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ISBN 0-315-62333-0
SYNTHETIC STUDIES DIRECTED TOWARDS THE ANTINEOPLASTIC MACROLIDE BRYOSTATINS

Abstract

This thesis describes stereocontrolled and practical routes to the C(1)–C(9), C(17)–C(20), and C(21)–C(27) synths of bryostatins, which are a closely related family of 20-membered ring lactones embedding 1,3-polyol units. Bryostatins are isolated in minute quantities from the marine Bryozoan Bugula neritina and possess exceptional antineoplastic activity.

Membrane-enclosed enantioselective enzymatic hydrolysis was successfully employed for the generation of gram quantities of the versatile building block (3R)-methoxymethoxypentadioic acid, monomethyl ester (51) (Chapter 2). This compound was used in the synthesis of the C(1)–C(5) segment of bryostatins.

Preliminary synthetic studies towards the C(1)–C(9) subunit are described in Chapter 3. Wittig and dithiane approaches were unfortunately unsuccessful for the connection of an enzymatically derived 5 carbon unit with a D-pantolactone derived 4 carbon unit.

Chapter 4 describes the practical synthesis of the C(1)–C(9) fragment of bryostatin in forms suitable for both structure/activity studies and synthetic elaboration. The pivotal step utilized a diastereoselective Mukaiyama aldol
condensation of a diketene derived silylenol ether with an enzymatically derived chiral β-alkoxyaldehyde.

Chapter 5 details the conversion of D-pantolactone and of D-galactono-1,4-lactone into the C(17)–C(20) and C(21)–C(27) synths of bryostatins via a chiron approach.

A study of nucleophilic additions onto chiral substituted γ-lactol templates is discussed in Chapter 6. This provided valuable information regarding the coupling of the C(17)–C(20) and C(21)–C(27) segments of bryostatins. As well, the results demonstrate the potential utility of γ-lactols as templates — a relatively unexplored area in asymmetric synthetic chemistry.
Acknowledgements

A global thank-you is extended to those who have, in various capacities, contributed directly and/or indirectly to the completion of this work. In particular, I must thank Dr. Clem Kazakoff for the mass spectroscopy service supplied, often on the same day. Also appreciated was the skillful NMR assistance provided by Raj Capoor and Dr. Heather Dettman.

I also acknowledge the advice and friendship extended to me by various people — especially those in Dr. Durst's, Dr. Morand's, and, most recently, Dr. Fallis' labs. Frequent conversations have led to valuable insights. My colleagues in Dr. Roy's lab made the past years enjoyable. Maintaining these friendships will be an important goal.

I must also express deep gratitude to my wife, Beth. Her constant support and unending patience (not to mention typing ability) have been of immense importance. She truly is a continual source of inspiration.

Finally, I must thank Dr. René Roy whose excellent guidance and perceptiveness made this project possible. His always open door and enthusiasm for chemistry were much appreciated.
Table of Contents

Abstract .............................................................................................................. i
Acknowledgements .......................................................................................... iii
Table of Contents ............................................................................................ iv
List of Figures ................................................................................................... viii
List of Tables .................................................................................................... x
List of Abbreviations ......................................................................................... xi

CHAPTER 1: INTRODUCTION
1.1 Isolation and Characterization ................................................................. 1
1.2 Biological Activities of Bryostatins ......................................................... 4
1.3 Previous Synthetic Approaches ............................................................... 5

CHAPTER 2: CHEMOENZYMATIC SYNTHESIS OF A C5 CHIRAL
BUILDING BLOCK: A SUBSTRATE MODIFICATION APPROACH
2.1 Introduction ............................................................................................... 22
2.2 Background ............................................................................................... 25
2.3 Reaction Conditions Control Approach ................................................... 26
2.4 Enantiomeric Excess and Absolute Configuration
   Determinations for 42 .................................................................................... 30
2.5 Pig Liver Esterase-Mediated Hydrolyses ................................................ 35
2.6 Substrate Modification Approach ............................................................. 36
2.7 Effect of Temperature ................................................................................ 45
2.8 Membrane-Enclosed Enzymatic Catalysis .............................................. 46
2.9a Enantiomeric Excess and Absolute Configuration
   Determinations for 49, 50, and 51 ............................................................. 48
2.9b Optical Purity of Methylbenzylamine ..............................................52
2.10 Chemical Modifications of 51 ...........................................................53
2.11 Conversion to a Chiral C₄–Synthon (63) ............................................55
2.12 Conclusions ......................................................................................56
2.13 Experimental ...................................................................................57

CHAPTER 3: WITTIG AND DIANION APPROACHS TOWARDS
THE C(1)–C(9) FRAGMENTS OF BRYOSTATINS

3.1 Introduction ......................................................................................75
3.2 Wittig Approach – Retrosynthetic Analysis .......................................75
3.3 Model Wittig Study ...........................................................................77
3.4 Dianion Approach – Retrosynthetic Analysis ...................................81
3.5 Preparation of the C₄ and C₅ Building Blocks 75 and 78 ..............83
3.6 Addition of 75 Onto C(5)-Activated Ester 78 ...............................85
3.7 Additions of 75 Onto the C(5) Aldehyde 83 ..................................89
3.8 Conclusions ......................................................................................93
3.9 Experimental ...................................................................................94

CHAPTER 4: SYNTHESIS OF THE C(1)–C(9) FRAGMENT OF
BRYOSTATIN BY LEWIS ACID MEDIATED ALDOL COUPLING

4.1 Introduction ......................................................................................104
4.2 Retrosynthetic Analysis ...................................................................104
4.3 Synthesis of the C(1)–C(5) Aldehyde Synthon (83): ....................107
4.4 Synthesis of the C(6)–C(9) Silylenol Ether Synthon (31): ............111
4.5 Condensation of C₄ and C₅ Synthons 31 and 83 .........................113
4.6 Synthesis of the C(1)–C(9) Fragment of Bryostatin in a
Form Suitable for Synthetic Elaboration (110): ...........................121
4.7 Synthesis of the C(1)–C(9) Fragment of Bryostatin in a Form Suitable for Structure/Activity Studies (29): 131

4.8 Conclusions 135

4.9 Experimental 136

CHAPTER 5: SYNTHESIS OF THE C(17)–C(20) AND C(21)–C(27) FRAGMENTS OF BRYOSTATIN BY THE CHIRON APPROACH

5.1 Introduction 153

5.2 Retrosynthetic Analysis 153

5.3 Synthesis of C(17)–C(20) Synthon (115) 158

5.4 Synthesis of the C(21)–C(27) Synthon (127) 159

5.5 Suggested Connection of the C(17)–C(20) (115) and the C(21)–C(27) (127) Synthons and
Complementation of the Synthesis of 37 164

5.6 Conclusions 166

5.7 Experimental 167

CHAPTER 6: MODEL STUDIES OF NUCLEOPHILIC ADDITIONS ONTO γ-LACTOL TEMPLATES

6.1 Introduction 180

6.2 Goal 180

6.3 Predictions 182

6.4 Synthesis of γ-Lactol Templates 115 and 76 185

6.5 Model Studies of 2-Lithio-1,3-Dithiane Additions
Onto γ-Lactols 115 and 76 186

6.6 Allyltrimethylsilane Addition onto γ-Lactols 115 and 77 198

6.7 Conclusions 206
6.8 Experimental ........................................207

APPENDIX A
Claims to Original Research ..............................227

APPENDIX B
Publications from Thesis ................................229
List of Figures

Figure 1 — The Bryostatins ----------------------------------------------- 2
Figure 2 — Masamune's Retrosynthetic Analysis for 1----------------------- 6
Figure 3 — Masamune's Retrosynthetic Analysis for 2----------------------- 7
Figure 4 — Masamune's Retrosynthetic Analysis for 3----------------------- 11
Figure 5 — Retrosynthetic Analysis for the C(1)–C(9) Subunit —
Mukaiyama Condensation Approach-------------------------------------- 17
Figure 6 — Retrosynthetic Analysis for the C(17)–C(27) Subunit —
Chiron Approach--------------------------------------------------------- 20
Figure 7 — Rate of α-CHY-Mediated Hydrolysis of 41 —
Percent Completion versus Reaction Time------------------------------- 28
Figure 8 — Capillary-GC Chromatogram of 44a and 44b-------------------- 33
Figure 9 — 1H NMR of 44a, 44b------------------------------------------ 34
Figure 10 — α-CHY Binding Site------------------------------------------ 37
Figure 11 — Effect of Temperature Upon the Rate of the
α-Chymotrypsin-Mediated Hydrolysis of 48------------------------------ 46
Figure 12 — 1H NMR Spectrum of 54-------------------------------------- 50
Figure 13 — Retrosynthetic Analysis for C(1)–C(9) Subunit —
Wittig Approach--------------------------------------------------------- 77
Figure 14 — Retrosynthetic Analysis for C(1)–C(9) Subunit —
Dianion Approach-------------------------------------------------------- 82
Figure 15 — Retrosynthetic Analysis for the C(1)–C(9) Subunit —
Mukaiyama Condensation Approach-------------------------------------- 106
Figure 16 — Danishefsky's Proposed Cage-Type Chelate------------------- 117
Figure 17 — BF$_3$Et$_2$O Electrostatic Repulsion Model ------------------- 119
Figure 18 — Transition State for β-Hydroxy Ketone Reduction ------- 123
Figure 19 — $^1$H NMR Spectrum of 108 ----------------------------- 126
Figure 20 — $^1$H NMR Spectrum of 110 ----------------------------- 130
Figure 21 — Comparison of $^{13}$C NMR Shifts for the C(1)–C(9) Segment of Bryostatin 1 versus 29 (in brackets) -------------- 133
Figure 22 — $^1$H NMR spectrum of 29 ----------------------------- 134
Figure 23 — Retrosynthetic Analysis for the C(17)–C(27) Subunit – Chiron Approach ------------------------------------------ 155
Figure 24 — Felkin-Ahn / Cram Model for Nucleophilic Addition
Onto 115--------------------------------------------------------------------- 183
Figure 25 — Chelation Model (Anti-Cram) for Nucleophilic
Addition Onto 76------------------------------------------------------------------ 185
Figure 26 — Configuration at C(20) of Adduct 138 –
$^1$H nOe Difference Results --------------------------------------------- 191
Figure 27 — $^1$H NMR of 138 --------------------------------------------- 192
Figure 28 — 1,4-Chelation Model for Nucleophilic Addition
Onto 115--------------------------------------------------------------------- 197
Figure 29 — Model for TiCl$_4$-Mediated Nucleophilic Additions
Onto 76--------------------------------------------------------------------- 201
Figure 30 — Configuration at C(4) of Adduct 147 –
$^1$H nOe Difference Results --------------------------------------------- 202
Figure 31 — $^1$H NMR of 147 --------------------------------------------- 203
Figure 32 — Configuration at C(4) of Adduct 151 –
$^1$H nOe Difference Results --------------------------------------------- 205
List of Tables

Table 1 — Summary of α-CHY-Mediated Hydrolysis of 41-------------------26
Table 2 — α-Chymotrypsin-Catalysed Hydrolysis of 41-------------------29
Table 3 — PLE-Mediated Hydrolysis of 41--------------------------------36
Table 4 — Chymotrypsin-Catalysed Hydrolysis of 45, 46, 47 and 48------------------40
Table 5 — Results from Santaniello's³⁸ Study---------------------------------42
Table 6 — PLE-Catalysed Hydrolysis of 41, 46, 47 and 48-------------------43
Table 7 — Results from Santaniello's³⁸ and Jones'⁴² Studies on PLE-Mediated Hydrolysies----------------------45
Table 8 — Enantiomeric Excess Determinations for 52, 53, and 54---------------------------49
Table 9 — Results for the Addition of 2-Lithio-1,3-Dithiane Onto 115 and 76-----------------------------------188
Table 10 — Comparison of the ⁱH NMR data of 1,3-O-Isopropylidene (136) and 1,3-O-Benzylidene (139) Acetals--------------------------193
Table 11 — Comparison of the ⁱH NMR data of 1,3-O-Isopropylidene (141) and 1,3-O-Benzylidene (143) Acetals--------------------------196
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
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<tbody>
<tr>
<td>Å</td>
<td>Angström</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>Ac₂O</td>
<td>acetic anhydride</td>
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<tr>
<td>ADEPT</td>
<td>Auto DEPT</td>
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<td>atmosphere</td>
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<td>BMS</td>
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<td>benzyl</td>
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<tr>
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<td>benzyl 2,2,2-trichloroacetimidate</td>
</tr>
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<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>cap</td>
<td>capillary</td>
</tr>
<tr>
<td>CDI</td>
<td>(N,N)-carbonylbis(imidazole)</td>
</tr>
<tr>
<td>α-CHY</td>
<td>α-chymotrypsin</td>
</tr>
<tr>
<td>Cl</td>
<td>chemical ionization</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
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<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
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doublet of doublets of doublets
diastereomeric excess
dicyclohexylcarbodiimide
distortionless enhanced polarization transfer
diisobutylaluminum hydride
N,N-diisopropylethylamine
4-dimethylaminopyridine
1,2-dimethoxyethane
N,N-dimethylformamide
2,2-dimethoxypropane
3,4-dimethoxyphenylmethyl
dimethylsulfoxide
doublet of triplets
ethyl chloroformate
(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
enantiomeric excess
electron impact
equivalent
ethyl
diethyl ether
ethyl acetate
fast atom bombardment
gram(s)
glacial acetic acid
gas chromatography
h ----------------------------------------------- hour(s)
His----------------------------------------------- histidine
HMPA ----------------------------------------------- hexamethylphosphoric triamide
HOAc----------------------------------------------- acetic acid
HOMCOR----------------------------------------------- homonuclear correlation
HPLC----------------------------------------------- high pressure liquid chromatography
HRMS----------------------------------------------- high resolution mass spectrometry
Hz----------------------------------------------- hertz
Im----------------------------------------------- imidazole
iPr----------------------------------------------- isopropyl
IR----------------------------------------------- infrared
L----------------------------------------------- litre
LAH----------------------------------------------- lithium aluminum hydride
LDA----------------------------------------------- lithium diisopropylamide
M----------------------------------------------- molar
M+----------------------------------------------- parent molecular ion
MBA----------------------------------------------- (R)-(−)-1-phenylethylamine
MCPBA----------------------------------------------- meta-chloroperoxybenzoic acid
MeCN----------------------------------------------- acetonitrile
Met----------------------------------------------- metal
min----------------------------------------------- minute(s)
μL----------------------------------------------- microlitre
mL----------------------------------------------- millilitre
mmol----------------------------------------------- millimole
mol----------------------------------------------- mole
mol. sieves---------------------------molecular sieves
MOM---------------------------------methoxymethyl
mp----------------------------------melting point
MPM---------------------------------4-methoxyphenylmethyl
MS----------------------------------mass spectrum
MTPA------(R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid
m/z---------------------------------mass to charge ratio
N-----------------------------------normal
nBuLi--------------------------------n-butyllithium
nq----------------------------------not quoted
NMR----------------------------------nuclear magnetic resonance
nOe----------------------------------nuclear Overhauser effect
NOESY-------------------------------nuclear Overhauser effect spectroscopy
N.R.---------------------------------no reaction
Nu----------------------------------nucleophile
PBS----------------------------------phosphate buffered saline
PCC----------------------------------pyridinium chlorochromate
Ph----------------------------------phenyl
PLE----------------------------------pig liver esterase
ppm---------------------------------parts per million
PPTS---------------------------pyridinium p-toluenesulfonate
py----------------------------------pyridine
q----------------------------------quartet
qu----------------------------------quintet
rf----------------------------------retention factor
R.T. ------------------------------- room temperature
s---------------------------------- singlet
sBuLi -------------------------------- s-butyllithium
t---------------------------------- triplet
T---------------------------------- temperature
tBu-------------------------------- --t-butyl
tBuLi-------------------------------- tert-butyllithium
TBDMS-Cl------------------------- tert-butyldimethylsilyl chloride
TBDMS-OTf--------- tert-butyldimethylsilyl trifluoromethanesulfonate
TBS-------------------------------- tert-butyldimethylsilyl
tBDPS-------------------------------- tert-butyldiphenylsilyl
TBDPS-Cl---------------------------------- tert-butyldiphenylsilyl chloride
tBuSH---------------------------------- tert-butyldithioli
TEMEDA-------------------------- N,N,N',N'-tetramethylethylenediamine
Tf---------------------------------- trifluoromethanesulfonate
THF---------------------------------- tetrahydrofuran
TIPS---------------------------------- tri-isopropylbenzenesulfonyl
tlc---------------------------------- thin layer chromatography
TLC---------------------------------- thick layer chromatography
TMS---------------------------------- trimethylsilyl
TMS-OTf---------------------------- trimethylsilyl trifluoromethanesulfonate
Ts---------------------------------- tosylate
TsOH------------------------------- p-toluenesulfonic acid
CHAPTER 1: INTRODUCTION

1.1 Isolation and Characterization

In 1965, Pettit, Kamano and their respective groups began a broad and systematic program to evaluate marine invertebrates and arthropods as sources of potentially useful anticancer drugs. By 1968, they had conclusively demonstrated that 9–10% of the marine invertebrates from exploratory collections displayed a confirmed level of activity in rats against U.S. National Cancer Institute's (NCI) murine P388 lymphocytic leukemia (PS System) or Walker carcinosarcoma 256. Subsequent efforts led to the isolation of numerous promising antineoplastic constituents. Of these, perhaps the two most striking examples are the macrocyclic lactones illustrated by bryostatin 1 (1a) (Figure 1) from Bugula neritina and the cyclic peptide of the dolostatin 3 class from the shell-less mollusc Dolabella auricularia.

---

Figure 1 — The Bryostatins

\[ \text{1a} \quad R=\text{COCH}_3; R_1=(2E,4E)\text{-octa-2,4-dienoyl} \] (Bryostatin 1)
\[ \text{1b} \quad R=\text{COCH}_2\text{C}(\text{CH}_3)_2; R_1=\text{COCH}_2\text{CH}_2\text{CH}_3 \] (Bryostatin 4)
\[ \text{1c} \quad R=\text{COCH}_2\text{CH}_2\text{CH}_3; R_1=\text{COCH}_3 \] (Bryostatin 6)
\[ \text{1d} \quad R=R_1=\text{COCH}_3 \] (Bryostatin 7)

Unlocking nature's important secrets can be fraught with difficulties. Pettit's endeavors towards the isolation and characterization of bryostatin 1 was no exception. The major obstacle was the low yield; one ton of wet organism delivers, after a lengthy isolation procedure, only 630 mg of bryostatin 1. In

1968, the initial collections of the invertebrate colonial filter-feeder *B. neritina* were made from the Gulf of Mexico. It was noted that extracts exhibited exceptional antineoplastic activity (100% life extension) against the NCI murine P388 lymphocytic leukemia\(^5\). Separation guided by these *in vitro* and/or *in vivo* systems led to the eventual isolation of the bioactive constituents — the bryostatins (1). The structure of the most abundant member of this family was unambiguously characterized by X-ray crystallography in 1982\(^2\).

*B. neritina* was formally described in 1758 and is now recognized as a cosmopolitan fouling organism resembling barnacles found on marine facilities and equipment\(^6\). Yet to be determined is whether bryostatins are endogenous or, alternatively, derived from common bryozoan food sources such as bacteria or phytoplankton. Likewise, the role for bryostatins is unknown. What is known is that cancer is essentially unknown among marine invertebrates\(^1a\).

Since the initial collection of *B. neritina*, subsequent collections have been made from the Eastern Pacific Ocean\(^7\), and the Gulfs of California, Mexico, and Sagami (Japan)\(^4\,6a\,8\). These collections have led to the isolation of a total of 17 bryostatins, all but one of which vary only in the C(7) and C(20) ester substituent. For example, bryostatin 1 has a C(7) acetate and a C(20)-(E,E)-octa-2,4-dieneoate substituent. Three C(20) deoxy bryostatins have recently been

discovered\textsuperscript{8a,b}. A representative sampling of the various bryostatins is shown in Figure 1. Interestingly, the other members of the bryostatin family are physiologically more active.

1.2 Biological Activities of Bryostatins

Pettit's efforts at isolating this scarce natural product appear to be well-justified. Bryostatins exhibit remarkable antineoplastic activity. The cause of this is a subject of intense interest. Results suggest that the bryostatin's mode of action depends upon its capacity to bind to the phorbol ester receptor of protein kinase C and, as a consequence, stimulate protein phosphorylation\textsuperscript{9}. Unlike phorbol esters (for instance, phorbol 12-myristate 13-acetate), bryostatins are not tumor promoters\textsuperscript{10}. In addition, bryostatins have immunoenhancing properties on cytotoxic T lymphocytes\textsuperscript{11} and inhibit RNA synthesis\textsuperscript{12}. Like avermectins, bryostatins do not appear to have antibacterial properties typical of other macrolide antibiotics\textsuperscript{13}. These promising biological activities have warranted pharmacological studies on the bryostatins. In this regard, they have currently reached Phase 2 of clinical trials.

\textsuperscript{13}G.R. Pettit, Unpublished results.
1.3 Previous Synthetic Approaches

By virtue of their attractive stereostructural features, promising biological profile, and relative scarcity, bryostatins represent an attractive synthetic target. The most advanced synthesis of bryostatin 1 has been accomplished by Masamune\textsuperscript{14} who is near completion. Evans\textsuperscript{15} is also engaged in the total synthesis. Partial syntheses have been accomplished by Thomas\textsuperscript{16} who has synthesized the C(10)–C(16) fragment and Lavallée\textsuperscript{17} and Garner\textsuperscript{18} who have outlined approaches towards the C(1)–C(9) and C(19)–C(25) segments, respectively. Of these syntheses, Masamune's will be examined.

Masamune's major disconnections were at the lactonic linkage and C(16)-C(17) double bond of 1 to yield the two major fragments 2 and 3 as depicted in Figure 2.

\textsuperscript{17}P. Lavallée, R. Ruel, L. Grenier, and M. Bissonnette, \textit{Tetrahedron Lett.}, 27, 679 (1986).
Figure 2 — Masamune’s Retrosynthetic Analysis for 1

1a R = (2E,4E)-octa-2,4-dienoyl (Bryostatin 1)

\[ \text{TBDPSO} \] + \[ \text{PhO}_2\text{S} \] = \[ \text{MOMO} \]
Dissection of 2 at the C(10)-C(11) bond revealed fragments 4 and 5 corresponding to the C(1)-C(10) and C(11)-C(16) segments of bryostatin 1 (Figure 3). The C(1)-C(10) intermediate 4 was further divided into 5 subunits.

Figure 3 — Masamune’s Retrosynthetic Analysis for 2

Masamune’s synthetic approach to 4 demonstrated the power of his chiral borolane mediated aldol methodology. It constituted the crucial step for the conversion of 6 to 8 and 9 to 11. Thus, the external chiral boron reagent effectively controlled the stereoselectivity in the creation of the chiral centres at C(3) (9:1 selectivity) and C(7) (3.9:1 selectivity). Another stereocontrolled reaction in this 12 step sequence was the chelation-controlled reduction of 11.
with the Saskena-Evans\textsuperscript{19} reagent tetrabutylammonium triacetoxyborohydride (11 to 12) to relay the stereochemistry at C(7) to C(5).

\[
\begin{align*}
\text{TBDPSO} & \quad \text{CHO} & & \quad \text{B(OAc)}_3 \\
\text{6} & & \quad \text{7} & & \quad \text{TBDPSO} \\
& & & & \quad \text{8} \\
\text{TBDPSO} & \quad \text{SC(Et)_3} & & \quad \text{B(OAc)}_3 \\
& & \quad \text{9} & & \quad \text{10} & & \quad \text{11} \\
& & & & & & \quad \text{12} & & \quad \text{4}
\end{align*}
\]

The 7-step synthesis of the achiral fragment 5 [C(10)–C(16)] was straightforward. The coupling of 4 and 5 was achieved with good stereocontrol (6:1) at C(11) again via a chiral-borolane mediated aldol reaction. The steps involved in the elaboration of 13 into the key intermediate 2 were as follows.

The C(1)–C(9) δ-lactol formation (13 to 14) was triggered by deacetonization and the C(11)–C(15) tetrahydropyran formation (14 to 15) assisted by Hg(OAc)$_2$. The problem of lack of stereocontrol at C(15) for this mercury-mediated cyclization was alleviated since treatment of 2 with Al$_2$O$_3$ effected equilibration to a 9:1 equatorial/axial mixture of C(16) aldehydes.
The lower-half of bryostatin 1 (3) was disconnected at the C(19) glycosidic linkage to afford the acyclic intermediate 17. Further disconnection at C(20)-C(21) revealed 18 and 19 as shown in Figure 4.
Fragment 18 derived its chirality from a Sharpless epoxidation\textsuperscript{20} of an allylic alcohol (20 to 22). Other important steps included selective epoxide ring opening\textsuperscript{21} (22 to 23) and periodate cleavage (23 to 18). This somewhat


lengthy 15-step synthesis of the four carbon fragment 18 \([C(17)-C(20)]\) is summarized below.

Fragment 19 was further disassembled into aldehyde 21 \([C(23)-C(27)]\) obtained from L-threonine (7 steps) and allenyl zinc bromide \([C(21)-C(22)]\). The coupling of these two pieces occurred with good stereocontrol (8:1) through chelation with the C(25) oxygen to afford 24 having the desired configurations at C(23). Pier's method\(^2\) was used to convert the acetylenic compound 24 into the tributyltin-E-olefin 25 in three steps. Conversion into the desired lithiated compound 19 involved changing the oxidation state at C(35) and halogen/metal exchange (4 steps). Coupling 19 with 18 occurred with 6:1 stereoselection at C(20) towards the desired diastereomer 26. Here the chirality at C(19) controlled the C(20) configuration by metal chelation. The phenyl sulfide 26 was

converted to the major fragment 3 by a six step sequence of straightforward functional group interconversions.
Difficulties were encountered in the Julia-Lythgoe\textsuperscript{23} olefin coupling of the C(1)–C(16) (2) and C(17)–C(27) (3) subunits of bryostatin 1. The presumed difficulty was steric congestion at C(17) and this problem was resolved by use of phenyllithium as base. Conversion of the coupled fragment 27 to 28 required 2 steps. Adjustment of the oxidation states at C(31) and C(35) and conversion to the C(20) acetate afforded 28 (5 steps). The remaining significant tasks to prepare the bryostatins is hydrolysis of the C(9) and C(19) methyl glycosides and macrolactonization.

Our retrosynthetic analysis of bryostatin 1 (1a) was similar to Masamune's in that the same major disconnections were made (Figure 2). However, our approaches to these major fragments differ considerably.
For the C(1)–C(9) segment, our strategy varies from Masamune’s by virtue of its simplicity and convergency. In comparison with Masamune’s synthesis which required the coupling of 4 fragments [C(1)–C(3); C(4)–C(5); C(6); C(7)–C(9)], ours requires only 2 fragments (Figure 5). The stereoselective coupling of a diketene derived 4 carbon unit [C(6)–C(9), 31] with a chiral, enzymatically derived, 5 carbon unit [C(1)–C(5), 32] was envisioned. Our efforts involved in the synthesis of the latter versatile chiral building block are detailed in Chapter 2. A prime consideration was the optimization of the enzymatic reaction in order to obtain, in a practical manner, gram quantities of 34 in high enantiomeric excess (> 95%).
Figure 5 — Retrosynthetic Analysis for the C(1)–C(9) Subunit —
Mukaiyama Condensation Approach

The use of 32 settles the stereochemical issue at C(3) of bryostatin. The synthetic plan was to employ this stereocentre to induce the desired configuration at C(5) upon addition of 31 via β-chelation. A Mukaiyama aldol condensation was viewed as the best method to accomplish this goal. Once the correct stereochemistry at C(5) is established, the stereocentre at C(7) should be
readily secured by the use of the highly anti-selective β-hydroxy ketone reduction technology recently developed by Saskena and Evans. The presence of a thiol ester at C(9) of 30 should enable regioselective mercury assisted lactonization to form the desired δ-lactone. This can be readily transformed into 29 which represents the C(1)–C(9) segment of bryostatin 1 (1a) in a form suitable for structure/activity studies. This route is described in Chapter 4.

