxyphenyl
PNO	pyridine-*N*-oxide
PNP	*para*-nitrophenyl
PPL	porcine pancreatic lipase

ppm	parts per million
PPTS	pyridinium *para*-toluene sulfonate
Pr	propyl
PTFP	*para*-trifluorophenyl
Py	pyridine
RB	Rose Bengal
RML	*rhizomucor miehei* lipase
RT	room temperature
SEMCl	2-trimethylsilylethyoxymethyl chloride
Sia_2BH	disiamylborane
SiO_2	silica gel
t-BuOH	*tert*-butanol
(*S*)-*t*-BuPhox	(*S*)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenylsilyl difluoride
TBDMS	*tert*-butyl dimethylsilyl
TBDMSOTf	*tert*-butyldimethylsilyl triflate
TBHP	*tert*-butyl hydroperoxide
TEA	triethylamine
TES	triethylsilyl
TFA	trifluoro acetic acid
TFAA	trifluoro acetic acid anhydride
TfO	triflate (trifluoromethylsulfonate)
THF	tetrahydrofuran
$Ti(O\textit{i}\text{-}Pr)_4$	titanium isopropoxide
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
Trisyl	triisopropylbenzenesulfonyl
VLA-4	Very Late Antigen 4

Introduction

Cyclopentane moiety is an integral part of many naturally occurring and synthetic structures which bear interesting biological properties. For example, these cyclopentane derivatives include antiviral carbocyclic nucleoside analogues[1–6] (Figure 1), antibiotics,[7] tumor necrosis factor-α inhibiting agents[8] and anti-cancer agents,[9–11] prostaglandins and their analogues,[12–14] phyto-[15] and isoprostanes[16] as local hormones and rhetrolones as natural pesticides,[17,18] cyclopentanols as neurokinin-1 inhibitors,[19] glycosidase inhibitors[20] and natural lipid analogues.[21–25]

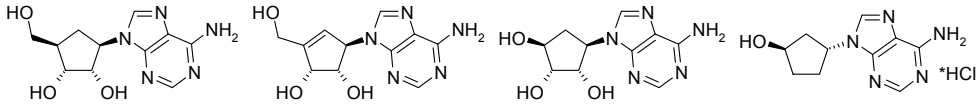


Figure 1. Some examples of carbocyclic nucleoside analogues

Furthermore, many sesquiterpenic compounds found in nature contain alkyl-branched cyclopentanoic motifs in their structures[26–29] (Figure 2).

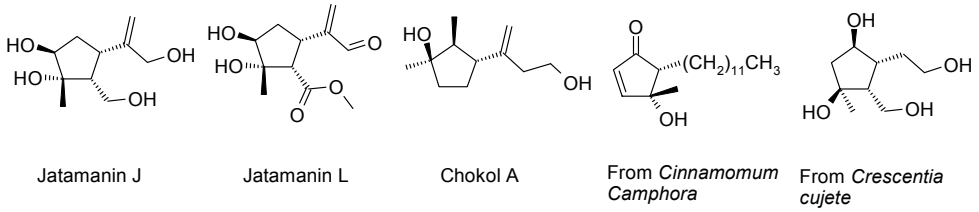


Figure 2. Some naturally occurring sesquiterpenes

The importance of the cyclopentane motif in nature, as mentioned above, has inspired scientists to pursue the synthetic methods of those structures. Therefore, the synthesis of differently substituted cyclopentanes and pentofuranose carba-analogues has generated considerable interest in the last few decades.[30–32] Among others, there have been several publications on methods for stereoselective and stereocontrolled synthesis of these structures.[33–35]

No less intriguing are the compounds containing tetrahydrofuran structural elements, which are essential parts of many naturally occurring compounds: communiols,[36] acetogenins,[37,38] polycyclic marine toxins,[39–41] lignans[42] etc. Furthermore, alkylbranched natural compounds, such as leiodolides,[43] pectenotoxins,[44] davana acid, davanone,[45] (-)-isocyclocapitelline,[46] (-)-isochrysotricine[46] and polycyclic ethers,[47] also exhibit interesting biological properties (Figure 3). More specifically, the derivatives of 2,2-disubstituted tetrahydrofurans have received attention as anti-

tumor agents[48] and potent VLA-4 antagonists,[49,50] for the treatment of various VLA-4 dependent inflammatory diseases, such as asthma, multiplex sclerosis and arthritis (Figure 4). A small unique class of compounds comprised of variously substituted 1,7-dioxaspiro[4.4]nonane (spiroditetrahydrofuran) skeletons also exists in nature, inspiring the synthetic community to find methods for the synthesis of spironucleosides[51]: prehispanolones,[52] leopersins,[53] syringolides[54] and fructose-derived molecular scaffolds.[55]

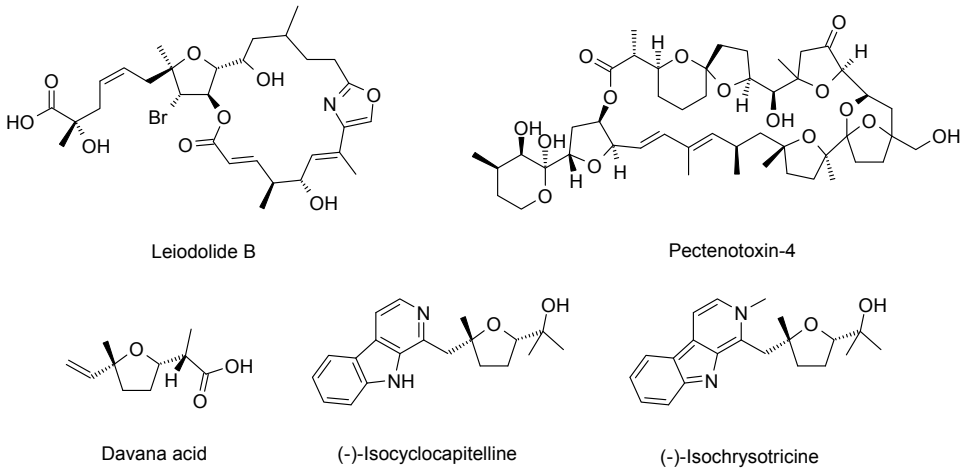


Figure 3. THF-derivatives bearing quaternary centers found in nature

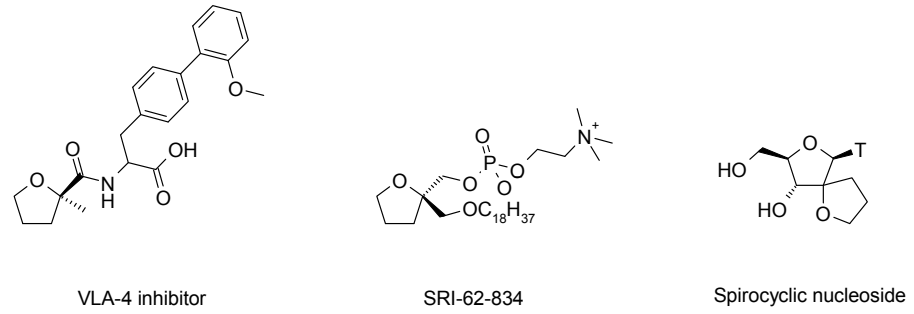


Figure 4. Some drug-like THF-derivatives

For synthetic chemists, various cyclopentane derivatives and tetrahydrofurans have been, and continue to be, interesting and challenging synthetic targets: many diastereoselective[56–59] and enantiospecific[16,60] methods for synthesizing differently substituted tetrahydrofurans have been developed in recent years. Even the relatively rare 1,7-dioxaspiro[4.4]nonane framework has been synthesized by various methods.[61–63] However, only a few methods exist to obtain chiral 2,2-disubstituted tetrahydrofuran derivatives.[64–67]

In the present work, the possibilities of synthesizing alkylbranched cyclopentane and tetrahydrofuran derivatives are examined. The synthesis of the cyclopentane derivative is presented in Articles I and III. Article I deals mainly with the asymmetric synthesis and the stereochemistry of dihydroxy cyclopentanones, and Article III deals with the diastereoselective synthesis of polyhydroxylated cyclopentanes. In Article II, we report a convenient method for obtaining several novel chiral tetrahydrofurans from the corresponding lactones.

1. Literature overview

1.1. Cyclopentane derivatives. Synthetic methods

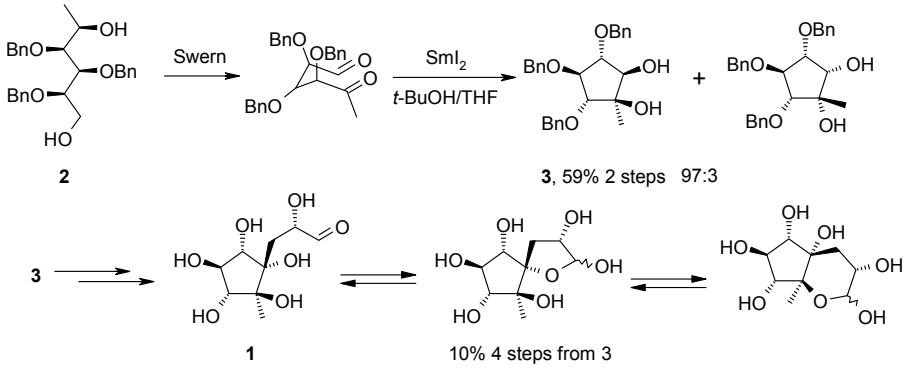
Synthetic methods for accessing polyhydroxy cyclopentanes and cyclopentanones can be divided roughly into four categories: methods that rely on natural chiral compounds,[63,68–73] enzymatic processes[34,74–77] or asymmetric synthesis[78–82] to establish stereogenic centers, and those that do not lead to chiral products, although they usually involve diastereo- or regioselectivity.[83–85] As the number of synthetic methods for yielding oxo- and/or hydroxyl-substituted cyclopentanes is too voluminous to cover fully, the focus is on methods leading to alkylbranched cyclopentanol and cyclopentanone derivatives.

1.2. Enantiomeric cyclopentane derivatives

1.2.1 Starting from a chiral pool

Naturally occurring compounds have been widely used in organic synthesis as starting material and often lend a stereogenic unit to the target molecule.

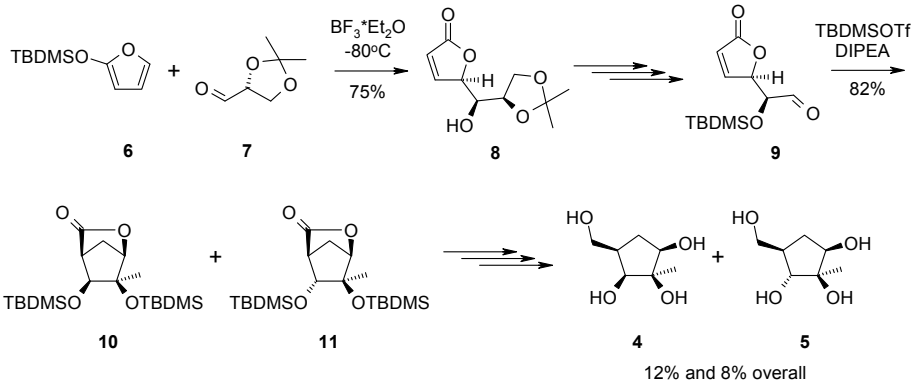
In the synthesis of naturally occurring carbocyclic sugar analogue caryose, **1** Adinolfi *et al.*[86] used 3,4,5-tri-*O*-benzyl-1-deoxy-D-iditol 2 as starting material and SmI_2 mediated cyclization as the key reaction to obtain the cyclopentane core structure **3** (Scheme 1). Further transformations led to a caryose **1** as a mixture of hemiacetals.



Scheme 1. Total synthesis of caryose

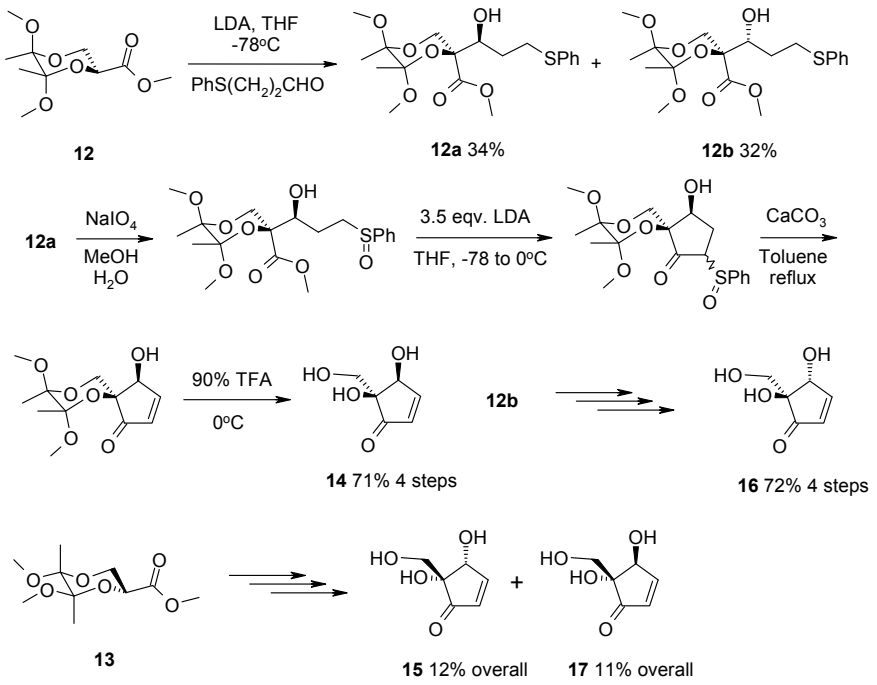
Another relevant example using a chiral pool was developed by Rassu *et al.*[35] The synthesis of carbafuranoses **4** and **5** started with a cross-aldol reaction between 2-[(*tert*-butyldimethylsilyl)oxy]furan **6** and D-glyceraldehyde acetonide **7**, catalyzed by Lewis acid (Scheme 2). The obtained lactone **8** was further elaborated to the

prerequisite aldehyde **9** in four steps to afford bicyclo[2.2.1]heptane derivatives **10** and **11** byTBDMSOTf/DIPEA-mediated intramolecular aldol reaction. Subsequent transformations gave *cis*-compound **4** and *trans*-compound **5**.



Scheme 2. Rassu's synthesis of alkyl-branched carbasugars

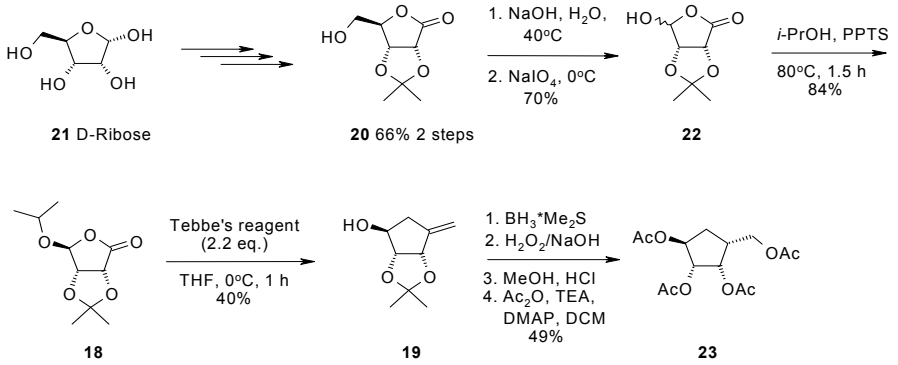
Relying on the chiral building blocks **12** and **13** of Ley *et al.,*[87] a novel route to the naturally occurring antibiotic (-)-pentenomycin **14**,[88] its enantiomer **15** and epimers **16** and **17** was devised by Pohmakotr *et al.* (Scheme 3).[89]



Scheme 3. Pohmakotr's synthesis of (-)-pentenomycin

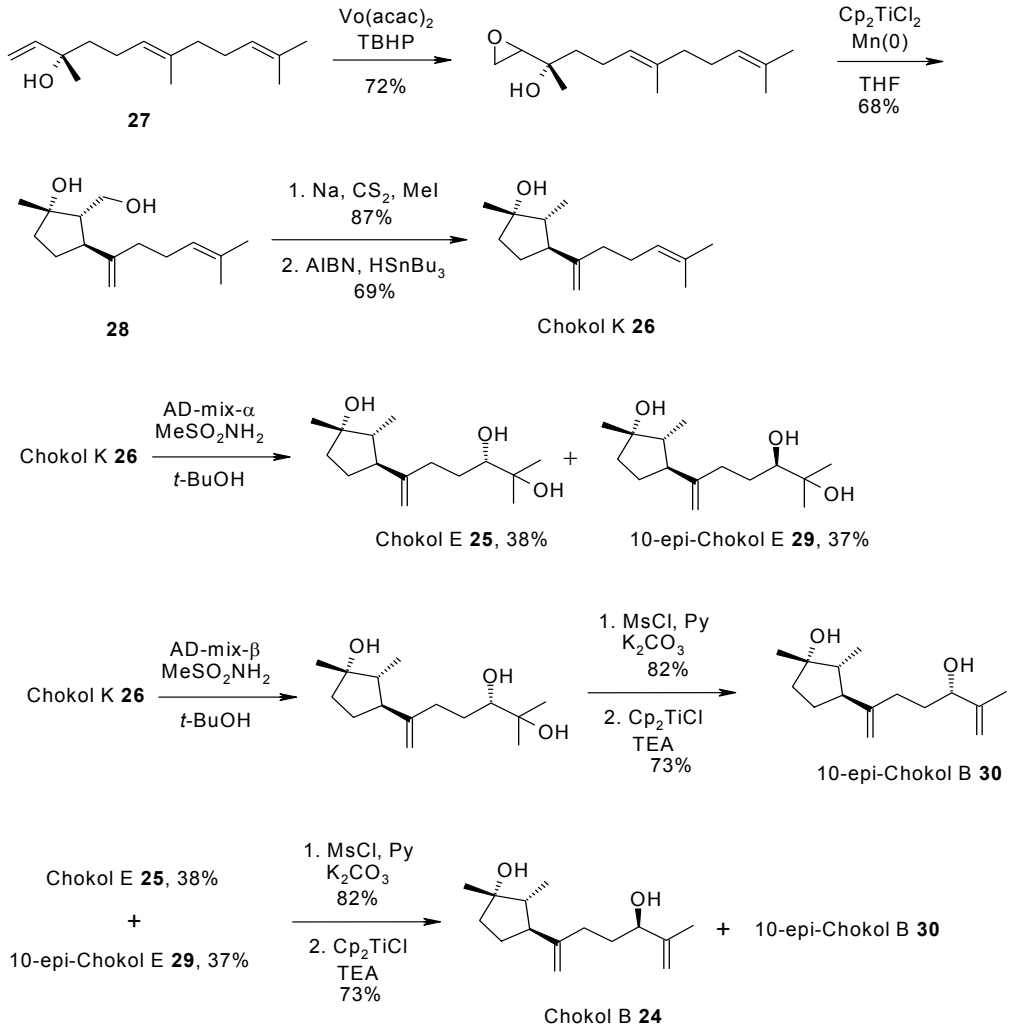
Although the synthesis featured low diastereoselectivity (1:1) at the secondary hydroxyl group, it allowed for the synthesizing of 3-epipentenomycin **16**, *ent*-pentenomycin **15** and *ent*-epipentenomycin **17**, according to a general reaction sequence.

A successful use of Tebbe's reagent in the cyclization of lactone **18** to cyclopentane **19** was reported by Rao *et al.*[90] (Scheme 4). Ribonolactone **20** was synthesized starting with D-ribose **21**.[91,92] Subsequent demethylation was achieved by basic hydrolysis and the oxidative cleavage of the formed *vic*-diol by $NaIO_4$, resulting in lactone acetal **22**. *Anti*-Isopropylacetal **18** was obtained stereoselectively under acidic catalysis and the key transformation was carried out with Tebbe's reagent, to afford a cyclopentane core structure **19**. This compound was further converted to the final product **23** by a hydroboration, deprotection and acetylation sequence.



Scheme 4. Tebbe's reagent in cyclization

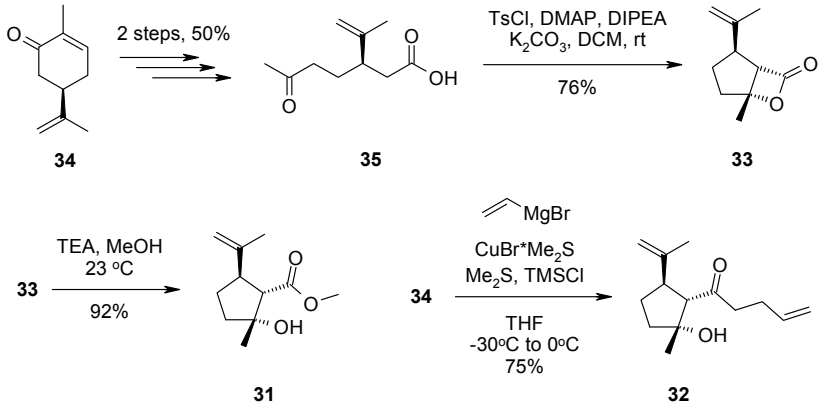
Barreros' synthesis of Chokol B **24**, E **25** and K **26** started with commercially available (+)-nerolidol **27** (Scheme 5).[93] An attempted radical oxirane opening cyclization reaction led to a mixture of six different compounds, while the use of a catalytic amount of Cp_2TiCl_2 resulted in only two major products. They concluded that Ti-complex was the main driving force of diastereoselectivity. The best results were obtained using two equivalents of TEA. The synthesis of Chokols B **24**, E **25** and K **26** started with an epoxidation of (+)-nerolidol **27** by using vanadium catalysis, followed by cyclization to afford a cyclopentane derivative **28**. Further derivatization with CS_2 and subsequent radical reduction with Bu_3SnH gave Chokol K **26** in 29% overall yield. Chokol E **25** was obtained from Chokol K **26**, together with its 10 epimer **29** *via* dihydroxylation with AD-mix-α.



Scheme 5. Synthesis of Chokols B, E and K

Chokol K **26** was also used as the starting material for the synthesis of C-10-epi-Chokol B **30** over a three-step sequence involving the use of AD-mix-β, epoxidation over mesylate and a Ti(III) catalyzed epoxide opening-elimination reaction. A mixture of Chokol E **25** and epi-Chokol E **29** underwent an epoxidation and epoxide opening sequence to afford Chokol B **24** as a 1:1 mixture of its epi-congener **30**.

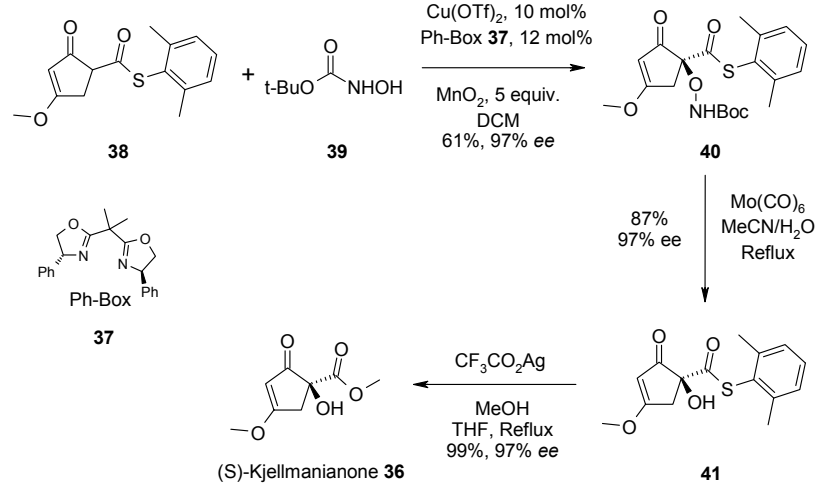
Cyclopentanols **31** and **32** were synthesized *via* the key intermediate β-lactone **33**, which was obtained by an intramolecular diastereoselective aldol reaction of *(R)*-carvone **34** derived oxo-acid **35** by Romo's group (Scheme 6).[94] The overall yield was good for both cyclopentanol derivatives: 34% for **31** and 28% for **32**.



Scheme 6. Cyclopentane derivative by intramolecular aldol reaction

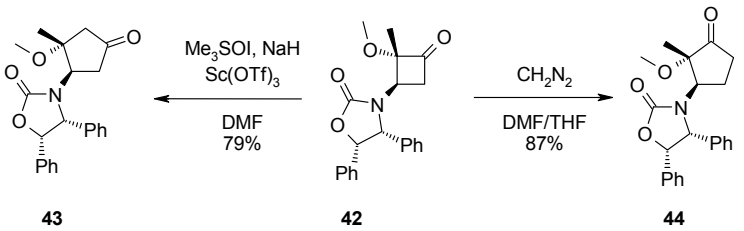
1.2.2 Asymmetric synthesis

A recent example of asymmetric (S)-Kjellmanianone **36**[95] synthesis was reported by Yamamoto (Scheme 7), who used a chiral Ph-Box ligand **37** and $Cu(OTf)_2$ to facilitate a **38** derived enolate addition to the N-nitrosocarbonyl compound **39** as the key step. Intermediate **40** was obtained in high *ee* (97%). The sequence was completed by the cleavage of the O-N bond with $Mo(CO)_6$ and the transesterification of **41** with MeOH.



Scheme 7. Synthesis of Kjellmanianone

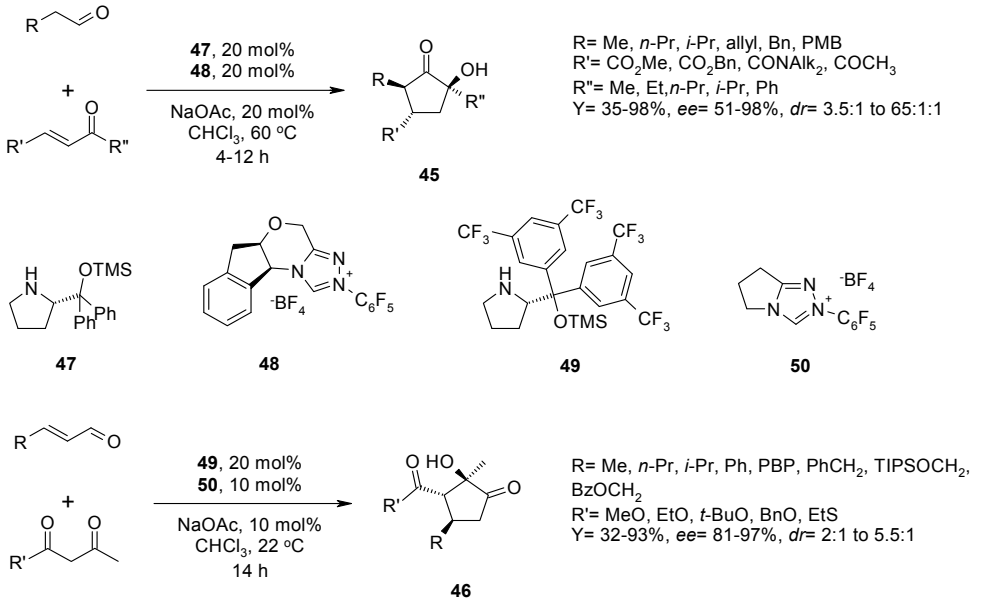
A review of the ring expansion reactions to afford cyclopentane derivatives has recently been published.[96] Especially relevant, in our opinion, is the method of ring expansion of cyclobutanones **42** developed by Hegedus *et al.*, [97–99] leading directly to regioisomeric methyl-susbstituted hydroxyl-cyclopentanones **43** and **44** (Scheme 8).



Scheme 8. Regioselective ring expansion reaction

β-Substitution to the oxo-group has been extensively studied, leading to the formation of 2,3-disubstituted cyclopentanone **44** when diazomethane was used. To obtain 3,4-substituted cyclopentanones **43**, an epoxide rearrangement was used. In both cases, the relative configuration was inherited from cyclobutanone synthesis. In the case of chiral oxazolidinone substituent at the β-position, high asymmetric induction was observed (97% ee).

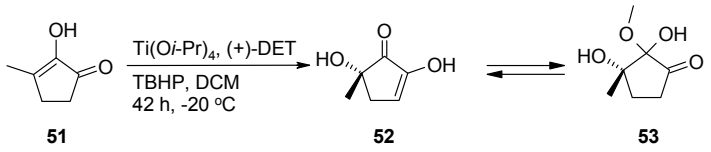
Cascade reactions can provide easy access to complex compounds, e.g. in the organocatalytic cyclization reported by the Rovis group (Scheme 9).[100,101] The Michael addition aldol reaction sequence led to 2,2,4,5-substituted **45** and to 2,2,3,4-substituted cyclopentanones **46** catalyzed by **47**, **48, 49** and **50** catalyst pairs, respectively. The substrate scope was wide (15 examples for 2,2,4,5-substituted cyclopentanones **45** and 16 examples for 2,2,3,4-substituted cyclopentanones **46**).



Scheme 9. NHC catalyzed cyclization of Michael adducts to cyclopentanones

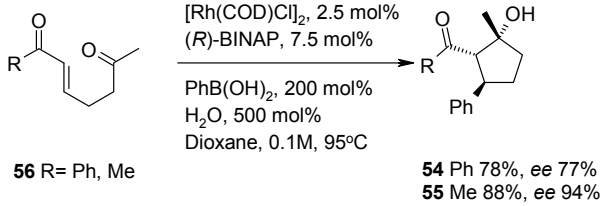
In our laboratory, a method for the asymmetric oxidation of 3-alkyl-1,2-diketones **51** with a Ti(O*i*-Pr)$_4$-tartaric ester-TBHP complex, affording 3-hydroxylated 3-alkyl diketones **52** in high enantiomeric purity has been developed[102] (). Commercially available diketone **51** was subjected to oxidation with TBHP in the presence of a

Ti(O*i*-Pr)$_4$/(+)-DET complex. Chiral tertiary hydroxydiketone **52** in a mixture with its hemiacetal **53** was obtained.



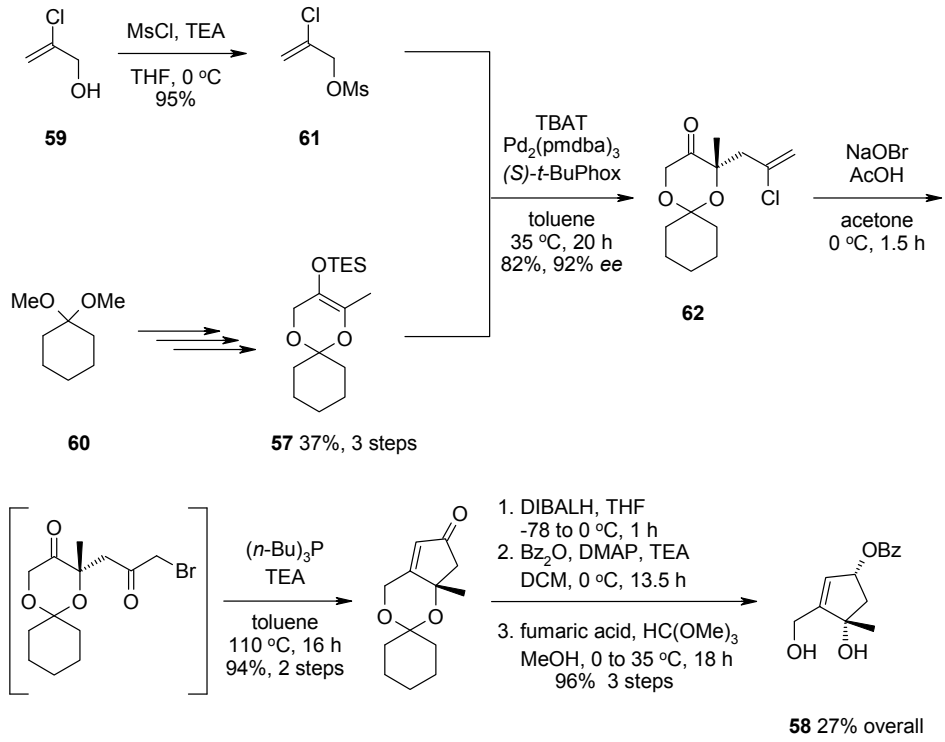
Scheme 10. Asymmetric oxidation with Ti(OiPr)$_4$-tartaric ester complex

Cauble *et al*.[103] have reported a highly diastereoselective and enantioselective method for the synthesis of aryl-substituted methyl-branched cyclopentanols **54** and **55** *via* an Rh(I) catalyzed one-pot conjugate addition aldol reaction sequence (Scheme 11). While high diastereoselectivity was observed in all cases, a good enantioselectivity was observed only with methylketone **56** as a substrate.



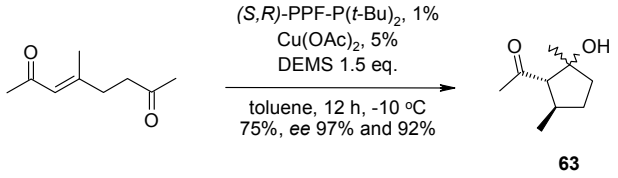
Scheme 11. One-pot conjugate addition aldol reaction

An asymmetric palladium-catalyzed alkylation of enone **57** was developed for cyclopentenol **58** by Stoltz *et al.* (Scheme 12).[104] The synthesis started with the commercially available compounds **59** and **60**. The intermediate **57** was alkylated with **61** under mild conditions to afford **62** in good yield (82%) and enantioselectivity (92%). Cyclization, reduction of the oxo-group, benzoylation and removal of the cyclohexylidene group gave a chiral building block **58**.



Scheme 12. Craig's approach to cyclopentenediol

A CuH catalyzed asymmetric conjugate addition aldol reaction was used to construct three stereogenic centers to a cyclopentane derivative **63** in good enantio- but poor diastereoselectivity[105] (Scheme 13). The substrate scope was limited to one example for cyclopentanes, although 10 examples for cyclohexane derivatives with excellent diastereo- and good enantioselectivity were presented.



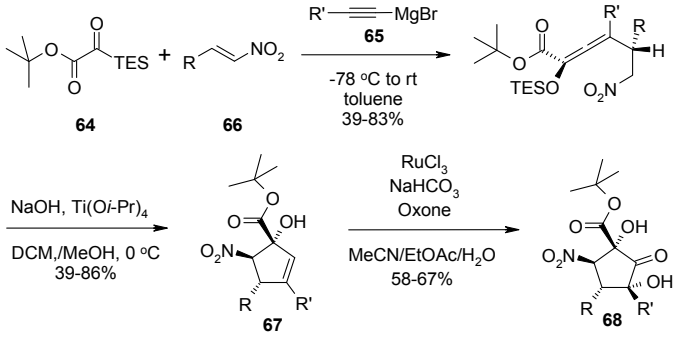
63

Scheme 13. CuH catalyzed conjugate addition aldol sequence.

1.3. Racemic cyclopentane derivatives

Boyce's synthesis of nitrocyclopentanones (Scheme 14) *via* a three-component coupling of silyl glyoxylates **64**, acetylide nucleophiles **65** and nitroalkenes **66**, a subsequent Ti(O*i*-Pr)$_4$ catalyzed cyclization to cyclopentane **67** and a $RuCl_3$ mediated oxidation of double bond to α-hydroxy ketone **68** proceeded with good diastereoselectivity.[83] In the latter reaction, the substrate scope was limited only to three different substitution patterns, although the observed diastereomeric ratio was

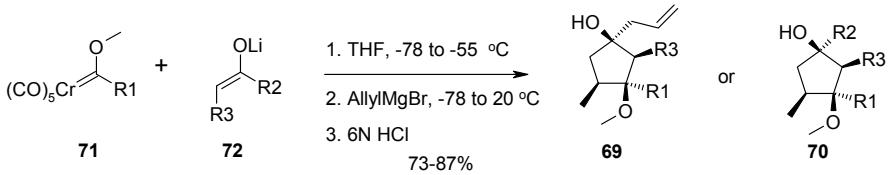
in line with the previous two steps (*dr* >20:1), and the overall yields were good (23-42%, three steps). A significant decline in yields was observed (42-56% *vs.* 67-83% for one step and 39-57% *vs.* 60-86%), when the R-group was comprised of alkyl chains (C_5H_{11} or *i*-Pr) instead of aryl groups (Ph, thienyl, furyl).



In **68** R'= Me and R= Ph, 2-thienyl or 2-furyl

Scheme 14. Three-component reaction to construct a cyclopentane core

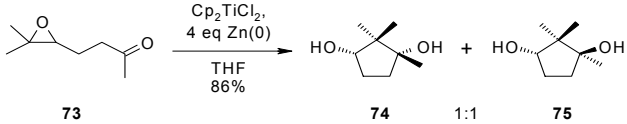
Another example of a multicomponent reaction to yield cyclopentanols **69** and **70** is the Fischer carbene **71** reaction with lithium enolates **72** and Grignard reagent (Scheme 15).[84] The reaction proceeded with good diastereoselectivity, though an additional equivalent of Grignard reagent was needed in the case of R_2= MeO to form an allyl-substituted cyclopentane derivative.



69: R1= 2-furyl, 2-naphtyl, cyclopentyl; R2= MeO; R3= Me
70: R1= Ph; R2= Et; R3= Me
R1= 2-naphtyl; R2, R3= $(CH_2)_4$

Scheme 15. Multicomponent reaction using Fischer carbenes

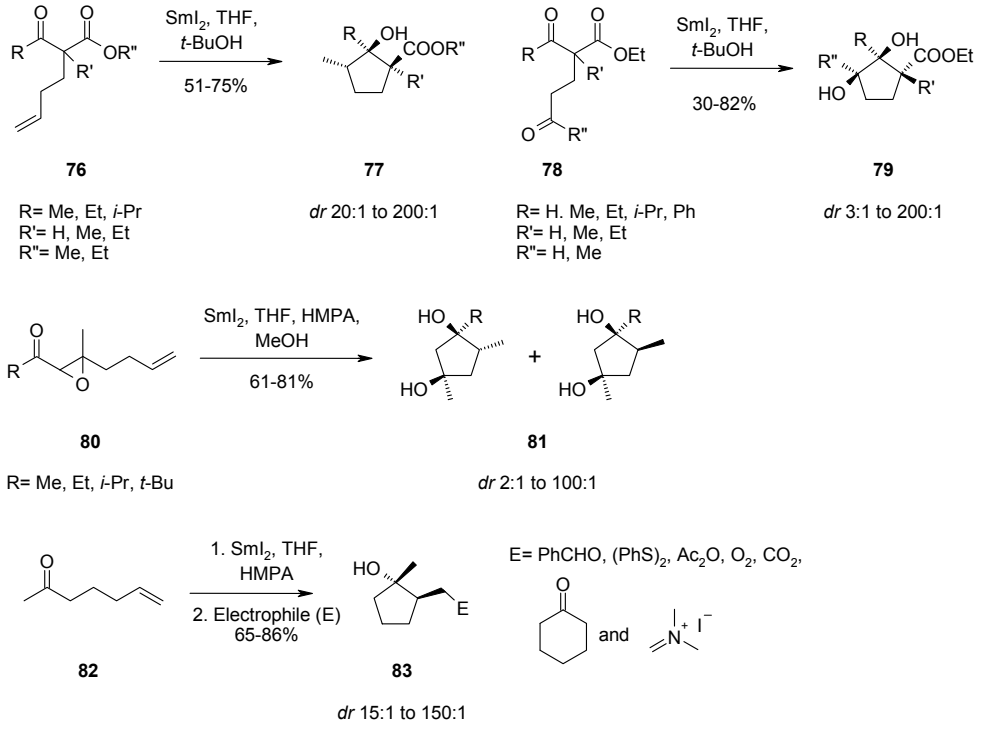
Ti(III) induced a regioselective opening of oxirane in **73** and the subsequent addition to the oxo-group led to the formation of methyl substituted cyclopentanediols **74** and **75** with good yield but with low diastereoselectivity, reaching a 4:1 ratio at best (Scheme 16).[106] The only exceptions were in the case of cyclopropane and cyclobutane formation (from ketone), although the latter was accompanied by a substantial amount of β-elimination (64%).



Scheme 16. Radical induced epoxide opening

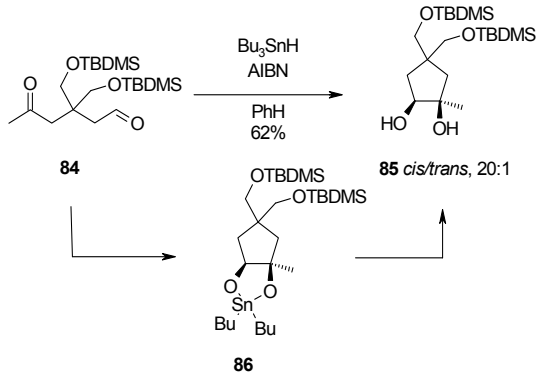
SmI_2-induced reductive radical intramolecular coupling reactions produced different cyclopentane derivatives (Scheme 17).[107–109] In all reactions, the first formation of an

active ketyl radical occurred, which then reacted with the appropriate functional group. Thus, β-oxoesters with an olefinic side chain **76** reacted in the presence of SmI_2 to provide 2'-hydroxy-cyclopentane carboxylic acid esters **77** in good yield (51-75%) and high diastereoselectivity (*dr* 20:1 to 200:1). When the side chain contained an oxo-group (compound **78**), *cis*-oriented *vic*-diols **79** were formed. An oxo group in the side chain in conjunction with β-keto functionality failed to afford diastereoselectivity above 3:1 *dr* and good yield. A similar effect had hydrogen substitution at the α-position to the ester group (*dr* 5:2). In the case of epoxide **80**, the oxirane opening followed by cyclization resulted in *cis*-1,3-cyclopentanediols **81** (*dr* 2:1 to 100:1). Oxo-olefin **82** afforded diastereoselectively 1,2-disubstituted cyclopentanols **83** (*dr* 15:1 to 150:1). The lower diastereoselectivity of *t*-Bu-substituted epoxides **80** can be attributed to the steric effects.



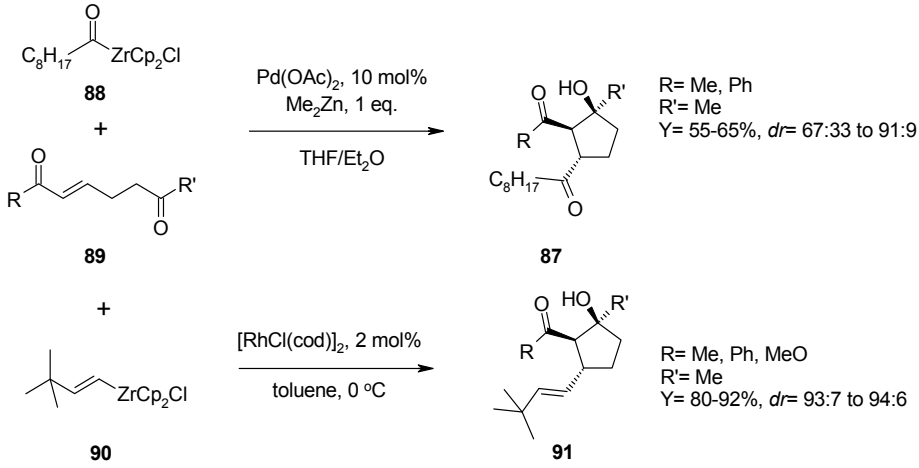
Scheme 17. SmI_2 in reductive cyclization

A tin-mediated radical reductive cyclization of ketoaldehyde **84** to cyclopentanediol **85** was reported (Scheme 18).[110] Although acceptable yields (46-64%) and diastereoselectivities (*dr* 20:1 to 99:1) were reported for cyclopentane derivatives, less rigid cyclohexane derivatives led to a higher yield (84-95%), but lower diastereoselectivity (*dr* 1:1.6 to 2.1:1). The latter was thought to depend on the formation of intermediate 1,3-dioxa-2-stannolane **86**, which should preferably give a less strained [3.3.0]bicyclic system **86** and *cis*-product.



