Synthetic Studies toward the Total Synthesis of Berkelic Acid and Lytophilippine A

DISSERTATION

Zur Erlangung des akademischen Grades
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von

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2010

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Die vorliegende Arbeit wurde auf Vorschlag und unter Anleitung von Herrn Prof. Dr. M. Hiersemann im Zeitraum von April 2007 bis Mai 2010 am Institut für Organische Chemie der Technischen Universität Dortmund angefertigt.

Es haben bisher keine Promotionsverfahren stattgefunden.

Ich erkenne die Promotionsordnung der Technischen Universität Dortmund für die Fachbereiche Mathematik, Physik und Chemie vom 24.06.1991 an.

_____

Nikola Stiasni

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Abstract

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Keywords: berkelic acid, lytophilippine A, total synthesis

C16–C20 part of natural product berkelic acid containing two adjacent stereogenic centers has been synthesized employing catalytic asymmetric Gosteli-Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ether as a key step. Synthetic sequence leading to the both fragments included 11 linear steps and afforded final products in good to excellent diastereoselectivity and good enantioselectivity. Model study exploring Oxa-Pictet-Spengler condensation as a key coupling step toward the tetracyclic core of berkelic acid has been successfully accomplished.

C20–C27 fragment of lytophilippine A has been synthesized in a sequence of 13 linear steps, and in total yield of 8.4%. The synthesis commenced with readily available natural (+)-L-ascorbic acid and features Evans asymmetric alkylation and asymmetric aldol condensation with norephedrine-derived auxiliary as key steps to install the required C21–C23 *anti*, *syn* stereotriad.

“A month in the laboratory can often save an hour in the library.”

-- F. H. Westheimer

To my parents

Research presented in this thesis was carried out between April 2007 and May 2010 at the Technical University Dortmund under the guidance of Prof. Dr. Martin Hiersemann.

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I am grateful to my parents Maja and Velimir, my brother Sasha, and my girlfriend Serra for their endless support without which this endeavor would not have been possible.

Ac	Acetyl
BBN	9-borabicyclo[3.3.1]nonane (9-BBN)
Bn	Benzyl
box	*bis*(oxazoline)
c-Hex	Cyclohexyl
CoA	Coenzyme A
cod	1,5-Cyclooctadiene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DMAP	*N*,*N*-4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
ee	Enantiomeric excess in %
Et	Ethyl
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
IBX	2-Iodoxybenzoic acid
Ipc	Isopinocamphenyl
i-Pr	Isopropyl
LDA	Lithium diisopropylamide
Me	Methyl
Mes	Mesityl
MOM	Methoxymethyl
Ms	Methanesulfonyl
MS	Molecular sieves
MTBE	Methyl *t*-butyl ether
MTPA	α-Methoxy-α-(trifluoromethyl)phenylacetic acid
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine oxide
n-Bu	*n*-Butyl
n-Oct	*n*-Octyl
Ph	Phenyl
Piv	Pivaloyl
PMB	*p*-methoxybenzyl
PNB	*p*-nitrobenzyl
PPTS	Pyridinium *p*-toluenesulfonate
Py	Pyridine
s-Bu	*sec*-Butyl
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy free radical
TES	Triethylsilyl
t-Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl-
TFA	Trifluoroacetic acid
thexyl	1,1,2-trimethylpropyl
THF	Tetrahydrofuran
THP	2-tetrahydropyranyl
TMS	Trimethylsilyl
TMU	Tetramethylurea
TPS	*tert*-Butyldiphenylsilyl
Ts	*p*-Toluenesulfonyl

1. Prospects in Organic Synthesis

Since the first formal total synthesis of quinine by Woodward and Doering in 1944,[1] considered as an important milestone in organic synthesis, the field has experienced explosive growth. It was primarily the advent of NMR technology in 1960's, which significantly simplified analysis of molecules and accelerated discoveries of new reactions. Some of these reactions ultimately found direct application in chemical industry, especially in the field of asymmetric synthesis of small molecules. Multistep syntheses toward complex natural products on a commercial scale remain even today prohibitively expensive and inefficient. However, since many natural products have been regarded as promising targets for cancer therapy, their natural scarcity has made total synthesis the last resort to obtain sufficient quantities for further examination of their biological activity.

It is undoubtful that organic synthesis will continue to play important role in the following years, but it will need to adopt new technologies to reduce its impact on environment. According to Anastas and Warner[2] major principles of sustainable chemistry that would be desired are: minimization of waste, atom economy (synthetic methods are designed to maximize the incorporation of all materials used in the process into the final product), avoidance of toxic by-products, safer solvents and auxiliaries, design for energy efficiency (if possible, reactions should be conducted at room temperature and pressure), use of renewable feedstocks, reduction of derivatives (protective groups should be avoided whenever possible), and use of catalytic amount of reagents. These principles result from the requirements set forth by Agenda 21[3] in 1992 and will be imposed upon chemical industry by taxing waste and fining pollution. Pharmaceutical sector is of all different chemical manufacturing sectors clearly a frontrunner in terms of waste production.[4] Therefore, major pharmaceutical companies have either terminated or considerably scaled down their natural product operations, despite the fact that many successful drugs in the past years were natural products.[5] Unfortunately, research at universities still lags behind these developments and many commonly used reactions violate almost all of the principles of sustainable chemistry. Therefore, there is still huge potential for exciting environmentally friendly chemistry methodologies to be developed in the following years.

[1] (a) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 849. (b) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860-874.
[2] Green Chemistry: Theory and Practice, Paul Anastas and John Warner, Oxford University Press: Oxford UK, **1998**.
[3] Earth Summit Agenda 21: http://www.un.org/esa/dsd/agenda21
[4] Handbook of Green Chemistry & Technology, James Clark and Duncan Macquarrie, Blackwell Science, **2002**.
[5] Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141-2153.

2. Formulation of the Problem

The following thesis encompasses two different projects, namely studies toward the total synthesis of berkelic acid (**1**) and toward the synthesis of C19–C27 fragment of lytophilippine A **2** (Figure 1). The synthetic sequences would need to be carefully planned in order to afford the final products in acceptable yield and also high enantio- and diastereoselectivity.

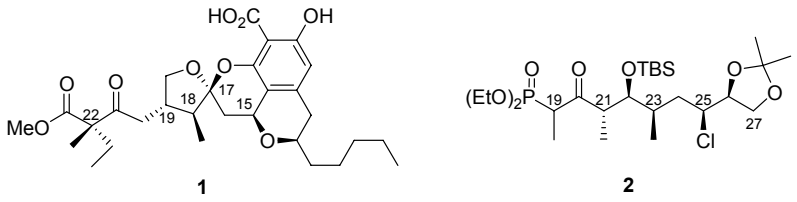


Figure 1: Berkelic acid (**1**) and C19–C27 fragment of lytophilippine A **2**.

In our analysis of berkelic acid (**1**), we recognized that the moiety containing two adjacent *anti*-configured stereogenic centers C-18 and C-19 could be accessible in high enantio- and diastereoselectivity by our **catalytic asymmetric Gosteli-Claisen rearrangment**.[6] Suitable allyl vinyl ether would have to be synthesized and subjected to asymmetric Gosteli-Claisen rearrangment to form an intermediate that could be further elaborated into the natural product by convergent synthesis with two literature-known fragments.

Second project involved the design of an efficient synthetic approach toward the C19–C27 fragment of lytophilippine A **2**. Our starting material was readily available (+)-L-ascorbic acid that contains two of the five stereogenic centers found in the C19–C27 fragment **2**. Chlorine atom at C-25 would be introduced through a sequence of two S_N2 processes resulting in a net retention of configuration. The sequence of stereoselective methylation and *anti*-selective asymmetric aldol reaction would allow for the generation of C21–C23 *anti*, *syn* stereotriad. The studies toward the C19–C27 fragment **2** using similar approach were commenced in our group by Tobias Jaschinski,[7] however, the stereoselective installation of the C-23 methyl group proved challenging and resulted in low diastereoselectivity. In order to circumvent this problem, a modified synthetic approach would have to be developed.

[6] Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4700-4703.
[7] Tobias Jaschinski – Diplomarbeit **2008**

3. Introduction to Berkelic Acid

Berkelic acid (**1**) is a tetracyclic isochroman spiroketal isolated along with spiciferone A (**3**) from a *Penicillium* species growing in the highly acidic (pH around 2.5) and heavy-metal polluted Berkley Pit Lake, a former open-pit copper mine in Butte, Montana.[8] The highly toxic lake harbors broad diversity of fungi, algae and bacteria and has therefore been subject of attention. These circumstances have provided impetus to unravel the structure of berkelic acid (**1**) and confirm it by total synthesis. The unique carbon skeleton of berkelic acid (**1**) contains an all-carbon quaternary stereocenter (C-3) and two contiguous stereogenic centers on an aliphatic chain, structural features also found in spicifernin (**4**), isolated from the strain of *Cochliobolus spicifer*.[9] Isochroman part of berkelic acid (**1**) contains two stereogenic centers and resembles fungal metabolite pulvilloric acid (**5**) (Figure 2), isolated from *Penicillium pulvillorum*.[10] The relative configuration of berkelic acid (**1**), apart from that at C-22, was originally assigned on the basis of NMR experiments,[8] thereafter revised by Fürstner,[11] and the absolute configuration finally established through total synthesis by Snider.[12]

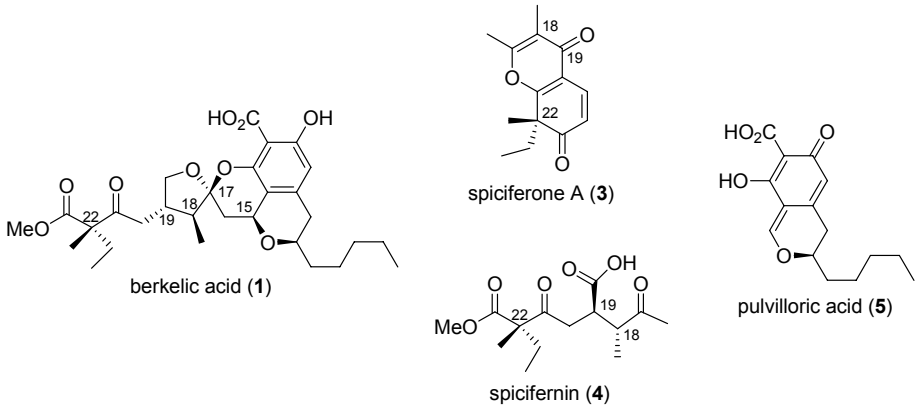
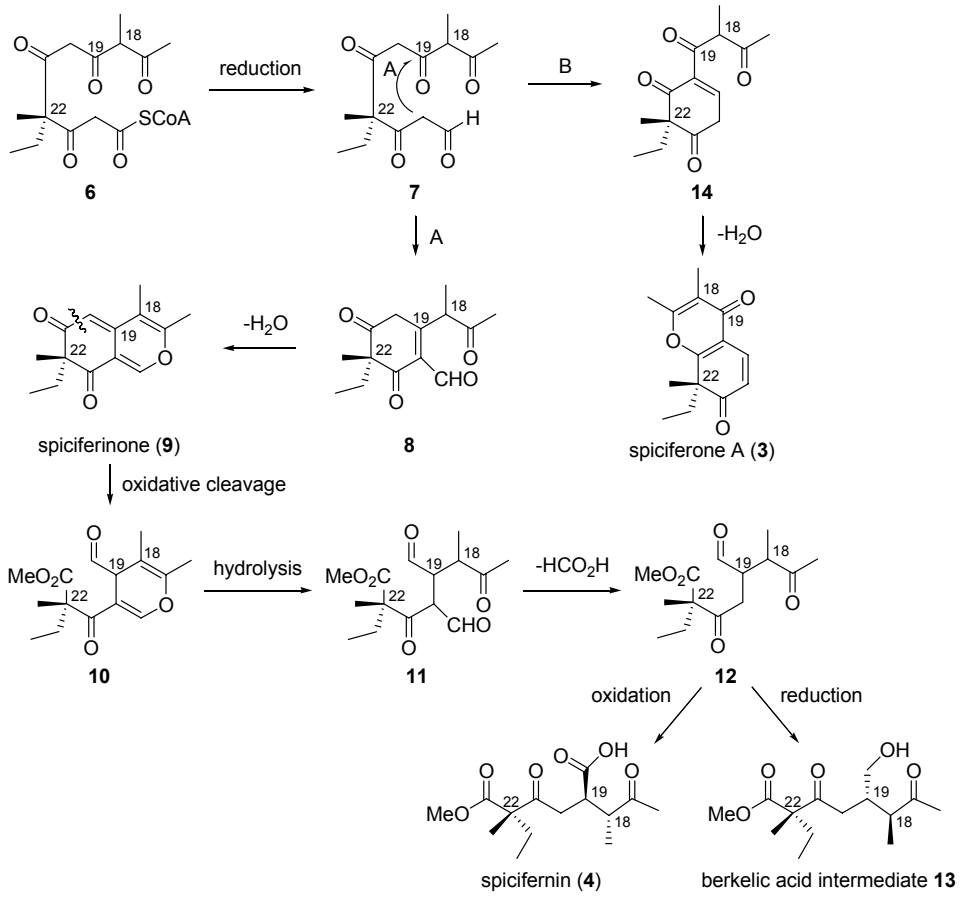


Figure 2: Berkelic acid and related natural products.

Despite different carbon skeletons, the quaternary stereogenic center C-22 suggests that fungal metabolites berkelic acid (**1**), spiciferone A (**3**) and spicifernin (**4**) are of the same biosynthetic origin. The discrepancy between absolute configuration at C-18 and C-19 in spicifernin (**4**) and berkelic acid (**1**) was explained by Snider[12] who revisited the existing

[8] Stierle, A. A.; Stierle, D. B.; Kelly, K. *J. Org. Chem.* **2006**, *71*, 5357-5360.
[9] Nakajima, H.; Hamasaki, T.; Maeta, S.; Kimura, Y.; Takeuchi, Y. *Phytochemistry* **1990**, *29*, 1739-1743.
[10] Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Norris, G. L. F. *Trans. Brit. Mycol. Soc.* **1957**, *40*, 369-374.
[11] Buchgraber, P.; Snaddon, T. N.; Wirtz, C.; Mynott, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8450-8454.
[12] (a) Xiaoxing, W.; Jingye, Z.; Snider, B. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 1283-1286. (b) Xiaoxing, W.; Jingye, Z.; Snider, B. B. *J. Org. Chem.* **2009**, *74*, 6245-6252.

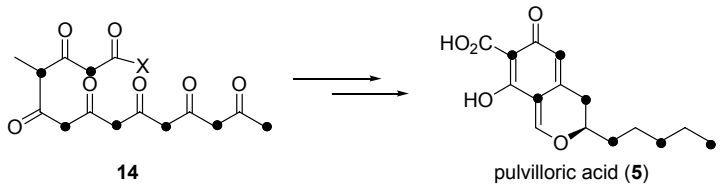
spicifernin biosynthesis studies by Nakajima et al.[13] According to his proposed biosynthesis (Scheme 1) polyketide **6** would be reduced to aldehyde **7**, which would undergo intramolecular aldol condensation to afford **8** (path A, condensation between C-19 and C-24). Subsequent dehydration of **8** would give spiciferinone (**9**), which would be oxidatively cleaved to furnish aldehyde ester **10**. Hydrolysis of the pyran ring would afford β-ketoaldehyde **11**, which could easily lose formic acid to form aldehyde **12**. Aldehyde **12** could be either oxidized to form spicifernin (**4**) or reduced to berkelic acid intermediate **13**. Whereas the stereochemistry of quaternary stereogenic center C-22 is already set in the intermediate **6**, aldehyde **12** can undergo epimerization at either C-18 or C-19. Thus, the proposed biosynthesis provides a simple explanation for the differing stereochemistry at C-18 and C-19 of spicifernin (**4**) and berkelic acid (**1**). It also plausibly explains the formation of spiciferone A (**3**) via intermediate **14**, formed from aldehyde **7** by aldol condensation between C-20 and C-25 (path B).



Scheme 1: Proposed biosynthesis of spicifernin, spiciferone A and berkelic acid intermediate.

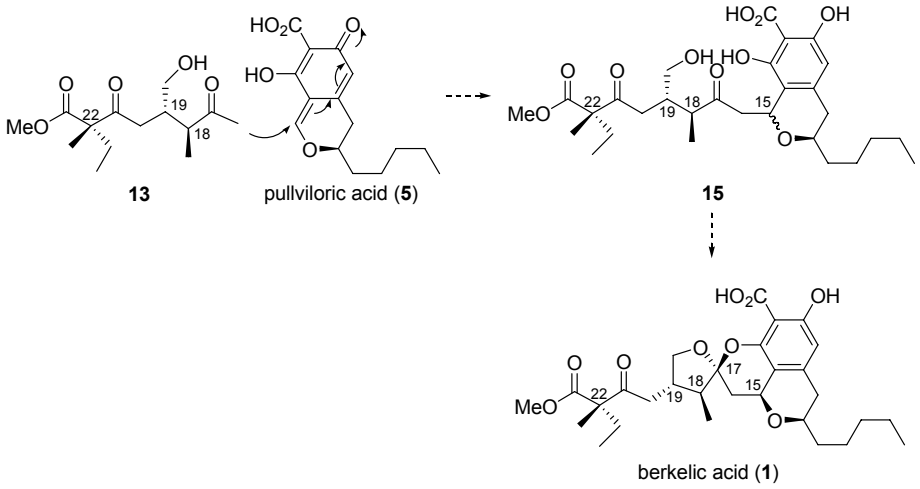
[13] (a) Nakajima, H.; Matsumoto, R.; Kimura, Y.; Hamasaki, T. J. *Chem. Soc. Commun.* **1992**, 1654-1656. (b) Nakajima, H.; Fujimoto, H.; Matsumoto, R.; Hamasaki, T. *J. Org. Chem.* **1993**, *58*, 4526-4528. (c) Nakajima, H.; Fukuyama, K.; Fujimoto, H.; Baba, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1865-1869.

^{14}C labeling biosynthetic studies of pullviloric acid (**5**)[14] and its analog citrinine[15] strongly suggest that isochroman part of berkelic acid is of polyacetate nature (seven acetate units), except for the exocyclic carboxyl group believed to originate from a single-carbon transfer pool. There are some doubts, however, as to whether *n*-pentyl side chain is formed from the polyketo acyl precursor **14** (Scheme 2) or results from malonyl extensions of lower fatty acids.



Scheme 2: Proposed polyketo acyl precursor of pulvilloric acid.

Although berkelic acid (**1**) biosynthesis has not been studied, it can be assumed that pulvilloric acid (**5**) could react as an electrophile with an enol form of intermediate **13** through a 1,6-conjugate addition to afford **15**, which would finally undergo acetalization under acidic conditions to afford berkelic acid (**1**) (Scheme 3). Since berkelic acid (**1**) was discovered in a highly acidic environment, it was expected that newly formed stereogenic centers C-15 and C-17 would be thermodynamically controlled.[16]



Scheme 3: Proposed berkelic acid biosynthesis.

[14] (a) Tannenbaum, S. W.; Nakajima, S. *Biochemistry* **1969**, *8*, 4626-4631. (b) Tanenbaum, S. W.; Nakajima, S.; Marx, G. *Biotechnol. Bioeng*. **1969**, *11*, 1135-1156.
[15] (a) Birch, A. J.; Fitton, P.; Pride, E.; Ryan, A. J.; Smith, H.; Whalley, W. B. *J. Chem. Soc.* **1958**, 4576-4581. (b) Rodig, O. R.; Ellis, L. C.; Glover, I. T. *Biochemistry* **1966**, *5*, 2451-2458. (c) Colombo L.; Gennari C.; Potenza, D.; Scolastico, C. *J. Chem. Soc. Perkin Trans 1* **1981**, 2594-2597.
[16] This was confirmed independently by Fürstner and Snider via synthetic studies.

3.1 Chemistry of Berkelic Acid

Discovery of berkelic acid (**1**) in an unusual environment of Berkelic Pit Lake immediately caught attention of several research groups and prompted them to embark on its synthesis. Berkelic acid (**1**) was initially reported to exhibit selective activity toward ovarian cancer OVCAR-3,[8] however, these findings could not be corroborated with synthetic berkelic acid (**1**) in the NCI human disease-oriented 60-cell line in vitro antitumor screening protocol.[12] Fürstner, Snider, and De Brabander[17] research groups revisited originally proposed relative structure, established absolute configuration, and presented successful routes toward the molecule. Several other studies describing partial syntheses were also published,[18] but these will not be discussed in the following short review.

3.1.1 *Fürstner's Synthesis*

Fürstner's retrosynthetic analysis of the originally proposed structure of berkelic acid **16** divides the molecule into three parts: aldehyde **17**, methyl ketone **18**, and aromatic aldehyde (*R*)-**19** (Figure 3).[11]

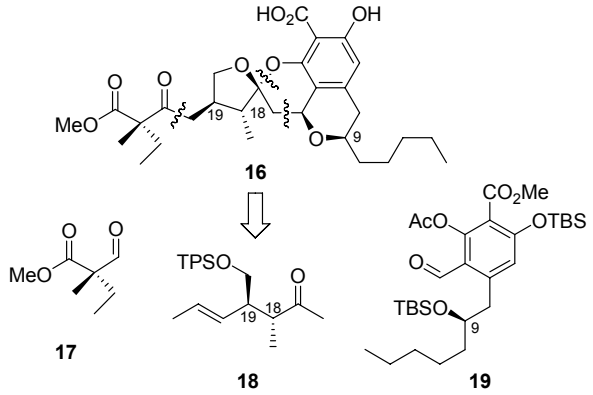
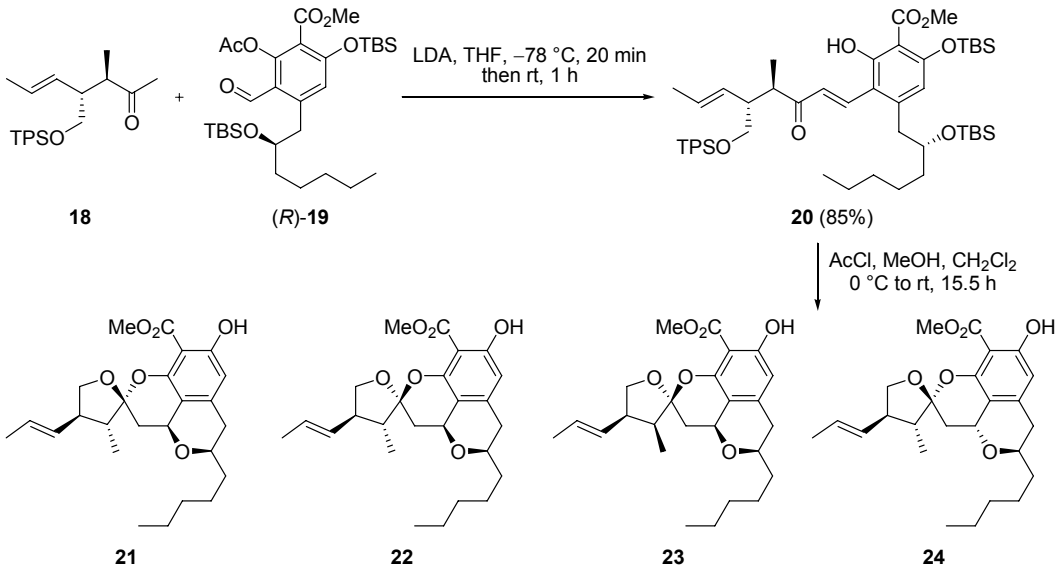


Figure 3: Originally proposed berkelic acid structure and retrosynthetic analysis.

To establish the tetracyclic core of **16**, aldol condensation between the lithium enolate of **18** and aromatic aldehyde (*R*)-**19** was utilized**,** followed by acid-induced Michael addition/spiroacetalization cascade. The synthesized tetracyclic core was, however, obtained as a statistical mixture of four diastereomers **21**-**24** (Scheme 4) and all attempts to equilibrate the crude mixture by treatment with various acids were not successful. The unexpected results cast doubt on the originally proposed relative configuration of berkelic acid **16** and

[17] Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 11350-11352.
[18] (a) Hung, Y.; Pettus, T. R. R. *Synlett* **2008**, *9*, 1353-1356. (b) Wilson, Z. E.; Brimble, M. A. *Org. Biomol. Chem.* **2010**, *8*, 1284-1286.

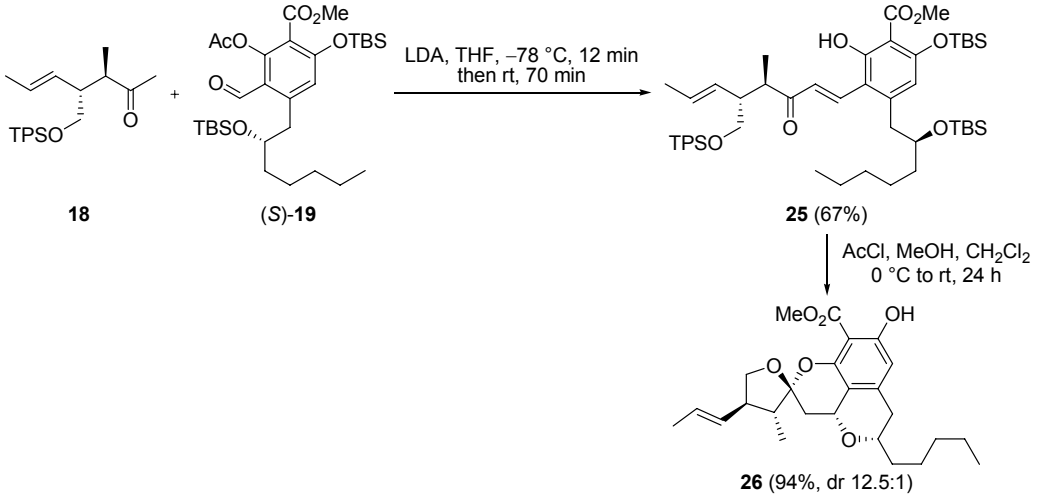
reexamination of the original NMR data led to the conclusion that either configuration at C-9 or configurations at C-18 and C-19 should be inverted.



18 (*R*)-**19** **20** (85%) **21** **22** **23** **24**

Scheme 4: Synthetic study leading to a mixture of diastereomers.

The inversion of stereochemistry at C-9 of fragment **19** was carried out using *p*-nitrobenzoic acid under Mitsunobu conditions.[19] Aldol coupling between lithium enolate of **18** and (*S*)-**19** was performed analogously as described above to afford **25** (Scheme 5). Acid-induced cyclization afforded tetracyclic core **26** as a single diastereomer (dr = 12.5:1).



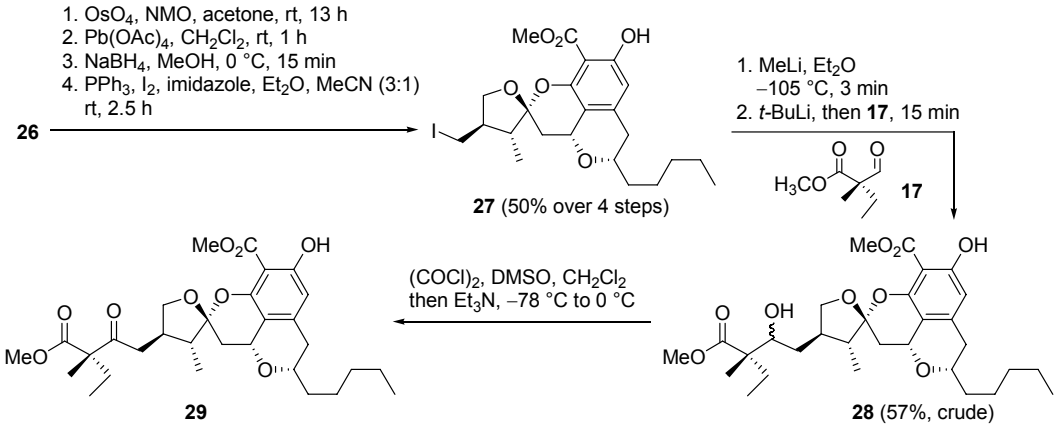
18 (*S*)-**19** **25** (67%) **26** (94%, dr 12.5:1)

Scheme 5: Synthesis of the tetracyclic core.

In the next four steps, **26** was transformed into iodide **27**. Iodine-lithium exchange furnished a precursor for the subsequent coupling with aldehyde **17** (Scheme 6). To complete the

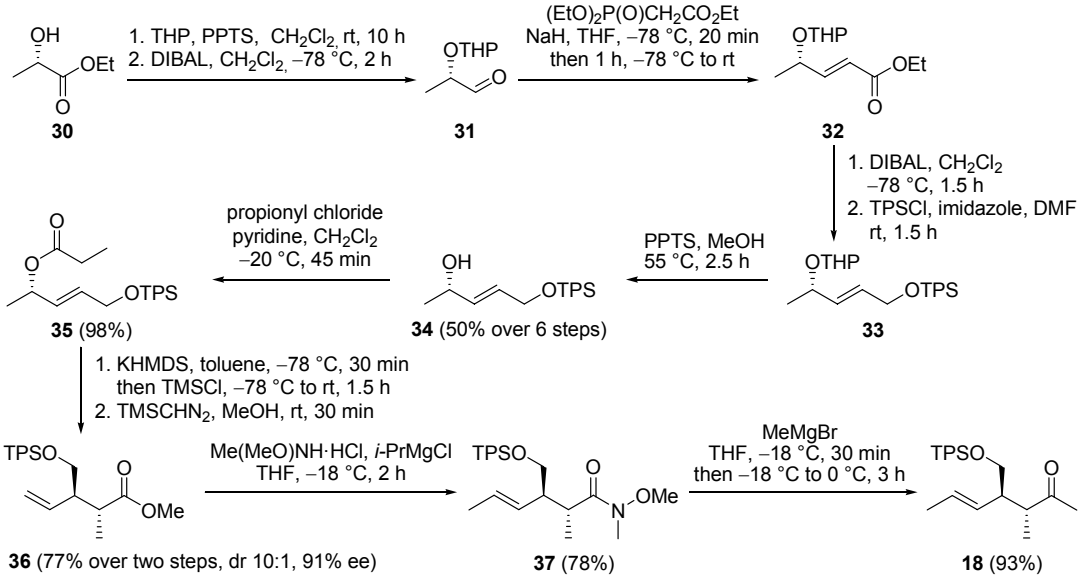
[19] Mitsunobu, O.; Yamada, Y. *Bull. Chem. Soc. Japan* **1967**, *40*, 2380-2382.

synthesis, the resulting alcohol **28** had to be oxidized in the presence of oxidation-sensitive aromatic phenol, which turned out to be difficult; nevertheless, Swern oxidation[20] of **28** afforded methyl berkelate (**29)** in sufficient quantity to allow for an unambiguous analysis.



Scheme 6: Completion of the synthesis of methyl berkelate.

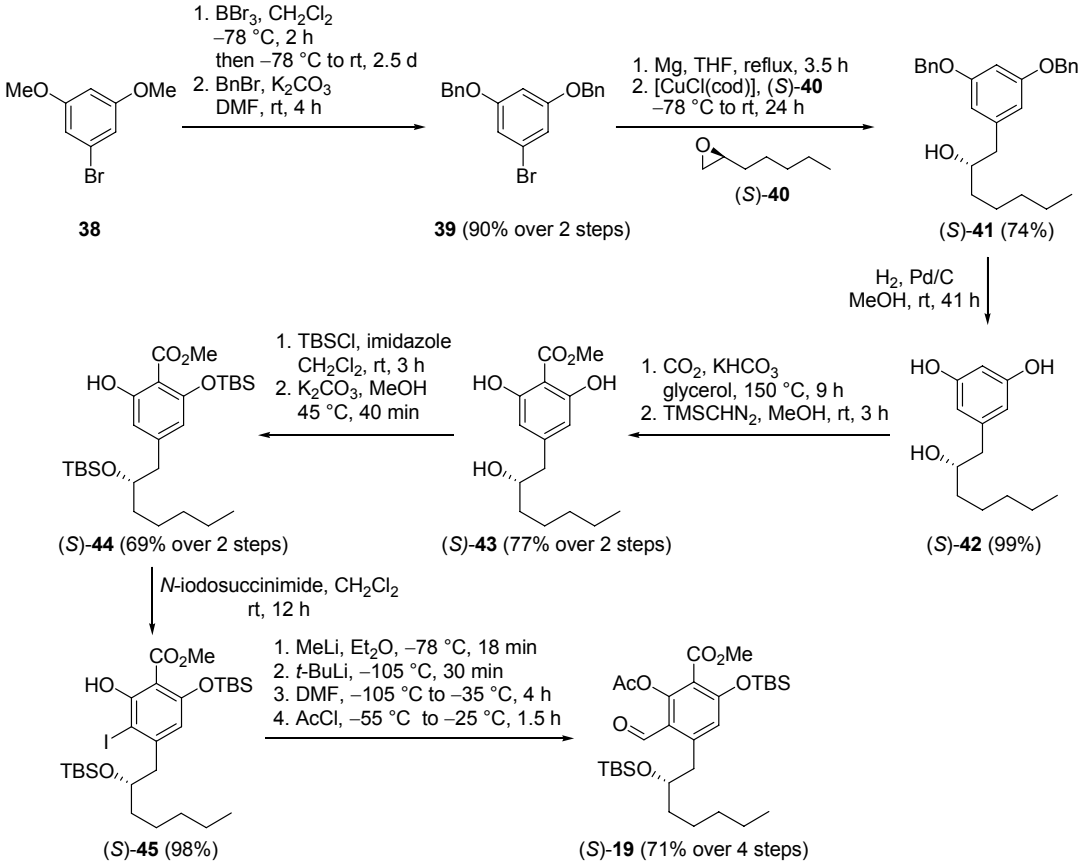
Synthesis of metyl ketone **18** commenced with (*S*)-ethyl lactate (**30**), which was transformed to allyl alcohol **34** in six steps (Scheme 7). Esterification with propionyl chloride in the presence of pyridine gave **35**, which after Ireland-Claisen rearrangement,[21] and *in situ* esterification with trimethylsilyldiazomethane afforded *anti*-configured ester **36** in a good diastereoselectivity (dr = 10:1). Subsequently, ester **36** was converted into Weinreb amide **37** and minor *syn*-diastereomer was separated by flash chromatography. Methyl ketone **18** was obtained from **37** on treatment with methylmagnesium bromide.



Scheme 7: Synthesis of methyl ketone **18**.

[20] Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.
[21] Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897-5898.

The synthesis of aromatic fragment (*S*)-**19** started with 1-bromo-3,5-dimethoxybenzene (**38**), which was first demethylated by boron tribromide, and then benzylated by $BnBr/K_2CO_3$ in DMF to give **39** (Scheme 8). Copper-catalyzed opening of (*S*)-2-pentyloxirane ((*S*)-**40**) by Grignard reagent derived from **39** afforded (*S*)-**41**.[22] Benzyl group deprotection by hydrogenation over palladium on charcoal, Kolbe-Schmitt carboxylation, and *in situ* esterification of the resulting acid with trimethylsilyldiazomethane gave (*S*)-**43**. TBS protection of free hydroxyl groups, followed by selective monodesilylation furnished (*S*)-**44**. Formyl group was introduced through a sequence of regioselective iodination, iodine-lithium exchange, and trapping of the resulting organolithium reagent with DMF. The remaining hydroxyl group was protected as acetate to afford fragment (*S*)-**19.**

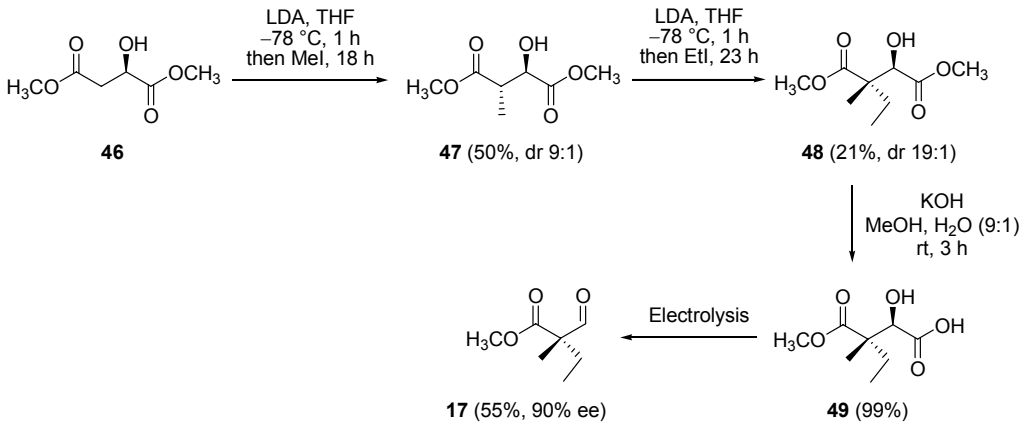


Scheme 8: Synthesis of the aromatic fragment (*S*)-**19**.

Aldehyde **17** was obtained according to the literature procedure starting from (*R*)-dimethyl malate (**46**) in four steps (Scheme 9).[23] Alkylation with LDA/MeI afforded **47**, which was then alkylated with LDA/EtI to obtain **48** as a single diastereomer (dr = 19:1). **48** was

[22] Rödel, T.; Gerlach, H. *Liebigs Ann. Chem.* **1997**, 213-216.
[23] (a) Wasmuth, D.; Arigoni, D.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 344-352. (b) Renaud, P.; Hürzeler, M.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 292-298.

selectively hydrolysed by potassium hydroxide to α-hydroxyacid **49**, and in the final step, electrolytic oxidation of α-hydroxyacid **49** afforded aldehyde **17** as a volatile liquid.



Scheme 9: Synthesis of aldehyde **17**.

3.1.2 *Snider's Synthesis*

Snider identified Oxa-Pictet-Spengler condensation [24] between ketal aldehyde **50** and literature-known aromatic fragment (*R*)-**51** as an efficient way toward the tetracyclic core of the originally proposed structure of berkelic acid **16**.[12]

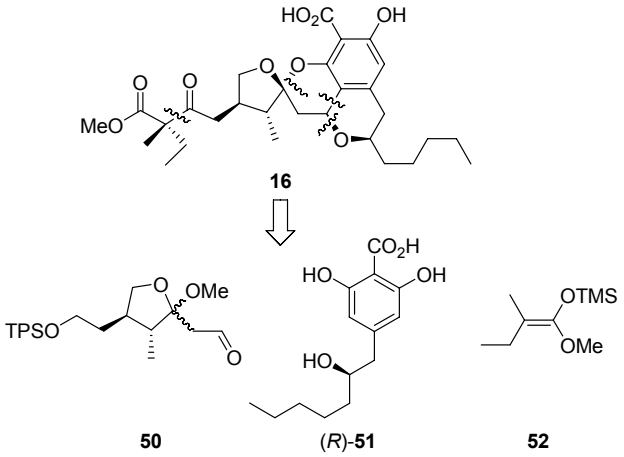
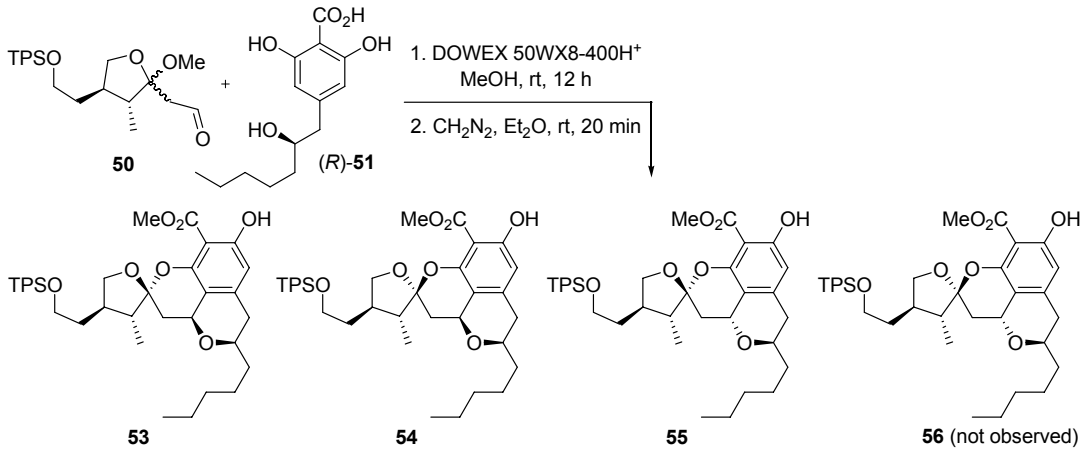


Figure 4: Snider's retrosynthetic analysis.