Another strategically similar approach to the C(1)–C(9) subunit of bryostatin involves the coupling of a suitable form of 34 with a (R)-pantolactone derived C(6)–C(9) unit (35 or 36).

Using a fragment obtained from (R)-pantolactone for the C(6)–C(9) segment of the bryostatins provides the desired stereochemistry at C(7) and gem-dimethyl functionality at C(8). The critical C(5)–C(6) bond connection may be accomplished by a Wittig reaction between synthon 35 and the suitable phosphorane derived from 34. An alternate approach involves the coupling of the dithianyl anion of 36 with a C(5) electrophilic version of 34. Investigations into the viability of both these strategies are discussed in Chapter 3.
Retrosynthetic analysis of the C(17)–C(27) fragment of bryostatin (37) suggested the chiron approach (Figure 6). Thus, for the C(17)–C(20) and C(22)–C(27) segments (38 and 39), the judicious choice of starting materials [(R)-pantolactone for 38 and D-galactono-1,4-lactone for 39] allows high correspondence of stereogenicities while keeping group interconversions to a minimum. Evidence of this is that, in both cases, the syntheses compare well in terms of efficiency to Masamune's syntheses of similar fragments. This work is described in Chapter 5.
Integral to our C(17)–C(27) synthetic design was the use of the dithiane moiety as a linchpin to link the principal intermediates 38 and 39. Therefore, a key question is whether the stereocentre at C(19) of the γ-lactol 38 could induce the desired stereochemistry at C(20) upon connection with the C(21)–C(27) synthon. Results from a model study are detailed in Chapter 6. Other aspects
regarding the relatively unexplored area of using γ-lactol templates possessing α-chirality in asymmetric organic synthesis are also described in Chapter 6.

The synthetic work presented in this thesis should aid in the establishment of another stereocontrolled route to the bryostatins (1). Also, the successful synthesis of fragments of 1 permits biological activity studies which may provide insights regarding the promising biological profile of bryostatins. Finally, useful methodologies have been examined in the course of these synthetic studies which may have general applicability.
CHAPTER 2: CHEMOENZYMATIC SYNTHESIS OF A C_5 CHIRAL BUILDING BLOCK: A SUBSTRATE MODIFICATION APPROACH

2.1 Introduction

A close inspection of the bryostatin molecule (1) reveals that this product embeds masked 1,3-diol units. This functionality also occurs in the medicinally important polyene macrolides and in numerous natural products. This motivated us to develop a reiterative strategy for these units:

Recent developments show that the diastereoselective reduction of β-hydroxy ketones to form either anti or syn 1,3-diols is possible. Evans and Saskena, using tetrabutylammonium triacetoxyborohydride in acetic acid/acetonitrile at -40°C, obtained the 1,3-anti diol relationship with diastereoselectivities ranging from 20:1 up to 50:1 (for an example, see conversion of 96 and 97 to 106 and 107, Chapter 4.6). Likewise, Prasad has developed methodology for obtaining the 1,3-syn diol relationship with up to 98:2 diastereoselection. In this case, sodium borohydride in the presence of alkoxydialkylboranes as complexing agents was used. Thus, we envisioned that a chiral 3-hydroxylated 5-carbon template having unsymmetrically disposed 1,5-functionality would be a suitable general precursor. Other methods for the stereoselective construction of 1,3-diols include carbon-carbon bond forming.

---

reactions on β-alkoxy aldehydes and the enantioselective reduction of 1,3-diketones.

The asymmetric synthetic opportunities provided by exploiting the chiral catalytic properties of enzymes is well-documented. This area has witnessed explosive growth in the past decade. Enzymatic reactions — in both aqueous, and more recently, non-aqueous media — have been added to the organic chemist's arsenal. An early example was the α-chymotrypsin (α-CHY) mediated hydrolysis of dimethyl 3-hydroxyglutarate (41) to provide methyl hydrogen (3R)-hydroxyglutarate (42a).

---


The product 42a represents the 1,3-diol precursor we desired in our synthesis of the C(1)–(C9) fragment of bryostatin. Furthermore, it represents an excellent starting material for the synthesis of several biologically important natural products such as pimaricin\textsuperscript{25b}, the lactone portion of mevinic acids\textsuperscript{32}, L-carnititine\textsuperscript{33}, and (R)-4-amino-3-hydroxybutanoic acid (GABOB)\textsuperscript{33}. Also noteworthy is the fact that there are few 5-carbon chiral building blocks and that 42a is analogous to the popular 4-carbon malic acid synthon.


2.2 Background

The enzymatic reaction shown above was reported in 1961 by Cohen and Khedouri\textsuperscript{31}. They claimed that the stereospecificity of the hydrolysis was "essentially complete" and the absolute stereochemistry to be R. This was based upon derivatization of 42a to (-)-1-(3-acetoxy-4-methoxycarbonylbutanoyl)-1,3-bis-(dimethylaminophenyl)-urea. The optical rotation of this material was then compared to one reported previously\textsuperscript{34} for the same material prepared from completely resolved (+)-methyl hydrogen 3-acetoxyglutarate.

Heathcock (1984)\textsuperscript{35}, Brooks (1987)\textsuperscript{36}, Roy (1987)\textsuperscript{24}, Tamm (1987)\textsuperscript{37}, and Santaniello (1988)\textsuperscript{38} repeated this hydrolysis and found that the ee was not high enough to be of synthetic value. The enantiomeric excesses obtained and reaction conditions in these studies are tabulated on the next page.

\textsuperscript{34}K. Serck-Hansen, \textit{Arkiv. Kemi.}, 10, 135(1956).
Table 1 — Summary of α-CHY-Mediated Hydrolysis of 41

<table>
<thead>
<tr>
<th>Group</th>
<th>Year</th>
<th>Reported ee (Absolute Config.)</th>
<th>Conditions</th>
<th>41:CHY Ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen and Khedouri</td>
<td>1961</td>
<td>100% (R)</td>
<td>pH 7.8</td>
<td>2:1</td>
<td>31</td>
</tr>
<tr>
<td>Heathcock</td>
<td>1984</td>
<td>&quot;enantiomerically enriched&quot;</td>
<td>nq*</td>
<td>nq*</td>
<td>35</td>
</tr>
<tr>
<td>Brooks</td>
<td>1987</td>
<td>80% (R)</td>
<td>pH 6.7</td>
<td>2:1</td>
<td>36</td>
</tr>
<tr>
<td>Roy</td>
<td>1987</td>
<td>57-67 (R)</td>
<td>pH 6.7–7.8</td>
<td>5:1 to 1:2</td>
<td>24</td>
</tr>
<tr>
<td>Tamm</td>
<td>1987</td>
<td>60-69 (R)</td>
<td>pH 7.0–7.8</td>
<td>2:1</td>
<td>37</td>
</tr>
<tr>
<td>Santaniello</td>
<td>1988</td>
<td>55±5 (R)</td>
<td>nq</td>
<td>nq</td>
<td>38</td>
</tr>
</tbody>
</table>

*nq = not quoted.

2.3 Reaction Conditions Control Approach

Heathcock's\(^{35}\) observation that the enantioselectivity of this hydrolysis was dependent upon the reaction conditions motivated us to investigate the effect of the pH, substrate to enzyme ratio, and solvent system on the ee. The aim was to optimize the ee in order to obtain 42 of sufficient optical purity (>90%
ee) for asymmetric synthesis. Studies\textsuperscript{39} have already led to striking improvements in similar situations. For instance, Jones\textsuperscript{40} noted an increase in ee from 71\% to 91\% by addition of 20\% methanol to the buffer solution and lowering the temperature (20°C to 0°C) for the pig liver esterase (PLE, E.C. 3.1.1.1 Sigma Type II)-mediated hydrolysis of dimethyl 3-methylglutarate.

The substrate 41 used in this study was prepared using a procedure similar to the one employed by Cohen and Khedouri\textsuperscript{31}. Thus, commercially available dimethyl 3-ketoglutarate (40) was reduced by sodium borohydride in methanol to afford the prochiral alcohol 41 in 92\% yield. The α-CHY-mediated hydrolyses were also conducted in a similar manner to the one described by Cohen and Khedouri. The enzyme was dissolved in the buffer solution (generally 0.01N Na\textsubscript{2}HPO\textsubscript{4}) and the substrate added. This solution was stirred at room temperature and the pH was maintained at the desired level (6.7 to 7.8) by addition of 0.25N NaOH. Each reaction was worked up when 0.90 equivalents of hydroxide were added. Although complete reaction (ie. ~1.0 equivalents of hydroxide) could be reached, it lengthened the reaction time considerably since the rate of hydrolysis began to plateau as the reaction neared completion (Figure 7). Also, experimentation has demonstrated that the enantiomeric excess was not dependent upon the extent of reaction. The acid, ester product 42 was removed by an extractive workup. The graph (percent completion verses time) in Figure 7 illustrates the rate obtained for a typical hydrolysis.

Figure 7 — Rate of α-CHY-Mediated Hydrolysis of 41 —

Percent Completion versus Reaction Time

![Chemical structure and graph](image)

As shown in Table 2, the enantiomeric excesses obtained for the hydrolysis of 41 were disappointingly constant and low (55–65%) — even after exhaustive variations in reaction conditions.
Table 2 — α-Chymotrypsin-Catalysed Hydrolysis of 41

<table>
<thead>
<tr>
<th>α-CHY:</th>
<th>pH</th>
<th>Solvent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Absolute Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subst</td>
<td>(w/w)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:2</td>
<td>6.7</td>
<td>A</td>
<td>100</td>
<td>66</td>
<td>R</td>
</tr>
<tr>
<td>1:5</td>
<td>7.0</td>
<td>A</td>
<td>92</td>
<td>64</td>
<td>R</td>
</tr>
<tr>
<td>1:2</td>
<td>7.0</td>
<td>A</td>
<td>86</td>
<td>60</td>
<td>R</td>
</tr>
<tr>
<td>1:1</td>
<td>7.0</td>
<td>A</td>
<td>95</td>
<td>67</td>
<td>R</td>
</tr>
<tr>
<td>1:5</td>
<td>7.8</td>
<td>A</td>
<td>83</td>
<td>59</td>
<td>R</td>
</tr>
<tr>
<td>1:2</td>
<td>7.8</td>
<td>A</td>
<td>99</td>
<td>65</td>
<td>R</td>
</tr>
<tr>
<td>1:1</td>
<td>7.8</td>
<td>A</td>
<td>61</td>
<td>65</td>
<td>R</td>
</tr>
<tr>
<td>1:2</td>
<td>7.8</td>
<td>B</td>
<td>100</td>
<td>57</td>
<td>R</td>
</tr>
<tr>
<td>2:1</td>
<td>7.0</td>
<td>C</td>
<td>67</td>
<td>64</td>
<td>R</td>
</tr>
</tbody>
</table>

<sup>a</sup>A = 0.01M Na<sub>2</sub>HPO<sub>4</sub> buffer; B = A + 20% MeOH; C = PBS. Reactions performed at room temperature.

<sup>b</sup>Yields of isolated 42 based on recovered 41.

<sup>c</sup>Determined by GC and <sup>1</sup>H NMR analysis on 44.

The explanation for the moderate enantioselectivity can only be rationalized in terms of non-specific binding of the substrate in the enzymatic binding site. This alternate binding mode is independent of reaction conditions. For example, a 13 fold decrease in hydroxide ion concentration (pH 7.8 to 6.7) had essentially no effect upon the ee obtained. Clearly, competing chemical hydrolysis was too slow to be a factor. This conclusion was further substantiated by the following experiment. In the absence of α-CHY, but otherwise identical
reaction conditions (0.01N Na₂HPO₄ buffer; pH = 7.8), the rate of hydrolysis of 41 was extremely low (~0.15% /hour). In contrast to Jones’ observations with PLE, addition of an organic co-solvent (20% methanol) decreased the ee. Changing to the PBS buffer system had no effect. Likewise, the substrate to enzyme ratio had little effect upon the enantioselectivity of the hydrolysis: however, it did effect the rate of reaction. While this investigation was in progress, Tamm²⁷ determined the effect of pH upon the ee obtained for this hydrolysis. His results and conclusions are in agreement with ours.

2.4 Enantiomeric Excess and Absolute Configuration

Determinations for 42

The enantiomeric excesses for these trials were determined by conversion of the crude acid, ester products (42a,42b) to their corresponding (R)-1-phenylethyl amide derivatives (43a,44b) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and (R)-(+-)-α-methylbenzylamine in tert-butanol in 60% yield. Subsequent formation of the tert-butyldimethylsilyl (TBDMS) ether using a standard procedure (TBDMS-OTf, imidazole, CH₂Cl₂) afforded diastereomeric protected amides 44a and 44b in 83% yield (50% overall yield from 42).
The ratio of the diastereomeric amides 44a and 44b could be conveniently determined by capillary GC (near-baseline separation, conditions are given in the Experimental section of this Chapter) or by the relative intensities of the respective tert-butyl or methoxy resonances in the $^1$H NMR (300 MHz) spectrum of the mixture (0.85 versus 0.79 ppm for the C(CH$_3$)$_3$ protons; 3.65 versus 3.68 ppm for the CO$_2$CH$_3$ protons for 44a and 44b, respectively). This method is an adaptation of a HPLC method described by Heathcock$^{35}$. The only other criterion for assaying the optical purity of 42 was its low specific rotation ($[\alpha]_D = -1.7^\circ$ (c = 12.5%, CHCl$_3$)$^{31}$. However, Heathcock$^{35}$ and others$^{37}$ have demonstrated that optical purity evaluation of a viscous oil by its optical rotations can be unreliable due to the fact that this physical property is sensitive to temperature and substrate concentrations.

The accuracy and precision of these techniques (GC and $^1$H NMR) for determining the ee of 42 was verified by two methods. Thus, the ee was determined for racemically prepared 42 (via saponification of 41) and was, within experimental error, 0% using either technique. In the second, there was
good agreement (±1.5%) between the enantiomeric excesses determined by these techniques. Figure 8 illustrates a typical chromatogram of the diastereomeric amides 44a and 44b and Figure 9 shows a typical $^1$H NMR spectrum.
Figure 8 — Capillary-GC Chromatogram of 44a and 44b

Column: vitreous silica bonded BP1 (megabore) (0.22 mm X 0.33 mm)
Length: 10 m
Split Ratio: 20:1
Temperatures:
Column: 180°C
Injector: 230°C
Detector: 300°C
Gas Chromatograph:
Varian 3300
Carrier Gas: N₂
Detector: FID
Figure 9 — $^1$H NMR of 44a, 44b
2.5 Pig Liver Esterase-Mediated Hydrolyses

We were unable to affect the diastereomeric transition state energy differences between the competing enantiotopic ester group hydrolysis pathways by this reaction conditions control approach (Table 2). Even the highest ee obtained (67%) was still too low for chemoenzymatic synthesis. A solution was still required.

We were reluctant to abandon the use of α-CHY as being the enzyme of choice for this transformation for several reasons. It is a relatively inexpensive enzyme (10 g, $105.30 US, Sigma). Also, α-CHY is a hardy enzyme which may be stored for extended periods of time (years) and is obtained in a highly crystalline, monomeric form. It exhibits no allosteric effects and, finally, does not require cofactors. However, since the optical purity of 42 obtained by this method was too low to be of use in our future synthetic plans, we explored the possibility of using PLE. In an analogous trial to the one described for α-CHY, the PLE-mediated hydrolysis of 41 afforded methyl hydrogen (3S)-hydroxyglutarate (42b) as the major enantiomer formed. The ee was a low 15%; obviously, the use of PLE does not constitute a solution either. Similar results have been obtained by others (Table 3).
Table 3 — PLE-Mediated Hydrolysis of 41

<table>
<thead>
<tr>
<th>Group</th>
<th>Year</th>
<th>Reported ee (Absolute Config.)</th>
<th>Conditions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamm</td>
<td>1983</td>
<td>12% (S)</td>
<td>pH 7.8</td>
<td>41:PLE Ratio&lt;sup&gt;a&lt;/sup&gt; 1.8:200</td>
</tr>
<tr>
<td>Jones</td>
<td>1986</td>
<td>nq&lt;sup&gt;b&lt;/sup&gt;</td>
<td>pH 7.0</td>
<td>1.0:400</td>
</tr>
<tr>
<td>Roy</td>
<td>1987</td>
<td>15% (S)</td>
<td>pH 7.0</td>
<td>0.5:70</td>
</tr>
<tr>
<td>Tamm</td>
<td>1987</td>
<td>22% (S)</td>
<td>pH 7.8</td>
<td>1.8:200</td>
</tr>
<tr>
<td>Santaniello</td>
<td>1988</td>
<td>30±5% (S)</td>
<td>pH 7.0</td>
<td>0.5:130</td>
</tr>
<tr>
<td>Baader&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1988</td>
<td>76% (S)</td>
<td>pH 7.0</td>
<td>nq&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Jones</td>
<td>1989</td>
<td>16% (S)</td>
<td>pH 7.0</td>
<td>1.0:400</td>
</tr>
</tbody>
</table>

<sup>a</sup> Grams of 41: units of PLE.

<sup>b</sup>nq = not quoted.

<sup>c</sup> di-n-propyl-3-hydroxyglutarate used as substrate at 0°C.

### 2.6 Substrate Modification Approach

As discussed, it was hypothesized that two orientations of the substrate within the binding site of α-CHY were responsible for the lack of enantioselectivity. Therefore, the solution was realized by modification of the substrate in a logical manner in order to prevent the alternate mode of binding leading to the undesired S-monoacid 42<sub>b</sub>. We were aided in these

modifications to the substrate by the fact that there is considerable information available regarding catalysis by α-CHY and the nature of the binding site\textsuperscript{43}. In other words, we wished to vary the substrate in order to take better advantage of the enzyme's active site.

For substrate 41, it seemed likely that the h (hydrogen) domain was not sterically congested enough to prevent the binding of the unprotected 3-hydroxy group in competition for the am (amide) domain as illustrated in Figure 10.

![Figure 10 — α-CHY Binding Site](image)

This undesired orientation would permit the pro-R ester to be hydrolyzed. Therefore, to prevent this binding, a suitable derivatization could constrain the 3-hydroxyl function of the substrate to bind to the am domain provided that the pro-R ester group would still have a higher affinity for the ar (aromatic) domain. To

test this postulate, the dimethyl 3-hydroxyglutarate substrate was derivatized as shown.

These straightforward transformations utilized well-known protecting group methodology. The only difficulty occurred when making the benzyl ether protected substrate 46. Due to the sensitivity of 41 to strong base, the benzylation attempts using sodium hydride–benzyl bromide conditions\(^\text{44}\) were unsuccessful. The benzyl group was incorporated by the use of the acid

\(^{44}\text{For instance, S. Czernecki, C. Georgoulis, and C. Provelegniou, }\textit{Tetrahedron Lett.}, \textit{17}, 3535 (1976).\)
catalysed reaction of 41 with benzyl trichloroacetimidate in 61% yield. This methodology was developed by Bundle\textsuperscript{45}. Treatment of 41 with chloromethyl methyl ether (MOM-Cl) under standard conditions\textsuperscript{46} afforded the MOM ether 48 in good yield (88%). However, the less utilized procedure\textsuperscript{47} with dimethoxymethane and P$_2$O$_5$ also completed the task in 94% yield. The latter method was preferred since the yield was better and the use of the carcinogenic MOM-Cl was avoided.

A number of results using this substrate modification approach are summarized in Table 4.

Table 4 — Chymotrypsin-Catalysed Hydrolysis of 45, 46, 47 and 48

<table>
<thead>
<tr>
<th>Entry</th>
<th>CHY:Sub (w/w)</th>
<th>pH</th>
<th>Solvent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>Absolute Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2:1 (45)</td>
<td>7.8</td>
<td>A,B,C</td>
<td>~0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>1:1 (46)</td>
<td>7.8</td>
<td>B</td>
<td>68</td>
<td>86</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>1:2 (47)</td>
<td>7.8</td>
<td>B&lt;sup&gt;d&lt;/sup&gt;</td>
<td>42</td>
<td>86</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>1:1 (47)</td>
<td>7.8</td>
<td>B</td>
<td>86</td>
<td>94</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>1:2 (47)</td>
<td>7.8</td>
<td>B&lt;sup&gt;e&lt;/sup&gt;</td>
<td>68</td>
<td>93</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>1:2 (48)</td>
<td>7.8</td>
<td>A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>100</td>
<td>90</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>1:2 (48)</td>
<td>7.0</td>
<td>A</td>
<td>95</td>
<td>95</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>1:1 (48)</td>
<td>7.8</td>
<td>A</td>
<td>100</td>
<td>95</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>2:1 (48)</td>
<td>7.8</td>
<td>A&lt;sup&gt;d&lt;/sup&gt;</td>
<td>92</td>
<td>95</td>
<td>R</td>
</tr>
</tbody>
</table>

<sup>a</sup>A = 0.01M Na<sub>2</sub>HPO<sub>4</sub> buffer; B = A + 20% 1,4-dioxane; C = A + 20% MeOH. Reactions performed at room temperature unless indicated otherwise.

<sup>b</sup>Yields of isolated 49, 50, and 51 based on recovered 46, 47, and 48. Yields may vary depending on the extent of completion which was followed by the equivalent of base consumed.

<sup>c</sup>Determined by GC and/or 1H-NMR analysis on 52, 53, and 54 (Chapter 2.9a).

<sup>d</sup>Accomplished at 36°C.

<sup>e</sup>Membrane-Enclosed Enzymatic catalysis (MEEC).

Some general comments regarding Table 4 are as follows. The configuration of the major enantiomer for substrates 46, 47, and 48 remained R which suggested that the orientation of the substrate within the active site was as predicted and corresponded to the pro-S ester binding in the n (active) site. As well, the postulate of obtaining more selective binding was rewarded since higher enantiomeric excesses were obtained.
The only substrate of those made that did not work was dimethyl 3-[(tert-butyldimethylsilyl)oxy]glutarate (45) (entry 1). A plausible explanation for this was that, even with organic co-solvents such as methanol and 1,4-dioxane added, this substrate was too insoluble in the buffer media. Another less likely explanation is that the tert-butyldimethylsilyl group was overly bulky to fit into the enzymatic active site.

The next substrate tried was the benzyl ether 46. For this substrate, the maximum ee obtained was 86% (entry 2). A problem with this substrate was that, like 45, it had relatively low solubility in the buffer media. This resulted in a slow rate of hydrolysis (1 day for 50% completion) — even at high α-CHY to 46 ratios. It also required the addition of 1,4-dioxane as a co-solvent [up to 20% (v/v), greater 1,4-dioxane concentrations denatured the enzyme]. Thus, although substrate 46 demonstrated that we were on the right track, there were practical difficulties.

The next substrate tested was dimethyl benzoylglutarate 47 (entries 3, 4, and 5). The rate of hydrolysis was slightly better (50% completion in 20 hours) relative to 46 under the same conditions (pH 7.8, 1:1 substrate to α-CHY ratio, 20% 1,4-dioxane). More significantly, this substrate allowed a more enantioselective hydrolysis. The ee of the product obtained was 94% (entry 4). In order to improve the utility of this reaction (ie. permit the use of lower α-CHY:47 ratio) the temperature of the reaction media was increased to 36±1°C (entry 3). This had the desired effect upon the rate of reaction with 50% completion being reached in 5 hours. Unfortunately, this benefit was counterbalanced by a decrease in the enantioselectivity of the hydrolysis (ee = 86%).
Clearly, what was required was a 3-hydroxyl protected substrate which was water soluble. The answer was dimethyl 3-methoxymethoxyglutarate (48) (entries 6, 7, 8, and 9). Under identical conditions to those used for 46 and 47, the rate of hydrolysis was much faster (50% completion in 2.5 hours, pH = 7.8, 1:1 α-CHY/48 ratio). Also, in contrast to 47, the rate of hydrolysis could be improved substantially (50% completion in less than 2 hours) by increasing the temperature without resulting in a loss in optical purity (entry 9). Summarizing, the α-CHY mediated hydrolysis of the MOM-protected substrate 48 allowed the practical, low-cost [1:5 (w/w) α-CHY/42 ratio] synthesis of the versatile chiral building block 51 with acceptable optical purity (ee = 95%) for chemoenzymatic synthesis. Shortly after publication of these results (1987), Santaniello\textsuperscript{38} also reported results (1988) from a similar substrate modification approach strategy. His results are summarized in Table 5.

Table 5 — Results from Santaniello's\textsuperscript{38} Study: α-CHY–Mediated Hydrolyses

<table>
<thead>
<tr>
<th>Substrate</th>
<th>α-CHY: Subst. (w/w)</th>
<th>pH</th>
<th>ee (%)</th>
<th>Absolute Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl 3-acetoxy-glutarate</td>
<td>1:3</td>
<td>7.8</td>
<td>84</td>
<td>R</td>
</tr>
<tr>
<td>Diethyl 3-acetoxy-glutarate</td>
<td>1:3</td>
<td>7.8</td>
<td>95</td>
<td>R</td>
</tr>
</tbody>
</table>
This substrate modification approach appears not to be general since it does not apply to the other enzymatic system studied (PLE) as the results in Table 6 demonstrate.

Table 6 — PLE-Catalysed Hydrolysis of 41, 46, 47 and 48

<table>
<thead>
<tr>
<th>Substrate</th>
<th>PLE: Substrate Ratioa</th>
<th>pH</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Absolute Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>70:1</td>
<td>7.0</td>
<td>A</td>
<td>100</td>
<td>15</td>
<td>S</td>
</tr>
<tr>
<td>46</td>
<td>370:1</td>
<td>7.0</td>
<td>B</td>
<td>78</td>
<td>12</td>
<td>S</td>
</tr>
<tr>
<td>47</td>
<td>180:1</td>
<td>7.0</td>
<td>B</td>
<td>77</td>
<td>60</td>
<td>S</td>
</tr>
<tr>
<td>47</td>
<td>160:1</td>
<td>7.0</td>
<td>C</td>
<td>79</td>
<td>33</td>
<td>S</td>
</tr>
<tr>
<td>48</td>
<td>330:1</td>
<td>7.0</td>
<td>A</td>
<td>100</td>
<td>14</td>
<td>S</td>
</tr>
</tbody>
</table>

aUnits of PLE:mmol of substrate.
bA = 0.01M Na2HPO4 buffer; B = A + 20% 1,4-dioxane; C = A + 20% methanol.

Points to note about these PLE-catalysed hydrolyses include that the rate of hydrolysis was much faster relative to that for α-CHY-mediated hydrolyses and, unlike α-CHY, PLE hydrolyzed the pro-R ester of 41, 46, 47, and 48. Unfortunately, the enantiomeric excesses were never high. The highest ee obtained was for the 3-benzoylated material 47 (ee = 60%). Although this represents considerable improvement relative to the ee of 15% obtained for the 3-hydroxylated material 41, it is still not synthetically useful. Furthermore, for the benzyl- and MOM-protected substrates (46 and 48), the enantioslectivity of hydrolysis relative to 41 was reduced [ee = 12% (46); ee = 14% (48)].
Rationalizing the stereochemical outcome for PLE-mediated hydrolyses for a glutarate based substrate clearly represents a formidable interpretative challenge. The results presented in Table 6 are consistent with those obtained by Jones and Santaniello in subsequent studies. Their results are given in Table 7.