Scheme 18. Tin mediated pinacol coupling

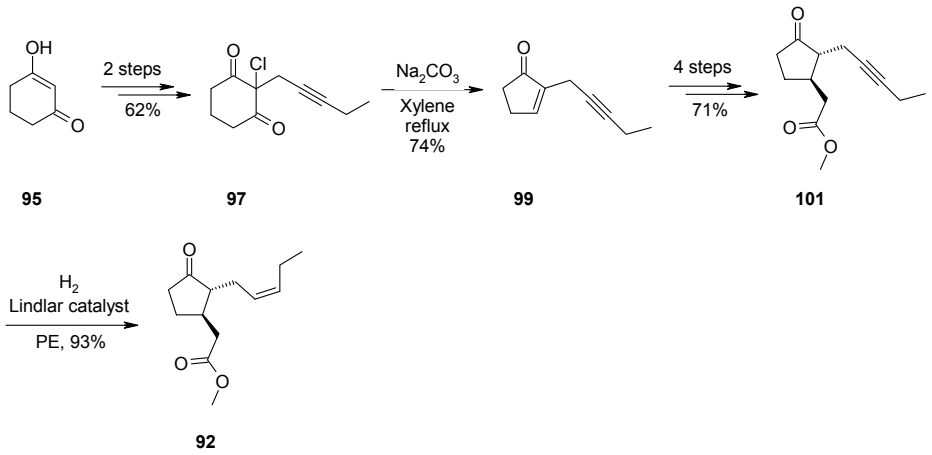
According to Hanzawa *et al.* 1,2,3-substituted cyclopentanols **87** were obtained by a Pd(II)-catalyzed (accelerated by Zn(II) additive) 1,4-addition of acylzirconocene **88** to conjugated ketones **89**, followed by an intramolecular aldol reaction, in 55-65% yield and fair diastereoselectivity (*dr* 67:33 to 91:9, Scheme 19).[111] The assistance of Zn in the enolate formation was predicted. A more efficient Rh(I)-catalyzed 1,4-addition/ aldol reaction with vinylzirconocene **90** and ketone **89**, affording higher yields (80-92%) and better diastereoselectivity (*dr* 93:7 to 94:6) for vinylsubstituted cyclopentanols **91** was reported by the same group.[112]



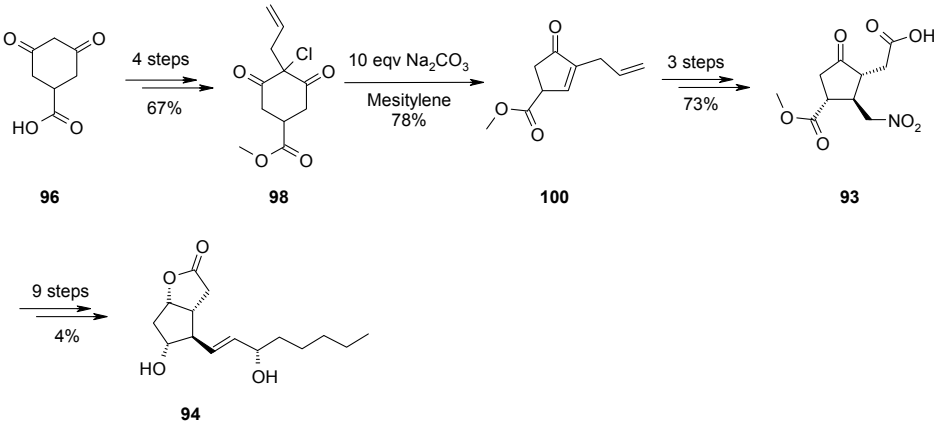
Scheme 19. Pd(II) and Rh(I) catalyzed 1,4-addition-cyclization reactions

A Favorskii-type ring contraction reaction, first described by Büchi and Egger[113] in their synthesis of methyl jasmonate **92** (Scheme 20), was used to synthesize a nitromethyl substituted cyclopentanone intermediate **93** by Kienzle *et al.*[114] (Scheme 21). This approach was further elaborated to a prostaglandins intermediate **94** by the same group. In both cases, a straightforward functionalization of suitable 1,3-diketones **95** and **96** to 2-chloro derivatives **97** and **98** was used as a starting point (62% for two steps and 67% for four steps, respectively). The ring contraction was effected smoothly in the presence of an inorganic base to furnish cyclopentenones

99 and **100**. Further derivatization by conjugate addition gave cyclopentanones **101** and **93** in a diastereoselective manner in good overall efficiency.

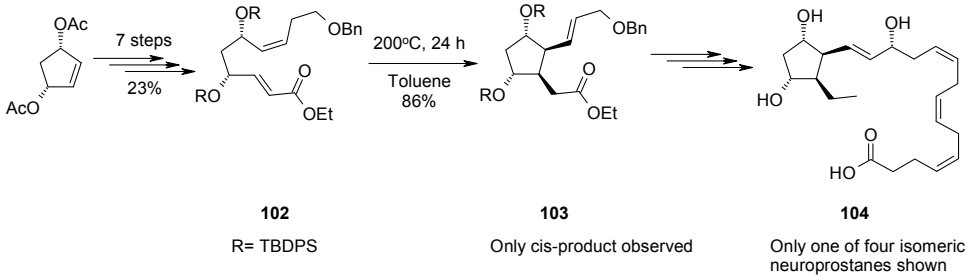


Scheme 20. Büchi synthesis of methyl jasmonate



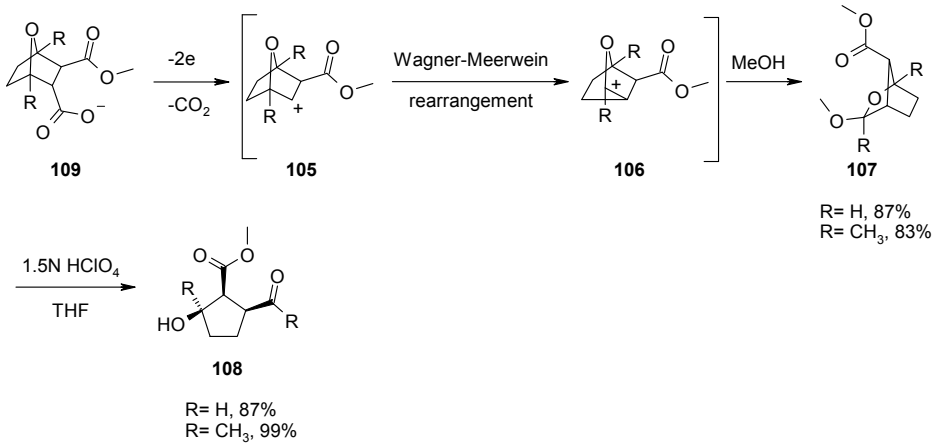
Scheme 21. Kienzles synthesis of racemic prostaglandin intermediate

Taber *et al.* used a thermal cyclization of suitably substituted dialkene **102**, obtaining the intermediate cyclopentane scaffold **103** in 86% yield and with high diastereospecificity, in their synthesis of target neuroprostanes **104** (Scheme 22).[115]



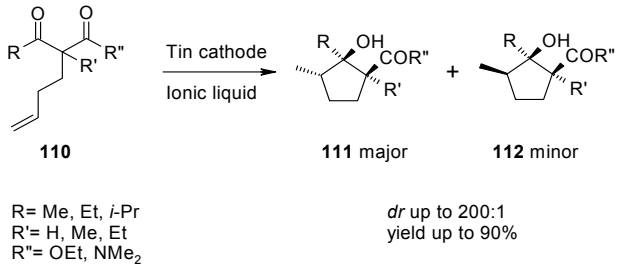
Scheme 22. Neuroprostane intermediate by thermal cyclization

Electrochemistry has been applied to the synthesis of various substituted cyclopentanes by Akiyama *et al.*[116] They reported the electrolytic formation of the cation **105** in MeOH at the carbon anode in the presence of Na. This cation rearranged to a 2-oxabicyclo[2.2.1]heptane cation **106**, which was trapped by MeOH. They obtained bicyclic intermediate **107**, which upon acidic hydrolysis gave cyclopentane derivative **108** in good yield (Scheme 23). Unfortunately, the yields for the Diels-Alder reaction leading to the compound **109** were not reported, and thus the efficiency of the process remains unclear.



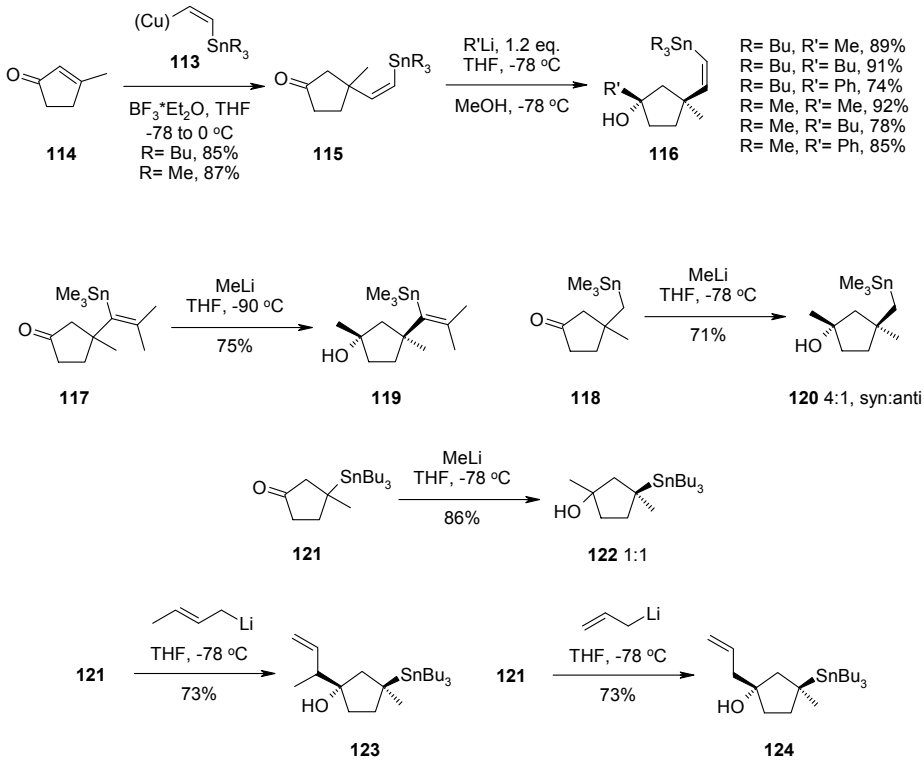
Scheme 23. Electrochemically induced Wagner-Meerwein shift

More recently, an electroreductive cyclization reaction in an ionic liquid media was presented by Yadav's group (Scheme 24).[117] β-ketoesters and -amides **110** were cyclized in a mixture of [MOEMIM]Ms-isopropanol (9:1) at a tin cathode to obtain the desired products **111** and **112** in 75-90% yield and with diastereoselectivities ranging from 80:1 to 200:1.



Scheme 24. Electroreductive cyclization in an ionic liquid

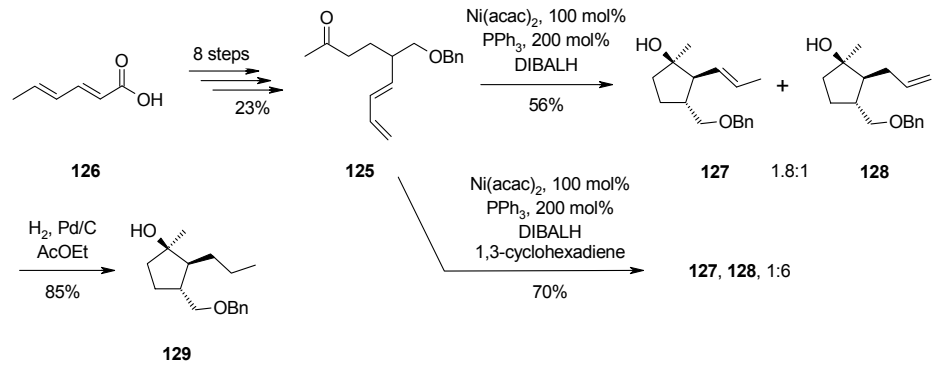
A unique tin-regulated diastereoselective addition of alkyllithiums to a carbonyl group was observed by Barbero *et al.*[118] The substrates for alkylation were synthesized by the conjugate addition of (Z)-2-(trialkylstannyl)vinyl cyanocuprates **113** to 3-methylcyclopent-2-en-1-one **114** in high yield (Scheme 25).



Scheme 25. Tin as a diastereoselectivity inducer

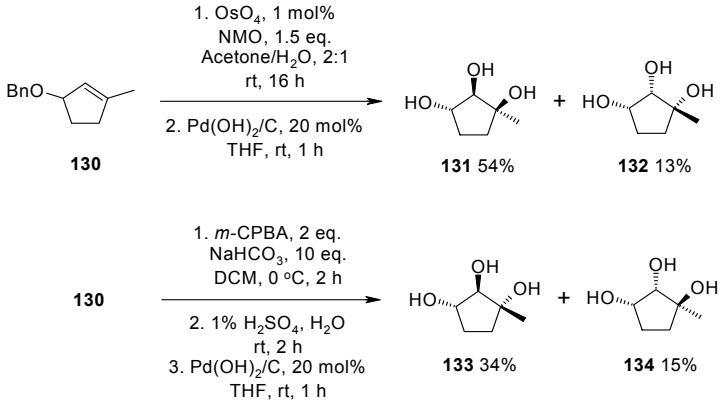
They found that diastereoselectivity was dependent on the distance of the tin atom from the carbonyl group, and on the type of alkyllithium compound. The tin atom at the δ-position **115** gave a fully diastereoselective outcome of **116**, whereas the tin atom at the γ-position (in **117** and **118**) led to full diastereocontrol with isobutene substituent (compound **119**) and to diminished diastereocontrol (4:1, *syn/anti*) with a methylene group (compound **120**). Substrates with a β-tin atom (**121**) exerted no diastereoselectivity in the case of the methyllithium reagent **122**, whereas the reaction with allyllithium gave only one diastereomer (compounds **123** or **124**).

Sato *et al.*[119] pursued a Ni catalyzed cyclization of oxo-olefins **125** (Scheme 26). Most of the substrates (four out of five) were synthesized starting with sorbic acid **126** in six to nine steps. They always observed a *syn* configuration for the hydroxyl group and alkene substituent, and *anti* for the hydroxyl group and benzyloxymethyl substituent. Furthermore, it was discovered that 1,3-cyclohexadiene as an additive reversed the regioselectivity for exocyclic double bond formation from 1.8:1 (internal/terminal) to 1:6 (internal/terminal) in favor of the terminal alkene. The overall yield was 13% for alkenes **127** and **128,** and 11% for cyclopentane **129**.



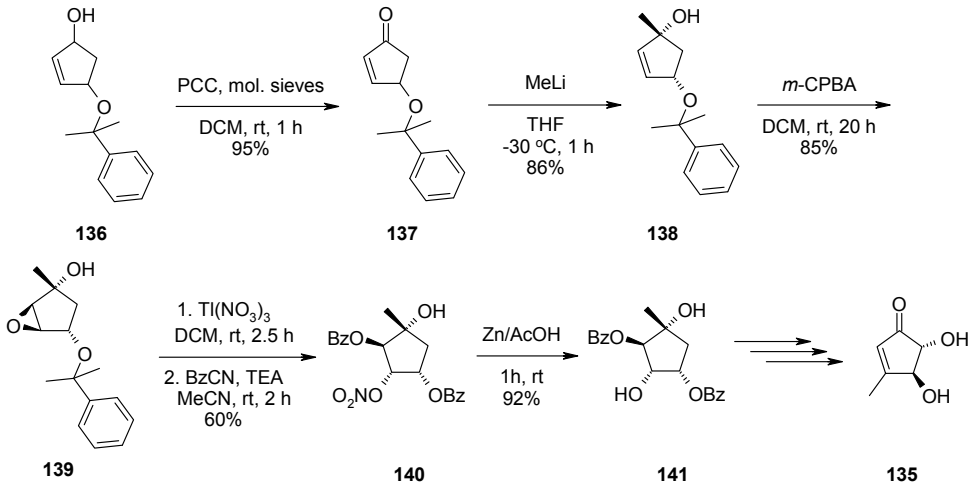
Scheme 26. Ni catalyzed cyclization of oxo-diene

Janda *et al.*[120] have synthesised the relevant cyclopentanols (Scheme 27), starting with benzylprotected cyclopentane **130**, which was reacted with OsO_4 or *m*-CPBA to afford diastereomeric cyclopentane-triols **131, 132, 133 and 134** after deprotection respectively in 13-54% overall yield.



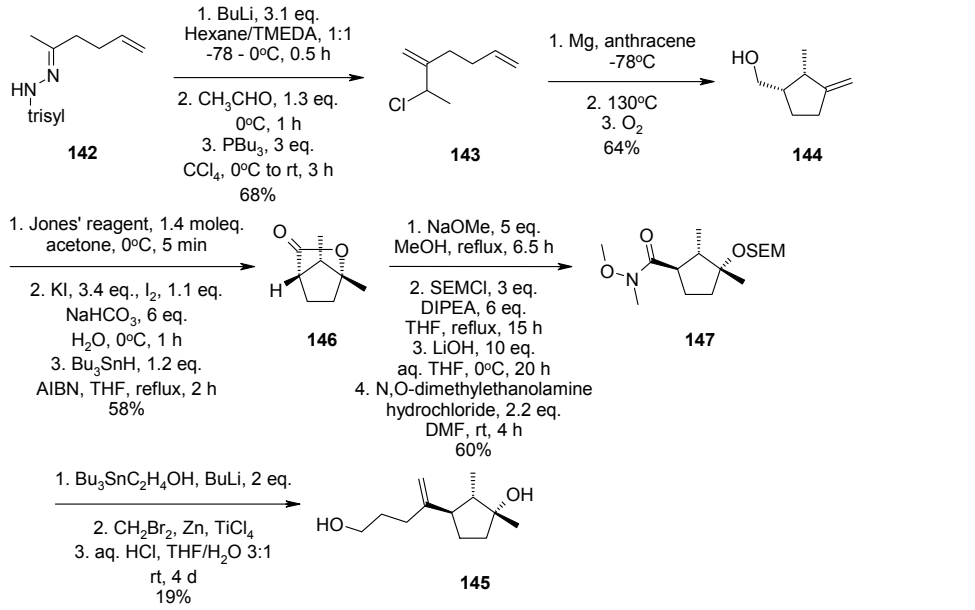
Scheme 27. Short synthesis of racemic cyclopentanetriols

A route to a C-ring fragment of Trichothecenes **135** developed by Hua and Venkataraman featured three consecutive diastereoselective transformations after the oxidation of a readily available cumene-protected cyclopentene-diol **136**:[121] alkylation of ketone **137** with MeLi afforded *anti*-product **138**, the subsequent epoxidation with *m*-CPBA afforded **139** and the epoxide opening with $Tl(NO_3)_3$ afforded nitrate-compound **140** (Scheme 28). The latter was reduced by Zn/AcOH to obtain the compound **141** in 38% overall yield.



Scheme 28. Synthetic route to a C-ring fragment of Trichothecenes

Oppolzer *et al.* have used a Mg-ene reaction of hydrazone **142** derived chloroalkene **143** to construct a cyclopentane core **144** with *cis*-configuration in the synthesis of (±)-Chokol A **145** (Scheme 29).[122] A subsequent Jones oxidation and iodolactonization, followed by a tin hydride promoted reduction, gave oxabicyclo[2.2.1.]heptane derivative **146** in 58% yield. Isomerization at the C-3 position was carried out in a methanolic solution of NaOMe. The hydroxyl group was protected with SEM-Cl, and the ester was saponified with LiOH and then reacted with N,O-dimethyl-ethanolamine hydrochloride to afford intermediate **147** (60% from **146**), followed by conversion to (±)-Chokol A **145** in 4.7% overall yield.



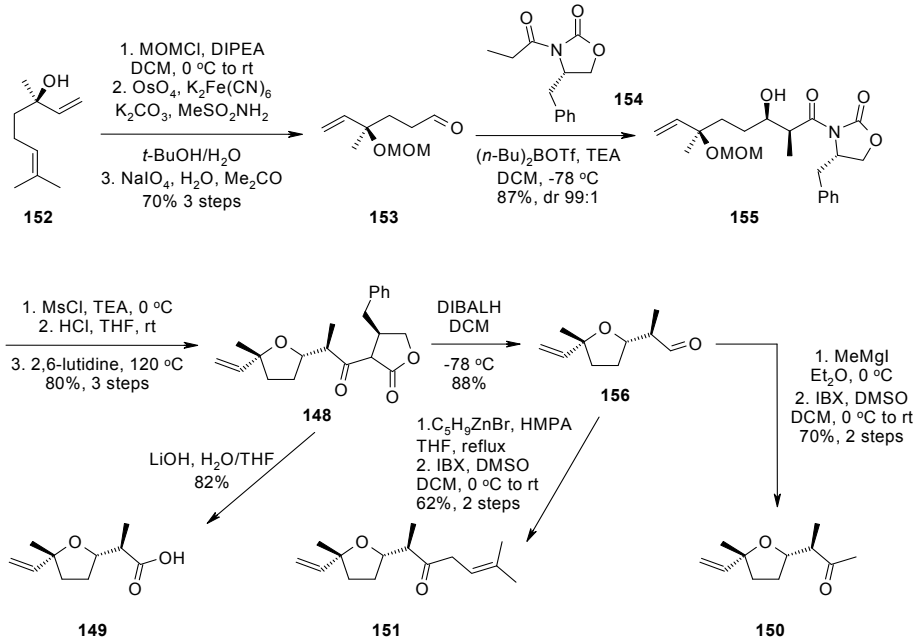
Scheme 29. Oppolzer's synthesis of (±)-Chokol-A

1.4. Tetrahydrofuran derivatives. Synthetic methods

As in the case of cyclopentane derivatives reviewed above, an overview of tetrahydrofuran derivatives synthesis is divided into categories by origin of chirality or lack thereof. An additional section contains only syntheses describing the construction of 1,7-dioxa[4.4]nonane derivatives.

1.4.1 Synthesis by the use of a chiral pool

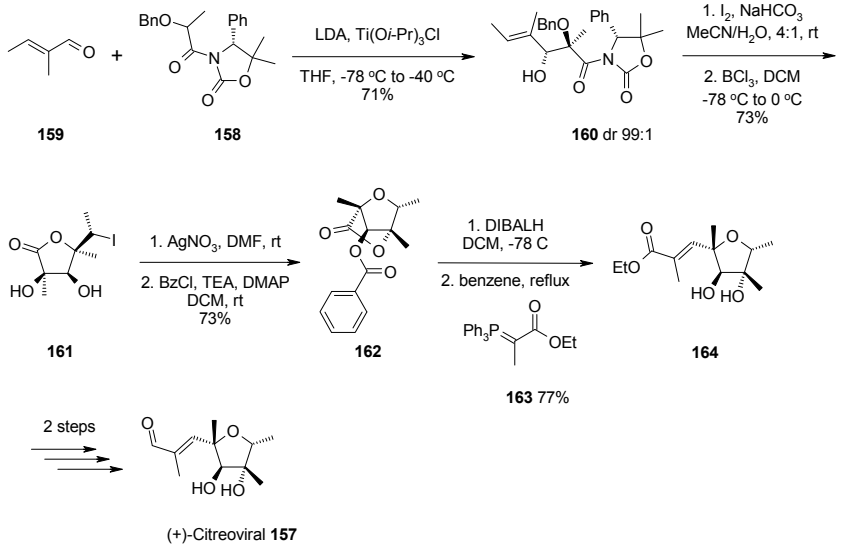
Yadav's approach to davana oil constituents was comprised of a six-step sequence to arrive at key intermediate **148**, which was converted to davana acid **149**, nordavanone **150** and davanone **151** in one or three steps (Scheme 30).[123] (-)-Linalool **152** was chosen as a starting compound. A diastereoselective aldol reaction afforded second and third stereogenic centers under Evans aldol conditions with aldehyde **153** as a substrate and *N*-propionyl oxazolidinone **154** as an auxiliary to afford carbonyl compound **155** in good yield (87%) and excellent diastereoselectivity (*dr* 99:1). The activation of the hydroxyl group, removal of the protecting group and subsequent basic cyclization afforded intermediate tetrahydrofuran derivative **148** with three stereogenic centers. Davana acid **149** was obtained by a simple basic hydrolysis of **148** in 40% overall yield. Davanone **151** and nordavanone **150** were furnished *via* common aldehyde **156** by alkylating it with an appropriate reagent and by subsequent oxidation with IBX in 27% and 30% overall yields, respectively.



Scheme 30. Total synthesis of davana oil components

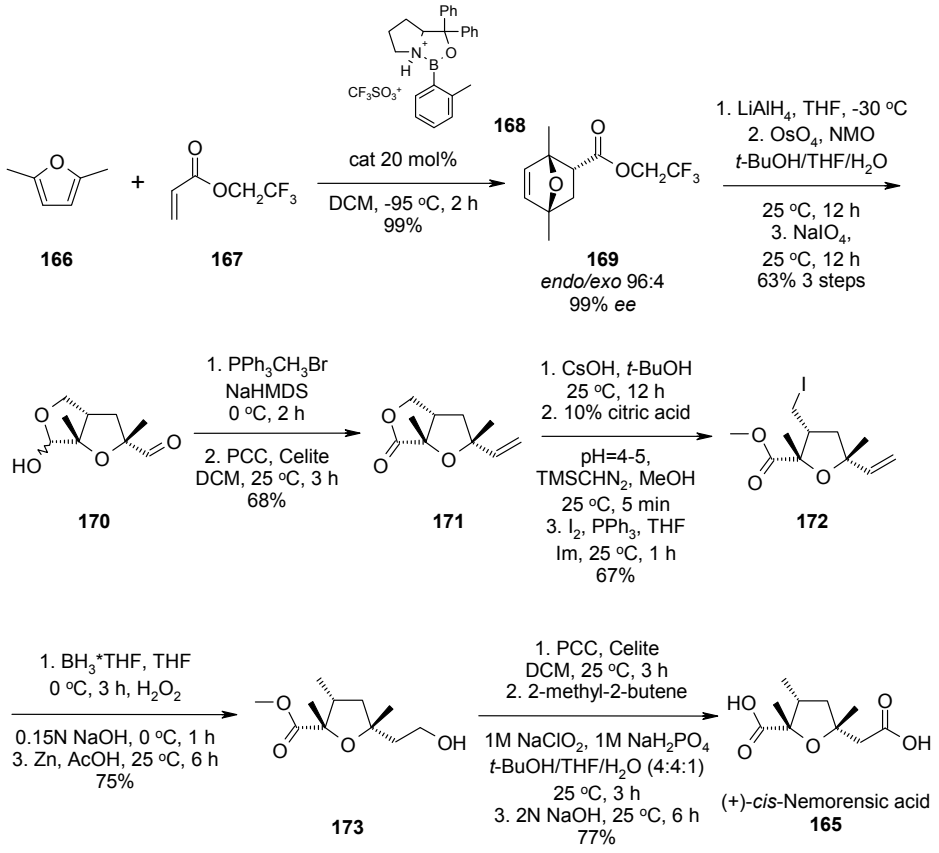
1.4.2 Asymmetric synthesis

Murata's approach to (+)-Citreoviral **157**[124] consisted of an eight-step sequence, including the addition of chiral auxiliary oxazolidinone **158** to 2-methyl-2-butenal **159**. Intermediate **160** was obtained in 71% yield with *dr* 99:1, followed by iodolactonization (iodo-derivative **161**) and by silver-promoted cyclization, to result in bicyclic intermediate **162** (Scheme 31). The reduction of the latter with DIBALH followed by a Wittig reaction with suitable ylide **163** afforded an advanced precursor **164**. (+)-Citreoviral **157** was obtain in two steps and in 14% overall yield.



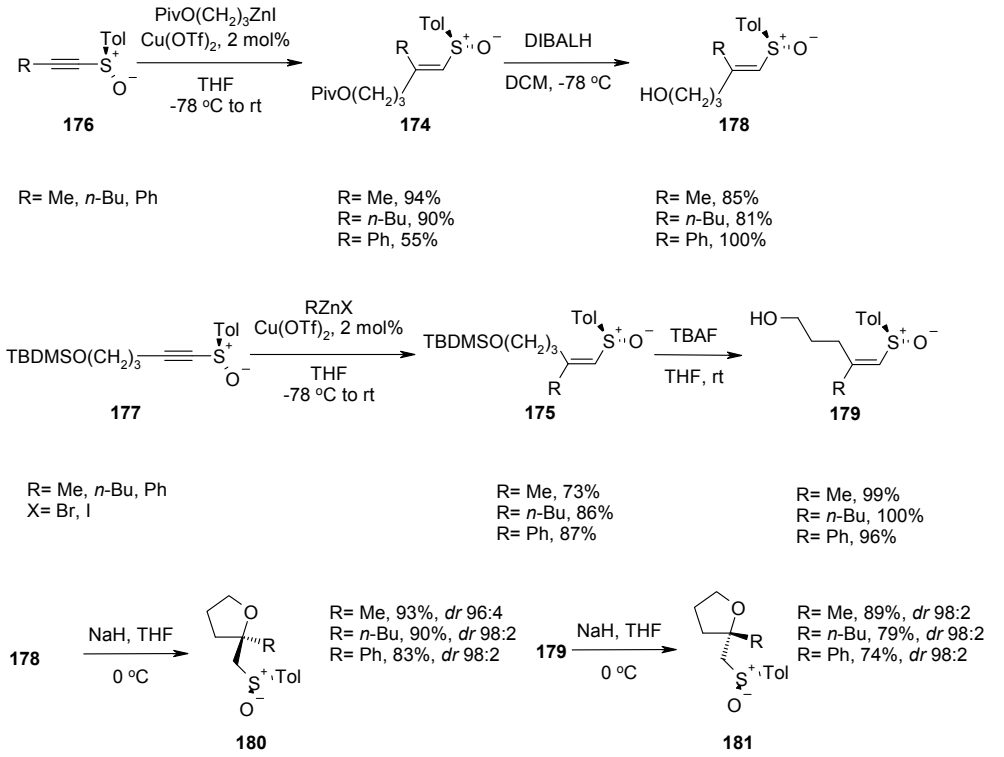
Scheme 31. Murata's synthesis of (+)-Citreoviral

Sim *et al.*[60] reported a synthesis of (+)-*cis*-nemorensic acid **165** (Scheme 32) employing an asymmetric Diels-Alder reaction of 2,5-dimethylfuran **166** and trifluoroethyl acrylate **167**, catalyzed by a cationic chiral oxazaborolidium catalyst **168**. Bicyclic adduct **169** was obtained in high yield (99%) and with high *endo-exo*-selectivity (96:4) and enantioselectivity (*ee* for *endo* 99%). The reduction of the ester moiety with $LiALH_4$ and cleavage of the double bond by a dihydroxylation-oxidation sequence gave bicyclic aldehyde **170**, which after treatment with a Wittig reagent and subsequent oxidation led to lactone **171**. Subsequent hydrolysis, methylation and iodination yielded iodinated alkene **172**. Hydroboration and iodine reduction afforded intermediate **173**. Double oxidation (PCC and Pinnick) and hydrolysis furnished the desired (+)-*cis*-nemorensic acid **165**.



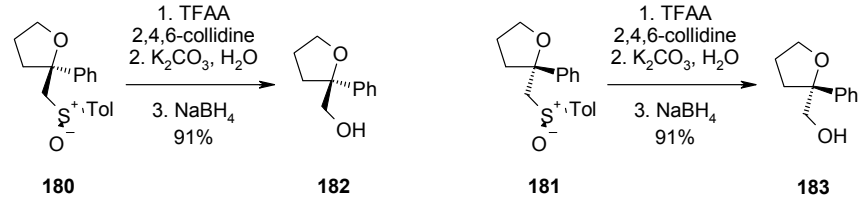
Scheme 32. Synthesis of (+) *cis*-nemorensic acid

A method of synthesizing chiral 2,2-substituted THF-derivatives was developed by Tanaka's group at Osaka University (Scheme 33).[65] First, both geometric isomers of disubstituted chiral vinylic sulfoxide **174** and **175** were obtained from the appropriately substituted alkynyl sulfoxides **176** and **177** *via* a *syn*-specific addition of an alkylzinc reagent. Removal of the protecting group gave precursors **178** and **179** to an asymmetric intramolecular Michael addition, effected by NaH in THF, to afford chiral cyclic ethers **180** and **181** in good yield (74-93%) and high diastereomeric ratio (*de* 96:4 to 98:2). Asymmetry was induced by using a chiral sulfoxide auxiliary group, presumably by coordinating sodium metal in alkoxide group and thus directing an alkoxide attack to the double bond.



Scheme 33. Asymmetry induced by chiral sulfoxides in the synthesis of 2,2-substituted THF-derivatives

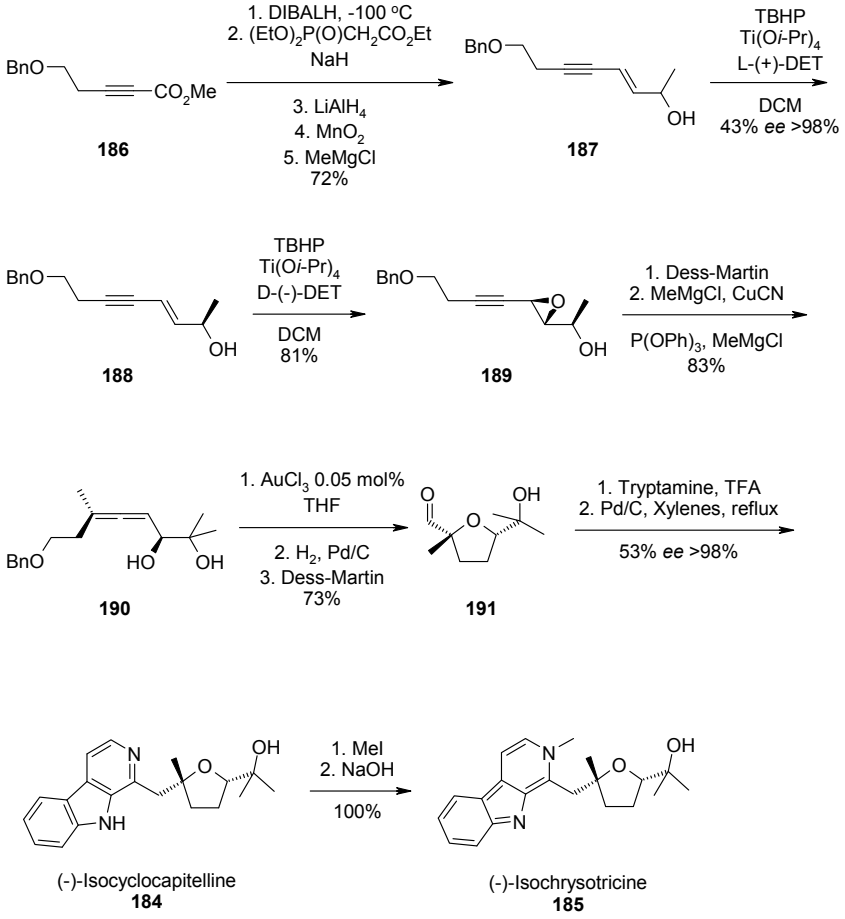
The chiral sulfoxides were converted to known compounds **182** and **183** to confirm the absolute stereochemistry (Scheme 34).[125] A Pummerer reaction with TFAA, hydrolysis of formed *S,O*-acetal by aq. K_2CO_3 and reduction of aldehydes with $NaBH_4$ gave the compounds **182** and **183** in 91% yield for both isomers. It was concluded that the precursors had (*R*,2*S*) and (*R*,2*R*) configuration around stereogenic centers, respectively.



Scheme 34. Confirmation of absolute stereochemistry

Volz and Krause proposed a synthesis of (-)-isocyclocapitelline **184** and (-)-isochrysotricine **185** by using a strategy which included Katsuki-Sharpless epoxidation to introduce chiral oxirane moiety and a diastereoselective conjugate epoxide opening as the key transformations (Scheme 35).[126] The sequence started with the known propargylic ester **186**, which was converted to the substrate **187** for kinetic resolution in five steps. Resolution of the enantiomers proceeded with high stereoselectivity for both products (*ee* >98 %) and good yield (43% for **188**).

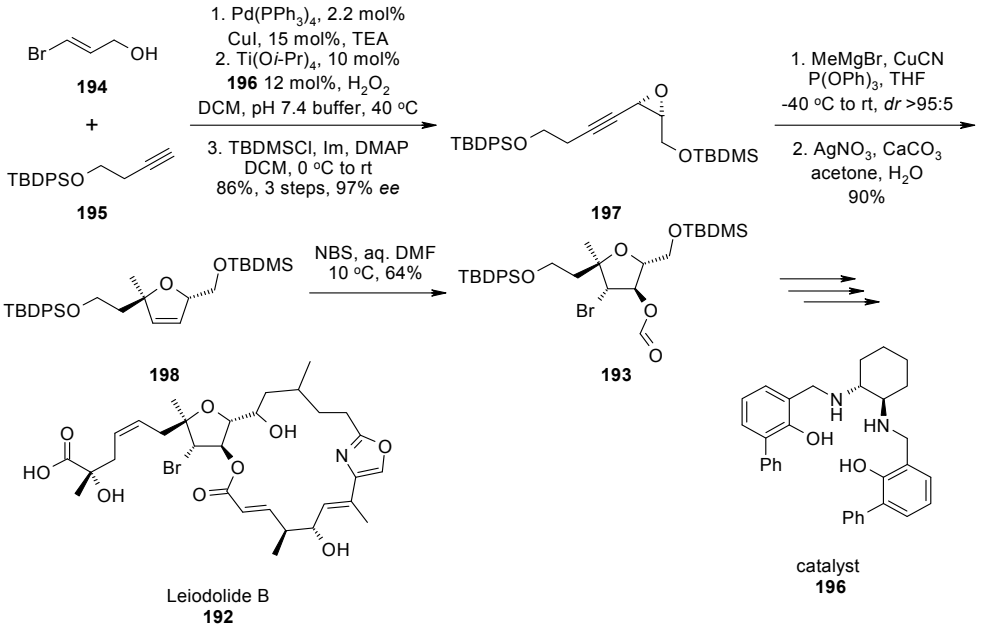
Subsequent Sharpless epoxidation gave a chiral oxirane **189** in good yield (81%), followed by Dess-Martin oxidation and a copper-mediated conjugate addition of a methyl-group to a propargylic triple bond, resulting in an allenic intermediate **190** in 83% yield. The latter was cyclized in the presence of a gold catalyst to a lead THF-derivative **191** after reduction of the double bond, removal of the benzyl group and Dess-Martin oxidation of the formed primary hydroxyl to aldehyde. The following Pictet-Spengler reaction and aromatization furnished (-)-isocyclocapitelline **184** in 53% yield. Finally (-)-isochrysotricine **185** was obtained by quantitative methylation of (-)-isocyclocapitelline **184**.



Scheme 35. Synthesis of (-)-isocyclocapitelline and (-)-isochrysotricine

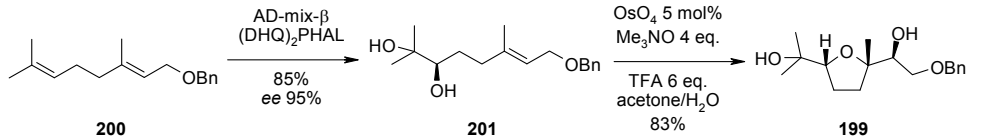
A similar strategy of a conjugate opening of chiral epoxide was employed to the structure of Leiodolide B **192** (found in the sponges of the rare genus *Leiodermatium*) by Fürstner's group. They synthesized an appropriate tetrahydrofuran intermediate **193** in high *ee* (97%) and overall yield (54%, Scheme 36).[127] Bromoalkenol **194** and alkyne **195** were coupled under Sonogashira conditions, followed by asymmetric epoxidation with catalytic Ti(O*i*-Pr)$_4$ in the presence of salen **196** as a chiral ligand, and protection of the hydroxyl group

yielding chiral epoxide **197** in 86% yield (three steps) and 97% *ee*. A conjugate oxirane opening was effected by a reagent derived from MeMgBr, CuCN and $P(OPh)_3$ in high diastereoselectivity (*dr* >95:5), followed by $AgNO_3$-promoted cyclization to afford dihydrofuran **198** (90% yield), which was then further converted to tetrahydrofuran **193** in 64% yield. Unfortunately, the macrocycles synthesized *via* the described intermediates did not afford the desired Leiodolide B and left the exact structure of the named target compound unclear.



Scheme 36. Fürstner's approach to Leiodolide B

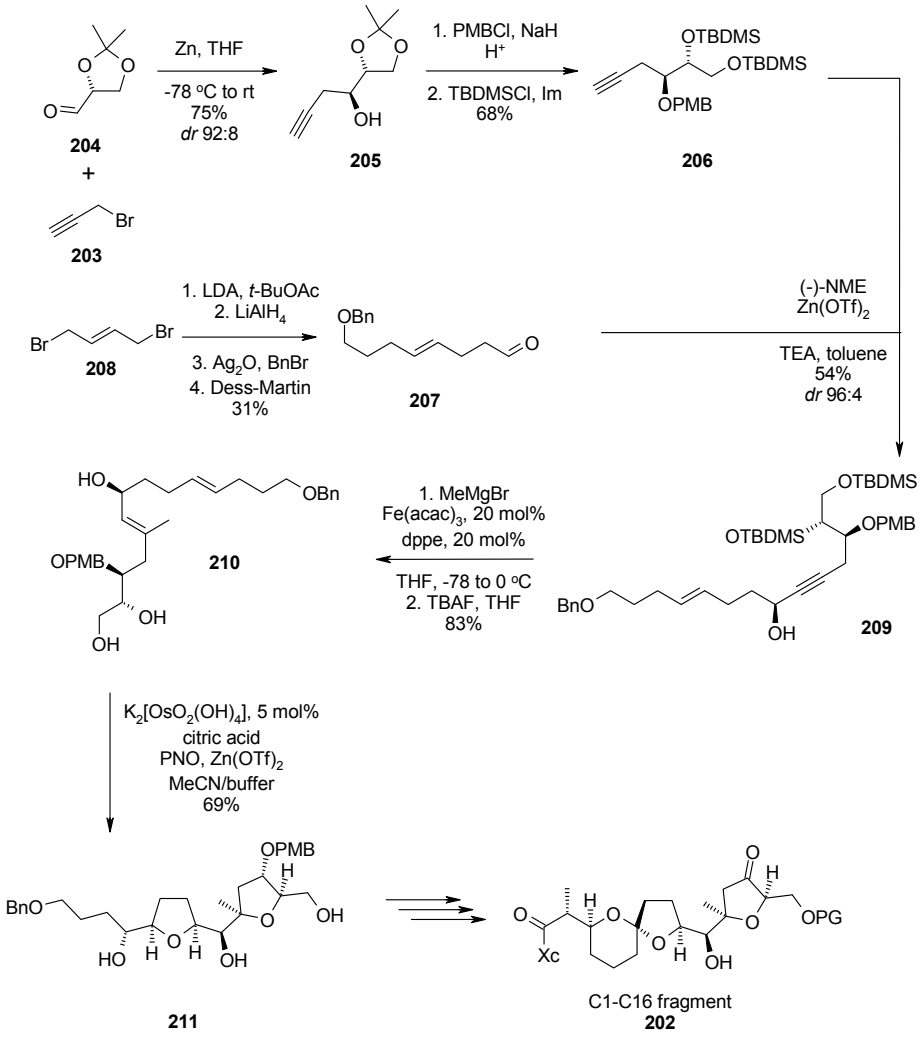
Donohoe *et al.*[66] applied an Os-catalyzed oxidative cyclization to the synthesis of an enantiomerically enriched tetrahydrofuran derivative **199** from 1,5-diene **200** in a two-step sequence, involving asymmetric Sharpless dihydroxylation to obtain chiral diol **201**, followed by oxidative cyclization (Scheme 37). In order to facilitate the cyclization step, an isoprene or cyclohexene additive was used to increase the amount of available Os(VI) catalyst in the reaction mixture.