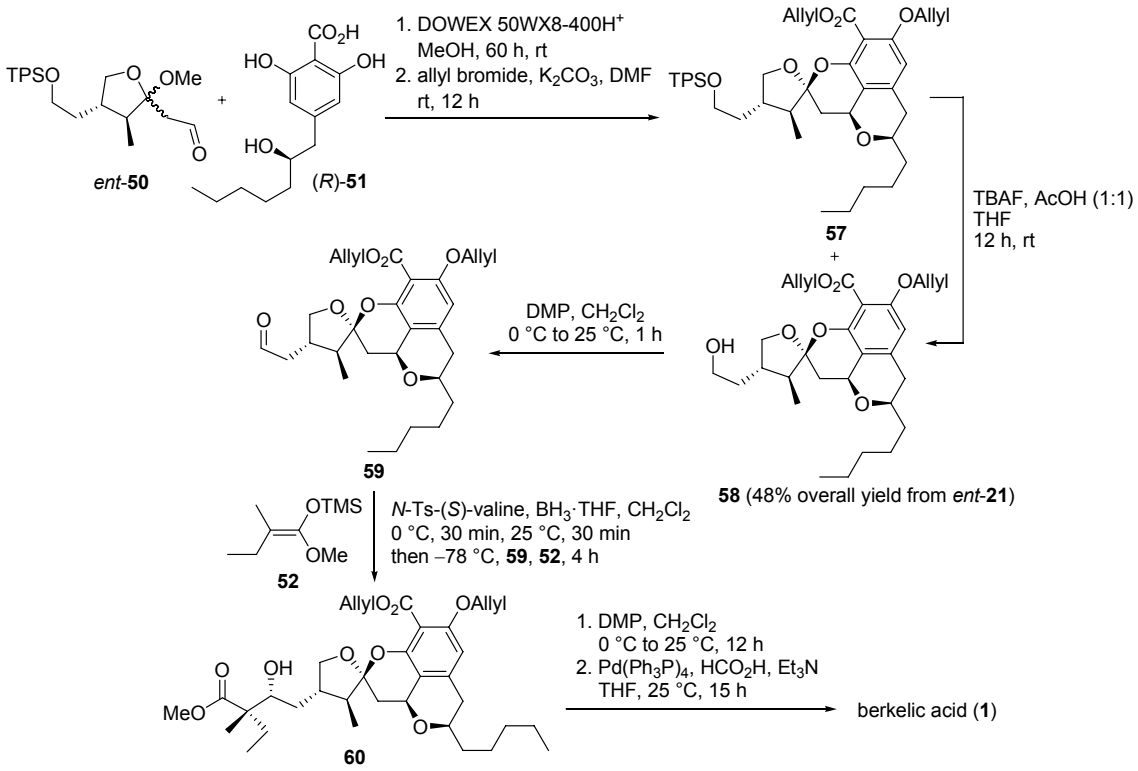
In analogy to Fürstner's findings condensation of **50** with (*R*)-**51**, catalyzed by Dowex 50WX8-400H$^+$ in MeOH, and subsequent diazomethane esterification gave a mixture of diastereomers **53-56** in approximately 4:1:3:0 ratio (Scheme 10). Since attempted equilibration with 0.2% trifluoroacetic acid had little effect, Snider concluded independently from Fürstner that originally assigned relative configuration must be revised.

[24] Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, *2*, 187-220.



Scheme 10: First synthetic approach leading to a mixture of diastereomers.

MMX computer calculations and analysis of NOE spectrum suggested that the correct structure of berkelic acid (**1**) should have opposite stereochemistry at both C-18 and C-19. Condensation of *ent*-**50** with (*R*)-**51** catalyzed by Dowex 50WX8-400H$^+$ in MeOH, and treatment of the crude product with allyl bromide/K_2CO_3[25] in DMF gave a mixture of **57** and alcohol **58** resulting from the concomitant cleavage of TPS group (Scheme 11).

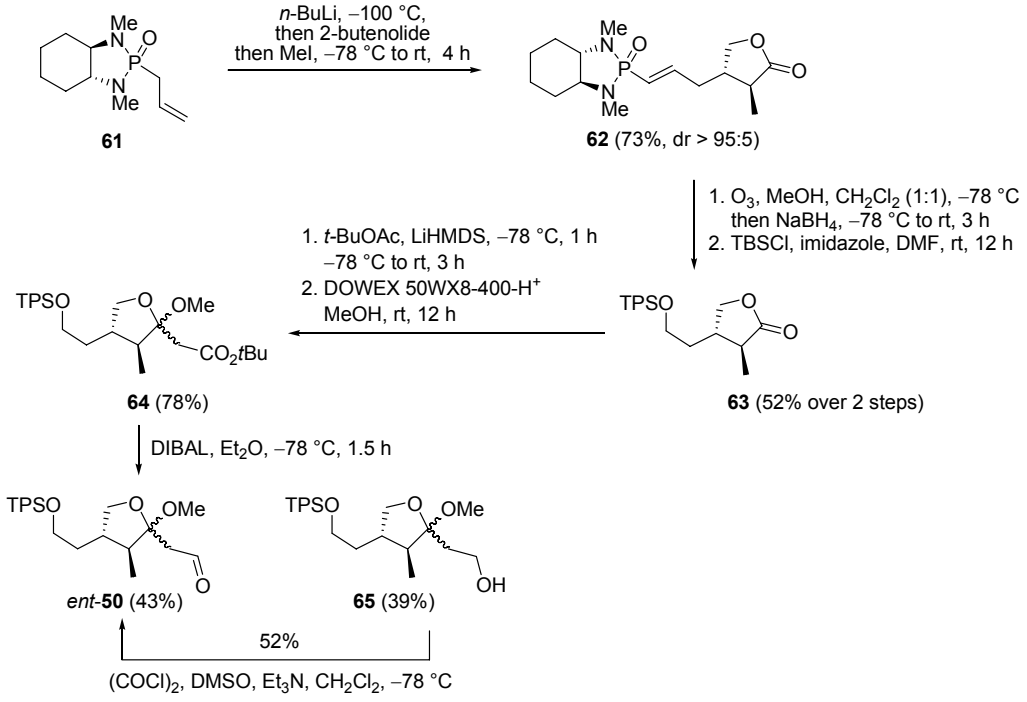


Scheme 11: Completion of synthesis.

[25] Allyl protecting group was chosen in preference over methyl group to avoid difficulties of hydrolyzing aromatic methyl ester in the presence of aliphatic methyl ester, as reported by Fürstner.

Remaining TPS ether **57** was desilylated to alcohol **58** with TBAF/AcOH (1:1) in THF, and subsequent Dess-Martin oxidation afforded aldehyde **59**.[26] Aldol condensation of aldehyde **59** and trimethylsilyl ketene acetal **52** induced by stoichiometric amount of oxazaborolidinone, prepared *in situ* from *N*-Ts-(*S*)-valine and BH_3·THF, gave **60** along with another diastereomer separable by preparative TLC. Berkelic acid (**1**) was obtained after oxidation of **60** under Dess-Martin conditions[26] and cleavage of both allyl groups.

The requisite ketal aldehyde *ent*-**50** was obtained by the method of Hanessian et al. (Scheme 12).[27] Chiral auxiliary **61** was deprotonated by *n*-butyllithium at −100 ºC, followed by addition of 2-butenolide. Trapping with excess methyl iodide afforded **62** in good diastereoselectivity (dr > 95:5). Ozonolysis, *in situ* reduction with sodium borohydride, and protection of free hydroxyl group as TPS ether gave lactone **63**. Addition of the lithium enolate of *tert*-butyl acetate and ketal formation afforded **64**. Diisobutylaluminium hydride reduction of **64** gave ketal aldehyde *ent*-**50** with considerable amount of alcohol **65**, which could be recycled by Swern oxidation.[20]



Scheme 12: Synthesis of ketal aldehyde *ent*-**50**.

[26] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
[27] Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623-5631.

3.1.3 *De Brabander's Synthesis*

De Brabander retrosynthetic approach is based on the recognition that berkelic acid (**1**) can be divided into two fragments **66a/66b** and **67** resembling natural products spicifernin (**4**) and pulvilloric acid (**5**), respectively (Figure 5).[17] These fragments could be coupled utilizing a unique Ag-catalyzed cascade dearomatization-cycloisomerization-cycloaddition sequence.

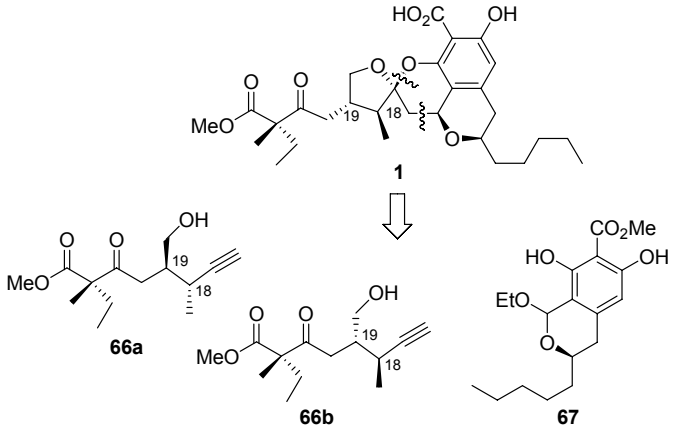
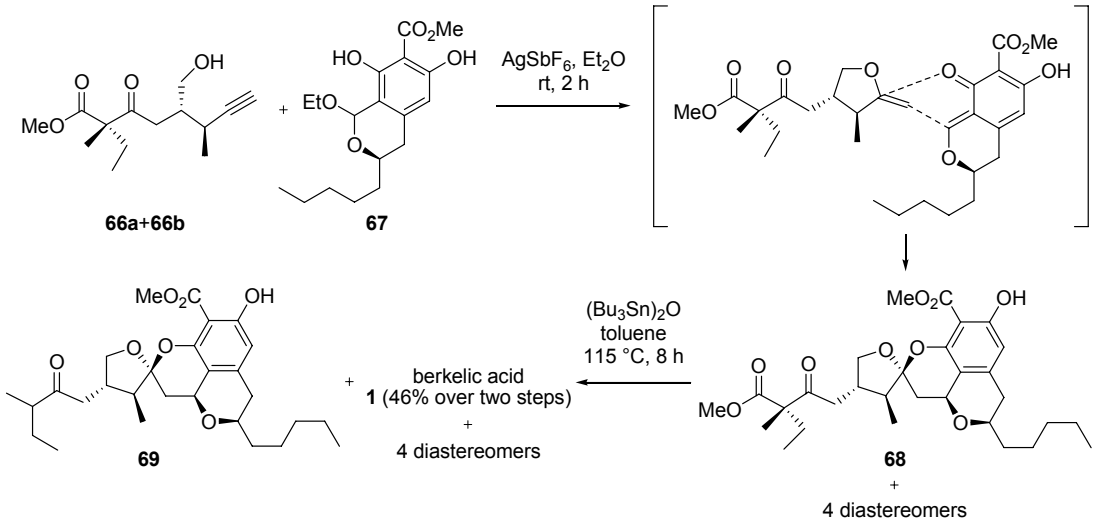


Figure 5: Bond disconnections and retrosynthetic analysis.

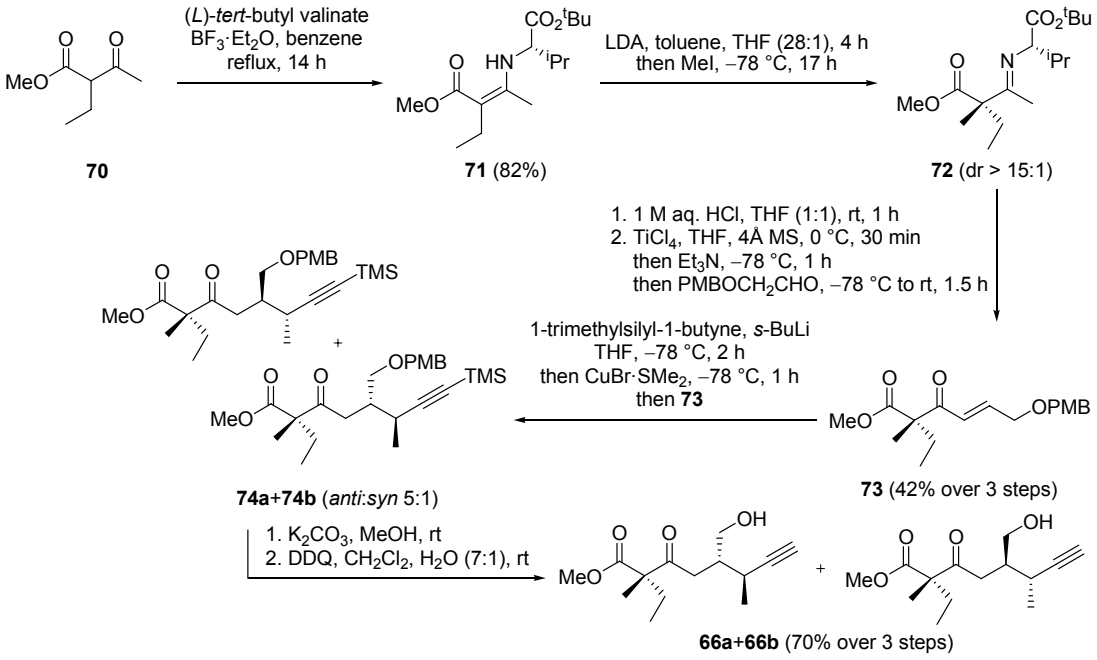
Stirring a solution of lactol **67** and alkynols **66a** and **66b** in the presence of silver(V)-hexafluoroantimonate resulted in the formation of methyl berkelate **68** along with four additional diastereomeric berkelates in a ratio of approximately 6:4 (Scheme 13). The methyl berkelate diastereomers were not separable by chromatography at this stage, so they were treated with tributyltin oxide in toluene to bring about the selective deprotection of methyl benzoate in the presence of aliphatic methyl ester.



Scheme 13: Condensation of fragments and completion of synthesis.

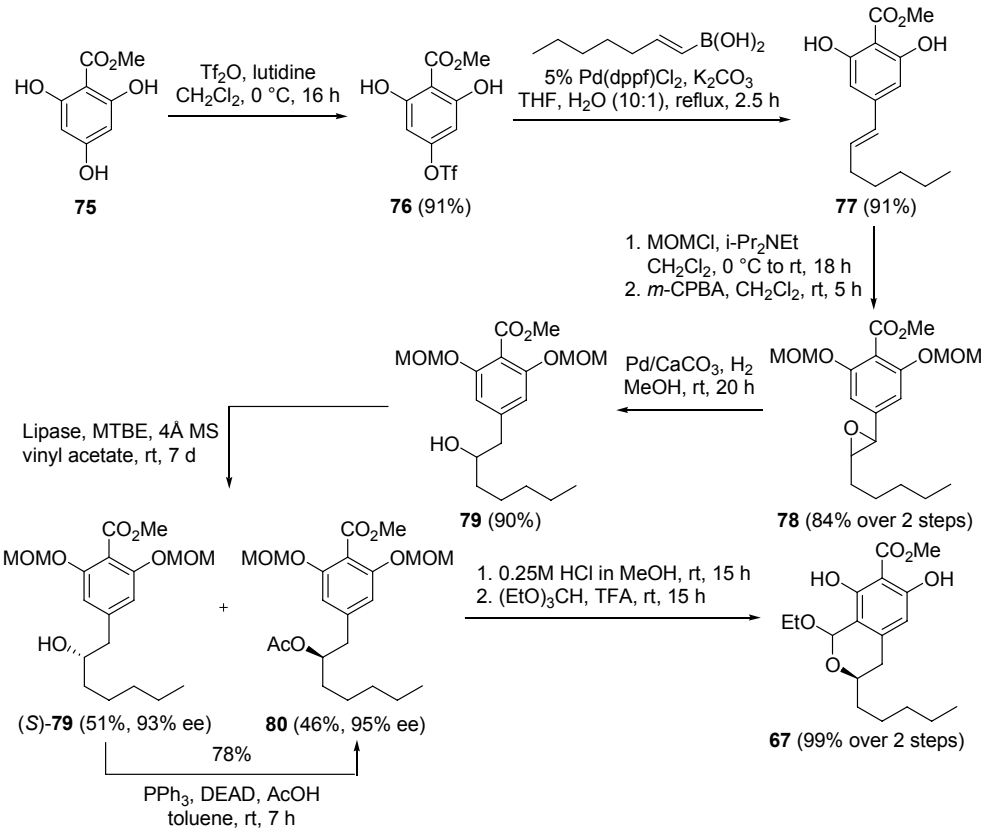
Since prolonged reaction times at elevated temperature led to the formation of decarboxylated side product **69**, the reaction had to be interrupted at partial conversion and unreacted methyl ester **68** resubjected to the reaction conditions. Pure berkelic acid (**1**) was obtained by separating the crude mixture by semi-preparative HPLC.

Starting material toward alkynols **66a** and **66b** was commercially available 2-ethyl-3-oxobutanoate (**70**), which was first converted to the corresponding (L)-^{t}Bu-valinate derived enamine **71** (Scheme 14). Subsequent α-methylation with LDA/MeI afforded imine derivative **72** with quaternary stereogenic center in high diastereoselectivity (dr > 15:1). Hydrolysis of the crude imine **72** with 1 M aq. HCl in THF followed by titanium(IV)-tetrachloride mediated dehydrative aldol reaction with (4-methoxybenzyloxy)ethanal afforded enone **73**. Subsequent *anti*-selective conjugate propargylation was effected by adding enone **73** to a solution of a cuprate derived from adding (4-(trimethylsilyl)but-3-yn-2-yl)lithium to a suspension of $CuBr{\cdot}SMe_2$ in THF at −78 ºC. The *anti*-selectivity of the reaction was acceptable (*anti*:*syn* = 5:1), however, the crude product consisted of an inseparable equimolar mixture of (*R*,*R*)- and (*S*,*S*)-diastereomers **74a** and **74b**. The alkynols **66a** and **66b** were obtained on treatment with methanolic potassium carbonate, followed by oxidative removal of PMB group with DDQ.



Scheme 14: Synthesis of alkynol fragment.

The synthesis of aromatic fragment **67** commenced with commercially available methyl 2,4,6-trihydroxybenzoate (**75**), which was first transformed to triflate **76**, and then coupled under palladium catalysis with 1-heptenylboronic acid to afford styrene derivative **77** (Scheme 15). MOM protection of free hydroxyl groups, followed by treatment with *m*-chloroperbenzoic acid gave epoxide **78**, which was converted to racemic alcohol **79** by palladium-catalyzed hydrogenation. Enzyme-mediated kinetic resolution afforded the desired acetate **80** along with the unreacted alcohol (*S*)-**79** that could be easily recycled to the acetate **80** via Mitsunobu esterification. The removal of the MOM protecting groups was achieved on treatment with HCl in methanol, and subsequent condensation with triethyl orthoformate afforded the aromatic fragment **67**.



Scheme 15: Synthesis of aromatic lactol fragment.

4. Synthetic Part – Studies toward the Berkelic Acid

4.1 *Retrosynthesis of the Tetracylic Core of Berkelic Acid*

In our analysis of the tetracyclic core of berkelic acid **81**, we recognized that spiroketal moiety containing two adjacent *anti*-configured stereogenic centers C-18 and C-19 could be constructed by Claisen rearrangement. Since the absolute configuration of these two stereogenic centers was unknown at the time the project was initiated, it was desirable to have versatile synthetic pathway providing both (*S*,*R*) and (*R*,*S*) enantiomeric building blocks. Our well-established **catalytic asymmetric Gosteli-Claisen rearrangement** of 2-alkoxycarbonyl-substituted allyl vinyl ethers allows access to chiral β,γ-branched α-ketoesters and would serve as a key step in our synthetic route. Initial retrosynthetic strategy, as outlined in Figure 6, disconnects **81** to the literature-known *p*-quinone methide pulvilloric acid (**5)** and silyl enol ether **82**. We reasoned that pulvilloric acid (**5**) could due to its electrophilic properties react with a nucleophilic silyl enol ether **82** through a 1,6-conjugate addition.[28] Silyl enol ether **82** would be derived from α-keto ester **84**, which would be available by **catalytic asymmetric Gosteli-Claisen rearrangement**[4] of achiral allyl vinyl ether (*Z*,*Z*)-**85**.

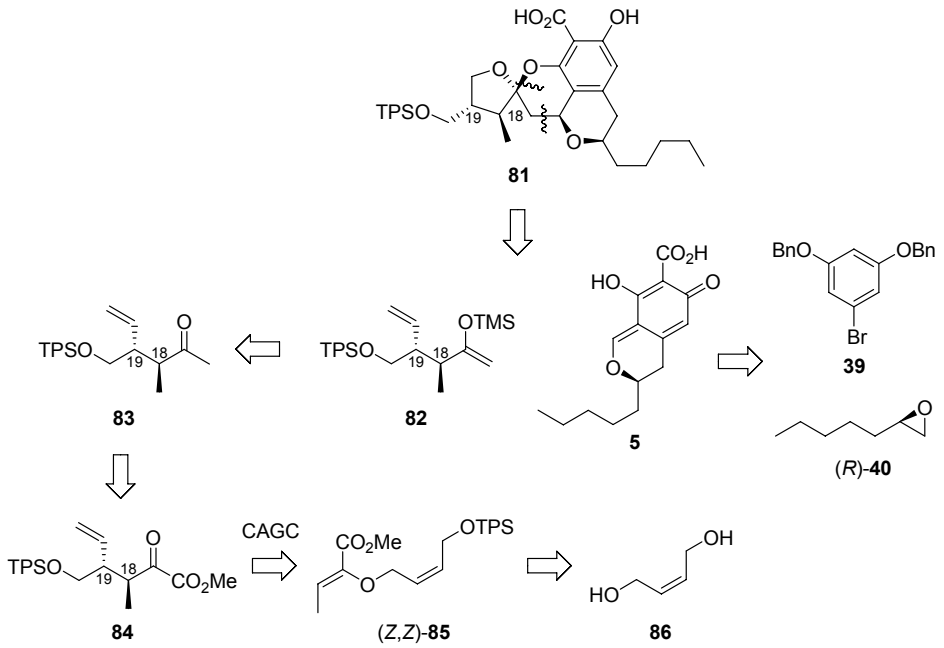


Figure 6: Retrosynthetic analysis of the tetracyclic core of berkelic acid.

[28]For similar 1,6-additions see: (a) Inagaki, M.; Haga, N.; Kobayashi, M.; Ohta, N.; Kamata, S.; Tsuri, T. *J. Org. Chem.* **2002**, *67*, 125-128. (b) Zjawiony, J. K.; Bartyzel, P.; Hamann, M. T. *J. Nat. Prod.* **1998**, *61*, 1502-1508.

Second alternative retrosynthetic plan was also devised, as outlined in Figure 7, which would utilize Oxa-Pictet Spengler condensation[24] for the coupling of literature-known (*S*)-**51** and acetal **88**. Acetal **88** would be synthesized from α-keto ester **90**, accessible by **catalytic asymmetric Gosteli-Claisen rearrangement** of achiral allyl vinyl ether (*E*,*Z*)-**85**.

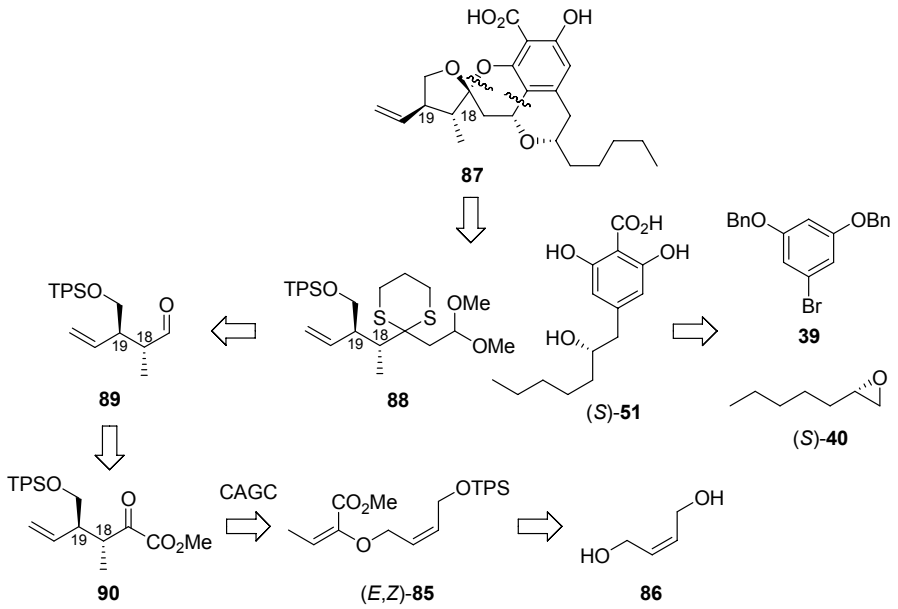
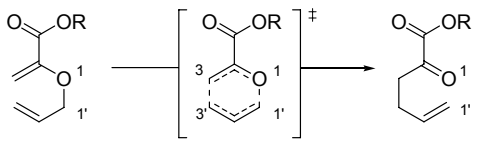


Figure 7: Alternative retrosynthetic analysis of the tetracyclic core of berkelic acid.

4.2 *Gosteli-Claisen Rearrangement - Theory*

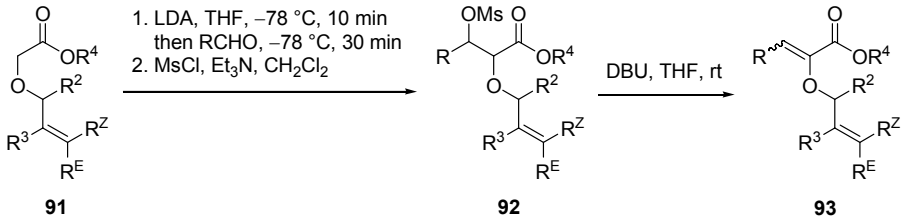
The first uncatalyzed [3,3]-rearrangment of 2-alkoxycarbonyl-substituted allyl vinyl ether to δ,ε-unsaturated α-keto ester (Scheme 16) was reported by Gosteli in 1972 in the course of synthesis of the antifungal antibiotic pyrrolnitrin.[29] The general strategy toward various acyclic 2-alkoxycarbonyl-substituted allyl vinyl ethers was reported by Hiersemann in 2000,[30] and shortly thereafter the first Lewis acid catalyzed Gosteli-Claisen rearrangement[31] was developed, which paved the way for the discovery of the first **catalytic asymmetric Gosteli-Claisen rearrangement**.[32]



Scheme 16: Gosteli-Claisen rearrangment of 2-alkoxycarbonyl-substituted allyl vinyl ether.

[29] Gosteli, J. *Helv. Chim. Acta* **1972**, *55*, 451-460.
[30] Hiersemann, M. *Synthesis* **2000**, *9*, 1279-1290.
[31] (a) Hiersemann, M.; Abraham, L. *Org. Lett.* **2001**, *3*, 49-52. (b) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461-1471.
[32] (a) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. *Adv. Synth. Catal.* **2004**, *346*, 1281-1294. (b) Abraham, L.; Körner, M.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 3647-3650.

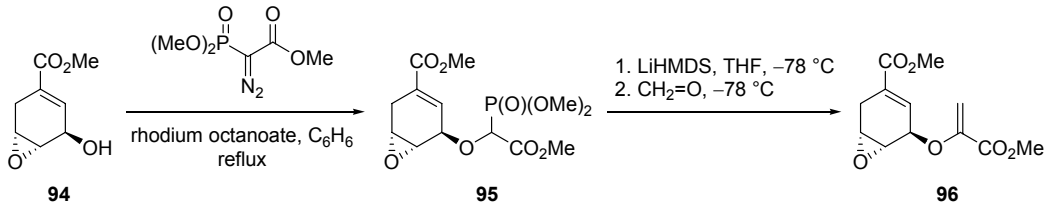
The access to 2-alkoxycarbonyl-substituted allyl vinyl ethers is difficult and very few useful synthetic approaches are known. The key sequence of the Hiersemann's synthesis is an aldol addition between the α-allyloxy-substituted ester **91** and an aldehyde RCHO, followed by mesylation and DBU mediated elimination of **92** to afford the 2-alkoxycarbonyl-substituted allyl vinyl ethers **93** as a mixture of double bond isomers (Scheme 17).



Scheme 17: Hiersemann's synthesis of 2-alkoxycarbonyl-substituted allyl vinyl ethers.

The disadvantage of the procedure is the lack of general stereocontrol over the vinyl ether double bond configuration, which can only be influenced in favor of *Z*-isomer by increasing the steric bulk of the vinyl ether double bond substituent "R". The separation of the double bond isomers is achieved with the help of preparative HPLC.

The sequence of rhodium-catalyzed OH-insertion and olefination was utilized in the synthesis of 2-alkoxycarbonyl-substituted allyl vinyl ether chorismic acid.[33] Berchtold et al. used Horner-Wadsworth-Emmons reaction to install the exocyclic double bond of the chorismic acid precursor **96** (Scheme 18). Because of the inherent (*E*)-selectivity of the Horner-Wadsworth-Emmons reaction, this sequence is suitable to selectively gain access to 2-alkoxycarbonyl-substituted allyl vinyl ethers with an (*E*)-configured vinyl ether double bond.[34]

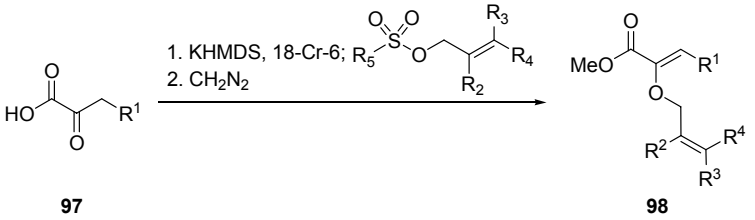


Scheme 18: Rhodium-catalyzed OH-insertion/olefination strategy.

Alternatively, 2-alkoxycarbonyl-substituted allyl vinyl ethers with (*Z*)-configured vinyl ether double bond can be obtained by *O*-alkylation of the α-ketoacid **97** enolate with allyl mesylate. To ensure selective *O*-alkylation, potassium *bis*(trimethylsilyl)amide is used as a

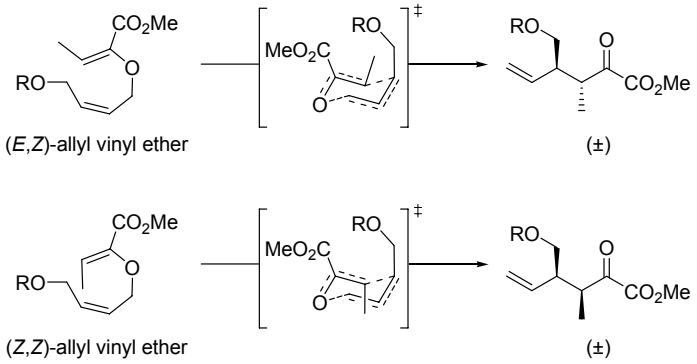
[33] (a) Ganem, B.; Ikota, N.; Muralidharan, V. B.; Wade, W. S.; Young, S. D.; Yukimoto, Y. *J. Am. Chem. Soc.* **1982**, *104*, 6787-6788. (b) Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765-1771.
[34] (a) Pollex, A.; Hiersemann, M. *Org. Lett.* **2005**, *7*, 5705-5708. (b) Körner, M.; Hiersemann, M. *Synlett* **2006**, *1*, 121-123.

deprotonating base together with 18-Crown-6. Subsequently, the carboxyl group is esterified with diazomethane to provide allyl vinyl ether **98** (Scheme 19). [35]



Scheme 19: Jacobsen synthesis of 2-alkoxycarbonyl-substituted allyl vinyl ethers.

Aliphatic 2-alkoxycarbonyl-substituted allyl vinyl ethers containing two stereogenic double bonds rearrange preferably via a chairlike transition-state structure to afford racemic α-ketoesters featuring two chiral carbon atoms, whose relative configuration can be reliably predicted (Scheme 20). (*E*,*Z*)- and (*Z*,*E*)-allyl vinyl ethers rearrange to give rise to *anti*-configured α-ketoesters, whereas (*E*,*E*)- and (*Z*,*Z*)-allyl vinyl ethers afford *syn*-configured α-ketoesters.[36]

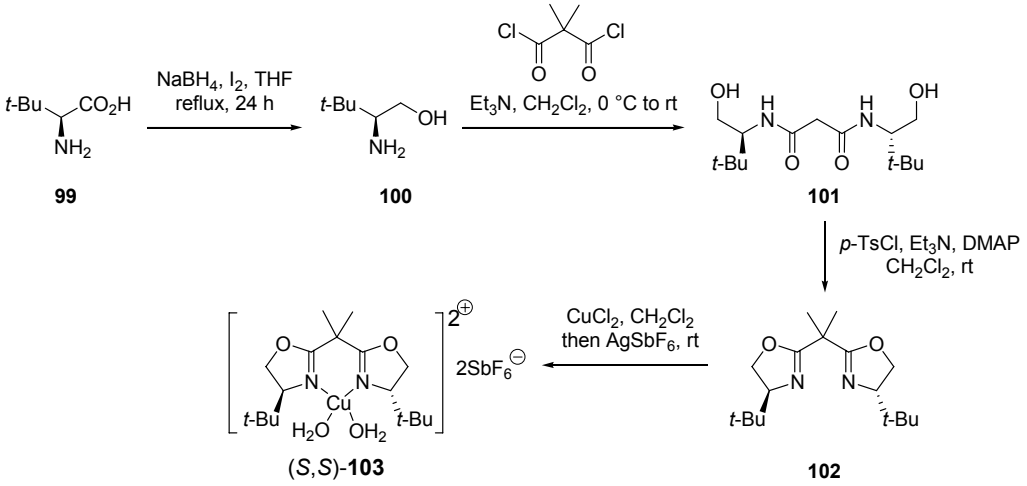


Scheme 20: Gosteli-Claisen rearrangment of (*E*,*Z*)- and (*Z*,*Z*)-allyl vinyl ethers.

The rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers was found to be very efficiently catalyzed by Lewis acids copper(II)-triflate and ytterbium(III)-triflate.[31a] By using chiral *bis*(oxazoline)copper(II) catalysts[37] it was possible to effect rearrangement of diverse 2-alkoxycarbonyl-substituted allyl vinyl ethers in high diastereo- and enantioselectivities. Chiral *bis*(oxazoline)copper(II) catalyst (*S*,*S*)-**103** can be easily synthesized in four steps starting from the commercially available amino acid (*S*)-*tert*-leucine (**99**) (Scheme 21).[38] In the first step (*S*)-*tert*-leucine is reduced to (*S*)-tert-leucinol (**100**) with *in situ* generated borane. Subsequent reaction with dimethylmalonyl chloride and triethylamine affords diamide

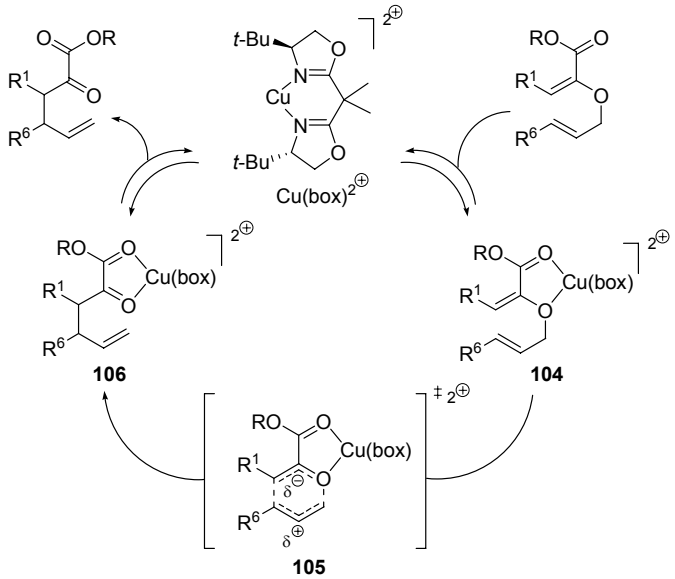
[35] Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228-9229.
[36] Rehbein, J.; Leick, S.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1531-1540.
[37] Chiral *bis*(oxazoline) ligands in asymmetric catalysis: Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561-3651.
[38] Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824-5825.

101, which on treatment with *p*-toluenesulfonic acid, triethylamine, and catalytic amount of 4-dimethylaminopyridine is converted to (*S*,*S*)-*bis*(*tert*-butyloxazoline) (**102**). To obtain the catalyst (*S*,*S*)-**103**, ligand **102** is first reacted with copper(II)-chloride in CH_2Cl_2, followed by treatment with silver(V)-hexafluoroantimonate.



Scheme 21: Synthesis of chiral *bis*(oxazoline)copper(II) catalyst.

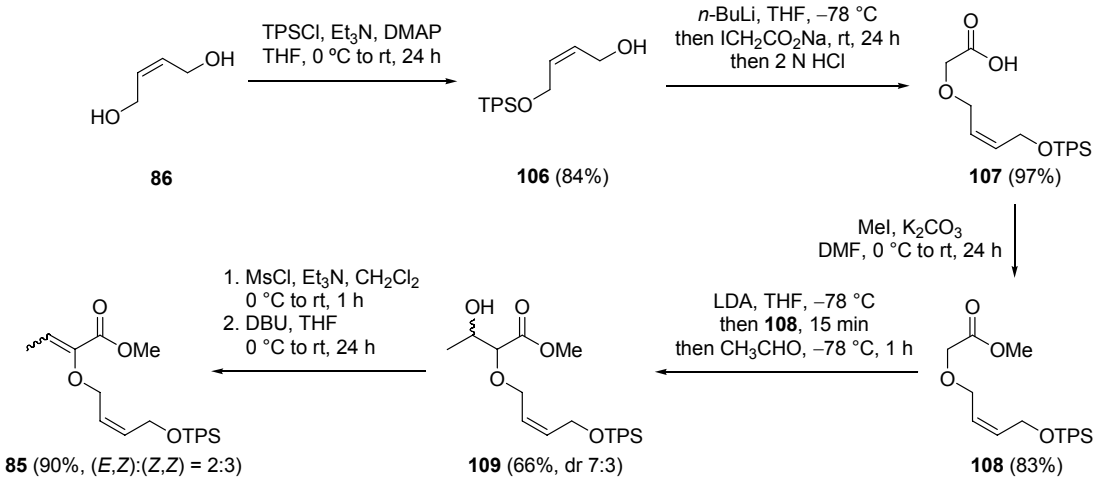
It can be assumed that at the beginning of the catalytic cycle, Cu-(box)-catalyst forms distorted square-planar complex **104** with allyl vinyl ether in which the copper ion coordinates simultaneously the allylic ether and the ester carbonyl oxygen atom. The strong inductive effect of the copper ion polarizes the allyl ether oxygen/carbon bond, and facilitates the formation of the highly polarized transition state **105** (Scheme 22).[32]



Scheme 22: Proposed catalytic cycle for the catalyzed Gosteli-Claisen rearrangement.