Table 7 — Results from Santaniello's$^{38}$ and Jones$^{42}$ Studies on PLE-Mediated Hydrolyses

<table>
<thead>
<tr>
<th>Substrate</th>
<th>PLE:Subst Ratio$^a$</th>
<th>ee (%)</th>
<th>Absolute Conf.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl 3-acetoxy glutarate</td>
<td>60:1</td>
<td>90</td>
<td>R</td>
<td>Santaniello$^{38}$</td>
</tr>
<tr>
<td>Diethyl 3-acetoxy glutarate</td>
<td>60:1</td>
<td>83</td>
<td>R</td>
<td>Santaniello$^{38}$</td>
</tr>
<tr>
<td>Dimethyl 3-methoxy-ethoxyglutarate</td>
<td>70:1</td>
<td>39</td>
<td>R</td>
<td>Jones$^{42}$</td>
</tr>
<tr>
<td>Dimethyl 3-benzyl-oxyglutarate</td>
<td>70:1</td>
<td>40</td>
<td>S</td>
<td>Jones$^{42}$</td>
</tr>
</tbody>
</table>

$^a$Units of PLE:mmol of substrate.

2.7 Effect of Temperature

Modern synthetic organic chemistry places great emphasis on obtaining highly-enantioselective reactions. While satisfied with the 95% ee obtained for the α-CHY mediated hydrolysis of 48, we questioned whether we could improve the enantioselectivity even further by lowering the temperature. The results demonstrated that, besides causing a significant decrease in the rate of reaction (Figure 11), conducting the hydrolysis at 0°C did not improve the ee obtained. In fact, the enantiomeric excesses were a constant 95% at 0°C, 25°C, and 36°C.
2.8 Membrane-Enclosed Enzymatic Catalysis

A potential drawback of using α-CHY is that, relative to PLE, it is an inefficient enzyme on the basis of stoichiometry. Thus, a high enzyme to substrate ratio must be employed to obtain satisfactory rates of reaction. Although this problem is somewhat diminished by the low cost of α-CHY, it was felt that a better solution would be offered by a method that allowed reuse of the
enzyme. Stated differently, we wished to take advantage of the catalytic property of enzymes. The possibility of immobilizing the α-CHY on a polymer support was explored, however, an operationally more convenient alternative was to simply enclose the enzyme in a cellulose acetate dialysis bag having a molecular weight cut-off point of 10,000 Daltons. After the hydrolysis was complete, the dialysis bag (containing the enzyme) was removed from the reaction mixture and was ready for the next hydrolysis. A slight disadvantage of using membrane-enclosed α-CHY was that the rate of hydrolysis was decreased by a factor of 2.5 compared to an analogous trial using free α-CHY. Importantly, the enantioselectivity of the hydrolysis was not affected (entry 6, Table 4). There was little deterioration in the performance (rate and stereoselectivity) of the enzyme upon reuse. However, a storage period of five weeks at 4°C did result in a substantial loss of enzymatic activity. Methods for improving the storage stability of membrane-enclosed α-CHY are available (for instance, by addition of 1% bovine serum albumin); however, they were not pursued in this study. For an experimental procedure using MEEC, see Chapter 4.9 (Experimental, Preparation of 51). During the course of this study, Whitesides49 formally published the methodology of enclosing enzymes in dialysis bags.

2.9a Enantiomeric Excess and Absolute Configuration Determinations for 49, 50, and 51

The method used to determine the ee of the 3-protected monoacids 49 (Bn), 50 (Bz), and 51 (MOM) was analogous to the one described for the ee determination of 42 (ie. integration of the $^1$H NMR spectrum and/or capillary-GC chromatogram of their respective diastereomeric amides 52, 53, and 54.

![Diagram of reaction and structures](image)

Fortunately, the ratio of amides 52, 53, and 54 could be conveniently determined by examination of the $^1$H NMR spectrum (for an example see Figure 12; $^1$H NMR of 54) of the diastereomeric mixtures and/or capillary GC. These methods are summarized in Table 8. Exact GC conditions are given in the Experimental section (2.13).
<table>
<thead>
<tr>
<th>Diastereomeric Amides</th>
<th>Technique</th>
<th>Elution Time (minutes)</th>
<th>Chemical Shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52a</td>
<td>Cap. GC</td>
<td>23.0</td>
<td>—</td>
</tr>
<tr>
<td>52b</td>
<td></td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>52a</td>
<td>$^1$H NMR (300 MHz)</td>
<td>—</td>
<td>3.65 (CO$_2$CH$_3$)</td>
</tr>
<tr>
<td>52b</td>
<td></td>
<td></td>
<td>3.67 (CO$_2$CH$_3$)</td>
</tr>
<tr>
<td>53a</td>
<td>Cap. GC</td>
<td>25.1</td>
<td>—</td>
</tr>
<tr>
<td>53b</td>
<td></td>
<td>25.9</td>
<td></td>
</tr>
<tr>
<td>54a</td>
<td>$^1$H NMR (300 MHz)</td>
<td>—</td>
<td>3.31</td>
</tr>
<tr>
<td>54b</td>
<td></td>
<td></td>
<td>(OCH$_2$OCH$_3$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.26 (OCH$_2$OCH$_3$)</td>
</tr>
</tbody>
</table>
Figure 12 — 1H NMR Spectrum of 54

- OCH$_2$OCH$_3$(RR)(54a)
- OCH$_2$OCH$_3$(SR)(54b)
The accuracy of these ee determinations was verified by demonstrating that the ee for racemically prepared 49, 50, and 51 (via saponification of 46, 47, and 48) was, as expected, 0% (within experimental error). Also, the individual assaying techniques correlated well with each other.

The determination of the absolute configuration of 49, 50, and 51 was accomplished by correlation to the known methyl hydrogen (3R)-hydroxyglutarate (36a). Thus, the (R)-1-phenylethyl amide derivative (43) of the monoacid 42 was formed as previously discussed. The sample of 42 that was used for this was obtained by the α-CHY-mediated hydrolysis of 41 and had a known ee of 61% with the major enantiomer corresponding to 3R (42a). The 3-hydroxyi of 43 was protected in the standard fashion to yield the benzyl ether (60%, 52), the benzoate (89%, 53), and the MOM ether (81%, 54) as shown on the next page. Inspection of the $^1$H NMR spectra and/or the GC chromatograms permitted assignment of the signals arising from the major (3R)-diastereomer.
2.9b Optical Purity of Methylbenzylamine

The optical purity of the (R)-(+)-methylbenzylamine used for the above ee determinations (Chapter 2.9a) was assessed by forming the diastereomeric amide 55a (52%) using optically pure (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(R)-MTPA]. The use of MTPA for determinations of this type was developed by Mosher\textsuperscript{50}. Also, the optical purity of the (R)-MTPA used in this study had been established by measurement of its optical rotation.

Careful examination of the $^1$H NMR spectrum of 55a (specifically, integration of the methoxy protons) revealed that the (R)-(−)-methylbenzylamine contained 1.5±0.2% (S)-(−)-α-methylbenzylamine (55b). Diastereomeric amide 55b was prepared from (S)-(−)-α-methylbenzylamine in 61% yield and contained 1.6±0.2% (R)-(−)-methylbenzylamine. The relevant enantiomeric excesses quoted in this Chapter have been corrected for this fact.

2.10 Chemical Modifications of 51

As stated in Chapter 2.1, the initial objective in this study was to afford a chiral building block for molecules having 1,3-polyol fragments. An example of this was accomplished in the synthesis of the C(1)–C(9) fragment of bryostatins (1) (Chapter 4) which embeds 1,3-anti diol functionality at C(3), C(5), and C(7).
Formation of 1,3-syn diols from synthons of this type was accomplished by Tamm\textsuperscript{51} as depicted below.

\[ \text{MeO}_2\text{C} - \text{CO}_2\text{H} \rightarrow \text{MeO}_2\text{C} - \text{CH}_2\text{Cl} \]

\[ 57 \]

\[ \begin{array}{c}
\text{Me} \\
\text{OH} \\
\text{OTBS}
\end{array} \rightarrow 
\begin{array}{c}
\text{Me} \\
\text{OTBS}
\end{array} \text{CH}_2\text{Cl} 
\]

\[ 58 \]

\[ \begin{array}{c}
\text{Me} \\
\text{CH}_2\text{Cl}
\end{array} \rightarrow 
\begin{array}{c}
\text{Me} \\
\text{CH}_2\text{Cl}
\end{array} \text{OTBS} \]

\[ 59 \]

\[ \begin{array}{c}
\text{Me} \\
\text{CH}_2\text{Cl}
\end{array} \rightarrow 
\begin{array}{c}
\text{Me} \\
\text{CH}_2\text{Cl}
\end{array} \text{OR} \]

\[ 60 \] \( R = \text{TBS} \)

\[ 61 \] \( R = \text{H} \)

\[ \begin{array}{c}
\text{Me} \\
\text{CH}_2\text{Cl}
\end{array} \rightarrow 
\begin{array}{c}
\text{Me} \\
\text{CH}_2\text{Cl}
\end{array} \text{OH} \]

\[ 62 \]

\[ \text{(Bu)}_3\text{B, NaBH}_4 \]

\[ \text{(syn:anti; >10:1)} \]

It is noteworthy to mention that, if desired, the absolute configuration at the C(3) position of the synthon 51 can be changed from R to S by two reasonably facile methods. Thus, selective reduction of the methyl ester of 51 followed by lactonization and ring opening by sodium methoxide, would yield the hydroxy ester of opposite configuration relative to the hydroxy ester obtained

by reduction of the carboxylic acid. An alternate procedure would involve the removal of the MOM group and subsequent inversion of the resulting C(3) alcohol by use of the Mitsunobu\textsuperscript{52} reaction (after suitable protection of the C(5) carboxylic acid).

2.11 Conversion to a Chiral C\textsubscript{4}–Synthon (63)

It was mentioned that a synthon of this type would represent an attractive starting material for the synthesis of various natural products. Thus, in an effort to demonstrate this point and the versatility of the chiral building block 51, it was converted into the four carbon chiral template 63 possessing three differentiated functional groups by a modified Hunsdiecker\textsuperscript{53} rearrangement (62\%, 51, Br\textsubscript{2}, HgO, CCl\textsubscript{4}, reflux 1.5 hours). This C\textsubscript{4}-synthon represents an excellent starting material for compounds such as the unnatural isomers of GABOB [(S)-4-amino-3-hydroxybutanoic acid] and carnitine\textsuperscript{33}.

\begin{equation}
\begin{array}{c}
\text{MeO}_2\text{C} \quad \text{OMOM} \\
\text{CO}_2\text{H}
\end{array}
\xrightarrow{\text{Br}_2, \text{HgO}, \text{reflux, 62\%}}
\begin{array}{c}
\text{MeO}_2\text{C} \quad \text{OMOM} \\
\text{CH}_2\text{Br}
\end{array}
\end{equation}

2.12 Conclusions

In summary, we have been able to gain access to a versatile chiral synthon (51) on the gram-scale and of acceptable optical purity for chemoenzymatic synthesis. Logical targets for this synthon include molecules having 1,3-polyol fragments. The practicality of this reaction was optimized using reaction condition control and the technique of membrane enclosed enzymatic catalysis.

In a general sense, this work also establishes another facet for the utilization of enzymes in asymmetric synthesis. Thus, a closer look at the enzyme's active site should be undertaken before abandoning their usage. From this information, modifications can be made to the substrate in a controlled manner in order to improve the enantioselectivity of the transformation. The above strategy should therefore be considered complementary to existing ones.
2.13 Experimental

Melting points were determined by use of a Gallenkamp digital melting point apparatus and are uncorrected. Boiling points are uncorrected. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Infrared (IR) spectra were taken from films on sodium chloride plates for oils, and from chloroform or dichloromethane (as indicated) solutions for solids, using a Perking Elmer 783 spectrophotometer. Mass spectra were recorded on a VG-7070E instrument (El-MS 70 eV; Cl-MS 70 eV ionizing potential, ether was used as reagent gas) unless otherwise indicated. The peak intensities are given as a percent of the base peak (100%) intensity. Combustion analyses were performed by Guelph Chemical Laboratories Ltd. (Guelph, Ont.) or M-H-W Laboratories (Phoenix, AZ).

Unless otherwise indicated all proton NMR spectra (1H NMR) were taken in deuterochloroform (CDCl₃) at 60 MHz on a Varian EM-360 spectrometer or 200 MHz on a Varian Gemini 200 spectrometer or 300 MHz on a Varian XL-300 spectrometer (as indicated). The chemical shifts are reported in ppm downfield relative to the internal standard tetramethylsilane (delta scale). The coupling patterns are noted as singlets (s), doublets (d), triplets (t), quartets (q), quintets (qu), doublets of doublets (dd), broad (br), or multiplets (m). Spectral assignments were aided by HOMCOR, NOESY, and nOe experiments. Unless otherwise indicated all carbon NMR (13C NMR) spectra were recorded in CDCl₃ at 50.3 MHz on a Varian Gemini 200 spectrometer or at 75.4 MHz on a Varian XL-300 spectrometer (as indicated). The number of protons attached to each carbon was determined by DEPT or ADEPT spectra. The numbering system
used for both carbon and proton NMR assignments refers to bryostatin unless otherwise indicated.

Gas chromatography was accomplished on a Varian 3300 or Varian 6000 instrument. Column chromatography was done using Baker or Terochem 60-200 mesh silica as the adsorbent. Flash chromatography was accomplished using Merck type 9385 silica gel (Terochem). Thin layer chromatography (TLC) was performed on Kieselgel 60 F254 precoated silica gel plates of 0.25 mm thickness and visualized by means of U.V., I2 or by charring. Preparative layer chromatography was done on PSC-Fertig platten Kieselgel 60 F254 precoated silica gel plates (Merck 13895) of 1.0 mm thickness. HPLC separations were performed with a Waters PREP LC/system 500A using a PrepPAK-500 silica column. Purifications by radial chromatography were performed on a Harrison Research Chromatotron model 7924 using silica gel coated rotors (1 mm, 2 mm, and 4 mm thickness).

Tetrahydrofuran (THF) was distilled over sodium-benzophenone ketyl under a nitrogen atmosphere prior to use. Diisopropylamine, triethylamine (NEt3), hexamethylphosphoramide (HMPA), and N,N-dimethylformamide (DMF) were distilled from calcium hydride under a nitrogen atmosphere. Dichloromethane was dried by distillation from phosphorus pentoxide. Butyllithium was used as received from Aldrich after titration with diphenylacetic acid54. LDA was prepared by adding an appropriate amount of n-butyllithium in hexane solution to a 1.1 equivalent excess of diisopropylamine in THF at -20°C. Sodium hydride was obtained as a 50% dispersion and washed with pentane.

prior to use. All other solvents or reagents were distilled or were of reagent grade quality.

Solutions in organic solvents were dried over anhydrous sodium sulfate or magnesium sulfate and the solvent removed with a Büchi evaporator connected to a water aspirator. Unless otherwise indicated all reactions were conducted under a nitrogen atmosphere.

**Dimethyl 3-hydroxyglutarate (41):**

This material was prepared using a procedure similar to one described by Cohen and Khedouri\(^\text{31}\). Thus, to 50 mL of water was added 3 drops of a 40% aqueous NaOH solution followed by 5.00 g (0.132 mol) of NaBH\(_4\). This solution was added dropwise to 50 g (0.287 mol) of dimethyl 1,3-acetonedicarboxylate (40, Aldrich) in 50 mL of methanol at 0°C over a 45 minute period with vigorous stirring. The mixture was allowed to warm to room temperature and an excess of Amberlite IR-120 resin in the H\(^+\) form was carefully added. The resin was removed by filtration and the water/methanol was removed *in vacuo*. The residual viscous oil was co-evaporated several times with 100 mL of a 5% acetic acid in methanol solution. Distillation using a short-path distillation apparatus (boiling point 138-140°C at 8 Torr; literature\(^\text{31}\): 138-140°C at 8 Torr) gave 46.5 g (92%) of the alcohol 41 as a colourless oil. IR (thin film) \(\nu\): 3505, 2962, 1740, 1441, 998 cm\(^{-1}\). \(^1\)H NMR (300 MHz) \(\delta\): 4.42 - 4.50 (app qu, 1H, H\(_3\)), 3.70 (s, 6H, 2 X CO\(_2\)CH\(_3\)), 3.32 - 3.43 (br s, 1H, OH, exchangeable), 2.55 (d, J = 6.3 Hz,
4H, 2 X CH₂). ¹³C NMR (50.4 MHz) δ: 172.0 (CO₂CH₃), 64.3 (C₃), 51.4 (CO₂CH₃), 40.3 (CH₂).

3-Hydroxypentanediolic acid monomethyl ester (42):

Procedure 1 — Enzyme Catalyzed Hydrolysis:

The following procedure is representative. The diester 41, (0.50 g, 2.84 mmol) was dissolved in 0.01N Na₂HPO₄ buffer solution (20 mL) and stirred rapidly at ambient temperature. α-Chymotrypsin (E.C. 3.4.21.1, Sigma Type II from bovine pancreas, 0.25 g, 15 µmol) or porcine liver esterase (E.C. 3.1.1.1, Sigma Type I, 70 units) was then added. The pH was kept constant at 7.8 by addition of 0.25N NaOH using a Radiometer automatic titrator. The extent of the reaction was estimated by volume of base consumed during the course of the reaction. When the reaction was 90% complete (~9 hours), the solution was extracted with ether (2 X 30 mL) to remove remaining 41. The aqueous layer was then acidified to pH ~2 using 2.5N HCl and extracted with ethyl acetate (4 X 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to yield 0.41 g (89 %) of the monoacid 42 as a colourless oil which was pure by tlc and ¹H NMR analysis. The reaction conditions (pH, substrate to enzyme ratio, solvent) were varied in a systematic manner. The results obtained (yield, ee) are summarized in Table 2, Chapter 2.
Procedure 2 — Preparation of Racemic 42:

The diester 41 (1.50 g, 8.51 mmol) was rapidly stirred in 20 mL of water and 34.0 mL of a 0.25N NaOH solution (8.51 mmol) was added dropwise over a 0.5 hour period. A further period of 1 hour was allowed for this saponification whereupon the aqueous solution was extracted with 2 equal portions (30 mL) of ether to remove remaining 41 and the aqueous layer was acidified to pH ~2 using 2.5 N HCl and extracted with four 40 mL portions of ethyl acetate. The organic layers were combined over Na₂SO₄ and concentrated in vacuo to afford a yellowish oil. Purification by SiO₂ flash chromatography (1:9 methanol/dichloromethane, 1% acetic acid) removed the diacid leaving 0.57 g (41%) of racemic monoacid 42 as a colourless syrup. IR (CHCl₃) ν: 3490, 2982, 1733, 1718, 1439, 1422, 1269, 1178 cm⁻¹. ¹H NMR (300 MHz) δ: 4.46 (qu, J = 6.2 Hz, 1H, H₃), 3.71 (s, 3H, CO₂CH₃), 2.60 (d, J = 6.2 Hz, 2H, RCH₂R), 2.57 (d, J = 6.2 Hz, 2H, RCH₂R).

(3R,S,1'R)-N-(1'-Phenylethyl)-3-hydroxy-4-carbomethoxybutanamide (43):

To a solution of the carboxylic acid (+)-42 (0.30 g, 1.85 mmol) in tert-butanol (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.46 g, 2.4 mmol) and R-(+)-α-methylbenzylamine (311μL, 2.41 mmol). After stirring for 1 hour at 25°C, the solution was the solvent removed in vacuo and the residue was taken up in ethyl acetate (50 mL) and washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (30 mL portions), dried over
Na₂SO₄, and concentrated in vacuo, providing 0.32 g (65%) of diastereomeric amides 43a and 43b as a colourless syrup. When data for the (3S,1'R)-diastereomer differs, it appears in brackets. ¹H NMR (300 MHz) δ: 7.31 (7.32) (m, 5H, aromatic), 6.29 (6.32) (br d, J = 6.6 Hz, 1H, NH), 5.11 (app qu, 1H, CHPh), 4.38 (m, 1H, H₃), 3.69 (s, 3H, CO₂CH₃), 2.38 - 2.55 (m, 4H, H₂, H₄), 1.47 (1.48) (d, J = 6.9 Hz, 3H, CH₃CH).

**(3R,S,1'R)-N-(1'-Phenylethyl)-3-[(tert-butyldimethylsilyl)oxy]-4-carbomethoxybutanamide (44)**:

The hydroxy amide 43 (0.15 g, 0.57 mmol) was stirred in 5 mL of dichloromethane and 85.1 mg (1.25 mmol) of imidazole and 196 μL (0.854 mmol) of trimethylsilyl trifluoromethanesulfonate were sequentially added. After stirring at room temperature for 5 hours, the solution was diluted with additional dichloromethane (40 mL) and washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (20 mL of each), dried over Na₂SO₄, and concentrated in vacuo to yield a colourless oil. Preparative TLC (2:1 ether/hexane) of the crude material afforded 0.18 g (83%) of silylated amide 44 as a colourless oil. When data for the (3S,1'R)-diastereomer (44b) differs, it appears in brackets. IR (thin film) ν: 3450, 3370, 2950, 2850, 1730, 1660 cm⁻¹. ¹H NMR (300 MHz) δ: 7.32 (m, 5H, aromatic), 6.55 (br d, J = 7.6 Hz, 1H, NH), 5.12 (app qu, 1H, CHPh), 4.50 (4.53) (m, 1H, H₃), 3.65 (3.68) (s, 3H, CO₂CH₃), 2.55 (dd, A of ABX, J = 5.1, 15.0 (5.2, 15.0) Hz, 1H, H₂), 2.48 (2.59) (d, J = 1.8 (6.1) Hz, 1H (2H), H₄), 2.45 (d, J =

⁵⁵¹H NMR spectrum identical to the one described by Heathcock (ref. 32c).
2.4 Hz, 1H, H₄), 2.39 (2.40) (dd, B of ABX, J = 5.2, 15.0 (4.9, 15.0) Hz, 1H, H₂): 1.47 (1.50) (d, J = 6.7 (6.8) Hz, CHCH₃), 0.85 (0.79) (s, 9H, C(CH₃)₃), 0.10, 0.07 (0.06, 0.02) (s, 6H, Si(CH₃)₂). Determination of the ee was accomplished by ¹H NMR (300 MHz) integration of the well-resolved carbomethoxy protons [3.65, 3.68 ppm for (3R,1'R)-, (3S,1'R)- diastereomers (44a and 44b), respectively]. An alternate method was gas chromatography (GC) taken on a vitreous silica bonded BP1 capillary column (0.22 mm ID X 0.33 mm OD, 10 m) and 20:1 split ratio. The column, injector, and detector (FID) temperatures were 180°, 230°, and 300°C, respectively. With these conditions, the (3R,1'R)- and (3S,1'R)- diastereomers eluted at 17.6 and 18.2 minutes, respectively. The correlation between these methods was good (± 2%) and the calculated ee of racemically prepared 42 (Procedure 2) was within experimental error, 0%.

**Dimethyl 3-[[tert-butyldimethylsilyl]oxy]glutarate (45):**

This material was prepared using a procedure similar to the one described by Heathcock. Thus, to 0.58 g (8.52 mmol) of imidazole in dichloromethane (30 mL) was added 0.642 g (4.26 mmol) of tert-butyldimethylsilyl chloride followed by dropwise addition of 0.50 g (2.83 mmol) of dimethyl 3-hydroxyglutarate (41) in 5 mL of dichloromethane over a 10 minute period. The mixture was stirred for 18 hours at ambient temperature whereupon it was diluted with ether (80 mL). The ethereal layer was washed with water and brine (40 mL of each). The combined aqueous washing were extracted with 100 mL of ether. The ethereal layers were combined and dried over Na₂SO₄ and the
solvent was removed in vacuo. The yellow oil was purified by SiO₂ flash chromatography (1:3 ether/hexane) to yield 0.70 g (85%) of the silyl ether 45 as a colourless oil. ¹H NMR (300 MHz) δ: 4.50 (qu, J = 6.1 Hz, H₃), 3.65 (s, 6H, 2 X CO₂CH₃), 2.53 (d, J = 6.1 Hz, 4H, 2 X CH₂), 0.84 (s, 9H, C(CH₃)₃), 0.08 (s, 6H, 2 X SiCH₃).

**Dimethyl 3-benzyloxyglutarate (46)⁵⁶:**

Trifluoromethanesulfonic acid (catalytic amount, 4 drops) was added to 1.50 g (8.51 mmol) of dimethyl 3-hydroxyglutarate (41) followed by 3.31 mL (17.8 mmol) of benzyl 2,2,2-trichloroacetimidate in cyclohexanedicloromethane (2:1, 100 mL). The reaction was stirred overnight at room temperature whereupon 100 mL of cyclohexane was added. The organic layer was then filtered and washed twice with saturated aqueous NaHCO₃ (50 mL) and once with brine (50 mL) and dried over Na₂SO₄. Concentration in vacuo yielded a reddish oil which was purified by SiO₂ flash chromatography (ether/hexane 1:3) affording 1.38 g (61%) of the benzyl ether 46 as a colourless oil. ¹H NMR (300 MHz) δ: 7.28 (br s, 5H, aromatic), 4.57 (s, 2H, OCH₂Ph), 4.31 (app qu, 1H, H₃) 3.66 (s, 6H, 2 X CO₂CH₃), 2.68 (dd, A of ABX, J = 6.8, 15.5 Hz, 2H, H₂, H₄), 2.60 (dd, B of ABX, J = 5.8, 15.5 Hz, 2H, H₂', H₄').

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⁵⁶¹H NMR and IR spectrum identical to those described by Jones (ref. 42).
**Dimethyl 3-benzoylglutarate (47):**

Dimethyl 3-hydroxyglutarate (41, 2.00 g, 11.4 mmol) was dissolved in 15 mL of pyridine containing 2.65 mL (22.8 mmol) of benzoyl chloride. After overnight contact, the excess benzoyl chloride was destroyed by addition of 2 g of crushed ice for 1 hour. The solution was stripped of solvent in vacuo and the residue diluted in dichloromethane (100 mL) and washed with 60 mL portions of 0.2N HCl, saturated aqueous NaHCO₃, and brine. The organic layer was dried over Na₂SO₄, treated with activated charcoal, and concentrated in vacuo to afford 2.94 g (92%) of the benzoate 47 as a colourless oil and of sufficient purity to be used without further purification. IR (thin film) ν: 3005, 2961, 2859, 1745, 1725, 1608, 1589, 1455, 1441, 1278, 1114 cm⁻¹. ¹H NMR (200 MHz) δ: 7.95 - 7.99 (m, 1H, aromatic), 7.44 - 7.99 (m, 5H, aromatic) 5.71 (qu, J = 6.3 Hz, 1H, H₃), 3.67 (s, 6H, 2 X CO₂CH₃), 2.84 (d, J = 6.3 Hz, 4H, 2 X CH₂). ¹³C NMR (50.4 MHz) δ: 170.4 (2 X CO₂CH₃), 166.0 (PhCO₂), 133.3,129.9, 128.5 (aromatic), 67.5 (C₃), 51.8 (2 X CO₂CH₃), 38.1 (2 X CH₂). MS (EI) m/z: 175 (M⁺-105, 9%), 159 (M⁺-121, 9%). MS (Cl ether) m/z: 281 (M⁺+1, 59%), 249 (M⁺-31, 16%). HRMS calcd. for C₇H₁₁O₅ (M⁺-PhCO): 175.0607; found: 175.0608.