Scheme 37. Oxidative cyclization of alkene-diols

Later, Donohoe's group continued the oxidative cyclization topic with the synthesis of a C1-C16 fragment **202** of Pectenotoxin 4 (Scheme 38).[128] The first two stereogenic centers were introduced by a diastereoselective (*dr* 92:8) Zn-promoted coupling of propargylbromide **203** with glyceraldehyde **204**. The derived acetonide **205** after a subsequent protection-deprotection-protection sequence gave the first substrate **206** for the (-)-N-methylephedrine-mediated diastereoselective coupling in

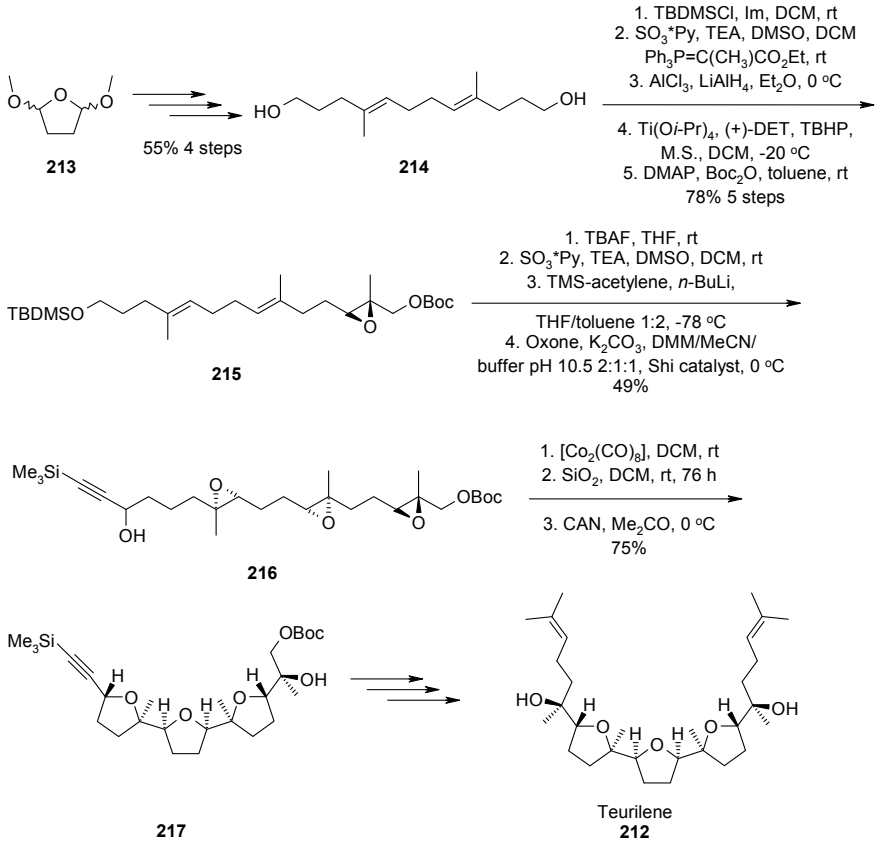
51% yield over three steps. The second substrate, compound **207** was obtained *via* a double derivatization of dibromoalkene **208** with *t*-BuOAc, followed by reduction with $LiAlH_4$, benzylation with BnBr and Ag_2O (31% yield over four steps) and Dess-Martin oxidation. These building blocks were subjected to Carreira[129] conditions to afford alkyne **209** in high diastereoselectivity (*dr* 96:4). Regio- and stereoselective methylation and subsequent removal of silyl groups gave substrate **210** for the cascade oxidative cyclization, which proceeded in good yield (69%). The four stereogenic centers were introduced in one step to furnish a key-intermediate **211** *en route* to the C1-C16 fragment **202** of Pectenotoxin 4.



Scheme 38. Synthesis of C1-16 fragment of Pectenotoxin 4

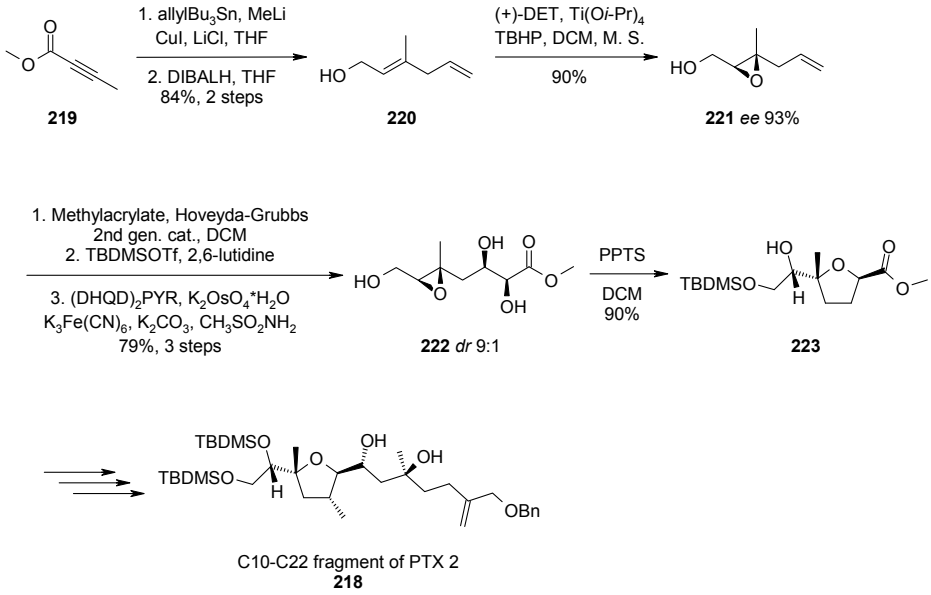
Although the synthetic efforts for polycyclic ethers *via* epoxide-opening cascades started in the early 1980s,[47] only one more recent example has appeared in literature. Rodriguez-Lopez *et al.* reported a total synthesis of teurilene **212** in 6.5% overall yield, achieved in 21 steps (Scheme 39).[130] The known diacetal **213** was used as

starting material to reach diene-diol **214** in four steps and 55% yield.[131] The next five steps, which included chain elongation by Wittig reaction and Sharpless epoxidation to install first stereogenic centers, led to chiral epoxide **215** in 78% yield. The following four steps featured a second chain elongation reaction (silylacetylene coupling to aldehyde) and double Shi epoxidation as key transformations, to afford a precursor **216**. This compound was subjected to a cascade epoxide opening reaction with Co-complex, affording intermediate **217,** bearing three THF-rings with appropriate stereochemistry for further elaboration to teurilene **212**.



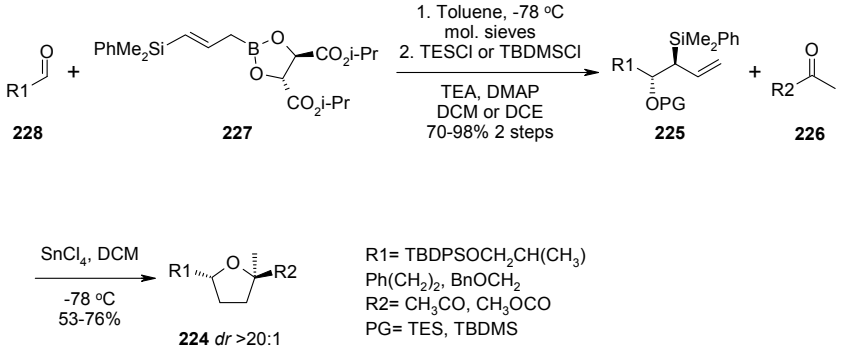
Scheme 39. Cascade epoxide opening

Pihko *et al.* have established an approach to C10-C22 fragment **218**[132] of pectenotoxin 2, featuring allylation of alkynyl ester **219** and a reduction of it with DIBALH to yield hydroxyalkene **220** (84%, two steps). This compound was subjected to stereoselective Katsuki-Sharpless epoxidation (**221** 90% yield and *ee* 93%), cross-metathesis and asymmetric dihydroxylation to obtain the cyclization precursor **222**, which after treatment with PPTS gave tetrahydrofuran intermediate **223** obtained in seven steps and 54% overall yield (Scheme 40).



Scheme 40. C10-C22 fragment of Pectenotoxin 2

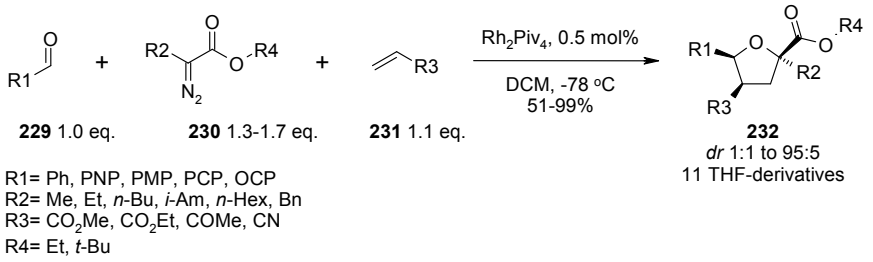
A highly diastereoselective annulation method to afford pentasubstituted tetrahydrofurans was developed by Micalizio and Roush.[133] THF-derivatives bearing a quaternary center at C-2 **224** were obtained *via* annulation of enantioenriched allylic silanes **225** with ketones **226** in the presence of $SnCl_4$ (Scheme 41). Silanes were synthesized by a previously reported method by reacting chiral allylboronate **227** with appropriately substituted aldehydes **228**.[134] High diastereoselectivity (*dr* >20:1, in favor of 2,5-*trans/cis* substitution) of the transformation was attributed to the chelating effect of Lewis acid (with BF_3*Et_2O and, when aldehydes were used instead of ketones, a reversal of diastereoselectivity was observed).



Scheme 41. Annulation of allylsilanes with ketones

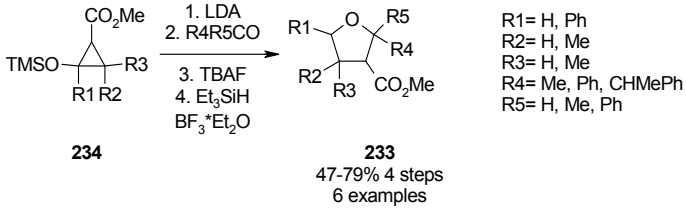
1.5. Racemic tetrahydrofuran derivatives

Fox *et al.* reported the use of carbonyl ylides derived from aldehydes **229**, diazoesters **230** and alkenes **231** in an Rh_2Piv_4-catalyzed multicomponent reaction in the synthesis of 26 different di- and tetrahydrofuran derivatives **232** with diastereomeric ratios up to 95:5 (low temperatures were essential to reach high diastereoselectivities) and yields ranging from 51 to 99% (Scheme 42, only tetrahydrofurans shown).[58] This method is not suitable for sterically more demanding diazocompounds (*tert*-butyl 2-diazo-isovalerate and *tert*-butyl 2-diazo-2-cyclohexyl-acetate), because these gave, with aliphatic aldehydes (propanal and pivalal), mainly β-hydride elimination. Phenylacetylene, vinyltrimethylsilane and norbornene gave dioxolanes as main products and ethyl crotonate, pent-3-yne-2-one, acrolein and methyl maleate afforded the respective tetrahydrofuran derivatives in minuscule yields (less than 10%).



Scheme 42. Three component reactions of dipolarophiles

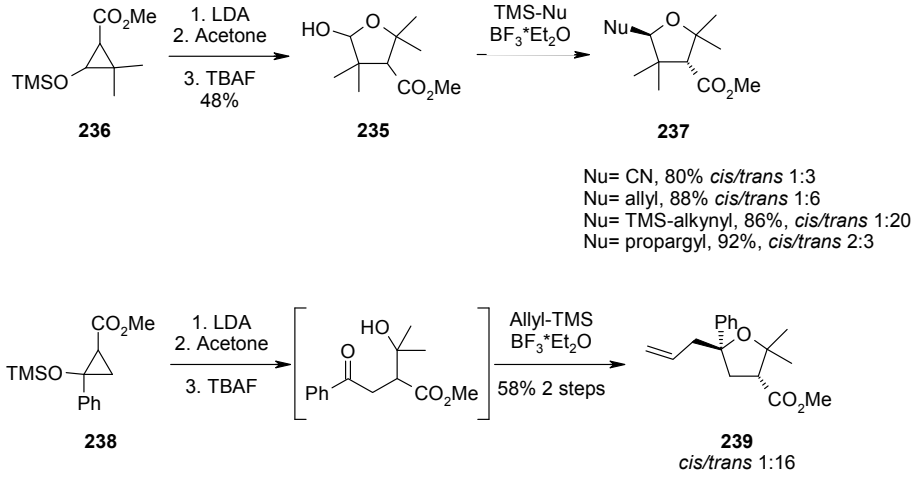
One of the first to utilize silicon nucleophiles to modify a tetrahydrofuran core was the Reissig group from Würtzburg (Scheme 43).[135] Tetrahydrofuran derivatives **233** were obtained from suitably substituted cyclopropanes **234** by reacting the cyclopropane enolate with a carbonyl compound (formaldehyde, acetone, benzaldehyde, benzophenone or 2-phenylpropanal) and then opening the ring with a fluoride anion. Spontaneous cyclization into lactol was observed. Reduction of the latter with an Et_3SiH/BF_3*Et_2O system afforded tetrahydrofurans **233**.



Scheme 43. Tetrahydrofurans from cyclopropanes

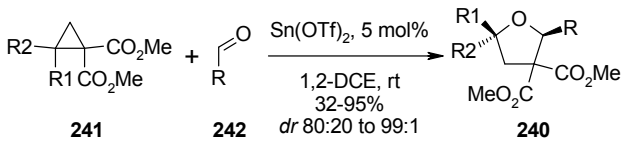
A further elaboration of the method led to the addition of silyl-nucleophiles other than silylhydrid to intermediate lactol **235** obtained from cyclopropane **236** (48%, Scheme 44). Four different nucleophiles were used to produce pentasubstituted tetrahydrofurans **237** in good yield (80-92%) with poor to good diastereoselectivity (3:2 to 20:1). One more example to illustrate the power of the current approach was also reported *ibid*.: phenyl-substituted cyclopropane **238** was treated with allylsilane

in the presence of BF_3*Et_2O to afford sterically congested tetrahydrofuran **239** in good yield (58%, two steps) and high diastereoselectivity. In most cases, a *trans* nucleophilic attack in respect to the ester-group in the lactol-ring dominated.



Scheme 44. Silyl-nucleophiles in reaction with lactols

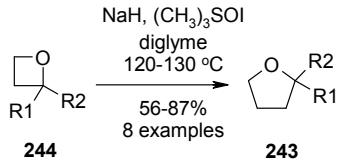
Another method using cyclopropanes to get THF-derivatives **240** was published by Johnson *et al.*[136] The reaction of electron deficient cyclopropanes **241** with various aliphatic and aromatic aldehydes **242** in the presence of $Sn(OTf)_2$ as a Lewis acidic catalyst was described (Scheme 45). In most cases, excellent results were obtained with a diastereomeric ratio better than 19:1. The yields exceeded 74% (up to 95% in some cases).



R= Et, *i*-Pr, Ph, PMP, *o*-Tol, PCP, PTFP
R1= isoprenyl, Ph, 4-CN-C_6H_4, PMP
R2= Me, allyl, Bn

Scheme 45. Annulation of cyclopropanes with aldehydes

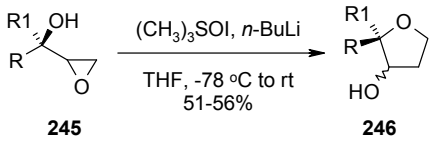
A relatively simple ring expansion method was developed by Butova *et al.*[137] to afford 2,2-disubstituted tetrahydrofuran derivatives **243** in an efficient manner (Scheme 46). Eight tetrahydrofuran derivatives **243** were synthesized by treating 2,2-disubstituted oxetanes **244** with dimethylsulfoxonium methylide at elevated temperatures in fair to good yields (56-87%). When a chiral substrate was used, full retention of enantiomeric purity was observed. Unfortunately, only aliphatic compounds were investigated, providing no information about the tolerance to the other functional group.



R1= H, Me, *n*-Bu, Ph
R2= *n*-Bu, *n*-Hex, Ph, *p*-Tol, PFP, Naphtyl

Scheme 46. Ring expansion of oxetanes

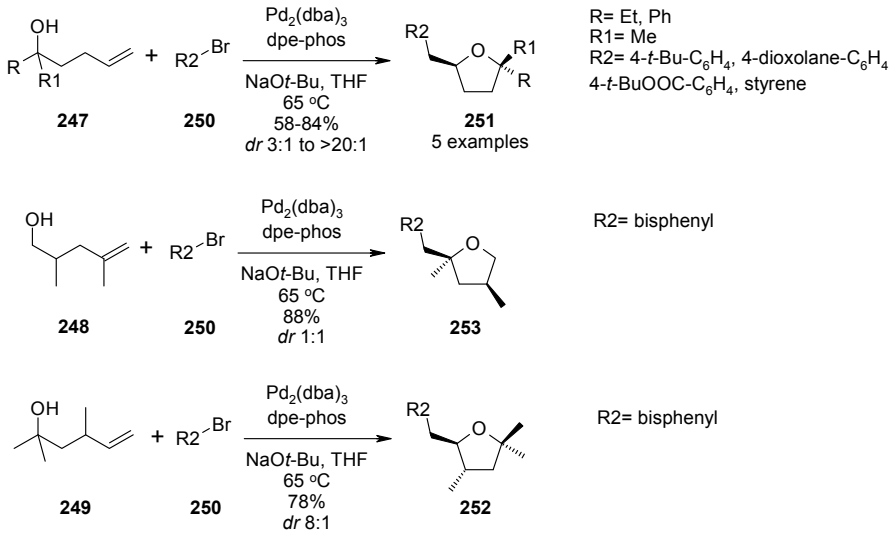
Schomaker *et al.* reported an epoxide opening cyclization sequence employing sulphur ylide as the reaction initiator (Scheme 47).[138] Two examples describe reacting terminal epoxides **245** with sulphur ylide generated from trimethylsulphoxonium iodide and *n*-BuLi at -78 °C, resulting in tetrahydrofuran derivatives **246** in 51% to 56% yield.



R= 4-methyl-3-pentene, R1= Me
R=R1= -$(CH_2)_4$-

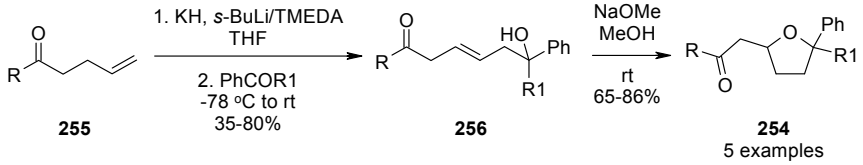
Scheme 47. Sulphur ylide promoted epoxide opening-cyclization sequence

The cyclization of γ-hydroxyalkenes **247**, **248** and **249** and coupling the latter with aromatic bromides **250** under palladium catalysis was developed by Wolfe's group (Scheme 48).[139] The obtained aliphatic THF-derivatives (seven selected examples) exhibited various substitution patterns: 2,2,5- **251**, 2,2,3-trisubstitution **252** and 2,2,4,5-tetrasubstitution **253** were afforded in fair to good yields (55-88%) and from non- to good diastereoselectivity (*dr* 1:1 to >20:1). The yields were dependent on both the electronic and steric factors of aryl compounds and alcohols, whereas diastereoselectivity was found to be mainly influenced by the substitution pattern in alcohol.



Scheme 48. Pd-catalyzed cyclization

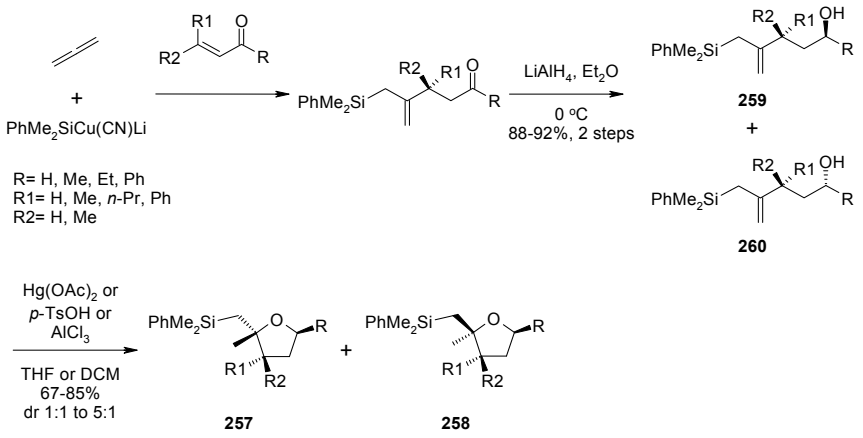
Pohmakotr and Seebach have reported a cyclization method to afford tetrahydrofurans **254** with an oxo group in the side chain (Scheme 49).[140] The method involves electrophilic substitution of a dianion formed from oxo-alkene **255** with ketone, to give hydroxyketone **256** in moderate to good yield. A subsequent basic cyclization into a THF-derivative occurred with relatively high efficiency, but low diastereoselectivity (*dr* 1.6:1).



R= Me, *t*-Bu, Ph
R1= Me, Ph, homoallyl

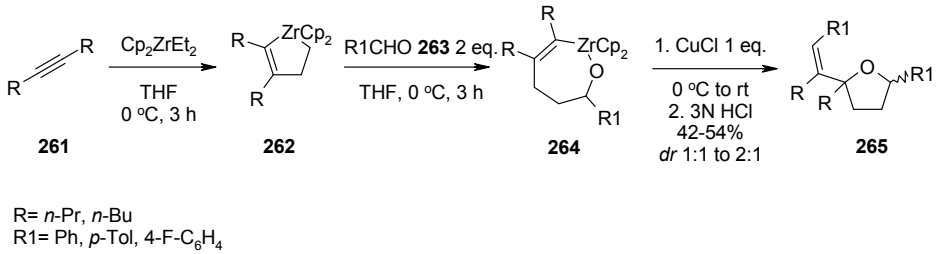
Scheme 49. Seebach synthesis of 2,2,5-trisubstituted THF-derivatives

A comparative study of reactants to obtain silylsubstituted tetrahydrofurans **257** and **258** *via* the cyclization of corresponding allylsilyl alcohols **259** and **260** was conducted recently by Pulido *et al.,*[141] using three different acids: $Hg(OAc)_2$, *p*-TsOH and $AlCl_3$ (Scheme 50). Mercury salts (Lewis acid) afforded the desired compounds in good yield (68-85%) and low diastereoselectivity (*dr* 1:1 to 1.9:1), whereas Brønsted acid gave better yields (72-87%; in only one case was mercury salt better) and diastereoselectivities (*dr* up to 5:1). The yields with $AlCl_3$ were lower (65-69%) than those for mercury salt and *p*-TsOH. However, the diastereomeric ratios (*dr* 2.3:1 to 3.5:1) were similar to those of *p*-TsOH-catalyzed reactions. In all cases, the dominant diastereomer was the isomer where silylmethyl- and R1-groups are in *trans*-configuration. Thus, diastereoselectivity seemed to depend mainly on the cyclization catalyst.



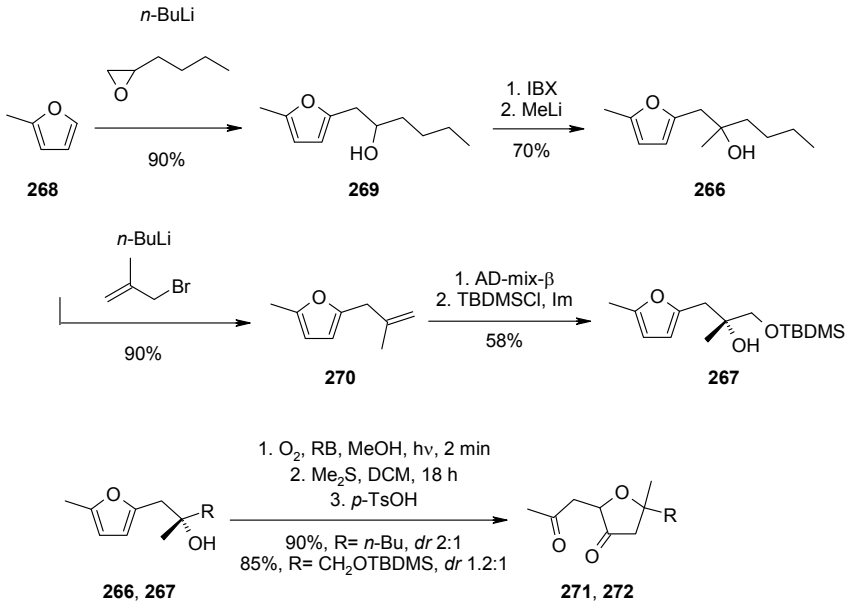
Scheme 50. Cyclization of allylic silanes

Zhao *et al.*[142] showed the utility of zircono-rings in the synthesis of arylsubstituted THF-derivatives (Scheme 51). Alkyne **261** was treated with diehtylzirconecene to form a five-member zirconocycle **262**, which after the addition of two equivalents of the appropriate aromatic aldehyde **263** led to zirconocycloheptene **264**. The latter was exposed to CuCl and 3N HCl to afford THF-derivatives **265** in fair yield and low diastereoselectivity (*dr* 2:1 at best). Also, a failure to perform the transformation with aliphatic aldehydes was reported.



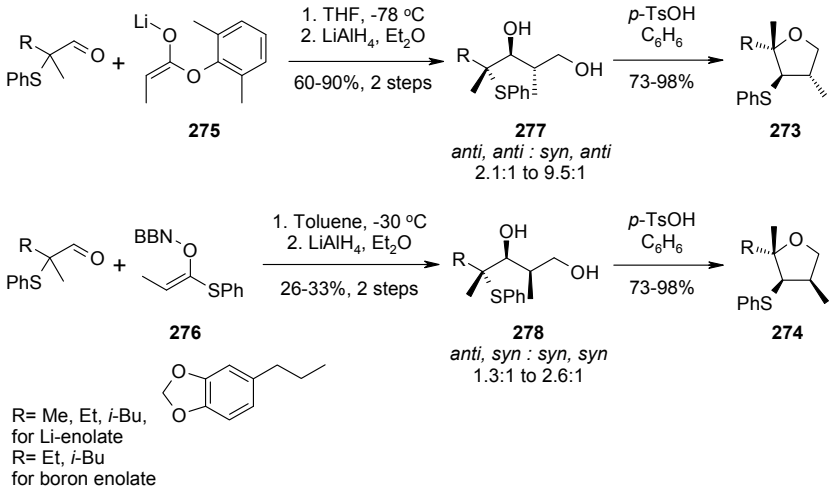
Scheme 51. Tetrahydrofurans *via* zirconocycle

Singlet oxygen was used to construct a tetrasubstituted THF-ring in a one-pot four-step sequence, as a unique example.[143] Both substrates **266** and **267** were synthesized starting with methylfuran **268** by alkylating lithiated starting material with an appropriate reagent, leading to the intermediates **269** and **270** in 90% yield in both cases. The first substrate **266** was furnished by oxidation with IBX, followed by alkylation with MeLi (70%, two steps). The second substrate **267** required dihydroxylation with AD-mix-β and subsequent protection with TBDMSCl/Im (58%, two steps). Crucial transformations were carried out in one-pot fashion with solvent exchange. Oxygen was bubbled through the reaction mixture in the presence of Rose Bengal, and irradiated with visible light for two minutes in MeOH. Then the solvent switch was begun and dimethylsulphide was added to reduce the hydroperoxy groups present, affording intermediate enedione, which in the presence of acid, *via* an intramolecular Michael addition, furnished the desired tetrahydrofurans **271** and **272** in 90% and 85% yields, respectively (Scheme 52).



Scheme 52. Synthesis of THF-ring by using singlet oxygen

Aggarwal *et al.*[144] published a synthesis route of sulphur containing tetrahydrofurans **273** and **274** with *anti* or *syn* configuration depending on the enolate configuration in the starting material **275** and **276**. The latter were transformed to cyclization precursors **277** (the ratio of *anti, anti* to *syn, anti* ranged from 2.1:1 to 9.5:1) and **278** (the ratio of *anti, syn* to *syn, syn* ranged from 1.3:1 to 2.6:1). (Scheme 53).

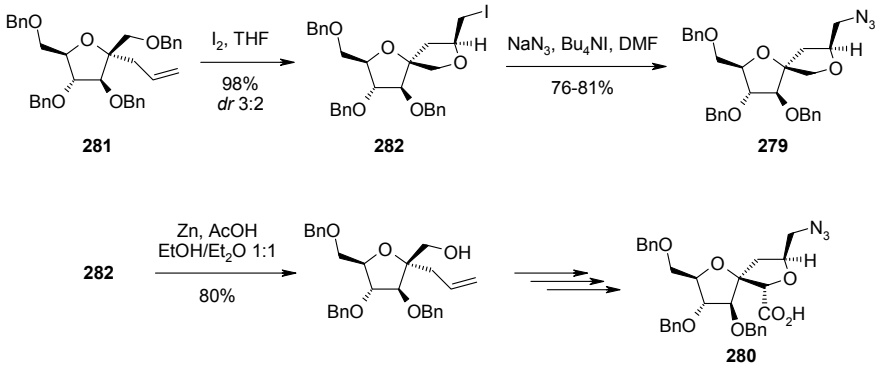


Scheme 53. THF-derivatives *via* episulphonium ion

1.6. Spiroditetrahydrofurans

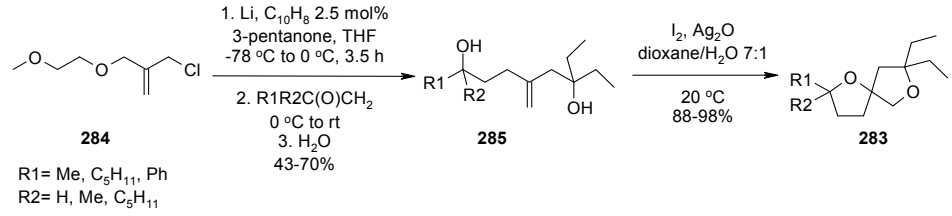
Below are some examples of the syntheses of the spirotetrahydrofuran core, focused on the 1,7-dioxaspiro[4.4]nonane skeleton, as the latter is the most relevant to our own work. Spirodilactone syntheses, although conceivable as spirodiether precursors, were deemed to be out of the scope of the current overview and left out.

Cipolla *et al.*[55] have reported the synthesis of the spirocyclic THF-derivatives **279** and **280**. The known allylic fructose derivative **281** was used as a starting compound to get iodine-promoted cyclization product **282**, which served as a starting material for spiro-compounds **279** (obtained in one step by treatment with sodium azide; the diastereomers were reacted separately) and for compound **280**. The latter required six steps and was obtained as a single diastereomer (*dr* 98:2) (Scheme 54).



Scheme 54. Molecular scaffolds

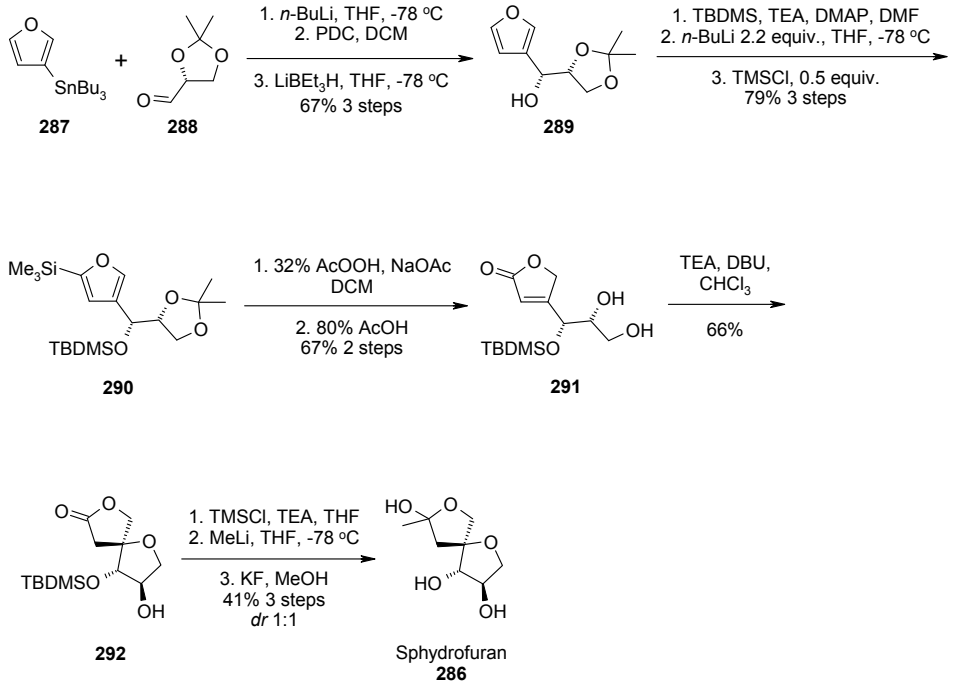
The Yus group at the University of Alicante constructed 1,7-dioxaspiro[4.4]nonanes **283** starting with 2-chloromethyl-3-(2-methoxy-ethoxy)propene **284** by using a sequential one-pot protocol (Scheme 55).[61] Naphthalene mediated lithiation of chloro-compound **284** with excess powdered lithium metal, the subsequent addition of 3-pentanone, raising the temperature to cleave the methoxy-ethoxy group and treatment with epoxide afforded ene-diol **285**. Upon reaction with molecular iodine and silver(I)oxide spirotetrahydrofurans **283** were formed in good to excellent yields (88-98%), but in the absence of or in low diastereoselectivity (*dr* 1:1 to 3.5).



Scheme 55. Synthesis of spirotetrahydrofurans

Wong *et al*. synthesized sphydrofuran **286** in 12 steps (Scheme 56)[40], using electrophilic substitution of stannulated furan **287** with glyceraldehyde derivative **288** to afford a chiral intermediate **289**. The second stereogenic center was introduced *via syn*-selective reduction with Super-Hydride (67%, three steps),

followed by a protection-silylation sequence resulting in furan derivative **290** (79%, three steps) and lactone **291** (67%, two steps). The latter upon treatment with a TEA/DBU system gave spirocyclic lactone **292** as a 1:1 mixture of diastereomers. Further elaboration to sphydrofuran **286** afforded a silylation-methylation-deprotection sequence in 4.8% overall yield.



Scheme 56. Synthesis of sphydrofuran

1.7. Summary of literature overview

From the literature survey, it is very clear that both classes of compounds, alkylbranched cyclopentanes and tetrahydrofuran derivatives, have received plenty of attention from the synthetic community. This is even more clearly revealed by the fact that the literature overview covers only a limited number of examples and references. This shows the importance of the topic for both synthetic chemists and bio-medicinal researchers. Also, one can conclude that the topic is not a simple one. The synthesis strategies for both classes of compounds – cyclopentanes and tetrahydrofurans – are similar. Most of the synthetic methods used to afford both classes of compounds consist of various cyclization reactions: base, acid or metal catalyzed (e. g. Ag_2O, SmI_2, Ti, Zr, Hg, Pd etc. catalysis), asymmetrically and/or diastereoselectively performed. Many different types of substrates, including epoxides, diols, substituted alkenes and halides, have been used. Far fewer examples have involved ring expansion and contraction reactions, modification of a preformed cyclic core or electrochemical or multicomponent reactions. Besides chemical activity, the main problems are connected with stereoselectivity, enantioselectivity

and especially diastereoselectivity - because uncontrolled reactions lead to a huge number of inseparable stereoisomers. These are the main problems that still wait for an elegant solution.

The synthesis of substituted cyclopentane and tetrahydrofuran derivatives in a stereochemically controlled way is an important chemical target in itself. The existence of such structural motifs in many active ingredients of pharmaceuticals stresses that importance and adds a practical value to it. In our case, we particularly focused on the synthesis of antiviral agents, which is a long term co-operation project of our research team.

Over the years, a simple and enantioselective method for synthesizing chiral lactone carboxylic acids has been developed by our group. That approach has been utilized in the synthesis of 2-alkyl-substituted 2-hydroxyglutaric acid γ-lactones [145], homocitric acid [146] and nucleoside analogues [147], [148]. As a continuation of these efforts, the current study is expected to widen the scope of that method and furnish new products.

2. Aims of the current study

The current study directs its efforts to widening the scope of the use of tertiary substituted cyclopentanes and lactones in chemical synthesis, focusing on the synthesis of substituted cyclopentanes and tetrahydrofurans. The results are expected to afford new methods of the synthesis and furnish new synthons for bioactive compounds.

The main tasks are as follows:

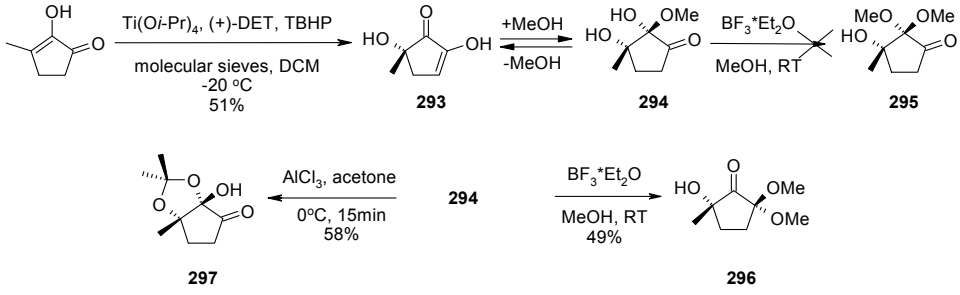
- Elucidation of the possibilities of the synthesis of chiral cyclopentane derivatives from mono-oxidation of 1,2-diketones
- Development of a lactone-acid-based method for the synthesis of cyclopentane derivatives: use of γ-lactones as starting compounds in the synthesis of 1-alkyl-1,2- and 1-alkyl-1,3-cyclopentanediols.
- Elaboration of a method for the synthesis of chiral tetrahydrofuran derivatives from γ-alkyl-γ-lactone carboxylic acids.
- Stereochemical assignment of the differently substituted cyclopentanols.

3. Results and discussion

3.1. Dihydroxycyclopentanones

3.1.1 Differentiation of C-1 and C-2 carbonyl groups (Article I)

The approach is based on differentiating the 1- and 2-oxo groups in hydroxylated diketone **293**. We found that it is possible *via* the formation of different types of ketals from it. The starting diketone **293** is isolated from the reaction mixture of the asymmetric oxidation of 3-methyl-1,2-cyclopentanedione with a Ti(O*i*-Pr)$_4$-tartaric ester-TBHP complex usually in a stable hemiacetal form **294**.[102] In order to obtain 1,3-dihydroxy compound, we first made an attempt to reduce keto-hemiacetal **294** directly with $NaBH_4$. However, from these experiments we learned that this produced a complex mixture of diols and triols in low total yield, and some amount of unreacted starting material. This prompted us to look for a more stable carbonyl protective group than hemiacetal. We proposed that by using distinct protecting groups in the compound **293** it would be possible to differentiate the carbonyl functions at C-1 and C-2. To convert hemiacetal **294** to dimethyl acetal **295,** we first used ordinary reaction conditions for acetalization (catalytic amounts of *p*-TsOH and MeOH). However, our attempts failed even when up to two equivalents of the catalyst were used. This result prompted us to explore the action of active Lewis acid catalysts. Fortunately, with 0.5 equivalents of boron trifluoride etherate and MeOH hemiacetal **294** converted mainly to the dimethyl acetal **296** in 49% yield. It is worth mentioning that during that process the carbonyl group at C-1 was protected and the group at C-2 became unprotected. This means that a selective trans-acetalization also occurred. Increasing the amount of the Lewis acid to one equivalent did not improve the yield; instead, the yield decreased considerably (to 17%) (Scheme 57).



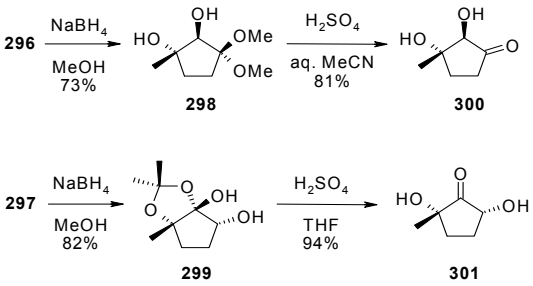
Scheme 57. Differentiation of C-1 and C-2-carbonyl groups

With different Lewis acids, we obtained selectively a full set of differently protected diketones. Thus, in order to protect the C-2 carbonyl group, we transformed hemiacetal **294** to acetonide **297**. Under typical conditions,[149,150] when the substrate was refluxed in a solvent (usually toluene or benzene) in the presence of an acid catalyst (*p*-TsOH or H_2SO_4) and 2,2-dimethoxypropane, the yield of **297** was low and acetalization was accompanied by side reactions (elimination of the tertiary hydroxyl group, deacetalization of the hemiacetal group in **294** and formation of

ketoenol **293**). Also, using acetone or 2-methoxypropene as the acetalization reagent and/or applying lower reaction temperatures (from RT to 60°C) and long reaction times did not improve the expected reaction and acetonide **297** was obtained only in low yield (in the range 13% to 32%). The change of a Brønsted acid to a Lewis acid (BF_3*Et_2O) was also not successful. Finally, when using the procedure proposed by Lal *et al.*[151] (three equivalents of $AlCl_3$ in a dry 1:1 mixture of acetone and ether), we obtained the acetonide **297** in acceptable yield (58%). Using that procedure, we obtained the intermediate **297** with the C-2 carbonyl group protected and the C-1 carbonyl free (Scheme 57). As a result, we succeeded in differentiating the carbonyl groups in compounds **296** and **297**, which could be used for further modifications.

3.1.2 Stereoselective reduction of C-1 and C-2 carbonyl groups

The reduction of acetal **296** with a 1.2 equivalent of $NaBH_4$ in MeOH led stereoselectively, with good yield (73%), to diol **298**. The same exclusive stereoselectivity and excellent yield were observed in the case of the reduction of acetonide **297**. Compound **299** was obtained as a single isomer in 82% yield.



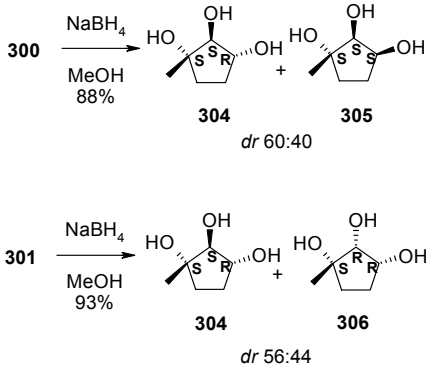
Scheme 58. Synthesis of ketodiols

Deprotection of hydroxy acetals **298** and **299** with sulphuric acid in MeCN or THF furnished dihydroxyketones **300** and **301**, respectively, in good yield (81% and 94%, Scheme 58). It should be mentioned that using HCl as an acid catalyst in deprotection resulted in the elimination of tertiary hydroxyl groups in **300** and **301**, and therefore could not be used. Also, during the purification of the crude reaction mixture on silica gel, a tendency towards the elimination of the hydroxyl group was observed. Therefore, the crude product was only filtered through a Celite pad after water-ethyl acetate extraction. The obtained products **300** and **301** were identified and characterized by NMR analysis and found to be stereochemically homogeneous.