4.3 *Allyl Vinyl Ether Synthesis*[30]

The synthesis commenced with commercially available *cis*-2-butene-1,4-diol (**86**), which was selectively monosilylated by treatment with *tert*-butyldiphenylsilyl chloride and triethylamine in dichloromethane (Scheme 23). The formation of disilylated product was also observed but could be largely suppressed by slowly adding a solution of *tert*-butyldiphenylsilyl chloride to the excess diol **86**. Alcohol **106** was then deprotonated with *n*-butyllithium at −78 ºC and treated with sodium iodoacetate at room temperature to furnish acid **107** in excellent yield and purity. TPS protecting group is acid-sensitive, and subsequent esterification had to be performed under mild conditions. DCC-mediated esterification[39] of acid **107** with methanol afforded methyl ester **108** in modest yield (63%) along with a considerable amount of unidentified side product. Interestingly, satisfactory results were obtained when methanol was replaced by isopropyl alcohol. In an effort to increase yield, we turned our attention to esterification by alkylation of carboxylate salts.[40] Gratifyingly, upon exposure to potassium carbonate and methyl iodide in DMF, **107** underwent esterification to provide methyl ester **108** in good yield. Subsequently, ester enolate generated by treatment of **108** with lithium diisopropylamide at −78 ºC was reacted with acetaldehyde to afford β-hydroxyester **109** in modest yield (dr = 7:3). The two-step sequence involving mesylation of **109**, and DBU-mediated elimination provided mixture of 2-methoxycarbonyl-substituted allyl vinyl ethers (*Z*,*Z*)-**85** and (*E*,*Z*)-**85** in a 3:2 ratio, which could be readily separated by preparative HPLC.



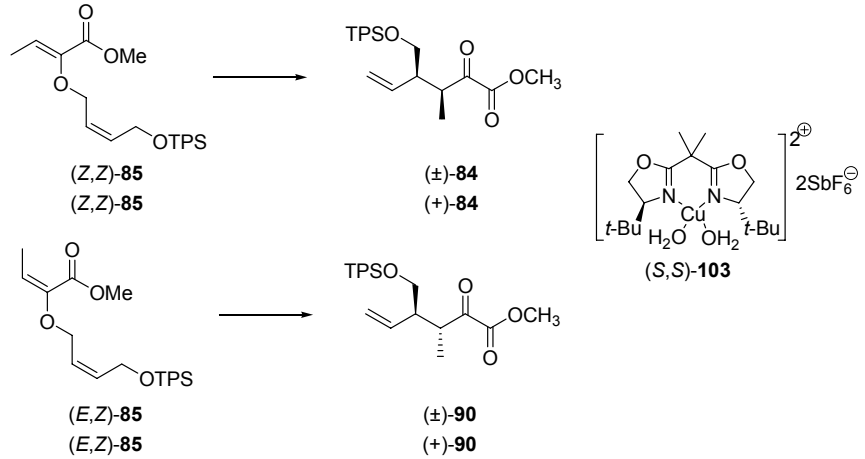
Scheme 23: Allyl vinyl ether synthesis.

[39] Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17*, 522-524.
[40] Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1976**, *41*, 1373-1379.

4.4 *Uncatalyzed and Catalyzed Gosteli-Claisen Rearrangement*

With (*Z*,*Z*)-**85** and (*E*,*Z*)-**85** in hand, we first explored their uncatalyzed rearrangement at elevated temperatures to obtain the corresponding racemic *syn*- and *anti*-configured α-ketoesters. Since uncatalyzed Gosteli-Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ether proceeded very slowly at temperatures below 100 ºC (one to five days), we decided to develop an easy and convenient protocol for microwave-assisted synthesis. After some optimization, it was found that quantitative conversion can be reached in only 30 minutes at 140 ºC (Table 1, entries 1 and 2).[41]

TABLE 1: Uncatalyzed and catalyzed Gosteli-Claisen rearrangement of allyl vinyl ethers.



	compound	solvent	T (ºC)	time (h)	(*S*,*S*)-103 (mol%)	yield[a]	dr[b]	ee[c]
1	(*Z*,*Z*)-**85**	trifluorethanol	140	0.5		95%	> 95:5	
2	(*E*,*Z*)-**85**	trifluorethanol	140	0.5		88%	> 95:5	
3	(*Z*,*Z*)-**85**	dichloromethane	rt	24	8	96%	> 95:5	> 90%
4	(*E*,*Z*)-**85**	dichloromethane trifluorethanol (3:2)	rt	24	8	95%	82:18	> 90%

[a] isolated yield. [b] determined by ^{1}H-NMR. [c] determined by Mosher's ester method.

Catalyzed Gosteli-Claisen rearrangement was performed at room temperature in the presence of chiral *bis*(oxazoline)copper(II) catalyst (*S*,*S*)-**103**. Although (*Z*,*Z*)-**85** afforded the corresponding α-ketoester (+)-**84** in very good diastereoselectivity, the opposite was the case with (*E*,*Z*)-**85**, which provided (+)-**90** only in modest diasteroselectivity (Table 1, entry 4). Suspecting that (*Z*,*Z*)-**85** contaminant might be responsible for the lower diastereoselectivity, (*E*,*Z*)-**85** was subjected to multiple rounds of preparative HPLC, however, the problem persisted. It was hypothesized that the disappointing *anti*/*syn* diastereoselectivity might be a

[41] The reaction is accelerated because of increase in temperature and not because of so-called "microwave effects". For further studies see: Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417-1424.

consequence of a competing catalyzed rearrangment via a boat-like transition state arrangement caused by the bulkiness of chiral *bis*(oxazoline) and the TPS protecting group.[32a] Attempts to separate enantiomers of α-ketoesters **84** and **90** on various chiral HPLC columns (Chiralcel OD, Chiralpak AD, Chiralpak IA) were not successful. Consequently, to control the enantiomeric purity of the α-ketoesters, they were transformed in four steps to the Mosher's esters **110-113** (Figures 8 and 9), which were then analyzed by ^{1}H-NMR.[42] All Mosher's esters contained an unidentified impurity, which could not be separated by column chromatography, but did not interfere with the spectra analyses.

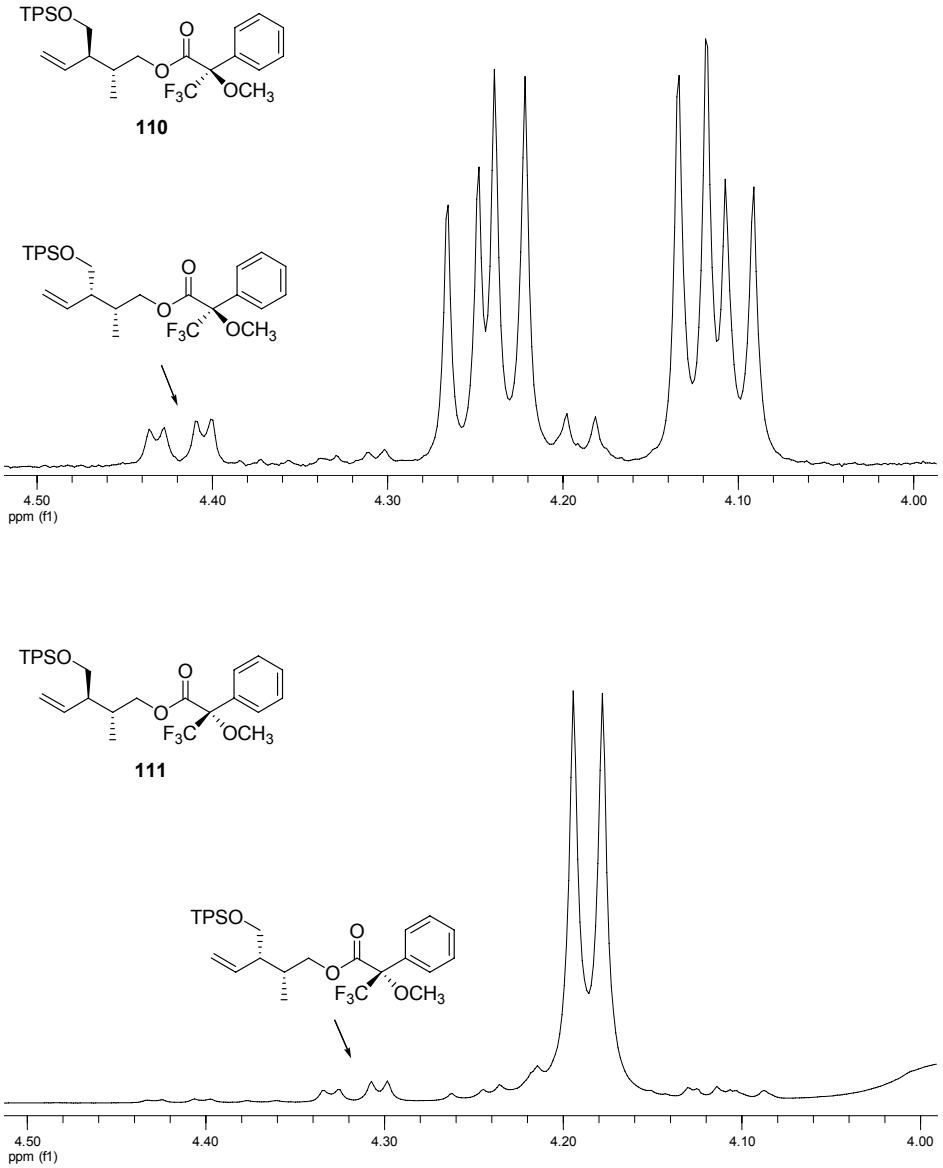


Figure 8: ^{1}H-NMR signals of –$COOCH_2$ protons of Mosher's esters **110** and **111**.

[42] Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

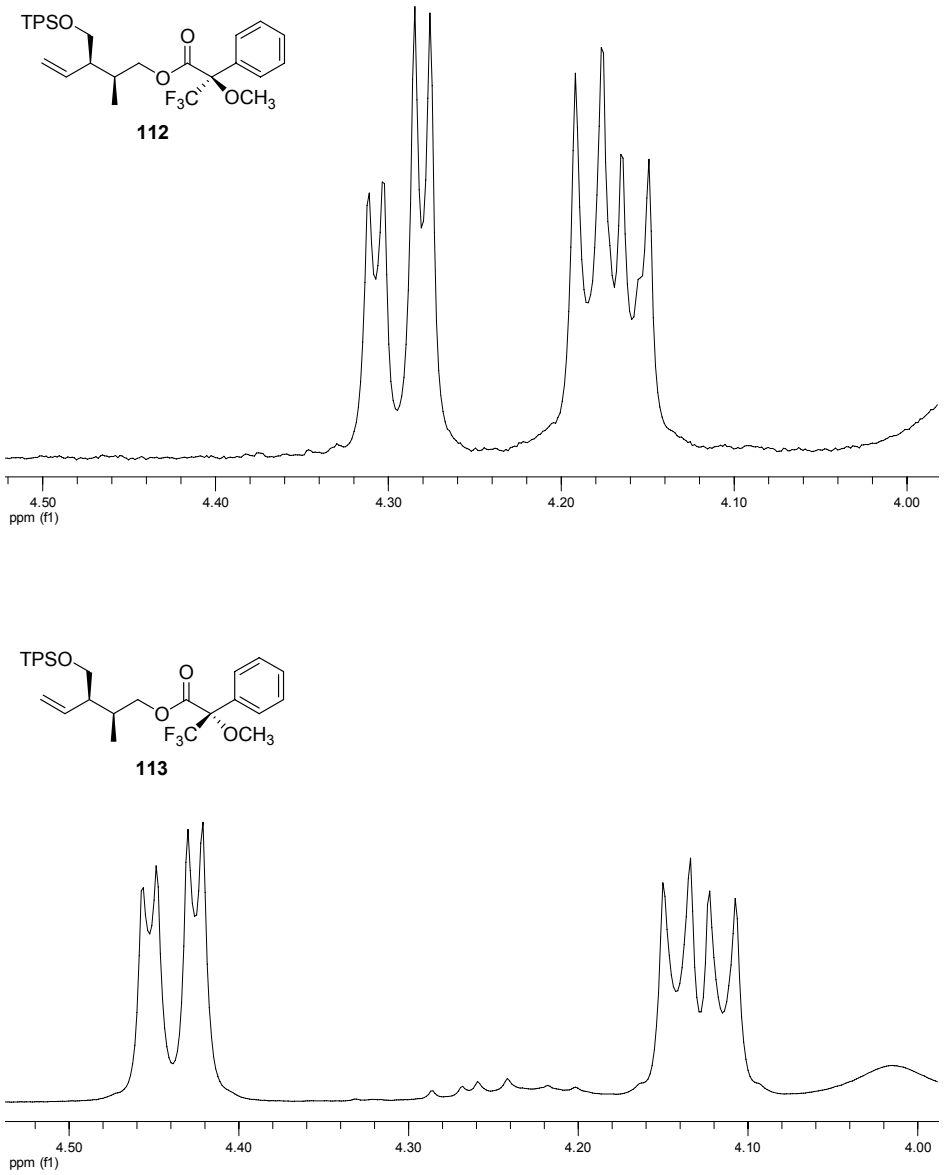
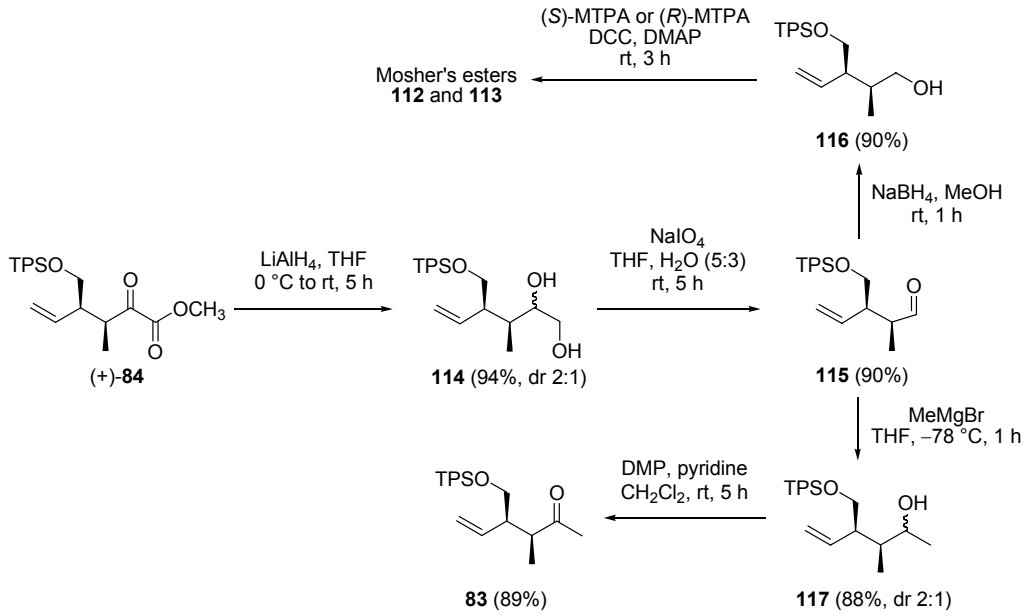


Figure 9: ^{1}H-NMR signals of –$COOCH_2$ protons of Mosher's esters **112** and **113**.

4.5 *Synthesis of the Ketone 83*

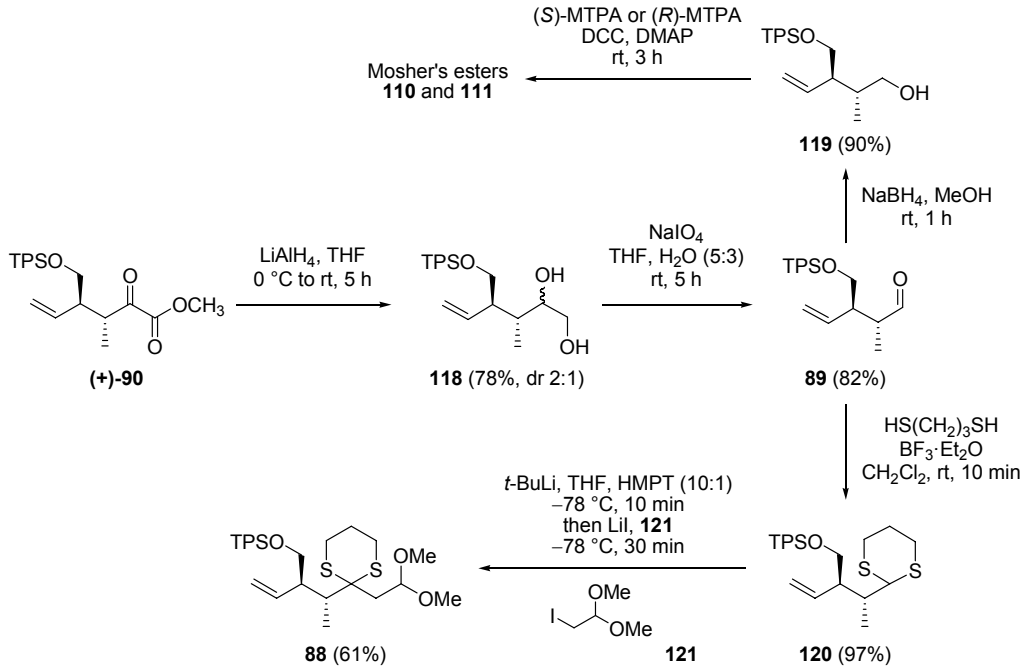
α-Ketoester (+)-**84** was reduced with lithium aluminium hydride to afford diol **114** (dr = 2:1) (Scheme 24). The latter was oxidatively cleaved by sodium periodate to provide aldehyde **115**. To synthesize Mosher's esters **112** and **113**,[42] aldehyde **115** was reduced with sodium borohydride to alcohol **116**, which was then treated with (*R*)- or (*S*) -α-methoxy-α-(trifluoromethyl)phenylacetic acid under Steglich conditions.[39] Reaction of methylmagnesium bromide with aldehyde **115** at −78 ºC, gave rise to alcohol **117** (dr = 2:1), and subsequent oxidation under Dess-Martin conditions provided ketone **83**.[26]



Scheme 24: Synthesis of ketone **83** and Mosher's esters **112** and **113**.

4.6 *Synthesis of the Acetal 88*

Analogously to the synthesis of ketone **83**, α-Ketoester (+)-**84** was converted in two steps to aldehyde **89** (Scheme 25). Reduction of **89** with sodium borohydride and esterification with (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid under Steglich conditions[39] provided the Mosher's esters **110** and **111**.[42]

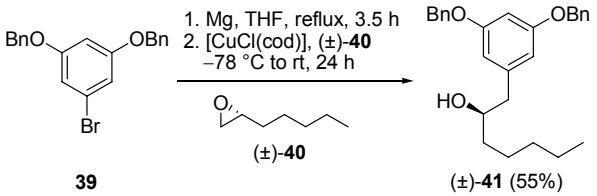


Scheme 25: Synthesis of acetal **88** and Mosher's esters **110** and **111**.

Upon treatment with 1,3-propanedithiol and boron trifluoride etherate, aldehyde **89** was smoothly converted to dithiane **120**. Subsequent alkylation of lithiated dithiane **120**[43] with bromoacetaldehyde dimethyl acetal proved unfruitful, and we reasoned that upon addition of lithium iodide, more reactive iodoacetaldehyde dimethyl acetal (**121**) would be formed *in situ*. Under such conditions the alkylated product was built, however, only in trace amounts. Pure iodoacetaldehyde dimethyl acetal (**121**) was synthesized from vinyl acetate (**122**)[44] and employed directly in the alkylation reaction, but surprisingly no product was formed. To our delight, the reaction of lithiated dithiane **120** with iodoacetaldehyde dimethyl acetal (**121**) in the presence of lithium iodide gave the desired product **88** in modest yield.[45]

4.7 *Model Study toward the Tetracyclic Core of Berkelic Acid*

To obtain alcohol (±)-**41**, Grignard reagent derived from 1,3-*bis*(benzyloxy)-5-bromobenzene (**39**) was reacted with (±)-2-pentyloxirane (**40**) under copper catalysis (Scheme 26).[22] The requisite copper catalyst CuCl(cod) was freshly synthesized from copper(I)-chloride, triethyl phosphite and 1,5-cyclooctadiene.[46] The formation of the Grignard reagent was sluggish, and **39** was added to magnesium turnings over a period of several hours in order to avoid undesired side reactions. The reaction of bromide ion with **40** led to the formation of undesired 1-bromheptan-2-ol, but this could be largely suppressed by lowering the reaction temperature.

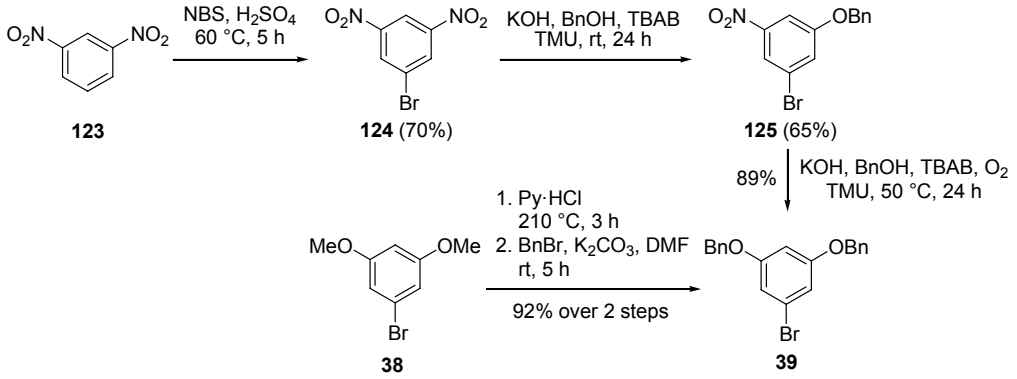


Scheme 26: Synthesis of racemic alcohol **41**.

The synthesis of **39** was easily accomplished by demethylation of commercially available 1-bromo-3,5-dimethoxybenzene (**38**) with pyridinium hydrochloride at 210 °C,[47] and subsequent benzylation (Scheme 27). Alternatively, **39** was synthesized starting with commercially available 1,3-dinitrobenzene (**123**), which was selectively brominated with *N*-bromosuccinimide in sulfuric acid at 60 °C to afford 1-bromo-3,5-dinitrobenzene (**124**).[48] On treatment with benzyl alcohol, potassium hydroxide, and catalytic amount of

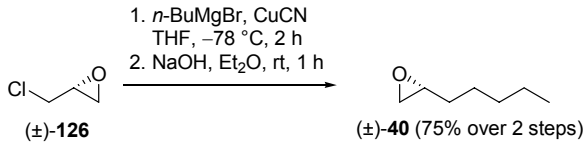
[43] For the alkylation of 2-substituted 1,3-dithianes HMPA must be added.
[44] Onoe, A.; Uemura, S.; Okano, M. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2818-2821.
[45] The yield could be further increased by reisolating the unreacted dithiane **120**, and subjecting it to the same reaction conditions.
[46] Cook, B. W.; Miller, R. G. J.; Todd, P. F. *J. Organometal. Chem.* **1969**, *19*, 421-430.
[47] Tabaka, A. C.; Murthi, K. K.; Pal, K.; Teleha, C. A. *Org. Proc. Res. Dev.* **1999**, *3*, 256-259.
[48] Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem.* **2007**, *72*, 5867-5869.

tetrabutylammonium bromide in tetramethylurea, **124** underwent nucleophilic substitution of one of its nitro groups to afford 1-(benzyloxy)-3-bromo-5-nitrobenzene (**125**). The substitution of the second nitro group was conducted under oxygen atmosphere at 50 °C using the same reagents.[49] In the absence of oxygen, considerable amount of unidentified byproduct was formed, which hindered the recrystallization of the crude product.



Scheme 27: Synthesis of 1,3-*bis*(benzyloxy)-5-bromobenzene.

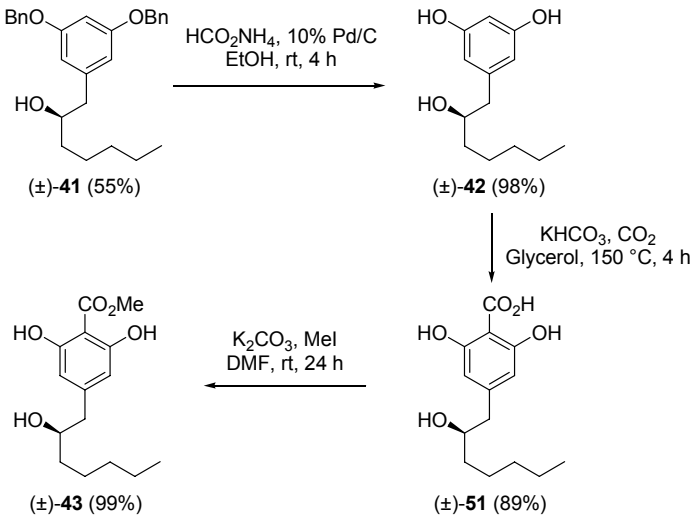
(±)-2-pentyloxirane (**40**) was conveniently synthesized from (±)-epichlorohydrine (**126**) in two steps. (±)-Epichlorohydrine (**126**) was first reacted with *n*-butylmagnesium bromide in the presence of copper(I)-cyanide to afford 1-chloroheptan-2-ol, which rapidly underwent oxirane formation on treatment with sodium hydroxide in diethyl ether (Scheme 28).[50]



Scheme 28: Synthesis of (±)-2-pentyloxirane.

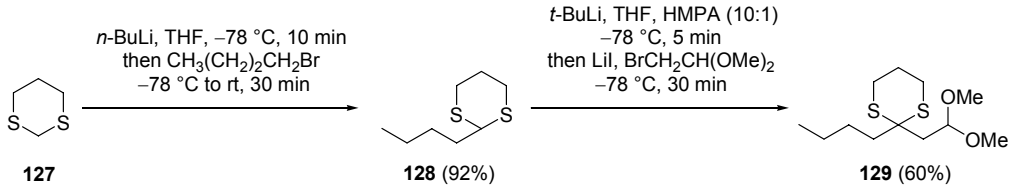
Alcohol (±)-**41** was easily deprotected by catalytic transfer hydrogenation with ammonium formate to afford (±)-**42** (Scheme 29).[51] The stage was now set for the Kolbe-Schmitt reaction to introduce carboxyl group in between two phenol groups. The reaction was conducted at 150 °C under carbon dioxide atmosphere with potassium bicarbonate in glycerol to afford acid (±)-**51** in excellent yield. Subsequent selective protection of free acid with methyl iodide and potassium carbonate in dimethylformamide afforded methyl ester (±)-**43**.

[49] Effenberger, F.; Koch, M.; Streicher, W. *Chem. Ber.* **1991**, *124*, 163-173.
[50] Dewi-Wülfing, P.; Gebauer, J.; Blechert, S. *Synlett* **2006**, *3*, 487-489.
[51] Bieg, T.; Szeja, W. *Synthesis* **1985**, *1*, 76-77.



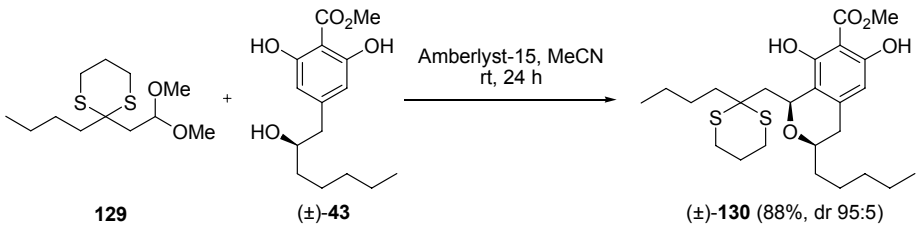
Scheme 29: Synthesis of the aromatic fragment (±)-**43**.

1,3-Dithiane (**127**) was deprotonated with *n*-butyllithium, and then alkylated with 1-bromobutane to give rise to **128** (Scheme 30). Subsequent alkylation of 2-substituted 1,3-dithiane **128** with bromoacetaldehyde dimethyl acetal was accomplished in the presence of lithium iodide to afford acetal **129**, a model compound of acetal **88**.



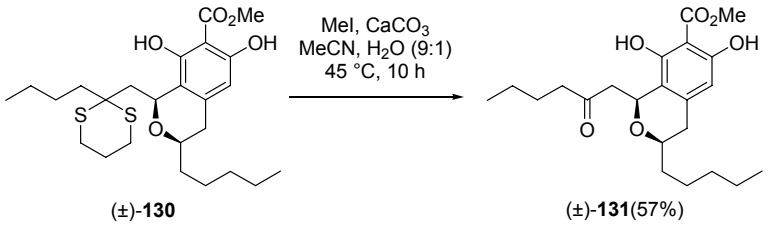
Scheme 30: Synthesis of acetal **128**.

With aromatic fragment (±)-**43** and acetal **129** in hand, we set out to explore the Oxa-Pictet-Spengler condensation. After some optimization it was found that Amberlyst-15 resin in acetonitrile smoothly effected the desired condensation to afford the product (±)-**130** as a *cis* diastereomer (dr > 95:5) according to NOESY correlations (Scheme 31).



Scheme 31: Oxa-Pictet-Spengler condensation.

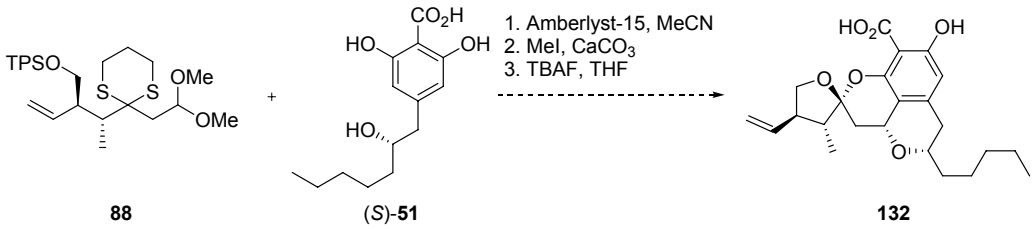
The last challenge was to find mild reaction conditions to hydrolyse thioketal (±)-**130**. Attempt to effect this transformation with mercury(II)-chloride in the presence of calcium carbonate failed.[52] Fortunately, methyl iodide in the presence of calcium carbonate converted thioacetal into ketone (±)-**131** in a moderate yield.[53]



Scheme 32: Deprotection of thioketal.

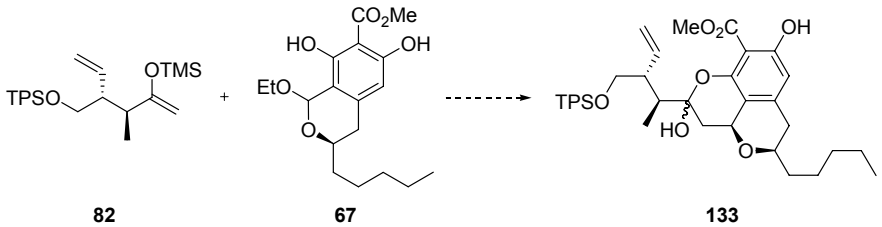
4.8 *Outlook*

The substituted enantiomerically pure acetal **88** could be reacted with aromatic acid (*S*)-**51** via acid-catalyzed Oxa-Pictet-Spengler condensation, followed by thioketal hydrolysis and TPS cleavage to afford the tetracyclic core **132**, which resembles **26** in the Fürstner's synthesis (Scheme 33). As it has been shown by Snider, the absolute configuration of the natural berkelic acid (**1**) is exactly opposite.



Scheme 33: Synthesis of the tetracyclic core of *ent*-berkelic acid.

The acid-catalyzed condensation of silyl enol ether **82** and pulvilloric acid (**5**) failed, however, the acid-catalyzed coupling of silyl enol ether **82** and lactol **67** might be worth investigating (Scheme 34).



Scheme 34: Proposed approach toward the berkelic acid.

[52] Seebach, D. *Synthesis* **1969**, *1*, 17-36.
[53] Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382-383.

5. Introduction to Lytophilippine A

Chloro-containing 14-membered polyketide macrolactone lytophilippine A (**134**) was isolated from the Red Sea hydroid *Lytocarpus Philippinus*, collected in the Gulf of Aqaba in Israel.[54] The macrolactone moiety of lytophilippine A (**134**) resembles structurally Haterumalides (from Okinawan sponge *Ircinia sp.* and Okinawan ascidian *Lissoclinum sp.*)[55] and to a lesser extent Amphidinolides (from marine dinoflagellates *Amphidinium*)[56]; the complex chloro-containing side chain is, however, unique to this natural product.

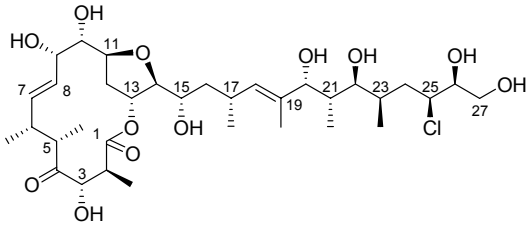
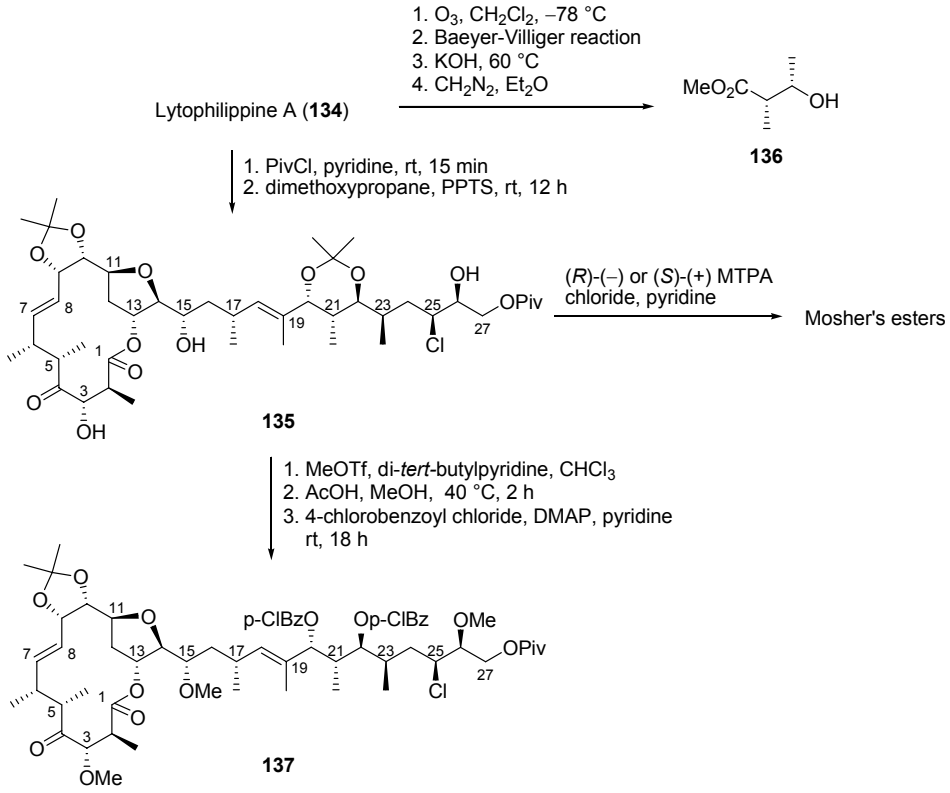


Figure 10: Lytophilippine A (**134**).

The structure of lytophilippine A (**134**), as depicted in Figure 10, was assigned based on extensive NMR experiments, IR and UV spectrometric measurements, coupled with chemical degradation and derivatization. To elucidate the relative stereochemistry, lytophilippine A (**134**) was converted to derivative **135** by protecting the primary hydroxyl group at C-27 as pivaloyl ester, and C-20/C-22 and C-9/C-10 hydroxyl groups as isopropylidene acetals (Scheme 35). Based on the NOESY spectrum of H-2 and H-3 protons, the relative stereochemistry C-2/C-3 was determined to be in *threo* relationship. C-9/C-10 stereochemistry could be determined as *syn* based on NOESY correlations and vicinal coupling constants. Tetrahydrofuran ring stereochemistry was determined using ROESY and selective 1D-NOE experiments. The relative configurations at C-14, C-15, and C-17 were elucidated on the basis of ^{1}H-^{1}H and ^{1}H-^{13}C coupling constants and NOESY correlations. C-20/C-22 relative configuration was established as *anti* by Rychnovsky's method.[57] Analysis of vicinal coupling constants $J_{5,6}$, $J_{20,21}$, $J_{21,22}$ and $J_{22,23}$ indicated *threo* relationship between C-5/C-6, C-20/C-21 and C-22/C-23, and *erythro* relationship between C-21/C-22. *J*-based configuration analysis developed by Murata[58] for the elucidation of relative stereochemistry in acyclic structures using $^{3}J_{H,H}$ values, coupled with additional NOE experiments helped to

[54] Řezanka, T.; Hanuš, L. O.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 12191-12199.
[55] Takada, N.; Sato, H.; Suenaga, K.; Arimoto, H.; Yamada, K.; Ueda, K.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 6309-6312.
[56] Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77-93.
[57] Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9-17.
[58] Murata, M.; Matsuoka, S.; Matsumori, N.; Kaneno, D.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870-871.

confirm *threo* relationship between C-25/C-26. To determine absolute configuration at C-5 and C-6, lytophilippine A (**134**) was degraded by ozonolysis and Baeyer-Villiger reaction. The resulting mixture was hydrolysed and treated with diazomethane to give methyl 3-hydroxy-2-methyl butyrate (**136**), which was then compared with synthetic methyl (2*S*,3*S*)-3-hydroxy-2-methyl butyrate.



Scheme 35: Degradation and derivatization reactions to determine the relative and absolute configuration.

The absolute configuration of C-20 and C-22 was determined by CD exciton chirality method[59] applied on 20,22-*bis*-*p*-chlorobenzoate **137**, which was obtained from **135** in three steps. The stereochemistry of the remaining asymmetric centers C-3, C-15 and C-26 was ascertained by NMR analysis of Mosher's esters obtained by treating **135** with *R*-(–) and *S*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in pyridine.

[59] Harada, N.; Saito, A.; Ono, H.; Gawronski, J.; Gawronska, K.; Sugioka, T.; Uda, H.; Kuriki, T. *J. Am. Chem. Soc.* **1991**, *113*, 3842-3850.

6. Synthetic Part – Lytophilippine A

6.1 *Retrosynthesis of Lytophilippine A and C19–C27 Fragment*

In our retrosynthetic analysis, lytophilippine A (**134**) is disconnected at C13–O acyl, and C18–C19 and C7–C8 alkene bonds, to provide three fragments as depicted in Figure 11. It was envisioned that C7–C8 connection would be established by methathesis, C13–O acyl bond by macrolactonization, and finally C18–C19 by Horner-Wadsworth-Emmons reaction.