**Dimethyl 3-methoxymethoxyglutarate (48):**

**Procedure 1:**

To 4.00 g (22.7 mmol) of the alcohol 41 in 30 mL of dry N,N-dimethylformamide was added 11.9 mL (68.1 mmol) of N,N-
diisopropylethylamine and 4.31 mL (56.8 mmol) of chloromethyl methyl ether. After stirring for 5 hours at room temperature, the mixture was transferred to a separatory funnel charged with 250 mL of ether. The ethereal layer was washed five times with water, once with 0.2N HCl, once with saturated aqueous NaHCO₃, and once with brine (50 mL portions). It was then dried over Na₂SO₄ and concentrated in vacuo to yield a pale yellow oil. Purification by SiO₂ flash chromatography (2:1 hexane/ether) yielded 4.40 g (88%) of methoxymethyl ether 48 as a colourless oil.

**Procedure 2:**

A solution of 7.00 g (39.7 mmol) of alcohol 41 and 40 mL (0.45 mol) of dimethoxymethane in chloroform (40 mL) was added to a slurry of phosphorus pentoxide (20 g, 0.14 mol) in chloroform (40 mL) at 0°C. After 5 hours, the reaction mixture was poured onto 100 mL of saturated aqueous Na₂CO₃ at 0°C and extracted with ether (3 x 80 mL). The combined ethereal extracts were washed with brine (100 mL) and dried over Na₂SO₄. The solvent was removed in vacuo and the resulting crude oil was purified as in Procedure 1 above to give 8.22 g (94%) of methoxymethyl ether 48. IR (thin film) ν: 2961, 1742, 1442, 1155, 1042 cm⁻¹. ¹H NMR (300 MHz) δ: 4.67 (s, 2H, OCH₂O), 4.40 (app qu, 1H, H₃), 3.68 (s, 6H, 2 X CO₂CH₃), 3.33 (s, 3H, OCH₃), 2.69 (dd, A of ABX, J = 6.8, 14.8 Hz, 2H, H₂, H₄), 2.62 (dd, B of ABX, J = 5.8, 14.8 Hz, 2H, H₂', H₄'). ¹³C NMR (50.4 MHz) δ: 171.2 (2 X CO₂CH₃), 96.4 (OCH₂O), 71.3 (C₃), 55.4 (OCH₃),
51.4 (2 X CO₂CH₃), 39.5 (2 X CH₂). MS (EI) m/z: 189 (M⁺-31,12%), 175 (M⁺-45, 2%). HRMS calcd. for C₈H₁₃O₅ (M⁺-CH₃O): 189.0763; found: 189.0755.

*Enzyme Catalyzed Hydrolyses of 3-Protected Substrates (46, 47, 48) to Form Chiral Monoacids (49, 50, 51):*

A similar protocol to the one described previously for the conversion of dimethyl 3-hydroxyglutarate to 3-hydroxypentanedioic acid, monomethyl ester (41 to 42, Procedure 1) was followed. The specific results obtained for substrates 46, 47, and 47 are summarized in Table 4, Chapter 2.

*(3R)-3-Benzylxypentanedioic acid monomethyl ester (49)*₅₆:

IR (thin film) ν: 1736, 1714 cm⁻¹. ¹H NMR (300 MHz) δ: 10.4 (br s, 1H, COOH, exchangeable), 7.33 (br s, 5H, aromatic), 4.60 (s, 2H, OCH₂Ph), 4.32 (app qu, 1H, H₃), 3.70 (s, 3H, CO₂CH₃), 2.69 (d, J = 6.0 Hz, 2H, H₂, H₄), 2.68 (d, J = 6.0 Hz, 2H, H₂', H₄').

*(3R)-3-Benzoylpentanedioic acid monomethyl ester (50):*

IR (thin film) ν: 3200, 2961, 1741, 1721, 1455, 1418, 1320, 1279 cm⁻¹. ¹H NMR (300 MHz) δ: 11.15 (br s, 1H, COOH, exchangeable), 7.32 - 8.04 (m, 5H, aromatic), 5.70 (qu, J = 6.2 Hz, 1H, H₃), 3.62 (s, 3H, CO₂CH₃), 2.82 - 2.90 (m,
4H, H2, H4). 13C NMR (50.4 MHz) δ: 175.5 (CO2H), 170.5 (CO2CH3), 165.5 (PhCO2), 133.2, 129.6, 129.6, 128.3 (aromatic), 67.1 (C3), 51.7 (CO2CH3), 37.8 (C2, C4). MS (Cl ether) m/z : 267 (M+1, 63%), 235 (M+-31, 4%), 145 (M+-121, 30%). Anal. calcd. for C13H14O6: C, 58.65, H, 5.30; found: C, 58.51, H, 5.21.

(3R)-3-Methoxymethoxypentanedioic acid monomethyl ester (51):

[α]D = -3.3°. IR (thin film) ν: 3150, 2961, 1734, 1442, 1152, 1103 cm⁻¹. 1H NMR (300 MHz) δ: 11.1 (br s, 1H, COOH, exchangeable), 4.68 (s, 2H, OCH2O), 4.40 (app qu, 1H, H3), 3.68 (s, 3H, CO2CH3), 3.34 (s, 3H, OCH3), 2.58 - 2.75 (m, 4H, 2 X CH2). 13C NMR (50.4 MHz) δ: 176.5 (CO2H), 171.4 (CO2CH3), 96.4 (OCH2O), 71.2 (C3), 55.5 (OCH3), 51.6 (CO2CH3), 39.5, 39.4 (C2, C4). MS (El) m/z: 175 (M+-31, 4%). MS (Cl ether) m/z: 207 (M+1, 15%), 175 (M+-31, 100%); Anal. calcd. for C8H14O6: C, 46.60, H, 6.85; found: C, 47.08, H, 6.91.

(3R,S,1'R)-N-(1'-Phenylethyl)-3-protected-4-carboxyloxybutanamides (52, 53, 54):

A similar protocol to the one described previously for the conversion of the carboxylic acid 42 to the diastereomeric amide 43 was followed.

Characterization Data:
(3R,1'R)-N-(1'-Phenylethethyl)-3-benzyloxy-4-carbomethoxybutanamide (52):

Yield: 66%, colourless syrup. When data for the (3S,1'R)-diastereomer differs (52b), it appears in brackets. $^1$H NMR (300 MHz) $\delta$: 7.28 (br s, 5H, aromatic), 6.32 (6.34) (br d, J = 6.6 Hz, 1H, NH), 5.08 (app qu, 1H, CHPh), 4.62 (4.56) (d, A of AB, J = 11.2 (11.1) Hz, 1H, CH$_2$Ph), 4.53 (4.44) (d, B of AB, J = 11.2 (11.1) Hz, 1H, OCH$_2$Ph), 4.31 (4.32) (app qu, 1H, H$_3$), 3.65 (3.67) (s, 3H, CO$_2$CH$_3$), 2.57 (d, J = 6.0 Hz, 2H, H$_2$), (2.65) (d, J = 3.4 Hz, 1H, H$_2$), (2.63) (d, J = 3.0 Hz, 1H, H$_2$), 2.53 (dd, A of ABX, J = 4.8, 14.1 Hz, 1H, H$_4$), 2.45 (dd, B of ABX, J = 7.0, 14.1 Hz, 1H, H$_4$), (2.54) (d, J = 6.3 Hz, 1H, H$_4$), (2.50) (d, J = 10.0 Hz, 1H, H$_4$), (1.42) (d, J = 6.9 Hz, 3H, CHCH$_3$), 1.40 (d, J = 7.0 Hz, 3H, CHCH$_3$). GC-MS (EI) m/z: 278 (M$^+$-77, 15%), 167 (M$^+$-188, 35%).

(3R,1'R)-N-(1'-Phenylethyl)-3-benzoyl-4-carbomethoxybutanamide (53):

Yield: 71%, colourless syrup. IR (thin film) $\nu$: 3310, 2962, 2938, 1745, 1733, 1658, 1549, 1441, 1279. $^1$H NMR (300 MHz) $\delta$: 7.18 - 7.95 (m, 5H, aromatic), 5.99 (br d, J = 6.3 Hz, 1H, NH), 5.69 (app qu, 1H, H$_3$), 5.09 (app qu, 1H, CHPh), 3.65 (s, 3H, CO$_2$CH$_3$), 2.93 (dd, A of ABX, J = 5.3, 16.2 Hz, 1H, H$_2$), 2.82 (dd, B of ABX, J = 6.9, 16.2 Hz, 1H, H$_2$), 2.72 (d, J = 3.6 Hz, 1H, H$_4$), 2.70 (d, J = 3.4 Hz, 1H, H$_4$), 1.42 (d, J = 6.8 Hz, 3H, CHCH$_3$). GC-MS (EI) m/z: 369 (M$^+$, 2%), 264 (M$^+$-105, 6%). MS (Cl ether) m/z: 370 (M$^+$+1, 100%), 264 (M$^+$-105, 3%), 248 (M$^+$-121, 54%).
(3R,1'R)-N-(1'-Phenylethyl)-3-methoxymethoxy-4-carbomethoxybutanamide (54):

Yield: 62%, colourless syrup. When data for the (3S,1'R)- diastereomer (54b) differs, it appears in brackets. IR (thin film) ν: 3301, 2940, 1741, 1645, 1545, 1440, 1211, 1105, 1041 cm⁻¹. ¹H NMR (300 MHz) δ: 7.42 - 7.34 (m, 5H, aromatic), 6.22 (broad d, J = 6.6 Hz, 1H, NH), 5.17 (app qu, 1H, CHPh), 4.68 (4.61) (s, 2H, OCH₂O), 4.36 (app qu, 1H, H₃), 3.66 (3.67) (s, 3H, CO₂CH₃), 3.31 (3.26) (s, 3H, OCH₃), 2.56 (app d of t, 4H, H₂, H₄), 1.47 (d, J = 6.9 Hz, 3H, CH₃CH). ¹³C NMR (50.4 MHz) δ: 171.5 (CO₂CH₃), 169.1 (CONH), 143.3, 128.7, 127.4, 126.2 (aromatic), 96.7 (OCH₂O), 72.3 (C₃), 55.7 (OCH₃), 51.7 (CO₂CH₃), 48.6 (CHCH₃), 41.9, 39.3 (C₂, C₄), 21.7 (CH₃CH). MS (EI) m/z: 278 (M⁺-31, 6%), 277 (M⁺-32, 13%), 264 (M⁺-45, 17%). MS (CI ether) m/z: 310 (M⁺+1, 100%). HRMS calcd. for C₁₄H₁₈O₄N (M⁺-CH₂OCH₃): 264.1272; found 264.1222.

Absolute Configuration and Enantiomeric Excess Determinations:

In all cases (49, 50, and 51) correlations were made to the known (3R)-hydroxyglutarate, monomethyl ester (42a)³¹.

(3R,S,1'R)-N-(1'-Phenylethyl)-3-benzoyloxy-4-carbomethoxybutanamide (52):

Method 1:

Determination of ee was accomplished by GC taken on a vitreous silica bonded BP1 capillary column (0.22 mm ID X 0.33 mm OD, 10 m) and 50:1 split
ratio. The column, injector, and detector (FID) temperatures were 150°, 300°, and 300°C, respectively. With these conditions, the (3R,1'R)- and (3S,1'R)-diastereomers (52a and 52b) eluted at 23.0 and 24.1 minutes, respectively.

Method 2:

Determination of the ee was accomplished by ¹H NMR (300 MHz) integration of carbomethoxy protons [3.65, 3.67 ppm for (3R,1'R)-, (3S,1'R)-diastereomers (52a and 52b), respectively].

The correlation between method 1 and 2 was good (± 1.5%) with method 1 being preferred.

(3R,S,1'R)-N-(1'-Phenylethyl)-3-benzoyl-4-carbomethoxybutanamide (53):

Determination of ee was accomplished by GC on a vitreous silica bonded BP1 capillary column (0.22 mm ID X 0.33 mm OD, 10 m) and 50:1 split ratio. The column, injector, and detector (FID) temperatures were 200°, 300°, and 300°C, respectively. With these conditions, the (3R,1'R)- and (3S,1'R)- diastereomers (53a and 53b) eluted at 25.1 and 25.9 minutes, respectively.
(3R,S,1'R)-N-(1'-Phenylethyl)-3-methoxymethoxy-4-carbomethoxybutanamide (54):

Determination of the ee was accomplished by $^1$H NMR (300 MHz) integration of the well-resolved methoxy singlets on the methoxymethyl ether group [3.313 and 3.256 ppm for the (3R,1'R)- and (3S,1'R)- diastereomers (54a and 54b), respectively].

Saponification of 46, 47, and 48 [using a procedure identical to the one described for preparation of the racemic-42 (Method 2)] afforded racemic-49, 50, and 51. Conversion to their diastereomeric amides using optically pure (R)-(+)-α-methylbenzylamine (as described above) provided racemic-52, 53, and 54. In all cases, the calculated ee was, within experimental error, 0% (as predicted).

**Determination of the Optical Purity of R-(+)-α-Methylbenzylamine**

(2R,1'R)-N-(1'-Phenylethyl)-2,2-methoxy(trifluoromethyl)phenylacetamide (55a):

To 58.1 mg (0.248 mmol) of R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid in 2 mL of tert-butanol at 25°C was added 72.5 mg (0.378 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and R-(+)-α-methylbenzylamine (48 µL, 0.37 mmol) and the solution was stirred for 1 hour. The solution was stripped of solvent and the
residue taken up in ethyl acetate (30 mL) and washed successively with 0.2N HCl, saturated aqueous NaHCO₃, and brine (20 mL of each). The organic layer was dried over Na₂SO₄ and concentrated in vacuo to yield 43.3 mg (52%) of the (2R,1'R)-diastereomeric amide (55a) as a colourless oil. ¹H NMR (300 MHz) δ: 7.24 - 7.55 (m, 10H, aromatic), 6.99 (br d, J = 7.7 Hz, 1H, NH), 5.18 (app qu, 1H, CHPh), 3.35 (q, J = 1.6 Hz, 3H, OCH₃), 1.45 (d, J = 6.9, 3H, CH₃CH). MS (EI) m/z: 337 (M⁺,2%), 305 (M⁺-32, 5%), 202 (M⁺-135, 3%), 189 (M⁺-148, 100%).

(2R,1'S)-N-(1'-Phenylethyl)-2-methoxy(trifluoromethyl)phenylacetamide (55b):

The same procedure as described above was used except that S-(−)-α-methylbenzylamine was used instead of R-(+)−α-methylbenzylamine. Thus, 67.5 mg (0.288 mmol) of (R)-(+)−α-methoxy−α-(trifluoromethyl)phenylacetic acid yielded 59.5 mg (61%) of the (2R,1'S)- diastereomeric amide 55b as a colourless oil. ¹H NMR (300 MHz) δ: 7.22 - 7.42 (m, 10H, m, aromatic), 6.96 (br d, J = 6.6 Hz, 1H, NH), 5.16 (app qu, 1H, CHPh), 3.39 (q, J = 1.6 Hz, OCH₃), 1.53 (d, J = 6.9 Hz, 1H, CH₃CH).

¹H NMR (300 MHz) integration of the protons of the methoxy groups revealed that the (R)-(+)−α-methylbenzylamine contained 1.5% (± 0.2%) (S)-(−)-α-methylbenzylamine. Likewise, the (S)-(−)-α-methylbenzylamine contained 1.6% (± 0.2%) (R)-(+)−α-methylbenzylamine. The appropriate corrections have been made to the relevant enantiomeric excesses quoted in this Chapter.
(3R)-Methyl 4-bromo-3-methoxymethoxy-1-butanoate (63):

In the dark, a solution of the monoacid 51 (0.36 g, 1.75 mmol) and red mercuric oxide (0.40 g, 1.85 mmol) in carbon tetrachloride was stirred and refluxed. Bromine (95μL, 1.84 mmol) was added and the reaction stirred 1.5 hours at which point it was cooled and 1 mL of saturated aqueous NaHCO₃ was added. After stirring a further hour at ambient temperature, it was diluted with 20 mL of chloroform and passed through a pad of Celite. The Celite was rinsed with another 15 mL of chloroform and the organic extracts were combined and washed with saturated aqueous NaHCO₃ and brine (15 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo to afford a yellowish oil. Purification by SiO₂ flash chromatography (4:6 ether/hexane) delivered 0.26 g (62%) of the bromide 63 as a colourless oil. ¹H NMR (300 MHz) δ: 4.73 (dd, A of AB, J = 7.1 Hz, 1H, OCH₂O), 4.68 (d, B of AB, J = 7.1 Hz, 1H, OCH₂O), 4.18 (app qu, 1H, H₃) 3.69 (s, 3H, CO₂CH₃), 3.55 (s, 1H, RCH₂Br), 3.53 (d, J = 0.8 Hz, RCH₂Br), 3.38 (s, 3H, OCH₃), 2.75 (dd, A of ABX, J = 5.2, 16.1 Hz, 1H, H₂), 2.67 (dd, B of ABX, J = 7.4, 16.1 Hz, 1H, H₂). GC-MS (EI) m/z: 211, 209 (M⁺-31, 3%), 181, 179 (M⁺-61, 9%), 147 (M⁺-95 (CH₂Br), 18%).
CHAPTER 3: WITTIG AND DIANION APPROACHES TOWARDS THE C(1)–C(9) FRAGMENTS OF BRYOSTATINS

3.1 Introduction

Presented in this Chapter are the results from our preliminary investigation into the development of a viable synthetic route towards the C(1)–C(9) subunit of bryostatins (1). The two approaches which will be discussed relied upon the coupling of an enzymatically derived 24 five carbon unit [C(1)–C(5), 51, Chapter 2] with a four carbon unit [C(6)–C(9)] derived from (R)-pantolactone (67). In each case, the routes were aborted due to difficulties encountered in making the C(5)-C(6)-bond connection. However, valuable insights were gained regarding the chemistry of these chiral templates which eventually culminated in the successful synthesis of the C(1)–C(9) fragment as discussed in Chapter 4. It is also noteworthy that a synthon originating from (R)-pantolactone was used in the synthesis of the C(17)–C(20) fragment of bryostatin (Chapter 5.3).

3.2 Wittig Approach - Retrosynthetic Analysis

The pivotal step in the first approach examined employed the Wittig reaction to couple the phosphorus ylide 65 and α-substituted γ-lactol 66 (Figure 13). It was anticipated that the acyclic C(1)–C(9) olefin 64 would undergo
regioselective halolactonization\textsuperscript{57} to assemble the desired C(5)–C(9) β-lactone. The required \textit{6-Endo-Trig} ring closure will be, hopefully, preferred relative to the also favoured \textit{5-Exo-Trig} cyclization mode\textsuperscript{57a}. The chiral Wittig precursor could be obtained by straightforward transformations of chiral building blocks 51 and 67.

3.3 Model Wittig Study

Before embarking upon the synthesis of the phosphorane 65, it was felt that a model study was in order. Thus, the ylide derived from the commercially available phosphonium salt ethyltriphenylphosphonium bromide was reacted
with (R)-benzoypantolactol (66). This provided information regarding the
electrophilicity of the γ-lactol template 66 as well as indicating the expected
trans:cis alkene ratio which could be expected. For the latter point, there exists
substantial literature precedent\textsuperscript{58} which demonstrates that variations in the
reaction conditions can be made to encourage the formation of the desired
trans-olefin.

The (R)-benzoypantolactol was prepared in a two-step sequence from
the commercially available (R)-pantolactone (67). Thus, 67 was benzyolated in
near-quantitative yield (95\%) using standard methodology (BzCl, pyridine, 25°C,
15 hours) to afford the α-benzyolated γ-lactone 68. Subsequent
diisobutylaluminum hydride reduction of 68 proceeded smoothly to furnish the γ-
lactol 66 in 80\% yield (DIBAL, THF, -78°C, 3 hours).

Wittig olefination of 66 with ethylenetriphenylphosphorane was, unfortunately, sluggish and low-yielding. In fact, barely detectable amounts (~5% yield) of the olefinic products 69 were obtained. Efforts to improve the yields by varying reaction conditions (temperature, reaction time, solvent, base) were unsuccessful.

To account for these results, we speculated that perhaps the gem-dimethyl and \(\alpha\)-benzoyl substituents combined with the favourable five-membered ring entropy conspired to drive the equilibrium constant far towards the closed \(\gamma\)-lactol form of 66. Thus, the external phosphorane was not exposed to the \(\gamma\)-hydroxy aldehyde tautomer. This notion is consistent with the absence of
any aldehyde resonances in the $^1$H NMR and $^{13}$C NMR spectrum — even when using the extremely polar dimethylsulfoxide as the NMR solvent.

It is noteworthy that 66 was receptive to other types of nucleophilic additions (for instance, methyl Grignard and phenyllithium) and Wittig reactions on other γ-lactols are known. On the other hand, there are cases where this type of reaction failed (for example, in Fuchs' synthetic efforts towards the quassinoid bruceantin). Clearly, the nature of the γ-lactol has substantial influence on the success of the Wittig reaction. Taken together, the results from the model study discouraged us from attempting the addition of phosphorane 65 directly onto 66.

Opening of the benzyolated γ-lactone 68 using technology developed by Wessel or Weinreb was considered. For example, the use of Weinreb's methodology would convert 68 to its N-methoxy-N-methylamide 70. Protection of the released primary alcohol as its tert-butylidimethylsilyl ether 71 and DIBAL reduction to the aldehyde would provide 72 which was considered a promising alternative to 66 since it would virtually guarantee the success of the Wittig coupling.

61 P. Fuchs, private communication.
However, while this avenue was being explored, a more appealing route to the C(1)–C(9) fragment became apparent and the Wittig olefination approach was discontinued.

3.4 Dianion Approach – Retrosynthetic Analysis

Another route to the C(1)–C(9) fragment of bryostatin is depicted retrosynthetically in Figure 14.
Figure 14 — Retrosynthetic Analysis for C(1)–C(9) Subunit — Dianion Approach
This route has conceptual similarities to the Wittig approach. For instance, the starting materials 51 and 67 are the same. However, the umpolung reactivity involved in the connection of the four and five carbon units is changed. The new strategy depended upon the addition of the 2-lithiodithianyl fragment 75 onto a suitably activated C(1)–C(5) synthon 74 to accomplish the critical C(5)-C(6) bond connection. The stereochemistry at C(7), originating from (R)-pantolactone, could then be relayed to C(5) using the highly anti-selective Evan's β-hydroxy ketone reduction methodology\textsuperscript{19}. The C(5)–C(9) 8-lactone is assembled by a series of straightforward manipulations to the C(1)–C(9) adduct 73. A definite advantage of this route is that the stereogenicities at C(3), C(5), and C(7) should all be secure.

3.5 Preparation of the C\textsubscript{4} and C\textsubscript{5} Building Blocks 75 and 78

The preparation of the dithianyl synthon 75 was straightforward. (R)-Pantolactone 67 was reduced directly to the γ-lactol 76 using borane-tetrahydrofuran complex\textsuperscript{64} in 83% yield (BH\textsubscript{3}-THF, THF, 0°C to 25°C, 12 hours). This reaction is discussed in greater detail in Chapter 6.4. Treatment of 76 with 1,3-propanedithiol and a catalytic amount of boron trifluoride etherate furnished the acyclic 1,3-propanedithioacetal 77 in 75% yield (1,3-propanedithiol, BF\textsubscript{3}-Et\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, 25°C, hours). The primary hydroxyl [C(9) of bryostatin] was then selectively protected as its tert-butylidiphenylsilyl ether (75%, TBDPSCI, DMAP, imidazole, DMF, 25°C, 6 hours) using technology developed by

Hanessian. This provided the α-hydroxy dithianyl synthon 75 in 49% overall yield from (R)-pantolactone.

\[
\begin{align*}
67 & \xrightarrow{BH_3\text{-THF}} 83\% & 76 \\
75 & \xrightarrow{1,3\text{-propanedithiol, BF}_3\text{-Et}_2O} 79\% & 77 \\
\end{align*}
\]

To permit connection of 75 with a suitable C(1)–C(5) synthon derived from 51 (Chapter 2), it was decided to make the C(5) succinimidyld ester. This was accomplished by activating the C(5) carboxylic acid with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) followed by

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esterification with N-hydroxysuccinimide (EDC, N-hydroxysuccinimide, tBuOH, 2 hours). The yield of the succinimidyl ester 78 was 82%.

3.6 Addition of 75 Onto C(5)-Activated Ester 78

With fragments 75 and 78 in hand, we were in a position to attempt the crucial C(5)-C(6) linkage. Thus, the dithianyl compound 75 was treated with tert-butyllithium to presumably form the dianion (tBuLi, THF, -20°C, 4 hours) whereupon the electrophile 78 was added. After four hours at -20°C, the reaction had gone to completion. Preliminary examination of the spectral data (1H NMR; CIMS) of the isolated product suggested that the desired C-acylated compound 73 had been formed in acceptable yield (71%). However, the possibility of the transesterified product 79 arising from O-acylation was not ruled out.
$78$ + $75$ → $79$

$tBuLi, \text{THF} \rightarrow 75\%$

$79$ → $41$

$\text{NaOMe, MeOH} \quad \text{pH} = 10$

$41$ + $75$ → $73$

$73$ → $73$
Indeed, treatment of the adduct 79 with a catalytic amount of sodium methoxide in methanol (pH ~9.5) resulted in the quantitative formation of dimethyl 3-hydroxyglutarate 41 (ironically, the achiral precursor of 51!) and 75. This methanolytic reaction unambiguously confirmed that the undesired transesterified product 79 was formed.

A solution to avoid O-acylation was required if this route was to be made viable. The first effort involved changing the nature of the C(5) electrophile. Literature$^{67}$ indicated that the N-methoxy-N-methyl amides couples in good yields with Grignard, organolithium, ester enolate, and enolate nucleophiles to give ketones. This is probably due to the formation of the stable metal-chelated intermediate as depicted below.

Thus, we derivatized the monoacid 51 as its N-methoxy-N-methyl amide 80 using N,N'-carbonylbis(imidazole)$^{67b}$ as the activating agent (N,N'-carbonylbis(imidazole), N,O-dimethylhydroxylamine.HCl, CH$_2$Cl$_2$, 25°C, 16 hours). The yield of 80 was 62%.

Unfortunately, the coupling of 75 with 80 was also unsuccessful. At low temperatures (-20°C, 5 hours), no reaction was noted by tlc. Workup simply afforded the starting materials. Pushing the reaction by increasing the reaction temperature led to decomposition of the relatively base-labile amide 80. A complex mixture of products were isolated. Clearly, the N-methoxy-N-methyl amide is not electrophilic enough to be a synthetically useful alternative for this transformation or the dienion of 75 was not formed.

Protection of both hydroxyls on the 1,3-propanedithioacetal 77 represented another method for preventing O-acylation to occur. Thus, the benzylicene acetal was formed in 86% yield using standard methodology (benzaldehyde dimethyl acetal, TsOH, benzene, 25°C, 2 hours).
Unfortunately — and perhaps — not surprisingly, attempts to generate the 2-lithiodithianyl anion of 81 invariably led to decomposition via β-elimination to form the ketene dithioacetal 82 and benzaldehyde.

3.7 Additions of 75 Onto the C(5) Aldehyde 83

Since the crucial C(5)-C(6) connection was thwarted by O-acylation when employing various C(5) activated ester electrophiles, it was decided to investigate the use of the C(5) aldehydic electrophile 83. In this case, successful C-alkylation would provide the C(5) hydroxylated adduct 84 having the desired oxidation state at C(5). This advantage is offset by the expected inability to obtain significant levels of asymmetric induction at C(5).