However, the NMR spectroscopic data were insufficient to determine the relative stereochemistry of acetonide **299** and dihydroxyketone **301**. The determination of the relative configuration of substituents in the cyclopentane ring is not a trivial matter (compared to the corresponding cyclohexane derivatives). Therefore, the diols were converted to triols and their relative configuration was additionally investigated on NMR spectra. Additionally, the spectra of the separately synthesized model compounds **302** and **303** were studied.

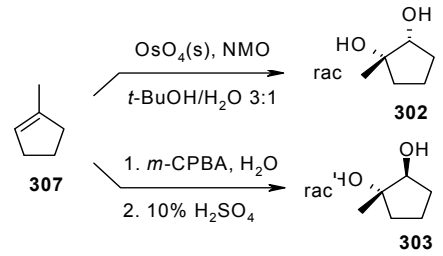
3.1.3 The relative and the absolute configuration of hydroxylated cyclopentanones and cyclopentanes

Dihydroxyketones **300** and **301** were reduced with $NaBH_4$, affording, in both cases, a mixture of triols **304, 305 and 306** (in 88% yield as a sum of the isomers for **300** and in 93% for **301**; Scheme 59). The NMR spectra of the triols were thoroughly investigated. Also, the obtained information enabled us to verify the established relative stereochemistry of acetonide **299** and dihydroxyketone **301** presented above.



Scheme 59. Reduction of ketones to triols

It is known that the ^{13}C chemical shift of the methyl group that is vicinal to the hydroxyl group in cyclic alkanols is dependent on the relative configuration of substituents.[152–154] The same phenomenon was also observed in the case of compounds **300**, **304**, **305** and **306**. To confirm the proposed stereochemistry for these compounds, the model compounds 1-methyl-1,2-cyclopentanols **302** and **303** were separately synthesized from cyclopentene **307**, using two different pathways: dihydroxylation of **307** with an OsO_4/NMO system, which afforded a *cis*-diol **302** and epoxidation of **307** with *m*-CPBA in water, followed by treatment with H_2SO_4, which afforded a *trans*-diol **303** (Scheme 60).



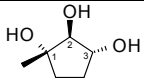
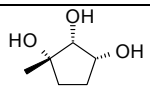
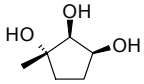
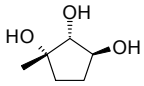
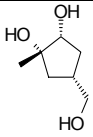
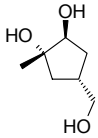
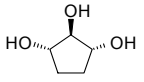
Scheme 60. Synthesis of model compounds

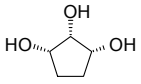
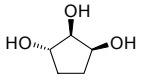
Although the difference in chemical shifts was larger (3.78 ppm) in the case of diols (Entries 5 and 6, Table 1) than that for triols, the general trend was clearly expressed: when the methyl group was located *cis* to the neighboring hydroxyl group, the shift was 2.02 to 2.65 ppm up field relative to that for the compounds with *trans* configuration of those groups. This regularity enabled us to determine the

relative configuration of the substituents around the carbons C-1 and C-2 as follows: *cis* for compounds **300**, **304** and **305**, and *trans* for compound **306**.

The chemical shifts of three adjacent carbon atoms attached to hydroxyl groups are also shown by the relative configuration of the corresponding substituents (see Table 1, entries 1-4 and 9-11). The ^{13}C chemical shifts of the compounds where OH-groups at carbons C-2 and C-3 are *cis* to each other were approximately 4 ppm up field compared to the corresponding *trans*-compounds.[154] In the case of compounds **304** (Table 1, entry 1), **305** (Table 1, entry 3) and **306** (Table 1, entry 2), a difference of five ppm was observed, which allows us to make suggestions about the relative configurations of groups around atoms C-2 and C-3 as follows: in the compound **304** the C-2 and C-3 hydroxyls are in *trans*- and in compounds **305** and **306** in *cis*-configuration.

Table 1. ^{13}C chemical shifts of cyclopentanols

Entry	Compound	C-1	C-2	C-3	C-4	C-5	CH_3
1		77.6	85.1	76.87	29.3	36.3	23.3
2		76.5	77.5	71.6	29.6	35.7	25.9
3		78.7	79.2	72.0	29.9	35.9	23.9
	Ref. 120						
4		78.0	85.2	77.5			26.2
5		78.3	78.4	31.6	19.1	37.1	25.3
6		80.8	80.0	30.9	18.8	37.0	21.5
7		79.1	78.6	35.6	36.4	41.2	25.2
8		81.1	81.1	36.2	38.4	41.5	22.1
	Ref. 152						
9		76.6	85.1	76.6	29.1	29.1	-

10	Ref. 152 	72.8	74.8	72.8	29.9	29.9	-
11	Ref. 152 	76.8	79.9	72.5	29.0	29.0	-

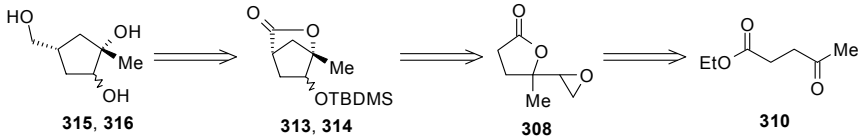
Thus, the results obtained from NMR spectra enabled us to assign correct stereochemical structures to all synthesized cyclopentanediols and -triols. Furthermore, the absolute configuration of the carbon C-1 in triols was determined by the oxidation step and was well established earlier.[102] This all enables us to determine unambiguously both the relative and the absolute stereochemistry of the triols as depicted in Scheme 59.

Later, similar regularities were observed in the ^{13}C NMR spectra of 4-hydroxymethyl-1-methyl-1,2-cyclopentanediols (Entries 7 and 8, Table 1), which also gave us additional confirmation of the stereochemistry of relevant bicyclic intermediates.

3.2. Dihydroxy-hydroxymethyl-cyclopentanes (Article III)

3.2.1 Cyclopentanes from cyclization of lactone epoxides

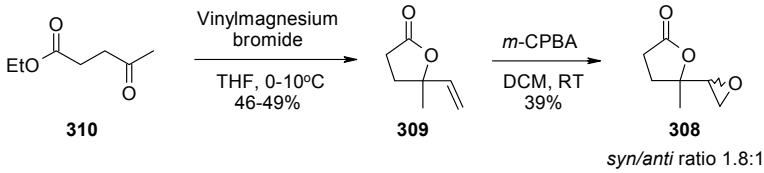
First, we focused our efforts on 3'-desoxycarbaribose analogue synthesis, which according to our retrosynthetic strategy (Scheme 61) would be accessed *via* intramolecular cyclization[155–158] of epoxides **308**, allowing perfect control over the relative configuration: the stereochemistry of epoxide is responsible for the stereochemistry of the hydroxyl group.



Scheme 61. Retrosynthetic analysis of regioisomeric cyclopentane synthesis

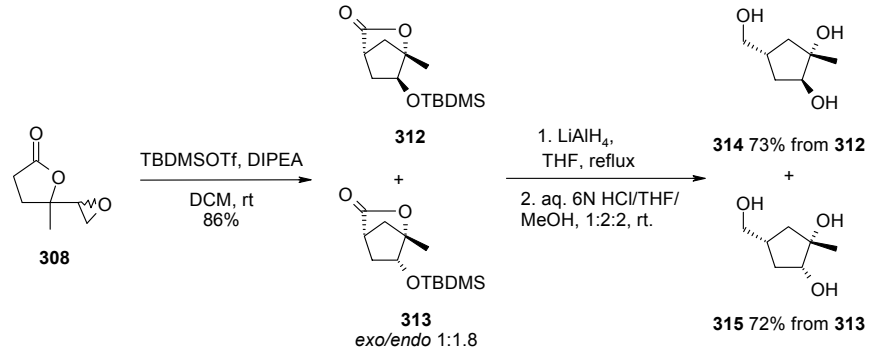
The intermediate epoxide could be easily synthesized via the γ-vinyl lactone **309**. The latter could be obtained from the cyclization of ethyl levulinate **310** after a vinylmagnesium bromide addition. Thus, ethyl levulinate **310** was allowed to react with vinylmagnesium bromide in THF to obtain γ-vinyl lactone **311** in 49% after distillation, as described by Wechter and coworkers[159] (Scheme 62). Subsequent oxidation of the double bond with *m*-CPBA at 24°C gave the epoxides **308** in satisfactory yield (39%) as a mixture of diastereomers in a 2:1 ratio. Raising the temperature of the reaction mixture (refluxing DCM) or prolonging the reaction time (from 45 h to 96 h) gave substantial amounts of the epoxide opening product with *m*-

CPBA (10% to 29%) and did not improve the yield of the epoxide. The sluggish reaction and low yield can be attributed to the steric factors, since in our attempts the corresponding γ-allyl lactone, which is one carbon homologue to the γ-vinyl lactone **309**, under similar conditions gave 67% yield in 22 h at 22 °C.



Scheme 62. Synthesis of epoxy-lactones

Having the epoxides **308** (mixture of diastereomers) in hand we performed the epoxide opening (Scheme 63). We were very pleased to find that the epoxide opening proceeded in a regioselective manner resulting in a diastereomeric mixture of bicycloheptanes **312** and **313** in an *exo-endo* ratio of 1.8:1, in good yield (83-86%).

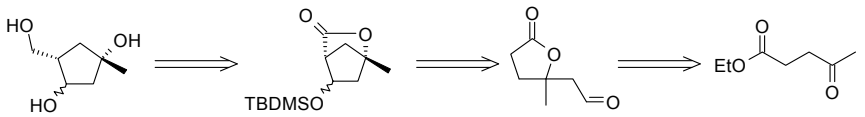


Scheme 63. Synthesis of 3'-desoxycarbasugar analogues

Subsequently, the *exo*-diastereomer **312** was treated consecutively with $LiAlH_4$ in refluxing THF (quenched with aqueous NaOH) and aq. 6 N HCl in a mixture of MeOH and THF to afford *trans*-diol **314** in 73% yield over two steps. The *endo*-diastereomer **313** afforded *cis*-diol **315** directly in 72% yield after treatment with $LiAlH_4$ in refluxing THF and quenching with aqueous NaOH.

3.2.2 Cyclopentanes from cyclization of lactone aldehydes

To gain access to 1-methyl-5-silyloxy regioisomeric bicyclic products **316** and **317**, a route through aldehyde **318** was envisioned.

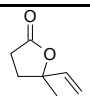
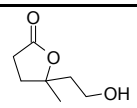
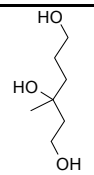
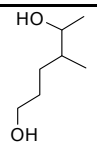
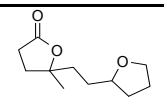


Scheme 64. Retrosynthetic approach to 1,3-cyclopentanediols

To reach the goal, synthesis of the aldehyde **318** needed to be accomplished. First, we tried to use the same starting compound γ-vinyl lactone **309** as in the previous case. Hydroboration of the intermediate vinyl lactone **309** with the subsequent oxidation of lactone alcohol seemed to lead to the desired aldehyde **318**.

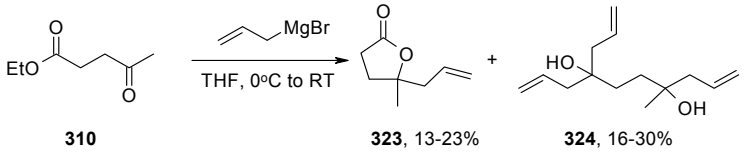
Despite many attempts to hydroborate the alkene **309** by using Me_2S*BH_3 in THF followed by oxidation with $NaBO_3*4H_2O$, at best we got a mixture of the products (Table 2). When two equivalents of BH_3*Me_2S were used for hydroboration (Table 2, entry 1), the yield of desired alcohol **319** was moderate (33%) and was accompanied by overreduction products **320** (8.5%) and 321 (22%). The latter was produced by a hydroboration-elimination-hydroboration sequence[160] of double bond carbon adjacent to the tertiary hydroxyl group in starting material **309**. Increasing the reaction time to 48 h at 22 °C (Table 2, entry 2) led to complete consumption of the starting material **309** but also an increased amount of overreduction products **320** and **321** (25% and 29% respectively), while the yield of product **319** (25%) decreased. Increasing the amount of BH_3 used in the reaction to three equivalents and conducting the reaction at 0 °C for two hours led to a somewhat better yield of product **319** (39%), but almost the same amounts of overreduction products **320** (8%) and **321** (24%) (Table 2, entry 3; compare with Table 2, entry 1). Changing the temperature regimen of the reaction led to complete consumption of the starting alkene **309**, a slightly decreased yield of alcohol **319** (32%) and increased amounts of overreduction products **320** (12%) and **321** (38%) (Table 2, entry 4). When the steric bulk of the boron reagent was increased, the reaction became sluggish and after 44 hours at RT 25% of the starting material **309** and only 8% of the desired alcohol **319** was still formed, giving a radical coupling product **322** of alkene **309** and THF as the main component of the reaction mixture instead (35%; Table 2, entry 5),

Table 2. Hydroboration of γ-vinyllactone

Entry	**Conditions**	 **309**	 **319**	 **320**	 **321**	 **322**
1	BH_3, 67 mol%	11%	33%	8.5%	22%	-

	1 h at 0°C and 16 h at 22°C					
2	BH_3, 67 mol% 48 h at 22°C	-	25%	25%	29%	-
3	BH_3, 100 mol% 2 h at 0°C	8%	39%	8%	24%	-
4	BH_3, 100 mol% 1 h at 0°C and 1.5 h at 22°C	-	32%	12%	38%	-
5	Sia_2BH, 110 mol%, 0-RT, 44 h	25%	8%	-	-	35%

As a result, poor chemo- (at best 1.2:1 in favor of hydroboration) and regioselectivity (at best 2:1 in favor of terminal alkene carbon) and the unfavorable steric effect of bulky borane to the outcome of the hydroboration reaction prompted us to pursue a different synthetic path to obtain the desired aldehyde **318**. Thus, we turned to the oxidative cleavage of the double bond in allylic γ-lactone **323**. We started with a straightforward allylic Grignard addition to 4-oxopentanoic ester **310** to accomplish the first step (Scheme 65). Unfortunately, the Grignard reaction gave unsatisfactory results, leading to mixtures of mono- and triaddition adducts in various ratios (Table 3): at 5 °C the yields of compounds **310**, **323** and **324** were 39%, 13% and 30%, respectively (Table 3, entry 1), while at -40 °C they were 55%, 23% and 17% (Table 3, entry 2) and at -78°C 58%, 16% and 16% (Table 3, entry 3). These results clearly indicate the non-feasibility of the Grignard reaction to produce the desired allylic lactone **323**. Allylmagnesium chloride proved to possess similar reactivity towards the starting material **310** and also to the primary product **323** under the applied conditions. In the literature, we found another possibility introduced by Estevez *et al.*[161] – a Ti(III)-mediated Barbier type allylation of ethyl levulinate **310**.



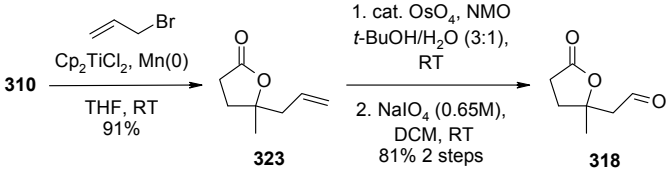
Scheme 65. Grignard reaction of levulinic acid ester

Table 3. Grignard reaction of ethyl levulinate*

Entry	310	323	324	Temperature
1	39%	13%	30%	5 °C
2	55%	23%	17%	-40 °C
3	58%	16%	16%	-78 °C

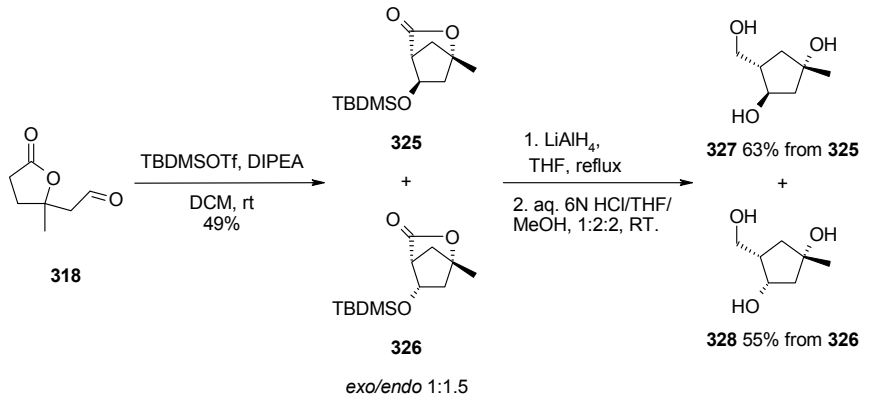
* All the reactions were run with 1.1 eq. of Grignard reagent in 1.1 M THF solution and the yields were determined from NMR spectra of crude

When we attempted allylation of substrate **310** by using the above-mentioned method with the use of allylbromide instead of allylchloride, we obtained the desired allylic lactone **323** in 63% yield, when a halide twofold excess was used, and in 91% yield when using only a 1.5-fold excess of the reagent (Scheme 66); the main side product was compound **324** in a small amount. Thus, a reduced amount of allylating reagent can be used in comparison to the original publication if allyl magnesium bromide is used instead of allyl magnesium chloride.



Scheme 66. Synthesis of lactone aldehyde

Having the allylic γ-lactone **323** in hand, we set out to produce aldehyde **318** *via* an osmium-catalyzed dihydroxylation of double bond with subsequent $NaIO_4$-induced oxidative cleavage of the formed diol. Indeed, we got the desired product **318** in 70-81% yield over two steps. The cyclization of **318** that was effected under the conditions previously reported by Rassu *et al.*[162] with the TBDMSOTf/DIPEA system resulted in a diastereomeric mixture of bicycloheptanes **325** and **326** in 47 to 49% isolated yield (Scheme 67), with an *exo/endo* ratio ranging from 1:1.4 to 1:1.8, depending on the addition time (the reaction time was increased from 10 min to 70 min). Separation of the diastereomers **325** and **326** was achieved by a simple chromatography and the subsequent transformations were carried out on the relevant *exo*- or *endo*-isomers separately. Thus, **325** was treated with $LiAlH_4$ in THF and then with a 1:2:2 mixture of aqueous 6N HCl, MeOH and THF to afford the *trans*-1,3-carbasugar analogue **327** in 63% yield over two steps. Treatment of **326** gave *cis*-1,3-carbasugar analogue **328** in 55% yield in just one step after the work-up of the reduction reaction mixture.



Scheme 67. Synthesis of 2'-desoxycarbasugar analogues

3.3. Configuration of bicyclic intermediates

For the determination of configurations of bicyclic intermediates **312**, **313**, **325** and **326**, well known regularities in the NMR spectra of the related bicyclo[2.2.1]heptane derivatives were used (Figure 5).[163–165] In ^{13}C NMR spectra, when C-5 or C-6 have *exo*-OX substituents, the C-7 signal is shifted up field.[166,167] In our case, for the C-7 of the *exo*-isomer **312**, the chemical shift was 40.6 ppm and for the *endo*-isomer **313** 42.7 ppm; in **325** and **326** the corresponding values were 41.9 and 43.4 ppm (see Tables 4 and 5). In ^1H NMR spectra, the ^3J for H-5, *exo*-H-4 is always larger than the ^3J for H-5*endo*-H-4. In the compound **325** the relevant coupling constant (4.3 Hz) was smaller than that in **326** (1.3 Hz), thus revealing the *exo*-configuration of the H-5 proton (Table 5). In compound **312**, two H-5 protons were present, with H-5*exo*-H-4 value 4.3 Hz and H-5*endo*-H-4 value 0.7 Hz, whereas in **313** the corresponding values were 4.6 and 0.6 Hz respectively (Table 4).

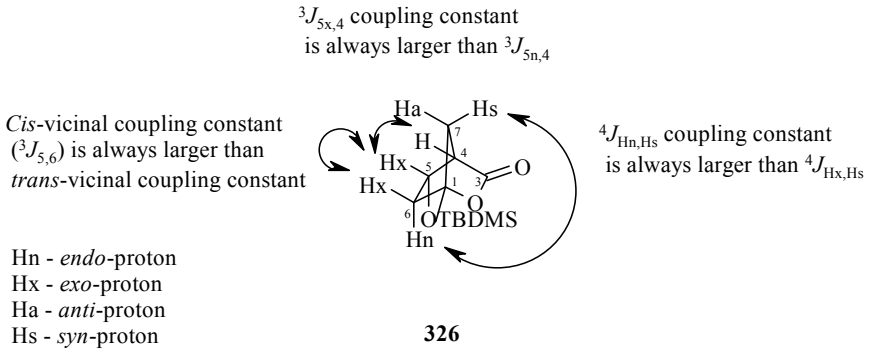
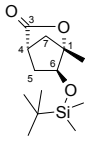
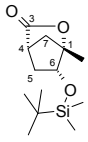


Figure 5. Relevant interactions for the structure determination

As a rule, the vicinal proton-proton couplings ^3J have higher values when protons are *cis*-oriented. In the case of compounds **312** and **313**, having established H-5-*exo*- and H-5-*endo*-protons, the relative configuration of H-6 was revealed by inspecting

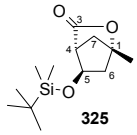
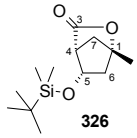
the relevant ^{3}J coupling values H-5-*exo*-H-6 and H-5-*endo*-H-6, which for **312** were 2.7 and 6.6 Hz and for **313** 9.0 and 3.3 Hz, respectively (Table 4).

Table 4. ^{1}H *J* coupling constants of 6-*exo*/*endo*-1-methylbicyclic compounds

Compound	δ^{13}C	δ^{1}H	Atom	4	5x	5n	6n	7s	7a
 **312**	41.14	2.72	**4**		-	-	-	-	-
	36.16	1.59	**5x**	4.3		-	-	-	-
		2.17	**5n**	0.7	13.2		-	-	-
	73.27	3.82	**6n**	-	2.7	6.6		-	-
	40.65	1.88	**7s**	1.6	-	2.3	1.6		-
		1.98	**7a**	1.2	-	-	-	10.6	
Compound	δ^{13}C	δ^{1}H	**Atom**	**4**	**5x**	**5n**	**6x**	**7s**	**7a**
 **313**	43.63	2.79	**4**		-	-	-	-	-
	35.64	2.31	**5x**	4.6		-	-	-	-
		1.50	**5n**	0.6	13.3		-	-	-
	74.61	4.14	**6x**	-	9.0	3.3		-	-
	42.74	1.95	**7s**	1.9	-	3.4	-		-
		1.72	**7a**	1.0	-	-	-	10.8	

^{4}J between H-7-*syn* and H-6 (and H-5) *endo*-protons is equally informative for the determination of configurations in **312**, **313**, **325** and **326** by ^{1}H NMR spectra. Thus, the ^{4}J for *endo*-protons is always larger than that for *exo*-protons.[163] The H-6-*endo* of **312** is coupled to H-7-*syn* with 1.6 Hz value (Table 4), whereas the H-5-*endo* of **325** is coupled to H-7-*syn* with 1.3 Hz value (Table 5).

Table 5. ^{1}H *J* coupling constants of 5-*exo*/*endo*-1-methylbicyclic compounds

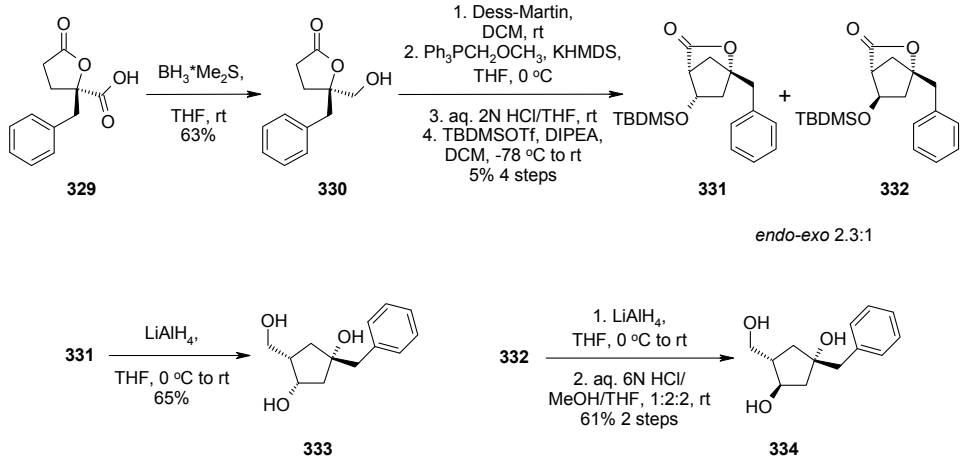
Compound	δ^{13}C	δ^{1}H	Atom	4	5n	6x	6n	7s	7a
 **325**	53.31	2.71	**4**		-	-	-	-	-
	70.22	4.26	**5n**	1.3		-	-	-	-
	47.03	1.52	**6x**	1.3	2.0		-	-	-
		2.18	**6n**	-	6.6	13.8		-	-
	41.87	1.92	**7s**	1.3	1.3	-	2.8		-
		2.15	**7a**	1.4	-	-	-	10.4	
Compound	δ^{13}C	δ^{1}H	**Atom**	**4**	**5x**	**6x**	**6n**	**7s**	**7a**
 **326**	51.72	2.92	**4**		-	-	-	-	-
	70.61	4.54	**5x**	4.3		-	-	-	-
	43.72	2.10	**6x**	-	8.7		-	-	-
		1.64	**6n**	-	3.1	13.7		-	-
	43.40	1.96	**7s**	1.6	-	-	3.9		-
		1.65	**7a**	1.2	-	-	-	10.7	

Taking into account all the relevant information given above, the relative configuration of bicyclic compounds **312**, **313**, **325** and **326** was unambiguously determined, thus letting us also establish the relative configurations of the derived diols **314**, **315**, **327** and **328**. On the other hand, the obtained information about the relative configuration of compounds **314** and **328** was in good accordance with our

previous observation[168] that ^{13}C chemical shifts of 1-methyl-substituted vicinal diols were dependent on the *cis*-*trans* substitution pattern. The CH_3-group should have a ^{13}C chemical shift up field in *trans*-diol relative to *cis*-diol; in the case of **314**, the CH_3-group had a chemical shift at 22.08 ppm and, in the case of **315**, at 25.24 ppm. Furthermore, the C-1 and C-2 carbons in 1-methyl-1,2-cyclopentanediols should have chemical shifts up field when *cis*-substitution is observed relative to the *trans*-substituted diol. Indeed, chemical shifts for C-1 and C-2 carbons in **315** were 79.05 and 78.63 ppm, whereas in **314** the corresponding shifts were 81.81 and 81.07 ppm. These results correlate with the observation that reduction of **312** and **313** should give **314** and **315**, respectively, and thus this confirmed the assignment of the relative configuration of the bicyclic intermediates **312** and **313**.

3.3.1 Synthesis of chiral benzyl-2'-desoxycarbasugar analogue

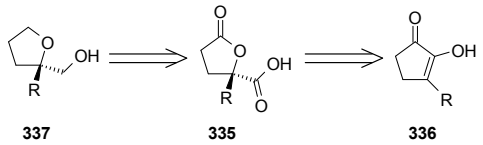
Since we had relatively convenient access to the enantiomeric γ-lactone acid **329**,[145] it was most appropriate to confirm the utility of the above-described method in the synthesis of a carbasugar analogue, thus complementing our synthetic endeavors. Thus, substrate **330** obtained from lactone acid by borane reduction was oxidized according to the Dess-Martin procedure,[169] followed by the Wittig reaction, hydrolysis with aqueous hydrochloric acid and TBDMSOTf, and DIPEA-induced cyclization at -78°C (Scheme 68), as described previously by Rassu *et al*.[162] The silylated bicyclic intermediates as a mixture of *endo*-*exo*-isomers **331** and **332** in 2.3:1 ratio and in moderate overall yield (5.4%) over four steps starting with carboxylic acid **329** were obtained. Further elaboration of lactones to *cis*-diol **333** and *trans*-diol **334** was achieved by reduction of the ester moiety with $LiAlH_4$ and, in the case of *trans*-diol **334**, additionally by removal of the silyl protecting group. As a result, it was shown that hydroxymethyl-1,3-diols can be accessed starting with lactones **329** from asymmetric oxidation. However, the overall efficiency of the process needs to be further improved.



Scheme 68. Synthesis of chiral 2'-desoxycarbasugar derivatives by a semi-telescoped process

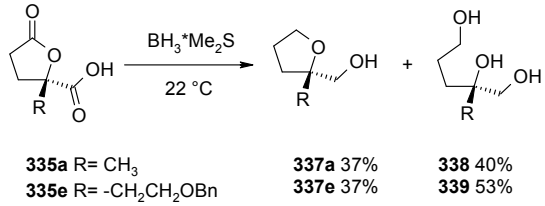
3.4. Enantiomeric tetrahydrofuran analogues (Article II)

In recent years, our group has developed a simple and enantioselective method for synthesizing chiral lactone carboxylic acids **335** from diketones **336**.[170,171] The ease of access and wide possible structural variability of the chiral building block **335** motivated us to broaden the practical scope of the compounds: to use the lactone carboxylic acids **335** for the synthesis of chiral tetrahydrofuran derivatives **337** as proposed in Scheme 69.



Scheme 69. Proposed retrosynthetic route to chiral THF-derivatives

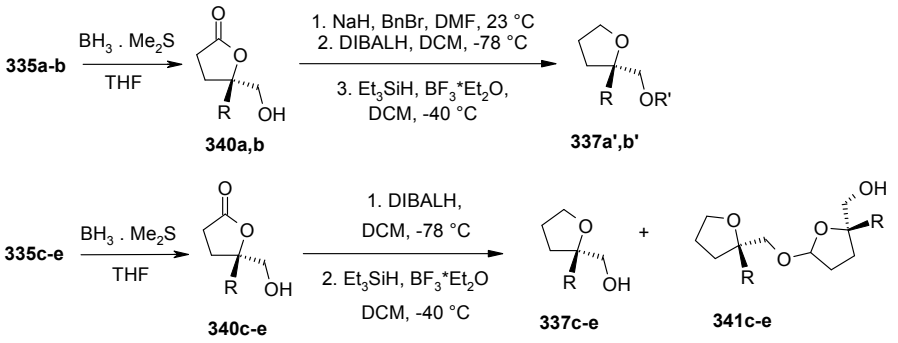
To transform the lactone acid skeleton to a tetrahydrofuran ring, an attempt to use the direct reduction approach proposed by Verma *et al.*[172] for triarylsubstituted dihydrofuranones with neat $BH_3 \cdot Me_2S$ (11 eq.) was made. However, with methylsubstituted lactone **335a,** this single-step procedure at room temperature gave a two-component mixture: hydroxymethyl tetrahydrofuran alcohol **337a** and triol **338** with 77% combined isolated yield in 1:1 ratio (Scheme 70). Also, with benzyloxyethyl lactone acid **335e,** the reaction was not selective, resulting in tetrahydrofuran alcohol **337e** and triol **339** with 90% overall isolated yield, in 1:1.4 ratio. Using different borane complexes as reductive agents, e.g. $BH_3 \cdot NH_3$, $BH_3 \cdot THF$, $BH_3 \cdot Me_2S/BF_3 \cdot Et_2O$, did not improve the result of ether **337a** from **335a**.



Scheme 70. Direct reduction of carboxylic acids

According to the literature, there are several reduction options to transform lactones into cyclic ethers, e.g. $NaBH_4/BF_3 \cdot Et_2O$[173], $DIBALH/Et_3SiH/BF_3 \cdot Et_2O$[174], manganese acetyl complexes/$PhSiH_3$[175], titanocene complexes/ PMHS/Et_3SiH/Amberlyst 15[176], $TiCl_4$/TMSOTf/Et_3SiH[177], and ruthenium complexes/ $EtMe_2SiH$.[178] The approach developed by Kraus *et al.*[174], where DIBALH at –78ºC with Et_3SiH and $BF_3 \cdot Et_2O$ in DCM are used, was selected by us and applied to our synthetic scheme. Thus, a three-step sequence involving triple reduction (with $BH_3 \cdot Me_2S$[179], DIBALH and Et_3SiH) of lactone carboxylic acids **335** to the tetrahydrofuran alcohols **337** was commenced. Reduction of the free carboxylic group afforded lactone alcohols **340a-e** in yields ranging from 68 to 77% (Scheme 71, Table 6). These alcohols were subjected to standard benzylation conditions and then reduced by DIBALH/Et_3SiH when R= CH_3 or CH_2CH_3 and directly with DIBALH/Et_3SiH, when R= Bn, CH_2OBn or CH_2CH_2OBn. The 2,2-

disubstituted THF-derivatives **337a-e** were obtained in 48-75% yield over three or two steps, respectively (Table 6).



R = a) -CH_3, b) -C_2H_5, c) -Bn, d) -CH_2OBn, e) -C_2H_4OBn
R' = a'-b') -Bn

Scheme 71. Three-step sequence to THF-derivatives

Table 6. Synthesis of tetrahydrofuran derivatives

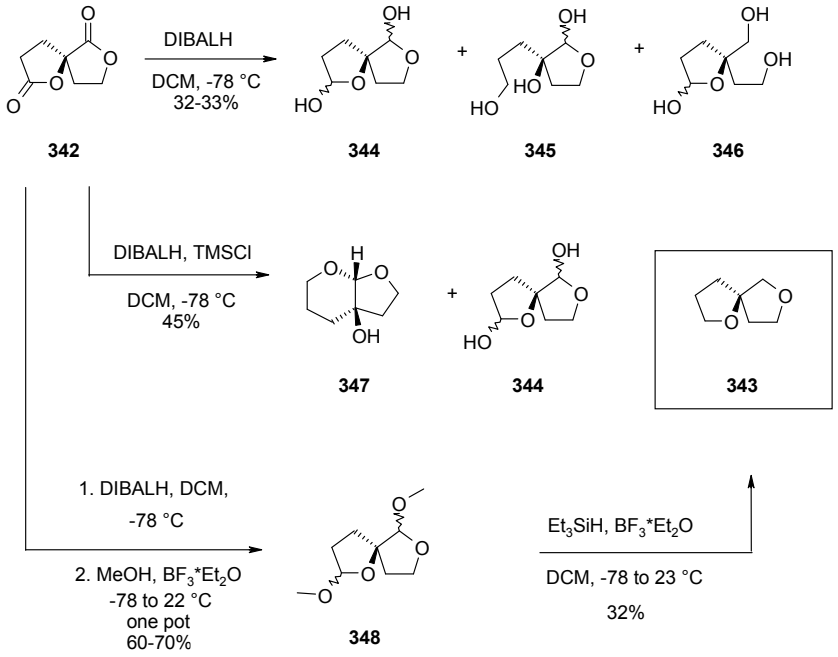
Entry	Substrate	340	337
1	**335a**	74%	
2	**b**	73%	
3	**c**	71%	
4	**d**	68%	
5	**e**	77%	
6	**340a**		48%†
7	**b**		57%†
8	**c**		75%
9	**d**		64%
10	**e**		70%

†The yields over two steps (protection and reduction)

The yields of the reduction step were somewhat lower for compounds without protecting groups than for the protected compounds. During the direct Lewis acid promoted silane reduction of **340**, intermolecular acetalization of the product **337** with the starting compound **340** was observed, leading to byproducts **341c-e** in 7-10% yield. This reaction transformed some amount of the starting material to an unreactive acetal, and so diminished the overall yield. The byproduct itself is easily separable from the target product by simple chromatography. However, the yields of the target tetrahydrofuran derivatives **337c-e** were higher (64–75%) than the overall yield of compounds **337a'-b'** with the corresponding protection steps (48% and 57%, Table 6). Deprotection would additionally decrease the yield of the whole

reaction sequence. Thus, for the synthesis of compounds **337** the protection-free approach is favorable.

Spirodilactone **342,** for which a synthetic method has been described earlier,[180] can be envisioned as a starting point to arrive at spiro-tetrahydrofuran compound **343**. Thus, we pursued the reduction of **342** with DIBALH and obtained a mixture of diastereomeric acetal **344** and hemiacetal diols **345** and **346**, as determined by NMR analysis of the crude product (Scheme 72). These results led us to search for more suitable methods for reducing spirodilactone **342**. A similar over-reduction problem was also observed in the synthesis of conformationally restricted spirocyclic nucleosides by Paquette *et al.*[182], and they solved the problem by using low concentration DIBALH in the presence of an excess of a Lewis acid (4.5 eq. Me_3SiCl). We applied that method to the reduction of spirodilactone **342** and obtained lactol **344**, together with bicyclic acetal **347** as a single diastereomer (up to 45% yield; Scheme 72).



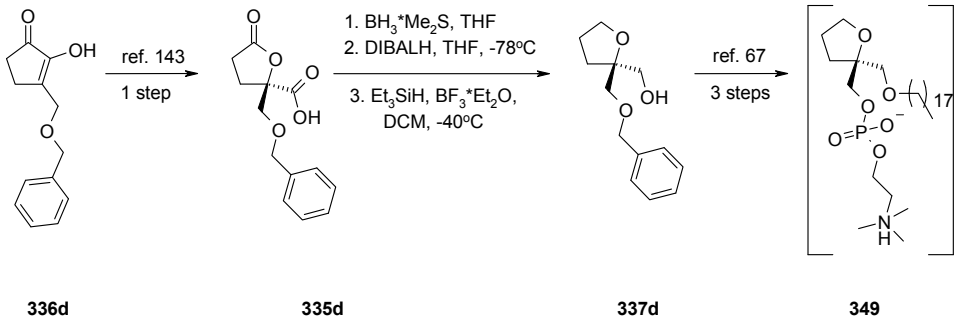
Scheme 72. Synthesis of spirodiether

Separation of the lactols from the reaction mixture after hydrolysis (containing $Al(OH)_3$) is sometimes complicated. In order to improve the yield of acetal **344** (to extract it from the aluminum hydroxide), we used an in situ trapping of the formed lactols as methylacetals **348** by quenching the DIBALH reaction with an excess of dry MeOH in the presence of one equiv of $BF_3{\cdot}Et_2O$. This method afforded stable yields of **348** (~70%). This compound was used in the following step without purification. Silane reduction[135,183] of **348** proceeded smoothly, with a slight modification of the original protocol: a stoichiometric amount of $BF_3{\cdot}Et_2O$ was used at -45ºC to rt. instead of a catalytic amount at rt, to furnish the volatile spiro-tetrahydrofuran **343** exclusively in 32% isolated yield after purification (the product

partly co-evaporated during solvent removal, reducing the isolated yield) (Scheme 72).

3.5. Formal synthesis of (S)-SRI-62-834

THF-derivative **337d** is a key intermediate for the synthesis of the anti-tumor agent (S)-SRI-62-834 **349**[48] (Scheme 73). This compound has been obtained previously by a multi-step sequence that includes enzymatic resolution of the acetylated tetrahydrofuran-2,2-methanol.[67] Our approach involves asymmetric oxidation,[145] which affords lactone acid **335d** in good yield (75%) and high stereoselectivity (*ee* 96%). Moreover, both enantiomers can be accessed by simply switching the ligand from (+)-DET to (-)-DET.



336d **335d** **337d** **349**

Scheme 73. Formal synthesis of (S)-SRI-62-834 **349**

The **335d** was transformed to the key intermediate **337d** by three consecutive reductions: borane dimethylsulfide complex, DIBALH and Et_3SiH in the presence of BF_3*Et_2O. Further transformations to reach **349** followed the literature route described by Repic *et al*.[67]

Conclusions

- A method of synthesizing regioselectively chiral 3-methyl-2,3-dihyroxy- and 2-methyl-2,5-dihydroxy cyclopentanones, starting with mono-oxidation of 3-methyl-cylopentanone-1,2-dione, was developed.

- γ-Lactones were shown to be feasible starting compounds for the synthesis of regioisomeric cyclopentane 1,2- and 1,3-diols:

  a) γ-Vinyl oxide of cyclopentane γ-lactone led to 4-hydroxymethyl-1-methyl-1,2-cyclopentanediols after intramolecular regioselective epoxide opening, effected by the TBDMSOTf/DIPEA system and reduction

  b) γ–(2-oxomethyl)-γ-lactone led to 4-hydroxymethyl-1-methyl-1,3-cyclopentanediols after intramolecular regioselective addition reaction, also effected by the TBDMSOTf/DIPEA system and reduction.

  c) γ-Benzyl-γ-lactone carboxylic acid from asymmetric oxidation afforded access to chiral 1-benzyl-4-hydroxymethyl-1,3-cyclopentanediols, offering a general method for those 1-alkyl-substituted cyclopentanediols.

- A simple route to chiral 2,2-disubstituted tetrahydrofuran derivatives was developed, starting with enantiomeric γ-lactones. Tetrahydrofurans were obtained. A three-step reaction sequence was applied to the synthesis of 1,7-dioxaspiro[4.4]nonane from enantiomeric spirodilactone.

- A formal synthesis of the key intermediate of the anti-tumor agent SRI-62-834 was developed.

- ^{13}C NMR study of cyclopentanetriols and cyclopentanediols enables unambiguous determination of their relative configurations.

Experimental

Materials and methods

Chemicals were purchased from the Aldrich Chemical Co and Lancaster and were used as received. DCM was distilled over CaH_2 and stored on 3Å molecular sieve pellets. THF and ether were distilled over $LiAlH_4$. Acetone was refluxed on K_2MnO_4 after persisting color was distilled, dried over K_2CO_3 2d, then distilled and stored over 4 Å molecular sieve pellets. Pre-coated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40-100 μm was used. NMR spectra were determined in $CDCl_3$, CD_3OD or DMSO-d_6 on a Bruker AMX-500 or Avance USLA 400 spectrometer. Solvent peaks ($CHCl_3$ δ=7.27, CHD_2OD δ=3.30, $CDCl_3$ δ=77.00, and CD_3OD δ=49.00) were used as chemical shift references. 2D FT methods were used for the analysis of synthesized compounds. IR spectra were measured on a Perkin-Elmer Spectrum BX FTIR spectrometer. Mass spectra were recorded on a Hitachi M80B spectrometer using EI (70 eV) or CI (isobutane) mode or on a Shimadzu GCMSQP2010 spectrometer using EI (70 eV). High resolution mass spectra were recorded on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer and utilizing AJ-ESI ion sources. Elemental analyses were performed on a Perkin Elmer C,H,N,S-Analyzer 2400. Optical rotations were obtained using a Krüss Optronic GmbH Polarimeter P 3002. All reactions sensitive to moisture or oxygen were carried out under an Ar atmosphere in oven-dried glassware.

Bicyclic intermediates

To the stirred solution of Dess-Martin periodinane (1.14 g, 2.7 mmol) in DCM (11 mL) at 23°C, lactone alcohol **330** (500 mg, 2.42 mmol) was added in DCM (9 mL) dropwise and the reaction mixture was stirred at 23°C for 25 min, after which precipitation occurred. The reaction mixture was diluted with DCM (50 mL) and poured into aq. saturated mixture of $NaHCO_3$ and $Na_2S_2O_3$ (15 mL). The organics were separated and washed with sat. $NaHCO_3$ (15 mL) and water (15 mL), dried over $MgSO_4$ and filtered, and the volatiles were evaporated to give crude aldehyde (562 mg) as light yellow oil. The crude aldehyde in THF (2 mL) was added to the preformed ylide (1.06 g, 3.08 mmol $PhPCH_2OCH_3$ Cl^- and 610 mg, 3.05 mmol KHMDS) in THF (11 mL) at 0°C and stirred for 10 min at the same temperature, after which the reaction was quenched by adding the reaction mixture to aq. sat. NH_4Cl (5 mL) at 0°C. The water phase was extracted with EtOAc, dried over Na_2SO_4 and filtered, and the solvents were evaporated to yield crude vinyl ether (1.25 g), which was taken up in THF (10 mL), and then aq. 2N HCl was added at 0°C. After stirring the reaction mixture for 3.5 h, aq. sat. $NaHCO_3$ (20 mL) was added. The obtained solution was extracted with EtOAc, dried over $MgSO_4$ and filtered, and the volatiles were removed. The resulting crude (1.02 g) was dissolved in DCM (10 mL) and added dropwise to the solution of DIPEA (0.96 mL, 5.5 mmol) and TBDMSOTf (1.26 mL, 5.5 mmol) in DCM (20 mL) at 0°C, stirred at 23°C for 3 h and quenched with NH_4Cl (5 mL). The layers were separated and the water phase

extracted with DCM (5×15 mL), dried over $MgSO_4$ and filtered, and the solvents were evaporated. The crude product was purified by flash chromatography (SiO_2, PE/Acetone 50:1) to yield **331** as colorless oil (33 mg, 4 %, four steps) and **332** as colorless oil (12 mg, 1.4 %, four steps).