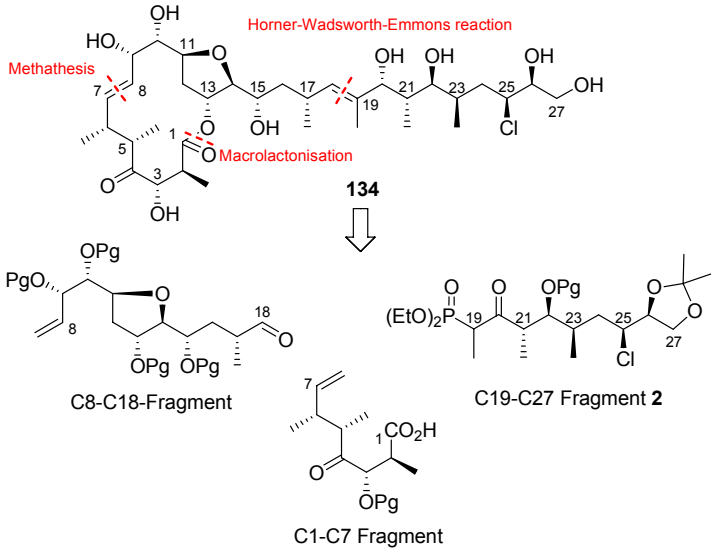


Figure 11: Retrosynthetic analysis of the lytophilippine A.

Chloro-containing C19–C27 fragment **2** was further simplified at C21–C22 to give α-chiral aldehyde **138**, which would be synthesized from the literature known lactone **140** or epoxide **141**, both available from natural (+)-L-ascorbic acid (**142**).

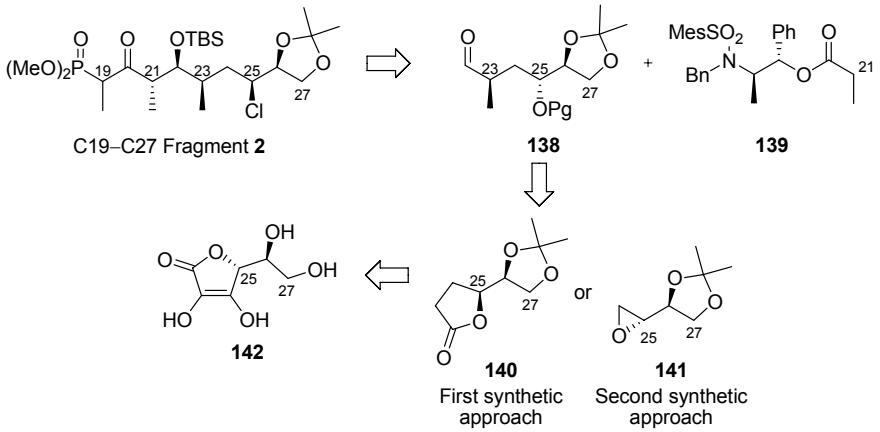
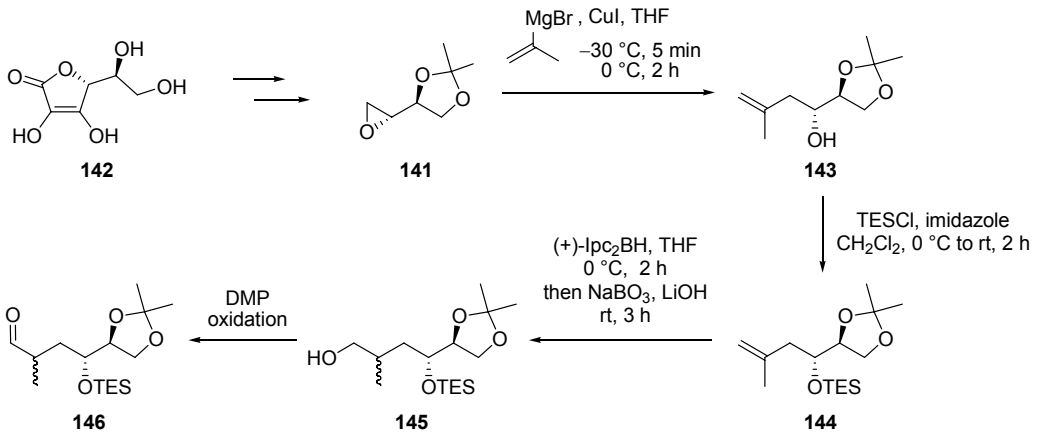


Figure 12: Retrosynthetic analysis of C19–C27 fragment of lytophilippine A.

6.2 *Challenge of the Stereoselective Methylation – Asymmetric Hydroboration*

The stereoselective introduction of C-23 methyl group proved to be difficult by relying on substrate-based 1,3-asymmetric induction. We initially envisioned an elegant synthetic approach toward aldehyde **146** by means of asymmetric hydroboration of terminal alkene **144** and subsequent oxidation (Scheme 36).[7] To synthesize **144**, commercially available (+)-L-ascorbic acid (**142**) was transformed to the epoxide **141** in six steps. Copper-catalyzed epoxide opening with isopropenylmagnesium bromide furnished alcohol **143**, which was protected as TES ether by treatment with chlorotriethylsilane in the presence of imidazole in CH_2Cl_2. Asymmetric hydroboration with (+)-$(Ipc)_2BH$ and subsequent organoborane oxidation provided alcohol **145** in good overall yield, but with low diastereoselectivity (dr 2:1),[60] which could not be improved by the use of other hydroboration reagents.



Scheme 36: Attempted asymmetric hydroboration of terminal alkene.

Evans has suggested a transition state model for 1,3-asymmetric induction in the hydroboration of terminal alkenes (Figure 13).[61] The model explains that useful alkene diastereofacial bias may be created when the sterically dominant ligand R_L adapts the illustrated *anti*-conformation, and that transition state T_2, leading to *anti*-diastereomer, is disfavoured by the developing methyl–R_M non-bonding interaction. Evans performed a series of hydroboration experiments with R_M=Me and concluded that high level of diastereoselectivity is reached only when R_L is large enough. The choice of hydroboration reagent had almost no influence.

[60] Major diastereomer was not identified.
[61] Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577-4580.

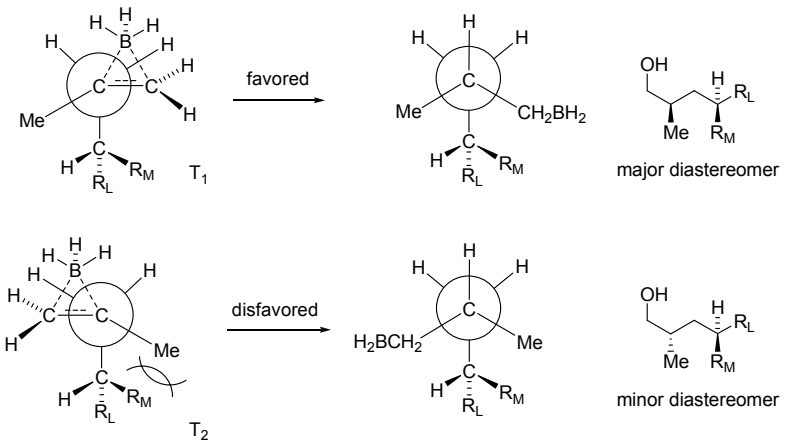
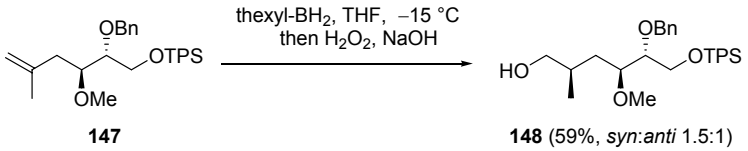


Figure 13: Proposed mechanism of 1,3-asymmetric induction in the hydroboration of terminal alkenes.

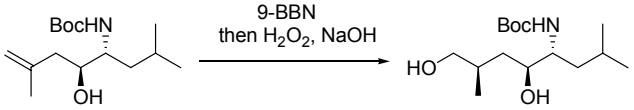
Morimoto, Shirahama et al. utilized asymmetric hydroboration in the synthesis of C10–C22 fragment of immunosuppressant FK506,[62] but attained only modest diastereoselectivities (dr = 1.5:1), which could not be increased despite many attempts under various conditons.



147 **148** (59%, *syn*:*anti* 1.5:1)

Scheme 37: Asymmetric hydroboration by Morimoto, Shirahama et al.

Asymmetric hydroboration of the terminal alkene **149** was reported by Pégorier and Larchevêque.[63] The diol **150** was obtained with the same sense of induction and disappointing level of diastereoselectivity (dr = 2.3:1) as observed previously with other related terminal alkenes.



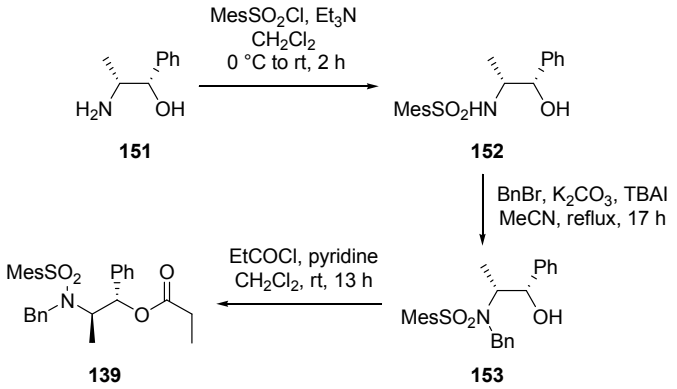
149 **150** (71%, *syn*:*anti* 2.3:1)

Scheme 38: Asymmetric hydroboration by Pégorier and Larchevêque.

[62] Morimoto, Y.; Mikami, A.; Kuwabe, S.; Shirahama, H. *Tetrahedron: Asymmetry* **1996**, *7*, 3371-3390.
[63] Pégorier, L.; Larchevêque, M. *Tetrahedron Lett.* **1995**, *36*, 2753-2756.

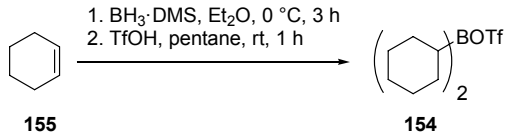
6.3 *Introduction of anti-3-hydroxy-2-methylcarbonyl Unit*

We envisioned that elaboration of the C21–C23 *anti*, *syn* stereotriad could be conveniently achieved by *anti*-selective asymmetric aldol reaction between aldehyde **138** and the (*E*)-boron enolate of propionate **139** (Figure 12).[64] The requisite propionate **139** can be easily prepared in three steps from commercially available (+)-norephedrine (**151**) by selective sulfonylation of the amino group with mesitylenesulfonyl chloride and triethylamine, selective *N*-alkylation with benzyl bromide in the presence of potassium carbonate in acetonitrile, and acylation with propionyl chloride and pyridine (Scheme 39).[65]



Scheme 39: Synthesis of propionate **139**.

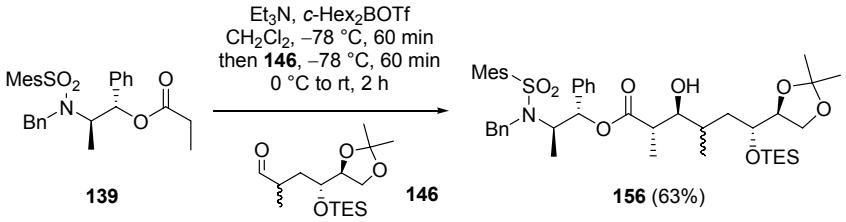
(*E*)-boron enolate of propionate **139**, which leads to the desired *anti*-aldol product,[66] is generated under kinetically controlled conditions at −78 ºC using dicyclohexylboron trifluoromethanesulfonate (**154**) and triethylamine as enolization reagents. **154** forms a complex with triethylamine in competition with deprotonation, and in order to achieve complete enolization two equivalents must be used.[67] It is air-sensitive reagent and needs to be prepared freshly from cyclohexene (**155**) prior to use (Scheme 40).[68] Preparation of the reagent turned out to be difficult and resulted in irreproducible yields.[69]



Scheme 40: Preparation of dicyclohexyl trifluoromethanesulfonate.

[64] (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586-2587. (b) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387-395.
[65] Abiko, A. *Org. Synth.* **2002**, *79*, 109-115.
[66] For explanation see Zimmerman-Traxler transition state model: Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.
[67] Abiko, A.; Liu, J.-F. *J. Org. Chem.* **1996**, *61*, 2590-2591.
[68] Abiko, A. *Org. Synth.* **2002**, *79*, 103-108.
[69] Trifluoromethansulfonic acid is very hygroscopic, and should be purchased in sealed ampules.

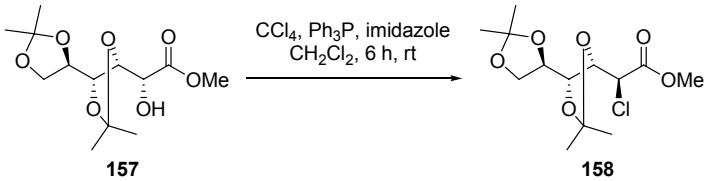
In initial studies toward the C19–C27 fragment **2**,[7] *anti*-selective asymmetric aldol reaction was successfully applied to afford the desired *anti*-aldol product **156** (Scheme 41).[70]



Scheme 41: Asymmetric aldol reaction.

6.4 *Introduction of Chlorine Atom through S_N2 Substitution*

Chlorination of the C-25 hydroxyl group with inversion of configuration would be accomplished late in the synthesis. Although there are many methods available to convert alcohols to the corresponding chlorides, the presence of an acetal precludes the use of acidic reagents.[71] A further complication is that some chlorination reactions of chiral alcohols proceed with partial racemization. Replacement of hydroxyl group by chlorine under mild conditions has been successfully utilized in the synthesis of several chloro-containing natural products: (+)-brasilenyne (CCl_4, (*n*-Oct)$_3$P, 60 ºC, toluene), (+)-rogioloxepane A (CCl_4, (*n*-Oct)$_3$P, 1-methylcyclohexene, Et_3BnNCl, 80 ºC), and (+)-obtusenyne (CCl_4, (*n*-Oct)$_3$P, 1-methylcyclohexene, 80 ºC, toluene or $Cl_2C{=}NMe_2^+Cl^-$, pyridine, dichloromethane, 0 ºC to rt).[72] Addition of imidazole to tetrachloromethane/triphenylphosphine reagent enables nucleophilic substitution to proceed at room temperature (Scheme 42).[73] It is presumed that the initial tetrachloromethane/triphenylphosphine adduct reacts with imidazole to form a species of higher reactivity.[74]

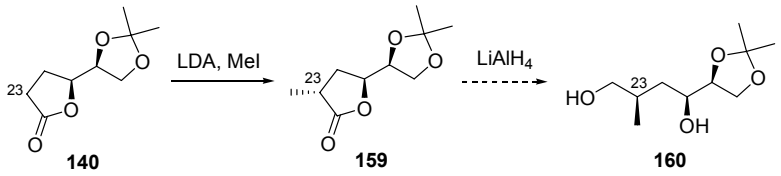


Scheme 42: Chlorination with tetrachloromethane, triphenylphosphine and imidazole.

[70] The aldehyde **146** was employed as a mixture of C-23 diastereomers (dr = 1.5:1).
[71] (a) Ph_3PCl_2: Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964-965. (b) NCS, PPh_3: Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, *40*, 3937-3940. (c) CCl_4, PPh_3: Appel, R. *Angew. Chem.* **1975**, *87*, 863-874. (d) $Cl_2C{=}NMe_2^+Cl^-$, pyridine: Klemer, A.; Brandt, B.; Hofmeister, U.; Rüter, E. R. *Liebigs Ann. Chem.* **1983**, 1920-1929. (e) CCl_4, (*n*-Oct)$_3$P: Hooy, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86-87. (f) CCl_3CONH_2, PPh_3: Pluempanupat, W.; Chavasiri, W. *Tetrahedron Lett.* **2006**, *47*, 6821-6823.
[72] (a) Denmark, S. E; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196-15197. (b) Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009-3011. (c) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592-7595. (d) Frankie Mak, S. Y.; Curtis, N. R.; Payne, A. N.; Congreve, M. S.; Wildsmith, A. J.; Francis, C. L.; Davies, J. E.; Pascu, S. I.; Burton, J. W.; Holmes, A. B. *Chem. Eur. J.* **2008**, *14*, 2867-2885.
[73] Vijayasaradhi, S.; Beedimane, M. N.; Aidhen, I. S. *Synthesis* **2005**, *13*, 2267-2269.
[74] Garegg, P. J.; Johansson, R.; Samuelsson, B. *Synthesis* **1984**, *2*, 168-170.

6.5 *Toward the C19-C27 Fragment of Lytophilippine A – First Approach*

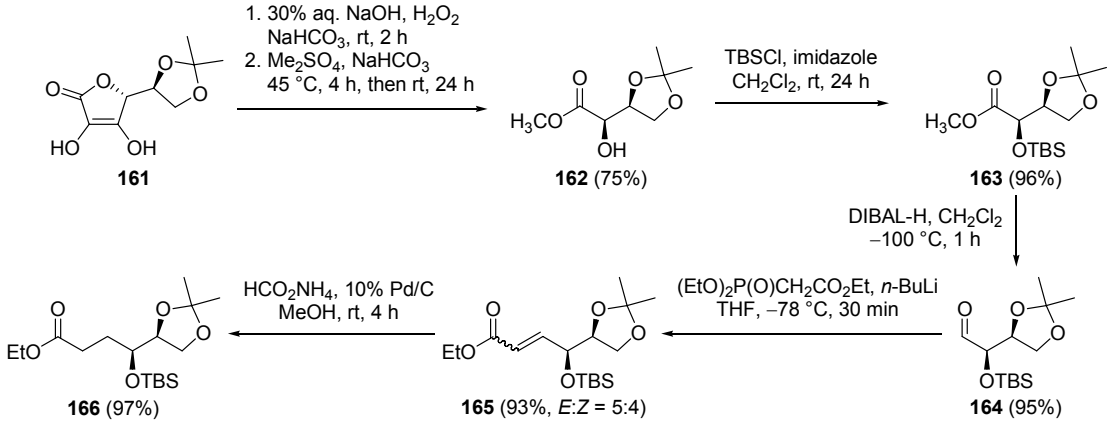
Remote stereocontrol in acyclic systems is a challenging problem, and reactions not involving cyclic transition state typically proceed with low diastereoselectivity. We hoped that stereoselective methylation of γ-butyrolactone **140** and subsequent reduction would provide an efficient way to synthesize diol **160** in high diastereoselectivity (Scheme 43). It was observed that the stereochemical course of γ-butyrolactone alkylations is mainly determined by the size of the group at the γ-position of the ring, leading to the conclusion that electrophilic attack occurs preferentially from the less hindered side. The method has been successfully applied in several syntheses.[75]



Scheme 43: Proposed stereoselective methylation of γ-butyrolactone **140**.

6.5.1 *Synthesis of γ-Butyrolactone 140*

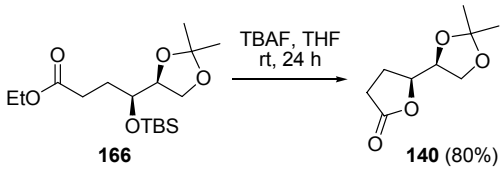
Protection of the vicinal diol of (+)-L-ascorbic acid (**142**) as the isopropylidene acetal **161** was achieved by reaction with acetone in the presence of anhydrous copper sulfate. Subsequent oxidative cleavage with sodium hydroxide and hydrogen peroxide, and *in situ* methylation with dimethyl sulfate afforded methyl ester **162**[76] in good yield and excellent purity, thus obviating the need for chromatography (Scheme 44).



Scheme 44: First synthetic approach

[75] (a) Ito, H.; Inoue, T.; Iguchi, K. *Org. Lett.* **2008**, *10*, 3873-3876. (b) Paquette, L. A.; Pissarnitski, D. ; Barriault, L. *J. Org. Chem.* **1998**, *63*, 7389-7398. (c) Ferrié, L. ; Reymond, S. ; Capdevielle, P. ; Cossy, J. *Org. Lett.* **2006**, *8*, 3441-3443. (d) Ghosh, A. K. ; Gong, G. *J. Org. Chem.* **2006**, *71*, 1085-1093.
(e) Hanessian, S.; Yang, G.; Rondeau, J.-M.; Neumann, U.; Betschart, C.; Tintelnot-Blomley, M. *J. Med. Chem.* **2006**, *49*, 4544-4567.
[76] Cho, B. H.; Kim, J. H.; Jeon, H. B.; Kim, K. S. *Tetrahedron* **2005**, *61*, 4341-4346.

Sodium carboxylate formed after the oxidative cleavage of **161** can be isolated and reacted with methyl iodide in DMF or MeCN; the two-step sequence, however, offers no advantage. On treatment with *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2, the free hydroxyl group in **162** was protected to afford TBS ester **163**.[77] Direct reduction of **163** to aldehyde **164** with diisobutylaluminium hydride at low temperature (–100 ºC) was achieved in excellent yield.[78] Although trace amounts of alcohol resulting from the overreduction of aldehyde **164** were difficult to separate by chromatography, they did not interfere in the next reaction. Two-carbon homologation of aldehyde **164** by means of Horner-Wadsworth-Emmons olefination was conveniently performed using *n*-butyllithium as a base at −78 ºC to furnish *α*,*β*-unsaturated ester **165** as a mixture of double bond isomers (*E*:*Z* = 5:4).[79] Palladium-catalyzed transfer hydrogenation with ammonium formate as hydrogen donor served to reduce alkene and provided ester **166**. [80] Finally, tetra-*n*-butylammonium fluoride mediated TBS deprotection with concomitant ring closure gave γ-butyrolactone **140** (Scheme 45).[81]



Scheme 45: γ-butyrolactone synthesis.

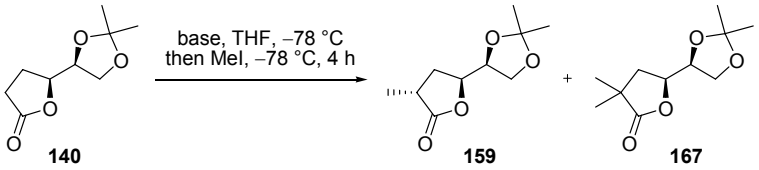
6.5.2 *Stereoselective Methylation*

With the γ-butyrolactone **140** in hand, the stage was now set for the stereoselective methylation. Unfortunately, the reaction proved unsatisfactory under a range of conditions and was accompanied by formation of dimethylated γ-butyrolactone **167**, not separable by flash chromatography (Table 2). Furthermore, it was observed that by reducing the amount of excess base and methyl iodide, formation of **167** could not be completely suppressed (Table 2, entries 3 and 7). The choice of deprotonating base seemed to play important role, and lithium diisopropylamide proved superior to more hindered and less basic lithium *bis*(trimethylsilyl)amide. These findings could be explained by two competing pathways for enolate **168**: reaction with methyl iodide to deliver desired **159**, or proton exchange with **159** to give γ-butyrolactone **140** and enolate **169**, which can further react with methyl iodide to

[77] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.
[78] Lilly, M. J.; Miller, N. A.; Edwards, A. J. Willis, A. C.; Turner, P.; Paddon-Row, M. N.; Sherburn, M. S. *Chem. Eur. J.* **2005**, *11*, 2525-2536.
[79] *E*:*Z* ratio of olefinic products formed in the Horner-Wadsworth-Emmons reaction increases with the reaction temperature. See: Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386.
[80] Paryzek, Z.; Koenig, H.; Tabaczka, B. *Synthesis* **2003**, *13*, 2023-2026.
[81] Dondoni, A.; Perrone, D.; Semola, M. T. *J. Org. Chem.* **1995**, *60*, 7927-7933.

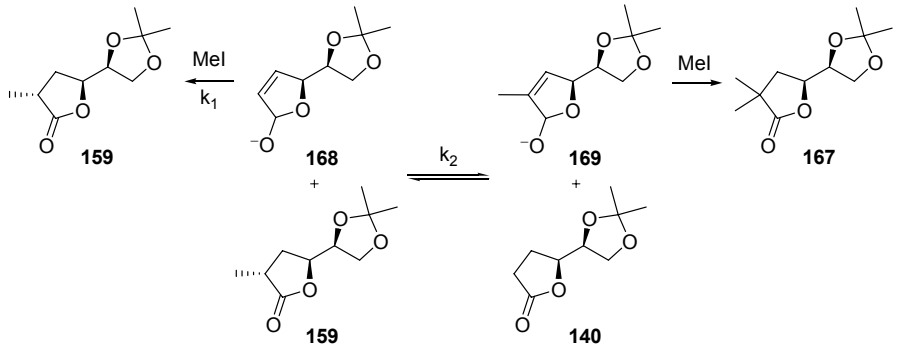
give dimethylated γ-butyrolactone **167** (Scheme 46).[82] It has been suggested[83] and experimentally proven[84] that enolate alkylation is accompanied by dialkylation because the less substituted enolates are more aggregated and thus less reactive. The addition of polar aprotic cosolvent HMPA, which serves to break up enolate aggregates, was reported to minimize dialkylation side product in lactone alkylations,[82] however, in our case it did not lead to any improvement (Table 2, entry 2). To our delight, the equilibrium outlined in Scheme 46 could be largely suppressed by reversing the order of reagent addition and slowly adding preformed enolate **168** to a large excess of methyl iodide (Table 2, entry 4). NOESY correlations of the monomethylated lactone **159** were in complete agreement with the expected stereochemical outcome of lactone alkylation, however, the diastereoselectivity was modest (dr = 4:1), and could not be improved. In view of these disappointing results, we decided to explore a different approach for the stereoselective introduction of the C-23 methyl group.

TABLE 2: Stereoselective methylation of γ-butyrolactone **140**.



entry	eq base	eq MeI	yield (%)[a]	dr[b]	159:167[b]
1	1.2 eq LDA	3.0	75	3:1	5:1
2[c]	1.2 eq LDA	4.0	74	4:1	4:1
3	1.1 eq LDA	1.5	79	3:1	8:1
4	1.1 eq LDA	8.0	69	4:1	9:1
5	1.5 eq LiHMDS	3.0	28	12:1	0.4:1
6	1.05 eq LiHMDS	3.0	53	9:1	1.4:1
7	1.05 eq LiHMDS	1.2	66	4:1	4:1

[a] Yield of the γ-butyrolactone **159**, determined from crude isolated yield and **159**:**167** ratio. [b] Determined from ^{1}H-NMR. [c] HMPA added.

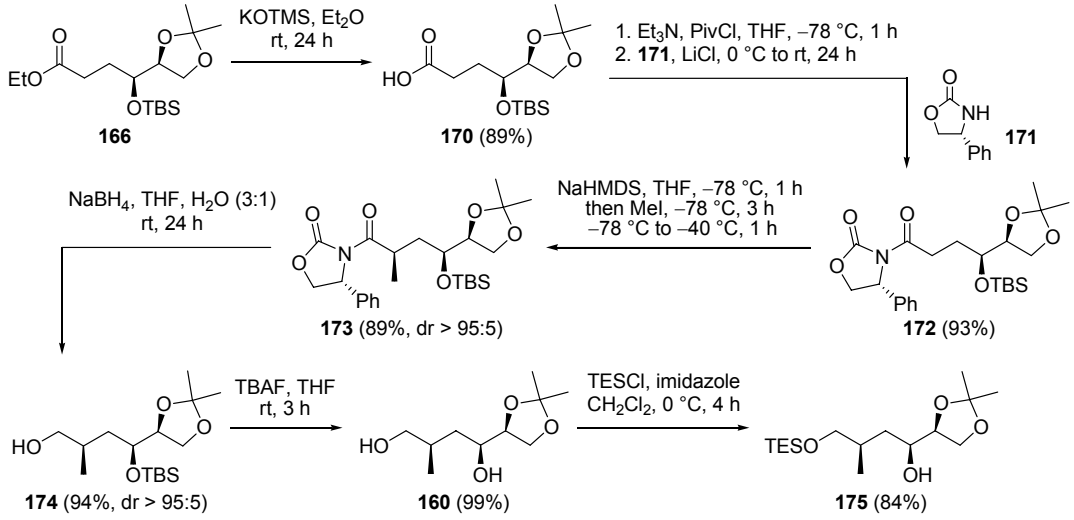


Scheme 46: Diastereoselective methylation – proposed competing pathways.

[82] Li, B.; Buzon, R. A.; Castaldi, M. J. *Org. Proc. Res. Dev.* **2001**, *5*, 609-611.
[83] House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361-2371.
[84] Streitwieser, A.; Kim, Y.-J.; Wang, D. Z.-R. *Org. Lett.* **2001**, *3*, 2599-2601.

6.5.3 *Evans Asymmetric Alkylation*[85]

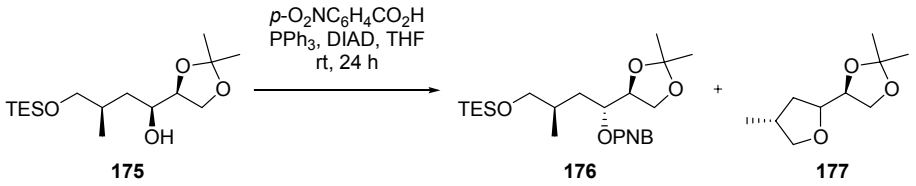
Ester **166** was hydrolyzed under mild conditions with potassium trimethylsilanolate to provide acid **170** (Scheme 47).[86] *N*-acyloxazolidinone **172** was prepared directly from acid **170** employing a one-pot procedure:[87] formation of the mixed anhydride of the acid by treatment with pivaloyl chloride and triethylamine followed by reaction with (*R*)-4-phenyloxazolidin-2-one (**171**) in the presence of lithium chloride.[88] Alkylation of **172** with sodium *bis*(trimethylsilyl)amide and methyl iodide delivered **173** as a single diastereomer (dr > 95:5 according to ^{1}H-NMR).[89] Reductive removal of chiral auxiliary with sodium borohydride in a mixture of THF and water afforded alcohol **174**.[90] Removal of the Evans chiral auxiliary with sodium borohydride is a mild method and proceeds free of racemization. The ensuing desilylation of **174** with tetra-*n*-butylammonium fluoride gave diol **160**, which was selectively protected at the primary hydroxyl as the triethylsilyl ether **175**. The reaction proceeded very fast at room temperature and was accompanied by the formation of significant amount of disilylated side product. Fortunately, the problem could be partially alleviated by lowering the reaction temperature and adding chlorotriethylsilane very slowly to the reaction mixture.



Scheme 47: Modification of the first synthetic approach.

[85] For a similar synthesis see: Ohi, K.; Shima, K.; Hamada, K.; Saito, Y.; Yamada, N.; Ohba, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2433-2440.
[86] Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *23*, 5831-5834.
[87] Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, Jr. J. F. *Tetrahedron* **1988**, *44*, 5525-5540.
[88] Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271-2273.
[89] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.
[90] Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067-7070.

Before chlorine atom could be introduced via S_N2 nucleophilic substitution, the configuration at C-21 had to be inverted. However, the Mitsunobu reaction[19] gave under standard conditions expected substitution product **176** in poor yield along with significant amount of tetrahydrofuran **177** as a side product (Scheme 48).

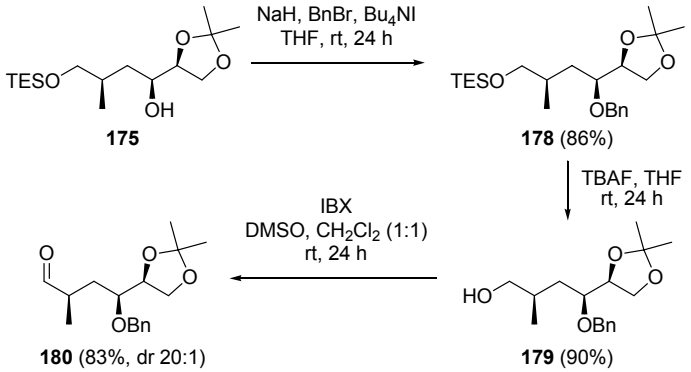


Scheme 48: Attempted Mitsunobu inversion.

Besides discouraging outcome of the Mitsunobu inversion, it is environmentally unfriendly reaction producing phosphine oxide and hydrazide byproducts, which are difficult to separate, thus compromising the elegance of the synthetic route. Although it would be possible to invert C-25 stereochemistry early in the synthesis via intramolecular S_N2 substitution, the present (*S*)-configuration was required for the stereoselective introduction of C-23 methyl group via asymmetric hydroboration or lactone alkylation. Evans asymmetric alkylation, on the contrary, is not dependent upon the configuration at the neighbouring C-25 group, and thus more efficient synthetic route could be developed.

6.6 *Toward the C19-C27 Fragment of Lytophilippine A – Second Approach*

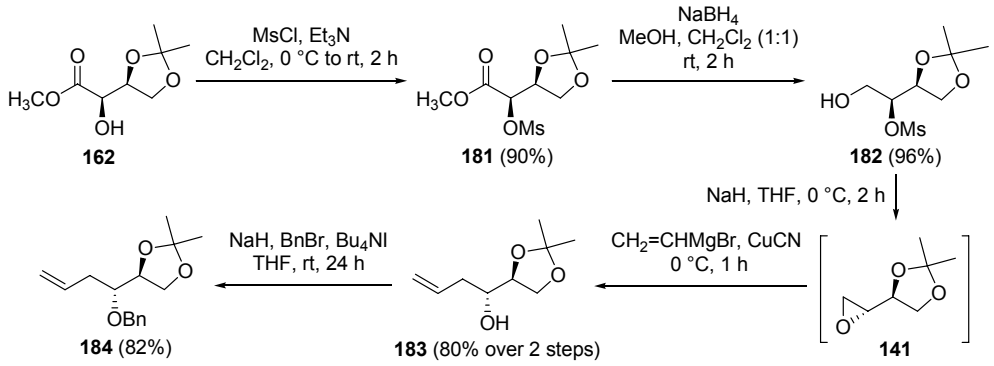
To successfully complete synthesis of the C19–C27 fragment **2**, C-25 hydroxyl group would have to be protected with a group that could be selectively cleaved in the presence of a silyl protecting group. Protection of the already available triethylsilyl ether **175** served as a model reaction to demonstrate the feasibility of the new approach (Scheme 49).



Scheme 49: Exploring the benzyl group introduction.

175 was subjected to benzylation of C-25 hydroxyl group by treatment with benzyl bromide and sodium hydride in THF.[91] Subsequent desilylation delivered alcohol **179** as a stable solid which could be stored at room temperature. Finally, IBX oxidation[92] in a mixture of DMSO and CH_2Cl_2 provided aldehyde **180** (dr = 20:1), a viable precursor for the projected *anti*-selective asymmetric aldol reaction. To efficiently obtain C-25 epimeric aldehyde, second synthetic approach was developed.

The new route started from methyl ester **162**, which was mesylated with methanesulfonyl chloride and triethylamine in CH_2Cl_2 (Scheme 50). Subsequent reduction of the ester functional group in mesylate **181** was performed with sodium borohydride and gave rise to alcohol **182** in excellent yield and purity. Upon exposure to sodium hydride, **182** underwent intramolecular S_N2 substitution to form epoxide **141**, which was treated *in situ* with vinylmagnesium bromide to provide homoallyl alcohol **183** with inverted configuration at C-25. Benzylation under the same conditions as described above for alcohol **179** furnished benzyl ether **184**.

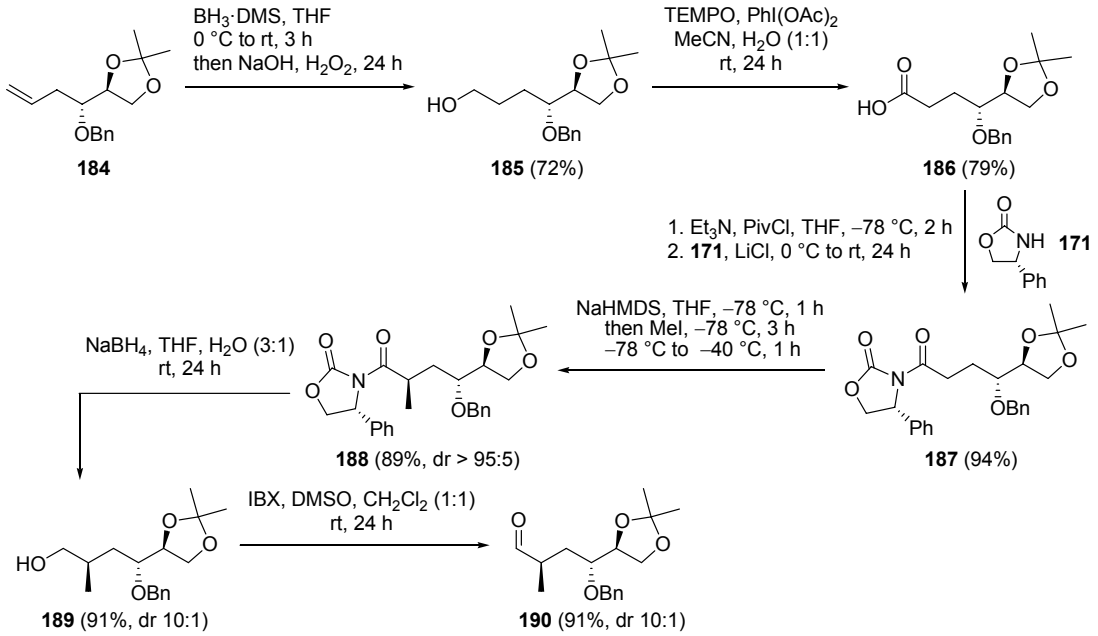


Scheme 50: Second synthetic approach.

Hydroboration of **184** with borane dimethyl sulfide complex,[93] and subsequent oxidation of the intermediate organoborane with sodium hydroxyde and hydrogen peroxide delivered alcohol **185** in acceptable yield accompanied by several unidentified side products, readily separable by flash chromatography (scheme 51).[94] One-pot protocol for direct oxidation of alcohol to carboxylic acid catalyzed by pyridinium chlorochromate in the presence of periodic acid as co-oxidant[95] failed, and no product could be isolated. Fortunately, oxidation catalyzed by TEMPO in the presence of [*bis*(acetoxy)iodo]benzene co-oxidant[96] effected the desired transformation and delivered acid **186** in good yield. In the course of the reaction

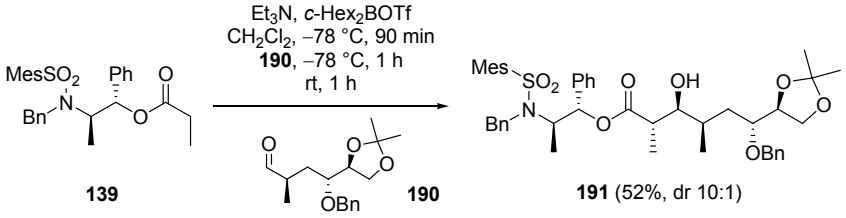
[91] Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *39*, 3535-3536.
[92] Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019-8022.
[93] Yadav, J. S.; Srinivas, C. *Tetrahedron Lett.* **2002**, *43*, 3837-3839.
[94] The use of sterically more demanding borane such as 9-borabicyclo[3.3.1]nonane might improve the yield of the hydroboration reaction.
[95] Hunsen, M. *Synthesis* **2005**, *15*, 2487-2490.
[96] (a) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293-295. (b) de Nooy, A. E. J.; Besemer, A. C. ; van Bekkum, H. *Synthesis* **1996**, *10*, 1153-1174.