The synthesis of the (R)-β-alkoxyaldehyde 83 is described in detail in Chapter 4.3. The attempted coupling of 75 with 83 using the standard lithiation procedure\(^{68}\) (75, nBuLi, THF, -20°C, 4 hours then 83) afforded no identifiable product; the major isolated compounds were the starting materials. Extensive variations in the reaction conditions (bases: nBuLi, sBuLi, tBuLi, MeLi, PhLi, PhLi,

LDA, NaH and combinations; solvents: THF, 1,2-dichloroethane, HMPA, TMEDA) gave the same negative result. In the extreme case, the dianion of 75 was given 30 hours at -10°C to form (nBuLi as base in 20% HMPA in THF). Once again, no coupled product was observed. In related experiments, quenches of the lithiation mixtures with D$_2$O and MeOD were made. This resulted in no deuterium incorporation ($^1$H NMR, CIMS). The inescapable conclusion was the dianion of the α-hydroxy dithianyl synthon 75 was either extremely short-lived or not formed$^{69}$.

Based upon inspection of Dreiding models of 75, it was speculated that perhaps the removal of the dithianyl proton was too sterically demanding (even with a small organolithium base such as MeLi). To test this hypothesis, we prepared the diethyl mercaptal derivative 85. This involved the dithioacetalization of 76 followed by treatment with ethanethiol and a catalytic amount of BF$_3$·Et$_2$O to afford the diethylthioacetal diol 85 in 61% yield (EtSH, BF$_3$·Et$_2$O, CH$_2$Cl$_2$, 25°C, 16 hours).

Selective protection of the primary alcohol of 85 using methodology identical to that described previously for the transformation of 77 into 75 provided the requisite four carbon synthon 86 in 68% yield (TBDPSCI, imidazole, DMAP, DMF, 25°C, 6 hours). Unfortunately, the dianion coupling of 86 with 83 under a wide variety of conditions was also unsuccessful.

Other modifications to the dithianyl synthons 75 and 86 included oxidation to the sulfoxide (58%, MCPBA, CHCl₃, 25°C, 30 minutes) in an effort to increase the acidity of the dithianyl proton. Formation of the dianion on these monosulfoxides did not occur either. Perhaps the remote tert-butyldiphenylsilyl protecting group was preventing dianion formation. To test this notion, protection of the primary hydroxyl of 85 as its benzyl ether was attempted. Standard
benzylation protocol (60%, BnBr, NaH, DMF, 25°C, 8 hours) led to exclusive benzylation of the secondary alcohol. The next thought was to form the benzylicidene acetal on 85 (using the same procedure as for the conversion of 77 to 81). Reductive benzylicdene-ring opening\textsuperscript{70} would then provide the desired primary benzyl ether. This sequence was prevented by difficulties encountered in formation of the benzylicdene acetal. The last idea for this seemingly trivial protection reaction was to tosylate the primary alcohol [C(9)] on 85 and, subsequently, displace it with the lithium salt of benzyl alcohol. The tosylation reaction (TsCl, pyridine, -10°C, 2 days) delivered the interesting, but not synthetically useful, product 87 in 77% yield.

\[ \begin{align*}
\text{EtS} & \quad \text{OH} \\
\text{EtS} & \quad \text{OH} \\
85 & \quad \text{TsCl, pyridine, -10°C, 77\%} \\
\text{EtS} & \quad \text{O} \\
\text{OTs} & \quad \text{9} \\
87 &
\end{align*} \]

Recent literature\textsuperscript{71} suggests that C-alkylation with dianions derived from \(\alpha\)-hydroxy 1,3-dithianes are possible. However, our results suggested that for the (R)-pantolactone derived synthons 75 and 86, this route was not viable. This encouraged us to search for other strategies and the dianion route was discontinued.


3.8 Conclusions

Although both the Wittig and dianion routes were unsuccessful, even in retrospect they seem sound and rational. Nevertheless, the experience gained in these preliminary studies regarding the chemistries of the (R)-pantolactone and methyl hydrogen (3R)-methoxymethoxyglutarate chiral building blocks was of value in our synthetic efforts towards the target bryostatin fragments [specifically, the C(17)–C(20) and C(1)–C(9) synthons].
3.9 Experimental

The general comments regarding instruments and reagents made in the Experimental section of Chapter 2.13 are applicable here as well.

(R)-Benzoylpantolactone (68):

To a stirred solution of 7.00 g, (53.8 mmol) of (R)-(−)-pantolactone 67 (dried using Dean-Stark apparatus, benzene) in pyridine (50 mL) was added 10.0 mL (86.1 mmol) of benzoyl chloride. After overnight contact, the excess benzoyl chloride was destroyed by addition of 3.0 g of crushed ice. After 2 hours, the mixture was stripped of solvent in vacuo and the residual syrup was taken up in ethyl acetate (250 mL) and washed with 0.5N HCl (100 mL), saturated aqueous NaHCO3 (100 mL), and brine (50 mL). The organic layer was dried over Na2SO4 and concentrated in vacuo leaving a white amorphous residue. This was recrystallized from hexane yielding 12.0 g (95%) of the benzyolated γ-lactone 68 as white needles melting at 51.1–52.2°C. [α]D = +3.2° (c = 1.5, CHCl3). IR (CH2Cl2 ν: 3018, 2962, 1788, 1728, 1267, 1118, 1013 cm\(^{-1}\). \(^1\)H NMR (300 MHz) δ: 7.43 - 8.10 (m, 5H, aromatic), 5.60 (s, 1H, H7), 4.12 (d, A of AB, J = 9.1 Hz, 1H, H9), 4.08 (d, B of AB, J = 9.1 Hz, 1H, H9), 1.26 (s, 3H, gem CH3), 1.21 (s, 3H, gem CH3). \(^13\)C NMR (50.4 MHz) δ: 172.4 (RCO2R), 165.3 (PhCO2R), 138.7, 129.9, 128.6, 128.5 (aromatic), 76.0 (C9), 75.2 (C7), 40.2 (C8), 22.6 (gem CH3), 19.6 (gem CH3). MS (El) m/z: 234 (M+, 3%), 105 (M+-129, 100%). Anal. calcd. for C\(_{13}\)H\(_{14}\)O\(_4\): C, 66.66, H, 6.02: found: C, 66.48, H, 6.00.
(R)-Benzoylpantolactol (66):

The benzyolated γ-lactone 68 (1.05 g, 4.48 mmol) was dissolved in 30 mL of THF and cooled to -78°C. Diisobutylaluminum hydride (1.0M in THF, 6.3 mL, 6.3 mmol) was added over a 15 minute period via a pressure-equalizing addition funnel. This mixture was stirred for 3 hours and then quenched by addition of Glauber's salt (Na₂SO₄·10H₂O, ~2 g). After warming to ambient temperature, the Glauber's salt was removed by filtration under suction. The filter cake was returned to the flask and refluxed with 50 mL of ethyl acetate (5 minutes), and filtered. This procedure was repeated with another 50 mL of ethyl acetate. The filtrates were combined and washed with 0.2N HCl (2 X 50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL), dried over Na₂SO₄, and concentrated in vacuo to yield a white amorphous solid. Purification by SiO₂ flash chromatography (2:8 ether/hexane) and recrystallization from hexane afforded 847 mg (80%) of the benzoylated γ-lactol 66 as white needles melting at 40.0-41.1°C. When different, the data for the minor anomer (2.0:1 anomic ratio) is given in brackets. [α]D = +30.1° (c = 1.0 in CHCl₃). IR (CH₂Cl₂) ν: 3405, 3018, 2962, 2878, 1718, 1601, 1272, 1118 cm⁻¹. ¹H NMR (300 MHz) δ: 7.42 - 8.08 (m, 5H, aromatic), 5.45 (d, J = 1.5 Hz, 1H, H₆), (5.66 - 5.75, m, 1H, H₆), 5.02 - 5.04 (m, 1H, H₇), 3.97 (d, A of AB, J = 8.6 Hz, 1H, H₉), 3.79 (d, B of AB, J = 8.6 Hz, 1H, H₉), (3.93) (d, A of AB, J = 8.3 Hz, 1H, H₉), (3.62) (d, B of AB, J = 8.3 Hz, 1H, H₉), 1.29 (s, 3H, gem CH₃), 1.14 (s, 3H, gem CH₃), (1.12) (s, 3H, gem CH₃), (1.16) (s, 3H, gem CH₃). ¹³C NMR (75.4 MHz) δ: 166.0 (PhCO₂R), 133.2, 129.6, 129.5, 128.4 (133.2, 129.7, 129.5, 128.4) (aromatic), 102.8 (97.0) (C₈), 86.0 (79.8) (C₇), 79.3, 77.3 (C₉), 41.7 (40.9) (C₈), 24.7, 20.8 (25.8, 20.4) (gem CH₃'s).
MS (Cl ether) m/z: 237 (M⁺+1, 12%), 235 (M⁺-1, 30%), 219 ((M⁺+1)-18, 100%). Anal. calcd. for C₁₃H₁₆O₄: C, 66.10, H, 6.84; found: C, 65.99, H, 6.91.

(2R)-2,4-Dihydroxy-3,3-dimethyl-1,1-(propane-1',3'-dithio)-butane (77):

To the γ-lactol 76 (Chapter 6.8), (1.05 g, 7.94 mmol) in dichloromethane (30 mL) was added 1,3-propanedithiol (1.03 mL, 10.3 mmol) and boron trifluoride etherate (196 μL, 1.59 mmol) and the solution was stirred at room temperature. After overnight contact, the reaction was diluted with another 70 mL of dichloromethane and extracted with 10% aqueous KOH (2 X 50 mL) and brine (1 X 50 mL), dried over Na₂SO₄, and concentrtrated in vacuo to yield an oil which was of sufficient purity (tlc, ¹H NMR) to be used in the next step without purification. This procedure provided 1.38 g (78%) of the dithianyl product 77 as a colourless oil. For analytical purposes, a sample was purified by preparative TLC (1:1 ethyl acetate/hexane). IR (thin film) ν: 3481, 3256, 2962, 2939, 2884, 1472, 1411, 1281, 1179, 1170, 1081, 1050 cm⁻¹. ¹H NMR (300 MHz) δ: 4.25 (d, J = 3.4 Hz, 1H, H₆), 3.71 (dd, J = 3.4, 4.5 Hz, 1H, H₇), 3.56 (dd, J = 4.8, 11.0 Hz, 1H, H₉), 3.49 (dd, J = 4.5, 11.0 Hz, 1H, H₉'), 3.04 (d, J = 4.5, 1H, R₂CHOH), 2.76 - 2.94 (m, 4H, CH₂(CH₂S), 2.56 (app t, J = 6.0 Hz, 1H, RCH₂OH), 1.88 - 2.10 (m, 2H, CH₂(CH₂S)₂), 1.02 (s, 6H, gem CH₃'s). ¹³C NMR (50.4 MHz) δ: 80.4 (C₆), 71.4 (C₉), 49.9 (C₇), 39.7 (C₈), 30.0 (CH₂(CH₂S), 29.0 (CH₃(CH₂S), 25.3 (CH₂(CH₂S)₂), 22.6, 20.0 (gem CH₃'s). MS (El) m/z: 222 (M⁺, 2%), 204 (M⁺-18,
2%), 119 (M^+-103, 100%). Anal. calcd. for C_9H_{18}O_2S_2: C, 48.61, H, 8.16, S, 28.84; found: C, 48.70, H, 8.09, S, 28.73.

(2R)-2-Hydroxy-3,3-dimethyl-4-[(tert-butyldiphenylsilyl)oxy]-1,1-(propane-1',3'-dithio)-butane (75):

To the 1,3-dithianyl diol 77 (1.20 g, 5.40 mmol) in N,N-dimethylformamide (30 mL) was added imidazole (0.53 g, 7.8 mmol), tert-butylchlorodiphenylsilane (1.97 mL, 7.58 mmol), and DMAP (0.33 g, 2.7 mmol). After stirring for 6 hours at ambient temperature, the solution was diluted with ether (200 mL) and extracted with water (3 X 70 mL), 0.2 N HCl, (1 X 70 mL), saturated aqueous NaHCO_3 (1 X 70 mL), and brine (70 mL). The ethereal layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by radial chromatography (2:8 ether/hexane) to yield 1.87 (75%) of the silyl ether 75 as a colourless oil. ^1H NMR (300 MHz) δ: 7.63 - 7.71 (m, 4H, aromatic), 7.34 - 7.43 (m, 6H, aromatic), 4.33 (d, J = 2.6 Hz, 1H, H_6), 3.82 (dd, J = 2.6, 4.9 Hz, 1H, H_7), 3.61 (d, A of AB, J = 9.8 Hz, 1H, H_g), 3.41 (d, J = 4.9 Hz, 1H, OH, exchangeable), 3.40 (d, B of AB, J = 9.8 Hz, 1H, H_g), 2.76 - 3.00 (m, 4H, CH_2(CH_2S)_2), 1.84 - 2.12 (m, 2H, CH_2(CH_2S)_2), 1.05 (s, 9H, C(CH_3)_3), 1.01, 0.98 (gem CH_3's). ^13C NMR (50.4 MHz) δ: 135.9, 134.9, 129.9, 127.8 (aromatics), 80.6 (C_6), 72.8 (C_9), 50.8 (C_7), 40.1 (C_8), 30.8 (CH_2(CH_2S)), 29.7 (CH_2(CH_2S)), 26.7 (C(CH_3)_3), 25.5 (CH_2(CH_2S)_2), 22.1, 20.5 (gem CH_3's), 19.0 (C(CH_3)_3). MS (Cl ether) m/z: 461 (M^+ + 1, 12%), 443 ((M^+ + 1)-18, 50%), 403 (M^+ - 57, 6%), 341 (M^+ - 119, 7%).
(3R)-4-(Carbo-N-hydroxysuccinimidyl)-3-methoxymethoxy-1-methylbutanoate (78):

In tert-butanol (20 mL) was added 0.55 g (2.67 mmol) of the monoacid 51 followed by 0.77 g (4.02 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 0.46 g (4.00 mmol) of N-hydroxysuccinimide. This mixture was stirred at room temperature for 2 hours and then stripped of solvent in vacuo. The residue was diluted in ethyl acetate (80 mL) and washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (50 mL portions). The organic layer was dried over Na₂SO₄ and the solvent was removed in vacuo. Purification by radial chromatography (9:1 ether/hexane) afforded 0.66 g (82%) of succinimidyl ester 78 as a colourless oil. [α]D = -6.6° (c = 2.0, CHCl₃). IR thin film ν: 2959, 1820, 1789, 1739, 1441, 1370, 1210, 1033 cm⁻¹. ¹H NMR (200 MHz) δ: 4.59 (s, 2H, OCH₂O), 4.33 (app qu, 1H, H₃) 3.58 (s, 3H, CO₂CH₃), 3.25 (s, 3H, OCH₃), 2.87 (d, J = 6.3 Hz, 2H, H₄), 2.73 (s, 4H, 2 X N(CO)CH₂R), 2.70 (dd, A of ABX, J = 9.2, 16.1 Hz, 1H, H₂), 2.58 (dd, B of ABX, J = 5.7, 16.1 Hz, 1H, H₂). ¹³C NMR (50.4 MHz) δ: 170.9 (CO₂CH₃), 169.2 (2 X NCOR), 166.0 (CO₂N), 96.7 (OCH₂O), 70.9 (C₃), 55.6 (OCH₃), 51.6 (CO₂CH₃), 39.2 (C₂), 36.6 (C₄), 25.3 (2 X NCOCH₂R). MS (EI) m/z: 272 (M⁺+1, 100%), 189 (M⁺-114, 8%).
(2'R,3R)-4-Carbomethoxy-1-[(2')-hydroxy-3',3'-dimethyl-4'-(tert-butyldiphenylsilyl)oxy]-1',1''-(propane-1'',3''-dithio)-butane]-3-methoxymethoxybutanoate (79):

A THF solution (10 mL) containing 52.4 mg (0.110 mmol) of the dithianyl compound 75 was cooled to -20°C and 0.35 mL (0.39 mmol) of tert-butyllithium (1.1M in pentane) was added. After stirring for 2 hours, the N-hydroxysuccinimidyl ester 78 (38.3 mg, 0.126 mmol) in 5 mL of THF was added dropwise. This mixture was stirred 4 hours at this temperature whereupon the reaction was quenched by addition of 2 mL of saturated aqueous NH₄Cl and allowed to warm to ambient temperature. The solution was diluted with 50 mL of ether. The ethereal layer was washed successively with 0.2N HCl, saturated aqueous NaHCO₃, and brine (30 mL of each), dried over Na₂SO₄, and concentrated in vacuo. The residual oil was purified by preparative TLC (4:6 ether/hexane) to yield 50.7 mg (71%) of the transesterified product 79 as a colourless oil. ¹H NMR (300 MHz) δ: 7.60 - 7.69 (m, 4H, aromatic), 7.34 - 7.42 (m, 6H, aromatic), 5.25 (d, J = 3.0 Hz, 1H, RCO₂CHR'), 4.44 (d, J = 3.0 Hz, 1H, RCH(SR'), 4.72 (d, A of AB, J = 6.9 Hz, 1H, OCH₂O), 4.61 (d, B of AB, J = 6.9 Hz, 1H, OCH₂O), 4.37 - 4.45 (m, 1H, H₃), 3.67 (s, 3H, CO₂CH₃), 3.40 (d, A of AB, J = 10.0 Hz, 1H, RCH₂OSi), 3.36 (d, B of AB, J = 10.0 Hz, 1H, RCH₂OSi), 3.34 (s, 3H, CH₂OCH₃), 2.52 - 2.84 (m, 8H, CH₂(CH₂S)₂, H₂, H₄), 1.64 - 2.04 (m, 2H, CH₂(CH₂S)₂), 1.07 (s, 9H, C(CH₃)₃), 1.02, 0.96 (s, 6H, gem CH₃'s). MS (Cl ether) m/z: 649 (M⁺+1, 3%), 617 (M⁺-31, 5%), 591 (M⁺-57, 1%), 443 (M⁺-205, 6%).
(3R)-3-Methoxymethoxy-1-methyl-4-(N-methyl-N-methoxycarbamoyl)-butanoate (80):

In 20 mL of dichloromethane was added the monoacid 51 (552 mg, 2.68 mmol) followed by 0.52 g (3.21 mmol) of N,N'-carbonylbis(imidazole) (recrystallized from THF and filtered under N₂ atmosphere). The mixture was stirred for 10 minutes at room temperature whereupon 0.29 g (2.97 mmol) of N,O-dimethylhydroxylamine hydrochloride was added. The reaction mixture was stirred overnight at room temperature, diluted with ether (80 mL), and washed successively with 0.2N HCl (2 x 30 mL), saturated aqueous NaHCO₃ (1 x 30 mL), and brine (1 x 30 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. Purification by SiO₂ flash chromatography (ether) yielded 412 mg (62%) of the N-methoxy-N-methylamide 80 as a colourless oil.

IR (thin film) ν: 2960, 1741, 1667, 1441, 1391, 1152, 1103, 1039 cm⁻¹. ¹H NMR (200 MHz) δ: 4.68 (d, A of AB, J = 6.9 Hz, 1H, OCH₂O), 4.63 (d, B of AB, J = 6.9 Hz, 1H, OCH₂O), 4.42 (app qu, 1H, H₃), 3.65 (s, 3H, CO₂CH₃), 3.64 (s, 3H, NOCH₃), 3.30 (s, 3H, OCH₃), 3.13 (s, 3H, NCH₃), 2.88 (dd, A of ABX, J = 6.9, 15.8 Hz, 1H, H₂), 2.64 (d, J = 5.8 Hz, 1H, H₄), 2.63 (d, J = 6.4 Hz, 1H, H₄'), 2.59 (dd, B of ABX, J = 6.2, 15.8 Hz, 1H, H₂'). 182.2 (CONR₂), 171.6 (CONR₂), 96.7 (OCH₂O), 71.6 (C₃), 61.2 (NOCH₃), 55.5 (CH₂OCH₃), 51.5 (CO₂CH₃), 40.0 (C₂), 37.2 (C₄), 32.0 (NCH₃). MS (El) m/z: 218 (M⁺-31, 3%), 189 (M⁺-60, 17%). MS (El ether) m/z: 250 (M⁺+1, 5%), 247 (M⁺-2, 50%), 218 (M⁺-31, 100%). HRMS calcd. for C₈H₁₃O₅ [M⁺-N(OCH₃)CH₃]: 189.0753; found: 189.0723.
(2R)-2,4-O-Benzylidene-3,3-dimethyl-1,1-(propane-1',3'-dithio)-butane (81):

To a solution of the 1,3-dithianyl diol 77 (42.5 mg, 0.191 mmol) in benzene (15 mL) was added benzaldehyde dimethyl acetal (37 μL, 0.25 mmol) and a catalytic amount of TsOH (~15 mg). After 2 hours, the reaction was diluted in ether (50 mL) and washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (40 mL portions). The organic layer was dried over Na₂SO₄ and concentrated in vacuo to yield 51.2 mg (86%) of the benzylidenated product 81 as a colourless oil. ¹H NMR (300 MHz) δ: 7.49 - 7.53 (m, 2H, aromatic), 7.29 - 7.38 (M, 3H, aromatic), 5.48 (s, 1H, PhCH), 4.33 (d, J = 5.2 Hz, 1H, H₆), 3.72 (d, J = 5.1 Hz, 1H, H₇), 3.66 (d, A of AB, J = 11.1 Hz, 1H, H₉), 3.58 (d, B of AB, J = 11.2 Hz, 1H, H₉'), 2.82 - 2.99 (m, 4H, CH₂(CH₂S)₂), 1.80 - 2.18 (m, 2H, CH₂(CH₂S)₂), 1.28, 0.95 (s, 6H, gem CH₃'s). MS (Cl ether) m/z: 311 (M+1, 36%), 205 ((M+1)-106, 100%), 191 (M+119, 93%).

(2R)-2,4-Dihydroxy-3,3-dimethyl-1,1-diethylthioacetal-butane (85):

To the γ-lactol 76, (0.50 g, 3.79 mmol) in dichloromethane (30 mL) was added ethanethiol (0.68 mL, 9.18 mmol) and boron trifluoride etherate (234 μL, 1.90 mmol) and the solution was stirred at room temperature. After overnight contact, the reaction was diluted with another 70 mL of dichloromethane and extracted with 10% aqueous KOH (2 X 50 mL) and brine (1 X 50 mL), dried over Na₂SO₄, and concentrated in vacuo to yield an oil which was purified by radial
chromatography (4:6 ether/hexane). This procedure provided 0.55 g (61%) of the diethyl thioacetal 85 as a colourless oil. $^1$H NMR (300 MHz) δ: 3.99 (d, J = 4.2 Hz, 1H, H₆), 3.65 (dd, J = 3.7, 4.2 Hz, 1H, H₇), 3.54 (d, A of AB, J = 9.8 Hz, 1H, H₉), 3.48 (d, B of AB, J = 9.8 Hz, 1H, H₉'), 3.30 (d, J = 9.8 Hz, 1H, OH, exchangeable), 2.60 - 3.02 (br s, 1H, OH, exchangeable), 2.59 - 2.78 (m, 4H, 2 X SCH₂CH₃), 1.27 (t, J = 7.5 Hz, 6H, 2 X SCH₂CH₃), 1.01 (s, 6H, gem CH₃'s). MS (Cl ether) m/z: 239 (M⁺+1, 8%), 177 (M⁺-61, 100%).

(2R)-2-Hydroxy-3,3-dimethyl-4-[(tert-butylidiphenylsilyl)oxy]-1,1-diethyl thioacetal-butane (86):

This material was prepared and purified in the same manner as described above for the conversion of 77 to 75. Thus, 221 mg (0.927 mmol) of the diethylthioacetal diol 85 yielded 0.30 g (68%) of the silyl ether 86 as a colourless oil $^1$H NMR (300 MHz) δ: 7.62 - 7.69 (m, 4H, aromatic), 7.33 - 7.42 (m, 6H, aromatic), 4.01 (d, J = 2.8 Hz, 1H, H₆), 3.94 (dd, J = 2.8, 4.5 Hz, 1H, H₇), 3.69 (d, A of AB, J = 9.7 Hz, 1H, H₉), 3.38 (d, B of AB, J = 9.7 Hz, 1H, H₉'), 3.36 (d, J = 4.5 Hz, 1H, OH, exchangeable), 2.61 - 2.76 (m, 4H, 2 X SCH₂CH₃), 1.24 (t, J = 7.4 Hz, 3H, SCH₂CH₃), 1.23 (t, J = 7.4 Hz, 3H, SCH₂CH₃), 1.05 (s, 9H, C(CH₃)₃), 1.01, 0.98 (s, 6H, gem CH₃'s). MS (Cl ether) m/z: 415 (M⁺-61, 11%), 341 (M⁺-135, 11%).
3,3-Dimethyl-4-O-tosyl-2-butanone (87):

p-Toluenesulfonyl chloride (102 mg, 0.54 mmol) in pyridine (15 mL) was added to the diethyl thiaoacetal diol 85 (50.3 mg, 0.21 mmol) and the reaction stirred at -10°C for 2 days. Water (1 mL) was added to destroy the excess sulfonyl chloride (1 hour) and the mixture was then stripped of solvent under reduced pressure. The residue was taken up in ether (40 mL) and washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (30 mL of each). The ethereal layer was dried over Na₂SO₄ and concentrated in vacuo. The oil was purified by preparative TLC (2:8 ether/hexane) to provide 53.1 mg (77%) of the ketone 87 as a colourless oil. IR (thin film) ν: 3022, 2982, 1711, 1697, 1373, 1361, 1192, 1180, 1102, 978 cm⁻¹. ¹H NMR (200 MHz) δ: 7.75 (d, J = 8.5 Hz, 2H, aromatic), 7.33 (d, J = 8.5 Hz, 2H, aromatic), 3.99 (s, 2H, H₉), 3.34 (s, 2H, H₈), 2.47 (q, J = 7.4 Hz, 2H, SCH₂CH₃), 2.44 (s, 3H, PhCH₃), 1.21 (s, 6H, gem CH₃'s), 1.20 (s, 3H, SCH₂CH₃). ¹³C NMR (50.4 MHz) δ: 206.7 (C₇), 145.1, 132.4, 129.9, 128.0 (aromatic), 75.2 (C₉), 47.2 (C₈), 36.5 (C₆), 25.8 (SCH₂CH₃), 21.9 (gem CH₃'s), 21.4 (PhCH₃), 13.8 (SCH₂CH₃). MS (El) m/z: 330 (M⁺, 18%), 227 (M⁺-103, 8%), 209 (M⁺-121, 24%). HRMS calcd. for C₁₅H₂₂O₄S₂ (M⁺): 330.0957; found: 330.0939.
CHAPTER 4: SYNTHESIS OF THE C(1)–C(9) FRAGMENT OF BRYOSTATIN BY LEWIS ACID MEDIATED ALDOL COUPLING72

4.1 Introduction

The results, as described in the last Chapter, suggested that an alternate strategy was required for the synthesis of the C(1)–C(9) fragment of bryostatin (1). Methyl hydrogen (3R)-methoxymethoxymethyglutarate (51) was still viewed as the best synthon for the C(1)–C(5) fragment of bryostatin. However, as demonstrated in the previous Chapter, a (R)-pantolactone derived C(6)–C(9) synthon was not feasible. Jonathan Swift's expression, "necessity is the mother of invention" rang true. A different strategy which was equally as elegant and more efficient became apparent.

4.2 Retrosynthetic Analysis

The new strategy is shown retrosynthetically in Figure 15. It differs considerably from the most advanced one14, since the actual synthesis requires only two synthons. Also, it permits a straightforward route to the δ-lactone 29 which is in a form appropriate for biological activity studies. It was anticipated that the C5 chiral building block 83, obtained from 51 in high enantiomeric excess (ee) by use of immobilized α-chymotrypsin24 (α-CHY) (Chapter 2), could induce its chirality from C(3) to C(5) upon addition of the C4 synthon 31 through

72This work has appeared in part in "A Direct Convergent Chemoenzymatic Synthesis of the C(1) – C(9) Fragment of Bryostatin. Unusual Diastereoselectivity During a Mukaiyama Aldol Condensation", R. Roy and A.W. Rey, Synlett., 1, 448 (1990).
β-chelation\(^{73}\) via a Lewis acid mediated aldol condensation\(^{74}\). The remaining stereogenic center at C(7) would then result from chelated β-hydroxy ketone reduction using tetramethylammonium triacetoxyborohydride\(^{19}\). The δ-lactone 29 would be readily available by regioselective mercury assisted lactonization\(^{75}\) of the hydroxyl at C(5) onto the thiol ester at C(9).