***endo*-(1*R*,5*R*,6*R*)-1-Benzyl-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-oxa-bicyclo[3.2.1]heptan-4-one 331**

$[\alpha]^{D}_{22}$= 0.12 ($CHCl_3$, c=7.27). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27-7.12 (m, 5H, -Bn), 4.40 (ddd, 1H, *J*= 3.1, 4.1, 8.6 Hz, 5C-Hx), 3.05 (m, 2H, Bn), 2.82 (d, 1H, *J*= 4.3 Hz, 4C-H), 2.05 (dd, 1H, *J*=8.7 Hz, *J*=13.6 Hz, 6C-Hn), 1.88 (ddd, 1H, *J*=1.5, 3.8, 10.7, 7C-Hs), 1.53-1.42 (m, 2H, 6C-Hx and 7C-Ha), 0.80-0.78 (s, 9H, *t*-Bu), 0.01 – (-0.01) (s, 6H, $Si(CH_3)_2$); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 174.54 (C-3), 135.45 (s), 130.02 (o), 128.50 (m), 126.97 (p), 91.07 (C-1), 70.26 (C-5), 50.88 (C-4), 41.57 (C-6), 39.77 (C-7), 25.68 (-$(CH_3)_3$), 17.97 (*tert*-C), -5.0 (Si-$(CH_3)_2$). IR (neat) 3063, 2952, 2856, 1786, 1605, 1471, 1361, 1321, 1252, 1109, 986, 900, 838, 777, 703; MS m/z: 275 $(M-57)^+$, 257, 155, 129, 91, 75 (Base). Anal. calcd. for $C_{19}H_{28}O_3Si$: C 68.63, H 8.49 found C 68.57, H 8.55.

***exo*-(1*R*,5*R*,6*R*)-1-Benzyl-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-oxa-bicyclo[3.2.1]heptane-4-one 332**

$[\alpha]^{D}_{22}$= 0.14 ($CHCl_3$, c=1.94). 1H-NMR (400 MHz, $CDCl_3$): δ 7.30-7.15 (m, 5H, -Bn), 4.26 (d, 1H, *J*= 6.0 Hz, 5C-Hn), 3.21-3.07 (m, 2H, -Bn), 2.72 (s, 1H, 4C-H), 2.20-2.10 (m, 2H, 7C-Ha), 1.95-1.90 (m, 1H, 7C-Hs), 1.59-1.54 (d, 1H, 6C-Hx), 0.79 (s, 9H, *t*-Bu), 0.02 (s, 6H, $Si(CH_3)_2$). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 176.24 (C-3), 135.77 (s), 129.95 (o), 128.42 (m), 126.95 (p), 92.67 (C-1), 69.78 (C-5), 52.56 (C-4), 45.18 (C-6), 39.93 (C-7), 25.69 (-$(CH_3)_3$), 17.94 (*tert*-C), -4.95 (Si-$(CH_3)_2$). IR (neat) 3030, 2954, 2857, 1781, 1605, 1471, 1361, 1256, 1173, 1097, 834, 701. MS m/z = 332 $(M)^+$, 275, 231, 91, 75 (base). Anal. calcd. for $C_{19}H_{28}O_3Si$: C 68.63, H 8.49 found C 68.53, H 8.48.

((1*R*,3*S*,4*S*)-1-Benzyl-4-hydroxymethyl)-cyclopentane-1,3-diol 333

Dissolve the *endo*-isomer (26 mg, 0.08 mmol) in THF (5 mL) and add $LiAlH_4$ (31 mg, 0.78 mmol) at 0°C. Stir until no starting material is detected by TLC and quench the reaction with sat. aq. Seignette's salt (5 mL). Add EtOAc (20 mL), separate the layers and extract the water phase with EtOAc (4×20 mL). Dry over $MgSO_4$, filter the solids off and evaporate the volatiles to get the crude product. Further purification was achieved by flash chromatography on SiO_2 eluting with DCM/MeOH 20:1 to 10:1 mixture to get **333** (10.5 mg, 0.05 mmol, 65%) as light yellow oil.

$[\alpha]^{D}_{25}$= -0.96 (MeOH, c=0.24). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.25 (t, *J*=4.2, 4H, Bn-*o*, Bn-*m*), 7.19 (m, 1H, Bn-*p*), 4.22 (td, *J*=4.8, 2.2, 1H, H-3), 3.77 (m, 1H, CH_2OH), 3.58 (m, 1H, CH_2OH), 2.82 (m, 2H, Ph-CH_2), 2.04 (m, 3H, H-4, H-5, H-2), 1.71 (m, 1H, H-2), 1.58 (m, 1H, H-5). ^{13}C NMR (101 MHz, CD_3OD) δ = 138.51 (Bn-*i*), 130.58 (Bn-*o*), 127.95 (Bn-*m*), 126.27 (Bn-*p*), 81.26 (C-1), 73.52 (C-3), 62.23 (*C*H_2OH), 47.51 (C-2), 47.39 (Ph-*C*H_2), 46.52 (C-4), 40.68 (C-5). IR, neat:

3374 (OH), 2931, 1434 (C-O), 1022 (C-O). MS m/z: 186 $(M-36)^+$, 171, 163, 131, 113, 92 (base), 91, 71, 67, 43. HRMS (ESI) calcd. for $C_{13}H_{18}O_3Na$: 245.1148 found 245.1128.

((1*R*,3*R*,4*S*)-1-Benzyl-4-hydroxymethyl)-cyclopentane-1,3-diol 334

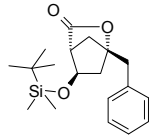
Dissolve the *exo*-isomer (18 mg, 0.05 mmol) in THF (5 mL) and add $LiBH_4$ (23 mg, 1.01 mmol) at 0°C. Stir until no starting material is detected by TLC and quench the reaction with saturated aq. NH_4Cl (2 mL) and saturated aq. 1M citric acid (5 mL). Add EtOAc (20 mL), separate the layers and extract the water phase with EtOAc (4×20 mL). Dry over $MgSO_4$, filter the solids off and evaporate the volatiles to get the crude product. Purify by flash chromatography (SiO_2, PE/Et_2O 4:1 to 1:1) to obtain TBDMS-derivative (12 mg, 0.04 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.15 (m, 5H, Bn), 4.29 (dt, J = 8.7, 6.3 Hz, 1H, H-3), 3.64 (qd, J = 10.4, 4.3 Hz, 2H, CH_2OH), 2.91 – 2.78 (m, 2H, PhCH_2), 2.13 (ddt, J = 15.2, 10.4, 7.7 Hz, 3H, H-5, H-4), 1.91 (ddd, J = 12.9, 6.6, 2.0 Hz, 1H, H-2), 1.71 (dd, J = 12.9, 8.7 Hz, 1H, H-2), 1.58 (s, 2H, OH), 1.39 (ddd, J = 12.9, 4.1, 2.0 Hz, 1H, H-5), 0.85 – 0.82 (m, 1H, H-5), 0.01 (t, J = 4.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.46 (Bn, *i*), 130.18 (Bn, *o*), 128.42 (Bn, *m*), 126.70 (Bn, *p*), 79.76 (C-1), 75.03 (C-3), 64.54 (*C*H_2OH), 49.42 (C-2), 48.85 (C-4), 47.41 (Ph*C*H_2), 40.24 (C-5), 25.83 (*t*-Bu, *C*H_3), 17.95 (*t*-Bu, *C*), -4.42 (*C*H_3Si), -4.78 (*C*H_3Si).

Subject the intermediate (6.8 mg, 0.02 mmol) to deprotection conditions (THF/MeOH/6N HCl, 1:1:0.4, total 1.2 mL) at rt for 2h. Evaporate the volatiles and purify the residue by flash chromatography on SiO_2, eluting with DCM/MeOH 20:1 to 10:1 mixture to get **334** (4.2 mg, 0.02 mmol, 94%) as light yellow oil.

$[\alpha]^D_{25}$= 1.34 (MeOH, c= 0.16). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.22 (m, 1H, Bn), 4.10 (m, 1H, H-3), 3.68 (dd, J=10.4, 5.3, 1H, H-6), 3.53 (dd, J=10.5, 7.0, 1H, H-6), 2.85 (m, 1H, PhCH_2), 2.15 (dd, J=13.9, 10.0, 1H, H-5), 1.95 (m, 1H, H-4, H-2), 1.69 (dd, J=13.0, 8.7, 1H, H-2), 1.43 (ddd, J=13.8, 6.1, 1.8, 1H, H-5). ^{13}C NMR (101 MHz, CD_3OD) δ = 139.56 (Bn, *i*), 131.59 (Bn, *o*), 128.94 (Bn, *m*), 127.23 (Bn, *p*), 80.61 (C-1), 75.18 (C-3), 65.68 (*C*H_2OH), 50.23 (C-4), 48.93 (C-2), 48.61 (Ph-*C*H_2), 41.45 (C-5). IR, neat: 3374 (OH), 2931, 1434 (C-O), 1022 (C-O). MS m/z: 186 $(M-36)^+$, 171, 163, 131, 113, 92 (base), 91, 71, 67, 43. HRMS (ESI) calcd. for $C_{13}H_{18}O_3Na$: 245.1148 found 245.1135.

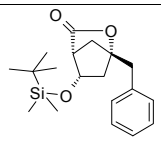
Appendix 1. ^{1}H *J* coupling constants of 5-*exo/endo*-bicyclic derivatives

Table 7. ^{1}H *J* coupling constants of 5-*exo*/*endo*-1-benzylbicyclic compounds



(1R,4R,5R)-1-Benzyl-5-(tert-butyl-dimethyl-silanyloxy)-2-oxa-bicyclo[2.2.1]heptan-3-one

δ^{13}C	δ^{1}H		**4**	**5n**	**6x**	**6n**	**7s**	**7a**		δ^{1}H	δ^{13}C
50.80	2.89	**4**		1.2	1.1	0.4	1.5	1.5	**4**	2.76	52.56
70.18	4.47	**5x**	4.3		2.0	6.7	1.5	-	**5n**	4.31	69.78
41.49	1.57	**6x**	-	8.8		13.9	-	0.5	**6x**	1.60	45.18
	2.31	**6n**	-	3.0	13.7		2.7	-	**6n**	2.19	
41.25	1.95	**7s**	1.7	-	-	3.9		10.4	**7s**	1.98	39.93
	1.58	**7a**	1.2	-	0.5	0.5	10.8		**7a**	2.20	
δ^{13}C	δ^{1}H		**4**	**5x**	**6x**	**6n**	**7s**	**7a**		δ^{1}H	δ^{13}C



(1R,4R,5S)-1-Benzyl-5-(tert-butyl-dimethyl-silanyloxy)-2-oxa-bicyclo[2.2.1]heptan-3-one

References

(1) Pinheiro, E.; Antunes, O.; Fortunak, J. *Antiviral Res.* **2008**, *79*, 143–165.

(2) De Clercq, E.; Neyts, J. *Rev. Med. Virol.* **2004**, *14*, 289–300.

(3) Clerq, E. D. *Nucleosides and Nucleotides* **1998**, *17*, 625–634.

(4) De Clercq, E. *Clin. Microbiol. Rev.* **1997**, *10*, 674–693.

(5) Simons, C.; Wu, Q.; Htar, T. T. *Curr. Top. Med. Chem.* **2005**, *5*, 1191–1203.

(6) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 1382–1384.

(7) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255–263.

(8) Watson, T. J. N.; Curran, T. T.; Hay, D. A.; Shah, R. S.; Wenstrup, D. L.; Webster, M. E. *Org. Process Res. Dev.* **1998**, *2*, 357–365.

(9) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272.

(10) Zhou, J.; Yang, M.; Akdag, A.; Wang, H.; Schneller, S. W. *Tetrahedron* **2008**, *64*, 433–438.

(11) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359–366.

(12) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286–3337.

(13) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533–1564.

(14) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185–210.

(15) Mueller, M. *Curr. Opin. Plant Biol.* **2004**, *7*, 441–448.

(16) Jahn, U.; Galano, J.-M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894–5955.

(17) Sarin, R. *Fitoterapia* **2004**, *75*, 62–64.

(18) Romanet, R. F.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 3701–3702.

(19) Kuethe, J. T.; Wong, A.; Wu, J.; Davies, I. W.; Dormer, P. G.; Welch, C. J.; Hillier, M. C.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5993–6000.

(20) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–554.

(21) Hancock, A. J.; Stokes, M. H.; Sable, H. Z. *J. Lipid Res.* **1977**, *18*, 81–92.

(22) Hancock, A.; Lister, M.; Sable, H. *J. Lipid Res.* **1982**, *23*, 183–189.

(23) Pajouhesh, H.; Hancock, A. J. *J. Lipid Res.* **1984**, *25*, 294–303.

(24) Pajouhesh, H.; Hancock, A. J. *J. Lipid Res.* **1984**, *25*, 310–312.

(25) Barlow, P. N.; Lister, M. D.; Sigler, P. B.; Dennis, E. A. *J. Biol. Chem.* **1988**, *263*, 12954–12958.

(26) Lin, S.; Chen, T.; Liu, X.-H.; Shen, Y.-H.; Li, H.-L.; Shan, L.; Liu, R.-H.; Xu, X.-K.; Zhang, W.-D.; Wang, H. *J. Nat. Prod.* **2010**, *73*, 632–638.

(27) Koshino, H.; Togiya, S.; Terada, S.; Yoshihara, T.; Sakamura, S.; Shimanuki, T.; Sato, T.; Tajimi, A. *Agric. Biol. Chem.* **1989**, *53*, 789–796.

(28) Takaoka, D.; Imooka, M.; Hiroi, M. *Phytochem.* **1979**, *18*, 488–489.

(29) Kaneko, T.; Ohtani, K.; Kasai, R.; Yamasaki, K.; Nguyen Minh Duc *Phytochem.* **1997**, *46*, 907–910.

(30) Arjona, O.; Gómez, A. M.; López, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919–2036.

(31) Kurteva, V. B.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 6809–6857.

(32) Lee, J. A.; Moon, H. R.; Kim, H. O.; Kim, K. R.; Lee, K. M.; Kim, B. T.; Hwang, K. J.; Chun, M. W.; Jacobson, K. A.; Jeong, L. S. *J. Org. Chem.* **2005**, *70*, 5006–5013.

(33) Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T.; Baba, M.; Yamaguchi, K.; Akita, H. *Chem. Pharm. Bull.* **1999**, *47*, 1256–1264.

(34) Audran, G.; Acherar, S.; Monti, H. *Eur. J. Org. Chem.* **2003**, *2003*, 92–98.

(35) Rassu, G.; Auzzas, L.; Zambrano, V.; Burreddu, P.; Battistini, L.; Curti, C. *Tetrahedron: Asymmetry* **2003**, *14*, 1665–1670.

(36) Che, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. *Tetrahedron Lett.* **2004**, *45*, 6891–6894.

(37) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303.

(38) Kladi, M.; Vagias, C.; Papazafiri, P.; Brogi, S.; Tafi, A.; Roussis, V. *J. Nat. Prod.* **2009**, *72*, 190–193.

(39) Yasumoto, T.; Muratat, M. *Chem. Rev.* **1993**, *93*, 1897–1909.

(40) Wong, H. N. C. *Eur. J. Org. Chem.* **1999**, 1757–1765.

(41) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279–282.

(42) Wu, J.; Li, N.; Hasegawa, T.; Sakai, J.; Kakuta, S.; Tang, W.; Oka, S.; Kiuchi, M.; Ogura, H.; Kataoka, T.; Tomida, A.; Tsuruo, T.; Ando, M. *J. Nat. Prod.* **2005**, *68*, 1656–1660.

(43) Sandler, J. S.; Colin, P. L.; Kelly, M.; Fenical, W. *J. Org. Chem.* **2006**, *71*, 7245–7251.

(44) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475–2480.

(45) Héthelyi, E.; Tétényi, P.; Kettenes-van den Bosch, J. J.; Salemink, C. A.; Heerma, W.; Versluis, C.; Kloosterman, J.; Sipma, G. *Phytochem.* **1981**, *20*, 1847–1850.

(46) Phuong, N. M.; Van Sung, T.; Porzel, A.; Schmidt, J.; Merzweiler, K.; Adam, G. *Phytochem.* **1999**, *52*, 1725–1729.

(47) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250–5281.

(48) Houlihan, W. J.; Lee, M. L.; Munder, P. G.; Nemecek, G. M.; Handley, D. A.; Winslow, C. M.; Happy, J.; Jaeggi, C. *Lipids* **1987**, *22*, 884 – 890.

(49) Doherty, G. A.; Yang, G. X.; Borges, E.; Chang, L. L.; Maccoss, M.; Tong, S.; Kidambi, U.; Egger, L. A.; Mccauley, E.; Riper, G. V.; Mumford, R. A.; Schmidt, J. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1501–1505.

(50) Khandelwal, A.; Narayanan, R.; Gopalakrishnan, B. *Bioorg. Med. Chem.* **2003**, *11*, 4235–4244.

(51) Babu, B. R.; Keinicke, L.; Petersen, M.; Nielsen, C.; Wengel, J. *Org. Biomol. Chem.* **2003**, *1*, 3514–3526.

(52) Lee, C.; Jiang, L.; Hang, H.-S.; Hon, P.-M.; He, Y.; Wong, H. N. C. *Br. J. Pharmacol.* **1991**, *103*, 1719–1724.

(53) Tasdemir, D.; Wright, A. D.; Sticher, O.; Çalis, I.; Linden, A. *J. Nat. Prod.* **1995**, *58*, 1543–1554.

(54) Midland, S. L.; Keen, N. T.; Sims, J. J.; Midland, M. M.; Stayton, M. M.; Burton, V.; Smith, M. J.; Mazzola, E. P.; Graham, K. J.; Clardy, J. *J. Org. Chem.* **1993**, *58*, 2940–2945.

(55) Cipolla, L.; Forni, E.; Jimenez-Barbero, J.; Nicotra, F. *Chem. Eur. J.* **2002**, *8*, 3976–3983.

(56) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290.

(57) Shin, C.; Oh, Y.; Cha, J. H.; Pae, A. N.; Choo, H.; Cho, Y. S. *Tetrahedron* **2007**, *63*, 2182–2190.

(58) DeAngelis, A.; Taylor, M. T.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 1101–1105.

(59) Mitchell, T. A.; Zhao, C.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5026–5029.

(60) Sim, J. Y.; Hwang, G.-S.; Kim, K. H.; Ko, E. M.; Ryu, D. H. *Chem. Commun.* **2007**, 5064–5065.

(61) Alonso, F.; Melendez, J.; Yus, M. *Tetrahedron Lett.* **2004**, *45*, 1717–1720.

(62) Donohoe, T. J.; Fisher, J. W.; Edwards, P. J. *Org. Lett.* **2004**, *6*, 465–467.

(63) Marco-Contelles, J.; Rodriguez-Fernandez, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 2249–2256.
(64) Masuda, T.; Osako, K.; Shimizu, T.; Nakata, T. *Org. Lett.* **1999**, *1*, 941–944.
(65) Maezaki, N.; Sawamoto, H.; Suzuki, T.; Yoshigami, R.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 8387–8393.
(66) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766–4768.
(67) Prasad, K.; Estermann, H.; Underwood, R. L.; Chen, C.-P.; Kucerovy, A.; Repic, O. *J. Org. Chem.* **1995**, *60*, 7693–7696.
(68) Choi, W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S. *J. Org. Chem.* **2001**, *66*, 6490–6494.
(69) Hong, J. H.; Shim, M. J.; Ro, B. O.; Ko, O. H. *J. Org. Chem.* **2002**, *67*, 6837–6840.
(70) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611–2613.
(71) Comin, M. J.; Leitofuter, J.; Rodriguez, J. B. *Tetrahedron* **2002**, *58*, 3129–3136.
(72) Ramana, C. V.; Sridhar Reddy, B.; Gurjar, M. K. *Tetrahedron Lett.* **2004**, *45*, 2817–2819.
(73) Bianco, A.; Celona, D.; Di Rita, S.; Guiso, M.; Melchioni, C.; Umani, F. *Eur. J. Org. Chem.* **2001**, *2001*, 4061–4066.
(74) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319–4348.
(75) Dauvergne, J.; Happe, A. M.; Jadhav, V.; Justice, D.; Matos, M. C.; McCormack, P. J.; Pitts, M. R.; Roberts, S. M.; Singh, S. K.; Snape, T. J.; others *Tetrahedron* **2004**, *60*, 2559–2567.
(76) Roy, A.; Schneller, S. W. *J. Org. Chem.* **2003**, *68*, 9269–9273.
(77) Roy, A.; Schneller, S. W. *Tetrahedron Lett.* **2005**, *46*, 8913–8915.
(78) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089–5090.
(79) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725.
(80) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459–2461.
(81) Stark, L. M.; Pekari, K.; Sorensen, E. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 12064–12066.
(82) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127–132.
(83) Boyce, G. R.; Liu, S.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 652–655.
(84) Barluenga, J.; Martinez, S. *Arkivoc* **2006**, *vii*, 129–147.
(85) Barluenga, J.; Alonso, J.; Fañanás, F. J. *Chem. Eur. J.* **2005**, *11*, 4995–5006.
(86) Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Manna, R. *Tetrahedron* **1997**, *53*, 11767–11780.
(87) Ley, S. V.; Michel, P.; Trapella, C. *Org. Lett.* **2003**, *5*, 4553–4555.
(88) Umino, K.; Furumai, T.; Matsuzawa, N.; Awataguchi, Y.; Ito, Y.; Okuda, T. *J. Antibiot.* **1973**, *26*, 506–512.
(89) Pohmakotr, M.; Kambutong, S.; Tuchinda, P.; Kuhakarn, C. *Tetrahedron* **2008**, *64*, 6315–6323.
(90) Mishra, G. P., Ramana, G. V., Rao, B. V. *Chem. Comm.* **2008**, 3423-3425.
(91) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457–5461.
(92) Stewart, A. J.; Evans, R. M.; Weymouth-Wilson, A. C.; Cowley, A. R.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2002**, *13*, 2667–2672.
(93) Morales, C. P.; Catalán, J.; Domingo, V.; González Delgado, J. A.; Dobado, J. A.; Herrador, M. M.; Quílez del Moral, J. F.; Barrero, A. F. *J. Org. Chem.* **2011**, *76*, 2494–2501.
(94) Liu, G.; Shirley, M. E.; Romo, D. *J. Org. Chem.* **2012**, *77*, 2496–2500.

(95) Baidya, M.; Griffin, K. A.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 18566–18569.
(96) Leemans, E.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2011**, *111*, 3268–3333.
(97) Hegedus, L. S.; Bates, R. W.; Soderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923–927.
(98) Reeder, L. M.; Hegedus, L. S. *J. Org. Chem.* **1999**, *64*, 3306–3311.
(99) Brown, B.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 1865–1872.
(100) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630.
(101) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835–1838.
(102) Paju, A.; Kanger, T.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2439–2448.
(103) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110–1111.
(104) Craig, R. A.; Roizen, J. L.; Smith, R. C.; Jones, A. C.; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5716–5719.
(105) Lipshutz, B. H.; Amorelli, B.; Unger, J. B. *J. Am. Chem. Soc.* **2008**, *130*, 14378–14379.
(106) Fernández-Mateos, A.; de la Nava, E. M.; Coca, G. P.; Silvo, A. R.; González, R. R. *Org. Lett.* **1999**, *1*, 607–610.
(107) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236–8246.
(108) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132–3139.
(109) Molander, G. A.; del Pozo Losada, C. *J. Org. Chem.* **1997**, *62*, 2935–2943.
(110) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 6375–6381.
(111) Hanzawa, Y.; Oka, Y.; Yabe, M. *J. Organomet. Chem.* **2007**, *692*, 4528–4534.
(112) Hanzawa, Y.; Takebe, Y.; Saito, A.; Kakuuchi, A.; Fukaya, H. *Tetrahedron Lett.* **2007**, *48*, 6471–6474.
(113) Buchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021–2023.
(114) Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P. *J. Org. Chem.* **1973**, *38*, 3440–3442.
(115) Taber, D. F.; Reddy, P. G.; Arneson, K. O. *J. Org. Chem.* **2008**, *73*, 3467–3474.
(116) Akiyama, T.; Fujii, T.; Ishiwari, H.; Imagawa, T.; Kawanisi, M. *Tetrahedron Lett.* **1978**, *19*, 2165–2166.
(117) Yadav, A. K.; Manju, M.; Kumar, M.; Yadav, T.; Jain, R. *Tetrahedron Lett.* **2008**, *49*, 5724–5726.
(118) Barbero, A.; Pulido, F. J.; Rincon, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 12049–12056.
(119) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624–1634.
(120) Tsuchikama, K.; Lowery, C. A.; Janda, K. D. *J. Org. Chem.* **2011**, *76*, 6981–6989.
(121) Hua, D. H.; Venkataraman, S. *Tetrahedron Lett.* **1985**, *26*, 3765–3768.
(122) Oppolzer, W.; Cunningham, A. F. *Tetrahedron Lett.* **1986**, *27*, 5467–5470.
(123) Sabitha, G.; Prasad, M.; Bhikshapathi, M.; Yadav, J. *Synthesis* **2009**, *2010*, 807–810.
(124) Murata, Y.; Kamino, T.; Aoki, T.; Hosokawa, S.; Kobayashi, S. *Angew. Chem. Int., Ed.* **2004**, *43*, 3175–3177.
(125) Akiyama, T.; Yasusa, T.; Ishikawa, K.; Ozaki, S. *Tetrahedron Lett.* **1994**, *35*, 8401–8404.
(126) Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519–1521.
(127) Larivée, A.; Unger, J. B.; Thomas, M.; Wirtz, C.; Dubost, C.; Handa, S.; Fürstner, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 304–309.
(128) Donohoe, T. J.; Lipiński, R. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2491–2494.
(129) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.
(130) Rodríguez-López, J.; Pinacho Crisóstomo, F.; Ortega, N.; López-Rodríguez, M.; Martín, V. S.; Martín, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 3659–3662.

(131) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

(132) Aho, J. E.; Salomäki, E.; Rissanen, K.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4179–4182.

(133) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461–464.

(134) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981–1998.

(135) Brückner, C.; Holzinger, H.; Reissig, H. U. *J. Org. Chem.* **1988**, *53*, 2450–2456.

(136) Smith, A. G.; Slade, M. C.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 1996–1999.

(137) Butova, E. D.; Barabash, A. V.; Petrova, A. A.; Kleiner, C. M.; Schreiner, P. R.; Fokin, A. A. *J. Org. Chem.* **2010**, *75*, 6229–6235.

(138) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, *126*, 13600–13601.

(139) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099–3107.

(140) Seebach, D.; Pohmakotr, M. *Tetrahedron* **1981**, *37*, 4047–4058.

(141) Pulido, F. J.; Barbero, A.; Val, P.; Diez, A.; González-Ortega, A. *Eur. J. Org. Chem.* **2012**, 5350–5356.

(142) Zhao, C.; Lu, J.; Yan, J.; Xi, Z. *Tetrahedron Lett.* **2003**, *44*, 6895–6898.

(143) Tofi, M.; Koltsida, K.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 313–316.

(144) Aggarwal, V. K.; Eames, J.; Villa, M.-J.; McIntyre, S.; Sansbury, F. H.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 533–546.

(145) Paju, A.; Laos, M.; Jõgi, A.; Päri, M.; Jäälaid, R.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron Lett.* **2006**, *47*, 4491–4493.

(146) Paju, A.; Kanger, T.; Pehk, T.; Eek, M.; Lopp, M. *Tetrahedron* **2004**, *60*, 9081–9084.

(147) Jõgi, A.; Ilves, M.; Paju, A.; Kailas, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2008**, *19*, 628–634.

(148) Jõgi, A.; Paju, A.; Pehk, T.; Kailas, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron* **2009**, *65*, 2959–2965.

(149) Kocienski, P. *Protecting groups*; 3rd ed.; Georg Thieme: Stuttgart; New York, 2004.

(150) Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*; 3rd ed.; Wiley, 1999.

(151) Lal, B.; Gidwani, R. M.; Rupp, R. H. *Synthesis* **1989**, *1989*, 711–713.

(152) Roberts, J. D.; Weigert, F. J.; Kroschwitz, J. I.; Reich, H. J. *J. Am. Chem. Soc.* **1970**, *92*, 1338–1347.

(153) Roberts, J. D.; Christl, M.; Reich, H. J. *J. Am. Chem. Soc.* **1971**, *93*, 3463–3468.

(154) Ritchie, R. G. S.; Cyr, N.; Korsch, B.; Koch, H. J.; Perlin, A. S. *Can. J. Chem.* **1975**, *53*, 1424–1433.

(155) Arteaga, J. F.; Diéguez, H. R.; González-Delgado, J. A.; Quílez del Moral, J. F.; Barrero, A. F. *Eur. J. Org. Chem.* **2011**, 5002–5011.

(156) Ushakov, D. B.; Navickas, V.; Ströbele, M.; Maichle-Mössmer, C.; Sasse, F.; Maier, M. E. *Org. Lett.* **2011**, *13*, 2090–2093.

(157) Takahashi, K.; Komine, K.; Yokoi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2012**, *77*, 7364–7370.

(158) Kim, M.-Y.; Kim, H.; Tae, J. *Synlett* **2009**, *2009*, 1303–1306.

(159) Wechter, W. J.; Kantoci, D.; Murray, E. D.; D'Amico, D. C.; Jung, M. E.; Wang, W. H. *Proc. Natl. Acad. Sci. U. S. A.* **1996**, *93*, 6002–6007.

(160) Brown, H. C.; Sharp, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 2915–2927.

(161) Estévez, R. E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García-Ruiz, J. M.; Robles, R.; Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Chem. Eur. J.* **2009**, *15*, 2774–2791.

(162) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G.; others *J. Org. Chem.* **2001**, *66*, 8070–8075.

(163) Marshall, J. L.; Walter, S. R. *J. Am. Chem. Soc.* **1974**, *96*, 6358–6362.

(164) Williamson, K. L. *J. Am. Chem. Soc.* **1963**, *85*, 516–519.

(165) Davis, J. C.; Van Auken, T. V. *J. Am. Chem. Soc.* **1965**, *87*, 3900–3905.

(166) Whitesell, J. K.; Minton, M. A. *Stereochemical analysis of alicyclic compounds by C-13 NMR spectroscopy*; Chapman and Hall: London; New York, 1987.

(167) Roberts, J. D.; Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 7107–7120.

(168) Niidu, A.; Paju, A.; Eek, M.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2678–2683.

(169) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(170) Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; M\ü\ürisepp, A. M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1565–1573.

(171) Jõgi, A.; Paju, A.; Pehk, T.; Kailas, T.; Müürisepp, A.-M.; Kanger, T.; Lopp, M. *Synthesis* **2006**, *2006*, 3031–3036.

(172) Verma, P.; Singh, S.; Dikshit, D. K.; Ray, S. *Synthesis* **1988**, *1988*, 68–70.

(173) PETTIT, G. R.; KASTURI, T. *J. Org. Chem.* **1961**, *26*, 4557–4563.

(174) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417–2419.

(175) Mao, Z.; Gregg, B. T.; Cutler, A. R. *J. Am. Chem. Soc.* **1995**, *117*, 10139–10140.

(176) Hansen, M. C.; Verdaguer, X.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 2360–2361.

(177) Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* **2001**, *57*, 5353–5359.

(178) Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem* **2002**, *67*, 4985–4988.

(179) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449–1452.

(180) Paju, A.; Kanger, T.; Niitsoo, O.; Pehk, T.; Müürisepp, A. M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2393–2399.

(182) Paquette, L. A.; Seekamp, C. K.; Kahane, A. L. *J. Org. Chem.* **2003**, *68*, 8614–8624.

(183) Chandrasekhar, S.; Tiwari, B.; Prakash, S. J. *ARKIVOC* **2006**, *2006*, 155–161.

Article I

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Synthesis of chiral hydroxylated cyclopentanones and cyclopentanes

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Abstract—A method for the synthesis of enantiomeric 1,3-dihydroxy and 2,3-dihydroxy cyclopentanones, starting from a commercially available 3-methyl-cyclopentane-1,2-dione **1**, is described. Dione **1** was subjected to asymmetric 3-hydroxylation to afford 3-methyl-3-hydroxy-1,2-dione **2**. The carbonyl groups in **2** were selectively differentiated by converting them either in dimethylacetal **5** or acetonide **6**. Stereoselective reduction of those acetals by using $NaBH_4$ afforded chiral methyl 1,2-dihydroxy cyclopentanone **9** and 1,3-dihydroxy cyclopentanone **10**, respectively. The diols obtained were further converted to the corresponding diastereomeric triols **11**–**13** by hydride reduction.

1. Introduction

The chiral multihydroxylated cyclopentane structure unit is present in various bioactive compounds, such as prostaglandins,[1,2] neurokinin-1,[3] glycosidase inhibitors[4] and natural lipid analogues.[5] These compounds are most widely used as building blocks in the synthesis of carbocyclic nucleoside analogues, which exhibit activity against a variety of diseases, for example, HIV, HSV, cancer and hepatitis.[6–9]

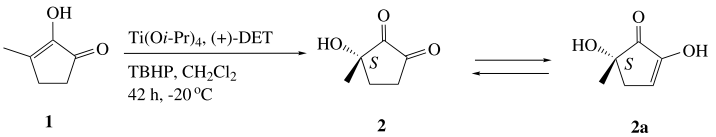
Many synthetic methods for the synthesis of polyhydroxy cyclopentanes and cyclopentanones rely on natural chiral compounds[7,10,11] or enzymatic processes.[12,13] Only a few examples of asymmetric synthesis of these compounds are described in the literature (e.g., Refs. 14 and 15).

In our laboratory, a method for the asymmetric oxidation of 3-alkyl-1,2-diketones **1** with Ti(O*i*Pr)$_4$-tartaric ester complex affording 3-hydroxylated 3-alkyl diketones **2** in high enantiomeric purity and with defined absolute configuration has recently been developed (Scheme 1).[16] Herein, we report our results of synthesizing different chiral dihydroxy cyclopentanones **9** and **10**, and cyclopentanetriols **11**–**13** starting from diketone **2**. The approach is based on differentiating the 1- and 2-oxo groups in hydroxylated diketone **2** via the formation of different types of acetals.

2. Results and discussion

2.1. Differentiation of C-1 and C-2 carbonyl groups

The starting diketone **2** is isolated from the reaction mixture of the asymmetric oxidation of 3-methyl-1,2-cyclopentanedione with a Ti(O*i*Pr)$_4$-tartaric ester complex



1 **2** **2a**

Scheme 1. Asymmetric oxidation with Ti(O*i*Pr)$_4$-tartaric ester complex.

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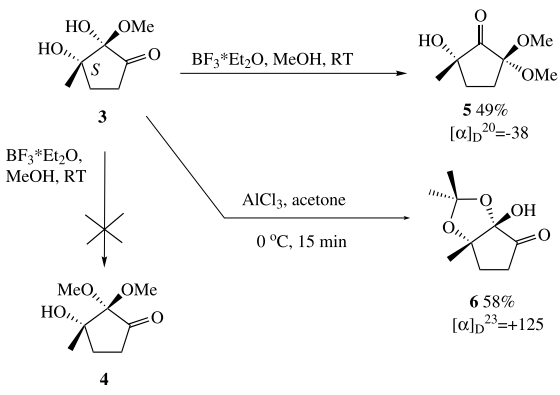
usually in a stable hemiacetal form **3**. In order to obtain a 1,3-dihydroxy compound we first made an attempt to reduce **3** directly with $NaBH_4$. However, from these experiments, a complex mixture of diols and triols in low total yield together with some amount of unreacted starting material was obtained. This prompted us to look for a more stable carbonyl protecting group. Also, we expected that using distinct protecting groups it would be possible to differentiate the carbonyl functions at C-1 and C-2 in diketone **2**.

To convert hemiacetal **3** to acetal **4**, first we used ordinary reaction conditions for acetalization (catalytic amount of *p*-TsOH and MeOH). However, our attempts failed even when up to 2 equiv of the catalyst were used. Surprisingly enough, when 0.5 equiv of boron trifluoride etherate with MeOH were used, hemiacetal **3** converted to the methyl acetal **5** in a 49% yield (the carbonyl group at C-1 was protected and the group at C-2 free for further transformations). Increasing the amount of Lewis acid to 1 equiv did not improve the yield, instead, the yield decreased considerably (17%) (Scheme 2).



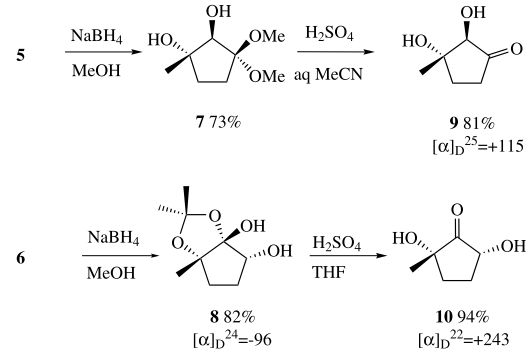
Scheme 2. Differentiation of C-1 and C-2-carbonyl groups.

In order to protect the C-2 carbonyl group, we selected the transformation of hemiacetal **3** to acetonide **6**. Under typical conditions,[17] when the substrate was refluxed in a solvent (usually toluene or benzene) in the presence of acid catalyst (*p*-TsOH, H_2SO_4) and 2,2-dimethoxypropane, the yield of **6** was low and acetalization was accompanied by side reactions (the elimination of tertiary hydroxyl group, deacetalization of hemiacetal **3** and formation of ketoenol **2a**). Also, using acetone or 2-methoxypropene as a reagent and/or applying lower reaction temperature (from rt to 60 °C) and long reaction times, resulted in acetonide **6** only but in low yield (13–32%). Neither was the change of a Brønsted acid to a Lewis acid ($BF_3{\cdot}Et_2O$) successful. Finally, using the procedure proposed by Lal et al.[18] (3 equiv of $AlCl_3$ in a dry 1:1 mixture of acetone and ether), we obtained acetonide **6** in an acceptable yield (58%). According to that procedure we obtained the intermediate **6** with C-2 carbonyl group protected and C-1 carbonyl free (Scheme 2).

2.2. Stereoselective reduction of C-1 and C-2 carbonyl groups

The reduction of acetal **5** with 1.2 equiv of $NaBH_4$ in MeOH led stereoselectively with good yield (73%) to diol **7**. The same exclusive stereoselectivity and excellent yield was observed in the case of reduction of acetal **6**. Thus, compound **8** was obtained as a single isomer in a 82% yield.

The deprotection of hydroxy acetals **7** and **8** with sulfuric acid in MeCN or THF furnished dihydroxyketones **9** and **10**, respectively, in a good yield (81% and 94%, Scheme 3). It should be noted that using HCl as an acid catalyst in deprotection resulted in the elimination of tertiary hydroxyl groups in **9** and **10**. Also, during the purification of the crude reaction mixture on silica gel, a tendency towards elimination of the OH-group was observed. Therefore, the crude product was only filtered through a Celite pad after water–ethyl acetate extraction. The obtained products **9** and **10** were identified and characterized by the NMR analysis and found to be stereochemically homogeneous.



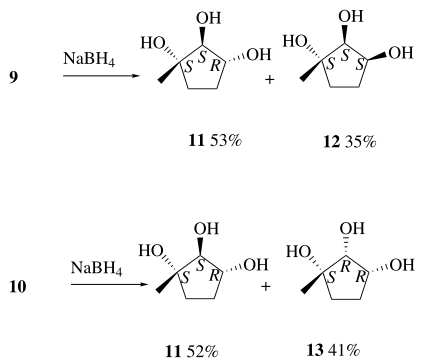
Scheme 3. Synthesis of ketodiols **9** and **10**.

However, NMR spectroscopic data was insufficient to determine the relative stereochemistry of acetonide **8** and dihydroxyketone **10**. Therefore, the diols were converted to triols and their NMR spectra together with the spectra of the model compounds **15** and **16** were additionally investigated.

2.3. The relative and the absolute configuration of hydroxylated cyclopentanones and cyclopentanes

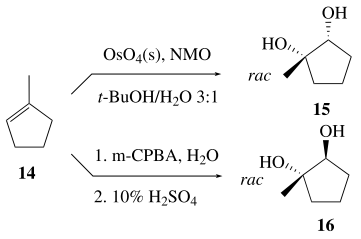
Dihydroxyketones **9** and **10** were further reduced with $NaBH_4$ affording, in both cases, a mixture of triols **11**–**13** (in a 88% yield as a sum of isomers for **9** and in a 93% for **10**; Scheme 4). The NMR spectra of the triols **11**–**13** were thoroughly investigated. Also, the information obtained enabled us to verify the established relative stereochemistry of acetonide **8** and dihydroxyketone **10** that was presented above.

It is known that the ^{13}C chemical shift of the methyl group vicinal to a hydroxyl group in cyclic alkanols is dependent



Scheme 4. Reduction of 3-methyl-2,3-dihydroxy-cyclopentanone and 2-methyl-2,5-dihydroxy-cyclopentanone to 1-methyl-1,2,3-cyclopentanetriols.

on the relative configuration of the substituents.[19–21] That phenomenon was also observed in the case of compounds **9**, **11**–**13**. To confirm the proposed stereochemistry for these compounds, model 1-methyl-1,2-cyclopentanols **15** and **16** were separately synthesized from cyclopentene **14**, using two different pathways: the dihydroxylation of **14** with an OsO_4/NMO system which should afford a *cis*-diol **15** and the epoxidation of **14** with MCPBA in water, followed by the treatment with H_2SO_4 which should afford a *trans*-diol **16** (Scheme 5).



Scheme 5. Synthesis of 1-methyl-1,2-cyclopentanediols **15** and **16**.

Although the difference in chemical shifts was larger (3.78 ppm) in the case of diols than that for triols, the general trend is clearly expressed: when the methyl group is located *cis* to the neighbouring hydroxyl group, the shift is 2.02–2.65 ppm upfield relative to that for the compounds with *trans* configuration of those groups. This regularity enabled us to determine the configuration of the substituents around carbons C1 and C2 as follows: *cis* for compounds **9**, **11** and **12** and *trans* for compound **13**.

The chemical shifts of three adjacent carbon atoms attached to hydroxyl groups are also determined by the relative configuration of the corresponding substituents (see Table 1). The ^{13}C chemical shifts of the compounds where OH-groups at carbons C2 and C3 are *cis* to each other were approximately 4 ppm upfield compared to the corresponding *trans*-compounds.[20] In the case of compounds **11**–**13** a difference of 5 ppm was observed, which allows us to make suggestions about the relative configurations of groups around atoms C2 and C3 as follows: in compound **11** the C2 and C3 hydroxyls are in *trans*- and in compounds **12** and **13** in *cis*-configuration.

Thus, the results obtained from NMR spectra enable us to assign correct stereochemical structures to all diol and triol compounds synthesized. Furthermore, the absolute configuration of the carbon C1 in triols is determined by the oxidation step and it is already well established. This way, the relative and absolute stereochemistry of the triols was unambiguously determined as depicted in Scheme 4.