[*bis*(acetoxy)iodo]benzene is converted to the toxic iodobenzene, and on a larger scale should be replaced by the more environmentally friendly co-oxidant NaOCl/$NaClO_2$.[97] Formation of the *N*-acyloxazolidinone **187** was followed by stereoselective methylation to afford **188** as a single diastereomer (dr > 95:5) according to ^{1}H-NMR.



Scheme 51: Second synthetic approach.

Removal of the Evans chiral auxiliary with sodium borohydride and following IBX oxidation delivered aldehyde **190** in good yield and diastereoselectivity (dr = 10:1). The stage was now set for the *anti*-selective asymmetric aldol reaction. The kinetic (*E*)-Boron enolate of chiral propionate **139**, formed *in situ* upon treatment with freshly prepared dicyclohexylboron trifluoromethanesulfonate (**154**) and triethylamine, was reacted with aldehyde **190** to give exclusively the expected *anti*-aldol product **191**. Because the diastereomeric ratio of the obtained product reflected the diastereomeric ratio of the aldehyde **190** (dr = 10:1), the minor diastereomer was identified as 23-*epi*-**191**.

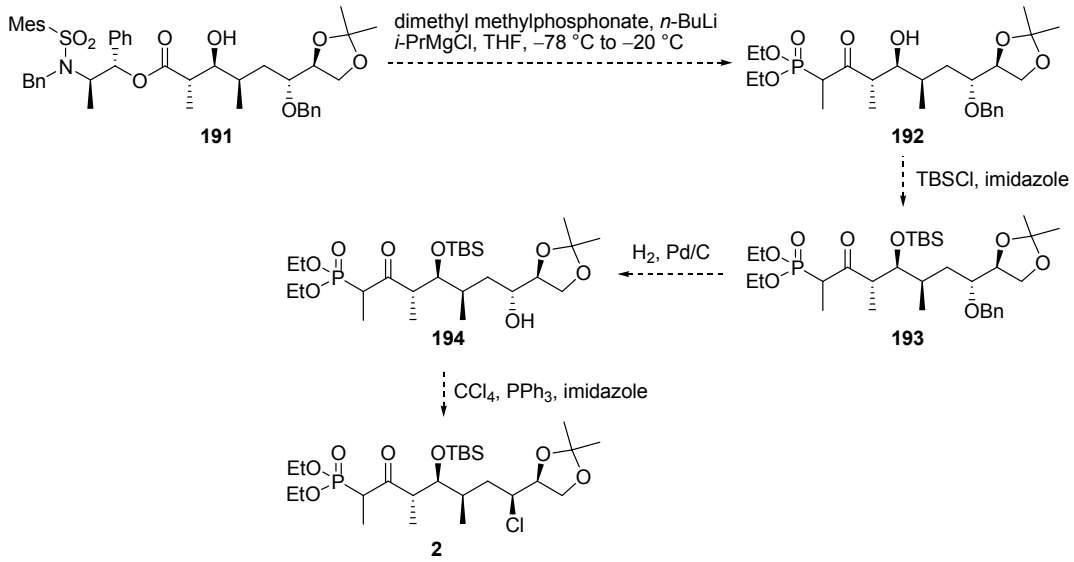


Scheme 52: Asymmetric aldol reaction.

[97] Zhao, M. M. ; Li, J. ; Mano, E. ; Song, Z. J. ; Tschaen, D. M. *Org. Synth.* **2005**, *81*, 195-203.

6.7 *Outlook*

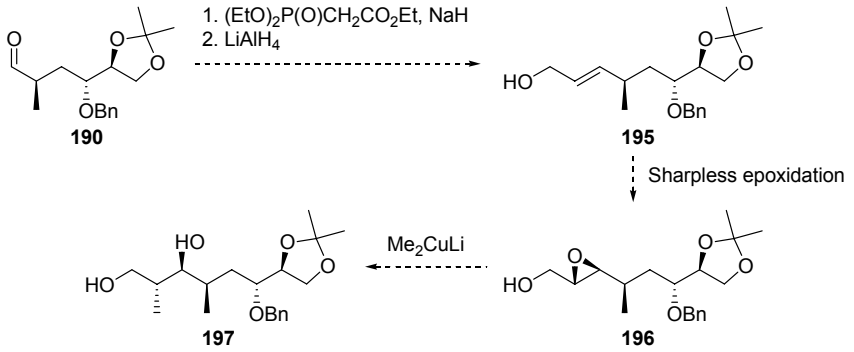
The auxiliary in fragment **191** could be directly displaced by dimethyl methylphosphonate on treatment with isopropylmagnesium chloride and *n*-butyllithium to afford β-ketophosphonate **192**. [98] Protection of free hydroxyl group as TBS ether by treatment with *tert*-butyldimethylsilyl chloride in the presence of imidazole would provide **193**. Benzyl group deprotection would be accomplished by hydrogenolysis, and finally chlorine would be introduced via an S_N2 nucleophilic substitution to provide C19–C27 fragment **2**.



Scheme 53: Proposed synthetic route toward the C19–C27 fragment of lytophilippine A.

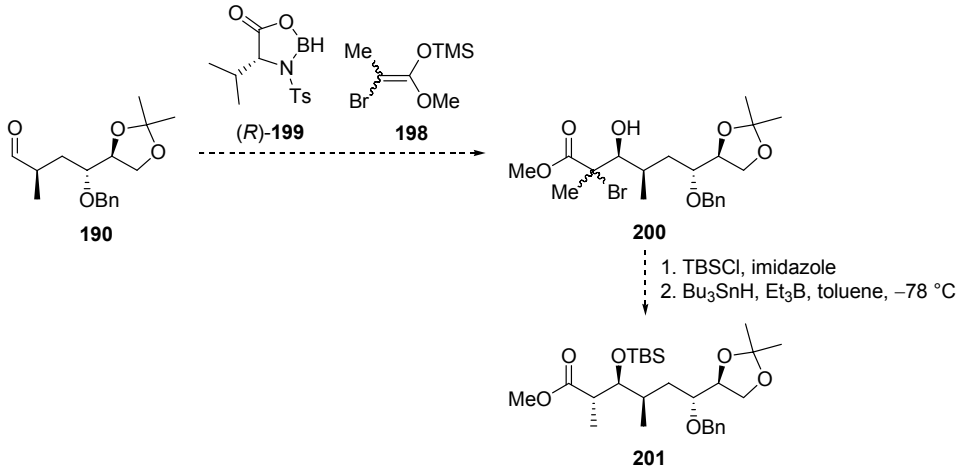
There are several other methods that could be used in place of *anti*-selective asymmetric aldol reaction. The non-aldol strategy that allows access to C21–C23 *anti*, *syn* stereotriad includes regioselective epoxide opening with lithium dimethyl cuprate (Scheme 54),[99] Aldehyde **190** could be converted via (*E*)-selective Horner-Wadsworth-Emmons reaction, and subsequent reduction to allyl alcohol **195**, a precursor for asymmetric Sharpless epoxidation. After epoxidation, cuprate-mediated epoxide opening would provide diol **197** with the desired configuration. However, compared to *anti*-selective aldol reaction, this strategy would require significantly more synthetic effort.

[98] Li, J.; Li, P.; Menche, D. *Synlett* **2009**, *15*, 2417-2420.
[99] (a) Kishi, Y.; Nagaoka, H. *Tetrahedron* **1981**, *37*, 3873-3888. (b) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307-309. (c) Jung, M. E.; Chaumontet, M.; Salehi-Rad, R. *Org. Lett.* **2010**, *12*, 2872-2875. (d) Reiss, T.; Breit, B. *Org. Lett.* **2009**, *11*, 3286-3289.



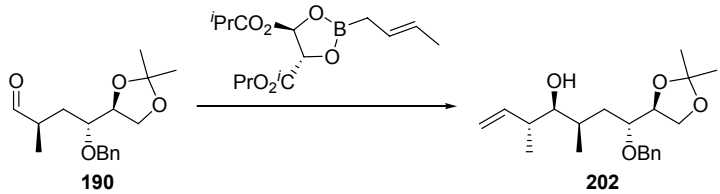
Scheme 54: Proposed alternative approach to stereotriad featuring regioselective epoxide opening.

Another efficient strategy would utilize highly diastereoselective Mukaiyama aldol reaction in combination with free radical reduction (Scheme 55).[100] Aldehyde **190** could react with silylketene acetal **198** in the presence of chiral borane (*R*)-**199**, prepared *in situ* by stirring *N*-*p*-toluenesulfonyl-(*R*)-valine and BH_3·THF in dichloromethane, to provide aldol adduct **200**. Subsequent TBS protection of the free hydroxyl group, and radical debromination would afford **201** with the C21–C23 *anti*, *syn* stereotriad.



Scheme 55: Tandem sequence of Mukaiyama aldol reaction and subsequent free radical reduction.

Well-established Roush crotylboration[101] could also be employed to install the required *anti*-3-hydroxy-2-methylcarbonyl unit (Scheme 56).



Scheme 56: Roush asymmetric crotylboration.

[100] Kiyooka, S.-I.; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967-7978.
[101] Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348.

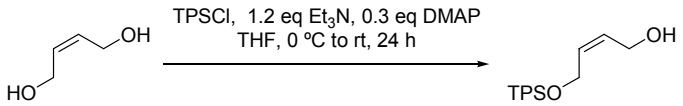
7. Experimental Part

7.1 *Working Techniques, Chemicals and Equipment*

Air and moisture sensitive reactions were carried out in heat gun-dried glassware under an argon atmosphere. Et_3N and diisopropylamine were dried by distillation over CaH_2 and stored over molecular sieves. MeOH was refluxed over Mg-turnings for 3 h, distilled and stored over molecular sieves. THF, CH_2Cl_2, MeCN and Et_2O were dried using MB-SPS 800 solvent purification system. Anhydrous DMSO and DMF were purchased from commercial sources. Cyclohexane and EtOAc for flash chromatography were distilled prior to use. pH 7 buffer was prepared by dissolving 1.42 g Na_2HPO_4 and 0.67 g NaH_2PO_4 in 100 mL H_2O. The concentration of *n*-BuLi and *t*-BuLi were determined by titration using diphenylacetic acid as an indicator.[102] **Flash chromatography**[103] was performed using silica gel 60 (40-63 μm) from Merck. Analytical **thin layer chromatography** was performed on Merck Silicagel 60 F254 plates. Visualization of substances was achieved by immersing the developed TLC plate briefly into *p*-anisaldehyde/sulfuric acid (23 mL anisaldehyde, 8.8 mL CH_3COOH, 835 mL EtOH and 31 mL conc. H_2SO_4) or phosphomolybdic acid/cerium(IV)-sulfate (25 g phosphomolybdic acid hydrate, 10 g cerium(IV)-sulfate, 60 mL conc. H_2SO_4 and 940 mL H_2O) reagent, and then heating the plate with a heat gun at 200 °C.[104] **Preparative HPLC** separation was performed on a Nucleosil 50-5 column (32 × 237) using heptane-EtOAc (25:1) as an eluent. The flow rate was 26 mL/min. **NMR spectra** were recorded on a Bruker DRX 400 (^{1}H: 400.1 Mhz, ^{13}C: 100.6 Mhz) or Bruker DRX 500 (^{1}H: 500.1 Mhz, ^{13}C: 125.8 Mhz). The signals in spectra were referenced against the residual protic solvent signal ($CDCl_3$: δ_H 7.26 ppm, δ_C 77.0 ppm; d6-acetone: δ_H 2.05 ppm, δ_C 29.8 ppm). The signal multiplicity was denoted using standard abbreviations (s: singlet, d: doublet, t: triplet, br: broad, dd: doublet of doublets, ddd: doublet of doublets of doublets, m: multiplet). The multiplicity in ^{13}C-NMR-spectra was assigned based on APT or DEPT-135 experiments. **FT-IR spectra** were recorded on Nicolet 320 FT-IR spectrometer. The characteristic IR absorption bands are represented in cm^{-1}. **Specific rotation values** $[\alpha]_D^{temp}$ of chiral compounds were measured on Perkin Elmer polarimeter 341 LC. All measurements were performed at a wavelength of 589 nm (sodium D-line). The concentration of compounds is given in g/100 mL. **Elemental analyses** were determined with a Leco CHNS-932.

[102] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879-1880.
[103] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
[104] All substances from "berkelic acid project" were visualized using anisaldehyde reagent and those from "lytophilippine project" with phosphomolybdic acid reagent.

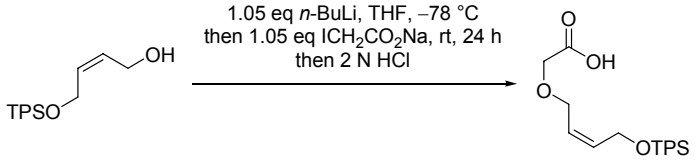
7.2 *Synthesis of Allyl Vinyl Ether*



86 **106** (84%)

alcohol 106: Et_3N (7.3 mL, 52.4 mmol, 1.2 eq) and DMAP (1.6 g, 13 mmol, 0.3 eq) were added sequentially to a solution of (*Z*)-2-butene-1,4-diol (**86**) (19 mL, 227 mmol, 5.2 eq) in THF (100 mL, 2.3 mL/mmol TPSCl) at 0 ºC. After the reaction mixture had been stirred for 5 min, a solution of TPSCl (12.0 g, 43.7 mmol, 1 eq) in THF (44 mL, 1 mL/mmol TPSCl) was added dropwise within 1 h. The resulting suspension was then allowed to warm to rt and stirred for 24 h. The solvent was removed under reduced pressure, the residue quenched with saturated aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1 to cyclohexane–EtOAc 3:1) afforded **106** (12 g, 84%) as a colorless oil.

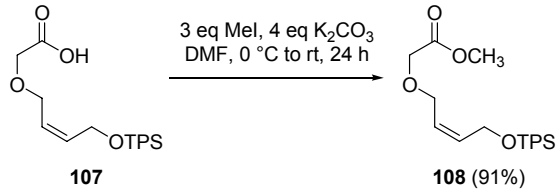
R_f = 0.37 (cyclohexane–EtOAc 3:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.68-7.70 (m, 4H), 7.38-7.46 (m, 6H), 5.61-5.75 (m, 2H), 4.26 (d, J = 5.6 Hz, 2H), 4.01 (d, J = 6.0 Hz, 2H), 1.54 (br, 1H), 1.05 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 135.6 (4 × CH), 133.4 (2 × C), 130.9 (CH), 129.9 (CH), 129.7 (2 × CH), 127.7 (4 × CH), 60.2 (CH_2), 58.7 (CH_2), 26.7 (3 × CH_3), 19.1 (C); IR (neat) ν 3342, 3071, 2958, 2891, 1472, 1112. Anal. Calcd. for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03, Found: C, 73.7; H, 7.8.



106 **107** (99%)

acid 107: *n*-BuLi in hexane (36.8 mmol, 1.05 eq) was added slowly to a solution of allyl alcohol **106** (11.5 g, 35.1 mmol, 1 eq) in THF (35 mL, 1 mL/mmol **106**) at –78 °C. The reaction mixture was then allowed to warm to rt and stirred for 1 h until the solution color turned light brown. Subsequently, ICH_2CO_2Na (7.66 g, 36.8 mmol, 1.05 eq) was added at once. After the reaction had been stirred for 24 h at rt, it was quenched with H_2O (20 mL) and acidified with 2N HCl (40 mL). The product was extracted with CH_2Cl_2 (3 × 60 mL), the combined organic phases were washed with saturated brine (60 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude acid **107** (13.4 g, 99%) as a dark-brown thick oil which was used in the next step without further purification.

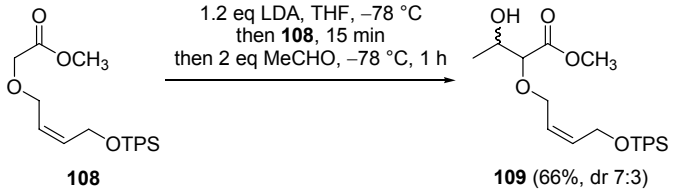
^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.66-7.68 (m, 4H), 7.37-7.46 (m, 6H), 5.80-5.86 (m, 1H), 5.54-5.60 (m, 1H), 4.25 (d, J = 6.0 Hz, 2H), 4.01 (d, J = 6.8 Hz, 2H), 3.99 (s, 2H), 1.05 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 174.0 (C), 135.5 (4 × CH), 133.4 (CH), 133.3 (2 × C), 129.7 (2 × CH), 127.7 (4 × CH), 125.6 (CH), 67.1 (CH_2), 66.6 (CH_2), 60.2 (CH_2), 26.7 (3 × CH_3), 19.1 (C).



107 **108** (91%)

ester 108: To a solution of acid **107** (13.4 g, 34.8 mmol, 1 eq) in DMF (70 mL, 2 mL/mmol **107**) was added K_2CO_3 (19.2 g, 139 mmol, 4 eq). The suspension was stirred for 30 min and cooled down to 0 °C, before MeI (6.6 mL, 105 mmol, 3 eq) was added. The reaction was allowed to warm to rt and stirred 24 h before being poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with H_2O (200 mL), 2N HCl (150 mL) and again with H_2O (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained yellow oil was purified by flash chromatography (cyclohexane–EtOAc 20:1) to afford **108** (12.6 g, 91%) as a colorless oil.

R_f = 0.43 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.64-7.71 (m, 4H), 7.35-7.47 (m, 6H), 5.76-5.86 (m, 1H), 5.54-5.64 (m, 1H), 4.25 (d, J = 5.8 Hz, 2H), 3.99 (d, J = 7.0 Hz, 2H), 3.97 (s, 2H), 3.71 (s, 3H), 1.05 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 170.6 (C), 135.5 (4 × CH), 133.4 (CH), 133.0 (2 × C), 129.7 (2 × CH), 127.7 (4 × CH), 126.0 (CH), 67.1 (CH_2), 67.0 (CH_2), 60.2 (CH_2), 51.8 (CH_3), 26.7 (3 × CH_3), 19.1 (C); IR (neat) ν 2954, 2857, 1757, 1428, 1112. Anal. Calcd. for $C_{23}H_{30}O_4Si$: C, 69.31; H, 7.59, Found: C, 69.4; H, 7.6.

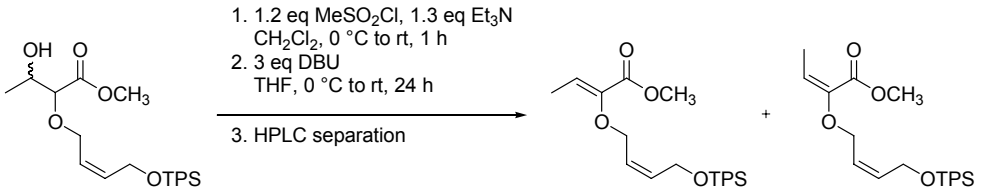


108 **109** (66%, dr 7:3)

β-hydroxyester 109: LDA was prepared in situ by adding *n*-BuLi in hexane (33.7 mmol, 1.2 eq) to a solution of diisopropylamine (5.1 mL, 36.5 mmol, 1.3 eq) in THF (56 mL, 2 mL/mmol **108**) at –78°C. Methyl ester **108** (11.2 g, 28.1 mmol, 1 eq) was dissolved in THF (56 mL, 2 mL/mmol **108**), cooled down to –78 °C and then added to a solution of LDA. After stirring the reaction mixture for 15 min, a freshly distilled and to –78 °C precooled MeCHO (3.2 mL, 56.2 mmol, 2 eq) was added. After 1 h the mixture was quenched with saturated aq.

NH_4Cl (80 mL) and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 10:1 to cyclohexane–EtOAc 3:1) afforded **109** (8.2 g, 66%, dr 7:3) as a yellow oil.

R_f = 0.30 (cyclohexane–EtOAc 3:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.63-7.72 (m, 4H), 7.34-7.50 (m, 6H), 5.74-5.86 (m, 1H), 5.53-5.65 (m, 1H), 4.25 (d, J = 5.2 Hz, 2H), 4.08-4.17 (m, 1H), 3.88-4.07 (m, 2H), 3.80 (d, J = 4.4 Hz, $1H^{major}$), 3.69 (s, 3H), 3.64 (d, J = 5.2 Hz, $1H^{minor}$), 2.34 (br s, 1H), 1.14-1.21 (m, 3H), 1.05 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 171.1 (C), 135.5 (4 × CH), 133.4 (2 × C), 132.9 (CH), 129.7 (2 × CH), 127.7 (4 × CH), 126.0 (CH), 81.7 (CH), 68.3 (CH), 66.6 (CH_2), 60.3 (CH_2), 51.9 (CH_3), 26.7 (3 × CH_3), 19.1 (CH_3), 18.1 (C); IR (neat) ν 3475, 2955, 2858, 1749, 1428, 1112. Anal. Calcd. for $C_{25}H_{34}O_5Si$: C, 67.84; H, 7.74, Found: C, 68.1; H, 7.8.



109 **85** (90%, *Z*:*E* = 3:2)

allyl vinyl ether 85: Et_3N (3.2 mL, 22.9 mmol, 1.3 eq) and $MeSO_2Cl$ (1.65 mL, 21.1 mmol, 1.2 eq) were added sequentially to a solution of β-hydroxy ester **109** (7.79 g, 17.6 mmol, 1 eq) in CH_2Cl_2 (53 mL, 3 mL/mmol **109**) at 0 °C. The mixture was allowed to warm to rt and stirred for 1 h before being quenched with saturated aq. $NaHCO_3$ (50 mL). The product was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was dissolved in THF (53 mL, 3 mL/mmol **109**), the solution cooled down to 0 °C, and DBU (7.9 mL, 52.9 mmol, 3 eq) added. The mixture was allowed to warm to rt and stirred for 24 h. After quenching with H_2O (50 mL), the product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1) gave 3:2 mixture of (*Z*,*Z*)-**85**:(*E*,*Z*)-**85** (6.73 g, 90% over two steps), which were separated by preparative HPLC (R_t(*Z*,*Z*) = 31.5 min, R_t(*E*,*Z*) = 38.0 min; baseline separation with 200 mg/injection) to provide (*Z*,*Z*)-**85** and (*E*,*Z*)-**85**[105] as colorless oils.

[105] To obtain (*E*,*Z*)-**5** completely free of (*Z*,*Z*)-**5** (<5%), second HPLC separation was needed.

R_f = 0.35 (cyclohexane–EtOAc 10:1)

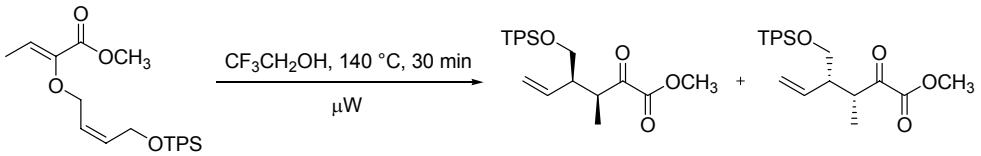
(*Z*,*Z*)-**85**

^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.62-7.71 (m, 4H), 7.34-7.48 (m, 6H), 6.32 (q, *J* = 7.1 Hz, 1H), 5.76-5.84 (m, 1H), 5.63-5.72 (m, 1H), 4.26 (d, *J* = 5.6 Hz, 4H), 3.68 (s, 3H), 1.71 (d, *J* = 7.2 Hz, 3H), 1.04 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 164.2 (C), 145.3 (C), 135.5 (4 × CH), 133.5 (2 × C), 132.9 (CH), 129.7 (2 × CH), 127.7 (4 × CH), 125.9 (CH), 124.8 (CH), 67.7 (CH_2), 60.2 (CH_2), 51.8 (CH_3), 26.7 (3 × CH_3), 19.1 (C), 11.4 (CH_3); IR (neat) *v* 2932, 2857, 1726, 1112. Anal. Calcd. for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60, Found: C, 70.8; H, 7.5.

(*E*,*Z*)-**85**

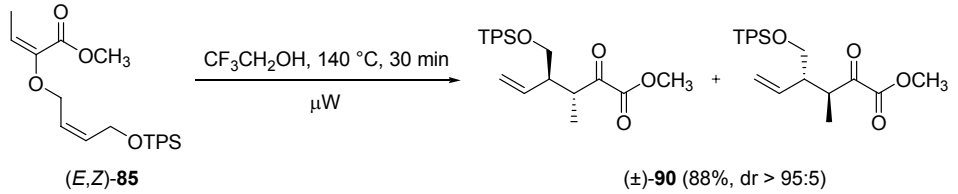
^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.67-7.73 (m, 4H), 7.35-7.48 (m, 6H), 5.76-5.85 (m, 1H), 5.60-5.70 (m, 1H), 5.26 (q, *J* = 7.4 Hz, 1H), 4.29 (d, *J* = 5.8 Hz, 2H), 4.19 (d, *J* = 5.8 Hz, 2H), 3.76 (s, 3H), 1.95 (d, *J* = 7.4 Hz, 3H), 1.07 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 164.0 (C), 144.7 (C), 135.5 (4 × CH), 133.3 (2 × C), 132.1 (CH), 129.7 (2 × CH), 127.7 (4 × CH), 125.6 (CH), 112.2 (CH), 64.9 (CH_2), 60.5 (CH_2), 51.7 (CH_3), 26.7 (3 × CH_3), 19.1 (C), 12.5 (CH_3); IR (neat) *v* 2931, 2857, 1726, 1112. Anal. Calcd. for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60, Found: C, 70.6; H, 7.5.

7.3 *Uncatalyzed Gosteli-Claisen Rearrangment*



(*Z*,*Z*)-**85** (±)-**84** (95%, dr > 95:5)

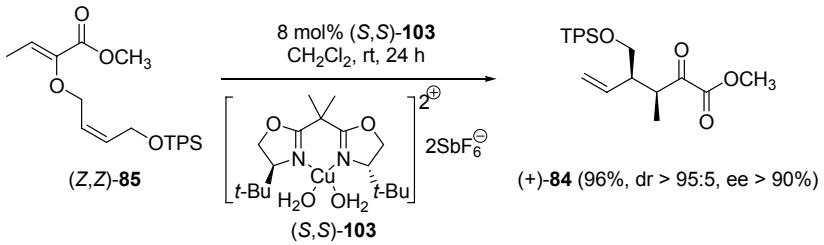
α-ketoester (±)-**84**: (*Z*,*Z*)-**85** (200 mg, 0.47 mmol) and CF_3CH_2OH (3 mL, 6.4 mL/mmol **85**) were placed in a 5 mL vial equipped with a magnetic stirring bar, and then sealed with a Teflon septum and an alumina crimp top. The vessel was inserted into the microwave cavity of the CEM Discover^{TM}, irradiated at 140 °C for 30 min (power 250 W), and subsequently cooled by rapid gas-jet cooling. The solvent was removed under reduced pressure, and the crude product purified by flash chromatography (cyclohexane–EtOAc 20:1) to yield (±)-**84** (190 mg, 95%, dr > 95:5) as a colorless oil.



(*E*,*Z*)-**85** (±)-**90** (88%, dr > 95:5)

α-ketoester (±)-**90**: (*E*,*Z*)-**85** (200 mg, 0.47 mmol) and CF_3CH_2OH (3 mL, 6.4 mL/mmol **85**) were placed in a 5 mL vial equipped with a magnetic stirring bar, and then sealed with a Teflon septum and an alumina crimp top. The vessel was inserted into the microwave cavity of the CEM Discover™, irradiated at 140 °C for 30 min (power 250 W) and subsequently cooled by rapid gas-jet cooling. The solvent was removed under reduced pressure, and the crude product purified by flash chromatography (cyclohexane–EtOAc 20:1) to yield (±)-**90** (175 mg, 88%, dr > 95:5) as a colorless oil.

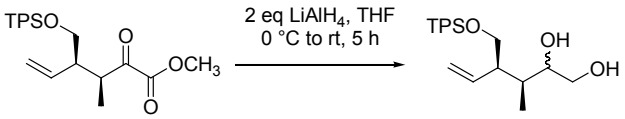
7.4 *Catalytic Asymmetric Gosteli-Claisen Rearrangment of (Z,Z)-85*



(*Z*,*Z*)-**85** (*S*,*S*)-**103** (+)-**84** (96%, dr > 95:5, ee > 90%)

α-ketoester (+)-**84**: To a solution of [Cu{(*S*,*S*)-*tert*-Bu-box}]$(H_2O)_2(SbF_6)_2$ **103** (81 mg, 0.094 mmol, 8 mol%) in CH_2Cl_2 (3 mL, 3 mL/mmol **85**) was added (*Z*,*Z*)-**85** (0.5 g, 1.18 mmol, 1 eq) in CH_2Cl_2 (3 mL, 3 mL/mmol **85**) at rt. The solution was stirred for 24 h before it was filtered through a short plug of silica to remove the catalyst. Evaporation of the solvent and purification by flash chromatography (cyclohexane–EtOAc 20:1) furnished the α-ketoester (+)-**84** (478 mg, 96%, dr > 95:5, ee > 90%) [106] as a clear oil: R_f 0.34 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.62-7.64 (m, 4H), 7.36-7.45 (m, 6H), 5.81 (ddd, J = 8.7, 10.3, 17.3 Hz, 1H), 5.00-5.08 (m, 2H), 3.80 (s, 3H), 3.65-3.67 (m, 2H), 3.56-3.63 (m, 1H), 2.67-2.73 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 1.04 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 196.7 (C), 161.8 (C), 136.8 (CH), 135.6 (4 × CH), 133.3 (C), 133.1 (C), 129.7 (2 × CH), 127.6 (4 × CH), 117.5 (CH_2), 64.1 (CH_2), 52.7 (CH_3), 48.3 (CH), 42.6 (CH), 26.7 (3 × CH_3), 19.2 (C), 12.5 (CH_3); IR (neat) ν 2930, 2860, 1730, 1430, 1112, 703. Anal. Calcd. for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60, Found: C, 70.6; H, 7.6; $[\alpha]^{25}_D$ +38.1 (*c* 1.0, $CHCl_3$).

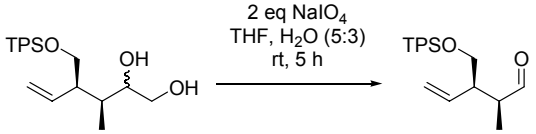
[106] Diastereoselectivity determined from ^{1}H-NMR; Enantioselectivity determined via Mosher's method.



(+)-**84** **114** (94%, dr 2:1)

diol 114: α-Ketoester (+)-**84** (605 mg, 1.42 mmol, 1 eq) was dissolved in THF (5 mL, 3.5 mL/mmol **84**) and the solution cooled down to 0 °C. $LiAlH_4$ (108 mg, 2.84 mmol, 2 eq) was added in small portions over a period of 2 min and the resulting suspension warmed up to rt and stirred for 5 h. The reaction mixture was then cooled down to 0 °C and excessive $LiAlH_4$ was destroyed by slow addition of pH 7 buffer (5 mL). The product was extracted with EtOAc (3 × 20 mL), the combined organic phases were dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 10:1 to 3:1) afforded **114** (533 mg, 94%, dr 2:1)[107] as a colorless oil.

R_f = 0.39 (cyclohexane–EtOAc 1:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.64-7.73 (m, 4H), 7.36-7.50 (m, 6H), 5.71-5.85 (m, 1H), 4.94-5.14 (m, 2H), 3.13-3.94 (series of multiplets, 6H), 2.26-2.60 (series of multiplets, 2H), 1.74-2.03 (m, 1H), 1.08 (s, 9H), 0.90 (d, J = 7.0 Hz, 3H^{minor}), 0.86 (d, J = 7.0 Hz, 3H^{major}); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 139.0 (CH^{minor}), 137.8 (CH^{major}), 135.5-135.6 (4 × CH), 133.0 (2 × C^{minor}), 132.6 (2 × C^{major}), 129.8 (2 × CH^{major}), 129.8 (2 × CH^{minor}), 127.8 (4 × CH^{major}), 127.7 (4 × CH^{minor}), 116.5 (CH_2^{major}), 116.2 (CH_2^{minor}), 74.0 (CH^{major}), 73.7 (CH^{minor}), 65.7 (CH_2^{minor}), 64.8 (2 × CH_2^{major}), 64.4 (CH_2^{minor}), 49.8 (CH^{minor}), 47.2 (CH^{major}), 38.2 (CH^{major}), 36.4 (CH^{minor}), 26.8 (3 × CH_3), 19.2 (C^{minor}), 19.1 (C^{major}), 12.8 (CH_3^{major}), 9.6 (CH_3^{minor}); IR (neat) ν 3387, 2931, 2857, 1384, 1112, 702. Anal. Calcd. for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60, Found: C, 72.0; H, 8.4.; $[\alpha]^{25}_D$ +19.9 (*c* 1.01, $CHCl_3$).

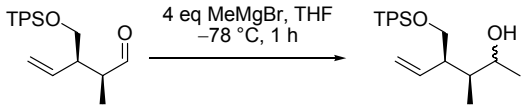


114 **115** (90%)

aldehyde 115: To a solution of diol **114** (1.39 g, 3.49 mmol, 1 eq) in 5:3 THF/H_2O (16 mL, 4.6 mL/mmol **114**) was added $NaIO_4$ (1.49 g, 6.97 mmol, 2 eq). The resulting suspension was stirred for 5 h at rt before being diluted with H_2O (6 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The CH_2Cl_2 extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1) afforded aldehyde **115** (1.15 g, 90%) as a colorless oil.

[107] Diastereoselectivity determined from ^{1}H-NMR.

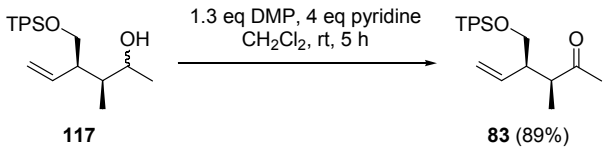
R_f = 0.35 (cyclohexane–EtOAc 20:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 9.76 (d, J = 1.2 Hz, 1H), 7.60-7.70 (m, 4H), 7.35-7.49 (m, 6H), 5.76 (ddd, J = 8.2 Hz, 10.4 Hz, 17.3 Hz, 1H), 5.01-5.14 (m, 2H), 3.67 (d, J = 6.4 Hz, 2H), 2.70-2.81 (m, 1H), 2.55-2.65 (m, 1H), 1.09 (d, J = 7.0 Hz, 3H), 1.04 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 204.6 (CH), 136.4 (CH), 135.6 (4 × CH), 133.1 (2 × C), 129.7 (2 × CH), 127.7 (4 × CH), 117.4 (CH_2), 64.0 (CH_2), 47.2 (2 × CH), 26.7 (3 × CH_3), 19.2 (C), 9.9 (CH_3); IR (neat) ν 2931, 2858, 1726, 1428, 1112, 702. Anal. Calcd. for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25, Found: C, 75.1; H, 8.0.; $[\alpha]^{25}_D$ +47.7 (c 1.11, $CHCl_3$).



115 **117** (94%, dr 2:1)

alcohol 117: To a solution of **115** (1.12 g, 3.05 mmol, 1 eq) in THF (6 mL, 2 mL/mmol **115**) at –78 °C was slowly added 1.0 M MeMgBr solution in THF (12.2 mL, 12.2 mmol, 4 eq). The mixture was stirred at this temperature for 1 h and then quenched with saturated aq. NH_4Cl (10 mL). The product was extracted with EtOAc (3 × 60 mL), the combined organic layers dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chomatography (cyclohexane–EtOAc 20:1 to 2:1) to afford **117** (1.1 g, 94%, dr 2:1)[107] as a colorless oil.

R_f = 0.54 (cyclohexane–EtOAc 3:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.62-7.75 (m, 4H), 7.33-7.50 (m, 6H), 5.72-5.88 (m, 1H), 4.92-5.13 (m, 2H), 3.58-4.08 (series of multiplets, 3H), 2.14-2.76 (series of multiplets, 2H), 1.60-1.84 (m, 1H), 1.19 (d, J = 6.5 Hz, 3H^{major}), 1.15 (d, J = 6.2 Hz, 3H^{minor}), 1.06 (s, 9H), 0.90 (d, J = 7.0 Hz, 3H^{major}), 0.85 (d, J = 7.0 Hz, 3H^{minor}); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 139.7 (CH), 135.6 (4 × CH), 133.2 (2 × C), 129.7 (2 × CH), 127.7 (4 × CH), 115.8 (CH_2), 69.1 (CH), 64.7 (CH_2), 50.2 (CH), 40.6 (CH), 26.8 (3 × CH_3), 21.2 (CH_3), 19.2 (C), 8.7 (CH_3); IR (neat) ν 3433 (br), 2964, 2931, 2858, 1428, 1112, 702. Anal. Calcd. for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96, Found: C, 75.2; H, 9.0; $[\alpha]^{25}_D$ +25.8 (c 1.16, $CHCl_3$).

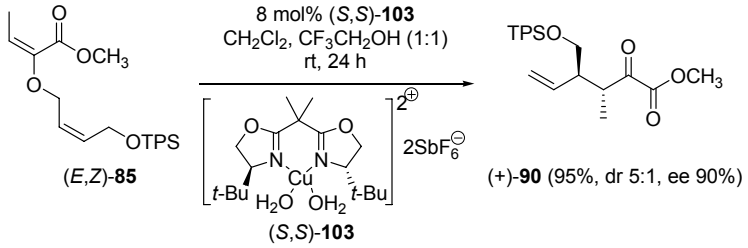


117 **83** (89%)

ketone 83: To a solution of **117** (1.1 g, 2.87 mmol, 1 eq) in CH_2Cl_2 (6 mL, 2 mL/mmol **117**) was added pyridine (0.91 g, 11.5 mmol, 4 eq) and DMP[108] (1.6 g, 3.8 mmol, 1.3 eq). The white suspension was stirred for 5 h at rt before being quenched with saturated aq. $Na_2S_2O_3$ (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc 20:1) to afford **83** (0.98 g, 89%) as a colorless oil.

R_f = 0.27 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.64-7.66 (m, 4H), 7.37-7.45 (m, 6H), 5.77-5.86 (m, 1H), 5.00-5.08 (m, 2H), 3.67 (d, J = 5.2 Hz, 2H), 2.82 (m, 1H), 2.43-2.49 (m, 1H), 2.12 (s, 3H), 1.04-1.05 (m, 12H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 211.8 (C), 137.7 (4 × CH), 135.6 (CH), 133.4 (2 × C), 129.7 (2 × CH), 127.6 (4 × CH), 116.9 (CH_2), 64.3 (CH_2), 48.6 (CH), 47.6 (CH), 29.4 (CH_3), 26.8 (3 × CH_3), 19.3 (C), 13.7 (CH_3); IR (neat) ν 2931, 2858, 1713, 1428, 1112, 703. Anal. Calcd. for $C_{24}H_{32}O_2Si$: C, 75.74; H, 8.47, Found: C, 75.6; H, 8.3.; $[\alpha]^{25}_D$ +31.8 (c 0.97, $CHCl_3$).