Figure 15 — Retrosynthetic Analysis for the C(1)–C(9) Subunit – Mukaiyama
Condensation Approach

Bryostatin 1
R = (2E,4E)-octa-2,4-dienoyl
4.3 Synthesis of the C(1)–C(5) Aldehyde Synthon (83):

The synthesis of the key chiral (3R)-β-alkoxyaldehyde 83 is depicted below.

\[ \text{MeO}_2\text{C} \quad \text{OMOM} \quad \text{CO}_2\text{Me} \quad \alpha - \text{Chymotrypsin} \quad \text{quantitative, 95% ee} \quad \text{MeO}_2\text{C} \quad \text{OMOM} \quad \text{CO}_2\text{H} \]

1. ECF / NEt₃
2. NaBH₄, 81%

\[ \text{MeO}_2\text{C} \quad \text{OMOM} \quad \text{CH}_2\text{OH} \quad \text{PCC, NaOAc} \quad 84\% \quad \text{MeO}_2\text{C} \quad \text{OMOM} \quad \text{CHO} \]

89 → 83

The preparation of the dimethyl 3-methoxymethoxyglutarate substrate 48 was described in Chapter 2. A multi-step synthesis of this type necessitates access to substantial quantities of enantiomerically homogeneous product in the early stages of the synthesis. Thus, considerable effort was devoted to making the enzymatic step (48 to 51) both efficient and economical. Immobilization of the α-CHY in dialysis bags permitted the use of a flow-through reactor as described in the Experimental section of this Chapter 4.9. This allowed the inexpensive synthesis of gram-quantities of 51 of acceptable optical purity (>95% ee) for chemoenzymatic synthesis²⁴.
Transformation of the carboxylic acid at C(5) to an aldehyde was problematic. Initially, we explored methods which would permit the one-pot reduction of 51 to 83. The two most successful methods we examined were developed by Fujisawa\textsuperscript{76} and Guibe\textsuperscript{77}.

Fujisawa's method\textsuperscript{76} employs N,N-dimethylchloromethyléniminium chloride for the chemoselective conversion of the carboxylic acid into the carboxymethyleniminum chloride which is subsequently reduced \textit{in situ} by lithium tri(tert-butoxy)aluminum hydride (oxayl chloride, DMF, pyridine, CuI, LiAlH(OBu)\textsubscript{3}, THF, acetonitrile). This yields a presumed stable betaine which decomposes upon workup to provide the aldehyde. This methodology did convert 51 into 83, however the yields were low and non-reproducible (20–40\%). Optimization of this rather complicated procedure by variations in reaction conditions did \textbf{not} improve the yields. Moreover, scale-up (5 mmol of 51) gave even poorer results (<30\%).

Guibe's\textsuperscript{77} methodology was tried as well. Briefly, this method relies upon the formation of an acid chloride (oxayl chloride, CH\textsubscript{2}Cl\textsubscript{2}, 0\textdegree C, 1 hour) and, without isolation, the subsequent palladium-catalysed reduction with tributyltin hydride [Pd(PPh\textsubscript{3})\textsubscript{4} (10\textsuperscript{-2} equiv), Bu\textsubscript{3}SnH, benzene, 25\textdegree C, 30 minutes]. Again, low yields (35\%) of the aldehyde 83 were obtained. Explanations for the low yields included loss of the MOM-protecting group and over-reduction to the alcohol (89). The low yields coupled with the expense of the catalyst discouraged the use of this method.

In a similar situation, Baader\textsuperscript{32a} noted that the Rosenmund reduction\textsuperscript{78} of the acid chloride 90 provided low yields (20–30\%) of the aldehyde 91. Thus, this method was not examined.

\[
\text{\begin{tikzpicture}
\node (n0) at (0,0) {90};
\node (n1) at (2,0) {10\% \text{ Pd/C}, H_2 (1 \text{ atm})};
\node (n2) at (4,0) {DIEA, 20–30\%};
\node (n3) at (6,0) {91};
\draw (n0) -- (n1) -- (n2) -- (n3);
\end{tikzpicture}}
\]

Considerable effort was spent exploring novel methodology for the one-pot conversion of carboxylic acids to aldehydes. Briefly, the principal idea was to employ mild reducing agents such as sodium cyanoborohydride (NaBH\textsubscript{3}CN) for the reduction of various carboxylic acid derivatives of 51 (for instance, the acid chloride, various mixed anhydrides, DCC– and EDC– adducts). The hope was that the reduction would stop at the aldehyde oxidation level since NaBH\textsubscript{3}CN does not reduce aldehydes at neutral pH's\textsuperscript{79}. Unfortunately, predominant alcohol formation did occur, presumably via a reduction pathway which does not pass through the aldehyde. Attempts at decreasing the reducing agent's strength even further by, for example, immobilization onto anion exchange resin, were unsuccessful.

The next strategy to accomplish this functional group interconversion was the two-step procedure involving reduction to the C(5) alcohol (89) followed by oxidation to the C(5) aldehyde (83). The first thought was to use the

chemoselective reducing agent borane-methyl sulfide complex (BMS). Indeed, this reagent did permit the clean reduction of methyl hydrogen (3R)-hydroxyglutarate and other 3-protected analogues (3-benzyloxy and 3-benzoyl) to the corresponding alcohols. However, for the 3-MOM-protected monoacid 51, a 65% yield of the hemi-orthoester 92 was obtained (BMS, THF, -78°C, 2 hours). This product presumably arises from MOM-group removal followed by hemi-orthoester formation.

Another plausible alternative for the structure of 92 is 93.

However, this possibility was rejected on the basis of the 1H NMR and 13C NMR data. For instance, the characteristic resonances of the methylene protons

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(OCH₂OCH₃) and methoxy protons (OCH₂OCH₃) on the MOM group at ~4.6 ppm and ~3.3 ppm, respectively, were absent. Likewise, the ¹³C NMR shifts at ~96.0 ppm (OCH₂O) and ~55.5 ppm (OCH₂OCH₃) were not observed. Also consistent with the proposed structure of 92 (and not with 93) is that the spectroscopic data suggested the presence of a carbomethoxy group (¹H NMR: CO₂CH₃, 3.71 ppm; ¹³C NMR: CO₂CH₃, 171.1 ppm and CO₂CH₃, 51.9 ppm).

A seldom used procedure developed in 1964 by workers at Bristol-Myers® for the reduction of various N-substituted 6-aminopenicillanic acids did provide the desired alcohol 89. This methodology involved the formation of the mixed anhydride of 51 (ECF, NEt₃, THF, 0°C, 1 hour) and, without isolation, borohydride reduction (NaBH₄, 7 equiv). This two-step, one-pot, reaction provided 89 in 81% yield.

Pyridinium chlorochromate oxidation (PCC, 4Å molecular sieves, CH₂Cl₂, 25°C, 30 minutes) of 89 proceeded smoothly to furnish key aldehyde 83 in 84% yield. The overall yield for 83 from 51 was 68% and this sequence was amenable to large scale (30 mmol) preparation.

4.4 Synthesis of the C(6)–C(9) Silylenol Ether Synthon (31):

The synthesis of the C(6)–C(9) synthon 31 is depicted on the next page.

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Briefly, using a procedure developed by Ley\textsuperscript{83}, addition of the anion of 2-methylpropane-2-thiol onto diketene (33) provided the known S-tert-butyl-3-oxobutanethioate 94 (71\%, tBuSH, NaH, THF, 1 hour). Introduction of the gem-dimethyl functionality at the C(8) position of this synthon was achieved by dimethylation using potassium tert-butoxide as base and methyl iodide as electrophile (86\%, KOtBu, MeI, THF, 25°C, 2 hours). This protocol was based upon work done in 1946 by Renfrow\textsuperscript{84} involving the alkylation of various

acetoacetate esters. In our situation, the use of THF as solvent (Renfrow uses tert-butyl alcohol) was preferred.

The silylenol ether derived from 95 was formed by the trimethylsilyl-trifluoromethanesulfonate (TMS-OTf) trapping of the enol tautomer (94%, TMS-OTf, NEt₃, benzene, 5°C to 25°C, 4 hours) of 95. The choice of benzene as solvent facilitated the workup procedure since the triethylammonium trifluoromethanesulfonate salt is insoluble in this medium. This allowed isolation of the key silylenol ether 31 in the supernatant benzene layer.

4.5 Condensation of C₄ and C₅ Synthons 31 and 83

The key condensation of the C₄ and C₅ synthons was accomplished as shown on the next page.

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Initially, a direct aldol condensation between the lithium enolate derived from 95 and the β-alkoxyaldehyde 83 was attempted (95, LDA, CeCl₃, THF, -20°C, 30 minutes then 83, -78°C, 1 hour). This afforded the diastereomeric aldol products 96 and 97 in 62% yield without significant diastereoselection (1.05:1; determined by ¹H NMR spectroscopy). Addition of CeCl₃ to the enolate before addition of the electrophile was utilized since it reduced the formation of unwanted side-products[86] for instance, olefinic products arising from the β-elimination of the C(3) MOM ether.

The cornerstone of this approach was the Lewis acid promoted (Mukaiyama) aldol condensation. The critical question was whether the chirality at C(3), which was settled by the enzymatic reaction, could be used to induce the desired chirality at C(5). In view of ample literature precedent[73] on simple model compounds, we anticipated that addition of 31 onto 83 should proceed with

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high diastereofacial selectivity towards the desired anti stereoisomer (97) under Ti(IV) or Sn(IV) tetrachloride chelation control addition. For instance, Reetz\textsuperscript{73a} obtains impressive diastereoselectivity (92:8 anti to syn) for the TiCl\textsubscript{4} catalysed addition of the enol silane derived from acetophenone (99) onto the β-benzzyloxyaldehyde 98.

\[
\begin{align*}
\text{Mg} & \quad \text{OBN} \\
\text{Ph} & \quad \text{Ph} \\
98 & \quad \text{OTMS} \\
\text{TICl}_4 & \quad -78^\circ\text{C} \\
\text{Me} & \quad \text{OBn} \\
100 & \quad \text{Nu} \\
\text{Me} & \quad \text{OBn} \\
101 & \quad (92\%) \\
\text{Me} & \quad \text{OBn} \\
102 & \quad (8\%)
\end{align*}
\]

The predominant formation of the anti product (101) is rationalized in terms of chelation-controlled addition of the enol silane from the less hindered side of the 6-membered chelate opposite to the pseudo-axial methyl group\textsuperscript{87} of intermediate 100. Considerable evidence supports this model\textsuperscript{88}.

We considered that having a β-MOM ether instead of a β-benzyl ether as in Reetz's\textsuperscript{73a} case should improve the diastereofacial selectivity for this


condensation. For instance, Danishefsky\textsuperscript{73c} reported in his tunicamycin synthesis improved anti selectivity when a MOM ether was in the $\beta$-position of the chiral aldehyde 101.

\begin{center}
\includegraphics[width=\textwidth]{103_104_105.png}
\end{center}

| C(5')-C(7')-relationship (anti / syn) | \hline
| R = Ph | 0:1 |
| R = OCH$_2$Ph | 1:2 |
| R = OMe | 3:1 |

To rationalize these results, Danishefsky postulates a cage-type chelate as shown in Figure 16. The explanation for the C(5') benzylxy protecting group forming the syn product is that the SnCl$_4$ is coordinated between the C(7') aldehyde and the tetrahydrofuran oxygen of 104. Thus, the diastereomeric outcome for this series of C(5')-protected aldehydes reflects a competition between the C(5')-C(7')-chelate and the ring oxygen-C(7')-chelate.
A most interesting and, at the time, disturbing result was that the \( \text{SnCl}_4 \)-mediated addition of 31 onto 83 (83, \( \text{SnCl}_4 \), \( \text{CH}_2\text{Cl}_2 \), \(-78^\circ\text{C}, 15 \) minutes then 31, \(-78^\circ\text{C}, 1 \) hour) did not lead to the anticipated and desired C(3) chelation control product 97. Rather, we obtained the C(5)-C(7)-syn diastereomer 96 as the major product (96:97, 1.5:1). The ratio of 96 to 97 was unchanged with \( \text{TiCl}_4 \), but the MOM protecting group was also lost. Although 96 and 97 were obtained as an inseparable mixture of diastereomers, their stereocchemical assignments were inferred by subsequent transformations.

This surprising 1.5:1 syn to anti ratio can only be rationalized on the basis of a long range chelation effect played by the C(1) carbomethoxy group which favoured Re-face attack. Remote chelation has recently been invoked to
rationalize some stereoselective reactions. The modest diastereoselectivity obtained here is a consequence of an interplay of 1,3- versus 1,5-chelation.

To test the hypothesis of long range chelation and to obtain improved yields of the C(3)-C(5)-anti product 97, the mono-coordinating Lewis acid boron trifluoride etherate (BF$_3$·Et$_2$O) was used. This prevented possible C(1)-C(5)-cage type chelation and encouraged single Lewis acid activation. Furthermore, the β-alkoxyaldehyde 83 might be expected to form a rigid conformation due to electrostatic repulsion (Figure 17). Attack of the silylenol ether 31 would occur from the less hindered diastereotopic π-face of the aldehyde (in this case, the Si-face) to provide 97 as the major product. In effect, the BF$_3$·Et$_2$O catalysed aldol condensation would simulate C(3) chelation control.

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A model of this type was proposed by Reetz\textsuperscript{73b} to accommodate the observations shown below.
These postulates were duly rewarded since the BF$_3$-Et$_2$O catalysed aldol condensation of 31 with 83 (83, BF$_3$-Et$_2$O, CH$_2$Cl$_2$, -78°C, 15 minutes then 31, -78°C, 1 hour) provided a 81% yield of the aldol products 96 and 97 with improved diastereoselectivity (anti: syn, 1.9:1).

As mentioned, the diastereomers 96 and 97 were not separable chromatographically. The diastereomeric ratio was assessed by integration of the $^1$H NMR resonances for the methoxy peak on the MOM group (3.37, 3.33 ppm for 97 and 96, respectively). Protection of the C(5) hydroxyl did permit separation of the diastereomers (for instance, the 3,5-dinitrobenzoate and mandelate esters). Unfortunately, deprotection using a variety of techniques invariably led to destruction of the molecule due to facile β-elimination to form the α,β-unsaturated ketone. The only alternative was to proceed in the synthesis with this mixture of β-hydroxy ketones. Perhaps separation would be possible at a later stage.
4.6 Synthesis of the C(1)–C(9) Fragment of Bryostatin in a Form Suitable for Synthetic Elaboration (110):

The β-hydroxy ketones 96 and 97 were subjected to the directed reduction method of Evans and Saskena\(^{19}\) (Me\(_4\)NHB(OAc)\(_3\), MeCN, HOAc, -40\(^\circ\)C, 9 hours) to afford the desired C(5)-C(7)-anti diol 107 and its C(5)-C(7)-epimeric diastereomer 106 in 84% combined yield.

\[
\begin{align*}
\text{MeO} & \quad \text{OMOM} & \quad \text{OH} & \quad \text{O} & \quad \text{O} & \quad \text{StBu} \\
1 & \quad 3 & \quad 5 & \quad 7 & \quad 9 & \\
97 & & & & & \\
\downarrow & & & & &
\end{align*}
\]

\[
\begin{align*}
\text{Me}_4\text{NBH(OAc)}_3, \text{CH}_3\text{CN}, \\
\text{HOAc}, -40^\circ \text{C}, 84%
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{OMOM} & \quad \text{OH} & \quad \text{OH} & \quad \text{O} & \quad \text{StBu} \\
1 & \quad 3 & \quad 5 & \quad 7 & \quad 9 & \\
107 & & & & & \\
\downarrow & & & & &
\end{align*}
\]

\[
\begin{align*}
\quad + & \quad \text{C(5) - epimer} \\
96 & & & & & \\
\quad \text{C(5),C(7) - epimer} \\
106 & & & & & \\
\end{align*}
\]

The stereoselection was excellent (anti/syn; 44:1). Moreover, the trace amounts of C(5)-C(7)-syn diastereomers that were formed were readily removed by silica gel flash chromatography. The cause of the high anti-
selectivity for reductions of this type is well-understood\textsuperscript{19}. Briefly, ligand exchange between the C(5) hydroxyl and the labile borohydride ligands affords the intermediate substrate-bound alkoxycacetone borohydride which is a stronger hydride donor than the parent borohydride (reductions of this type can be done in acetone). The hydride is delivered internally to the C(7) ketone via the chair-like transition states pictured in Figure 18. Clearly, the transition state leading to the C(5)-C(7)-anti diol is favoured relative to the transition state leading to the corresponding syn diol since it has both the C(5) and C(7) substituents in equatorial positions.
Figure 18 — Transition State for β-Hydroxy Ketone Reduction

\[
\begin{array}{c}
\text{DI-equatorial} \\
\text{Axial-equatorial}
\end{array}
\]

The high stereoselectivity of this reduction meant that we were still dealing with two diastereomers (106 and 107). Unfortunately they were chromatographically inseparable.

Interestingly, the desired anti-diol 107 was prone to acid-catalysed lactonization of the C(5) hydroxyl through the C(1) methyl ester to afford δ-lactone 108. Thus, when the mixture of 1,3-anti diols 106 and 107 were treated
with TsOH in benzene at room temperature, the δ-lactone 108 was obtained in 89% yield (based upon the amount of 107 present) together with unreacted C(5)-C(7)-epi anti diol 106.

This reactivity difference may be rationalized as follows. The δ-lactone 108 is formed from 107 since it allows the substituents at C(3) and C(5) to adopt the diequatorial relationship in the chair form. This may be contrasted to the less thermodynamically favourable situation for 106; the δ-lactone which would be formed for this product requires an axial/equatorial relationship between these substituents. The greater thermodynamic stability of 108 was mirrored at the
kinetic level. Recently, Danishefsky\textsuperscript{90} neatly employed this phenomena in his synthetic efforts towards FK-506.

The identification of the $\delta$-lactone 108 was quite straightforward by spectroscopic techniques. The $^1$H NMR resonances for the methyl ester protons at 3.7 ppm were absent as well as the characteristic $^{13}$C NMR resonance at 52 ppm for the CO$_2$CH$_3$ carbon. Additionally, $^1$H NMR and $^{13}$C NMR demonstrated that we were dealing with one diastereomer since there was no doubling of the resonance signals. The proton assignments were aided by a HOMCOR–$^1$H NMR experiment. The $^1$H NMR spectrum of 108 is given in Figure 19.

Figure 19 — $^1$H NMR Spectrum of 108
This preferential mode of lactonization for 107 was more than an experimental curiosity. Indeed, it was utilized to unequivocally assign the absolute configuration at C(5) relative to that at C(3). There was a 7.4% $^1$H nuclear Overhauser effect (nOe) difference enhancement between the protons on C(3) and C(5) which is consistent with their trans-diaxial relationship.

Many positive aspects had been realized in this synthesis to this point. The chirality at C(3) was successfully used to induce the desired chirality at C(5). The chirality at C(5) was then relayed to C(7) using a highly selective $\beta$-hydroxy ketone reduction. The absolute stereochemistries at C(3), C(5), and C(7) were established by $^1$H nOe difference spectroscopy studies. The only problem was that the diastereomeric anti diols 106 and 107 were still inseparable chromatographically (including HPLC). Separation was absolutely essential; the once desirable preparation of a chiral compound in enantiomerically pure form has become, in recent years, a virtual necessity.

This requirement was finally accomplished by derivatization of the intractable mixture of 106 and 107 with a solution of 2,2-dimethoxypropane in benzene and a catalytic amount of TsOH to provide the corresponding C(5)-C(7)-dioxane acetonides 109 and 110 in near quantitative yields.
Importantly, these acetonides were separable by silica gel flash chromatography. Acetonide removal was subsequently accomplished by acidic methanolysis (MeOH, PPTS, 25°C, 5 hours) to afford the desired homochiral
C(5)-C(7)-anti diol 107. Before complete acetonide removal, concomitant lactonization at C(1) also occurred to form 108. By carefully monitoring the reaction, formation of this δ-lactone was minimized (<10%).

Recently, Rychnovsky\textsuperscript{91} has noted that the $^{13}$C NMR chemical shifts of the acetonide methyl groups for syn and anti 1,3-acetonides vary in a predictable manner. Specifically, the $^{13}$C NMR chemical shifts for the 1,3-anti acetonide methyl groups occur at ~24 ppm whereas 1,3-syn acetonides occur at ~19 and ~30 ppm. For acetonide 110, the methyl resonances occur at 24.3 and 24.0 ppm, thereby confirming the C(5)-C(7)-anti acetonide relationship for this product.

It is worth mentioning that acetonide 110 [(α)\textsubscript{D} = -19.4° (c=1.0, CHCl\textsubscript{3})] constitutes an appropriate intermediate for further synthetic elaboration of the bryostatin molecule. Structurally, it is closely related to Masamune's\textsuperscript{14} C(1)-C(9) synthon 12 [(α) = -12.8° (c=0.80, CHCl\textsubscript{3}); Chapter 1.3] — the primary difference being the oxidation states at C(1) and C(9). From a synthetic viewpoint, synthon 110 has advantages. For instance, the probable next step (which Masamune accomplished) is one carbon homologation at C(9) to form the C(9)-C(10) methyl ketone. This permits enolate chemistry for the connection of C(10) to C(11). The methyl ketone can be formed directly from 110 by methylcuprate addition to the thiol ester. This may be contrasted to Masamune's synthon which necessitated a four step sequence. The $^1$H NMR spectrum for 110 is given in Figure 20.

4.7 Synthesis of the C(1)–C(9) Fragment of Bryostatin in a Form Suitable for Structure/Activity Studies (29):

The C(1)–C(9) subunit of bryostatin 1 occurs as a substituted δ-lactol. Thus, it was considered that the C(5)–C(9) δ-lactone 29 would mimic the δ-lactol portion and provide a stable molecule for biological testing. Selection of the thiol ester functionality at C(9) was predicated upon the ability of this functionality to allow facile mercury-assisted lactonization\textsuperscript{75}. Thus, treatment of the anti-diol 107 with mercury trifluoroacetate [Hg(CF\textsubscript{3}CO\textsubscript{2})\textsubscript{2}, THF, 25°C, 30 min] allowed selective cyclization between the C(5) hydroxyl group and the C(9) thiol ester to provide δ-lactone 111 in 85% yield.

\[
\begin{align*}
\text{MeO} & \quad \text{OMOMOH} & \quad \text{OH} & \quad \text{O} & \quad \text{StBu} & \quad \text{Hg(CF}_3\text{CO}_2)\text{2} \\
& & & \quad \text{OR} & & \quad \text{MeO} \\
\text{107} & \quad \text{111: R=MOM, R'=H} & \quad \text{112: R=MOM, R'=Ac} & \quad \text{29: R=H, R'=Ac} \\
& & & \quad \text{Ac}_2\text{O, py, 91\%} & & \quad \text{TiCl}_4, -78°C, 85\%}
\end{align*}
\]

The structure of 111 was confirmed by spectral analysis. For example, \textsuperscript{1}H NMR revealed the loss of the tert-butylthiol group by the disappearance of the resonance for the C(CH\textsubscript{3})\textsubscript{3} protons at 1.4 ppm. An unlikely product would have been lactonization of 107 through the C(7) hydroxyl group to afford the β-lactone. This possibility was rejected by use of IR spectroscopy. The carbonyl
stretching frequency for \(\beta\)-lactones occurs at \(\sim 1810\ \text{cm}^{-1}\) whereas 111 had a carbonyl stretching frequency at 1721 cm\(^{-1}\) (consistent with \(\delta\)-lactones). The assignments of the protons in the \(^1\)H NMR spectrum were ascertained by HOMCOR- and NOESY- \(^1\)H NMR experiments.

Bryostatin 1 (1a) has the C(7) hydroxyl protected as its acetate. Thus, the \(\delta\)-lactone 111 was acetylated using standard methodology (Ac\(_2\)O, pyridine, 6 hours) to provide the C(7) acetate 112 in excellent yield (91%).

The final step in the synthesis of the target \(\delta\)-lactone 29 was deprotection of the MOM-ether at C(3). During the experimentation regarding the effect of the Lewis acid upon the stereochemical outcome of the Mukaiyama reaction (Chapter 4.5), it was noted that the TiCl\(_4\)-mediated aldol provided the adduct along with loss of the MOM-protecting group. Based upon this result, the acetylated \(\delta\)-lactone 112 was subjected to the conditions discovered above (TiCl\(_4\), CH\(_2\)Cl\(_2\), -78°C, 1 hour followed by a saturated aqueous NaHCO\(_3\) quench). This procedure cleanly removed the MOM-group in 85% yield to afford the \(\delta\)-lactone 29 [(\(\alpha\))\(_D\) = +42° (c=0.50, CHCl\(_3\))], thereby completing the synthesis. Figure 21 compares the \(^{13}\)C NMR chemical shifts of 29 with those found in bryostatin 1. The \(^1\)H NMR spectrum of 29 is given in Figure 22.
Figure 21 — Comparison of $^{13}$C NMR Shifts for the C(1)–C(9) Segment of Bryostatin 1 versus 29 (in brackets)
Figure 22 — $^1$H NMR spectrum of 29
4.8 Conclusions

The transformations described herein provide a practical enantioselective route to gram quantities of the useful C(1)–C(9) bryostatin fragments 110 and 29 using only two synthons. A long range chelation effect was proposed to explain the reversal of diastereoselectivity during a Lewis acid mediated aldol condensation. However, a non-chelating Lewis acid provided the desired diastereomer. In addition, a new mild and efficient method has been utilized for the removal of the MOM–protecting group.
4.9 Experimental

The general comments regarding instruments and reagents made in the Experimental section of Chapter 2.13 are applicable here as well.