3. Conclusions

A useful regioselective method for the differentiation of the carbonyl groups in 3-alkyl-3-hydroxy cyclopentane-1,2-dione was developed. The synthesized acetals **5** and **6** were converted in a stereoselective manner to dihydroxy ketones **9** and **10**, respectively. The NMR investigation of diastereomeric triols **11**–**13** and diols **15** and **16** enables us to draw regularities in the chemical shifts from relative configuration of hydroxyl groups in the compounds. The data obtained help to establish the stereochemical structure of similar cyclopentanols.

4. Experimental

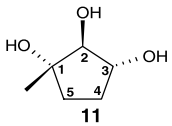
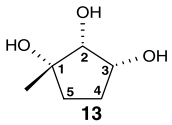
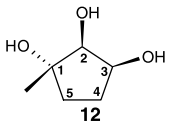
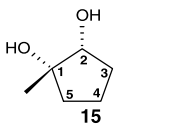
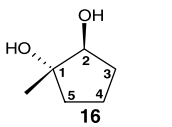
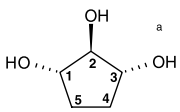
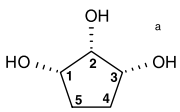
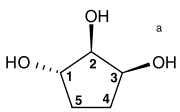
4.1. Materials and methods

Chemicals were purchased from Aldrich Chemical Co. or Lancaster and were used as received. DCM was distilled over CaH_2 and stored on the 3 Å molecular sieve pellets. THF and ether were distilled over $LiAlH_4$. Acetone was refluxed on $KMnO_4$ after persisting colour distilled, dried over K_2CO_3 2d, then distilled and stored over 4 Å molecular sieve pellets. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40–100 μm was used. NMR spectra were determined in $CDCl_3$, CD_3OD or DMSO-d_6 on Bruker AMX-500 spectrometer. 2D FT methods were used for the analysis of synthesized compounds. IR spectra were measured on a Perkin–Elmer Spectrum BX FTIR spectrometer. Mass spectra were recorded on a Hitachi M80B spectrometer using EI (70 eV) or CI (isobutane) mode. Optical rotations were obtained using a Krüss Optronic GmbH Polarimeter P 3002. All reactions sensitive to the moisture or oxygen were carried out under Ar atmosphere in an oven-dried glassware. Chiral starting material **3** was synthesized according to the conditions described in the literature from commercially available 2-methyl-1,2-cyclopentanedione. The reference compounds **15** and **16** were obtained from 1-methyl-cyclopent-1-ene purchased from Lancaster, following the recommendations of FiberCat™ catalyst manufacturer (Johnson Matthey) and an example of Fringuelli et al.,[22] respectively.

4.2. (2*S*)-2-Hydroxy-5,5-dimethoxy-2-methyl-cyclopentanone 5

To hemiacetal **3** (72 mg, 0.45 mmol) in dry MeOH (5 mL) under Ar atmosphere at 0 °C $BF_3{\cdot}Et_2O$ (29 μL, 0.23 mmol)

Table 1. ^{13}C Chemical shifts of cyclopentanols

Compound	C-1	C-2	C-3	C-4	C-5	CH_3
 **11**	*77.63*	*85.08*	*76.87*	29.25	36.27	**23.27**
 **13**	*76.51*	*77.46*	*71.61*	29.61	35.70	25.92
 **12**	*78.71*	*79.23*	*71.96*	29.91	35.88	**23.90**
 **15**	*78.32*	*78.40*	*31.57*	19.14	37.10	25.28
 **16**	*80.80*	*79.96*	*30.94*	18.76	36.95	**21.50**
 [a]	*76.60*	*85.10*	*76.60*	29.10	29.10	—
 [a]	*72.8*	*74.8*	*72.8*	29.90	29.90	—
 [a]	*76.80*	*79.90*	*72.50*	29.00	29.00	—

[a] Chemical shifts were abstracted directly from Ref. 21.

was added. The reaction mixture was allowed to reach ambient temperature and stirred for 26 h. To neutralize the solution, 5% $NaHCO_3$ (8 mL) was added at 0 °C. MeOH was removed from the mixture by evaporation and the water phase was extracted with dry AcOEt (6×25 mL). The organics were dried over Na_2SO_4, filtered, concentrated and purified over silica gel column (hexanes/acetone 20:1–10:1) to yield dimethylacetal (38 mg,

0.22 mmol, 49%) as a light yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (s, 3H, 2-CH_3), 1.96 and 2.15 (m, 2H, H-4), 1.98 (m, 2H, H-3), 2.45 (br s, 1H, 2-OH), 3.28 (s, 3H, 5-OCH_3), 3.34 (s, 3H, 5-OCH_3); ^{13}C (125 MHz, $CDCl_3$): δ 24.44 (2-CH_3), 29.83 (C-4), 32.38 (C-3), 50.23 (OCH_3), 50.32 (OCH_3), 74.77 (C-2), 100.64 (C-5), 210.18 (C-1); IR (neat): 3417, 2983 2949, 2839, 1760, 1455, 1391, 1373, 1220, 1208, 1145, 1094, 1048, 1024; $[\alpha]_D^{20} = -38$ (*c* 2.47, $CHCl_3$); MS: *m*/*z*: 174, 156, 141, 126 (base), 113, 94, 81, 69, 55, 41, 27, 15.

4.3. (3a*S*,6a*S*)-3a-Hydroxy-2,2,6a-trimethyl-tetrahydro-cyclopenta[1,3]dioxol-4-one 6

To ketone **3** (91 mg, 0.364 mmol) dissolved in dry acetone (1.5 mL) was added $AlCl_3$ (207 mg, 1.091 mmol) in dry Et_2O (1.5 mL) dropwise at 0 °C. After stirring for 15 min, the reaction mixture was quenched with cold $NaHCO_3$ (2.0 mL). Et_2O (10 mL) was added and the layers were separated. Water phase was extracted with Et_2O (4 × 10 mL). Combined organics were dried over $MgSO_4$, filtered and purified by column chromatography (silica gel, petroleum ether/acetone 20:1). Product **6** was obtained as a white solid (39 mg, 0.209 mmol, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 3H, 2-CH_3), 1.46 (s, 3H, 6a-CH_3), 1.55 (s, 3H, 2-CH_3), 1.71 (ddd, $J = 8.2$, 11.9 and 13.7 Hz, 1H, H-6), 2.22 (ddd, $J = 2.9$, 10.2 and 13.7 Hz, 1H, H-6), 2.27 (ddd, $J = 2.9$, 8.2 and 17.4 Hz, 1H, H-5), 2.86 (ddd, $J = 10.2$, 11.9 and 17.4 Hz, 1H, H-5), 3.92 (br s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.73 (6a-CH_3), 28.06 (2-CH_3), 28.47 (2-CH_3), 32.35 (C-5), 32.49 (C-6), 86.60 (C-6a), 101.52 (C-3a), 112.02 (C-2), 208.79 (C-4); IR (CCl_4): 3341, 2996, 2946, 1764, 1452, 1412, 1380, 1264, 1215, 1153, 1098, 1029; $[\alpha]_D^{23.5} = +125$ (*c* 1.75, $CHCl_3$); MS 10 eV *m*/*z*: 186, 171, 141, 128, 113, 100 (base), 82, 69, 59; HRMS calcd for $(M-CH_3)^+$ $C_8H_{11}O_4$: 171.0656; found: 171.0655.

4.4. (1*S*,2*R*)-3,3-Dimethoxy-1-methyl-cyclopentane-1,2-diol 7

To the starting ketone **5** (141 mg, 0.81 mmol) in 1 mL dry MeOH on the ice bath $NaBH_4$ (40 mg, 0.97 mmol) in three portions was added. After 15 min of stirring, the reaction mixture was quenched by adding acetone (200 μL) and subsequent filtering through Celite path. Concentrated mixture was purified by flash chromatography (silica gel, petroleum ether/acetone 5:1) to furnish alcohol **7** (105 mg, 0.60 mmol, 73.5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (s, 3H, 1-CH_3), 1.74 and 1.84 (m, 2H, H-5), 1.87 and 1.93 (m, 2H, H4), 3.26 and 3.29 (2s, 6H, OCH_3), 3.69 (br s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.52 (1-CH_3), 30.55 (C-4), 34.97 (C-5), 49.40 (OCH_3), 49.57 (OCH_3), 79.31 (C-1), 80.55 (C-2), 108.32 (C-3).

4.5. (3a*R*,4*R*,6a*S*)-2,2,6a-Trimethyl-tetrahydro-cyclopenta[1,3]dioxole-3a,4-diol 8

Compound **6** (38 mg, 0.204 mmol) was dissolved in MeOH (1.5 mL) and treated with $NaBH_4$ (9 mg, 0.238 mmol) at −5 °C. After stirring for 0.5 h, the excess of hydride was destroyed by adding acetone (0.5 mL) to the solution. The mixture was quenched with brine (10 mL) and extracted with AcOEt (1 × 20 mL and 3 × 10 mL). The resulting organic solution was dried over Na_2SO_4. The concentrated filtrate was purified by flash chromatography (silica gel, hexanes/acetone 5:1) to afford product **8** (28 mg, 0.149 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 3H, 6a-CH_3), 1.43 and 1.53 (2s, 2 × 3H, 2-CH_3), 1.35 and 1.82 (m, 2H, H-6), 1.53 and 1.83 (m, 2H, H-5), 3.02 (d, $J = 10.9$ Hz, 1H, 4-OH), 3.73 (m, 1H, H-4), 4.93 (s, 1H, 3a-OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.59 (6a-CH_3), 27.78 (2-CH_3), 28.27 (2-CH_3), 29.01 (C-5), 34.14 (C-6), 78.74 (C-4), 88.09 (C-6a), 108.49 (C-3a), 109.93 (C-2); $[\alpha]_D^{24} = -96$ (*c* 3.55, $CHCl_3$).

4.6. (2*R*,3*S*)-2,3-Dihydroxy-3-methyl-cyclopentanone 9

Acetal **7** (70 mg, 0.40 mmol) was dissolved in MeCN (3.0 mL). To the obtained solution was added aq 0.2 M H_2SO_4 (1.5 mL) dropwise. After stirring for 1.5 h at ambient temperature, the reaction was quenched with 2 M $NaHCO_3$ (0.4 mL). MeCN was removed under reduced pressure and the remaining water phase was extracted with AcOEt (8 × 10 mL). The solution was dried over $MgSO_4$, filtered through Celite path and the solvents evaporated to give ketodiol **9** (47 mg, 0.36 mmol, 80.5%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (s, 3H, CH_3), 2.09 and 2.11 (m, 2H, H-4), 2.24 and 2.56 (m, 2H, H-5), 4.22 (d, $J = 1.5$ Hz, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.33 (CH_3), 31.40 (C-4), 32.97 (C-5), 76.88 (C-3), 83.82 (C-2), 214.25 (C-1); $[\alpha]_D^{25} = +115$ (*c* 0.34, acetone); MS *m*/*z*: 130, 112, 97, 84, 71, 58 (base), 43, 27, 15; HRMS calcd for M^+ $C_6H_{10}O_3$: 130.0629; found: 130.0626.

4.7. (2*S*,5*R*)-2,5-Dihydroxy-2-methyl-cyclopentanone 10

To the solution of **8** (55.2 mg, 0.277 mmol) in THF (1.5 mL) aq 2 N H_2SO_4 (0.5 mL) was added. The mixture obtained was stirred at room temperature for 3 h, after which the reaction mixture was treated with 5% $NaHCO_3$ (1 mL). AcOEt (20 mL) was added and the layers separated. Water phase was extracted with AcOEt (10 × 10 mL), dried over Na_2SO_4 and filtered through Celite plug to yield ketodiol **10** (34 mg, 0.261 mmol, 94%) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD): δ 1.22 (s, 3H, 2-CH_3), 1.70 (ddd, $J = 6.8$, 11.0 and 13.7 Hz, 1H, H-3), 1.82 (dddd, $J = 7.3$, 10.1, 11.0 and 12.2 Hz, 1H, H-4), 2.00 (ddd, $J = 3.0$, 7.3 and 13.7 Hz, 1H, H-3), 2.19 (dddd, 1H, $J = 3.0$, 6.8, 8.5 and 12.2 Hz, H-4), 4.14 (dd, $J = 8.5$ and 10.1 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD): δ 23.59 (2-CH_3), 27.27 (C-4), 32.90 (C-3), 73.27 (C-2), 73.59 (C-5), 218.28 (C-1). $[\alpha]_D^{22} = +243$ (*c* 0.80, MeOH); MS *m*/*z*: 130, 112, 84, 69, 58 (base), 43, 27, 15; HRMS calcd for $(M)^+$ $C_6H_{10}O_3$: 130.0629; found: 130.0630.

4.8. (1*S*,2*S*,3*R*)-1-Methyl-cyclopentane-1,2,3-triol 11 and (1*S*,2*S*,3*S*)-1-methyl-cyclopentane-1,2,3-triol 12

(2*R*,3*S*)-2,3-Dihydroxy-3-methyl-cyclopentanone **9** (10.8 mg, 0.083 mmol) was dissolved in MeOH (1 mL). The obtained solution was treated with $NaBH_4$ (3.8 mg, 0.100 mmol) at −5 °C for 1 h, after which acetone (0.2 mL) was added. The reaction mixture was filtered through Celite and concentrated. The product was purified

by flash chromatography (silica gel, DCM/MeOH, 15:1–10:1) to yield a mixture of two isomers as oil (9.7 mg, 0.073 mmol, 88%): (1*S*,2*S*,3*R*)-1-methyl-cyclopentane-1,2,3-triol **11** and (1*S*,2*S*,3*S*)-1-methyl-cyclopentane-1,2,3-triol **12** in 3:2 ratio by proton NMR. Compound **11**: (500 MHz, DMSO-d_6): δ 1.02 (s, 3H, 1-CH_3), 1.44 (m, 1H, H-4), 1.48 (m, 1H, H-5), 1.63 (m, 1H, H-5), 1.77 (m, 1H, H-4), 3.42 (t, 1H, H-2), 3.63 (m, 1H, H-3), 4.32 (s, 1H, 1-OH), 4.62 (d, 1H, 3-OH), 4.67 (d, 1H, 2-OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.27 (1-CH_3), 29.25 (C-4), 36.27 (C-5), 76.87 (C-3), 77.63 (C-1), 85.08 (C-2). Compound **12**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.14 (s, 3H, 1-CH_3), 1.39 and 1.64 (m, 2H, H-5), 1.39 and 1.87 (m, 2H, H-4), 3.31 (m, 1H, H-2), 4.17 (m, 1H, H-3), 4.22 (d, $J = 4.1$ Hz, 1H, 2-OH), 4.24 (s, 1H, 1-OH), 4.32 (d, $J = 7.0$ Hz, 1H, 3-OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.90 (1-CH_3), 29.91 (C-4), 35.88 (C-5), 71.96 (C-3), 78.71 (C-1), 79.23 (C-2).

4.9. (1*S*,2*S*,3*R*)-1-methyl-cyclopentane-1,2,3-triol (11) and (1*S*,2*R*,3*R*)-1-methyl-cyclopentane-1,2,3-triol (13)

(2*S*,5*R*)-2,5-dihydroxy-2-methyl-cyclopentanone **10** (9.3 mg, 0.071 mmol) was dissolved in MeOH (1 mL). The obtained solution was treated with $NaBH_4$ (3.2 mg, 0.086 mmol) at −5 °C for 1 h, after which acetone (0.1 mL) was added. The reaction mixture was filtered through Celite and concentrated. Diastereomers were separated by flash chromatography (silica gel, DCM/MeOH, 15:1–10:1) to yield (1*S*,2*S*,3*R*)-1-methyl-cyclopentane-1,2,3-triol **11** (4.9 mg, 0.037 mmol, 52%) and (1*S*,2*R*,3*R*)-1-methyl-cyclopentane-1,2,3-triol **13** (3.9 mg, 0.030 mmol, 41%). Compound **11**: NMR spectra identical to the data given in Section 4.8. Compound **13**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (s, 3H, 1-CH_3), 1.42 and 1.72 (m, 2H, H-5), 1.57 and 1.76 (m, 2H, H-4), 3.25 (m, 1H, H-3), 3.88 (bs, 1H, H-2), 4.15 (bs, 1H, 1-OH), 4.50 (bs, 2H, 2-OH, 3-OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.92 (1-CH_3), 29.61 (C-4), 35.70 (C-5), 71.61 (C-3), 76.51 (C-1), 77.46 (C-2).

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References

1. (a) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533–1564; (b) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185–210.
2. (a) Bickley, J. F.; Roberts, S. M.; Santoro, M. G.; Snape, T. J. *Tetrahedron* **2004**, *60*, 2569–2576; (b) Dauvergne, J.; Happe, A. M.; Roberts, S. M. *Tetrahedron* **2004**, *60*, 2551–2557.
3. Kuethe, J. T.; Wong, A.; Wu, J.; Davies, I. W.; Dormer, P. G.; Welch, C. J.; Hillier, M. C.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5993–6000.
4. Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553.
5. (a) Hancock, A. J.; Lister, M. D.; Sable, H. Z. *J. Lipid Res.* **1982**, *23*, 183–189; (b) Pajouhesh, H.; Hancock, A. J. *J. Lipid Res.* **1984**, *25*, 310–312; (c) Barlow, P. N.; Lister, M. D.; Sigler, P. B.; Dennis, E. A. *J. Biol. Chem.* **1988**, *263*, 12954–12958.
6. Gulick, R. M. *Clin. Microbiol. Infect.* **2003**, *9*, 186–193.
7. (a) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611–10670; (b) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272; (c) Borthwick, A.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571–623; (d) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768.
8. Gurjar, M. K.; Maheshwar, K. *J. Org. Chem.* **2001**, *66*, 7552–7554.
9. (a) Kim, H. O.; Yoo, S. J.; Ahn, H. S.; Choi, W. J.; Moon, H. R.; Lee, K. M.; Chun, M. W.; Jeong, L. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2091–2093; (b) Jeong, L. S.; Yoo, S. J.; Lee, K. M.; Koo, M. J.; Choi, W. J.; Kim, H. O.; Moon, H. R.; Lee, M. Y.; Park, J. G.; Lee, S. K.; Chun, M. W. *J. Med. Chem.* **2003**, *46*, 201–203.
10. (a) Choi, W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S. *J. Org. Chem.* **2001**, *66*, 6490–6494; (b) Hong, J. H.; Shim, M. J.; Ro, B. O.; Ko, O. H. *J. Org. Chem.* **2002**, *67*, 6837–6840; (c) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611–2613.
11. (a) Comin, M. J.; Leitofuter, J.; Rodriguez, J. B. *Tetrahedron* **2002**, *58*, 3129–3136; (b) Bianco, A.; Celona, D.; Di Rita, S.; Guiso, M.; Melchioni, C.; Umani, F. *Eur. J. Org. Chem.* **2001**, 4061–4066; (c) Marco-Contelles, J.; Rodríguez-Fernández, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 2249–2256; (d) Ramana, C. V.; Reddy, B. S.; Gurjar, M. K. *Tetrahedron Lett.* **2004**, *45*, 2817–2819.
12. Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319–4347.
13. (a) Dauvergne, J.; Happe, A. M.; Jadhav, V.; Justice, D.; Matos, M.-C.; McCormack, P. J.; Pitts, M. R.; Roberts, S. M.; Singh, S. K.; Snape, T. J.; Whittall, J. *Tetrahedron* **2004**, *60*, 2559–2567; (b) Roy, A.; Schneller, S. W. *Tetrahedron Lett.* **2005**, *46*, 8913–8915 (and references cited therein); (c) Audran, G.; Acherar, S.; Monti, H. *Eur. J. Org. Chem.* **2003**, 92–98.
14. (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089–5090; (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725.
15. (a) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459–2461; (b) Stark, L. M.; Pekari, K.; Sorensen, E. J. *Proc. Nat. Acad. Sci.* **2004**, *101*, 12064–12066; (c) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127–132.
16. Paju, A.; Kanger, T.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2439–2448.
17. (a) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, NY, 2004, pp 119–185, and references cited therein; (b) Green, T.; Wutts, P. G. M. *Protective Groups in Organic Chemistry*; John Wiley and Sons, NY, 2004; pp 201–245, and references cited therein.
18. Lal, B.; Gidwani, R. M.; Rupp, R. H. *Synthesis* **1989**, 711–713.
19. Christl, M.; Reich, H. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 3463–3468.
20. Ritchie, R. G. S.; Cyr, N.; Korsch, B.; Koch, H. J.; Perlin, A. S. *Can. J. Chem.* **1975**, *53*, 1424–1433.
21. Roberts, J. D.; Weigert, F. J.; Kroschwitz, J. I.; Reich, H. J. *J. Am. Chem. Soc.* **1970**, *92*, 1338–1347.
22. Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Synth. Commun.* **1989**, *19*, 1939–1943.

Article II

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Synthesis of chiral enantioenriched tetrahydrofuran derivatives

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Abstract
A simple and short synthetic pathway to novel chiral enantioenriched 2,2-disubstituted tetrahydrofuran derivatives, starting from enantiomeric lactone acids in 2 steps was developed in 36-54% overall yield. The method enables also to obtain enantioenriched 2,3'-spiro ditetrahydrofuran (1,7-dioxaspiro[4.4]nonane) starting from the spirodilactone (*R*-1,7-dioxaspiro[4.4]nonane-2,6-dione).

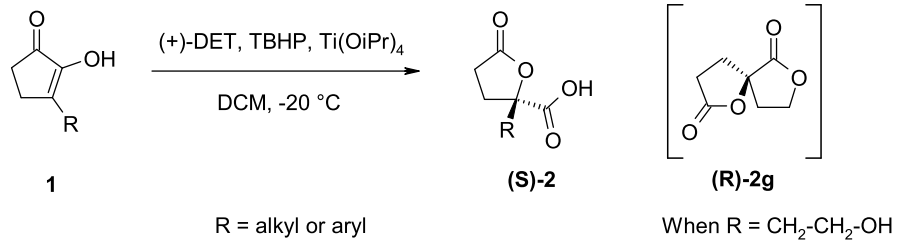
Keywords: Asymmetric oxidation, chiral tetrahydrofuran derivatives, reduction, 1,7-dioxaspiro[4.4]nonane

Introduction

The tetrahydrofuran structural elements are an essential part in many naturally occurring compounds, like communiols,[1] acetogenins,[2,3] polycyclic ethers,[4,5,6] lignans[7] etc. Derivatives of 2,2-disubstituted tetrahydrofurans have elicited attention as antitumor agents[8] and potent VLA-4 antagonists,[9,10] which could be useful in the treatment of various VLA-4 dependent inflammatory diseases such as asthma, multiple sclerosis and arthritis. 1,7-Dioxaspiro[4.4]nonane (spiro-ditetrahydrofuran) skeleton exists in the naturally occurring prehispanolones,[11] leopersins,[12] syringolides.[13] Also, this structural element is an essential part in synthetic spironucleosides[14] and fructose derived molecular scaffolds.[15]

Although, there exist many diastereoselective[16-19] and enantiospecific[16,20] methods for synthesizing differently substituted tetrahydrofurans, only a few methods exist to obtain chiral 2,2-disubstituted tetrahydrofuran derivatives.[21-24] Also, the synthesis of the spiro tetrahydrofuran skeleton, has been realized by many different routes,[5,25-27] however, only in a few cases has an asymmetric method been used to accomplish this goal.

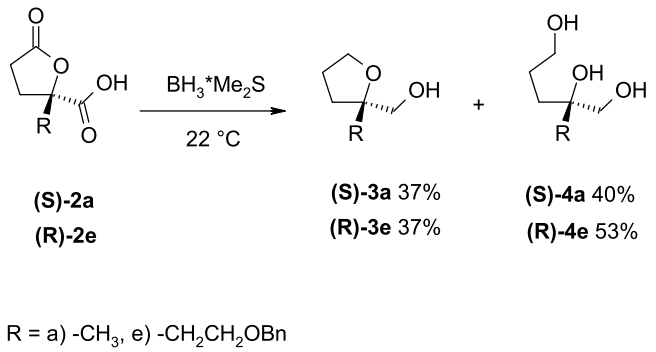
In recent years our group has developed a simple and enantioselective method for synthesizing chiral lactone carboxylic acids (Scheme 1).[28,29] This approach has been applied in the synthesis of 2-alkyl-substituted 2-hydroxyglutaric acid γ-lactones[30] homocitric acid[31], and nucleoside analogues.[32,33] The easy access and wide possible structural variability of that chiral building block **2** motivated us to broaden the practical scope of the compounds - to use the lactone carboxylic acids for the synthesis of chiral tetrahydrofuran derivatives. In this paper, we report a convenient method for obtaining several novel chiral tetrahydrofurans **3** and **7** from the corresponding lactone acids **2** and spiro ditetrahydrofuran from spirodilactone **2g**.



Scheme 1. Asymmetric synthesis of chiral lactone carboxylic acids.

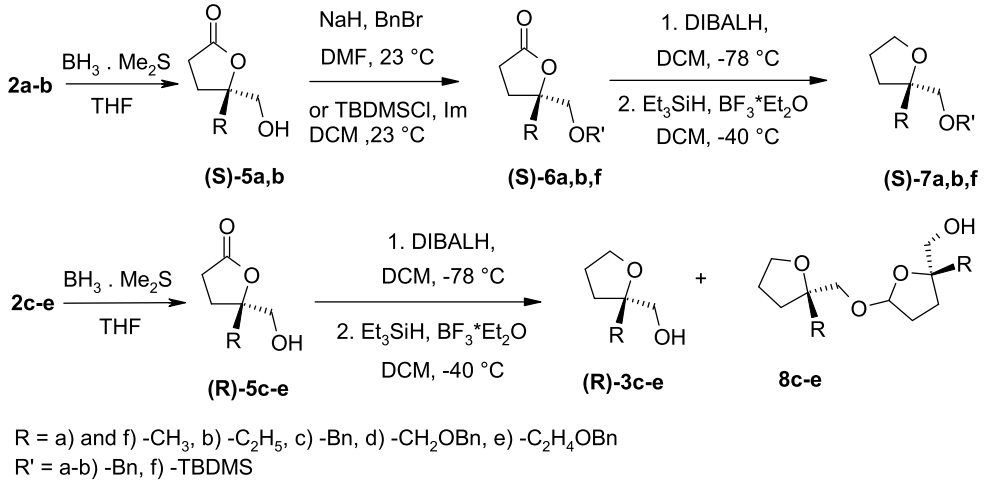
Results and Discussion

To transform the lactone acid skeleton to the tetrahydrofuran ring we made an attempt to use a direct reduction approach proposed by Verma *et al.*[34] for triarylsubstituted dihydrofuranones with neat $BH_3 \cdot Me_2S$ (11 eq). However, with methylsubstituted lactone **2a** this single step procedure at room temperature gave us a two component mixture – hydroxymethyl tetrahydrofuran alcohol **3a** and triol **4a** with 77% combined isolated yield in a 1:1 ratio (Scheme 2). Also, with benzyloxyethyl lactone acid **2e** the reaction was not selective, resulting in tetrahydrofuran alcohol **3e** and triol **4e** with 90% overall isolated yield, in a 1:1.4 ratio. Using different borane complexes as reductive agents e.g. $BH_3 \cdot NH_3$, $BH_3 \cdot THF$, $BH_3 \cdot Me_2S/BF_3 \cdot Et_2O$ did not afford ether **3a** from **2a**.



Scheme 2. Direct reduction of carboxylic acids.

To improve the yield of the target tetrahydrofuran derivatives, we applied a two step sequence involving the reduction of lactone carboxylic acid **2** in the first step and reduction of the formed lactone alcohol **5** to the ether alcohol **3** in the second step. For the reduction of the free carboxylic group we used a protocol proposed by Ravid *et al.*[35] For compounds **2a-e** the isolated yields of the resulted lactone alcohols **5a-e** were in a range of 68-77% (Scheme 3, Table 1).



Scheme 3. Synthetic routes to chiral THF-derivatives.

Table 1. Synthesis of tetrahydrofuran derivatives

Entry	Substrate	**5**	**3**	**7**†
1	**2a**	74%		
2	**2b**	73%		
3	**2c**	71%		
4	**2d**	68%		
5	**2e**	77%		
6	**5a**			48%
7	**5b**			57%
8	**5c**		75%	
9	**5d**		64%	
10	**5e**		70%	

†The yields over two steps (protection and reduction).

There are several options to transform the lactones into cyclic ethers, e.g. $NaBH_4/BF_3{\cdot}Et_2O$,[36] $DIBALH/Et_3SiH/BF_3{\cdot}Et_2O$,[37] manganese acetyl complexes/$PhSiH_3$,[38] titanocene complexes/ PMHS/Et_3SiH/Amberlyst 15,[39] and $TiCl_4$/TMSOTf/Et_3SiH,[40] ruthenium complexes/ $EtMe_2SiH$.[41] The most promising, according to us, is a method, described by Kraus *et al.*[37] where DIBALH at –78ºC with Et_3SiH and $BF_3{\cdot}Et_2O$ in DCM is used.

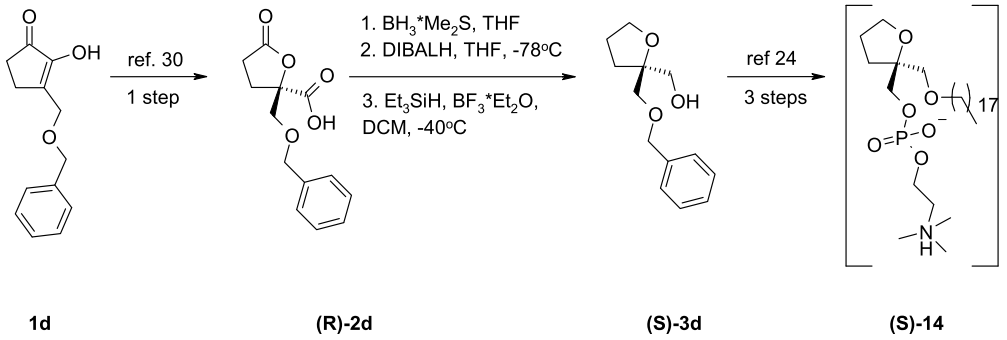
The latter conditions were applied to the starting material **5a**, affording in the first attempt a low yield – <20% according to GC analysis. The reason may be a low boiling point of the formed product which makes separation of the compound from the reaction mixture complicated when small quantities of starting material (100 mg) are used. Therefore, we protected the hydroxyl group in **5a** with a TBDMS protecting group (87-93% yield) and reduced the protected alcohol with $DIBALH/Et_3SiH/BF_3{\cdot}Et_2O$ at -78 ºC in DCM. The reduction proceeds smoothly, however, under the reaction conditions some cleavage of the TBDMS group occurred in the silane reduction step, giving rise to a mixture of the expected TBDMS ether **7f** together with free alcohol **3a** with 77% combined yield[47] (Scheme 3).

To avoid undesired deprotection of the starting material, we turned to the more stable benzyl protecting group. So, starting materials **5a** and **5b** were protected with benzyl bromide in the presence of an equimolar amount of NaH in DMF in 62% and 73% yield respectively and were then subjected to reduction with $DIBALH/Et_3SiH/BF_3{\cdot}Et_2O$ at -78 ºC in DCM (Scheme 3). As a result, the target tetrahydrofuran derivatives **7a** and **7b** were obtained with 77% and 78% yield. The overall yield starting from lactone alcohols **5a** and **5b** were 48% and 57% respectively.

The protection/deprotection steps are often complicating the synthetic technologies. Therefore, starting materials **5c-e** with an unprotected hydroxyl group were subjected to DIBALH and then $Et_3SiH/BF_3{\cdot}Et_2O$ reduction (Scheme 3). The obtained yield of the reduction step was somewhat lower than in the case of the protected compounds. During the direct Lewis acid promoted silane reduction of **5** intermolecular acetalization of the product **3** with the starting

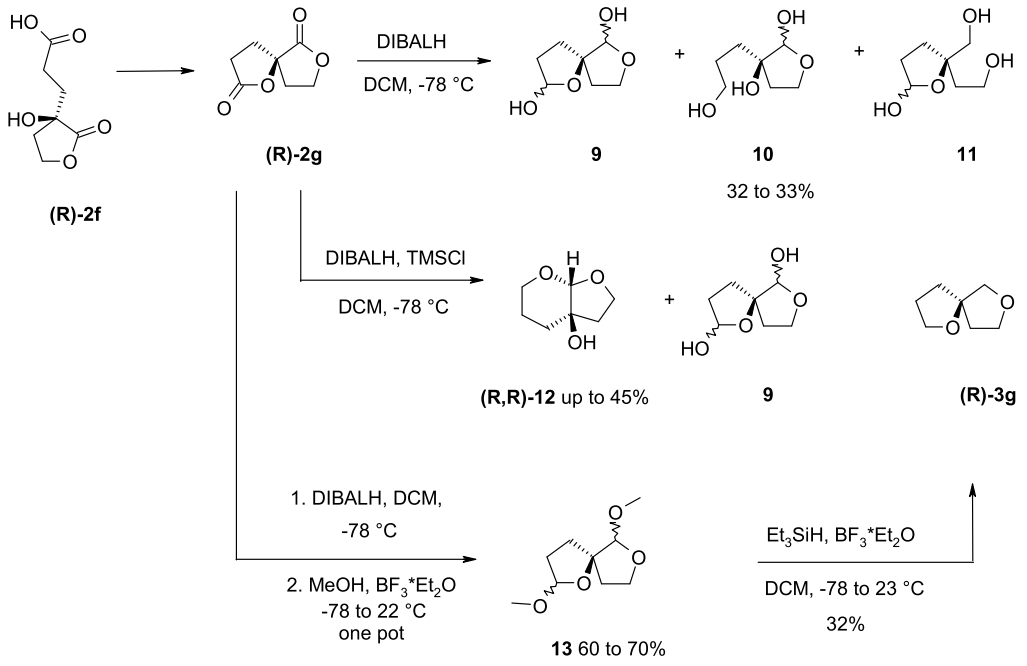
compound **5** was observed, leading to byproducts **8c-e** in 7-10% yield. This reaction transforms some amount of the starting material to an unreactive acetal and so, diminishes the yield. The byproduct itself is easily separable from the target product by simple chromatography. However, the yields of the target tetrahydrofuran derivatives **3c-e** were higher (64–75%) than the overall yield of compounds **7a** and **7b** with the corresponding protection steps (48% and 57%) (Table 1). Unmasking to obtain **3a** and **3b** would additionally decrease the yield of the whole reaction sequence. So, for the synthesis of compounds **3** the protection-free approach is favourable.

THF derivative **3d** is a key intermediate for the synthesis of the bioactive compound (S)-SRI-62-834 **14** (Scheme 4), an antitumor agent[8], that has been obtained previously by a multistep sequence that includes enzymatic resolution of the acetylated tetrahydrofuran-2,2-methanol.[24]



Scheme 4. Formal synthesis of (S)-SRI-62-834 14.

Spirodilactone **2g** was obtained from substituted lactone **2f** by simple lactonisation.[42] We made an attempt to apply the above described methodology to the reduction of spirodilactone **2g** in order to obtain spiro tetrahydrofuran compound **3g**. Thus, we pursued the reduction of **2g** with DIBALH and obtained a mixture of diastereomeric acetal **9** and hemiacetal diols **10** and **11** as determined by NMR analysis of the crude product (Scheme 5).[43] These results lead us to search more suitable methods for reducing spirodilactone **2g**. A similar over reduction problem was also observed in the synthesis of conformationally restricted spirocyclic nucleosides by Paquette *et al.*[44] and they solved the problem by using a low DIBALH concentration in the presence of an excess of Lewis acid (4.5 eq Me_3SiCl). We applied that method to spirodilactone **2g** and obtained lactol **9** together with bicyclic acetal **12** as a single diastereomer (up to 45% yield; Scheme 5).



Scheme 5. Synthesis of spirodiether.

Separation of the lactols from the reaction mixture after hydrolysis (containing $Al(OH)_3$) appeared to be complicated. In order to improve the yield of acetal **9** (to extract it from the aluminium hydroxide) we used an in situ trapping of the formed lactols as methylacetals **13** by quenching the DIBALH reaction with an excess of dry MeOH in the presence of 1 equiv of $BF_3{\cdot}Et_2O$. This method afforded stable yields of **13** (~70%). This compound was used in the following step without purification. Silane reduction[45,46] of **13** proceeded smoothly (with a modification of the original protocol: a stoichiometric amount of $BF_3{\cdot}Et_2O$ was used at -45 ºC to rt instead of a catalytic amount at rt) to furnish the volatile spiro tetrahydrofuran **3g** exclusively in 32% isolated yield after purification (the product partly co-evaporated during solvent removal) (Scheme 5).

In conclusion a short and convenient method for the synthesis of different 2,2-substituted chiral tetrahydrofuran derivatives was developed. The two step sequence gave better overall yield than the direct reduction of the chiral carboxylic acid – 54% and 37% respectively. In the case of starting material **2g**, the conversion of the hemiacetal **9** to the methyl acetal **13** contributes to the extraction of the latter from the reaction mixture and improves the yield of the reduction step. Subsequent silane reduction gave cleanly the desired compound **3g** with 32% yield.

Experimental Section

General. Chemicals were purchased from Aldrich Chemical Co or Alfa Aesar and were used as received. DCM and DMF were distilled over CaH_2 and stored on the 3Å molecular sieve pellets. THF and ether were distilled over $LiAlH_4$. Precoated silica gel 60 F254 plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40-100 μm was used. NMR spectra were determined in $CDCl_3$ on Bruker AMX-500 or Bruker Avance USLA 400 spectrometer. Solvent peaks were used as references. 2D FT methods were used for the analysis of synthesized compounds. IR spectra were measured on a Perkin-Elmer Spectrum BX FTIR spectrometer. Mass spectra were recorded on a Hitachi M80B spectrometer using EI (70eV) or a Shimadzu GCMSQP2010 spectrometer using EI (70eV). Optical rotations were obtained using a Krüss Optronic GmbH Polarimeter P 3002. Elemental analyses were performed on a PerkinElmer C, H, N, S-Analyzer 2400. All reactions sensitive to the moisture or oxygen were carried out under Ar atmosphere in oven-dried glassware. Chiral acids **2a-e** were synthesized according to previously published methods and each exhibited physical and spectroscopic properties in accordance with data given in literature.[34,36]

Direct reduction of carboxylic acids 2a and 2e. To the carboxylic acid (1.5 mmol) at -30 °C was added neat 10M $BH_3{\cdot}Me_2S$ (1.5 mL, 15 mmol) dropwise and the resulting mixture was stirred at 22 °C for 17 h. Then dry MeOH (3.0 mL) was added dropwise at -20 °C. After stirring at 22 °C for 1 h the volatiles were removed and the residue was purified by flash chromatography (petroleum ether/acetone 10:1 to 2:1) to give cyclic ether alcohol along with triol. Tetrahydrofuran **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 3.1, 3H, CH_3), 1.62 (ddd, J = 11.2, 10.0, 6.0, 1H, H-3), 1.82– 2.01 (m, 3H, H-3 and H-4), 3.42 – 3.46 (m, 2H, CH_2O), 3.77 – 3.90 (m, 2H, H-5), ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.33 (CH_3), 26.47 (C-4), 33.48 (C-3), 68.07 (C-5), 68.53 (CH_2O), 82.95 (C-2); triol **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3H, CH_3), 1.52 – 1.48 (m, 1H, H-4), 1.54 (dt, J = 7.0, 2.1, 1H, H-4), 1.69 – 1.57 (m, 2H, H-3), 3.38 – 3.35 (m, 2H, H-5), 3.59 – 3.53 (m, 2H, H-1), 4.90 (s, 3H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.89 (CH_3), 27.86 (C-4), 35.88 (C-3), 63.71 (C-5), 70.46 (C-1), 73.56 (C-2). Tetrahydrofuran **3e**: see below. Triol **4e**: ^{1}H NMR (500 MHz, DMSO-D_6) δ 1.35 (m, 2H, H-3), 1.44 (m, 2H, H-4), 3.19 (d, 2H, H-1), 3.35 (m, 2H, H-5), 3.54 (t, 2H, CH_2O), 4.03 (s, 1H, OH-2), 4.38 (s, 1H, OH-5), 4.43 (s, 2H, Bn CH_2), 4.46 (s, 1H, OH-1), 7.31 (m, 5H, Bn *p*, *o*, *m*); ^{13}C NMR (DMSO-D_6) δ 26.50 (C-4), 33.38 (C-3), 36.14 (C-1'), 61.65 (C-5), 66.23 (C-2'), 66.76 (C-1), 71.95 (Bn CH_2), 72.43 (C-2), 127.28 (Bn *p*), 127.39 (Bn *o*), 128.20 (Bn *m*), 138.72 (Bn *i*).

General method for synthesis of lactone alcohols 5a-e. 2-(*S*)-lactone carboxylic acid **2a** (3 g, 20.8 mmol) was dissolved in dry THF (15 mL) and cooled on ice bath to 4 °C after which, $BH_3{\cdot}Me_2S$ (2.37 mL, 24.0 mmol) was added dropwise over period of 20 min. The resulting mixture was stirred at 23 °C for 1.5 h to 2.0 h (endpoint was confirmed by TLC). Then MeOH (1.25 mL) was carefully added to destroy borane complex. The solvents were removed *in vacuo*, then MeOH (1.25 mL) was added and the volatiles were removed – the procedure was repeated

once to yield the crude product as light yellow viscous oil. Purification was achieved by flash chromatography (SiO_2, petroleum ether /EtOAc 3:1 to 1:1).

(*S*)-5-Hydroxymethyl-5-methyl-dihydro-furan-2-one 5a. The title compound was synthesized in 20.8 mmol scale and recrystallization from petroleum ether/Et_2O obtained as white solid (2.01 g, 15.5 mmol, 74%). $[\alpha]_D^{23}$= +12.7 (*c* 3.47, AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (s, 3H, CH_3), 1.92 (ddd, 1H, H-4), 2.36 (ddd, 1H, H-4), 2.58 (ddd, 1H, H-3), 2.69 (ddd, 1H, H-3), 2.73 (bs, 1H, OH) 3.51 (d, 1H, CH2-OH), 3.70 (d, 1H, CH2-OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.01 (CH_3), 29.54 (C-4), 29.57 (C-3), 68.31 (C-OH), 86.66 (C-5), 177.38 (C-2); IR (KBr) 3412, 2978, 2938, 1759, 1649, 1459, 1419, 1384, 1304, 1213, 1162, 1130, 1099, 1061, 1011, 945; MS (m/z): 131$(M+1)^+$, 115, 99 (base), 71, 56.

(*S*)-5-Ethyl-5-hydroxymethyldihydrofuran-2-one 5b. The title compound was synthesized in 0.7 mmol scale in good yield to obtain a colorless oil (73 mg, 73%), which solidified upon smearing with glass stick. $[\alpha]_D^{25}$= +11.5 (*c* 3.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, *J*=2×7.5 Hz, 3H, CH_3), 1.69 (dt, *J*=3×7.5, 14.2, 1H, CH_2), 1.71 (dt, *J*=3×7.5, 14.2, 1H, CH_2), 1.98 (ddd, *J*=7.3, 10.7, 13.0 Hz, 1H, H-4), 2.26 (ddd, *J*=5.8, 10.8, 13.0 Hz, 1H, H-4), 2.55 (ddd, *J*=5.8, 10.7, 18.2 Hz, 1H, H-3), 2.70 (ddd, *J*=7.3, 10.8, 18.2 Hz, 1H, H-4), 3.01 (bs, 1H, OH), 3.54 (d, *J*=12.1 Hz, 1H, CH_2OH), 3.73 (d, *J*=12.1 Hz, 1H, CH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 7.42 (Et CH_3), 26.87 (C-4), 28.97 (Et CH_2), 29.62 (C-3), 66.93 (*C*H_2OH), 89.39 (C-5), 177.90 (C-2); IR (KBr) 3433(OH), 2974, 2944, 2886, 1766(C=O), 1464, 1418, 1331, 1219, 1160, 1120, 1069, 976, 936; MS m/z: 145 $(M+1)^+$, 127, 113 (base), 98, 95, 71, 57, 55, 41; anal. calcd. for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found C, 57.95; H, 8.49.