7.5 *Catalytic Asymmetric Gosteli-Claisen Rearrangment of (E,Z)-85*

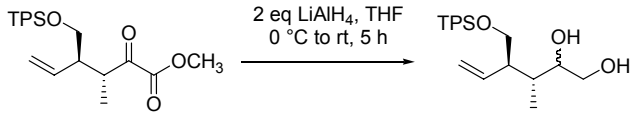


(*E*,*Z*)-**85** (*S*,*S*)-**103** (+)-**90** (95%, dr 5:1, ee 90%)

α-ketoester (+)-90: To a solution of [Cu{(*S*,*S*)-*tert*-Bu-box}]$(H_2O)_2(SbF_6)_2$ **103** (384 mg, 0.44 mmol, 8 mol%) in CF_3CH_2OH (11 mL, 2 mL/mmol **85**) was added (*E*,*Z*)-**85** (2.36 g, 5.55 mmol) in CH_2Cl_2 (17 mL, 3 mL/mmol **85**) at rt. The solution was stirred for 24 h, then the solvent was evaporated under reduced pressure, and the residue filtered through a short plug of silica gel (cyclohexane–EtOAc 1:1). Additional purification by flash chromatography (cyclohexane–EtOAc 50:1 to 20:1) furnished α-ketoester (+)-**90** (2.24 g, 95%, dr 5:1, 90% ee)[106] as a clear oil.

[108] DMP was synthesized in two steps (58%) starting from 2-iodobenzoic acid: a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538. b) Ireland, R. E.; Longbin, L. *J. Org. Chem.* **1993**, *58*, 2899.

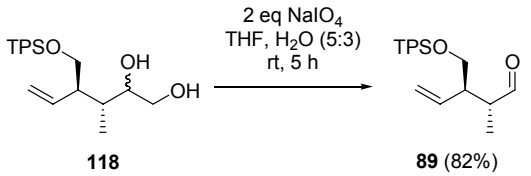
R_f = 0.35 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.62-7.64 (m, 4H), 7.36-7.45 (m, 6H), 5.54 (ddd, J = 17.1, 10.4, 9.3 Hz, 1H), 4.98-5.08 (m, 2H), 3.80 (s, 3H), 3.57-3.66 (m, 3H), 2.75-2.83 (m, 1H), 1.03-1.07 (m, 12H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 196.6 (C), 161.7 (C), 135.5 (4 × CH), 135.0 (CH), 133.2 (C), 133.1 (C), 129.7 (2 × CH), 127.6 (4 × CH), 118.5 (CH_2), 65.3 (CH_2), 52.7 (CH_3), 48.0 (CH), 42.4 (CH), 26.7 (3 × CH_3), 19.2 (C), 12.4 (CH_3); IR (neat) ν 2932, 2858, 1731, 1428. Anal. Calcd. for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60, Found: C, 70.8; H, 7.5; $[\alpha]^{25}_D$ +4.3 (c 0.99, $CHCl_3$).



(+)-**90** **118** (78%, dr 2:1)

diol 118: α-Ketoester (+)-**90** (2.22 g, 5.2 mmol, 1 eq) was dissolved in THF (25 mL, 5 mL/mmol **90**) and the solution cooled down to 0 °C. $LiAlH_4$ (0.4 g, 10.5 mmol, 2 eq) was added in small portions over a period of 2 min and the resulting suspension warmed up to rt and stirred for 5 h. The reaction mixture was then cooled down to 0 °C and excessive $LiAlH_4$ was destroyed by slow addition of pH 7 buffer (10 mL). The product was extracted with EtOAc (3 × 50 mL), the combined organic phases were dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc 10:1 to 3:1) to afford **118** (1.63 g, 78%, dr 2:1)[107] as a colorless oil.

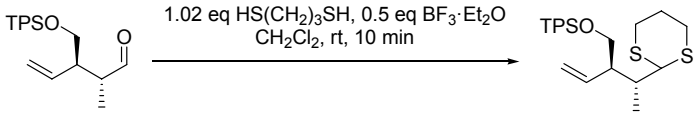
R_f = 0.20 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.67-7.69 (m, 4H), 7.38-7.46 (m, 6H), 5.61-5.83 (m, 1H), 4.97-5.11 (m, 2H), 3.48-3.82 (series of multiplets, 5H), 2.28-2.89 (series of multiplets, 3H), 1.79-1.98 (m, 1H), 1.07 (s, 9H), 0.90 (d, J = 7.0 Hz , $3H^{minor}$), 0.77 (d, J = 7.0 Hz, $3H^{major}$); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 137.3 (CH^{minor}), 136.4 (CH^{major}), 135.6 (4 × CH^{major}), 135.5 (4 × CH^{minor}), 133.5 (2 × C^{major}), 133.2 (2 × C^{minor}), 129.7 (2 × CH^{minor}), 129.6 (2 × CH^{major}), 127.7 (4 × CH^{minor}), 127.6 (4 × CH^{major}), 117.8 (CH_2^{major}), 117.4 (CH_2^{minor}), 74.4 (CH^{major}), 73.9 (CH^{minor}), 65.4 (CH_2^{major}), 65.2 (CH_2^{minor}), 65.0 (CH_2^{major}), 64.8 (CH_2^{minor}), 49.1 (CH^{minor}), 46.9 (CH^{major}), 36.3 (CH^{minor}), 36.1 (CH^{major}), 26.8 (3 × CH_3), 19.2 (C), 11.3 (CH_3^{major}), 10.6 (CH_3^{minor}); IR (neat) ν 3381, 2931, 2858, 1428. Anal. Calcd. for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60, Found: C, 72.2; H, 8.6; $[\alpha]^{25}_D$ +16.7 (c 0.905, $CHCl_3$).



118 **89** (82%)

aldehyde 89: To a solution of diol **118** (1.47 g, 3.69 mmol, 1 eq) in 5:3 THF/H_2O (16 mL, 4.3 mL/mmol **118**) was added $NaIO_4$ (1.58 g, 7.38 mmol, 2 eq). The resulting suspension was stirred for 5 h at rt before being diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The CH_2Cl_2 extracts were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1) provided aldehyde **89** (1.11 g, 82%) as a colorless oil.

R_f = 0.34 (cyclohexane–EtOAc 20:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 9.69 (d, J = 2 Hz, 1H), 7.65-7.66 (m, 4H), 7.38-7.46 (m, 6H), 5.53-5.62 (m, 1H), 5.04-5.13 (m, 2H), 3.59-3.73 (m, 2H), 2.67-2.80 (m, 2H), 1.01-1.10 (m, 12H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 204.6 (CH), 135.6 (4 × CH), 135.2 (CH), 133.2 (2 × C), 129.7 (2 × CH), 127.7 (4 × CH), 118.1 (CH_2), 64.7 (CH_2), 47.0 (CH), 46.8 (CH), 26.8 (3 × CH_3), 19.2 (C), 10.0 (CH_3); IR (neat) ν 3072, 2931, 2858, 1726, 1428. Anal. Calcd. for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25, Found: C, 75.3; H, 8.0; $[\alpha]^{25}_D$ +1.1 (*c* 1.03, $CHCl_3$).

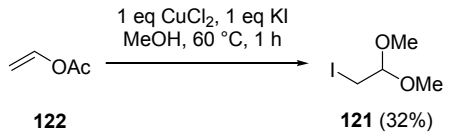


89 **120** (97%)

dithiane 120: 1,3-Propanedithiol (0.3 mL, 2.9 mmol, 1.02 eq) and $BF_3{\cdot}Et_2O$ (0.2 g, 1.4 mmol, 0.5 eq) were added to a solution of aldehyde **89** (1.04 g, 2.8 mmol, 1 eq) in CH_2Cl_2 (8.5 mL, 3 mL/mmol **89**) at rt. The reaction mixture was allowed to stir for 10 min and then quenched with saturated aq. $NaHCO_3$ (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the crude product which was further purified by flash chromatography (cyclohexane–EtOAc 50:1) to provide **120** (1.25 g, 97%) as a pale-yellow oil.

R_f = 0.46 (cyclohexane–EtOAc 20:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.65-7.71 (m, 4H), 7.36-7.44 (m, 6H), 5.70-5.79 (m, 1H), 5.07-5.19 (m, 2H), 4.05 (d, J = 6.0 Hz, 1H), 3.65-3.76 (m, 2H), 2.76-2.86 (m, 3H), 2.57-2.66 (m, 2H), 2.22-2.31 (m, 1H), 2.03-2.07 (m, 1H), 1.77-1.88 (m, 1H), 1.01-1.07 (m, 12H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 137.3 (CH), 135.7 (2 × CH), 135.6 (2 × CH), 133.6 (2 × C), 129.6 (2 × CH), 127.6 (4 × CH), 117.5 (CH_2), 65.0 (CH_2), 52.8 (CH), 47.9 (CH), 36.9 (CH), 30.7 (CH_2), 30.1 (CH_2), 26.8 (3 × CH_3), 26.2 (CH_2), 19.2 (C),

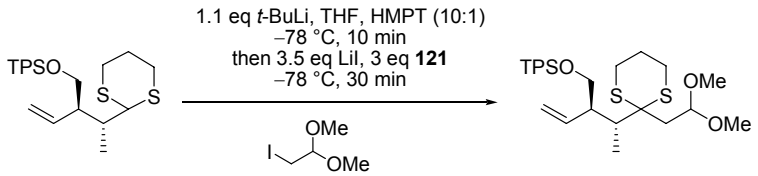
13.6 (CH_3); IR (neat) *v* 2930, 2896, 2857, 1427. Anal. Calcd. for $C_{26}H_{36}OS_2Si$: C, 68.37; H, 7.94, Found: C, 68.1; H, 8.0; $[\alpha]^{25}_D$ +20.9 (*c* 1.15, $CHCl_3$).



122 **121** (32%)

iodoacetaldehyde dimethyl acetal 121: Anhydrous $CuCl_2$ (6.7 g, 50 mmol, 1 eq) and KI (8.3 g, 50 mmol, 1 eq) were suspended in MeOH (40 mL, 0.8 mL/mmol **122**) and heated to 60 °C. Vinyl acetate (**122**) (4.3 g, 50 mmol, 1 eq) was added and the reaction mixture stirred for 1 h, whereby solid CuCl precipitated. The suspension was poured into H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). Combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Bulb-to-bulb distillation of the crude product (rt, 0.6 mbar) yielded **121** as a light-brown liquid (3.4 g, 32%).

^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.45 (t, J = 5.4 Hz, 1H), 3.35 (s, 6H), 3.19 (d, J = 5.2 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 103.2 (CH), 53.6 (2 × CH_3), 4.12 (CH_2); IR (neat) *v* 2930, 2896, 2857, 1427. Anal. Calcd. for $C_4H_9IO_2$: C, 22.24; H, 4.20, Found: C, 22.3; H, 4.1.

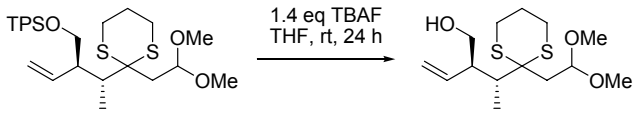


120 **121** **88** (61%)

acetal 88: To a solution of **120** (106 mg, 0.23 mmol, 1 eq) in THF (2 mL, 8.6 mL/mmol **120**) at –78 °C was added HMPA (0.3 mL, 1.3 mL/mmol **120**) and then slowly *t*-BuLi in pentane (0.16 mL, 0.26 mmol, 1.1 eq, 1.6 M solution in pentane). The resulting dark-red solution was stirred for further 10 min before iodoacetaldehyde dimethyl acetal **13** (150 mg, 0.69 mmol, 3 eq) and LiI (109 mg, 0.81 mmol, 3.5 eq) in THF (1 mL, 4.3 mL/mmol **120**) were added. The mixture was stirred for 30 min at –78 °C and then quenched with saturated aq. $NaHCO_3$ solution (3 mL). After extraction with CH_2Cl_2 (3 × 20 mL), the organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purifed by flash chromatography (cyclohexane–EtOAc 50:1 to 20:1) to afford unreacted **120** (20 mg) and acetal **88** (77 mg, 61%) as a colorless oil.

R_f = 0.20 (cyclohexane–EtOAc 20:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.68-7.70 (m, 4H), 7.38-7.45 (m, 6H), 5.69-5.78 (m, 1H), 5.06-5.17 (m, 2H), 4.81 (t, J = 4.0 Hz, 1H), 3.56-3.57 (m, 2H), 3.30-3.40 (m, 7H), 2.72-3.03 (m, 3H), 2.62-2.69 (m, 1H), 2.51-2.57 (m, 1H), 2.18-2.22 (m, 1H), 1.78-1.98 (m, 3H), 1.05-1.10 (m, 12H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 136.7

(CH), 135.6 (4 × CH), 133.6 (C), 133.5 (C), 129.6 (2 × CH), 127.6 (4 × CH), 118.1 (CH_2), 102.7 (CH), 66.8 (CH_2), 57.2 (C), 53.5 (CH_3), 52.5 (CH_3), 46.0 (CH), 39.5 (CH_2), 35.8 (CH), 26.9 (3 × CH_3), 25.8 (CH_2), 25.5 (CH_2), 24.5 (CH_2), 19.3 (C), 9.9 (CH_3); IR (neat) *v* 2930, 2903, 2857, 1427. Anal. Calcd. for $C_{30}H_{44}O_3S_2Si$: C, 66.13; H, 8.14, Found: C, 66.2; H, 8.1; $[\alpha]^{25}_D$ +21.0 (*c* 1.01, $CHCl_3$).

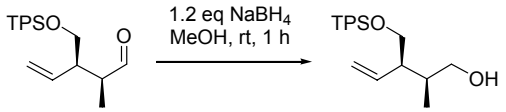


88 **88b** (89%)

alcohol 88b: Acetal **88** (236 mg, 0.43 mmol, 1 eq) was dissolved in THF (2 mL, 4.7 mL/mmol **88**) and to the solution was added 1.0 M TBAF in THF (0.6 mL, 0.60 mmol, 1.4 eq). The reaction mixture was stirred for 24 h at rt before being quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 ml). Combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Subsequent purification by flash chromatography (cyclohexane–EtOAc 3:1) afforded pure alcohol **88b** (118 mg, 89%) as a colorless oil.

R_f = 0.27 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 5.73-5.82 (m, 1H), 5.14-5.22 (m, 2H), 4.76 (t, *J* = 4.2 Hz, 1H), 3.50 (d, *J* = 7.4 Hz, 2H), 3.34 (s, 3H), 3.32 (s, 3H), 3.07-3.14 (m, 1H), 2.80-2.94 (m, 2H), 2.65-2.77 (m, 2H), 2.42-2.50 (m, 1H), 2.18-2.26 (m, 1H), 2.05-2.15 (m, 1H), 1.83-2.00 (m, 2H), 1.72 (br s, 1H), 1.13 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 136.8 (CH), 118.9 (CH_2), 102.7 (CH), 65.5 (CH_2), 57.2 (C), 53.3 (CH_3), 52.8 (CH_3), 46.6 (CH), 39.2 (CH_2), 37.7 (CH), 25.9 (CH_2), 25.8 (CH_2), 24.6 (CH_2), 11.1 (CH_3); IR (neat) *v* 3444, 2932, 2829, 1118, 1056. Anal. Calcd. for $C_{14}H_{26}O_3S_2$: C, 54.86; H, 8.55, Found: C, 54.9; H, 8.6; $[\alpha]^{25}_D$ +17.1 (*c* 0.87, $CHCl_3$).

7.6 *Mosher's Ester Analysis - Determination of the Enantiomeric Excess*

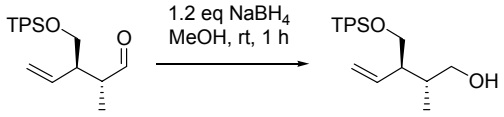


115 **116** (92%)

alcohol 116: To a solution of aldehyde **115** (269 mg, 0.73 mmol, 1 eq) in MeOH (2.2 mL, 3 mL/mmol **115**) was added $NaBH_4$ (33 mg, 0.88 mmol, 1.2 eq) and the solution stirred for 1 h at rt before being quenched with H_2O (2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced

pressure to yield the crude product. Purification by flash chromatography (cyclohexane–EtOAc 5:1) afforded **116** (249 mg, 92%) as a clear oil.

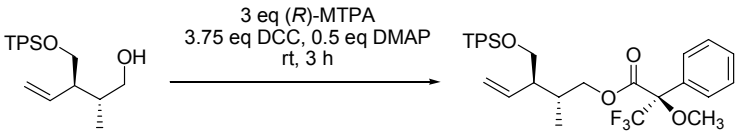
R_f = 0.32 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.64-7.72 (m, 4H), 7.34-7.50 (m, 6H), 5.83 (ddd, J = 9.2 Hz, 10.1 Hz, 17.2 Hz, 1H), 4.97-5.12 (m, 2H), 3.65-3.79 (m, 2H), 3.56-3.65 (m, 1H), 3.45-3.54 (m, 1H), 2.09-2.30 (m, 2H), 1.88-2.01 (m, 1H), 1.06 (s, 9H), 0.91 (d, J = 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 138.4 (CH), 135.6 (4 × CH), 133.2 (2 × C), 129.7 (2 × CH), 127.7 (4 × CH), 116.5 (CH_2), 66.2 (CH_2), 65.3 (CH_2), 49.4 (CH), 36.9 (CH), 26.8 (3 × CH_3), 19.2 (C), 14.5 (CH_3); IR (neat) ν 3349 (br), 3071, 2930, 2858, 1428, 1112, 702. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75, Found: C, 74.8; H, 8.5.; $[\alpha]^{25}_D$ +20.4 (c 0.85, $CHCl_3$).



89 **119** (95%)

alcohol 119: To a solution of aldehyde **89** (251 mg, 0.69 mmol, 1 eq) in MeOH (2 mL, 3 mL/mmol **89**) was added $NaBH_4$ (31 mg, 0.82 mmol, 1.2 eq) and the solution stirred for 1 h at rt before being quenched with H_2O (2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield the crude product. Purification by flash chromatography (cyclohexane–EtOAc 5:1) afforded **119** (241 mg, 95%) as a clear oil.

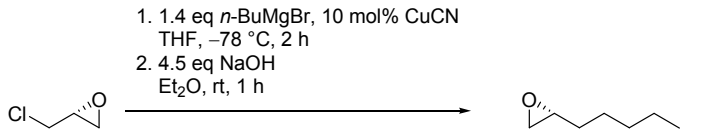
R_f = 0.38 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.67-7.69 (m, 4H), 7.38-7.46 (m, 6H), 5.59-5.68 (m, 1H), 4.99-5.10 (m, 2H), 3.68 (d, J = 6.3 Hz, 2H), 3.48-3.59 (m, 2H), 2.31-2.38 (m, 1H), 2.05 (br s, 1H), 1.89-1.99 (m, 1H), 1.07 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 137.2 (CH), 135.6 (4 × CH), 133.4 (2 × C), 129.7 (2 × CH), 127.6 (4 × CH), 117.1 (CH_2), 66.7 (CH_2), 65.7 (CH_2), 48.5 (CH), 36.5 (CH), 26.8 (3 × CH_3), 19.2 (C), 13.3 (CH_3); IR (neat) ν 3359 (br), 3071, 2930, 2858, 1428, 1112, 702 . Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75, Found: C, 74.7; H, 8.6; $[\alpha]^{25}_D$ +20.0 (c 0.66, $CHCl_3$).



119 **110**

Mosher's ester (General procedure): To a solution of alcohol **119** (65 mg, 0.176 mmol, 1 eq) in CH_2Cl_2 (2 mL) was added DMAP (11 mg, 0.09 mmol, 0.5 eq), DCC (136 mg, 0.66 mmol, 3.75 eq), and (*R*)-MTPA (124 mg, 0.53 mmol, 3 eq) dissolved in CH_2Cl_2 (1 mL). The mixture was stirred for 3 h at rt before being quenched with saturated aq. NaCl (3 mL). The product was extracted with CH_2Cl_2 (3 × 3 mL), the combined organic phases dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc 200:1 to 100:1) to afford ester **110** which was pure enough to be analyzed by ^{1}H-NMR.[109]

7.7 *Model Study toward the Tetracyclic Core of Berkelic Acid*

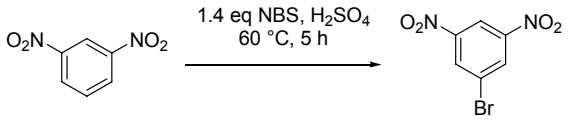


(±)-**126** (±)-**40** (75% over 2 steps)

2-pentyloxirane ((±)-**40**): To a suspension of Mg-turnings (2.8 g, 115.2 mmol, 1.7 eq) in THF (5 mL, 0.07 mL/mmol **126**) was added 1-bromobutane (13 g, 94.9 mmol, 1.4 eq) solution in THF (12 mL, 0.18 mL/mmol **126**) over 4 h. The solution was stirred for 30 min and then added over 1 h to a suspension of epichlorohydrin (**126**) (6.27 g, 67.8 mmol, 1 eq) and CuCN (607 mg, 6.78 mmol, 10 mol%) in THF (20 mL, 0.3 mL/mol **126**) at –78 °C. The reaction mixture was allowed to warm to rt over 4 h before being quenched with saturated aq. NH_4Cl (40 mL). The aqueous solution was extracted with Et_2O (3 × 60 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford crude 1-chloroheptan-2-ol (8.3 g, 90%), which was then immediately dissolved in Et_2O (60 mL, 0.9 mL/mmol), treated with finely ground NaOH (12.2 g, 305 mmol, 4.5 eq) and stirred for 3 h at rt. Subsequently, H_2O (40 mL) was added and the organic phase separated. Aqueous phase was extracted with Et_2O (2 × 30 mL), and the combined organic layers dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The obtained oil was purified by flash chromatography (pentane–Et_2O 20:1) to afford pure (±)-**40** (5.8 g, 75%) as a colorless liquid.

[109] All synthesized esters contained an unknown impurity, inseparable by flash chromatography, thus preventing accurate characterization. Enantiomeric excess could, nevertheless, be determined by analyzing 4-4.5 ppm interval in the ^{1}H-NMR spectra.

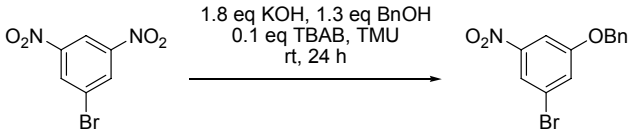
R_f = 0.31 (cyclohexane–EtOAc 20:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 2.84-2.92 (m, 1H), 2.72 (t, J = 4.5 Hz, 1H), 2.44 (dd, J = 2.7 Hz, J = 4.9 Hz, 1H), 1.12-1.59 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 52.3 (CH), 47.1 (CH_2), 32.4 (CH_2), 31.6 (CH_2), 25.6 (CH_2), 22.5 (CH_2), 13.9 (CH_3); IR (neat) ν 2930, 2859, 1037.



123 **124** (70%)

1-bromo-3,5-dinitrobenzene (**124**): 1,3-dinitrobenzene (**123**) (2.60 g, 15.5 mmol, 1 eq) was dissolved in concentrated H_2SO_4 (16 mL, 1 mL/mmol **123**) at 60 °C. NBS (3.85 g, 21.6 mmol, 1.4 eq) was added to the reaction mixture in three portions over 1 h. The mixture was stirred at 60 °C for 6 h before it was poured onto ice. The precipitated solid was dissolved in CH_2Cl_2 (40 mL) and washed with 2N KOH (30 mL) and then H_2O (2 × 30 mL). Organic phase was then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford crude **124** as a yellow oil which crystallized upon standing. The product was recrystallized from methanol and then dried in vacuum over P_4O_{10} for 48 h to afford pure **124** (2.66 g, 70%) as white crystals.

R_f = 0.42 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 8.96-9.05 (m, 1H), 8.66-8.76 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 148.8 (2 × C), 132.0 (2 × CH), 123.8 (C), 117.7 (CH); IR (neat) ν 3100, 1538, 1342, 1164, 1073, 725.

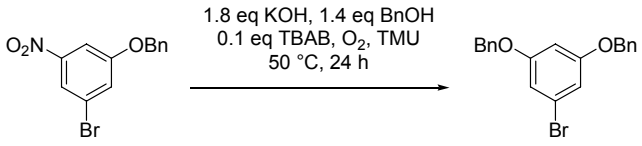


124 **125** (65%)

1-(benzyloxy)-3-bromo-5-nitrobenzene (**125**): A round-bottom flask was charged with **124** (28.5 g, 115.4 mmol, 1 eq), finely ground KOH (11.7 g, 208.5 mmol, 1.8 eq) and TBAB (3.72 g, 11.5 mmol, 0.1 eq). Subsequently TMU (115 mL, 1 mL/mmol **124**) was added, followed by slow addition of BnOH (15.5 mL, 150 mmol, 1.3 eq). The reaction mixture was stirred for 8 h at rt before being poured onto ice and extracted with Et_2O (2 × 600 mL). The combined organic layers were washed with H_2O (150 mL), 5N H_2SO_4 (2 × 150 mL) and again H_2O (2 × 150 mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc 20:1) to afford **125** (23 g, 65%) as pale-yellow crystals.

R_f = 0.44 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.94-8.00 (m, 1H), 7.73-7.78 (m, 1H), 7.34-7.48 (m, 6H), 5.13 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 159.6 (C),

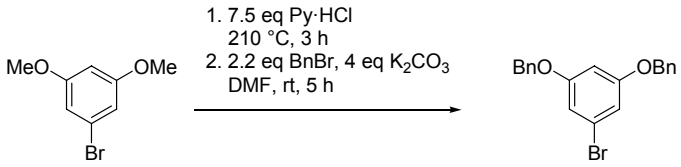
149.4 (C), 135.0 (C), 128.8 (2 × CH), 128.6 (CH), 127.6 (2 × CH), 124.6 (CH), 123.0 (C), 119.2 (CH), 108.6 (CH), 70.9 (CH_2); IR (neat) ν 3094, 1612, 1533, 1349, 1261, 1025, 742. Anal. Calcd. for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; N, 4.55, Found: C, 50.7; H, 3.4; N, 4.4.



125 **39** (89%)

1,3-*bis*(benzyloxy)-5-bromobenzene (**39**): In a round-bottom flask, fitted with thermometer and gas-inlet, **125** (5 g, 16.2 mmol, 1 eq), finely ground KOH (1.64 g, 29.2 mmol, 1.8 eq) and TBAB (0.56 g, 1.74 mmol, 0.1 eq) were added. Subsequently TMU (16 mL, 1 mL/mmol **125**) was added, and the suspension cooled down to 0°C. BnOH (2.5 mL, 22.7 mmol, 1.4 eq) was added slowly and oxygen introduction initiated. The mixture was then warmed up to 50°C[110] and stirred for 24 h at this temperature. The reaction mixture was poured onto ice-water and extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with H_2O (30 mL), 5N H_2SO_4 (2 × 30 mL) and again H_2O (2 × 30 mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc 20:1) to afford **39** (5.34 g, 89%) as pale-yellow crystals.

R_f = 0.39 (cyclohexane–EtOAc 20:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.31-7.50 (m, 10H), 6.79 (d, J = 2.2 Hz, 2H), 6.56 (t, J = 2.2 Hz, 1H), 5.01 (s, 4H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 160.3 (2 × C), 136.2 (2 × C), 128.6 (4 × CH), 128.1 (2 × CH), 127.5 (4 × CH), 122.9 (C), 111.0 (2 × CH), 101.3 (CH), 70.2 (2 × CH_2); IR (neat) ν 3032, 1596, 1575, 1438, 1159, 696. Anal. Calcd. for $C_{20}H_{17}BrO_2$: C, 65.05; H, 4.64, Found: C, 64.8; H, 4.8.

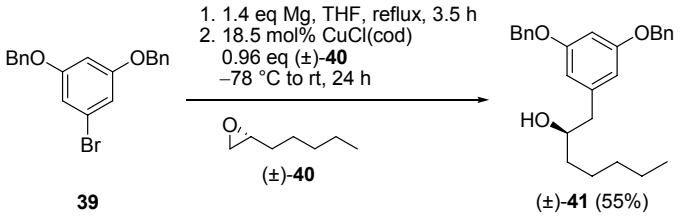


38 **39** (92% over two steps)

1,3-*bis*(benzyloxy)-5-bromobenzene (**39**): 1-Bromo-3,5-dimethoxybenzene (**38**) (5.0 g, 23.0 mmol, 1 eq) and pyridinium hydrochloride (20 g, 173 mmol, 7.5 eq) were heated under stirring at 210 °C for 3 h before being poured into H_2O (40 mL). After extraction with EtOAc (3 × 60 mL), the combined organic layers were washed with H_2O (60 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting reddish oil was purified by flash chromatography (cyclohexane–EtOAc 20:1 to 3:1) to afford 5-

[110] The reaction is exothermic and temperature should not exceed 50°C; oxygen introduction during the course of the reaction is absolutely essential to provide the pure product.

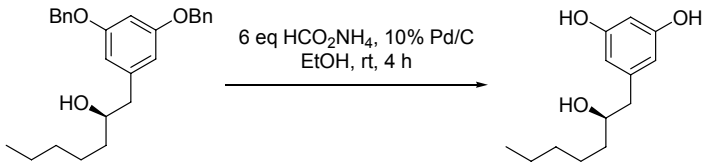
bromoresorcinol (4.1 g, 94%) as white crystals. To a solution of 5-bromoresorcinol (3.29 g, 17.4 mmol, 1 eq) in DMF (17 mL, 1 mL/mmol) were added K_2CO_3 (9.6 g, 69.5 mmol, 4 eq) and BnBr (4.5 mL, 38.3 mmol, 2.2 eq). Resulting suspension was stirred for 24 h at rt before being poured into H_2O (150 mL). Aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were washed with 2N HCl (40 mL), H_2O (100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting oil was purified by flash chromatography (cyclohexane–EtOAc 20:1) to yield **39** (6.27 g, 92% over two steps) as a white solid.



1-(3,5-*bis*(benzyloxy)phenyl)heptan-2-ol ((±)-**41**): To a suspension of Mg-turnings (184 mg, 7.6 mmol, 1.4 eq) in THF (4 mL, 0.74 mL/mmol **39**) was added 1,2-dibromoethane (205 mg, 1.1 mmol, 0.2 eq) and the suspension stirred for 1 h at rt before being heated to 78 °C. Subsequently, the solution of **39** (2.0 g, 5.4 mmol, 1 eq) and 1,2-dibromoethane (205 mg, 1.1 mmol, 0.2 eq) in THF (40 mL, 7.4 mL/mmol **39**) was added slowly over a period of 8 h. After the addition, the solution was cooled down to –78 °C and (±)-**40** (589 mg, 5.16 mmol, 0.96 eq) and CuCl(COD) (207 mg, 1.0 mmol, 0.19 eq) were added. After stirring the reaction mixture for 30 min at –78 °C, it was allowed to warm to rt, and stirred for further 24 h. The solution was quenched with H_2SO_4 (1 g H_2SO_4 in 5 mL H_2O) and then extracted with 110 mL Et_2O/cyclohexane mixture (2:1). The combined organic layers were washed with 20 mL H_2O, 2N KOH (3 × 20 mL), H_2O (3 × 20 mL), dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The crude product was dried under vacuo (80 °C, 0.05 mbar) for 1 h an then purified by flash chromatography (cyclohexane–EtOAc 20:1 to 5:1) to afford (±)-**41** (1.2 g, 55%) as a white powder.

R_f = 0.36 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.35-7.47 (m, 10H), 6.57 (t, J = 2.1 Hz, 1H), 6.53 (d, J = 2.2 Hz, 2H), 5.06 (s, 4H), 3.80-3.86 (m, 1H), 2.80 (dd, J = 4.1, J = 13.5 Hz, 1H), 2.62 (dd, J = 8.4 Hz, 13.5 Hz, 1H), 1.70 (s, 1H), 1.24-1.57 (m, 8H), 0.96 (t, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 159.9 (2 × C), 141.0 (C), 136.7 (2 × C), 128.5 (4 × CH), 127.9 (2 × CH), 127.4 (4 × CH), 108.4 (2 × CH), 100.0 (CH), 72.4 (CH), 69.9 (2 × CH_2), 44.3 (CH_2), 36.7 (CH_2), 31.8 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR

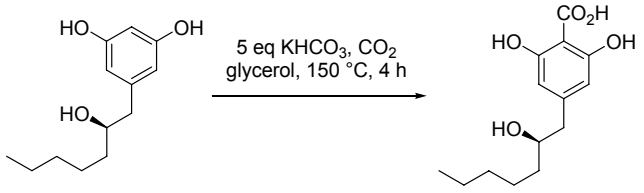
(neat) *v* 3412 (br), 2930, 2858, 1594, 1453, 1157, 1059, 697. Anal. Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97, Found: C, 80.5; H, 8.3.



(±)-**41** (±)-**42** (98%)

1-(3,5-dihydroxyphenyl)heptan-2-ol ((±)-**42**): To a solution of (+)-**41** (3.12 g, 7.7 mol, 1 eq) in EtOH (40 mL, 5.2 mL/mmol **41**) was added HCO_2NH_4 (2.92 g, 46.3 mmol, 6 eq) and 10% Pd/C (193 mg, 25 mg/mmol). The reaction mixture was stirred for 4 h at rt and then quenched with H_2O (30 mL). The product was extracted with EtOAc (3 × 70 mL), the combined organic layers dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was filtered through a short pad of silica (cyclohexane–EtOAc 1:1) to provide (±)-**42** (1.25 g, 98%) as a white powder.

R_f = 0.29 (cyclohexane–EtOAc 1:1); ^{1}H-NMR (acetone-d6, 400 Mhz) δ 8.05 (s, 2H), 6.22 (d, J = 2.3 Hz, 2H), 6.18 (t, J = 2.2 Hz, 1H), 3.66-3.80 (m, 1H), 3.48 (d, J = 4.9 Hz, 1H), 2.56 (d, J = 5.9 Hz, 2H), 1.17-1.58 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (acetone-d6, 100.6 Mhz) δ 159.1 (2 × C), 142.7 (C), 108.7 (2 × CH), 101.2 (CH), 72.8 (CH), 45.3 (CH_2), 37.6 (CH_2), 32.7 (CH_2), 26.2 (CH_2), 23.3 (CH_2), 14.3 (CH_3); IR (neat) *v* 3263 (br), 2931, 1599, 1485, 1330, 1163, 830. Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99, Found: C, 69.5; H, 8.8.

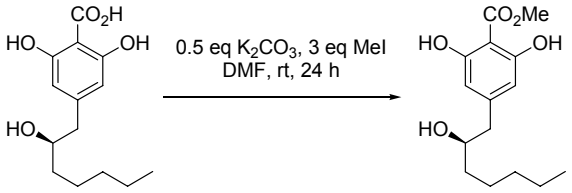


(±)-**42** (±)-**51** (89%)

2,6-dihydroxy-4-(2-hydroxyheptyl)benzoic acid ((±)-**51**)[9]: To a mixture of (±)-**42** (3.4 g, 15.2 mmol, 1 eq) and $KHCO_3$ (7.6 g, 75.9 mmol, 5 eq) was added glycerol (12 g) and the reaction suspension was stirred at 145 ºC for 5 h under CO_2 atmosphere (1 atm). Subsequently, the mixture was allowed to cool down under CO_2 atmosphere and quenched with aq. $KHCO_3$ solution (25 g in 200 mL). The aqueous solution was extracted with Et_2O (3 × 100 mL) and organic layer discarded. The water phase was acidified with conc. HCl (100 mL) and extracted with EtOAc (3 × 120 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The

crude product was washed with warm toluene (20 mL) and then dried in vacuo to afford (±)-**51** (3.61 g, 89%) as a white powder.

R_f = 0.31 (EtOAc–AcOH 20:1); ^{1}H-NMR[111] (acetone-d6, 400 Mhz) δ 9.09 (br s, 3H), 6.38 (s, 2H), 3.78-3.88 (m, 1H), 2.57-2.71 (m, 2H), 1.18-1.60 (m, 9H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C-NMR (acetone-d6, 100.6 Mhz) δ 172.2 (C), 161.5 (2 × C), 150.3 (C), 109.7 (2 × CH), 99.3 (C), 72.3 (CH), 45.2 (CH_2), 37.9 (CH_2), 32.6 (CH_2), 26.1 (CH_2), 23.3 (CH_2), 14.3 (CH_3); IR (neat) ν 2932, 2576 (br), 1672, 1640, 702. Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51, Found: C, 62.9; H, 7.4.

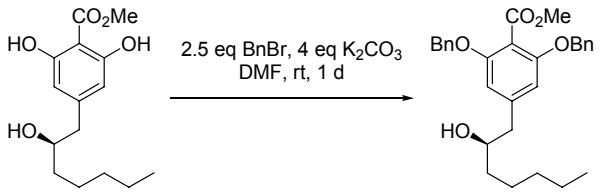


(±)-**51** (±)-**43** (99%)

methyl 2,6-dihydroxy-4-(2-hydroxyheptyl)benzoate ((±)-**43**): To a solution of (±)-**51** (1.0 g, 3.75 mmol, 1 eq) in DMF (7.5 mL, 2 mL/mmol **51**) was added K_2CO_3 (260 mg, 1.88 mmol, 0.5 eq) and the suspension was stirred for 2 h before MeI (0.7 mL, 11.2 mmol, 3 eq) was added. After 24 h the reaction mixture was poured into H_2O (40 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 3:1) afforded methyl ester (±)-**43** (1.04 g, 99%) as white crystals.

R_f = 0.35 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 9.63 (br s, 2H), 6.37 (s, 2H), 4.07 (s, 3H), 3.80-3.88 (m, 1H), 2.70 (dd, J = 13.4 Hz, 4.4 Hz, 1H), 2.56 (dd, J = 13.4 Hz, 8.4 Hz, 1H), 1.55 (d, J = 4.0 Hz, 1H), 1.26-1.51 (m, 8H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 169.8 (C), 160.7 (2 × C), 149.0 (C), 109.1 (2 × CH), 98.3 (C), 72.0 (CH), 52.8 (CH_3), 44.3 (CH_2), 36.9 (CH_2), 31.8 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (neat) ν 3446, 2930, 1674, 1644, 1570, 1194, 1097. Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85, Found: C, 63.9; H, 7.8.

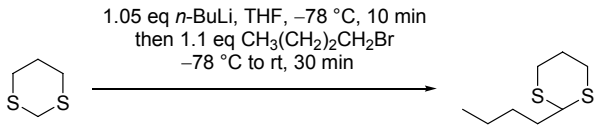
[111] The acid reacts slowly with d6-acetone to form the corresponding isochroman, therefore, prepared NMR-sample should be measured immediately.



(±)-**43** (±)-**43b** (93%)

methyl 2,6-*bis*(benzyloxy)-4-(2-hydroxyheptyl)benzoate ((±)-**43b**): To a solution of (±)-**43** (558 mg, 1.98 mmol, 1 eq) in DMF (5 mL, 2.5 mL/mmol **43**) was added K_2CO_3 (1.1 g, 7.96 mmol, 4 eq) and BnBr (845 mg, 4.94 mmol, 2.5 eq). The reaction mixture was stirred for 24 h, then poured into H_2O (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc 5:1) to afford (±)-**43b** (850 mg, 93%) as a colorless oil.