(3R)-Methoxymethoxypentanedioic acid monomethyl ester (51):

α-Chymotrypsin (E.C. 3.4.21.1, Sigma Type II from bovine pancreas, 1.00 g, 15 μmol) dissolved in 16 mL of 0.01N Na₂HPO₄ buffer was equally distributed in four dialysis bags (cellulose acetate M.W. cut off 12-14 kDa) which were added to a solution of 48 (1.00 g, 4.55 mmol) in 30 mL of the same buffer. The reaction mixture was stirred at room temperature and the pH was adjusted to 7.8 using 0.4N NaOH and kept constant throughout the reaction by a Radiometer automatic titrator. The extent of reaction was estimated by the volume of base consumed during the course of the reaction. After overnight contact, the reaction was complete. The solution was extracted with ether (2 x 30 mL) to remove remaining 48. The mixture was then acidified to pH ~2 using 2.5N HCl. This solution was extracted with ethyl acetate (4 x 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The products remaining in the dialysis bags were isolated by repeating the above steps after dialyzing the contents with a fresh solution of the buffer (50 mL). The (R)-monoacid 51 was thus isolated in a yield of 91% (0.85 g) and could be used without purification in the next step. A small sample was purified by SiO₂ flash chromatography (1:1 ethyl acetate/hexane) for analytical purposes. A reactor
such as the one described may be repeatedly used or the enzyme stored for a period of one month without a significant decrease in the rate or enantioselectivity of hydrolysis. Also, without a decrease in the enantioselectivity, the time of the reaction may be decreased 3 to 4 fold when the reactions are performed at 36°C. \([\alpha]_D = -3.3^\circ \text{ (c} = 3, \text{ CHCl}_3)\). IR (thin film) \(\nu:\)

\begin{align*}
3150, & \quad 2961, 1734, 1442, 1152, 1103 \text{ cm}^{-1}. \\
^{1} \text{H NMR} & \text{ (300 MHz) } \delta: 11.1 \text{ (br } s, \text{ 1H, COOH, exchangeable), } 4.68 \text{ (s, 2H, OCH}_2\text{O), } 4.40 \text{ (app qu, 1H, H}_3\text{), } 3.68 \text{ (s, 3H, CO}_2\text{CH}_3\text{), } 3.34 \text{ (s, 3H, OCH}_3\text{), } 2.58 - 2.75 \text{ (m, 4H, 2 X CH}_2\text{). } 13\text{C NMR (50.4 MHz) } \delta: 176.5 \text{ (CO}_2\text{H), } 171.4 \text{ (CO}_2\text{CH}_3\text{), } 96.4 \text{ (OCH}_2\text{O), } 71.2 \text{ (C}_3\text{), } 55.5 \text{ (OCH}_3\text{), } 51.6 \text{ (CO}_2\text{CH}_3\text{), } 39.5, 39.4 \text{ (C}_2\text{, } C_4\text{). MS (El) m/z: } 175 \text{ (M}^+\text{-31, 4%). MS (Cl ether) m/z: } 207 \text{ (M}^+\text{+1, 15%), } 175 \text{ (M}^+\text{-31, 100%). Anal. calcd. for } C_8\text{H}_{14}\text{O}_6: C, 46.60, H, 6.85; \text{ found: C, 47.08, H, 6.91.}
\end{align*}

**Hemi-Orthoester 92:**

To a solution of carboxylic acid 51 (0.51 g, 2.47 mmol) in THF (40 mL) at -78°C was added 1.82 mL (3.64 mmol) of borane-methyl sulfide complex (2.0M in THF) and the solution stirred at -78°C for 4 hour. It was quenched by careful addition of methanol (20 mL) and allowed to warm to room temperature. The mixture was co-evaporated several times with 50 mL of a 2% acetic acid in methanol solution and the residual yellowish oil purified by SiO₂ flash chromatography (1:1 ether/hexane) to afford 0.33 g (65%) of the hemi-orthoester 92 as the major product. IR (thin film) \(\nu:\)

\begin{align*}
3462, & \quad 2941, 2921, 1741, 1441, 1285, 1168, 1151, 1098 \text{ cm}^{-1}. \\
^{1} \text{H NMR} & \text{ (300 MHz) } \delta \text{ (major diastereomer): } 5.253 \text{ (s, 1H,}
\end{align*}
OCH₂O), 5.250 (s, 1H, OCH₂O), 4.42 - 4.51 (m, 1H, H₃), 3.71 (s, 3H, CO₂CH₃) 3.46 (s, 3H, OCH₃), 3.32 (br s, 1H, OH, exchangeable), 2.59 (d, J = 6.0, 2H, H₂), 2.56 (d, J = 6.3, 2H, H₄). ¹³C NMR (50.4 MHz) δ: 172.0 (C₅), 171.1 (CO₂CH₃), 90.6 (OCH₂O), 64.6 (C₃), 57.8 (OCH₃), 51.9 (CO₂CH₃), 40.7, 40.4 (C₂, C₄). MS (EI) m/z: 143 (M⁺-63, 3%), 127 (M⁺-79, 2%), 100 (M⁺-106, 10%). MS (Cl ether) m/z: 207 (M⁺+1, 4%), 189 (M⁺+1-18, 9%), 175 (M⁺-31, 100%). Anal. calcd. for C₆H₁₄O₆: C, 46.60, H, 6.84; found: C, 46.83, H, 6.99.

(3R)-Methyl-5-hydroxy-3-methoxymethoxypentanoate (89):

To a solution of carboxylic acid 51 (3.00 g, 14.5 mmol) in THF (100 mL) at 0°C was added 26.3 mL (18.9 mmol) of triethylamine and 16.6 mL (17.4 mmol) of ethyl chloroformate. After being stirred for 1 hour, 20 mL of methanol was added followed by proportional additions of NaBH₄ (3.29 g, 87.0 mmol) over a 30 minute period. The ice-bath was removed and the reaction mixture was allowed to warm to ambient temperature and then carefully poured into saturated aqueous NH₄Cl (50 mL) and transferred to a separatory funnel charged with 150 mL of ethyl acetate. The organic layer was washed with saturated aqueous NaHCO₃ and brine. The combined aqueous layers were re-extracted with an equal volume of ethyl acetate and subsequently dried over Na₂SO₄ and the solvent removed in vacuo to yield a colourless oil. Purification by SiO₂ flash chromatography (7:3 ethyl acetate/hexane) afforded 2.27 g (81%) of the alcohol 89 as a colourless oil. [α]D = +14.2° (c = 1.0, CHCl₃). IR (thin film) ν: 3450, 2960, 1740, 1442, 1153, 1103 cm⁻¹. ¹H NMR (300 MHz) δ: 4.72 (d, A of
AB, J = 6.9 Hz, 1H, OCH₂O), 4.64 (d, B of AB, J = 6.9 Hz, 1H, OCH₂O), 4.12 - 4.30 (m, 1H, H₃), 3.72-3.82 (m, 2H, H₅), 3.70 (s, 3H, CO₂CH₃), 3.37 (s, 3H, OCH₃). 2.66 (dd, A of ABX, J = 7.0, 15.5 Hz, 1H, H₂), 2.51 (dd, B of ABX, J = 5.7, 15.5 Hz, 1H, H₂), 2.25 (b, 1H, OH, exchangeable), 1.79 - 1.98 (m, 2H, H₄).¹³C NMR (50.4 MHz) δ: 171.8 (CO₂CH₃), 96.3 (OCH₂O), 72.9 (C₃), 58.8 (C₅), 55.4 (OCH₃), 51.3 (CO₂CH₃), 40.0 (C₂), 37.1 (C₄). MS (El) m/z: 161 (M⁺-31,3%). MS (Cl ether) m/z: 161 (M⁺-31, 72%), 131 (M⁺-61, 100%). MS (FAB glycerol) m/z: 193 (M⁺+1, 15%), 161 (M⁺-31,100%). Anal. calcd. for C₈H₁₆O₅: C, 49.99, H, 8.39; found: C, 49.87, H, 8.18.

(3R)-Methyl-3-methoxymethoxy-5-oxopentanoate (83):

To 50 mL of dichloromethane was added 2.00 g (10.4 mmol) of the alcohol 89, 2.56 g (31.2 mmol) of anhydrous sodium acetate, 6.73 g (31.2 mmol) of pyridinium chlorochromate and 2.0 g of 4 Å molecular sieves. The resulting brown slurry was stirred at ambient temperature for 30 minutes (over-oxidation to the monoacid 51 was noted for longer reaction times) whereupon an equal volume of ether was added. The precipitated solid was removed by filtration, through a pad of SiO₂ and the solvent removed in vacuo to provide a colourless oil. The oil was purified by SiO₂ flash chromatography (7:3 ether/hexane) to deliver 1.66 g of aldehyde 83 (84%). [α]D = +4.9° (c = 1.5, CHCl₃). IR (thin film) ν: 2960, 2818, 1740, 1441, 1150, 1105 cm⁻¹. ¹H NMR (300 MHz) δ: 9.76 (dd, J = 1.5, 2.2 Hz, 1H, CHO), 4.69 (d, A of AB, J = 7.1 Hz, 1H, OCH₂O), 4.65 (d, B of AB, J = 7.1 Hz, 1H, OCH₂O), 4.49 (app qu, 1H, H₃), 3.68
(s, 3H, CO₂CH₃), 3.32 (s, 3H, OCH₃), 2.72–2.81 (m, 2H, H₄), 2.69 (dd, A of ABX, J = 6.9, 15.7 Hz, 1H, H₂), 2.57 (dd, B of ABX, J = 5.9, 15.7 Hz, 1H, H₂). ¹³C NMR (50.4 MHz) δ: 200.4 (CHO), 171.2 (CO₂CH₃), 96.5 (OCH₂O), 69.9 (C₃), 55.6 (OCH₃), 51.6 (CO₂CH₃), 48.6 (C₄), 39.6 (C₂). MS (EI) m/z : 175 (M⁺−15, 1%), 159 (M⁺−31, 1%), 145 (M⁺−45, 4%). MS (Cl ether) m/z: 191 (M⁺+1, 3%), 159 (M⁺−31, 100%). Anal. calcd. for C₈H₁₄O₅·½H₂O: C, 48.24, H, 7.59; found: C, 48.50, H, 7.05. HRMS (recorded on a Kratos Concept 2H mass spectrometer) calcd. for C₇H₁₁O₅ (M⁺−CH₃): 175.0606; found: 175.0602.

**S-tert-Butyl-3-oxobutanethioate (94):**

This material was prepared according to the method of Ley⁹³. Thus, 2-methylpropane-2-thiol (12.5 mL, 0.11 mol) in THF (10 mL) was added via a pressure-equalizing dropping funnel to a slurry of sodium hydride (50% in mineral oil, washed with pentane) (6.00 g, 0.13 mol) in THF (300 mL) at -5°C. The rate of addition was such that a steady evolution of hydrogen was maintained. After complete addition, the solution was stirred at 0°C a further 15 minutes and then re-cooled to -5°C and diketene (33) (9.4 mL, 0.12 mol) was added over a 15 minute period. The mixture was allowed to warm to ambient temperature and the excess sodium hydride was quenched by addition of saturated aqueous NH₄Cl (150 mL) and transferred to a separatory funnel charged with ether (200 mL). The layers were separated and the organic layer was washed successively with water, saturated aqueous NaHCO₃, and brine (150 mL of each). The combined aqueous washes were re-extracted with ether
(200 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to yield 13.6 g (71%) of 94 as a red oil. A sample for analytical purposes was obtained by radial chromatography (10:1 hexane/ether). Distillation at 95-100°C (0.9 mm Hg). IR (thin film) ν: 1712, 1676, 1621 cm⁻¹. ¹H NMR (200 MHz) δ: 3.57 (s, 2H, CH₂), 2.26 (s, 3H, CH₃CO), 1.48 (s, 9H, C(CH₃)₃); 15% in enol-form: 5.33 (s, 1H, C=CH), 1.90 (s, 3H, CH₃C(OH)=C), 1.48 (s, 9H, C(CH₃)₃).

**S-tert-Butyl-2,2-dimethyl-3-oxobutanethioate (95):**

To 3.00 g (17.2 mmol) of 94 in THF (100 mL) was added 4.83 g (43.0 mmol) of potassium tert-butoxide. After stirring at room temperature for 30 minutes, 3.21 mL (51.6 mmol) of iodomethane was added. When tlc indicated the reaction to be complete (approximately 2 hours) it was processed by concentration in vacuo followed by dissolving the residue in saturated aqueous NH₄Cl (100 mL). This solution was transferred to a separatory funnel charged with 200 mL of ether. The ethereal layer was washed successively with 100 mL portions of 0.2N HCl, saturated aqueous NaHCO₃, and brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo leaving 3.00 g (86%) of the gem-dimethylated product 95 as a pale yellow oil. This product was used in the next step without purification. An analytical sample was obtained by radial chromatography (5:1 hexane/ether) for analytical purposes. IR (thin film) ν: 2973, 1722, 1675, 1461, 1368, 948 cm⁻¹. ¹H NMR (200 MHz) δ: 2.16 (s, 3H, CH₃CO), 1.48 (s, 9H, C(CH₃)₃), 1.37 (s, 6H, gem CH₃'s). ¹³C NMR (50.4 MHz) δ:
205.6 (C=O), 201.8 ((C=O)S), 63.9 (C(CH₃)₃), 48.0 (C₈), 29.4 (C(CH₃)₃), 25.5 (CH₃CO), 21.8 (gem CH₃'s). MS (EI) m/z: 202 (M⁺, 1%), 160 (M⁺-42, 2%), 146 (M⁺-56, 30%). MS (Cl ether) m/z: 203 (M⁺+1, 100%). HRMS calcd. for C₉H₁₀O₂S (M⁺-(CH₃)₂C=CH₂): 146.0453; found: 146.0400.

4-S-tert-Butyl-3,3-dimethyl-2-trimethylsilyloxy-1-butenethioate (31):

Triethylamine (0.414 mL, 2.97 mmol) and trimethylsilyl trifluoromethanesulfonate (0.526 mL, 2.72 mmol) were sequentially added to 0.500 g (2.47 mmol) of 95 in 50 mL of benzene at 5°C. After 5 minutes at this temperature, the mixture was allowed to warm to ambient temperature and stirred a further 4 hours. The stirring was discontinued and the triethylammonium trifluoromethanesulfonate was allowed to coalesce into a brown oil. The supernatant benzene layer was decanted into a separatory funnel containing 150 mL ether and 50 mL saturated aqueous NaHCO₃. The triethylammonium trifluoromethanesulfonate oil was washed with another 30 mL of dry benzene and the upper layer decanted into the separatory funnel. The ethereal layer was separated and washed successively with 50 mL portions of 0.2N HCl, saturated aqueous NaHCO₃, and brine. Drying over Na₂SO₄ and concentration in vacuo afforded 0.64 g (94%) of silylenol ether 31 as a yellowish oil which was used in the next step without purification. A small sample was purified by radial chromatography (9:1 hexane/ether) for analytical purposes. IR (thin film) ν: 2970, 1685, 1628, 1258, 1171, 1022 cm⁻¹. ¹H NMR (200 MHz) δ: 4.26 (d, A of AB, J = 2.0 Hz, 1H, H₂C=C), 4.11 (d, B of AB, J = 2.0 Hz, 1H, H₂C=C), 1.41 (s,
9H, C(CH₃)₃, 1.27 (s, 6H, gem CH₃’s), 0.19 (s, 9H, Si(CH₃)₃). ¹³C NMR (50.4 MHz) δ: 204.3 ([C=O]S), 161.8 (C=CH-O), 88.8 (CH₂=C), 56.0 (C(CH₃)₃), 46.8 (C₈), 29.7 (C(CH₃)₃), 23.9 (gem CH₃’s), -0.25 (Si(CH₃)₃). MS (El) m/z: 217 (M⁺-57, 22%). HRMS calcd. for C₉H₁₇O₂SSi (M⁺- C(CH₃)₃): 217.0719; found: 217.0706.

(3R,5R,S)-9-S-tert-Butylthioate-5-hydroxy-3-methoxymethoxy-8,8-dimethyl-7-oxononanoic acid, methyl ester (96, 97):

**Procedure 1:**

A solution of nBuLi (1.5M in hexane) (0.693 mL, 1.04 mmol) was added to a solution of diisopropylamine (0.155 mL, 1.11 mmol) in THF (10 mL) at -20°C and stirred for 30 minutes. The mixture was cooled to -78°C and 195 mg (0.963 mmol) of 95 in 2 mL of THF was added via cannula to the mixture and stirred a further 50 minutes. Anhydrous cerium (III) chloride (0.273 g, 1.11 mmol) was added at this point and, after 10 minutes, a solution of the aldehyde 83 (0.141 g, 0.741 mmol) in 3 mL of THF was added via cannula. Stirring was continued for 1 hour at -78°C whereupon the reaction was quenched by addition of 3 mL of saturated aqueous NH₄Cl and the mixture allowed to warm to room temperature. Dilution with 40 mL of ether and subsequent washing with 0.2N HCl (20 mL), saturated aqueous NaHCO₃ (20 mL) and brine (20 mL) was accomplished. The ethereal layer was dried over Na₂SO₄ and concentrated in vacuo to yield a yellow oil. Purification by radial chromatography (3:2 ether/hexane) afforded
0.18 g (62%) of the mixture of β-hydroxy ketones 96 and 97 as a colourless oil and 1:1 mixture of inseparable (3R, 5S)- and (3R, 5R)- diastereomers.

Procedure 2:

At -78°C, boron trifluoride etherate (0.837 mL, 6.81 mmol) was added to a solution of aldehyde 83 (0.432 g, 2.27 mmol) in 40 mL of dichloromethane. After stirring for 15 minutes, a solution of silylenol ether 31 (0.936 g, 3.41 mmol) in 5 mL of dichloromethane was added dropwise via cannula over a 20 minute period. The reaction was stirred a further 40 minutes after complete addition at which point it was quenched by addition of 10 mL of saturated aqueous NaHCO₃ and warmed to ambient temperature. The mixture was then diluted with 50 mL of dichloromethane and washed with saturated aqueous NaHCO₃ and brine (130 mL of each). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residual oil was purified as described in Procedure 1 above to afford 0.72 g (81%) of β-hydroxy ketones 96 and 97 as a colourless oil and 1.92:1 mixture of inseparable (3R,5R)- and (3R,5S)- diastereomers, respectively. Lewis acids other than boron trifluoride etherate were also utilized (TiCl₄, SnCl₄, ZnBr₂, ZnI₂, MgCl₂). The experimental protocol was identical. When data for the minor, and undesired, (3R, 5S)- diastereomer (96) differs, it appears in brackets. IR (thin film) ν: 3470, 2962, 2935, 1739, 1668, 1368, 1151, 1102, 1038 cm⁻¹. ¹H NMR (300 MHz) δ: 4.60 - 4.70 (m, 2H, OCH₂O), 4.10 - 4.32 (m, 2H, H₃, H₅), 3.66 (s, 3H, CO₂CH₃), 3.37 (3.33) (s, 3H, OCH₃), 3.25 (br s, 1H, OH, exchangeable), 2.51 - 2.66 (m, 4H, H₂, H₆), 1.72 - 1.90 (m, 1H, H₄), 1.45 - 1.70 (m, 1H, H₄), 1.44 (s, 9H, C(CH₃)₃), 1.36 (s, 3H, gem CH₃), 1.35 (s, 3H, gem
CH₃). ³¹C NMR (50.4 MHz) δ: 208.5 (C=O), 201.7 ((C=O)S), 171.7 (CO₂CH₃), 96.9 (96.1) (OCH₂O), 72.4 (73.0) (C₃), 64.1 (65.4) (C₅), 63.9 (C(CH₃)₃), 55.7 (55.6) (OCH₃), 51.4 (CO₂CH₃), 48.4 (C₈), 45.1 (45.0) (C₆), 41.6, 40.5 (40.9, 39.7) (C₂, C₄), 29.5 (C(CH₃)₃), 22.0 (gem CH₃), 21.8 (gem CH₃). MS (Cl ether) m/z: 361 (M+⁻31, 6%), 343 (M+⁻49, 5%), 313 (M+⁻79, 43%). Anal. calcd. for C₁₈H₃₂O₇S: C, 55.08, H, 8.22; found: C, 55.20, H, 8.34.

(5R,S,7R,S)-9-S-tert-Butylthioate-5,7-dihydroxy-3-methoxymethoxy-
8,8-dimethyl-Nonanoic acid, methyl ester (106, 107):

1.60 g (6.08 mmol) of tetramethylammonium triacetoxyborohydride was dissolved in 2.0 mL of anhydrous acetonitrile and 2.0 mL of anhydrous acetic acid and the mixture was stirred at ambient temperature for 30 minutes. It was cooled to -40°C and a solution of β-hydroxy ketones 96 and 97 (0.30 g, 0.76 mmol) (obtained by Procedure 2 above) in 1.0 mL of anhydrous acetonitrile was added via cannula. The mixture was stirred a further 8 hours whereupon it was quenched by addition of 4 mL of 0.5N aqueous sodium potassium tartrate. After allowing the reaction to warm to room temperature, it was diluted with 30 mL of dichloromethane and washed with saturated aqueous NaHCO₃ (40 mL). The aqueous layer was back extracted four times with 30 mL portions of dichloromethane and the combined organic layers were washed with saturated aqueous NaHCO₃ (40 mL). The aqueous layer was back extracted four times with 30 mL portions of dichloromethane and the combined organic layers were dried over Na₂SO₄ and stripped of solvent in vacuo. Analysis of the resulting
colourless syrup (\(^1\)H NMR, 300 MHz) revealed a 44:1 anti to syn (C\(_5\),C\(_7\))-diol ratio based upon integration of the methoxy protons on the MOM group (3.386, 3.349 and 3.376, 3.354 for syn and anti, respectively). The minor syn component was removed by radial chromatography (6:4 ethyl acetate/hexane) to yield 0.25 g (84\%) of an inseparable mixture of 106 and 107 as (3R,5S,7R)- and (3R,5R,7S)-diastereomers, respectively. When different, the \(^1\)H NMR and \(^{13}\)C NMR assignments for the undesired (3R,5S,7R)-diastereomer (106) are given in brackets. [\(\alpha\)]\(_D\) = -1.5° (c = 1.0, CHCl\(_3\)). IR (thin film) \(\nu\): 3468, 2960, 2938, 1742, 1669, 1368, 1153, 1103 cm\(^{-1}\). \(^1\)H NMR (300 MHz) \(\delta\): 4.64 - 4.73 (m, 2H, OCH\(_2\)O), 4.12 - 4.20 (m, 1H, H\(_3\)), 3.91 - 4.00 (m, 2H, H\(_5\), H\(_7\)), 3.67 (s, 3H, CO\(_2\)CH\(_3\)), 3.38 (3.35) (s, 3H, OCH\(_3\)), 2.48 - 2.79 (m, 2H, H\(_2\)), 1.48 - 1.90 (m, 4H, H\(_4\), H\(_6\)), 1.44 (s, 9H, C(CH\(_3\))\(_3\)), 1.19 (1.18) (s, 6H, gem CH\(_3\)'s). \(^{13}\)C NMR (50.4 MHz) \(\delta\): 208.7 ((C=O)S), 171.8 (CO\(_2\)CH\(_3\)), 97.1 (96.1) (OCH\(_2\)O), 73.7, 73.2 (74.7, 73.4) (C\(_3\), C\(_7\)), 65.1 (67.8) (C\(_5\)), 55.9 (55.8) (OCH\(_3\)), 54.2 (C(CH\(_3\))\(_3\)), 51.7 (CO\(_2\)CH\(_3\)), 47.6 (C\(_6\)), 41.9, 40.4, 37.9 (41.8, 40.1) (C\(_2\), C\(_4\), C\(_6\)), 29.6 (C(CH\(_3\))\(_3\)), 22.3 (22.0) (gem CH\(_3\)), 20.9 (gem CH\(_3\)). MS (Cl ether) m/z: 395 (M\(^+\)+1, 38\%), 363 (M\(^+\)-31\%). Anal. calcd. for C\(_{18}\)H\(_{34}\)O\(_7\)S: C, 54.80, H, 8.69; found: C, 54.83, H, 8.58.

(3R,5R,7S)-9-S-tert-Butylthioate-5,7-O-isopropyliden-e-3-methoxymethoxy-8,8-dimethylnonanoic acid, methyl ester (110):

The (C\(_5\),C\(_7\))-anti diols 106 and 107 (0.57 g, 1.4 mmol) were dissolved in 10 mL of a 30% solution of 2,2-dimethoxypropane in benzene. After stirring 1
hour at room temperature, the mixture was diluted with ether (70 mL) and washed with saturated aqueous NaHCO₃ (30 mL) and brine (30 mL). The ethereal layer was dried over Na₂SO₄ and concentrated *in vacuo* to afford 0.63 g of crude acetonide as a colourless syrup and a 1.92:1 mixture of (3R,5R,7S)- to a (3R,5S,7R)-diastereomers (110 and 109), respectively. Purification and separation of diastereomers was accomplished by a combination of careful SiO₂ flash chromatography (3.5% ethyl acetate in benzene and 120:1 SiO₂ (dried and activated overnight at 120°C) to compound ratio followed by preparative TLC (3 times elution with 4% ethyl acetate in benzene) of the mixed diastereomeric fractions. These procedures afforded 229 mg (57%) of homochiral and desired (3R,5R,7S)-diastereomer (110) (eluted first) along with 206 mg of mixed diastereomer (1.4:1 ratio of (3R,5R,7S)- to (3R,5S,7R)-diastereomers, respectively) which could be further separated if desired. The diastereomeric ratio was assessed by integration of the well-resolved methylene protons on the MOM group [δ: 4.653 (3R,5R,7S) and 4.636, 4.629 (3R,5S,7R)]. [α]D = -19.4° (c = 1.0, CHCl₃). IR (thin film) ν: 2950, 1745, 1675, 1382, 1228, 1141, 949 cm⁻¹. ¹H NMR (300 MHz) δ: 4.65 (s, 2H, OCH₂O), 3.96 - 4.10 (m, 1H, H₃), 4.02 (dd, J = 6.5, 9.7 Hz, 1H, H₇), 3.78 - 3.90 (m, 1H, H₅), 3.67 (s, 3H, CO₂CH₃), 3.33 (s, 3H, OCH₃), 2.57 (d, J = 5.5 Hz, 1H, H₂), 2.56 (d, J = 6.4 Hz, 1H, H₂), 1.50 - 1.88 (m, 4H, H₄, H₆), 1.42 (s, 9H, C(CH₃)₃), 1.28 (s, 3H, (CH₃)₂C(OR)₂), 1.27 (s, 3H, (CH₃)₂C(OR)₂), 1.17 (s, 3H, gem CH₃), 1.06 (s, 3H, gem CH₃). ¹³C NMR (50.4 MHz) δ: 206.1 ((C=O)S), 172.1 (CO₂CH₃), 100.6 ((CH₃)₂C(OR)₂), 97.2 (OCH₂O), 73.2 (C₃), 70.8 (C₇), 63.4 (C₅), 55.6 (OCH₃), 53.4 (C(CH₃)₃), 51.5 (CO₂CH₃), 47.1 (C₈), 41.4, 41.1 (C₂, C₆), 33.2 (C₄), 29.6 (C(CH₃)₃), 24.3 ((CH₃)₂C(OR)₂), 24.0 ((CH₃)₂C(OR)₂), 20.1 (gem CH₃), 20.0 (gem CH₃). MS (Cl
ether) m/z: 435 (M+1, 1%), 403 (M+3, 6%), 377 (M+57, 69%). Anal. calcd. for C\textsubscript{21}H\textsubscript{38}O\textsubscript{7}S: C, 53.04, H, 8.81; found: C, 58.19, H, 8.61.

(3R,5R,7S)-9-S-tert-Butylthioate-5,7-dihydroxy-3-methoxymethoxy-8,8-dimethylnonanoic acid, methyl ester (107):

The enantiomerically pure acetonide 110 (0.21 g, 0.48 mmol) was dissolved in methanol (10 mL) containing 6.5 mg of PPTS and the reaction was monitored by tlc (3:7 ether/hexane). After 5 hours at ambient temperature, tlc indicated that the reaction was complete, whereupon the reaction was quenched by addition of 30 mL of saturated aqueous NaHCO\textsubscript{3} and extracted with 100 mL of ether. The ethereal layer was washed with brine (30 mL) and dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The crude oil was purified by preparative TLC (3:2 ethyl acetate/hexane) to provide 0.16 g (85%) of homochiral (3R,5R,7S)-anti diol 107. [\textalpha]\textsubscript{D} = -1.5\textdegree (c = 1.0, CHCl\textsubscript{3}). IR (thin film) \nu : 3468, 2960, 2938, 1742, 1669, 1368, 1153, 1103 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz) \delta: 4.73 (d, A of AB, J = 6.8 Hz, 1H, OCH\textsubscript{2}O), 4.63 (d, B of AB, J = 6.8 Hz, 1H, OCH\textsubscript{2}O), 4.12 - 4.20 (m, 1H, H\textsubscript{3}), 4.01 - 4.11 (m, 1H, H\textsubscript{5}), 3.98 (dd, J = 6.5, 6.6 Hz, 1H, H\textsubscript{7}), 3.67 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.38 (s, 3H, OCH\textsubscript{3}), 2.65 (dd, A of ABX, J = 7.2, 15.5 Hz, 1H, H\textsubscript{2}), 2.52 (dd, B of ABX, J = 5.5, 15.5 Hz, 1H, H\textsubscript{2}), 1.48-1.90 (m, 4H, H\textsubscript{4}, H\textsubscript{6}), 1.44 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 1.19 (s, 6H, gem CH\textsubscript{3}’s). \textsuperscript{13}C NMR (50.4 MHz) \delta: 208.7 ((C=O)S), 171.8 (CO\textsubscript{2}CH\textsubscript{3}), 97.1 (OCH\textsubscript{2}O), 73.7, 73.2 (C\textsubscript{3}, C\textsubscript{7}), 65.1 (C\textsubscript{5}), 55.9 (OCH\textsubscript{3}), 54.2 (C(CH\textsubscript{3})\textsubscript{3}), 51.7 (CO\textsubscript{2}CH\textsubscript{3}), 47.6 (C\textsubscript{8}), 41.9, 40.4, 37.9 (C\textsubscript{2}, C\textsubscript{4}, C\textsubscript{6}), 29.6 (C(CH\textsubscript{3})\textsubscript{3}), 22.3 (gem CH\textsubscript{3}), 20.9 (gem CH\textsubscript{3}). MS (Cl ether) m/z: 395
(M+1, 38%), 363 (M+-31%). Anal. calcd. for C_{18}H_{34}O_7S: C, 54.80, H, 8.69; found: C, 54.83, H, 8.58.