(*R*)-5-Benzyl-5-hydroxymethyldihydrofuran-2-one 5c. The title compound was synthesized in 0.45 mmol scale to yield the title compound as white solid (67 mg, 0.33 mmol, 71%). $[\alpha]_D^{23}$= +56.6 (*c* 6.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (m, 1H, H-3), 2.07 (m, 1H, H-4), 2.21 (ddd, *J*=7.2, 10.4, 12.5 Hz, 1H, H-4), 2.45 (ddd, *J*=5.1, 10.4, 17.5 Hz, 1H, H-3), 2.85 (d, *J*=14.0 Hz, 1H, Bn CH_2), 3.06 (d, *J*=14.0 Hz, 1H, Bn CH_2), 3.60 (d, *J*=12.1 Hz, 1H, CH_2OH), 3.76 (d, *J*=11.9 Hz, 1H, CH_2OH), 7.29 (m, 5H, Bn *m, p, o*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.63 (C-4), 29.25 (C-3), 41.97 (Bn CH_2), 67.63 (CH_2OH), 88.19 (C-5), 127.21 (Bn *p*), 128.64 (Bn *m*), 130.43 (Bn *o*), 134.76 (Bn *i*), 177.15 (C-2); IR (film) 3434(OH), 2929, 1767(C=O), 1496, 1456, 1416, 1187, 1061, 942, 705; MS m/z: 206 $(M)^+$, 188, 175, 129, 115 (base), 91, 77, 65, 55, 41; HRMS calcd. for $(M)^+$ $C_{12}H_{14}O_3$: 206.0942; found: 206.0944.

(*S*)-5-Benzyloxymethyl-5-hydroxymethyldihydro-furan-2-one 5d. The title compound wa synthesized in 0.46 mmol scale to yield the title compound as light yellow liquid (74 mg, 0.31 mmol, 68%). $[\alpha]_D^{23}$= +8.1 (*c* 3.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (m, 2H, H-4), 2.61 (m, 2H, H-3), 3.55 (dd, *J*=10.2, 21.9 Hz, 2H, CH_2O), 3.70 (dd, *J*=12.0, 53.0 Hz, 2H, CH_2OH), 4.53 (s, 2H, Bn CH_2), 7.31 (m, 5H, Bn *m, p, o*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.82 (C-4), 29.31 (C-3), 65.62 (CH_2OH), 72.55 (CH_2O), 73.84 (Bn CH_2O), 87.67 (C-5), 127.74 (Bn *o*), 128.01 (Bn *p*), 128.62 (Bn *m*), 137.63 (Bn *i*), 177.47 (C-2); IR (neat) 3020, 2400, 1773, 1216, 752, 669; MS m/z: 205 $(M-31)^+$, 130, 115, 91, 55, 41; HRMS calcd. for $(M-106)^+$ $C_6H_{10}O_3$: 130.0630, found: 130.0635.

(R)-5-Benzyloxyethyl-5-hydroxymethyl-dihydrofuran-2-one 5e. The tilte compound was synthesized in 0.18 mmol scale yielded title compound as light yellow syrup (35 mg, 0.14 mmol, 77%). $[\alpha]_D^{24}$= -7.0 (*c* 7.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (m, 2H, Et CH_2), 2.06 (m, 1H, H-4), 2.27 (m, 1H, H-4), 2.56 (m, 2H, H-3), 3.58 (m, 2H, Et CH_2O), 3.60 (s, 2H, C*H*$_2$OH), 3,65 (m, 1H, Et CH_2O), 4.48 (s, Bn CH_2O), 7.30 (m, 5H, Bn); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.97 (C-3), 29.03 (C-4), 36.91 (Et CH_2), 65.77 (Et CH_2O), 66.85 (CH_2OH), 73.73 (Bn CH_2O), 87.63 (C-5), 128.03 (Bn *o*), 128.19 (Bn *p*), 128.77 (Bn *m*), 137.63 (Bn *i*), 177.06 (C-2); IR (neat) 3444, 2928, 2871, 1769, 1208, 1097; MS m/z: 219 $(M-31)^+$, 172, 159 (M-91), 126, 107, 91 (Base), 79, 65, 44; HRMS: calcd. for $(M-91)^+$ $C_7H_{11}O_4$: 159.0656; found: 159.0653.

Benzylation of 5a and 5b. To the lactone **5a** (100 mg, 0.77 mmol) dissolved in dry DMF (1.5 mL), sodium hydride (27 mg, 1.15 mmol) and BnBr (165 uL, 1.39 mmol) were added at 0 °C. The resulting solution was stirred at 23 °C for 48 h, after which water (0.5 mL) was added dropwise on ice bath to quench the reaction. Then DCM (2.5 mL) was added and the layers separated. Water phase was extracted with DCM (2×2.5 mL) and the organics washed with brine (1.0 mL), then dried over $MgSO_4$, filtered and concentrated to yield crude product, which was purified by flash chromatography (SiO_2, petroleum ether /EtOAc 3:1 to 1:1) giving compound (105 mg, 62%) as a colorless oil.

(*S*)-5-Benzyloxymethyl-5-methyldihydrofuran-2-one 6a. Synthesis in 0.77 mmol scale gave the title compound (105 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 3H, CH_3), 1.94 (ddd, *J*=8.4, 10.3, 12.8 Hz, 1H, H-4), 2.35 (ddd, *J*=4.8, 10.4, 12.8 Hz, 1H, H-4), 2.54 (ddd, *J*=4.8, 10.4, 17.9 Hz, 1H, H-3), 2.74 (ddd, *J*=8.4, 10.4, 17.9 Hz, 1H, H-3), 3.44 (d, *J*=10.1 Hz, 1H, CH_2O), 3.52 (d, *J*=10.1 Hz, 1H, CH_2O), 4.53 (d, *J*=12.1 Hz, 1H, Bn CH_2), 4.59 (d, *J*=12.1 Hz, 1H, Bn CH_2), 7.31 (m, 3H, *p*, *o*), 7.36 (m, 2H, *m*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.74 (CH_3), 29.68 (C-3), 30.73 (C-4), 73.52 (Bn CH_2), 75.82 (*C*H_2O), 85.30 (C-5), 127.48 (o-Bn), 127.73 (*p*-Bn), 128.41 (*m*-Bn), 137.68 (*i*-Bn), 177.13 (C-2); IR (neat) 4060, 3520, 3089, 3064, 3032, 2977, 2936, 2867, 1958, 1772, 1604, 1497, 1454, 1416, 1381, 1367,1286, 1231, 1212, 1158, 1099, 1028, 1011, 943; MS m/z: 220 $(M)^+$, 114, 99 (base), 91, 71, 65, 55, 43; anal. calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; found: C, 70.41; H, 7.29.

(*S*)-5-Benzyloxymethyl-5-ethyldihydrofuran-2-one 6b. Synthesis in 0.48 mmol scale gave benzyl ether (82 mg, 0.35 mmol, 73%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J*=7.5, 3H, CH_3), 1.66 (m, 2H, CH_2), 1.93 (ddd, *J*=8.5, 10.6, 12.9, 1H, H-4), 2.20 (ddd, *J*=4.5, 10.6, 12.9, 1H, H-4), 2.44 (ddd, *J*=4.5, 10.6, 15.1, 1H, H-3), 2.67 (ddd, *J*=8.5, 10.6, 18., 1H, H-3), 3.46 (q, *J*=10.1, 2H, CH_2O), 4.50 (q, *J*=12.0, 2H, Bn CH_2), 7.27 (m, 5H, Bn *o*, *p*, *m*); ^{13}C NMR (100 MHz, $CDCl_3$): d 7.62 (5-CH_3), 28.37 (C-4), 29.78 (5-CH_2), 29.84 (C-3), 73.75 (5-CH_2O), 74.73 (Bn-CH_2), 87.98 (C-5), 127.65 (*o*), 127.87 (*p*), 128.58 (*m*), 137.93 (*i*), 177.50 (C-2); IR 3030, 2972, 2926, 1770, 1496, 1454, 1416, 1366, 1221, 1158, 1100, 940, 738, 699; MS m/z: 205 $(M-29)^+$, 179, 159, 143, 128, 113 (base), 107, 91, 71, 57; anal. calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; found: C, 72.16; H, 7.72.

General method for synthesis of tetrahydrofurans 7a-b and 3c-e. Lactone benzyl ether **6a** (0.27 mmol) was dissolved in DCM (1.0 mL) and cooled to -78 °C, then DIBALH was added

dropwise and the resulting solution stirred for 3 h. Reaction mixture was quenched with water (200 uL) and the temperature was allowed to reach 0 °C, then DCM (2.5 mL) was added. The resulting mixture was stirred at 22 °C for 1 h, filtered through Celite and the solids were washed with DCM (3×2.5 mL). TLC showed presence of one product. After removal of solvents, the residue was dissolved in DCM (1.0 mL) and Et_3SiH (70 uL, 0.41 mmol) was added. Then the reaction mixture was cooled to -45 °C and $BF_3{\cdot}Et_2O$ (40 uL, 0.31 mmol) was added dropwise. After stirring for 3 h, the reaction was quenched with aq. $NaHCO_3$ solution (10%, 0.5 mL). The layers were separated and the water phase was extracted with DCM (3×2.5 mL). The combined organics were dried over $MgSO_4$ and concentrated to give crude product. Further purification was achieved by flash chromatography (petroleum ether /EtOAc 5:1 to 1:1).

(2*S*)-2-[(Benzyloxy)methyl]-2-methyltetrahydro-furan 7a Obtained as a colorless liquid (43 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, *J*=6.6, 3H, CH_3), 1.60 (m, 1H, H-1), 1.76 (m, 3H, H-1, H-5), 3.33 (dd, *J*=9.71, 2H, CH_2O), 3.84 (m, 2H, H-4), 4.56 (dd, 2H, *J*=12.35, 13.45, Bn CH_2O), 7.28 (m, 5H, Bn *o*, *p*, *m*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.32 (CH_3), 26.37 (C-5), 34.63 (C-3), 68.19 (C-5), 73.62 (Bn CH_2), 76.53 (CH_2O), 82.40 (C-2), 127.61 (*p*-Bn), 127.68 (*o*-Bn), 128.48 (*m*-Bn), 138.84 (*i*-Bn); IR (neat) 3088, 3064, 3030, 2970, 2866, 1810, 1604, 1497, 1454, 1370, 1310, 1272, 1206, 1103, 1050, 736, 698, 606; MS (m/z): 206 $(M)^+$, 191, 175, 148, 135, 119, 107, 91, 85 (base), 77, 65, 43; anal. calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; found: C, 75.56; H, 8.78.

(*S*)-5-Benzyloxymethyl-5-ethyltetrahydrofuran 7b. Synthesis in 0.26 mmol scale yielded the title compound as a colorless liquid (45 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.90 (m, 3H, Et CH_3), 1.63 (m, 3H, H-3 and Et CH_2), 1.86 (m, 3H, H-3 and H-4), 3.33 (q, *J*=9.5, 2H, CH_2O), 3.82 (q, *J*=6.1, 2H, H-5), 4.55 (m, 2H, Bn CH_2), 7.27 (m, 5H, Bn *o,p,m*); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 8.53 (Et CH_3), 26.53 (C-4), 29.73 (Et CH_2), 32.37 (C-3), 68.37 (C-5), 73.59 (Bn CH_2), 74.55 (CH_2O), 84.82 (C-2), 127.58 (*p*-Bn), 127.67 (*o*-Bn), 128.43 (*m*-Bn), 138.83 (*i*-Bn); IR (film): 3440, 3085, 3061, 3028, 2949, 2868, 1950, 1880, 1813, 1758, 1604, 1583, 1496, 1454, 1400, 1330, 1296, 1200, 1147, 1123, 1087, 1039, 957, 702; MS (m/z): 191 $(M\text{-}29)^+$, 161, 149, 114, 99 (base), 91, 57; anal. calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; found: C, 75.98; H, 9.21.

((*R*)-2-Benzyltetrahydrofuran-2-yl)-methanol 3c. Synthesis in 0.46 mmol scale yielded the title compound as a colorless liquid (66 mg, 75%).$[\alpha]_D^{23}$= -1.5 (*c* 12.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.67 (m, 2H, H-3, H-4), 1.83 (m, 2H, H-3, H-4), 2.13 (bs, 1H, OH), 2.80 (m, 2H, Bn CH_2), 3.49 (m, 2H, CH_2OH), 3.79 (m, 2H, H-5), 7.28 (m, 5H, Bn *o*, *p*, *m*); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 26.53 (C-4), 31.35 (C-3), 42.38 (Bn CH_2), 67.35 (CH_2OH), 68.63 (C-5), 85.69 (C-2), 126.47 (*p*-Bn), 128.39 (*o*-Bn), 130.75 (*m*-Bn), 137.82 (*s*-Bn); IR ($CHCl_3$): 3440, 3085, 3061, 3028, 2949, 2868, 1950, 1880, 1813, 1758, 1604, 1583, 1496, 1454, 1400, 1330, 1296, 1200, 1147, 1123, 1087, 1039, 957, 702; MS (m/z): 192 $(M)^+$, 161, 128, 115, 101 (base), 91, 83, 65; HRMS calcd. for $(M)^+$ $C_{12}H_{16}O_2$: 192.1149; found 192.1156; anal. calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; found: C, 74.72; H, 8.44.

((*S*)-2-Benzyloxymethyltetrahydrofuran-2-yl)-methanol 3d. Synthesis in 0.19 mmol scale yielded the title compound as a colorless liquid (23 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*

1.85 (m, 4H, H-3 and H-4), 2.10 (s, 1H, OH), 3.43 (dd, *J*=9.4, 39.4, 2H, C*H*$_2$O), 3.56 (dd, *J*=11.3, 37.0, 2H, C*H*$_2$OH), 3.84 (t, *J*=6.4, 2H, H-5), 4.54 (q, *J*=12.2, 2H, Bn C*H*$_2$O), 7.30 (m, 5H, Bn *o*, *p*, *m*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.38 (C-4), 30.67 (C-3), 66.43 (C-5), 68.86 (CH_2OH), 73.43 (CH_2O), 73.80 (Bn CH_2O), 84.39 (C-2), 127.80 (o-Bn), 127.85 (p-Bn), 128.60 (m-Bn), 138.38 (s-Bn); IR (neat): 3439, 3089, 3064, 3031, 2927, 2868, 1497, 1454, 1406, 1365, 1208, 1096, 1056, 737, 699; MS (m/z): 222 $(M)^+$, 207, 191, 181, 161, 143, 131, 116, 101, 91, 83, 65, 55, 43; HRMS: calcd. for $(M-31)^+$ $C_{12}H_{15}O_2$: 191.1071; found: 191.1064.

{(2*R*)-2-[2-(Benzyloxy)-ethyl]-tetrahydrofuran-2-yl}-methanol 3e. Synthesis in 0.49 mmol scale yielded THF-derivative as a colorless liquid (76 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (m, 1H, H-3), 1.89 (m, 5H, H-3, H-4, Et CH_2), 2.71 (bs, 1H, OH), 3.45 (m, 2H, CH_2OH), 3.57 (m, 1H, CH_2O), 3.65 (m, 1H, CH_2O), 3.82 (m, 2H, H-5), 4.51 (m, 2H, Bn CH_2), 7.32 (m, 5H, Bn *o*, *p*, *m*); ^{13}C NMR (100 MHz, $CDCl_3$): 26.11 (C-5), 33.15 (C-3), 36.86 (Et CH_2), 66.86 (Et CH_2O), 67.01 (C-5), 67.88 (CH_2OH), 73.33 (Bn CH_2), 84.35 (C-2), 127.65 (*p*-Bn), 127.76 (*o*-Bn), 128.46 (*m*-Bn), 137.91 (*s*-Bn); IR (neat): 3444, 3088, 3063, 3030, 2947, 2868, 1496, 1454, 1366, 1308, 1206, 1098, 1053, 926, 738, 698; MS (m/z): 205 $(M-31)^+$, 187, 169, 159, 143, 129, 113, 99, 91 (base), 81, 65; HRMS: calcd. for $(M-31)^+$ $C_{13}H_{17}O_2$: 205.1227; found: 205.1226; anal. calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; found: C, 70.89; H, 8.60.

(5*R*)-1,7-Dioxaspiro[4.4]nonane-2,6-dione 2g. Spirodilactone **2g** was synthesized with slight modification to previously reported method: To the solution of Ti(O*i*Pr)$_4$ (7.1 mL, 23.2 mmol) and (+)-DET (5.0 mL, 29.0 mmol) in DCM (180 mL) at -20 °C 2-hydroxy-3-(2-hydroxyethyl)cyclopent-2-en-1-one (3.3 g, 23.2 mmol) was added carefully. After stirring for 0.5 h *t*-BuOOH (9.4 mL, 58.0 mmol) was added dropwise over 20 min. The resulting mixture was kept at -20 °C for 68 h. The reaction was quenched with water (145 mL), then the mixture was stirred for 1 h and 10N NaOH solution (29 mL) was added. After stirring for 1 h the layers were separated and water phase was treated with 5.5N HCl solution (110 mL), then the water phase was extracted with DCM (10×100 mL). The extracts were dried over $MgSO_4$, filtered and the solvents evaporated to give 3.37 g of crude as yellow crystals, which upon crystallization from EtOAc/Et_2O mixture (1:4) gave spirodilactone **2g** as white solids (2.75 g, 17.6 mmol, 75%), which physical and spectroscopic properties were in accordance with data given in literature[42].

(*R*)-1,7-dioxaspiro[4,4]nonane 3g. Spirodilactone **2g** (786 mg, 5.04 mmol) was dissolved in DCM (200 mL, solution was 0.025M in substrate, dried over 4Å MS, amylenes as stabilizers) under Ar atmosphere. Resulting solution was cooled to -78 ºC and then DIBALH (7.0 mL, 10.6 mmol, 1.5M in toluene) was added dropwise. After 2 h stirring, MeOH (40 mL, dried over 3Å MS) and $BF_3{\cdot}Et_2O$ (1.48 mL, 12.0 mmol) were added sequentially and the reaction mixture was kept at -78 ºC for 14 h and then stirred 2 h at 23 ºC. The reaction was quenched with aq $NaHCO_3$ (30 mL, 10%) at +4 ºC and agitated for 1 h, after which the layers were separated and the aqueous phase was extracted with DCM (6×50 mL). Organic phase was dried over $MgSO_4$, filtered and the solvents were evaporated to yield methylacetal **13** (565 mg, 3.0 mmol, 60%) as yellow viscous oil, which was used in the next synthetic step without further purification. The crude and Et_3SiH (2.9 mL, 18.0 mmol) were dissolved in DCM (60 mL, 0.05M in substrate),

then the resulting solution was cooled to -78 ºC and $BF_3{\cdot}Et_2O$ (750 uL, 6.01 mmol) was added. The thus obtained reaction mixture was stirred for 3 h at -78 ºC and then the temperature was slowly allowed to reach 23 ºC (4 h). The reaction was quenched by adding aq $NaHCO_3$ (5.0 mL, 10%). The layers were separated and the water phase was extracted with DCM (4×30 mL). The organics were dried over $MgSO_4$, filtered and the solvents evaporated. Purification of the crude by flash chromatography (SiO_2, petroleum ether /acetone, 20:1 to 16:1) gave the title compound (123 mg, 0.96 mmol, 32%) as light yellow oil. Caution! The volatility of title compound is of concern! $[\alpha]_D^{21}$= -2.4 (*c* 12.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 – 1.92 (m, 1H, H-9), 1.89 – 2.01 (m, 2H, H-3), 1.90 – 1.97 (m, 2H, H-4), 2.02 – 2.10 (m, 1H, H-9), 3.59 (d, *J*=9.1 Hz, 1H, H-6), 3.77 (d, *J*=9.1 Hz, 1H, H-6), 3.78 – 3.88 (m, 2H, H-2), 3.87 – 3.97 (m, 2H, H-8) and ^{13}C (100 MHz, $CDCl_3$): δ 25.97 (C-3), 33.29 (C-4), 38.51 (C-9), 67.37 (C-2), 67.99 (C-8), 76.90 (C-6), 89.16 (C-5); IR ($CHCl_3$): 2971, 2870, 1461, 1059, 911; MS(m/z): 128, 98, 83, 70, 56 (base), 42, 27; HRMS calcd. for $(M)^+$ $C_7H_{12}O_2$: 128.0836; found 128.0827.

(3a*R*,7a*R*)-Tetrahydro-4*H*-furo[2,3-*b*]pyran-3a(7a*H*)-ol 12. Spirodilactone **2g** (156 mg, 1.0 mmol) was dissolved in dry DCM (40 mL, 0.025M in substrate) under Ar atmosphere. Then, to the obtained solution TMSCl (1.70 mL, 9.0 mmol) was added and the mixture was cooled to -78 ºC after which DIBALH (1.15 mL, 2.5 mmol) was added dropwise. Reaction mixture was stirred at -78 °C for 2 h and carefully quenched with aq $NaHCO_3$ (10%, 0.46 mL) and the temperature rised slowly to 23 ºC. Na_2SO_4 (2.28 g) was added and the stirring was continued for further 2 h. The solids were filtered off and washed with EtOAc (3×10 mL). Combined organics were concentrated and purified by flash chromatography (SiO_2, PE/acetone 10:1 to 3:1) to yield title compound as clear liquid (65 mg, 0.45 mmol, 45%). $[\alpha]_D^{21}$= -7.8 (*c* 9.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (m, 1H, H-4e), 1.64 (m, 1H, H-4a), 1.71 (m, 1H, H-7), 1.76 (m, 1H, H-5a), 2.13 (m, 1H, H-5e), 2.24 (m, 1H, H-7), 2.86 (bs, 1H, OH), 3.39 (m, 1H, H-3a), 3.83 (m, 1H, H-3e), 4.10 (m, 2H, H-8), 4.61 (s, 1H, H-1) and ^{13}C NMR (100 MHz, $CDCl_3$): 23.02 (C-4), 31.61 (C-5), 33.04 (C-7), 64.29 (C-3), 67.21 (C-8), 77.15 (C-6), 105.03 (C-1); IR (neat): 3428, 2948, 2899, 2862, 1447, 1252, 1213, 1128, 1100, 1070, 1034, 991, 966, 932, 726, 601, 588; MS (m/z): 144 $(M)^+$, 126, 116, 98, 97, 70 (base), 56; HRMS: calcd. for $(M)^+$ $C_7H_{12}O_3$: 144.0785; found: 144.0783.

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References and Notes

1. Che, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. *Tetrahedron Lett.* **2004**, *45*, 6891.
2. Bermejo, A.; Figad re, B.; Zafra-Polo, M.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269.
3. Kladi, M.; Vagias, C.; Papazafiri, P.; Brogi, S.; Tafi, A.; Roussis, V. *J. Nat. Prod.* **2009**, *72*, 190.
4. Yasumoto, T.; Muratat, M. *Chem. Rev.* **1993**, *93*, 1897.
5. Wong, H. N. C. *Eur. J. Org. Chem.* **1999**, 1757.
6. Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279.
7. Wu, J.; Li, N.; Hasegawa, T.; Sakai, J.; Kakuta, S.; Tang, W.; Oka, S.; Kiuchi, M.; Ogura, H.; Kataoka, T.; Tomida, A.; Tsuruo, T.; Ando, M. *J. Nat. Prod.* **2005**, *68*, 1656.
8. Houlihan, W. J.; Lee, M. L.; Munder, P. G.; Nemecek, G. M.; Handley, D.; Winslow, C. M.; Happy, J.; Jaeggi, C. *Lipids* **1987**, *22*, 884.
9. Doherty, G. A.; Yang, G. X.; Borges, E.; Chang, L. L.; Maccoss, M.; Tong, S.; Kidambi, U.; Egger, L. A.; Mccauley, E.; Riper, G. V.; Mumford, R. A.; Schmidt, J. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1501.
10. Khandelwal, A.; Narayanan, R.; Gopalakrishnan, B. *Bioorg. Med. Chem.* **2003**, *11*, 4235.
11. Lee, C.; Jiang, L.; Hang, H.; Hon, P.; He, Y.; Wong, H. N. C. *Br. J. Pharmacol.* **1991**, *103*, 1719.
12. Tasdemir, D.; Wright, A. D.; Sticher, O.; Çalis, I.; Linden, A. *J. Nat. Prod.* **1995**, *58*, 1543.
13. Midland, S. L.; Keen, N. T.; Sims, J. J.; Midland, M. M.; Stayton, M. M.; Burton, V.; Smith, M. J.; Mazzola, E. P.; Graham, K. J.; Clardy, J. *J. Org. Chem.* **1993**, *58*, 2940.
14. Babu, B. R.; Keinicke, L.; Petersen, M.; Nielsen, C.; Wengel, J. *Org. Biomol. Chem.* **2003**, *1*, 3514.
15. Cipolla, L.; Forni, E.; Jimenez-Barbero, J.; Nicotra, F. *Chem. Eur. J.* **2002**, 3976.
16. Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261.
17. Shin, C.; Oh, Y.; Cha, J. H.; Pae, A. N.; Choo, H.; Cho, Y. S. *Tetrahedron* **2007**, *63*, 2182.
18. DeAngelis, A.; Taylor, M. T.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 1101.
19. Mitchell, T. A.; Zhao, C.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5026.
20. Sim, J. Y.; Hwang, G.; Kim, K. H.; Ko, E. M.; Ryu, D. H. *Chem. Commun.* **2007**, 5064.
21. Masuda, T.; Osako, K.; Shimizu, T.; Nakata, T. *Org. Lett.* **1999**, *1*, 941.
22. Maezaki, N.; Sawamoto, H.; Suzuki, T.; Yoshigami, R.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 8387.
23. Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766.
24. Prasad, K.; Estermann, H.; Underwood, R. L.; Chen, C.; Kucerovy, A.; Repic, O. *J. Org. Chem.* **1995**, *60*, 7693.
25. Alonso, F.; Meléndez, J.; Yus, M. *Tetrahedron Lett.* **2004**, *45*, 1717.
26. Donohoe, T. J.; Fisher, J. W.; Edwards, P. J. *Org. Lett.* **2004**, *6*, 465.
27. Marco-Contelles, J.; Dominguez, L.; Anjum, S.; Ballesteros, P.; Soriano, E.; Postel, D.

Tetrahedron: Asymmetry **2003**, *14*, 2865.
28. Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; Müürisepp, A.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1565.
29. Jõgi, A.; Paju, A.; Pehk, T.; Kailas, T.; Müürisepp, A.; Kanger, T.; Lopp, M. *Synthesis* **2006**, *2006*, 3031.
30. Paju, A.; Laos, M.; Jõgi, A.; Päri, M.; Jäälaid, R.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron Lett.* **2006**, *47*, 4491.
31. Paju, A.; Kanger, T.; Pehk, T.; Eek, M.; Lopp, M. *Tetrahedron* **2004**, *60*, 9081.
32. Jõgi, A.; Ilves, M.; Paju, A.; Kailas, T.; Müürisepp, A.; Lopp, M. *Tetrahedron: Asymmetry* **2008**, *19*, 628.
33. Jõgi, A.; Paju, A.; Pehk, T.; Kailas, T.; Müürisepp, A.; Lopp, M. *Tetrahedron* **2009**, *65*, 2959.
34. Verma, P.; Singh, S.; Dikshit, D. K.; Ray, S. *Synthesis* **1988**, *1988*, 68.
35. Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449.
36. Pettit, G. R.; Kasturi, T. R. *J. Org. Chem.* **1961**, *26*, 4557.
37. Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.
38. Mao, Z.; Gregg, B. T.; Cutler, A. R. *J. Am. Chem. Soc.* **1995**, *117*, 10139.
39. Hansen, M. C.; Verdaguer, X.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 2360.
40. Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* **2001**, *57*, 5353.
41. Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem.* **2002**, *67*, 4985.
42. Paju, A.; Kanger, T.; Niitsoo, O.; Pehk, T.; Müürisepp, A.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2393.
43. The number of lactol carbons in the range of 94 to 110 ppm exceeds that of possible when only spirocyclic acetals **9** are counted (12 vs 8), thus indicating a presence of other lactols. Most probably accountable for lactolalcohols **10** and **11** as depicted on the scheme 5. Also the number of quaternary and oxygen-linked carbons support the hypothesis of presence of overreduction products in the crude product.
44. Paquette, L. A.; Seekamp, C. K.; Kahane, A. L. *J. Org. Chem.* **2003**, *68*, 8614.
45. Chandrasekhar, S.; Tiwari, B.; Prakash, S. J. *Arkivoc* **2006**, *2006*, 155.
46. Brueckner, C.; Holzinger, H.; Reissig, H. U. *J. Org. Chem.* **1988**, *53*, 2450.
47. According to Kraus' work (see ref 37) the TBDMS group should be stable under the reaction conditions described.

Article III

Niidu, A.; Paju, A.; Müürisepp, A.-M.; Järving, I.; Kailas, T.; Pehk, T.; Lopp, M. Stereoselective synthesis of 1-methyl-1,2- and 1,3-cyclopentanediols *via* γ-lactones. *Chemistry of Heterocyclic Compounds* **2013**, *48*, 1751-1760.

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STEREOSELECTIVE SYNTHESIS OF 1-METHYL-1,2- AND 1,3-CYCLOPENTANEDIOLS *via* γ-LACTONES

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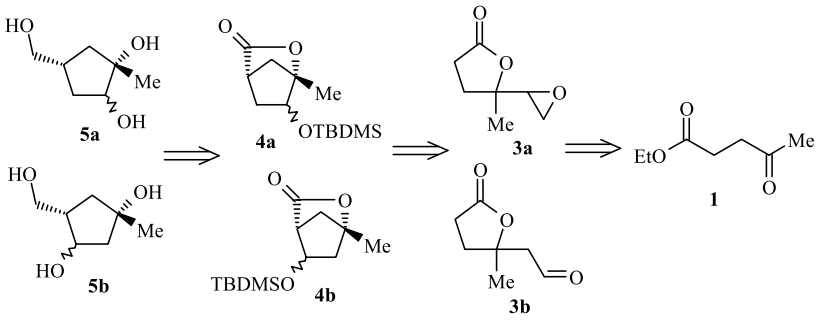
A method for the synthesis of 1-methylcarbapentofuranose derivatives was developed, where 1,2-cis- and 1,2-trans-4-hydroxymethyl-1-methylcyclopentanediols were obtained from intramolecular opening of a 4-epoxy-4-methyl-γ-lactone. An intramolecular aldol reaction of 4-methyl-4-(2-oxoethyl)-γ-lactone derivatives yielded 1,3-cis- and 1,3-trans-4-hydroxymethyl-1-methylcyclopentanediols.

Keywords: carbaribose, cyclopentane-1,2-diols, cyclopentane-1,3-diols, γ-lactone derivatives, oxabicyclo[2.2.1]heptanone, cyclization, epoxide opening.

Substituted cyclopentanediol structural subunits are essential parts of many important natural compounds and their analogs. Prostaglandins F [1, 2] and phytoprostanes [3], antiviral [4-6] and anticancer [7-9] carbacyclic nucleoside analogs present only a few examples of such compounds. It is obvious that the synthesis of differently substituted cyclopentane structures and pentofuranose carba analogs has attained considerable interest in the last few decades [10-12]. Also, several methods for stereoselective synthesis of compounds with structures of this type have been published [13-15].

We have been engaged in the synthesis of different 4'-substituted nucleoside analogs [16-18]. Now we have developed synthetic routes for obtaining 1'-methyl-substituted carbocyclic ribose analogs **5a**,**b** with controlled regio- and stereoselectivity from the key intermediates **3a**,**b** *via* bicyclic lactones **4a**,**b**.



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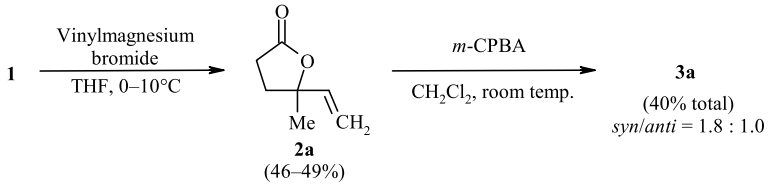
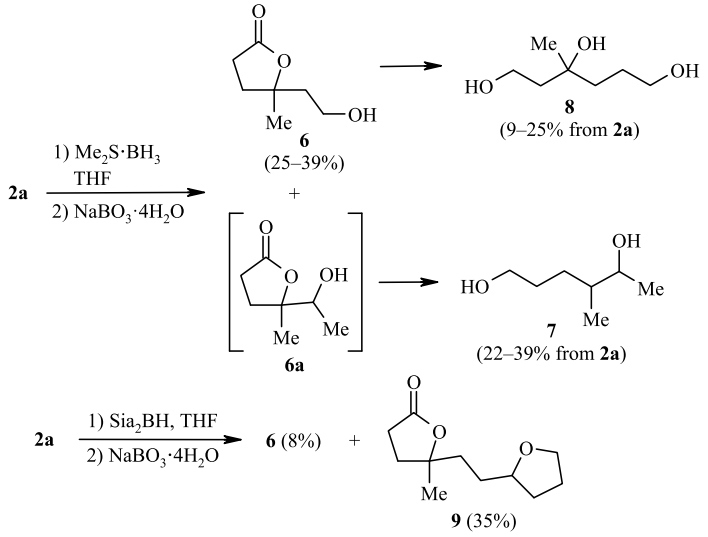
The location of the secondary OH group in the cyclopentane ring was determined by the key intermediate 3: compounds with 2-OH group are obtained from epoxide 3a, and compounds with 3-OH group, from the aldehyde 3b.

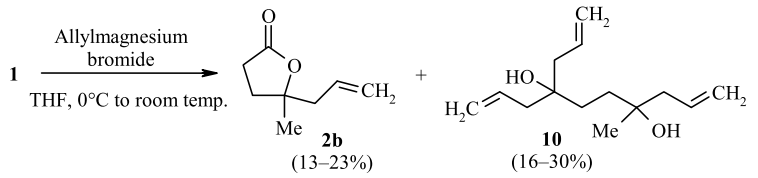
Lactone intermediates **2a**,**b** were prepared starting from ethyl levulinate **1**. Thus, addition of vinylic Grignard reagent to compound **1** [19], followed by intramolecular cyclization, afforded lactone **2a** (49% yield after distillation). The double bond of lactone **2a** was epoxidized with *m*-chloroperbenzoic acid (*m*-CPBA), resulting in a diastereomeric mixture of epoxy lactones **3a** in the *syn*/*anti* isomers ratio of 1.8:1.0, in 40% overall isolated yield.



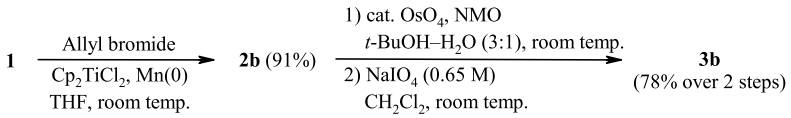
We also intended to obtain lactone aldehyde **3b** directly from vinyl lactone **2a** (*via* lactone alcohol **6**), by using a hydroboration–oxidation sequence. Despite our many attempts using $Me_2S{\cdot}BH_3$ in THF at different substrate/reactant ratios and reaction conditions, we always obtained a mixture of different products with the yield of the target lactone alcohol **6** after oxidation of borane with $NaBO_3{\cdot}4H_2O$ in the range of 25-39%, along with compound **7**, which very likely formed in 22-39% yield from regioisomer **6a**, after a hydroboration–elimination–rehydroboration sequence [20]. Also, we isolated 9-25% of the reduction product **8**. Even using a sterically bulky boron reagent disiamylborane (Sia_2BH) (110 mol%, from 0°C to room temperature, 44 h) did not improve the results – compound **6** was formed in only 8% yield after 44 h at room temperature; instead, a radical coupling reaction of alkene **2a** with THF occurred, yielding compound **9** in 35% yield.



Poor chemo- and regioselectivity (only 2:1 in favor of primary alcohol **6**, calculated from the **6**/**7** ratio) prompted us to pursue another synthetic path towards the key intermediate **3b**. Thus, a synthesis *via* allylic γ-lactone **2b** was performed. Direct Grignard reaction of ethyl levulinate **1** with allylmagnesium bromide gave unsatisfactory results, leading to mixtures of monoaddition adduct **2b** (after lactonization) and triple addition adduct **10** in variable ratios. The yield of monoaddition adduct **2b** did not exceed 23% in the best case.

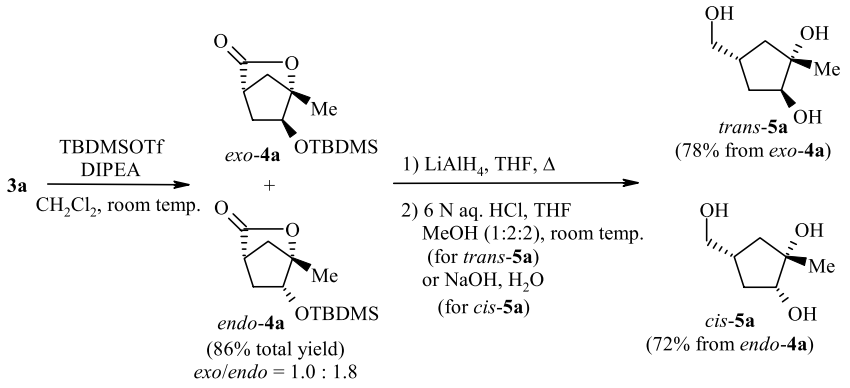


Fortunately, Ti(III)-mediated Barbier type allylation of ethyl levulinate **1** according to Estevez [21] with 1.5-fold excess of allyl bromide afforded allylic lactone **2b** in 91% yield. Two-step oxidation of γ-lactone **2b** and osmium-catalyzed dihydroxylation followed by $NaIO_4$-induced oxidative cleavage [22-24] afforded the key intermediate **3b** in 78% overall yield.



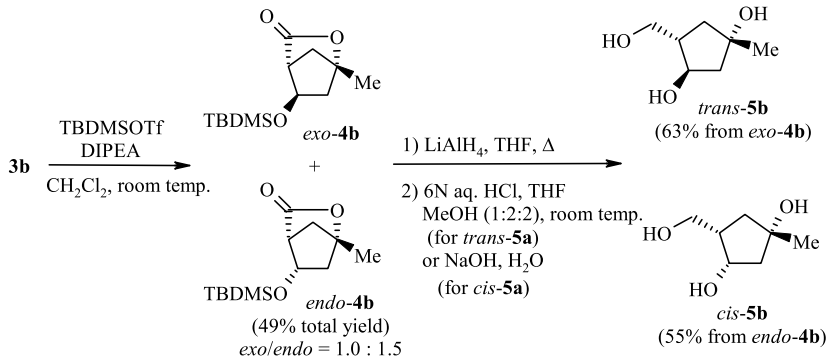
There are several reports in the literature where the intramolecular epoxide opening has been used to construct functionalized cyclopentane structural units. Some of the examples include NaH-assisted synthesis of the bicyclic skeleton of 9-deoxyenglerin A [25], Lewis acid (BF_3)-catalyzed intramolecular epoxide opening to synthesize brefeldin A [26], and a radical Ti-catalyzed stereoselective epoxide opening to construct functionalized cyclopentane structural units of terpenic compounds [27].

We found that lactone epoxide **3a** cyclizes smoothly in a regioselective manner by the use of TBDMSOTf–DIPEA reagent system [28].



The cyclization afforded stable diastereomeric silyl-protected alcohols **4a** in a good yield (86%) as the primary reaction products, in a similar *exo*/*endo* diastereomer ratio as the initial epoxide (1.8:1.0). This result indicates that the reaction is fully regio- and stereoselective. The diastereomers were easily separated on silica gel and subjected separately to reduction. Diastereomer *exo*-**4a** was treated with $LiAlH_4$ in refluxing THF, quenched with aqueous NaOH, and deprotected with 6 N HCl in a mixture of MeOH and THF to afford diol *trans*-**5a** in 78% yield over two steps. The compound *cis*-**5a** was obtained similarly from compound *endo*-**4a** in 72% yield after treatment of the reaction mixture with aqueos NaOH solution without the deprotection step.

Cyclization of the second key intermediate **3b** was performed under the same conditions used for compound **3a**. After separation on silica gel, isomers *exo*-**4b** and *endo*-**4b** were obtained in 49% total isolated yield, with the *exo*/*endo* ratio of ~1.0:1.5.



The subsequent transformations were carried out separately with the *exo* and *endo* isomers separately. Thus, compound *exo*-**4b** was treated with $LiAlH_4$ in THF, quenched with aqueous NaOH, followed by deprotection with a 1:2:2 mixture of aqueous 6 N HCl, MeOH, and THF to afford isomer *trans*-**5b** in 63% yield over two steps. A similar transformation of compound *endo*-**4b** to isomer *cis*-**5b** was achieved in 55% yield by a direct one-step quenching the mixture with aqueous NaOH.

To assign the configurations of bicyclic intermediates **4a**,**b**, well-known NMR spectral features of related bicyclo[2.2.1]heptane derivatives were used [29-31]. It is known that when C-5 or C-6 atoms in such compounds have an oxygen-derived *exo* substituent, the ^{13}C NMR signal of the C-7 carbon is shifted upfield [32, 33]. In the case of compound **4a**, the C-7 atom signal had a chemical shift of 40.7 ppm for the *exo* isomer and 42.7 ppm for the *endo* isomer, and in the case of compound **4b** the corresponding values were 41.9 and 43.4 ppm. In the ^1H NMR spectra, $^3J_{H\text{-}5x,H\text{-}4}$ was always larger than $^3J_{H\text{-}5n,H\text{-}4}$. In the case of compound **4b**, the corresponding values were 4.3 and 1.3 Hz, thus revealing the configuration of the H-5 proton. In the case of compound **4a**, both H-5 protons exhibited $^3J_{H\text{-}5x,H\text{-}4}$ constants of 4.6 Hz (for the *endo* isomer) and 4.3 Hz (for the *exo* isomer) and $^3J_{H\text{-}5n,H\text{-}4}$ constants of 0.6 and 0.7 Hz, respectively (Fig. 1).

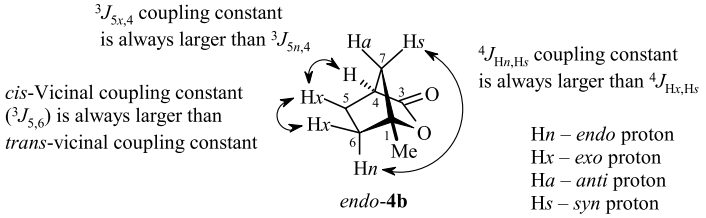


Fig. 1. Relevant interactions for the structure determination.
(TBDMSO group at position 5*n* is not shown)

As a rule, the vicinal proton-proton coupling constants ^3J have higher values when the protons were *cis*-oriented. In the case of compounds **4a**, the H-5*x* and H-5*n* protons being assigned, the relative configuration of H-6 was revealed by inspecting the relevant ^3J coupling constants of H-5*x*,H-6 and H-5*n*,H-6, which for the isomer *exo*-**4a** were 2.7 and 6.6 Hz and for the isomer *endo*-**4a** 9.0 and 3.3 Hz, respectively. Equally informative in H^1 NMR spectrum for the purpose of establishing the configuration of compounds **4a** and **4b** were ^4J constants between H-7*s* and H-6 (and H-5) *endo* protons, which were always larger in the case of *endo* protons than in the case of *exo* protons [29]. The H-6*n* proton of compound **4a** was found to be coupled to H-7*s* with $J = 1.6$ Hz, whereas the H-5*n* proton of compound **4b** was coupled to H-7*s* with $J = 1.3$ Hz.