R_f = 0.46 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.34-7.40 (m, 8H), 7.26-7.28 (m, 2H), 6.46 (s, 2H), 5.12 (s, 4H), 3.89 (s, 3H), 3.65-3.75 (m, 1H), 2.73 (dd, J = 4.1 Hz, J = 13.5 Hz, 1H), 2.57 (dd, J = 8.2 Hz, J = 13.4 Hz, 1H), 1.22-1.48 (m, 9H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 166.8 (C), 156.5 (2 × C), 142.4 (C), 136.7 (2 × C), 128.5 (4 × CH), 127.8 (2 × CH), 126.9 (4 × CH), 112.6 (C), 107.1 (2 × CH), 72.4 (CH), 70.5 (2 × CH_2), 52.3 (CH_3), 44.6 (CH_2), 36.7 (CH_2), 31.8 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (neat) ν 3445 (br), 2930, 1732, 1609, 1433, 1268, 1121. Anal. Calcd. for $C_{29}H_{34}O_5$: C, 75.30; H, 7.41, Found: C, 75.4; H, 7.6.

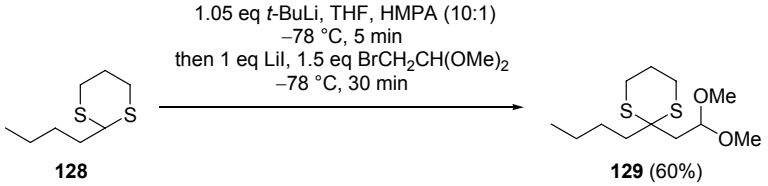


127 **128** (92%)

2-butyl-1,3-dithiane (**128**): To a solution of 1,3-dithiane (**127**) (684 mg, 5.69 mmol, 1 eq) in THF (11 mL, 2 mL/mmol **127**) was slowly added *n*-BuLi in hexane (5.97 mmol, 1.05 eq) at –78 °C. After the solution had been stirred for 5 min, 1-bromobutane (857 mg, 6.26 mmol, 1.1 eq) dissolved in THF (5.7 mL, 1 mL/mmol **127**) was added, and the reaction mixture allowed to warm to rt over 3 h. The reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1) afforded **128** (920 mg, 92%) as a colorless oil.

R_f = 0.32 (cyclohexane–EtOAc 20:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.03 (t, J = 7.2 Hz, 1H), 2.90-2.77 (m, 4H), 2.13-2.03 (m, 1H), 1.89-1.78 (m, 1H), 1.75-1.70 (m, 2H), 1.50-1.43 (m,

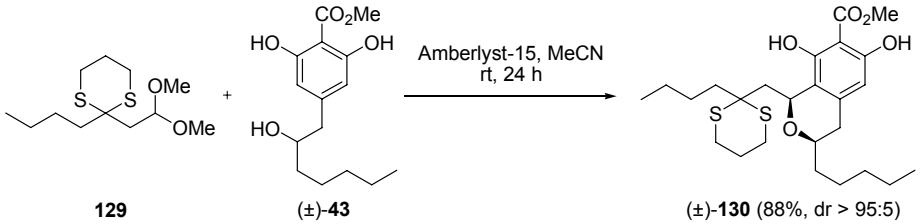
2H), 1.36-1.27 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 47.6 (CH), 35.1 (CH_2), 30.4 (2 × CH_2), 28.7 (CH_2), 26.0 (CH_2), 22.3 (CH_2), 13.8 (CH_3); IR (neat) ν 2954, 2930, 2899, 2871, 2857, 1422, 1275. Anal. Calcd. for $C_8H_{16}S_2$: C, 54.49; H, 9.15, Found: C, 54.5; H, 9.0.



128 **129** (60%)

2-butyl-2-(2,2-dimethoxyethyl)-1,3-dithiane (**129**): To a solution of **128** (682 mg, 3.87 mmol, 1 eq) in THF (8 mL, 2 mL/mmol **128**) and HMPA (0.8 mL) was added *t*-BuLi in pentane (4.06 mmol, 1.05 eq) at –78 °C. The red-colored reaction mixture was then stirred for 5 min before a solution of LiI (518 mg, 3.87 mmol, 1 eq) and bromoacetaldehyde dimethyl acetal (980 mg, 5.80 mmol, 1.5 eq) in THF (4 mL, 1 mL/mmol **128**) was added dropwise over 2 min. After stirring for 30 min at –78 °C, the pale green-yellow reaction mixture was quenched with saturated aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (cyclohexane–EtOAc 20:1) to afford **129** (614 mg, 60%) as a pale-yellow oil.

R_f = 0.27 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.61 (t, J = 4.4 Hz, 1H), 3.33 (s, 6H), 2.89-2.82 (m, 2H), 2.78-2.72 (m, 2H), 2.23 (d, J = 4.4 Hz, 2H), 2.03-1.84 (series of m, 4H), 1.50-1.42 (m, 2H), 1.35-1.26 (m, 2H), 0.90 (t, J = 7.2, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 102.7 (CH), 53.1 (2 × CH_3), 51.2 (C), 41.0 (CH_2), 39.0 (CH_2), 26.1 (3 × CH_2), 25.2 (CH_2), 22.9 (CH_2), 13.9 (CH_3); IR (neat) ν 2954, 2933, 2907, 2871, 2828, 1120, 1073. Anal. Calcd. for $C_{12}H_{24}O_2S_2$: C, 54.50; H, 9.15, Found: C, 54.6; H, 8.9.

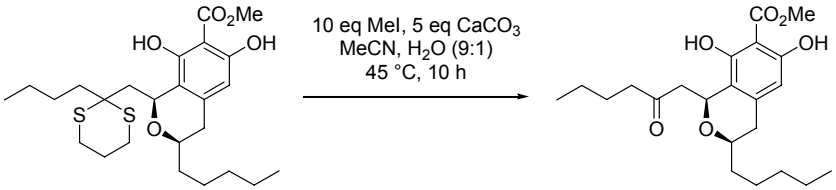


129 (±)-**43** (±)-**130** (88%, dr > 95:5)

thioketal (±)-**130**: To a solution of **129** (77 mg, 0.29 mmol, 1.05 eq) and (±)-**43** (78 mg, 0.28 mmol, 1 eq) in CH_3CN (2 mL, 7 mL/mmol **43**) wad added grinded Amberlyst-15 (11 mg). The reaction mixture was stirred for 24 h at rt before being quenched with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash

chromatography (cyclohexane–EtOAc 10:1) to afford thioketal (±)-**130** (117 mg, 88%, dr > 95:5) as a white solid.

R_f = 0.32 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 10.5 (br s, 1H), 9.16 (br s, 1H), 6.25 (s, 1H), 5.25 (d, J = 9.0 Hz, 1H), 4.07 (s, 3H), 3.32-3.48 (m, 1H), 3.14-3.26 (m, 1H), 2.98-3.08 (m, 1H), 2.86-2.98 (m, 1H), 2.64-2.80 (m, 2H), 2.52-2.64 (m, 1H), 2.40-2.50 (m, 1H), 2.14-2.28 (m, 1H), 1.82-2.12 (m, 4H), 1.22-1.66 (m, 12H), 0.82-0.98 (m, 6H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 170.1 (C), 158.0 (C), 157.3 (C), 146.4 (C), 117.3 (C), 108.0 (CH), 98.1 (C), 72.5 (CH), 72.3 (CH), 53.7 (C), 52.8 (CH_3), 42.0 (CH_2), 40.1 (CH_2), 36.3 (CH_2), 35.8 (CH_2), 31.9 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 25.3 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 14.1 (2 × CH_3); IR (neat) ν 3448, 2955, 2930, 2858, 1672, 1640. Anal. Calcd. for $C_{25}H_{38}O_5S_2$: C, 62.21; H, 7.93, Found: C, 62.2; H, 8.0.

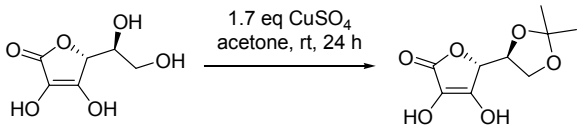


(±)-**130** (±)-**131** (57%)

ketone (±)-**131**: To a solution of (±)-**130** (69 mg, 0.14 mmol, 1 eq) in 9:1 MeCN/H_2O (2 mL, 14 mL/mmol **130**) was added $CaCO_3$ (72 mg, 0.72 mmol, 5 eq) and then MeI (0.09 mL, 1.4 mmol, 10 eq). The suspension was heated at 45 ºC for 5 h before being quenched with H_2O (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 5:1) afforded ketone (±)-**131** (32 mg, 57%) as a pale-yellow oil which solidifed upon standing.

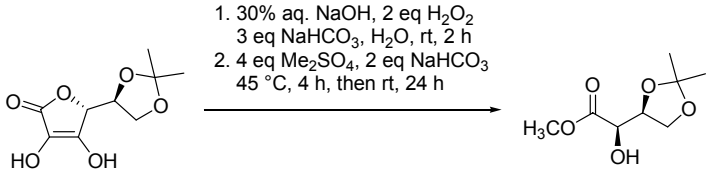
R_f = 0.28 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 6.26 (s, 1H), 5.24-5.26 (m, 1H), 4.06 (s, 3H), 3.41-3.47 (m, 1H), 3.30 (dd, J = 3.0, 15.0 Hz, 1H), 2.56-2.66 (m, 2H), 2.48-2.51 (m, 3H), 1.22-1.63 (m, 12H), 0.86-0.94 (m, 6H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 210.1 (C), 170.0 (C), 158.2 (C), 157.1 (C), 145.8 (C), 116.4 (C), 108.0 (CH), 98.0 (C), 72.8 (CH), 71.2 (CH), 52.8 (CH_3), 48.1 (CH_2), 43.2 (CH_2), 35.9 (CH_2), 35.5 (CH_2), 31.8 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 22.3 (CH_2), 14.0 (CH_3), 13.9 (CH_3); IR (neat) ν 3435, 2957, 2931, 2860, 1712, 1673, 1640. Anal. Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22, Found: C, 67.5; H, 8.2.

7.8 *Toward the C19-C27 Fragment of Lytophillipine A – First Approach*



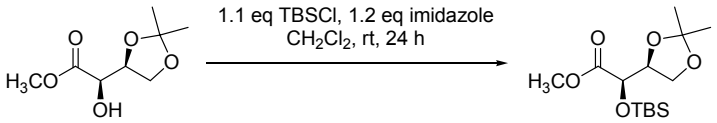
5,6-*O*-isopropylidene-L-ascorbic acid (**161**): To a suspension of ascorbic acid (**142**) (20.0 g, 113.6 mmol, 1 eq) in acetone (400 mL, 3.5 mL/mmol **142**) was added anhydrous $CuSO_4$ (30.8 g, 193 mmol, 1.7 eq), and the mixture was stirred for 24 h at rt. The suspension was filtered, and the filtrate washed with acetone (600 mL). The solution was evaporated under reduced pressure to give **161** (23.8 g, 97%) as a white solid.

^{1}H-NMR (acetone-d6, 400 Mhz) δ 4.72 (d, J = 3.1 Hz, 1H), 4.32-4.39 (m, 1H), 4.18 (dd, J = 7.0 Hz, 8.4 Hz, 1H), 4.00 (dd, J = 6.6 Hz, 8.4 Hz, 1H), 1.24-1.31 (m, 6H); ^{13}C-NMR (acetone-d6, 100.6 Mhz) δ 170.2 (C), 151.2 (C), 120.0 (C), 110.2 (C), 75.5 (CH), 75.0 (CH), 66.0 (CH_2), 26.2 (CH_3), 25.8 (CH_3); IR (neat) ν 3240, 2990, 1755, 1665, 1334. $[\alpha]^{25}_D$ +16.0 (*c* 1.05, MeOH).



methyl 3,4-*O*-isopropylidene-L-threonate (**162**): To a suspension of **161** (24.06 g, 111.3 mmol, 1 eq) in H_2O (111 ml, 1 mL/mmol **161**) was added NaOH (5 g in 10 mL H_2O) and the suspension stirred until it became clear solution. After $NaHCO_3$ (28.1 g, 333.9 mmol, 3 eq) was added, the reaction mixture was cooled down to 0 °C and 35% aq. H_2O_2 (21.7 g, 222.6 mmol, 2 eq) was added dropwise within 1 h. The reaction mixture was stirred for 2 h at rt, then Na_2SO_3 (1.75 g, 13.9 mmol, 0.125 eq) and $NaHCO_3$ (18.7 g, 222.6 mmol, 2 eq) were added and the suspension was heated to 45 °C. Me_2SO_4 (42 mL, 445.2 mmol, 4 eq) was added dropwise within 4 h, and the reaction mixture left to stir for another 24 h at rt. The reaction was quenched with H_2O (200 mL), and extracted with CH_2Cl_2 (4 × 250 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to furnish crude **162** (15.9 g, 75%), pure enough to be used in the next step. For analysis purposes, additional purification by flash chromatography (cyclohexane–EtOAc 10:1 to 1:2) was performed.

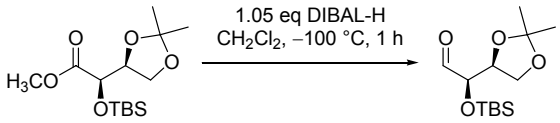
R_f = 0.25 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.37 (dt, J = 2.8 Hz, J = 6.7 Hz, 1H), 4.09 (m, 2H), 3.99 (dd, J = 6.9 Hz, J = 8.2 Hz, 1H), 3.80 (s, 3H), 2.98 (d, J = 8.2 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 172.5 (C), 109.9 (C), 76.2 (CH), 70.2 (CH), 65.5 (CH_2), 52.7 (CH_3), 26.0 (CH_3), 25.2 (CH_3); IR (neat) ν 3479, 2989, 1746. Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42, Found: C, 50.6; H, 7.3; $[\alpha]^{25}_D$ +19.4 (c 1.34, $CHCl_3$).



162 **163** (96%)

TBS-ester 163: To a solution of **162** (4.54 g, 23.9 mmol, 1 eq) in CH_2Cl_2 (31 mL, 1.3 mL/mmol **162**) was added imidazole (1.95 g, 28.6 mmol, 1.2 eq) and the suspension stirred for 5 min until imidazole dissolved. After cooling down to 0 °C, TBSCl (3.95 g, 26.2 mmol, 1.1 eq) dissolved in CH_2Cl_2 (17 mL, 0.7 mL/mmol **162**) was added dropwise over 10 min. The reaction mixture was left to stir for 24 h at rt and then quenched with H_2O (30 mL). The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1) provided TBS-ester **163** (6.99 g, 96%) as a clear oil.

R_f = 0.29 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.29-4.34 (m, 1H), 4.22 (d, J = 5.2 Hz, 1H), 4.03 (dd, J = 6.4 Hz, 8.5 Hz, 1H), 3.96 (dd, J = 6.4 Hz, 8.5 Hz, 1H), 3.73 (s, 3H), 1.39, 1.33 (6H, 2 × s), 0.90 (s, 9H), 0.09, 0.06 (6H, 2 × s); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 171.6 (C), 109.7 (C), 77.0 (CH), 73.0 (CH), 65.4 (CH_2), 51.9 (CH_3), 26.2 (CH_3), 25.6 (3 × CH_3), 25.3 (CH_3), 18.3 (C), –5.1 (CH_3), –5.3 (CH_3); IR (neat) ν 2954, 2932, 2858, 1742. Anal. Calcd. for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27, Found: C, 55.0; H, 9.3; $[\alpha]^{25}_D$ +27.0 (c 1.13, $CHCl_3$).

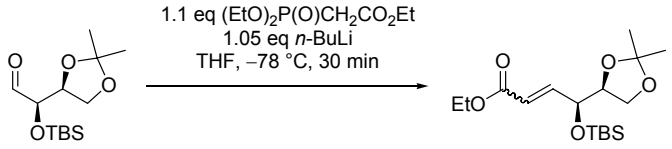


163 **164** (95%)

aldehyde 164: To a solution of TBS-ester **163** (7.0 g, 23 mmol, 1 eq) in CH_2Cl_2 (46 mL, 2 mL/mmol **163**) at –100 °C was slowly added 1.0 M DIBAL-H in CH_2Cl_2 (24 mL, 24 mmol, 1.05 eq). After the addition, the solution was left to stir for 15 min and then quenched with saturated Rochelle salt solution (190 mL). After extraction with CH_2Cl_2 (3 × 120 mL), the solution was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification

by flash chromatography (cyclohexane–EtOAc 20:1) provided aldehyde **164** (6.0 g, 95%) as a clear oil.

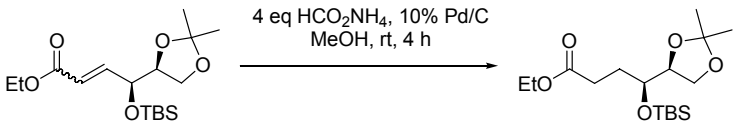
R_f = 0.26 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 9.69 (d, J = 1.0 Hz, 1H), 4.28-4.36 (m, 1H), 4.02-4.10 (m, 2H), 3.90-3.98 (m, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 202.3 (C), 109.7 (C), 77.6 (CH), 76.3 (CH), 65.0 (CH_2), 26.0 (CH_3), 25.6 (3 × CH_3), 25.1 (CH_3), 18.2 (C), –4.8 (CH_3), –5.1 (CH_3); IR (neat) ν 2932, 2858, 1737, 1256, 839.



164 **165** (93%, *E*:*Z* = 5:4)

α,β-unsaturated ester 165: To a solution of triethyl phosphonoacetate (4.8 g, 21.3 mmol, 1.1 eq) in THF (40 mL, 2 mL/mmol **164**) at –78 °C was added *n*-BuLi in hexane (20.4 mmol, 1.05 eq) and the solution stirred for 15 min before it was slowly added to the solution of aldehyde **164** (5.33 g, 19.4 mmol, 1 eq) in THF (40 mL, 2 mL/mmol) at –78 °C. The reaction was stopped after 30 min by quenching it with saturated aq. NH_4Cl (100 mL). The product was extracted with CH_2Cl_2 (3 × 80 mL), the combined organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1) afforded α,β-unsaturated ester **165** (6.23 g, 93%, *E*:*Z* = 5:4) as a clear oil.

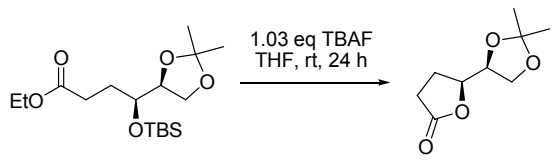
R_f(*E*) = 0.33, R_f(*Z*) = 0.41 (cyclohexane–EtOAc 10:1); ^{1}H-NMR (*E*-isomer) ($CDCl_3$, 400 Mhz) δ 6.99 (dd, J = 4.0 Hz, 15.6 Hz, 1H), 6.07 (dd, J = 1.9 Hz, 15.6 Hz, 1H), 4.44-4.50 (m, 1H), 4.11-4.24 (m, 3H), 3.93-3.99 (m, 1H), 3.74-3.81 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (*E*-isomer) ($CDCl_3$, 100.6 Mhz) δ 166.1 (C), 146.0 (CH), 122.1 (CH), 109.6 (C), 77.7 (CH), 71.9 (CH), 64.9 (CH_2), 60.3 (CH_2), 26.1 (CH_3), 25.7 (3 × CH_3), 25.0 (CH_3), 18.1 (C), 14.2 (CH_3), –4.9 (CH_3), –5.1 (CH_3); ^{1}H-NMR (*Z*-isomer) ($CDCl_3$, 400 Mhz) δ 6.19 (dd, J = 8.6 Hz, 11.8 Hz, 1H), 5.82 (dd, J = 0.9 Hz, 11.9 Hz, 1H), 5.38-5.45 (m, 1H), 4.10-4.24 (m, 3H), 3.87-4.01 (m, 2H), 1.41 (s, 3H), 1.33 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C-NMR (*Z*-isomer) ($CDCl_3$, 100.6 Mhz) δ 165.7 (C), 149.1 (CH), 119.9 (CH), 109.5 (C), 78.9 (CH), 68.2 (CH), 65.1 (CH_2), 60.2 (CH_2), 26.1 (CH_3), 25.7 (3 × CH_3), 25.5 (CH_3), 18.1 (C), 14.2 (CH_3), –4.7 (CH_3), –5.0 (CH_3); IR (neat) ν 2956, 2932, 2858, 1722. Anal. Calcd. for $C_{17}H_{32}O_5Si$: C, 59.27; H, 9.36, Found: C, 59.3; H, 9.4; $[\alpha]^{25}_D$ –21.1 (*c* 0.97, $CHCl_3$).



165 **166** (97%)

ester 166: To a solution of α,β-unsaturated ester **165** (6.23 g, 18.1 mmol, 1 eq) in MeOH (36 mL, 2 mL/mmol **165**) was added HCO_2NH_4 (4.56 g, 72.3 mmol, 4 eq) and 10% Pd/C (380 mg, 21 mg/mmol **165**). The suspension was stirred for 5 h at rt before being quenched with H_2O (20 mL). The product was extracted with EtOAc (3 × 60 mL), the combined organic layers dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc 20:1) to provide ester **166** (6.09 g, 97%) as a clear oil.

R_f = 0.32 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.09-4.14 (m, 2H), 4.00-4.04 (m, 1H), 3.93-3.97 (m, 1H), 3.71-3.74 (m, 2H), 2.31-2.49 (m, 2H), 1.74-1.83 (m, 1H), 1.57-1.67 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 173.5 (C), 109.2 (C), 78.5 (CH), 72.2 (CH), 65.4 (CH_2), 60.3 (CH_2), 30.2 (CH_2), 27.6 (CH_2), 26.4 (CH_3), 25.9 (3 × CH_3), 25.2 (CH_3), 18.1 (C), 14.2 (CH_3), –4.3 (CH_3), –4.8 (CH_3); IR (neat) ν 2956, 2932, 2858, 1737. Anal. Calcd. for $C_{17}H_{34}O_5Si$: C, 58.92; H, 9.89, Found: C, 58.6; H, 9.8; $[\alpha]^{25}_D$ –26.0 (*c* 1.00, $CHCl_3$).

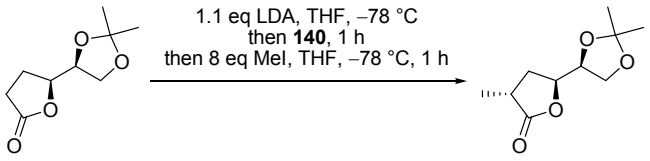


166 **140** (80%)

lactone 140: To a solution of ester **166** (3.71 g, 10.7 mmol, 1 eq) in THF (11 mL, 1 mL/mmol **166**) was added 1.0 M TBAF in THF (11 mL, 11.0 mmol, 1.03 eq). The solution was stirred for 24 h at rt and then evaporated under reduced pressure. The residue was taken up in little cyclohexane–EtOAc 5:1 and purified by flash chromatography (cyclohexane–EtOAc 5:1 to 2:1) to afford lactone **140** (1.60 g, 80%) as a clear oil.

R_f = 0.26 (cyclohexane–EtOAc 1:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.51 (ddd, J = 2.9 Hz, J = 5.0 Hz, J = 8.0 Hz, 1H), 4.17 (dt, J = 2.9 Hz, 6.9 Hz, 1H), 4.06 (dd, J = 6.9 Hz, 8.3 Hz, 1H), 3.90 (dd, J = 7.2 Hz, J = 8.2 Hz, 1H), 2.58-2.70 (m, 1H), 2.39-2.51 (m, 1H), 2.25-2.38 (m, 1H), 2.11-2.23 (m, 1H), 1.37 (s, 3H), 1.35 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 177.2 (C), 110.0 (C), 77.9 (CH), 77.5 (CH), 65.2 (CH_2), 27.9 (CH_2), 25.8 (CH_3), 25.5 (CH_3), 24.2

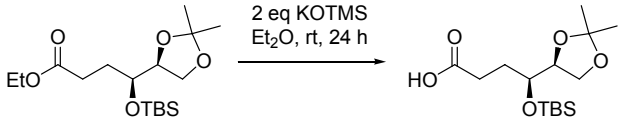
(CH_2); IR (neat) *v* 2987, 1777. Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58, Found: C, 57.8; H, 7.7; $[\alpha]^{25}_D$ +20.5 (*c* 1.10, $CHCl_3$).



140 **159** (69%, dr 4:1)

lactone 159: LDA was prepared in situ by adding *n*-BuLi in hexane (1.53 mmol, 1.1 eq) to a solution of diisopropylamine (0.23 mL, 1.67 mmol, 1.2 eq) in THF (2 mL, 1.4 mL/mmol **140**) at −78 °C. Lactone **140** (259 mg, 1.39 mmol, 1 eq) was dissolved in THF (2 mL, 1.4 mL/mmol **140**) and added dropwise to the LDA solution at −78 °C. After stirring for 1 h, the formed enolate was transferred to a solution of MeI (0.7 mL, 11.1 mmol, 8 eq) in THF (1 mL, 0.7 mL/mmol **140**) at −78 °C. The reaction was stirred at −78 °C for 1 h, and then quenched with saturated aq. NH_4Cl (3 mL). After extraction with EtOAc (3 × 20 mL) the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chomatography (cyclohexane–EtOAc 10:1 to 2:1) to give crude lactone (213 mg) as a mixture of monoalkylated lactone **159** (192 mg, 69%, dr 4:1), together with *gem*-dialkylated lactone (9:1 mixture).

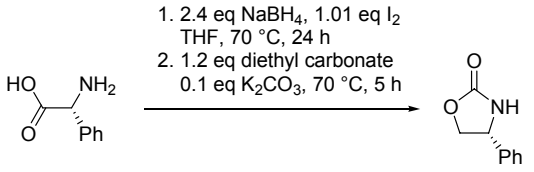
R_f = 0.42 (cyclohexane–EtOAc 1:1); ^{1}H-NMR ($CDCl_3$, 500 Mhz) δ 4.40-4.44 (m, 1H), 4.12-4.17 (m, 1H), 4.01-4.06 (m, 1H), 3.87-3.92 (m, 1H), 2.79-2.88 (m, 1H), 2.36-2.42 (m, 1H), 1.96-2.03 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.23 (d, *J* = 7.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 150.8 Mhz) δ 180.1 (C), 109.9 (C), 77.8 (CH), 75.3 (CH), 65.3 (CH_2), 33.6 (CH), 33.1 (CH_2), 25.7 (CH_3), 25.5 (CH_3), 16.0 (CH_3); IR (neat) *v* 2985, 2881, 1771, 1061. Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05, Found: C, 59.7; H, 8.0; $[\alpha]^{25}_D$ +27.2 (*c* 1.04, $CHCl_3$).



166 **170** (89%)

acid 170: To a solution of ester **166** (13.5 g, 39.0 mmol, 1 eq) in Et_2O (117 mL, 3 mL/mmol **166**) was added KOTMS (10 g, 78.0 mmol, 2 eq). The suspension was stirred for 24 h at rt before being quenched with saturated aq. NH_4Cl (400 mL). After extraction with EtOAc (3 × 240 mL), the organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 5:1 to 1:1) afforded acid **170** (11.1 g, 89%) as a clear thick oil.

R_f = 0.29 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.01-4.10 (m, 1H), 3.91-4.00 (m, 1H), 3.71-3.82 (m, 2H), 2.36-2.58 (m, 2H), 1.76-1.90 (m, 1H), 1.59-1.72 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 179.5 (C), 109.3 (C), 78.4 (CH), 71.9 (CH), 65.3 (CH_2), 30.0 (CH_2), 27.2 (CH_2), 26.4 (CH_3), 25.8 (3 × CH_3), 25.1 (CH_3), 18.1 (C), –4.3 (CH_3), –4.8 (CH_3); IR (neat) ν 2955, 2931, 2858, 1712. Anal. Calcd. for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.49, Found: C, 56.3; H, 9.5; $[\alpha]^{25}_D$ –28.8 (*c* 1.01, $CHCl_3$).



(*R*)-phenylglycine **171** (59%)

(*R*)-4-phenyloxazolidin-2-one 171[112]: Iodine (34 g, 134 mmol, 1.01 eq) dissolved in THF (80 mL, 0.6 mL/mmol (*R*)-phenylglycine) was added during 1 h to a suspension of (*R*)-phenylglycine (20 g, 132 mmol, 1 eq) and $NaBH_4$ (12 g, 317 mmol, 2.4 eq) in THF (160 mL, 1.2 mL/mmol (*R*)-phenylglycine) at 0 °C. Subsequently, the mixture was stirred for 2 h at rt and then refluxed for 24 h. After cooling down to rt, MeOH (105 mL, 0.8 mL/mmol (*R*)-phenylglycine) was added slowly, resulting in a clear solution. The solvents were removed under reduced pressure, and the white residue treated with 20% KOH (185 mL, 1.4 mL/mmol (*R*)-phenylglycine) and stirred for 2 h. After extraction with CH_2Cl_2 (5 × 100 mL), the combined organic phases were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Obtained crude product was purified by heating it under reduced pressure (75 °C, 1 mbar) for 30 min, and then distilling it (150 °C, 1 mbar). (*R*)-Phenylglycinol (10.8 g, 60%) was obtained as a white solid.

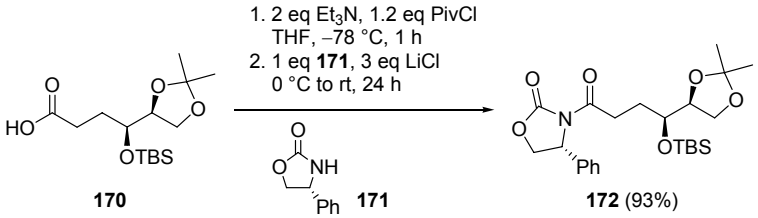
^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.24-7.33 (m, 5H), 4.03 (dd, J = 8.1 Hz, 4.4 Hz, 1H), 3.73 (dd, J = 10.6 Hz, 4.4 Hz, 1H), 3.53 (dd, J = 10.6 Hz, 8.1 Hz, 1H), 1.88 (br s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 142.4 (C), 128.5 (2 × CH), 127.3 (CH), 126.5 (2 × CH), 67.7 (CH_2), 57.3 (CH_2).

(*R*)-phenylglycinol (10.8 g, 78.4 mmol, 1 eq) was transferred to a distillation apparatus and diethyl carbonate (11.4 mL, 94.1 mmol, 1.2 eq) and K_2CO_3 (1.1 g, 7.84 mmol, 0.1 eq) added. The suspension was heated at 100°C for 4 h under atmospheric pressure. The resulting crude product was dried under reduced pressure, then filtered over Celite® and rinsed with CH_2Cl_2.

[112] a) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568-3571. b) Eur. Pat. Appl., 0232786, 19. Aug 1987.

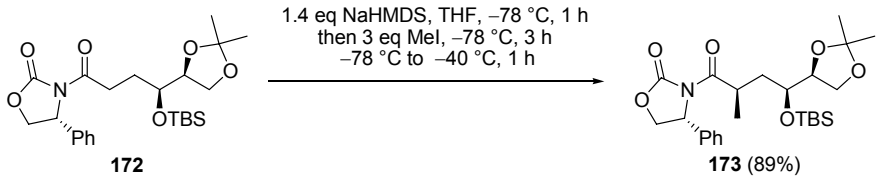
The solvent was removed under reduced pressure to afford (*R*)-4-phenyloxazolidin-2-one (**171**) (12.7 g, 59% over two steps) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 Mhz) δ 7.30-7.44 (m, 5H), 6.03 (br s, 1H), 4.91-4.99 (m, 1H), 4.73 (t, J = 8.7 Hz, 1H), 4.18 (dd, J = 7.1 Hz, 8.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 125.8 Mhz) δ 159.7 (C), 139.5 (C), 129.2 (2 × CH), 128.8 (CH), 126.0 (2 × CH), 72.5 (CH_2), 56.3 (CH); IR (neat) ν 3241, 1738, 1709, 1488, 1236, 1097, 1038, 924, 698. $[\alpha]^{25}_D$ +54.5 (*c* 1.15, $CHCl_3$).



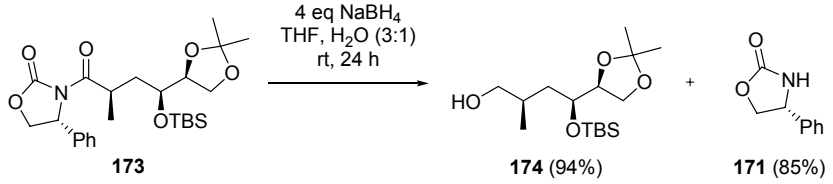
imide 172: To a solution of acid **170** (3.60g, 11.3 mmol, 1 eq) in THF (90 mL, 8 mL/mmol **170**) was added Et_3N (3.2 mL, 22.6 mmol, 2 eq) and the reaction mixture cooled down to –78 °C. PivCl (1.6 g, 13.6 mmol, 1.2 eq) was added slowly and the white suspension was left to stir in the cold for 2 h. After warming up to 0 °C, (*R*)-4-phenyloxazolidin-2-one **171** (1.8 g, 11.3 mmol, 1 eq) and LiCl (1.4 g, 34.0 mmol, 3 eq) were added at once. The reaction mixture was left to stir for 24 h at rt and then diluted with H_2O (40 mL). The aqueous phase was extracted with Et_2O (3 × 80 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc 10:1 to 2:1) to afford imide **172** (4.9 g, 93%) as a white solid.

R_f = 0.43 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.27-7.42 (m, 5H), 5.40 (dd, J = 3.6 Hz, 8.7 Hz, 1H), 4.68 (t, J = 8.8 Hz, 1H), 4.28 (dd, J = 3.6 Hz, 8.9 Hz, 1H), 4.00 (dd, J = 6.6 Hz, 13.1 Hz, 1H), 3.91 (dd, J = 6.8 Hz, 8.1 Hz, 1H), 3.66-3.77 (m, 2H), 2.93-3.15 (m, 2H), 1.72-1.85 (m, 1H), 1.52-1.69 (m, 1H), 1.38 (s, 3H), 1.31 (s, 3H), 0.88 (s, 9H), 0.07 (2 × s, 6H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 172.5 (C), 153.6 (C), 139.1 (C), 129.2 (2 × CH), 128.7 (CH), 125.9 (2 × CH), 109.2 (C), 78.5 (CH), 72.1 (CH), 70.0 (CH_2), 65.4 (CH_2), 57.5 (CH), 31.9 (CH_2), 26.5 (CH_2), 26.4 (CH_3), 25.8 (3 × CH_3), 25.2 (CH_3), 18.1 (C), –4.3 (CH_3), –4.8 (CH_3); IR (neat) ν 2930, 2857, 1785, 1708, 1383. Anal. Calcd. for $C_{24}H_{37}NO_6Si$: C, 62.17; H, 8.04; N, 3.02, Found: C, 62.2; H, 8.0; N, 2.9; $[\alpha]^{25}_D$ –59.7 (*c* 1.03, $CHCl_3$).



imide 173: To a solution of imide **172** (3.74 g, 8.06 mmol, 1 eq) in THF (16 mL, 2 mL/mmol **172**) at –78 °C was slowly added NaHMDS (2.07 g, 11.3 mmol, 1.4 eq) in THF (8 mL, 1 mL/mmol **172**), and the reaction mixture maintained at this temperature for 1 h. MeI (1.5 mL, 24.2 mmol, 3 eq) was added at once and the reaction mixture kept at –78 °C for 3 h, then warmed up over 1 h to –40 °C and quenched with saturated aq. NH_4Cl (20 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 10:1 to 5:1) afforded imide **173** (3.44 g, 89%) as a thick colorless oil.

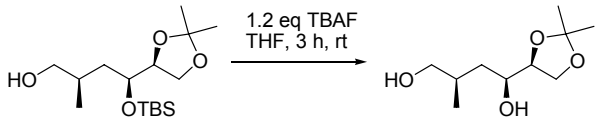
R_f = 0.31 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.25-7.42 (m, 5H), 5.44 (dd, J = 3.6 Hz, 8.8 Hz, 1H), 4.65 (t, J = 8.8 Hz, 1H), 4.25 (dd, J = 3.7 Hz, 8.9 Hz, 1H), 3.82-4.03 (m, 3H), 3.70 (t, J = 7.6 Hz, 2H), 1.90 (ddd, J = 2.7 Hz, 10.3 Hz, 13.3 Hz, 1H), 1.39 (s, 3H), 1.26-1.35 (m, 1H), 1.32 (s, 3H), 1.19 (d, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 175.6 (C), 152.9 (C), 139.2 (C), 129.2 (2 × CH), 128.6 (CH), 125.5 (2 × CH), 109.2 (C), 78.9 (CH), 71.7 (CH), 69.8 (CH_2), 65.6 (CH_2), 57.5 (CH), 35.4 (CH_2), 34.4 (CH), 26.4 (CH_3), 25.8 (3 × CH_3), 25.1 (CH_3), 19.0 (CH_3), 18.1 (C), –4.0 (CH_3), –5.0 (CH_3); IR (neat) ν 2931, 2857, 1785, 1703, 1383. Anal. Calcd. for $C_{25}H_{39}NO_6Si$: C, 62.86; H, 8.23; N, 2.93, Found: C, 63.1; H, 8.5; N, 2.7; $[\alpha]^{25}_D$ –88.0 (*c* 0.98, $CHCl_3$).



alcohol 174: To a solution of imide **173** (3.44 g, 7.20 mmol, 1 eq) in 3:1 THF/H_2O (22 mL, 3 mL/mmol **173**) was added $NaBH_4$ (1.09 g, 28.8 mmol, 4 eq). After stirring for 24 h at rt, aq. saturated NH_4Cl (30 mL) was added and the product extracted with EtOAc (3 × 60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was taken up in little 5:1 cyclohexane–EtOAc and filtered through a short plug of silica (cyclohexane–EtOAc 5:1) to separate (*R*)-4-phenyloxazolidin-2-one (**171**)

(1.0 g, 85%). Further purification by flash chromatography (cyclohexane–EtOAc 20:1 to EtOAc) afforded alcohol **174** (2.16 g, 94%) as a colorless oil.

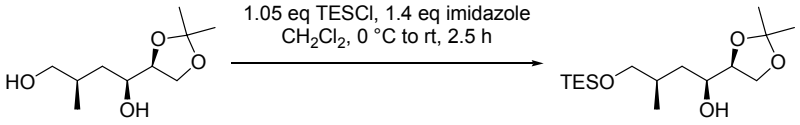
R_f = 0.19 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.10-4.19 (m, 1H), 3.95 (dd, *J* = 6.6 Hz, 8.1 Hz, 1H), 3.79-3.87 (m, 1H), 3.59-3.67 (m, 1H), 3.39-3.52 (m, 2H), 2.73 (br s, 1H), 1.76-1.92 (m, 1H), 1.44-1.54 (m, 1H), 1.32-1.42 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 0.85-0.94 (m, 12H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 109.2 (C), 78.4 (CH), 72.3 (CH), 67.8 (CH_2), 65.6 (CH_2), 38.1 (CH_2), 32.2 (CH), 26.5 (CH_3), 25.8 (3 × CH_3), 25.3 (CH_3), 18.6 (CH_3), 18.2 (C), –4.3 (CH_3), –4.8 (CH_3); IR (neat) ν 3440, 2955, 2930, 2857, 1254. Anal. Calcd. for $C_{16}H_{34}O_4Si$: C, 60.33; H, 10.76, Found: C, 60.2; H, 10.7; $[\alpha]^{25}_D$ –15.6 (*c* 1.01, $CHCl_3$).



174 **160** (99%)

diol 160: To a solution of alcohol **174** (1.92 g, 6.03 mmol, 1 eq) in THF (12 mL, 2 mL/mmol **174**) was added 1.0 M TBAF in THF (7.2 mL, 7.2 mmol, 1.2 eq). The solution was stirred for 3 h at rt, and then evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 5:1 to 1:2) afforded diol **160** (1.22 g, 99%) as a thick colorless oil.

R_f = 0.14 (cyclohexane–EtOAc 1:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 3.93-4.06 (m, 2H), 3.64-3.75 (m, 2H), 3.57 (dd, *J* = 4.7, 10.8 Hz, 1H), 3.50 (dd, *J* = 6.6, 10.9 Hz , 1H), 2.2-3.1 (br s, 2H), 1.90-2.05 (m, 1H), 1.48-1.59 (m, 1H), 1.36-1.44 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 0.95 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 109.5 (C), 79.2 (CH), 69.9 (CH), 67.3 (CH_2), 66.1 (CH_2), 37.6 (CH_2), 32.2 (CH), 26.7 (CH_3), 25.3 (CH_3), 17.3 (CH_3); IR (neat) ν 3443, 2933, 1372, 1064. Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87, Found: C, 58.4; H, 9.5; $[\alpha]^{25}_D$ –14.0 (*c* 0.98, $CHCl_3$).

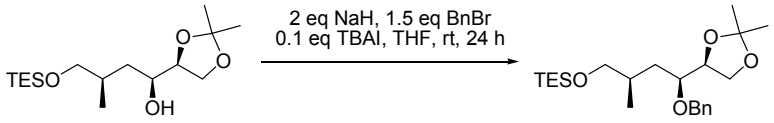


160 **175** (84%)

alcohol 175: To a solution of diol **160** (636 mg, 3.11 mmol, 1 eq) in CH_2Cl_2 (6 mL, 2 mL/mmol **160**) was added imidazole (297 mg, 4.35 mmol, 1.4 eq) and the reaction mixture stirred for 5 min at rt. After cooling down to 0 °C, TESCl (493 mg, 3.27 mmol, 1.05 eq) dissolved in CH_2Cl_2 (3 mL, 1 mL/mmol **160**) was added slowly over 30 min and the suspension stirred for 2 h at rt. Subsequently, the reaction was quenched with saturated aq. NH_4Cl (5 ml) and extracted with EtOAc (3 × 30 mL). The combined organic layers were

dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1 to 5:1) afforded alcohol **175** (829 mg, 84%) as a colorless oil.

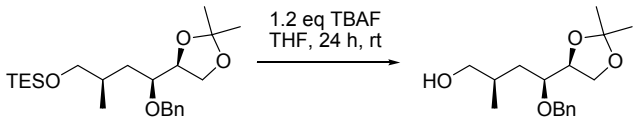
R_f = 0.32 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 3.95-4.05 (m, 2H), 3.63-3.77 (m, 2H), 3.54 (dd, J = 4.8 Hz, 9.9 Hz, 1H), 3.46 (dd, J = 6.3 Hz, 9.9 Hz, 1H), 2.91 (d, J = 4.6 Hz, 1H), 1.85-2.0 (m, 1H), 1.33-1.47 (m, 8H), 0.88-1.02 (m, 12H), 0.53-0.66 (m, 6H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 109.3 (C), 79.3 (CH), 70.1 (CH), 67.4 (CH_2), 66.1 (CH_2), 37.8 (CH_2), 32.2 (CH), 26.6 (CH_3), 25.4 (CH_3), 17.7 (CH_3), 6.7 (3 × CH_3), 4.3 (3 × CH_2); IR (neat) ν 3476, 2955, 2877, 1083, 742. Anal. Calcd. for $C_{16}H_{34}O_4Si$: C, 60.33; H, 10.76, Found: C, 60.2; H, 10.9; $[\alpha]^{25}_D$ –13.8 (c 1.36, $CHCl_3$).



175 **178** (86%)

ether 178: To a solution of alcohol **175** (2.43 g, 7.63 mmol, 1 eq) in THF (15 mL, 2 mL/mmol **175**) was added TBAI (282 mg, 0.763 mmol, 0.1 eq) and then slowly 60% NaH suspension in oil (610 mg, 15.3 mmol, 2 eq). After stirring for 10 min at rt, BnBr (1.4 mL, 11.4 mmol, 1.5 eq) was added at once and the reaction mixture left to stir for 24 h. After addition of pH 7 buffer (10 mL), the product was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc 50:1 to 20:1) to afford ether **178** (2.68 g, 86%) as a colorless oil.

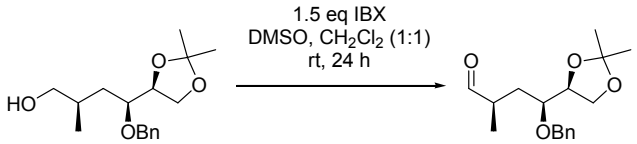
R_f = 0.35 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.24-7.39 (m, 5H), 4.81 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.14-4.22 (m, 1H), 3.98 (dd, J = 6.6 Hz, 8.1 Hz, 1H), 3.64-3.70 (m, 1H), 3.52-3.59 (m, 1H), 3.41 (dd, J = 5.2 Hz, 9.8 Hz, 1H), 3.34 (dd, J = 5.7 Hz, 9.8 Hz, 1H), 1.78-1.93 (m, 1H), 1.36-1.47 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.24-1.34 (m, 1H), 0.89-0.98 (m, 12H), 0.51-0.61 (m, 6H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 138.8 (C), 128.2 (2 × CH), 128.0 (2 × CH), 127.5 (CH), 109.3 (C), 79.1 (CH), 78.4 (CH), 72.7 (CH_2), 67.0 (CH_2), 66.1 (CH_2), 34.6 (CH_2), 32.1 (CH), 26.6 (CH_3), 25.5 (CH_3), 18.2 (CH_3), 6.8 (3 × CH_3), 4.3 (3 × CH_2); IR (neat) ν 2955, 2876, 1455, 1092, 742. Anal. Calcd. for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87, Found: C, 67.4; H, 9.8; $[\alpha]^{25}_D$ –36.0 (c 1.18, $CHCl_3$).



178 **179** (90%)

alcohol 179: To a solution of ether **178** (2.45 g, 6.0 mmol, 1 eq) in THF (6 mL, 1 mL/mmol **178**) was added 1.0 M TBAF in THF (7.2 mL, 7.2 mmol, 1.2 eq). The reaction was stirred for 24 h, then quenched with saturated aq. NH_4Cl (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc 10:1 to 2:1) to afford alcohol **179** (1.59 g, 90%) as a white solid.

R_f = 0.23 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 500 Mhz) δ 7.27-7.39 (m, 5H), 4.83 (d, J = 11.6 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.22-4.31 (m, 1H), 3.96-4.02 (m, 1H), 3.65-3.70 (m, 1H), 3.57-3.63 (m, 1H), 3.34-3.45 (m, 2H), 2.03-2.11 (m, 1H), 1.80-1.93 (m, 1H), 1.41-1.49 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125.8 Mhz) δ 138.3 (C), 128.4 (2 × CH), 128.1 (2 × CH), 127.7 (CH), 109.4 (C), 78.4 (CH), 77.8 (CH), 72.7 (CH_2), 67.4 (CH_2), 66.0 (CH_2), 34.8 (CH_2), 32.3 (CH), 26.6 (CH_3), 25.4 (CH_3), 17.9 (CH_3); IR (neat) ν 3438, 2932, 1455, 1371, 1212. Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90, Found: C, 69.6; H, 9.0; $[\alpha]^{25}_D$ –43.0 (c 0.965, $CHCl_3$).



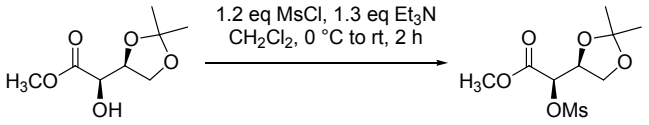
179 **180** (83%)

aldehyde 180: To a solution of alcohol **179** (589 mg, 2.0 mmol, 1 eq) in 1:1 DMSO/H_2O (4 mL, 2 mL/mmol **179**) was added IBX (841 mg, 3.0 mmol, 1.5 eq) and the suspension stirred for 24 h at rt. Then, IBX was filtered off and washed with CH_2Cl_2. To the filtrate H_2O (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 10:1 to 5:1) afforded aldehyde **180** (485 mg, 83%) as a pale-yellow oil.

R_f = 0.26 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 500 Mhz) δ 9.53 (d, J = 1.0 Hz, 1H), 7.25-7.37 (m, 5H), 4.74 (d, J = 11.3 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.20 (dd, J = 6.7 Hz, 13.6 Hz, 1H), 4.00 (dd, J = 6.6 Hz, 8.3 Hz, 1H), 3.72-3.77 (m, 1H), 3.51-3.58 (m, 1H), 2.54-2.62 (m, 1H), 1.69-1.77 (m, 1H), 1.58-1.67 (m, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125.8 Mhz) δ 204.0 (CH), 138.2 (C), 128.3 (2 × CH), 128.3

(2 × CH), 127.7 (CH), 109.5 (C), 78.4 (CH), 77.0 (CH), 73.0 (CH_2), 65.8 (CH_2), 42.6 (CH), 32.1 (CH_2), 26.5 (CH_3), 25.3 (CH_3), 13.9 (CH_3); IR (neat) ν 2984, 2934, 1723, 1381, 1213, 1071. $[\alpha]^{25}_D$ –45.0 (*c* 1.06, $CHCl_3$).

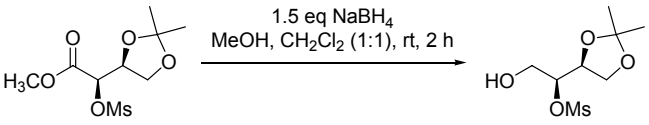
7.9 *Toward the C19-C27 Fragment of Lytophillipine A – Second Approach*



162 **181** (90%)

Ms-ester 181: To a solution of **162** (7.61 g, 40.0 mmol, 1 eq) in CH_2Cl_2 (120 mL, 3 mL/mmol **162**) was added Et_3N (7.3 mL, 52.0 mmol, 1.3 eq), followed by slow addition of MsCl (3.7 mL, 48.0 mmol, 1.2 eq) at 0 °C. The reaction mixture was stirred at this temperature for additional 2 h, and then quenched with saturated aq. $NaHCO_3$ (60 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). Combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure, and the crude crystalline product was dissolved in small amount of CH_2Cl_2 and subjected to flash chromatography (cyclohexane–EtOAc 1:1) to yield Ms-ester **181** (9.59 g, 90%) as white crystals.

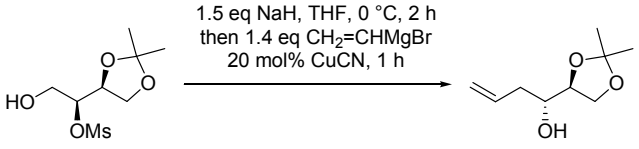
R_f = 0.25 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 4.98 (d, *J* = 4.8 Hz, 1H), 4.53 (dd, *J* = 5.3 Hz, 11.7 Hz, 1H), 4.12 (dd, *J* = 6.8 Hz, 9.0 Hz, 1H), 4.00 (dd, *J* = 5.5 Hz, 9.1 Hz, 1H), 3.81 (s, 3H), 3.17 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 167.1 (C), 110.5 (C), 77.2 (CH), 74.5 (CH), 65.4 (CH_2), 53.1 (CH_3), 39.1 (CH_3), 26.0 (CH_3), 25.1 (CH_3); IR (neat) ν 2989, 1757, 1364, 1335, 1217, 1173, 1112, 1062. Anal. Calcd. for $C_9H_{16}O_7S$: C, 40.29; H, 6.01, Found: C, 40.1; H, 5.9; $[\alpha]^{25}_D$ +40.3 (*c* 1.06, $CHCl_3$).



181 **182** (96%)

Ms-alcohol 182[11]: To a solution of Ms-ester **181** (8.33 g, 31.0 mmol, 1 eq) in 1:1 CH_2Cl_2/MeOH (62 mL, 2 mL/mmol **181**) was slowly added $NaBH_4$ (1.76 g, 46.5 mmol, 1.5 eq) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for further 2 h before being quenched with saturated aq. NH_4Cl (50 mL). The product was extracted with EtOAc (3 × 50 mL), organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to afford Ms-alcohol **182** (7.16 g, 96%) as a pale-yellow oil which required no further purification.

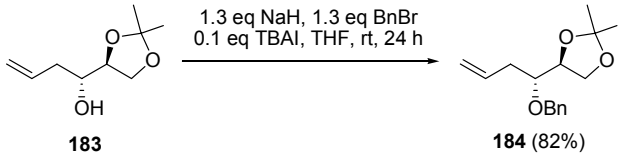
R_f = 0.20 (cyclohexane–EtOAc 1:1); ^{1}H-NMR ($CDCl_3$, 500 Mhz) δ 4.65-4.71 (m, 1H), 4.32-4.39 (m, 1H), 4.08-4.13 (m, 1H), 3.79-3.94 (m, 3H), 3.15 (s, 3H), 2.29 (br s, 1H), 1.44 (s, 3H), 1.36 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125.8 Mhz) δ 110.1 (C), 82.6 (CH), 74.6 (CH), 65.4 (CH_2), 62.4 (CH_2), 38.6 (CH_3), 26.2 (CH_3), 25.2 (CH_3); IR (neat) ν 3473 (br), 2988, 2939, 1349, 1173, 1074, 922. Anal. Calcd. for $C_8H_{16}O_6S$: C, 39.99; H, 6.71, Found: C, 40.0; H, 6.8; $[\alpha]^{25}_D$ –3.0 (*c* 1.00, $CHCl_3$).



182 **183** (80%)

allyl alcohol 183: To a solution of **182** (4.03 g, 16.8 mmol, 1 eq) in THF (84 mL, 5 mL/mmol **182**) was added slowly 60% NaH suspension in oil (1.0 g, 25.2 mmol, 1.5 eq) at 0 °C. The reaction mixture was left to stir at this temperature for 2 h, and then CuCN (300 mg, 3.35 mmol, 0.2 eq) was added at once, followed by slow addition of 1.0 M vinylmagnesium bromide in THF (23.5 mL, 23.5 mmol, 1.4 eq). After stirring for additional 90 min at 0 °C, the reaction was quenched with saturated aq. NH_4Cl (60 mL) and the product extracted with EtOAc (3 × 80 mL). Combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude oil was purified by flash chromatography (cyclohexane–EtOAc 20:1 to 2:1) to afford allyl alcohol **183** (2.31 g, 80%) as a colorless oil.

R_f = 0.35 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 500 Mhz) δ 5.78-5.90 (m, 1H), 5.10-5.23 (m, 2H), 3.97-4.07 (m, 2H), 3.88-3.97 (m, 1H), 3.73-3.82 (m, 1H), 2.28-2.38 (m, 1H), 2.14-2.26 (m, 1H), 2.03 (br s, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125.8 Mhz) δ 134.0 (CH), 118.3 (CH_2), 109.1 (C), 78.1 (CH), 70.4 (CH), 65.2 (CH_2), 37.6 (CH_2), 26.5 (CH_3), 25.3 (CH_3); IR (neat) ν 3464 (br), 2987, 1383, 1216, 1065. $[\alpha]^{25}_D$ –16.5 (*c* 0.90, $CHCl_3$).

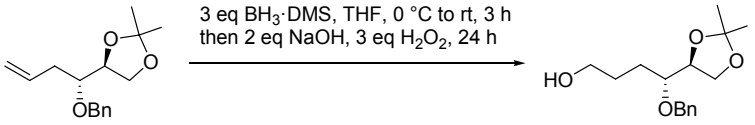


183 **184** (82%)

Bn-ether 184: To a solution of allyl alcohol **183** (1.8 g, 10.5 mmol, 1 eq) in THF (10.5 mL, 1 mL/mmol **183**) was added TBAI (386 mg, 1.05 mmol, 0.1 eq) and then slowly 60% NaH suspension in oil (544 mg, 13.6 mmol, 1.3 eq). After stirring for 20 min, BnBr (1.6 mL, 13.6 mmol, 1.3 eq) was added at once and the reaction mixture let to stir for 24 h at rt. The reaction was quenched with saturated aq. NH_4Cl (20 mL) and the product extracted with CH_2Cl_2

(3 × 50 mL). Combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure, and crude product purified by flash chromatography (cyclohexane–EtOAc 100:1 to 20:1) to afford Bn-ether **184** (2.26 g, 82%) as a colorless oil.

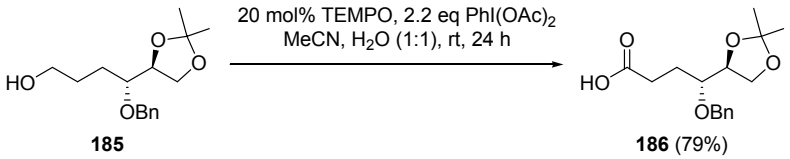
R_f = 0.36 (cyclohexane–EtOAc 10:1); ^{1}H-NMR ($CDCl_3$, 500 Mhz) δ 7.25-7.38 (m, 5H), 5.84-5.97 (m, 1H), 5.06-5.20 (m, 2H), 4.66 (d, J = 11.4 Hz, 1H), 4.60 (d, J = 11.4 Hz, 1H), 4.07-4.14 (m, 1H), 4.01-4.07 (m, 1H), 3.87-3.94 (m, 1H), 3.55-3.62 (m, 1H), 2.40-2.50 (m, 1H), 2.30-2.40 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125.8 Mhz) δ 138.4 (C), 134.2 (CH), 128.3 (2 × CH), 127.8 (2 × CH), 127.6 (CH), 117.5 (CH_2), 109.0 (C), 78.9 (CH), 77.2 (CH), 72.5 (CH_2), 66.4 (CH_2), 35.6 (CH_2), 26.6 (CH_3), 25.4 (CH_3); IR (neat) ν 2986, 2880, 1455, 1370, 1213, 1073 (br), 915, 856, 736, 698. Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45, Found: C, 73.3; H, 8.5; $[\alpha]^{25}_D$ –37.0 (c 1.01, $CHCl_3$).



184 **185** (72%)

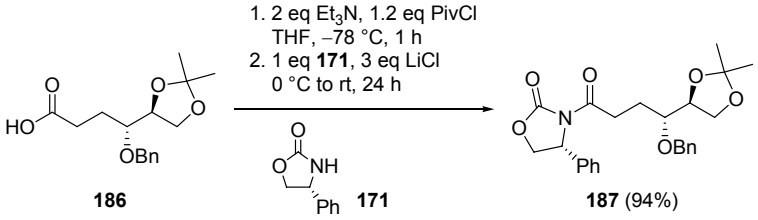
alcohol 185: To a solution of Bn-ether **184** (1.73 g, 6.60 mmol, 1 eq) in THF (26 mL, 4 mL/mmol **184**) was slowly added BH_3·DMS (2 mL, 19.8 mmol, 3 eq) at 0 °C. The reaction mixture was stirred for 4 h at rt before it was again cooled down to 0 °C and NaOH (528 mg, 13.2 mmol, 2 eq), dissolved in 2:1 EtOH/H_2O (13 mL, 2 mL/mmol **184**) was slowly added. Subsequently, H_2O_2 (1.92 g, 19.8 mmol, 3 eq) wad added and the reaction was stirred for 24 h at rt. The aqueous phase was separated and extracted with EtOAc (3 × 40 mL), the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure, and the crude product purified by flash chromatography (cyclohexane–EtOAc 5:1 to 2:1) to afford alcohol **185** (1.33 g, 72%) as a colorless oil.

R_f = 0.30 (cyclohexane–EtOAc 1:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.25-7.39 (m, 5H), 4.55-4.70 (m, 2H), 4.09-4.18 (m, 1H), 4.01-4.09 (m, 1H), 3.85-3.93 (m, 1H), 3.52-3.69 (m, 3H), 1.54-1.94 (m, 5H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 138.2 (C), 128.4 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 109.1 (C), 78.9 (CH), 77.5 (CH), 72.7 (CH_2), 66.5 (CH_2), 62.8 (CH_2), 28.1 (CH_2), 27.4 (CH_2), 26.6 (CH_3), 25.3 (CH_3); IR (neat) ν 3444 (br), 2935, 2875, 1454, 1381, 1212, 1070, 738, 698. Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63, Found: C, 68.3; H, 8.7; $[\alpha]^{25}_D$ –14.0 (c 1.01, $CHCl_3$).



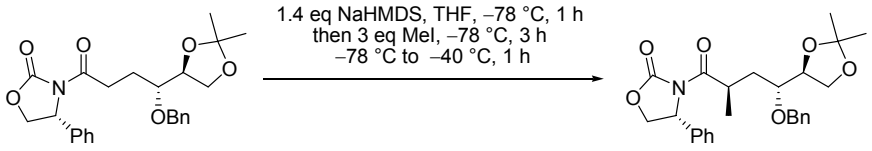
acid 186: Alcohol **185** (2.19 g, 7.81 mmol, 1 eq), TEMPO (244 mg, 1.56 mmol, 0.2 eq), $PhI(OAc)_2$ (5.54 g, 17.2 mmol, 2.2 eq) and $NaHCO_3$ (1.64 g, 19.5 mmol, 2.5 eq) were added to a flask and suspended in 1:1 $MeCN/H_2O$ mixture (16 mL, 2 mL/mmol **185**). The reaction mixture was stirred for 24 h at rt, and then quenched with saturated aq. NH_4Cl (40 mL). The product was extracted with EtOAc (3 × 60 mL), the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc 10:1 to 1:2) to afford acid **186** (1.81 g, 79%) as a pale-yellow oil.

R_f = 0.25 (cyclohexane–EtOAc 1:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.24-7.39 (m, 5H), 4.55-4.68 (m, 2H), 4.02-4.15 (m, 2H), 3.83-3.93 (m, 1H), 3.53-3.63 (m, 1H), 2.41-2.57 (m, 2H), 1.93-2.07 (m, 1H), 1.77-1.92 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 179.6 (C), 138.0 (C), 128.4 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 109.2 (C), 77.8 (CH), 77.2 (CH), 72.6 (CH_2), 66.4 (CH_2), 29.3 (CH_2), 26.5 (CH_3), 25.6 (CH_2), 25.2 (CH_3); IR (neat) ν 2986, 2935, 2884, 1709, 1371, 1213, 1074. Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53, Found: C, 65.5; H, 7.4; $[\alpha]^{25}_D$ –3.4 (*c* 1.05, $CHCl_3$).



imide 187: To a solution of imide **186** (1.78 g, 6.05 mmol, 1 eq) in THF (48 mL, 8 mL/mmol **186**) was added Et_3N (1.7 mL, 12.1 mmol, 2 eq) and the reaction mixture cooled down to –78 °C. PivCl (0.9 mL, 7.26 mmol, 1.2 eq) was added slowly and the white suspension was left to stir in the cold for 2 h. After warming up to 0 °C, (*R*)-4-phenyloxazolidin-2-one (**171**) (987 mg, 6.05 mmol, 1 eq) and LiCl (769 mg, 18.2 mmol, 3 eq) were added at once. The reaction mixture was left to stir for 24 h at rt and then diluted with H_2O (30 mL). The aqueous phase was extracted with Et_2O (3 × 60 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc 10:1 to 2:1) to afford imide **187** (2.49 g, 94%) as a pale-yellow oil.

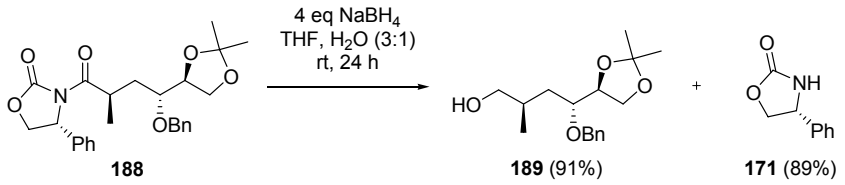
R_f = 0.33 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.23-7.42 (m, 10H), 5.33 (dd, J = 3.5 Hz, 8.7 Hz, 1H), 4.45-4.64 (series of multiplets, 3H), 4.23 (dd, J = 3.6 Hz, 8.9 Hz, 1H), 4.10 (dd, J = 6.3 Hz, 12.1 Hz, 1H), 4.02 (dd, J = 6.6 Hz, 7.9 Hz, 1H), 3.85 (dd, J = 6.6 Hz, 8.0 Hz, 1H), 3.51-3.59 (m, 1H), 3.20 (ddd, J = 6.1 Hz, 8.6 Hz, 17.6 Hz, 1H), 3.00 (ddd, J = 6.3 Hz, 8.5 Hz, 17.7 Hz, 1H), 1.90-2.02 (m, 1H), 1.77-1.89 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 172.4 (C), 153.6 (C), 139.1 (C), 138.3 (C), 129.1 (2 × CH), 128.7 (CH), 128.3 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 125.9 (2 × CH), 109.1 (C), 78.0 (CH), 77.5 (CH), 72.7 (CH_2), 69.9 (CH_2), 66.3 (CH_2), 57.6 (CH), 31.2 (CH_2), 26.5 (CH_3), 25.3 (CH_2), 25.2 (CH_3); IR (neat) ν 2984, 1782, 1706, 1383, 1204, 1071. Anal. Calcd. for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19, Found: C, 68.0; H, 6.9; $[\alpha]^{25}_D$ –37.5 (c 0.95, $CHCl_3$).



187 **188** (89%)

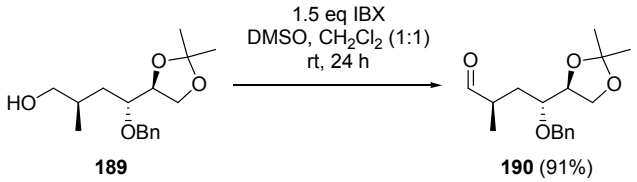
imide 188: To a solution of imide **187** (1.82 g, 4.14 mmol, 1 eq) in THF (8 mL, 2 mL/mmol **187**) at –78 °C was slowly added NaHMDS (1.06 g, 5.80 mmol, 1.4 eq) in THF (4 mL, 1 mL/mmol **187**), and the reaction mixture maintained at this temperature for additional 1 h. MeI (0.78 mL, 12.4 mmol, 3 eq) was added at once and the reaction mixture kept at –78 °C for 3 h, then warmed up to –40 °C over 1 h and quenched with saturated aq. NH_4Cl (20 mL). The aqueous phase was extracted with Et_2O (3 × 60 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 10:1 to 5:1) afforded imide **188** (1.67 g, 89%) as a thick colorless oil.

R_f = 0.51 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.25-7.42 (m, 8H), 7.14-7.21 (m, 2H), 4.97 (dd, J = 4.0 Hz, 8.8 Hz, 1H), 4.87 (d, J = 11.6 Hz, 1H), 4.53 (d, J = 11.6 Hz, 1H), 4.01-4.17 (m, 3H), 3.92-4.00 (m, 2H), 3.84-3.92 (m, 1H), 3.69-3.77 (m, 1H), 2.00-2.13 (m, 1H), 1.53 (td, J = 4.3 Hz, 14.1 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.06 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 176.2 (C), 153.4 (C), 139.4 (C), 138.7 (C), 129.1 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 127.4 (CH), 127.2 (2 × CH), 125.5 (2 × CH), 109.0 (C), 78.6 (CH), 77.5 (CH), 73.0 (CH_2), 69.3 (CH_2), 65.6 (CH_2), 57.5 (CH), 35.4 (CH_2), 34.6 (CH), 26.3 (CH_3), 25.1 (CH_3), 18.4 (CH_3); IR (neat) ν 2984, 2933, 2879, 1779, 1705, 1384, 1202, 1067. Anal. Calcd. for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09, Found: C, 68.5; H, 6.7; N, 2.9; $[\alpha]^{25}_D$ –81.6 (c 1.05, $CHCl_3$).



alcohol 189: To a solution of imide **188** (1.42 g, 3.13 mmol, 1 eq) in 3:1 THF/H_2O (12 mL, 3 mL/mmol **188**) was added $NaBH_4$ (473 mg, 12.5 mmol, 4 eq). After stirring for 24 h at rt, aq. saturated NH_4Cl (10 mL) was added and the product extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1 to EtOAc) afforded alcohol **189** (833 mg, 91%) as a colorless oil, and recovered (*R*)-4-phenyloxazolidin-2-one (**171**) (454 mg, 89%) as white crystals.

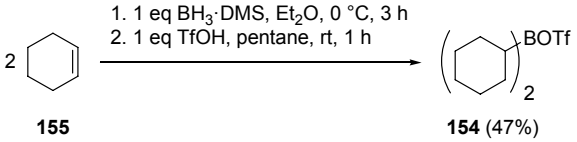
R_f = 0.23 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.25-7.39 (m, 5H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.10-4.18 (m, 1H), 4.01-4.08 (m, 1H), 3.89-3.96 (m, 1H), 3.69-3.76 (m, 1H), 3.36-3.53 (m, 2H), 1.80-1.95 (m, 2H), 1.52-1.64 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 1.27-1.40 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 138.2 (C), 128.4 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 109.0 (C), 78.7 (CH), 76.8 (CH), 73.2 (CH_2), 68.4 (CH_2), 65.7 (CH_2), 35.5 (CH_2), 32.6 (CH), 26.4 (CH_3), 25.2 (CH_3), 16.9 (CH_3); IR (neat) *v* 3441 (br), 2933, 2876, 1454, 1380, 1212, 1066. Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90, Found: C, 69.2; H, 9.2; $[\alpha]^{25}_D$ +10.2 (*c* 0.995, $CHCl_3$).



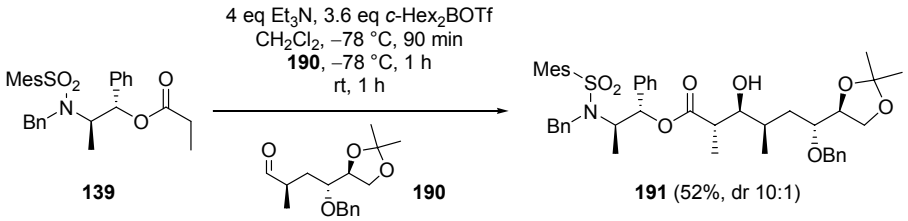
aldehyde 190: To a solution of alcohol **189** (375 mg, 1.28 mmol, 1 eq) in 1:1 DMSO/H_2O (2 mL, 2 mL/mmol **189**) was added IBX (535 mg, 1.91 mmol, 1.5 eq) and the suspension stirred for 24 h at rt. Then, IBX was filtered off and washed with CH_2Cl_2. To the filtrate H_2O (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 10:1 to 5:1) afforded aldehyde **190** (340 mg, 91%) as a pale-yellow oil.

R_f = 0.31 (cyclohexane–EtOAc 5:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 9.56 (d, *J* = 2.1 Hz, 1H), 7.25-7.39 (m, 5H), 4.72 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.09-4.17 (m, 1H), 4.01-4.08 (m, 1H), 3.83-3.94 (m, 1H), 3.57-3.69 (m, 1H), 2.49-2.66 (m, 1H), 1.89-2.02 (m,

1H), 1.40-1.52 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.12 (d, J = 7.2 Hz, 3H^{minor}), 1.04 (d, J = 7.1 Hz, 3H^{major}); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 204.4 (CH), 138.0 (C), 128.4 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 109.2 (C), 78.3 (CH), 76.5 (CH), 73.1 (CH_2), 65.8 (CH_2), 43.4 (CH), 32.9 (CH_2), 26.4 (CH_3), 25.1 (CH_3), 13.6 (CH_3); IR (neat) v 2985, 2934, 2877, 1723, 1455, 1380, 1212, 1072, 858. $[\alpha]^{25}_D$ +2.1 (c 1.105, $CHCl_3$).



dicyclohexylboron trifluoromethanesulfonate 154: To a solution of cyclohexene (**155**) (4.2 mL, 41.5 mmol, 2.08 eq) in Et_2O (12 mL, 0.3 mL/mmol **155**) at 0 °C was slowly added BH_3·SMe_2 (1.9 mL, 20 mmol, 1 eq). The suspension was stirred for 3 h at 0 °C, then the formed solid was allowed to settle without stirring. The supernatant organic phase was partially removed by syringe, while the rest was removed under reduced pressure to afford dicyclohexylborane as a white solid. The solid was immediately suspended in pentane (12 mL, 0.3 mL/mmol **155**) and CF_3SO_3H (1.8 mL, 20 mmol, 1 eq) was added very slowly under vigorous stirring at rt. After completed addition, the reaction was stirred for additional 1 h at rt. The solution was then placed in a −20 °C freezer for 24 h whereby crystalline product formed. The remaining liquid was taken out of the flask via syringe, and the crystalline solid was dried under reduced pressure to afford dicyclohexylboron trifluoromethanesulfonate (**154**) (3.07 g, 47%) as white crystals. To prepare 1.0 M solution for the use in the next step, the obtained crystals were dissolved in pentane (9.5 mL).



ester 191: To a solution of propionate **139** (558 mg, 1.16 mmol, 1 eq) in CH_2Cl_2 (5 mL, 5 mL/mmol **190**) was added Et_3N (0.65 mL, 4.65 mmol, 4 eq) and the mixture cooled down to −78 °C. 1.0 M c-Hex_2BOTf in pentane (4.3 mL, 4.2 mmol, 3.6 eq) was then added dropwise and the resulting suspension stirred for 90 min at −78 °C. Subsequently, aldehyde **190** (340 mg, 1.16 mmol, 1 eq) dissolved in CH_2Cl_2 (5 mL, 5 mL/mmol **190**) was added slowly and the reaction mixture stirred for 1 h at −78 °C, and 1 h at rt. The reaction was stopped by quenching with the pH 7 buffer (4 mL, 4 mL/mmol), MeOH (20 mL, 20 mL/mmol) and 35% H_2O_2 (2 mL, 2 mL/mmol). The mixture was stirred for further 1 h at rt, then the layers were

separated and aqueous layer extracted with CH_2Cl_2 (3 × 70 mL). Combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 20:1 to 5:1) afforded ester **191** (463 mg, 52%)[113] as a thick colorless oil.

R_f = 0.52 (cyclohexane–EtOAc 2:1); ^{1}H-NMR ($CDCl_3$, 400 Mhz) δ 7.15-7.37 (m, 13H), 6.80-6.92 (m, 4H), 5.79-5.87 (m, 1H), 4.64-4.84 (m, 2H), 4.46-4.63 (m, 2H), 4.01-4.16 (m, 3H), 3.88-3.93 (m, 1H), 3.57-3.75 (m, 2H), 2.46-2.55 (m, 7H), 2.25-2.32 (m, 3H), 1.77-1.92 (m, 1H), 1.45 (s, $3H^{major}$), 1.41 (s, $3H^{minor}$), 1.37 (s, $3H^{major}$), 1.35 (s, $3H^{minor}$), 1.32-1.58 (m, 2H), 1.06-1.24 (m, 4H), 0.96-1.03 (m, 3H), 0.86 (d, J = 6.9 Hz, $3H^{minor}$), 0.77 (d, J = 6.7 Hz, $3H^{major}$); ^{13}C-NMR ($CDCl_3$, 100.6 Mhz) δ 174.9 (C), 142.5 (C), 140.2 (2 × C), 138.7 (C), 138.3 (2 × C), 133.3 (C), 132.1 (2 × CH), 128.4 (4 × CH), 128.3 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 127.7 (CH), 127.6 (2 × CH), 127.1 (CH), 125.7 (2 × CH), 109.0 (C), 79.0 (CH), 78.1 (CH), 76.4 (CH), 75.5 (CH), 73.3 (CH_2), 65.5 (CH_2), 56.8 (CH), 48.1 (CH_2), 43.5 (CH), 36.5 (CH_2), 30.5 (CH), 26.4 (CH_3), 25.2 (CH_3), 22.9 (2 × CH_3), 20.9 (CH_3), 13.5 (CH_3), 13.3 (CH_3), 11.2 (CH_3); IR (neat) ν 3529, 2982, 2938, 1742, 1455, 1380, 1324, 1153, 1068, 858. $[\alpha]^{25}_D$ –14.1 (c 1.08, $CHCl_3$).

[113] Yield not optimized

8. *Compound Characterization List*

	IDENTITY								PURITY		
Compound, structure, or table-entry number	New compound	Known compound	IR	1H NMR	13C NMR	1H/1H COSY	1H/13C COSY	1H/1H NOESY	Copy of 1H/13C NMR spectrum in SI*	Elemental analysis	* SI = Supporting Information
alcohol 106		×	×	×	×				×	×	
acid 107		×		×	×				×		
ester 108		×	×	×	×				×	×	
β-hydroxyester 109		×	×	×	×				×	×	
AVE (*Z*,*Z*)-85		×	×	×	×				×	×	
AVE (*E*,*Z*)-85		×	×	×	×				×	×	
α-ketoester (±)-84		×		×	×				×		
α-ketoester (±)-90		×		×	×				×		
α-ketoester (+)-84		×	×	×	×				×	×	
diol 114	×		×	×	×				×	×	
aldehyde 115	×		×	×	×				×	×	
alcohol 117	×		×	×	×				×	×	
ketone 83	×		×	×	×				×	×	
α-ketoester (+)-90		×	×	×	×				×	×	
diol 118	×		×	×	×				×	×	
aldehyde 89	×		×	×	×				×	×	
dithiane 120	×		×	×	×				×	×	
acetal 121		×		×	×				×	×	
acetal 88	×		×	×	×		×		×	×	
alcohol 88b	×		×	×	×				×	×	
alcohol 116	×		×	×	×				×	×	
alcohol 119	×		×	×	×				×	×	
ester 110	×			×	×						
ester 111	×			×	×						
ester 112	×			×	×						
ester 113	×			×	×						

epoxide (±)-40		×	×	×	×				×		
bromobenzene 124		×	×	×	×				×		
bromobenzene 125		×	×	×	×				×	×	
bromobenzene 39		×	×	×	×				×	×	
alcohol (±)-41		×	×	×	×				×	×	
resorcine (±)-42		×	×	×	×				×	×	
acid (±)-51		×	×	×	×				×	×	
ester (±)-43		×	×	×	×				×	×	
ester (±)-43b	×		×	×	×				×	×	
dithiane 128		×	×	×	×				×	×	
acetal 129	×		×	×	×				×	×	
thioacetal (±)-130	×		×	×	×			×	×	×	
ketone (±)-131	×		×	×	×			×	×	×	
acetal 161		×		×	×				×		
ester 162		×	×	×	×				×	×	
TBS-ester 163		×	×	×	×				×	×	
aldehyde 164		×	×	×	×				×		
ester 165		×	×	×	×				×	×	
ester 166	×		×	×	×				×	×	
lactone 140		×	×	×	×				×	×	
lactone 159	×		×	×	×			×	×	×	
acid 170	×		×	×	×				×	×	
auxiliary 171		×	×	×	×				×		
imide 172	×		×	×	×				×	×	
imide 173	×		×	×	×				×	×	
alcohol 174	×		×	×	×				×	×	
diol 160	×		×	×	×				×	×	
alcohol 175	×		×	×	×				×	×	
ether 178	×		×	×	×				×	×	
alcohol 179	×		×	×	×				×	×	
aldehyde 180	×		×	×	×				×		
Ms-ester 181		×	×	×	×				×	×	
Ms-alcohol 182		×	×	×	×				×	×	
allyl alcohol 183		×	×	×	×				×		
Bn-ether 184		×	×	×	×				×	×	
alcohol 185		×	×	×	×				×	×	
acid 186	×		×	×	×				×	×	
imide 187	×		×	×	×				×	×	
imide 188	×		×	×	×				×	×	
alcohol 189	×		×	×	×				×	×	
aldehyde 190	×		×	×	×				×		
154		×									
ester 191	×		×	×	×	×	×		×		