Taking into account all the relevant information given above, we determined unambiguously the relative configuration of bicyclic compounds **4a**,**b**, thus letting us establish also the relative configurations of diols **5a**,**b**. On the other hand, the relative configuration of compound **5a** could have been determined based on our previous observation [34] that the ^{13}C chemical shifts of 1-methyl-substituted vicinal diols are dependent on the *cis*-*trans* substitution pattern. The methyl group should have ^{13}C chemical shift upfield in *trans*-diol relative to *cis*-diol; in the case of the isomer *trans*-**5a,** the methyl group had a 22.1 ppm chemical shift, and 25.2 ppm in the case of isomer *cis*-**5a**. Furthermore, the C-1 and C-2 carbons in compound **5a** should have chemical shifts moved upfield when *cis* substitution is observed relative to the *trans*-substituted diol. Indeed, the chemical shifts for C-1 and C-2 carbons in the isomer *cis*-**5a** were 79.1 and 78.6 ppm, whereas in the isomer *trans*-**5a** the corresponding shifts were 81.8 and 81.1 ppm. These results correlated with the observation that reduction of compounds *exo*-**4a** and *endo*-**4a** should yield triols *trans*-**5a** and *cis*-**5a**, respectively, and thus confirmed the assignment of the relative configuration for bicyclic intermediates **4a**.

Thus, through unprecedented use of the TBDMSOTf–DIPEA reagent system, a regio- and stereospecific epoxide opening reaction was investigated and efficiently applied to the synthesis of novel methyl branched cyclopentane derivatives *via* heterocyclic bicyclo[2.2.1]heptanes. Appropriate substrate selection allowed us to achieve the synthesis of regioisomeric 5- and 1-methyl-6-silyloxy-2-oxa-bicyclo[2.2.1]heptan-3-one derivatives, starting from (2-methyl-5-oxotetrahydrofuran-2-yl)acetaldehyde and 5-methyl-5-oxiranyldihydrofuran-2-one, respectively.

EXPERIMENTAL

The IR spectra were measured on a Perkin-Elmer Spectrum BX FTIR spectrometer. The NMR spectra were determined in $CDCl_3$ or CD_3OD on Bruker Avance USLA 400 or Bruker Avance 800 spectrometers. Residual solvent signals were used for reference. Mass spectra were recorded on Hitachi M80B or Shimadzu GCMSQP2010 spectrometers using EI ionization (70 eV). High-resolution mass spectra were recorded on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer utilizing AJ-ESI or APCI ion sources. Elemental analyses were performed on a Perkin-Elmer C,H,N,S-Analyzer 2400. Precoated silica gel 60 F254 plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40-100 μm was used. All reactions sensitive to moisture or oxygen were carried out under Ar atmosphere in oven-dried glassware. Vinyl lactone **2a** and allyl lactone **2b** were synthesized according to previously published methods (except that, for allylation reaction, allyl bromide instead of allyl chloride was used as alkylating reagent) and their physical and spectroscopic properties were in accordance with data given in the literature [19, 21]. Epoxides **3a** were synthesized by the literature method [35]. Chemicals were purchased from Aldrich Chemical Co. or Alfa Aesar and were used as received. MeOH was distilled from sodium. DCM was distilled over CaH_2 and stored on the 4Å molecular sieves pellets. THF was distilled from sodium benzophenone complex.

5-Methyl-5-oxiranyldihydrofuran-2-one (3a) (Mixture of Diastereomers). *m*-CPBA (551.3 mg, 2.46 mmol, 1.22 equiv) was added portionwise at 22°C to a solution of γ-vinyl lactone **2a** (253.6 mg, 2.01 mmol) in CH_2Cl_2 (5 ml). The resulting solution was stirred at 22°C for 25 h, during which precipitation occurred. A second portion of *m*-CPBA (764.4 mg, 3.10 mmol) was added, and stirring was continued for another 19 h (44 h total). The reaction was quenched with successive addition of 10% aqueous solution of $Na_2S_2O_3$ (5 ml) and 5% aqueous solution of $NaHCO_3$ (5 ml) with vigorous stirring. The layers were separated and the water phase extracted with CH_2Cl_2 (4×10 ml). The combined organic phases were washed sequentially with $NaHCO_3$ (10 ml) and saturated NaCl (10 ml), then dried over Na_2SO_4. Filtration and evaporation of volatiles afforded the crude product, from which, after purification by flash chromatography (silica gel, CH_2Cl_2–MeOH, 200:1), diastereomeric epoxides **3a** were obtained as a light-yellow oil (112 mg, 40%, *syn/anti* = 1.8:1.0). IR spectrum (thin layer), ν, cm^{-1}: 2984 (CH), 1778 (CO). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.20 (0.36H, *J* = 4.2, *J* = 2.7, 2'-CH *anti*); 3.03 (0.64H, dd, *J* = 4.0, *J* = 2.8, 2'-CH *syn*); 2.84

(0.36H, t, J = 4.3, 3'-CH_A *anti*); 2.80 (0.64H, dd, J = 5.0, J = 2.6, 3'-CH_A *syn*); 2.78-2.69 (1.28H, m, 3-CH_A *syn*, 3'-CH_B *syn*); 2.66-2.57 (1.08H, m, 3-CH_2 *anti*, 3'-CH_B *anti*); 2.55-2.39 (1.28H, m, 3-CH_B *syn*, 4-CH_A *syn*); 2.13-2.01 (1H, m, 4-CH_B *syn*, 4-CH_A *anti*); 1.90-1.78 (0.36H, m, 4-CH_B *anti*); 1.50 (1.92H, s, CH_3 *syn*); 1.48 (1.08H, s, CH_3 *anti*). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 176.5 (C-2 *syn*); 176.2 (C-2 *anti*); 84.7 (C-5 *anti*); 81.6 (C-5 *syn*); 56.7 (C-2' *syn*); 55.3 (C-2' *anti*); 43.6 (C-3' *anti*); 43.5 (C-3' *syn*); 32.5 (C-4 *syn*); 29.0 (C-3 *syn*); 29.0 (C-3 *anti*); 27.7 (C-4 *anti*); 23.5 (CH_3 *anti*); 23.3 (CH_3 *syn*). Mass spectrum, *m/z* (I_{rel}, %): 142 $[M]^+$ (1), 127 $[M\text{-}CH_3]^+$ (2), 112 $[M\text{-}CH_2O]^+$ (1), 99 $[M\text{-}C_2H_3O]^+$ (100). Found, %: C 58.90; H 7.09. $C_7H_{10}O_3$. Calculated, %: C 59.14; H 7.09.

(2-Methyl-5-oxotetrahydrofuran-2-yl)acetaldehyde (3b). OsO_4 in *t*-BuOH (2.5%, 2.2 ml, 0.175 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (50% in water, 1.1 ml, 5.32 mmol) were consecutively added to a solution of γ-allyl lactone **2b** (93%, 536.3 mg, 3.55 mmol) in *t*-BuOH (8.9 ml) and H_2O (3.0 ml). After stirring at 22°C for 23 h, the reaction mixture was treated with 20% aqueous Na_2SO_3 (10 ml) and Florisil (1 g) at the same temperature for 45 min. The resulting slurry was filtered through a pad of Celite and the latter washed with acetone (3×15 ml). The organic volatiles were evaporated, and 1 M $NaHSO_4$ (2 ml) was added to the residue to adjust the pH to 2. The water phase was extracted with EtOAc (15×15 ml, NaCl (2 g) was added to the water phase after the 10th extract), dried over $MgSO_4$, and filtered through a short pad of silica to yield crude 5-(2,3-dihydroxypropyl)-5-methyldihydrofuran-2-one (562.5 mg) as a 1:1 mixture of diastereomers, which was used in the next synthetic step without further purification. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.98-3.89 (1H, m, 2'-CH); 3.62-3.52 (1H, m) and 3.49-3.40 (1H, m, 3'-CH_2); 2.72-2.55 (2H, m, 3-CH_2); 2.49-2.21 (1H, m) and 2.12-1.99 (1H, m, 4-CH_2); 1.92-1.71 (2H, m, 1'-CH_2); 1.49 (1.5H, s) and 1.47 (1.5H, s, CH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 177.0 (C-2); 86.1 and 85.9 (C-5); 68.4 and 67.9 (C-2'); 66.6 and 66.6 (C-3'); 42.7 and 42.6 (C-1'); 33.4 and 32.7 (C-4); 28.7 and 28.5 (C-3); 26.4 and 25.6 (CH_3).

To the obtained intermediate diol (479 mg, 2.75 mmol) dissolved in CH_2Cl_2 (55.0 ml), $NaIO_4$ (0.65 M, 5.3 ml) and silica (5.22 g) were added at 22°C. The resulting slurry was stirred for 40 min and then filtered through a pad of silica. The solids on the filter were washed with CH_2Cl_2 (3×25 ml) and EtOAc (2×25 ml), and the solvents were evaporated to yield the crude aldehyde **3b** as a light-brown liquid. Yield 392.4 mg (78%). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1766 (CO), 1723 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.79 (1H, t, J = 1.9, CHO); 2.85 (2H, qd, J = 16.7, J = 1.8, C$\underline{H}_2$CHO); 2.71–2.62 (2H, m, 4-CH_2); 2.30–2.16 (2H, m, 3-CH_2); 1.52 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 198.6 (CHO); 175.7 (C-5); 83.2 (C-2); 53.3 ($\underline{C}H_2$CHO); 33.0 (C-4); 28.3 (C-3); 26.3 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 143 $[M+H]^+$ (1), 127 $[M\text{-}CH_3]^+$ (8), 114 $[M+H\text{-}CH_2O]^+$ (27), 99 $[M\text{-}C_2H_3O]^+$ (92). Found, *m/z*: 165.0521 $[M+Na]^+$. $C_7H_{10}O_3Na$. Calculated, *m/z*: 165.0522.

Synthesis of Cyclization Products *exo*-4a, *endo*-4a, *exo*-4b and *endo*-4b (General Method).

6-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (4a). To the mixture of DIPEA (255 μl, 1.45 mmol) and TBDMSOTf (340 μl, 1.45 mmol) in CH_2Cl_2 (6 ml), a solution of a diastereomeric mixture of epoxides **3a** (69 mg, 0.49 mmol) in CH_2Cl_2 (3 ml) was added dropwise at 25°C over a period of 10-15 min. The resulting solution (0.06 M of substrate) was stirred for 0.5 h at 25°C, after which the reaction mixture was added to a saturated aqueous NH_4Cl solution, and the layers were separated. The organic phase was extracted with CH_2Cl_2 (4×10 ml), dried over $MgSO_4$, filtered, and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, heptane–acetone, 40:1 to 10:1) to yield compounds *exo*-**4a** (66.6 mg, 54%) and *endo*-**4a** (39.0 mg, 32%) in the form of light-yellow oils.

6-*exo*-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (*exo*-4a). IR spectrum (thin layer), ν, cm^{-1}: 1776 (CO). ^{1}H NMR spectrum (800 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.82 (1H, ddd, J = 6.6, J = 2.7, J = 1.6, 6-CH*n*); 2.72 (1H, dddd, J = 4.3, J = 1.6, J = 1.2, J = 0.7, 4-CH); 2.17 (1H, dddd, J = 13.2, J = 6.6, J = 2.3, J = 0.7, 5-CH*n*); 1.98 (1H, dd, J = 10.6, J = 1.2, 7-CH*a*); 1.88 (1H, ddt, J = 10.6, J = 2.3, J = 1.6, 7-CH*s*); 1.59 (1H, ddd, J = 13.2, J = 4.3, J = 2.7, 5-CH*x*); 1.47 (3H, s, 1-CH_3); 0.87 (9H, s, $C(CH_3)_3$); 0.06 (3H, s) and 0.05 (3H, s, $Si(CH_3)_2$). ^{13}C NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 178.1 (C-3); 90.8

(C-1); 73.3 (C-6); 41.1 (C-4); 40.7 (C-7); 36.2 (C-5); 25.6 (SiC($\underline{C}$H$_3$)$_3$); 17.8 (Si$\underline{C}$(CH$_3$)$_3$); 15.6 (1-CH$_3$); -4.8 (SiCH$_3$); -5.1 (SiCH$_3$). Mass spectrum, *m/z* (I_{rel}, %): 257 [M+H]$^+$ (1), 241 [M-CH$_3$]$^+$ (2), 211 [M-COOH]$^+$ (1), 199 [M-*t*-Bu]$^+$ (31), 171 [M-*t*-Bu-CO]$^+$, (41), 155 [M-*t*-Bu-COOH]$^+$ (26), 141 [M-TBDMS]$^+$ (1), 127 [M+1-TBDMS-CH$_3$]$^+$ (9), 115 [TBDMS]$^+$ (28), 75 [C$_2$H$_7$SiO]$^+$ (100). Found, %: C 60.81; H 9.48. $C_{13}H_{24}O_3Si$. Calculated, %: C 60.89; H 9.43.

6-*endo*-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (*endo*-4a). IR spectrum (thin layer), ν, cm^{-1}: 1779 (CO). ^{1}H NMR spectrum (800 MHz, CDCl$_3$), δ, ppm (*J*, Hz): 4.14 (1H, dd, *J* = 9.0, *J* = 3.3, 6-CH*x*); 2.79 (1H, dddd, *J* = 4.6, *J* = 1.9, *J* = 1.0, *J* = 0.6, 4-CH); 2.31 (1H, ddd, *J* = 13.3, *J* = 9.0, *J* = 4.6, 5-CH*x*); 1.95 (1H, ddd, *J* = 10.8, *J* = 3.4, *J* = 1.9, 7-CH*s*); 1.72 (1H, dd, *J* = 10.8, *J* = 1.0, 7-CH*a*); 1.50 (1H, dtd, *J* = 13.3, *J* = 3.3, *J* = 0.6, 5-CH*n*), 1.48 (3H, s, 1-CH$_3$); 0.88 (9H, s, C(CH$_3$)$_3$); 0.06 (s, 3H) and 0.04 (s, 3H, Si(CH$_3$)$_2$). ^{13}C NMR spectrum (400 MHz, CDCl$_3$), δ, ppm: 178.2 (C-3); 90.1 (C-1); 74.6 (C-6); 43.6 (C-4); 42.7 (C-7); 35.6 (C-5); 25.6 (SiC($\underline{C}$H$_3$)$_3$); 18.0 (Si$\underline{C}$(CH$_3$)$_3$); 16.1 (1-CH$_3$), -4.7 (SiCH$_3$); -5.0 (SiCH$_3$). Mass spectrum, *m/z* (I_{rel}, %): 241 [M-CH$_3$]$^+$ (1), 211 [M-COOH]$^+$ (1), 199 [M-*t*-Bu]$^+$ (12), 171 [M-*t*-Bu-CO]$^+$ (23), 155 [M-*t*-Bu-COOH]$^+$ (46), 141 [M-TBDMS]$^+$ (1), 127 [M+1-TBDMS-CH$_3$]$^+$ (13), 115 [TBDMS]$^+$ (22), 75 [C$_2$H$_7$SiO]$^+$ (100). Found, %: C 60.89; H 9.48. $C_{13}H_{24}O_3Si$. Calculated, %: C 60.89; H 9.43.

5-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (4b) was obtained using aldehyde **3b** as starting material on a 2.75 mmol scale. Yield of isomer *exo*-**4b** 143 mg (20%), light-yellow liquid. Yield of isomer *endo*-**4b** 204 mg (29%), light-yellow amorphous solid.

5-*exo*-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (*exo*-4b). IR spectrum (CHCl$_3$), ν, cm^{-1}: 1783 (CO). ^{1}H NMR spectrum (400 MHz, CDCl$_3$), δ, ppm (*J*, Hz): 4.33 (1H, ddt, *J* = 6.6, *J* = 2.0, *J* = 1.3, 5-CH*n*); 2.79 (1H, quint, *J* = 1.3, 4-CH); 2.25 (1H, dd, *J* = 10.4, *J* = 1.4, 7-CH*a*); 2.25 (1H, ddd, *J* = 13.8, *J* = 6.6, *J* = 2.8, 6-CH*n*); 1.98 (1H, ddt, *J* = 10.4, *J* = 2.8, *J* = 1.3, 7-CH*s*); 1.59 (3H, s, 1-CH$_3$); 1.59 (1H, ddd, *J* = 13.8, *J* = 2.0, *J* = 1.3, 6-CH*x*); 0.88 (9H, s, C(CH$_3$)$_3$); 0.08 (3H, s) and 0.07 (3H, s, Si(CH$_3$)$_2$). ^{13}C NMR spectrum (101 MHz, CDCl$_3$), δ, ppm: 176.5 (C-3); 90.2 (C-1); 70.2 (C-5); 53.3 (C-4); 47.0 (C-6); 41.9 (C-7); 25.7 (C($\underline{C}$H$_3$)$_3$); 18.7 (1-CH$_3$); 17.9 ($\underline{C}$(CH$_3$)$_3$); -4.8 (SiCH$_3$); -5.0 (SiCH$_3$). Mass spectrum, *m/z* (I_{rel}, %): 256 [M]$^+$ (1), 241 [M-CH$_3$]$^+$ (1), 199 [M-*t*-Bu]$^+$ (33), 171 [M-*t*-Bu-CO]$^+$ (4), 155 [M-*t*-Bu-COOH]$^+$ (7), 115 [TBDMS]$^+$ (2), 75 [C$_2$H$_7$SiO]$^+$ (100). Found, *m/z*: 279.1391 [M+Na]$^+$. $C_{13}H_{24}NaO_3Si$. Calculated, *m/z*: 279.1387.

5-*endo*-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-one (*endo*-4b). IR spectrum (KBr), ν, cm^{-1}: 1776 (CO). ^{1}H NMR spectrum (400 MHz, CDCl$_3$), δ, ppm (*J*, Hz): 4.54 (1H, ddd, *J* = 8.7, *J* = 4.3, *J* = 3.1, 5-CH*x*); 2.92 (1H, dt, *J* = 4.3, *J* = 1.4, 4-CH); 2.10 (1H, dd, *J* = 13.7, *J* = 8.7, 6-CH*x*); 1.96 (1H, ddd, *J* = 10.7, *J* = 3.9, *J* = 1.6, 7-CH*s*); 1.65 (1H, dd, *J* = 10.7, *J* = 1.2, 7-CH*a*); 1.64 (1H, ddd, *J* = 13.7, *J* = 3.9, *J* = 3.1, 6-CH*n*); 1.51 (3H, s, 1-CH$_3$); 0.87 (9H, s, C(CH$_3$)$_3$); 0.09 (s, 3H) and 0.06 (s, 3H, Si(CH$_3$)$_2$). ^{13}C NMR spectrum (101 MHz, CDCl$_3$), δ, ppm: 174.8 (C-3); 88.6 (C-1); 70.6 (C-5); 51.7 (C-4); 43.7 (C-6); 43.4 (C-7); 25.7 (C($\underline{C}$H$_3$)$_3$); 19.3 (CH$_3$); 18.0 ($\underline{C}$(CH$_3$)$_3$); -4.8 (SiCH$_3$); -5.0 (SiCH$_3$). Mass spectrum, *m/z* (I_{rel}, %): 241 [M–CH$_3$]$^+$ (1), 199 [M–*t*-Bu]$^+$ (30); 171 [M–*t*-Bu–CO]$^+$ (8); 155 [M–*t*-Bu–COOH]$^+$ (6); 75 [C$_2$H$_7$SiO]$^+$ (100). Found (ESI), *m/z*: 279.1392 [M+Na]$^+$. $C_{13}H_{24}NaO_3Si$. Calculated, *m/z*: 279.1387.

1,2-*trans*-4-Hydroxymethyl-1-methylcyclopentane-1,2-diol (*trans*-5a). $LiAlH_4$ (91 mg, 2.28 mmol) was suspended in THF, and a solution of compound *exo*-**4a** (167 mg, 0.65 mmol) in THF (10 ml) was added at 0°C. The resulting suspension was heated to reflux for 1 h, then the reaction mixture was cooled to 0°C and water was added (100 μl). Stirring was continued for 0.5 h with gradual rise of temperature to 23°C. Then aqueous 10% NaOH (100 μl) at 23°C was added, and the stirring continued for an additional 0.5 h to complete the precipitation. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield the crude protected diol. Mass spectrum, *m/z* (I_{rel}, %): 243 [M+H-H$_2$O]$^+$ (1), 227 [M-H$_2$O-CH$_3$]$^+$ (1), 203 [M-*t*-Bu]$^+$ (12), 185 [M-H$_2$O-*t*-Bu]$^+$ (42), 129 [M+H-H$_2$O-TBDMS]$^+$ (2), 75 [C$_2$H$_7$SiO]$^+$ (100).

To a solution of the protected diol (130.3 mg, 0.50 mmol) in a mixture of THF (2 ml) and MeOH (2 ml), 6 N HCl (1 ml) was added dropwise at 25°C. The resulting solution was stirred for 1 h at 25°C, then the volatiles were evaporated to yield the crude product as a light-yellow oil. Further purification was achieved by

flash chromatography on silica gel eluting with CH_2Cl_2–MeOH, 10:1. Yield 57 mg (78%). Colorless oil. IR spectrum (thin layer), ν, cm^{-1}: 3341 (OH), 1118 (C–O), 1038 (C–O). ^1H NMR spectrum (400 MHz, CD_3OD), δ, ppm (*J*, Hz): 3.75 (1H, dd, *J* = 5.6, *J* = 3.3, 2-CH); 3.47 (2H, d, *J* = 6.0, C<u>H</u>$_2$OH); 2.44–2.27 (1H, m, 4-CH); 1.98-1.80 (2H, m, 3-CH_A, 5-CH_A); 1.77-1.65 (1H, m, 3-CH_B); 1.43 (1H, dd, *J* = 13.7, *J* = 5.3, 5-CH_B); 1.25 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, CD_3OD), δ, ppm: 81.8 (C-1); 81.1 (C-2); 67.6 (CH_2OH); 41.5 (C-5); 38.4 (C-4); 36.2 (C-3); 22.1 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 146 $[M]^+$ (1), 128 $[M-H_2O]^+$ (3), 115 $[M-CH_2OH]^+$ (28), 98 $[M+H-H_2O-CH_2OH]^+$ (17), 97 $[M-H_2O-CH_2OH]^+$ (37). Found, *m/z*: 169.0829 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0835.

1,2-*cis*-4-Hydroxymethyl-1-methylcyclopentane-1,2-diol (*cis*-5a). $LiAlH_4$ (50 mg, 1.29 mmol) was suspended in THF (7 ml), and a solution of the compound *endo*-**4a** (88 mg, 0.34 mmol) in THF (7 ml) was added at 0°C. The resulting suspension was heated to reflux for 1 h, then the reaction mixture was cooled to 0°C and water (100 μl) was added. Stirring was continued for 0.5 h with gradual rise of temperature to 23°C. Then aqueous 10% NaOH (100 μl) at 23°C was added, and the stirring continued for an additional 0.5 h to complete the precipitation. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield the crude diol *cis*-**5a**, which was purified by flash chromatography on silica gel, eluent CH_2Cl_2–MeOH, 10:1. Yield 36.4 mg (72%). Light to colorless oil. IR spectrum (thin layer), ν, cm^{-1}: 3381 (OH), 1086 (C–O), 1043 (C–O). ^1H NMR spectrum (400 MHz, CD_3OD), δ, ppm (*J*, Hz): 3.63 (1H, dd, *J* = 7.9, *J* = 6.4, 2-CH); 3.48 (2H, d, *J* = 6.0, C<u>H</u>$_2$OH); 2.17-2.01 (2H, m, 4-CH, 3-CH_A); 1.79 (1H, dd, *J* = 13.8, *J* = 9.3) and 1.56 (1H, dd, *J* = 13.8, *J* = 5.7, 5-CH_2); 1.48 (1H, dt, *J* = 12.7, *J* = 7.5, 3-CH_B); 1.22 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, CD_3OD), δ, ppm: 79.1 (C-1); 78.6 (C-2); 67.7 (<u>C</u>H_2OH); 41.2 (C-5); 36.4 (C-4); 35.6 (C-3); 25.2 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 146 $[M]^+$ (1), 128 $[M-H_2O]^+$ (5), 115 $[M-CH_2OH]^+$ (32), 98 $[M+H-H_2O-CH_2OH]^+$ (14), 97 $[M-H_2O-CH_2OH]^+$ (36). Found, *m/z*: 169.0828 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0835.

1,3-*trans*-4-Hydroxymethyl-1-methylcyclopentane-1,3-diol (*trans*-5b). $LiAlH_4$ (41 mg, 1.06 mmol) was suspended in THF (2.5 ml), and a solution of the compound *exo*-**4b** (130.3 mg, 0.51 mmol) in THF (2.5 ml) was added at 0°C. The resulting suspension was heated to reflux for 1 h, then the reaction mixture was cooled to 0°C, and water (41 μl) was added. Stirring was continued for 0.5 h with gradual rise of temperature to 23°C. Then aqueous 10% NaOH (41 μl) at 23°C was added, and the stirring was continued for an additional 0.5 h, upon which water (123 μl) was added. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield the crude protected diol, which was dissolved in CH_2Cl_2 (5 ml), and 6 N HCl (200 μl) was added. The resulting two-phase system was stirred vigorously for 5 min and then the volatiles were removed *in vacuo* to yield the crude diol *trans*-**5b**, which was purified by flash chromatography on silica gel, eluent CH_2Cl_2–MeOH, 20:1 to 10:1. Yield 46.7 mg (63%). Light-yellow oil. IR spectrum (thin layer), ν, cm^{-1}: 3331 (OH), 1057 (C–O), 1031 (C–O). ^1H NMR spectrum (400 MHz, CD_3OD), δ, ppm (*J*, Hz): 4.10 (1H, dd, *J* = 13.6, *J* = 7.6, 3-CH); 3.68 (1H, dt, *J* = 9.5, *J* = 5.9) and 3.58-3.55 (1H, m, C<u>H</u>$_2$OH); 2.07 (1H, ddd, *J* = 13.2, *J* = 7.1, *J* = 1.4, 4-CH); 2.01-1.94 (2H, m) and 1.67-1.52 (2H, m, 2,5-CH_2); 1.33 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, CD_3OD), δ, ppm: 77.8 (C-1); 75.2 (C-3); 65.4 (<u>C</u>H_2OH); 50.8 (C-4); 50.7 (C-2); 43.8 (C-5); 29.5 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 128 $[M-H_2O]^+$ (1), 113 $[M-H_2O-CH_3]^+$ (15), 98 $[M+H-H_2O-CH_2OH]^+$ (11), 97 $[M-H_2O-CH_2OH]^+$ (4). Found, *m/z*: 169.0824 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0835.

1,3-*cis*-4-hydroxymethyl-1-methylcyclopentane-1,3-diol (*cis*-5b). $LiAlH_4$ (43.5 mg, 1.12 mmol) was suspended in THF (2.5 ml), and a solution of the compound *endo*-**4b** (135.2 mg, 0.53 mmol) in THF (2.5 ml) was added at 0°C. The resulting suspension was heated to reflux for 1h, then the reaction mixture was cooled to 0°C, and water (44 μl) was added. Stirring was continued for 0.5 h with gradual rise of temperature to 19°C. Then aqueous 10% NaOH (100 μl) was added at 19°C, and the stirring continued for an additional 0.5 h, upon which water (132 μl) was added. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield the crude diol *cis*-**5b** which was purified by flash chromatography on silica gel, eluent CH_2Cl_2–MeOH 40:1 to 20:1 mixture. Yield 44.3 mg (55%). Light-yellow oil. IR spectrum (thin layer), ν, cm^{-1}: 3383 (OH), 1033 (C–O). ^1H NMR spectrum (400 MHz, CD_3OD), δ, ppm (*J*, Hz): 4.26 (1H, td, *J* = 4.9, *J* = 2.8, 3-CH); 3.79 (1H, dd, *J* = 10.7, *J* = 7.5) and 3.66-3.58 (1H, m, C<u>H</u>$_2$OH); 2.20–2.10 (1H, m, 4-CH); 1.90-1.81 (3H, m, 2-CH_2,

5-CH_A); 1.77-1.68 (1H, m, 5-CH_B); 1.30 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, CD_3OD), δ, ppm: 79.4 (C-1); 74.8(C-3); 63.2 ($\underline{C}H_2OH$); 50.8 (C-2); 47.7 (C-4); 43.8 (C-5); 29.8 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 147 $[M+H]^+$ (1), 128 $[M-H_2O]^+$ (2), 113 $[M-H_2O-CH_3]^+$ (2), 98 $[M+H-H_2O-CH_2OH]^+$ (10), 97 $[M-H_2O-CH_2OH]^+$ (5). Found, *m/z*: 169.0825 $[M+Na]^+$. $C_7H_{14}NaO_3$. Calculated, *m/z*: 169.0835.

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REFERENCES

1. S. Das, S. Chandrasekhar, J. S. Yadav, and R. Grée, *Chem. Rev.*, **107**, 3286 (2007).
2. P. W. Collins and S. W. Djuric, *Chem. Rev.*, **93**, 1533 (1993).
3. M. Mueller, *Curr. Opin. Plant Biol.*, **7**, 441 (2004).
4. E. Pinheiro, O. Antunes, and J. Fortunak, *Antiviral Res.*, **79**, 143 (2008).
5. E. De Clercq and J. Neyts, *Rev. Med. Virol.*, **14**, 289 (2004).
6. C. Simons, Q. Wu, and T. T. Htar, *Curr. Top. Med. Chem.*, **5**, 1191 (2005).
7. T. J. N. Watson, T. T. Curran, D. A. Hay, R. S. Shah, D. L. Wenstrup, and M. Webster, *Org. Process Res. Dev.*, **2**, 357 (1998).
8. M. T. Crimmins, *Tetrahedron*, **54**, 9229 (1998).
9. J. Zhou, M. Yang, A. Akdag, H. Wang, and S. W. Schneller, *Tetrahedron*, **64**, 433 (2008).
10. O. Arjona, A. M. Gómez, J. C. López, and J. Plumet, *Chem. Rev.*, **107**, 1919 (2007).
11. V. B. Kurteva and C. A. M. Afonso, *Chem. Rev.*, **109**, 6809 (2009).
12. J. A. Lee, H. R. Moon, H. O. Kim, K. R. Kim, K. M. Lee, B. T. Kim, K. J. Hwang, M. W. Chun, K. A. Jacobson, and L. S. Jeomg, *J. Org. Chem.*, **70**, 5006 (2005).
13. K. Kato, H. Suzuki, H. Tanaka, T. Miyasaka, M. Baba, K. Yamaguchi, and H. Akita, *Chem. Pharm. Bull.*, **47**, 1256 (1999).
14. G. Audran, S. Acherar, and H. Monti, *Eur. J. Org. Chem.*, **2003**, 92 (2003).
15. G. Rassu, L. Auzzas, V. Zambrano, P. Burredu, L. Battistini, and C. Curti, *Tetrahedron: Asymmetry*, **14**, 1665 (2003).
16. A. Jõgi, M. Ilves, A. Paju, T. Pehk, T. Kailas, A.-M. Müürisepp, and M. Lopp, *Tetrahedron: Asymmetry*, **19**, 628 (2008).
17. A. Jõgi, A. Paju, T. Pehk, T. Kailas, A.-M. Müürisepp, and M. Lopp, *Tetrahedron*, **65**, 2959 (2009).
18. A. Paju, M. Päri, A. Selyutina, E. Žusinaite, A. Merits, T. Pehk, K. Siirde, A.-M. Müürisepp, T. Kailas, and M. Lopp, *Nucleosides, Nucleotides Nucleic Acids,* **29**, 707 (2010).
19. W. J. Wechter, D. Kantoci, E. D. Murray, Jr, D. C. D'Amico, M. E. Jung, and W.-H. Wang, *Proc. Natl. Acad. Sci. U. S. A.*, **93**, 6002 (1996).
20. H. C. Brown and R. L. Sharp, *J. Am. Chem. Soc.*, **90**, 2915 (1968).
21. R. E. Estévez, J. Justicia, B. Bazdi, N. Fuentes, M. Paradas, D. Choquesillo-Lazarte, J. M. Garcia-Ruiz, R. Robles, A. Gansäuer, J. M. Cuerva, and J. E. Oltra, *Chem. Eur. J.*, **15**, 2774 (2009).
22. M. Schroeder, *Chem. Rev.*, **80**, 187 (1980).
23. V. VanRheenen, D. Y. Cha, and W. M. Hartley, in: *Organic Syntheses*, Vol. 6, (1988), p. 342.
24. D. N. Gupta, P. Hodge, and J. E. Davies, *J. Chem. Soc., Perkin Trans. 1*, 2970 (1981).
25. D. B. Ushakov, V. Navickas, M. Ströbele, C. Maichle-Mössmer, F. Sasse, and M. E. Maier, *Org. Lett.*, **13**, 2090 (2011).
26. M.-Y. Kim and H. Kim, J. Tae, *Synlett*, **2009**, 1303 (2009).
27. J. F. Arteaga, H. R. Diéguez, J. A. González-Delgado, J. F. Quílez del Moral, and A. F. Barrero, *Eur.*

J. Org. Chem., 5002 (2011).
28. G. Rassu, L. Auzzas, L. Pinna, V. Zambrano, L. Battistini, F. Zanardi, L. Marzocchi, D. Acquotti, and G. Casiraghi, *J. Org. Chem.*, **66**, 8070 (2001).
29. J. L. Marshall and S. R. Walter, *J. Am. Chem. Soc.*, **96**, 6358 (1974).
30. K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963).
31. J. C. Davis, Jr. and T. V. Van Auken, *J. Am. Chem. Soc.*, **87**, 3900 (1965).
32. J. K. Whitesell and M. A. Minton, *Stereochemical Analysis of Alicyclic Compounds by ^{13}C NMR Spectroscopy*, Chapman and Hall, London (1987).
33. J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970).
34. A. Niidu, A. Paju, M. Eek, A.-M. Müürisepp, T. Pehk, and M. Lopp, *Tetrahedron: Asymmetry*, **17**, 2678 (2006).
35. B. M. Trost, M. J. Bogdanowicz, W. J. Frazee, and T. N. Salzmann, *J. Am. Chem. Soc.*, **100**, 5512 (1978).

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Abstract

Cyclopentanes and tetrahydrofurans are abundant in nature and as such have received the widespread attention of the scientific community. The syntheses of said compounds have been realized by many different routes in asymmetric and diastereoselective manners. However, some cyclopentane and tetrahydrofuran derivatives remain elusive to the synthetic community, exemplified by the scarce appearance of cyclopentane diols and triols bearing quaternary carbon centers and 2,2-disubstituted tetrahydrofurans and 1,7-dioxa[4.4]nonane frameworks in the organic synthetic literature.

Our group has been working on ways to elaborate the lactone carboxylic acids into many types of valuable compounds, such as nucleosides (cyclic and acyclic), homocitric acid and 2-alkyl-substituted 2-hydroxyglutaric acid γ-lactones, which formed the basis for further studies in the field. Thus we set out to develop synthetic methods which would allow access to cyclopentanediols and susbstituted tetrahydrofurans, relying on our previous experience in the asymmetric oxidation of diketones to hydroxylated cyclopentanes and γ-lactone carboxylic acids.

A method to afford selectively regioisomeric 2-methyl-2,3- and 2-methyl-2,5-dihydroxycyclopentanones was developed, in the course of which the stereochemistry of the mentioned compounds was determined by synthesizing relevant methyl-substituted cyclopentanediols by known methods, and subsequent comparative study of ^{13}C NMR spectra of model compounds and triols obtained from regioisomeric cyclopentanones. These observations were later confirmed in the case of diastereomeric 1-methyl-4-hydroxymethyl-1,2-cyclopentanediols. Thus in certain types of compounds (differently substituted 1-methyl-1,2-cyclopentanediols) the relative stereochemistry can be generally determined by inspecting appropriate ^{13}C NMR spectra.

γ-Lactone carboxylic acids (five examples) were converted to 2,2-disubstituted tetrahydrofuran derivatives by a synthetic method comprised of three or four steps in good overall yield and high enantiomeric purity. A modified three-step sequence was also applied to the synthesis of 1,7-dioxa[4.4]nonane in acceptable yield.

γ-Lactones (γ-vinyl and -allyl) were transformed regioselectively to respective 1-methyl-4-hydroxymethyl-1,2- and -1,3-cyclopentanediols, featuring unprecedented epoxide opening by the TBDMSOTf/DIPEA reagent system to furnish 1,2-cyclopentandiols in an efficient manner.

The further utility of chiral γ-lactone carboxylic acids was demonstrated when benzyl-substituted carboxylic acid was converted to respective diastereomeric 1-benzyl-4-hydroxymethyl-1,3-cyclopentanediols *via* a semi-telescoped process, thus avoiding tedious separations and purifications in three of the six steps.

Kokkuvõte

Looduses laialt levinud tsüklopentaanid ja tetrahüdrofuraanid on pälvinud teadusliku üldsuse laialdase tähelepanu. Mainitud ühendeid on sünteesitud mitmetel erinevatel meetoditel nii asümmeetriliselt kui diastereoselektiivselt. Siiski on teatud tsüklopentaanide ja tetrahüdrofuraanide derivaadid jäänud sünteesikeemikute vaateväljalt kõrvale, mida ilmestab tsüklopentaandioolide ja -trioolide ja 2,2-diasendatud tetrahüdrofuraanide ja ka 1,7-dioksa[4.4]nonaanide vähene esindatus sünteesialases teaduskirjanduses.

Meie töörühmas on välja töötatud erinevaid viise laktoonhapete kasutamiseks mitmete väärtuslike ühendite saamiseks nagu seda on tsüklilised ja atsüklilised nukleosiidid, homosidrunhape ja 2-alküül-2-glutaarhappe-γ-laktoonid. Toetudes eelnevale kogemusele, liikusime edasi meetodite väljatöötamise suunas, mis võimaldaksid sünteesida tsüklopentaanide ja tetrahüdrofuraanide derivaate lähtudes asümmeetrilise oksüdatsiooni saadustest – hüdroksüleeritud diketoonist ja γ-laktoonhapetest.

Töö käigus töötati välja meetod uudsete regioisomeersete 2-metüül-2,3- ja 2-metüül-2,5-hüdroksütsüklopentanoonide saamiseks, mille käigus tuvastati vastavate ühendite suhteline stereokeemia selleks sünteesitud mudelühendite ja tsüklopentanoonidest saadud trioolide ^{13}C TMR võrdleva analüüsi teel. Viimase tulemusi kinnitasid lisaks hilisemad tähelepanekud 1-metüül-4-hüdroksümetüül-1,2-tsüklopentaandioolide korral, mistõttu võime väita, et erinevalt asendatud 1-metüül-1,2-tsüklopentaandioolide suhtelist stereokeemiat saab üldistel alustel määrata pelgalt ^{13}C TMR spektraalandmeid uurides.

γ-Laktoonhapped (5 näidet) viidi üle 2,2-diasendatud tetrahüdrofuraanideks kasutades 3 või 4 astmelist sünteesiskeemi hea saagise ja kõrge enantiomeerse puhtusega. Modifitseeritud 3-etapilist skeemi kasutati lisaks ka 1,7-dioksa[4.4]nonaani saamiseks rahuldava saagisega.

γ-vinüül- ja -allüüllaktoone kasutati vastavate1-metüül-4-hüdroksümetüül-1,2- ja 1,3-tsüklopentaandioolide regioselektiivseks sünteesiks. Teadaolevalt esmakordselt kasutati antud meetodi juures epoksiidi avamiseks bitsüklilise vaheühendi moodustumisel TBDMSOTf/DIPEA kombinatsiooni.

Käeliste γ-laktoonhapete kasutusala laiendamisvõimaluste näitlikustamiseks töötati välja osaliselt teleskopeeritud meetod bensüülasendatud karboksüülhappe korral, mis viis vastavate 1-bensüül-4-hüdroksümetüül-1,3-tsüklopentaandioolideni, seejuures võimaldades loobuda tülikatest eraldamise ja puhastamise operatsioonidest kolmel etapil kuuest.

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8. Original publications

1. Niidu, A.; Paju, A.; Müürisepp, A.-M.; Järving, I.; Kailas, T.; Pehk, T.; Lopp, M. Stereoselective synthesis of 1-methyl-1,2- and 1,3-cyclopentanediols *via* γ-lactones. *Chemistry of Heterocyclic Compounds* **2013**, *48*, 1751-1760.
2. Niidu, A.; Paju, A.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synthesis of cyclopentane hydroxy derivatives* Balticum Organicum Syntheticum. International Conference on Organic Synthesis, **2012**, Tallinn, Estonia. Program and Abstract Book PO95.
3. Paju, A.; Niidu, A.; Lumi, P.; Matkevitš, Katharina; Oja, Karolin; Pehk, T.; Lopp, M. *Catalytic asymmetric synthesis of enantiomeric γ-lactone acids* 30th Estonian Chemistry Days **2010**, Tallinn, Estonia. Abstract Book pp. 61.
4. Paju, A.; Niidu, A.; Lumi, P.; Matkevitš, Katharina; Oja, Karolin; Pehk, T.; Lopp, M. *Catalytic asymmetric synthesis of γ-lactone acids* Balticum Organicum Syntheticum. International Conference on Organic Synthesis, **2010**, Riga, Latvia. Program and Abstract Book PO108.
5. Niidu, A.; Kislitsõn, K.; Paju, A.; Lopp, M. *Synthesis of key intermediate en route to novel carbasugar analogues* Balticum Organicum Syntheticum. International Conference on Organic Synthesis, **2010**, Riga, Latvia. Program and Abstract Book PO103.
6. Niidu, A.; Paju, A.; Müürisepp, A.-M.; Kailas, T.; Pehk, T.; Lopp, M. *Synthesis of chiral enantioenriched tetrahydrofuran derivatives* Arkivoc, **2009**, *xiv*, 39-52.
7. Niidu, A.; Kislitsõn, K.; Paju, A.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synthesis of chiral THF-analogues* Balticum Organicum Syntheticum. International Conference on Organic Synthesis, **2008**, Vilnius, Lithuania. Program and Abstract Book pp 1008.

8. Niidu, A.; Paju, A.; Kislitsõn, K.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synthesis of chiral THF-analogues* 30th Estonian Chemistry Days (oral presentation) **2007**, Tartu, Estonia. Abstract Book pp. 104-105.
9. Niidu. A. „*Synthesis of chiral THF derivatives*" UTTP Doctoral School winterschool (oral presentation), **2007**, Haapsalu, Estonia.
10. Niidu, A.; Paju, A.; Eek, M.; Müürisepp, A.-M.; T.; Pehk, T.; Lopp, M. *Synthesis of chiral hydroxylated cyclopentanones and cyclopentanes* Tetrahedron: Asymmetry, **2006**, *17*, 2678-2683.
11. Niidu. A. „*Synthesis of chiral cyclopentane derivatives*" UTTP Doctoral School summerschool (oral presentation), **2006**, Saaremaa, Estonia.
12. Niidu, A.; Paju, A.; Eek, M.; Kanger, T.; Pehk, T.; Lopp, M. *Investigation of the synthesis of hydroxylated cyclopentanediones* Balticum Organicum Syntheticum **2004**, 27.06-01.07.2004, Riga, Latvia, Abstract Book PO64.
13. Niidu, A.; Paju, A.; Eek, M.; Kanger, T.; Pehk, T.; Lopp, M. *Regio- nad stereoselective synthesis of chiral dihydroxyketones* Komppa Centenary Symposium, **2003**, Espoo, Finland. Abstract Book A-70.
14. Niidu, A.; Maasalu, A.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synthesis of 3-cyano-2-methylcyclohex-2-ene-1-one* 25th days of Estonian Chemical Society **1999**, Tallinn, Estonia. Abstract Book pp113.

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