(3R,5R,7S)-9-S-tert-Butythioate-5,7-dihydroxy-3-methoxymethoxy-8,8-dimethyl-5-nonanolide (108):

The anti diol 107 (36.0 mg, 0.091 mmol) was stirred in 3 mL of benzene containing 5 mg of TsOH. Tlc (8:2 ethyl acetate/hexane) indicated the reaction to be complete after 2 hours. It was then diluted with 30 mL of ether and washed with saturated aqueous NaHCO_3 (15 mL) and brine (15 mL). The ethereal layer was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by preparative TLC (7:3 ethyl acetate/hexane) to give 29.1 mg (88%) of the δ-lactone 108 as a colourless oil. [α]_D = -24.1° (c = 0.50, CHCl_3). IR (thin film) ν: 3465, 2972, 2935, 1739, 1669, 1368, 1155, 1041 cm⁻¹. ¹H NMR (300 MHz) δ: 4.65 (s, 2H, OCH_2O), 4.46 - 4.56 (m, 1H, H₅), 4.12 (app qu, 1H, H₃), 3.96 (dd, J = 6.6, 11.4 Hz, 1H, H₇), 3.35 (s, 3H, OCH₃), 2.87 (dd, A of ABX, J = 6.0, 17.1 Hz, 1H, H₂), 2.57 (dd, B of ABX, J = 7.0, 17.1 Hz, 1H, H₂), 1.52 - 1.88 (m, 4H, H₄, H₆), 1.44 (s, 9H, C(CH₃)₃), 1.22 (s, 3H, gem CH₃), 1.18 (s, 3H, gem CH₃). ¹³C NMR δ: 209.2 ((C=O)S), 170.6 (RCO₂R'), 95.2 (OCH₂O), 73.7, 72.6 (C₂, C₇), 69.0 (C₅), 55.5 (OCH₃), 53.8 (C(CH₃)₃), 47.9 (C₈), 37.6, 37.1, 36.2 (C₃, C₄, C₆), 29.6 (C(CH₃)₃), 23.3 (gem CH₃), 20.3 (gem CH₃). MS (Cl ether) m/z: 363 (M++1, 89%), 331 (M+-31, 4%).
(3R,5R,7S)-5-(5,7-Dihydroxy-8,8-dimethyl-5,9-lactoyl)-3-methoxymethoxynonanoic acid, methyl ester (111):

In 30 mL of THF was added 0.11 g (0.28 mmol) of homochiral anti-diol 107 and 0.24 g (0.56 mmol) of mercuric trifluoroacetate. After stirring at room temperature for 2 hours, the THF was removed under reduced pressure and the heterogeneous red residue was taken up in 2 mL of ether and applied to a preparative TLC plate and eluted twice (8:2 ethyl acetate/hexane) to afford 71.1 mg (85%) of the δ-lactone 111 as a colourless oil. $[\alpha]_D = +19.1^\circ$ (c = 0.50, CHCl$_3$). IR (thin film) ν: 3450, 2961, 2938, 1727, 1441, 1392, 1268, 1155, 1032 cm$^{-1}$. $^1$H NMR (300 MHz) δ: 4.70 (d, A of AB, J = 6.8 Hz, 1H, OCH$_2$O), 4.68 (d, B of AB, J = 6.8 Hz, 1H, OCH$_2$O), 4.41 - 4.49 (m, 1H, H$_5$), 4.25 (app qu, 1H, H$_3$), 3.88 (dd, J = 4.1, 11.0 Hz, 1H, H$_7$), 3.67 (s, 3H, CO$_2$CH$_3$), 3.34 (s, 3H, OCH$_3$), 2.62 (dd, A of ABX, J = 6.6, 15.2 Hz, 1H, H$_2$), 2.56 (dd, B of ABX, J = 5.9, 15.2 Hz, 1H, H$_2$), 1.78 - 1.92 (m, 4H, H$_4$, H$_6$), 1.35 (s, 3H, gem CH$_3$), 1.27 (s, 3H, gem CH$_3$). $^{13}$C NMR (50.4 MHz) δ: 177.0 (RCO$_2$R'), 171.5 (CO$_2$CH$_3$), 97.0 (OCH$_2$O), 72.8, 71.6, 71.5 (C$_3$, C$_5$, C$_7$), 55.7 (OCH$_3$), 51.6 (CO$_2$CH$_3$), 44.4 (C$_8$), 42.0, 40.5 (C$_2$, C$_4$), 34.4 (C$_6$), 23.2 (gem CH$_3$), 20.1 (gem CH$_3$). MS (Cl ether) m/z: 305 (M$^+$+1, 2%), 289 (M$^+$-15, 5%), 273 (M$^+$-31, 100%). Anal. calcd. for C$_{14}$H$_{24}$O$_7$: C, 55.25, H, 7.95; found: C, 54.95, H, 7.86.
(3R,5R,7S)-5-(7-Acetoxy-5-hydroxy-5,8-dimethyl-5,9-lactoyl)-3-methoxymethoxynonanoic acid, methyl ester (112):

Acetic anhydride (0.3 mL) was added to a solution of hydroxy lactone 111 (61 mg, 0.20 mmol) in pyridine (1.5 mL) and DMAP (12 mg, 0.10 mmol) at 0°C. The ice-bath was then removed and the mixture was stirred for 6 hours at ambient temperature. The reaction was quenched by addition of 2 mL of methanol and stirred a further 1 hour. The mixture was concentrated in vacuo. Co-evaporation with toluene removed most of the pyridine. The residual oil was dissolved in 50 mL of ether and washed with 25 mL portions of 0.2N HCl, saturated aqueous NaHCO₃, and brine. The ethereal layer was then dried over Na₂SO₄ and concentrated in vacuo. The resulting slightly yellow oil was purified by preparative TLC (1:1 ethyl acetate/hexane) to afford 63 mg (91%) of 112. [α]D = +45° (c = 0.50, CHCl₃). IR (thin film) ν: 2930, 1740, 1375, 1238, 1155, 1032 cm⁻¹. ¹H NMR (300 MHz) δ: 4.97 (dd, J = 4.3, 10.4 Hz, 1H, H₇), 4.68 (s, 2H, OCH₂O), 4.50 - 4.61 (m, 1H, H₅), 4.25 (app qu, 1H, H₃), 3.67 (s, 3H, CO₂CH₃), 3.34 (s, 3H, OCH₃), 2.62 (dd, A of ABX, J = 5.86, 15.2 Hz, 1H, H₂), 2.55 (dd, B of ABX, J = 5.92, 15.2 Hz, 1H, H₂), 2.03 - 2.12 (m, 1H, H₄), 2.08 (s, 3H, CH₃CO₂), 1.70 - 1.82 (m, 3H, H₄, H₆), 1.29 (s, 3H, gem CH₃), 1.27 (s, 3H, gem CH₃). ¹³C NMR (50.4 MHz) δ: 175.7 (RCO₂R'), 171.3 (CH₃CO₂), 170.4 (CO₂CH₃), 96.9 (OCH₂O), 73.0, 72.6, 71.4 (C₃, C₅, C₇), 55.7 (OCH₃), 51.6 (CO₂CH₃), 42.9 (C₈), 42.0, 40.4 (C₂, C₄), 31.6 (C₆), 23.4 (gem CH₃), 21.5 (CH₃CO₂), 20.8 (gem CH₃). MS (El) m/z: 315 (M⁺-31, 1%). MS (Cl ether) m/z: 347 (M⁺+1, 10%), 315 (M⁺-31, 100%). Anal. calcd. for C₁₆H₂₆O₈: C, 55.48, H, 7.57; found: C, 55.36, H, 7.62.
(3R,5R,7S)-5-(7-Acetoxy-5-hydroxy-8,8-dimethyl-5,9-lactoyl)-3-hydroxynonanoic acid, methyl ester (29):

55 mg (0.16 mmol) of acetylated δ-lactone 112 in 5 mL of dichloromethane was cooled to -78°C and 70 μL (0.64 mmol) of TiCl₄ was added. After stirring for 30 minutes, the reaction was quenched by addition of 5 mL of saturated aqueous NaHCO₃ and allowed to warm to ambient temperature. Dichloromethane (25 mL) was added and the solution washed with saturated aqueous NaHCO₃ and brine (15 mL of each), dried over Na₂SO₄, and concentrated in vacuo. The residual syrup was purified by preparative TLC (6:2 ethyl acetate/hexane) to afford 41 mg (85%) of alcohol 29 as a colourless syrup. [α]D = +42° (c = 0.50, CHCl₃). IR (thin film) v: 3460, 2930, 2860, 1740, 1735, 1466, 1240, 1160 cm⁻¹. ¹H NMR (300 MHz) δ: 4.98 (dd, J = 4.3, 10.4 Hz, 1H, H₇), 4.62 - 4.73 (m, 1H, H₅), 4.32 - 4.43 (m, 1H, H₃), 3.70 (s, 3H, CO₂CH₃), 3.08 - 3.18 (br s, 1H, OH, exchangeable), 2.51 (dd, A of ABX, J = 3.5, 16.7 Hz, 1H, H₂), 2.42 (dd, B of ABX, J = 8.7, 16.7 Hz, 1H, H₂), 2.18 - 2.28 (m, 1H, H₄), 2.07 (s, 3H, CH₃CO₂), 1.68 - 1.92 (m, 3H, H₄, H₆), 1.30 (s, 3H, gem CH₃), 1.27 (s, 3H, gem CH₃). ¹³C NMR (50.4 MHz) δ: 175.8 (RCO₂R'), 173.1 (CH₃CO₂), 170.4 (CO₂CH₃), 73.1, 72.8 (C₅, C₇), 63.7 (C₃), 51.8 (CO₂CH₃), 42.9 (C₈), 42.7, 41.1 (C₂, C₄), 31.5 (C₆), 23.4 (gem CH₃), 21.5 (CH₃CO₂), 20.8 (gem CH₃). MS (Cl ether) m/z: 303 (M⁺+1, 100%), 271 (M⁺-31, 2%), 243 (M⁺-59, 5%). Anal. calcd. for C₁₄H₂₂O₇: C, 55.62, H, 7.33; found: C, 55.73, H, 7.48.
CHAPTER 5: SYNTHESIS OF THE C(17)–C(20) AND C(21)–C(27) FRAGMENTS OF BRYOSTATIN BY THE CHIRON APPROACH\textsuperscript{92}

5.1 Introduction

In a continuation of our synthetic endeavors towards bryostatin, we directed our attention towards the C(17)–C(27) segment. It was decided that the chiron approach\textsuperscript{93} was an appropriate strategy. In essence, the pre-existing chirality found in natural products was carried through to obtain the chirality found in these fragments. This method is complementary to existing chemistry which relies upon the development of reactions or reagents to induce the formation of stereogenic centres in the molecule which were not previously optically active. Examples include the enzymatic reaction discussed in Chapter 2 and the stereoselective Mukaiyama aldol condensation discussed in Chapter 4.

5.2 Retrosynthetic Analysis

Retrosynthetic analysis suggested disconnection of the bryostatin molecule (1) at the C(16)–C(17)–trans olefin and C(1) lactonic linkage to afford key intermediate 37. Further disconnection between C(20) and C(21) and the C(19)–glycosidic linkage revealed fragments 38 and 39 having four and seven


carbon frameworks, respectively (Figure 23). These fragments were transposed
to naturally occurring building blocks 67 and 113.
Figure 23 — Retrosynthetic Analysis for the C(17)–C(27) Subunit – Chiron
Although the choice of the masked aldehyde 38 was not obvious due to the ketonic nature at C(19) in the bryostatins, the judicious choice of this template was predicated upon the realization that it already possessed the gem-dimethyl functionality at C(18) and also because the chirality at C(19) could be temporarily used for 1,2-asymmetric induction. Indeed, it was anticipated that the C(19) stereocentre would allow high diastereofacial selectivity in the addition of the dithianyl fragment derived from 39. This nucleophilic addition reaction is explored in detail in Chapter 6. It was noteworthy that fragment 38 is an integral constituent of the C(6)–C(9) segment of the bryostatins (Chapter 3).

It was recognized that (R)-(−)-dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone [(R)-pantolactone, 67] was a suitable precursor for fragment 38. It should be mentioned that (R)-pantolactone has been identified as a potential synthon for an increasing number of biologically and structurally interesting natural products which possess a quaternary gem-dimethyl carbon centre flanked at both sides by either a carbonyl group and chiral carbinolic centre or two chiral carbinolic centres.

D-Galactone-1,4-lactone (113) was selected as a template for the synthesis of the fragment 39 when it became apparent that transposition of the predisposed stereogenicities at C(2) [C(23)], C(4) [C(25)], and C(5) [C(26)] (bryostatin numbering in brackets) would greatly simplify the synthetic task. Furthermore, the intrinsic 1,4-lactone functionality of 113 was known to undergo facile β-elimination at its C(3) [C(24)] substituent. Therefore, simultaneous deoxygenation at C(3) and C(6) (sugar numbering) was anticipated. One carbon homologation at C(1) [C(22)] was accomplished by

2-lithio-1,3-dithiane addition. In effect, the dithiane group acted as a linchpin\textsuperscript{95} to connect synthons 38 and 39. The dithiane moiety could then be unmasked by hydrolysis\textsuperscript{96} to provide the C(21) ketone which represents a suitable precursor for the stereoselective introduction of the trans-carbomethoxy acetylidene group using technology recently developed by Garner\textsuperscript{18a}.

Both (R)-pantolactone (67) and D-galactono-1,4-lactone (113) are commercially available in enantiomerically pure form and are relatively inexpensive [67: $18.55$ US for 25 grams (Aldrich); 113: $88.20$ US for 100 grams (Sigma)]. Care was exercised to avoid adventitious racemization in this synthesis, thereby providing a chirally safe route to the target molecules.

5.3 Synthesis of C(17)–C(20) Synthon (115)

As discussed in the retrosynthetic analysis, a (R)-pantolactone derived electrophilic synthon was required. A model study (Chapter 6) suggested that (2R)-[(tert-butyldimethylsilyl)oxy]pantolactol (115) was appropriate. This synthon was derived from (R)-pantolactone (67) using a straightforward sequence of high-yielding reactions. First, the hydroxyl on 67 was protected by formation of its bulky, non-chelating tert-butyldimethylsilyl ether 114 (95\%, TBDMSI, DMAP, NEt\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, 24 hours). DIBAL reduction\textsuperscript{97} of this α-silylated γ-lactone formed the γ-lactol 115 [87\%, DIBAL, THF, -78°C, 3 hours; (α)\textsubscript{D} = -13.3° (c=2.0, CHCl\textsubscript{3})]. When this reduction was attempted in toluene, overreduction occurred.

\textsuperscript{97}E. Winterfeldt, \textit{Synthesis}, 617 (1975) and references cited therein.
to a large extent. These simple transformations furnished the desired C(17)–C(20) synthon.

5.4 Synthesis of the C(21)–C(27) Synthon (127)

D-Galactono-1,4-lactone 113 was transformed via a high-yielding (88%) two step, one-pot, reaction into the known 2,3,5-tri-O-acetyl-6-bromo-D-galactono-1,4-lactone (116) using a procedure developed by Pederson.
Thus, treatment of the aldonolactone 113 with a 33% solution of HBr in acetic acid (33% HBr in HOAc, 25°C, 4 hours) formed the primary C(6) bromide (sugar numbering). Addition of acetic anhydride acetylated the remaining C(2), C(3), and C(5) hydroxyls to provide the known bromo triacetate (116) (mp: 100.0–101.5 °C; literature94: 98–100°C).

The next step involved the hydrogenolytic removal of the primary bromide and the concomitant stereoselective hydrogenation of the C(2)-C(3) enol acetate formed in situ by the added base. This step was experimentally more troublesome than the literature precedent94 would suggest. Inconsistent and frequently low yields (<50%) of the product 117 were obtained. Modifications were made to the literature procedure in order to minimize the suspected formation of the di-β-eliminated side-product 129 as depicted below.

These steps included the use of the more sterically hindered base N,N-diisopropylethylamine (instead of triethylamine) and pre-saturation of the ethyl acetate solvent and 5% palladium on carbon catalyst with hydrogen followed by
the simultaneous addition of the base and γ-lactone 116. Finally, the reaction was performed by bubbling hydrogen through the reaction mixture instead of using the Parr apparatus. With these variations, consistent yields (82%) of the crystalline 3,6-dideoxy derivative 117 were obtained. The virtually complete stereoselectivity in the hydrogenation step, through the intermediary enol acetate 128, was due to the steric hindrance of the bottom face caused by the orientation of the C(4) side chain.

The next step involved the reduction of the diacetoxylactone 117 using LiAlH₄. Isolation of the tetrol 118 was also troublesome, presumably due to stable aluminate complex formation. This difficulty was overcome by use of LiBH₄ followed by cation exchange resin treatment (LiBH₄, THF, 0°C, 14 hours) to afford improved yields (96%) of the known⁹⁴,⁹⁸ 3,6-dideoxy-D-xylo-hexitol (118) (mp: 95-96°C; literature⁹⁴: 90°C).

The original notion was to obtain the C(22)–C(23) epoxide 125 (bryostatin numbering will be used for the remainder of this Chapter) by direct tosylation (TsCl, pyridine, -10°C, 16 hours) of the primary hydroxyl group of the tetrol, followed by base treatment. This procedure failed due to the inevitable formation of the 1,4-anhydro diol 119 in near quantitative yields during the tosylation step. The structure of the cyclic ether 119 was suggested by ¹H NMR spectroscopy. Complete confirmation was provided by acetylation of 119 (88%, Ac₂O, pyridine, DMAP, 25°C, 4 hours) to provide the acetylated cyclic ether 120. Examination of the ¹H NMR spectrum of 120 suggested two acetate groups. If the mono-tosylated product had been obtained, then three acetates would have

been expected. Also, the $^1$H NMR spectrum was more consistent with the structure of 120 than the C(22)–C(23) epoxy diacetate.

To circumvent this problem, the bis-acetonide (121) of the tetrol 118 was formed (30% 2,2-dimethoxypropane in benzene, cat. TsOH, 25°C, 12 hours) in 87% yield. The more labile primary acetonide was then selectively removed by kinetic deacetonation. Methodology developed by Szarek$^{99}$ was employed for this transformation (1.5% I$_2$ in methanol, 25°C, ∼8 hours) and afforded 122 in 77% yield. An alternate procedure for the cleavage of the primary isopropylidene group was the use of acidic methanolysis (75%, TsOH, methanol, RT, ∼4 hours). With diol 122 in hand, we were in a position to form the C(22)–C(23) epoxide 125 by tosylation of the primary hydroxyl function followed by base treatment.

Transformation of the diol 122 with tosyl chloride (TsCl, pyridine, -10°C, 18 hours) furnished the mono-tosylated product 123 in 84% yield. Base treatment (K$_2$CO$_3$, methanol, 0°C, 2 hours) gave a satisfactory yield (83%) of the epoxide 125 along with a more polar impurity. Further investigation (GC-MS) demonstrated that this side-product (6% by weight) was the epimeric C(23) epoxide which must have originated from partial tosylation of the C(23) secondary hydroxyl group.

To test this hypothesis, the bulkier 2,4,6-tri-isopropylbenzenesulfonyl chloride (TIPS-Cl) was used for the sulfonation of the diol 122 (TIPS-Cl, pyridine, -10°C, 18 hours). The yield of the triisopropylsulfonate ester 124 was 78%. Treatment of 124 in the same manner as 123 (K$_2$CO$_3$, methanol, 0°C, 4 hours) provided a 52% yield of the epoxide 125 as the only diastereomer [ie. no

epimeric C(23) epoxide was noted\textsuperscript{100}. However, since the overall yield was somewhat lower, the first approach was preferred and enantiomerically pure epoxide 125 was obtained by silica gel flash chromatography [syrup, [\(\alpha\)]\textsubscript{D} = +23° (c=2.4, CHC\textsubscript{3}).]

Regioselective epoxide ring opening was then achieved by the addition of 2-lithio-1,3-dithiane\textsuperscript{71a,95,96} to 125 (nBuLi, 1,3-dithiane, THF, -20°C, 2 hours then 125, 18 hours). The 2-lithio-1,3-dithiane added to the less hindered C(22) position. This one carbon homologation transformed the electrophilic epoxide fragment into the desired nucleophilic C(21)–C(27) dithianyl fragment (126). Unfortunately, the yield for this step was poor (47%). The last step involved benzoylation of the C(23) hydroxyl on 126 (BzCl, pyridine, 25°C, 3 hours) to afford the benzoylated dithianyl C(21)–C(27) synthon of bryostatins (127) in 74% yield.

5.5 Suggested Connection of the C(17)–C(20) (115) and the C(21)–C(27) (127) Synthons and Completion of the Synthesis of 37

The next step in the synthesis will be the key connection of the dithianyl C(21)–C(27) synthon 127 with the (R)-pantolactone derived C(17)–C(20) synthon 115. Thus, a model study examining nucleophilic dithianyl additions onto pantolactol templates was undertaken at this stage and the results are presented and discussed in the following Chapter (Chapter 6). The important conclusion from this study was that the addition of 127 onto silylated-pantolactol 115 should favour formation of the desired C(19)-C(20)–anti diol 130 in accord

\textsuperscript{100}For a similar example see: S. Hanessian and P.J. Murray, \textit{Tetrahedron}, 43, 5055 (1987).
with non-chelation addition (anti/syn for addition of 2-lithio-1,3-dithiane was 96:4).

Elaboration of this adduct into the key intermediate 37 primarily involves protection/deprotection chemistry. A postulated step deserving comment is the stereoselective introduction of the C(21) exocyclic trans-acetylidene group. Briefly, Garner\textsuperscript{18a} has noted that stabilized phosphonium ylides undergo accelerated Wittig reactions with $\alpha$-hydroxy ketones to afford trans-trisubstituted olefins. Thus, hydrolysis of the C(21) dithiane and subsequent Wittig reaction with the commercially available methyl (triphenylphosphoranylidene)acetate should directly provide the desired C(21) trans-acetylidene group [trans to the C(20) hydroxyl].

The final challenges include formation of the phosphonium ylide at C(17) of 37 and the subsequent Wittig reaction with a C(16) aldehyde fragment (perhaps derived from Thomas' synthon\textsuperscript{16}) to form the desired C(16)-C(17)-trans olefin. Hydrolysis of the C(19) methyl glycoside and C(25)-C(26) isopropylidene group leaves, as the final task, the selective macrolactonization of the C(25) hydroxyl and a suitably activated C(1) ester. Masamune\textsuperscript{14} is faced with a similar problem in his synthetic effort (28 to 1, Chapter 1.3). Hopefully, his solution will be applicable to our situation.
5.6 Conclusions

Our contribution to the practical synthesis of fragments corresponding to the C(17)–C(20) and C(21)–C(27) segments of bryostatins was described. These enantiospecific sequences leading to fragments 115 and 127 compare well to the synthesis of similar fragments described by Masamune\textsuperscript{14} (18 and 19, Chapter 1.3). The judicious choice of the starting chiral templates allowed high correspondence of stereogenicities while keeping group interconversions to a minimum. This work illustrates the utility of the chiron methodology. As well, the strategy used here is, relative to Masamune's, more convergent. For purposes of comparison, Masamune's synthesis of the C(17)–C(27) subunit involved the coupling of 5 fragments \((C_3 + C_1 + C_2 + C_1 + C_4)\) as described in Chapter 1. Our synthesis requires only 3 fragments \((C_4 + C_1 + C_6)\). The next Chapter details model studies for the coupling of 115 and 127.
5.7 Experimental

The general comments regarding instruments and reagents made in the Experimental section of Chapter 2.13 are applicable here as well.

2,3,5-Tri-O-acetyl-6-bromo-D-galactono-1,4-lactone (116):

This material was prepared according to the method of Pederson\textsuperscript{94}. Thus, D-galactono-1,4-lactone (113, 20.0 g, 0.112 mol) was dissolved in 150 mL of a 33\% HBr in acetic acid solution and stirred at room temperature for 4 hours. Acetic anhydride (50.0 mL, 0.53 mol) was then added dropwise. When addition was completed, the mixture was stirred for 1 hour whereupon it was slowly poured into 1L of crushed ice and stirred vigorously using a mechanical stirrer. The stirring was maintained for 2 hours at which point the resulting white solid was filtered (Büchner) and rinsed with 200 mL of water. The solid was dissolved in ethyl acetate (300 mL) and washed with saturated aqueous NaHCO\textsubscript{3} (2 X 100 mL) and brine (100 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo to yield a light sensitive white solid which was recrystallized from ethanol to afford 35.8 g (88\%) of the bromotriacetate 116 as white needles melting at 100.0-101.5°C (literature\textsuperscript{94}: 98-100°C). \([\alpha]_D = -10.0^\circ\) (c = 2.5, CHCl\textsubscript{3}) (literature\textsuperscript{94}: -10.1°).
2,5-Di-O-acetyl-3,6-dideoxy-D-xylo-hexono-1,4-lactone (117):

This material was prepared using a modification of a procedure described by Pederson\textsuperscript{94}. Thus, 300 mL of ethyl acetate was added to 3.50 g of 5% palladium on carbon. In a well-ventilated fume hood, a 20 mL/min stream of hydrogen was bubbled through the reaction mixture and 55.0 mL (0.316 mol) of N,N-diisopropylethylamine and 38.0 g (0.104 mol) of 116 were added. After stirring at ambient temperature for 7 hours, the hydrogen flow was discontinued and the catalyst was removed by gravity filtration. (caution, pyrophoric) The filtrate was washed twice with 1N HCl (100 mL) and once with brine (100 mL). Drying over Na\textsubscript{2}SO\textsubscript{4} and concentration in vacuo yielded a yellowish syrup which was recrystallized from ether/pentane to afford 19.6 g (82%) of the diacetate 117 as white needles. Triethylamine may be used instead of N,N-diisopropylethylamine, however slightly lower and less consistent yields are obtained. Also, a decrease in reaction time (3 hours) is realized by use of a Parr apparatus and a hydrogen pressure of 3 atm. The melting point of 117 was 86.0–87.0°C (literature\textsuperscript{94}: 86–87°C). [α\textsubscript{D}] = -22.0° (c = 1.0, CHCl\textsubscript{3}) (literature\textsuperscript{94}: -22.8°). \textsuperscript{1}H NMR (300 MHz) δ: 5.49 (dd, J = 8.9, 10.5 Hz, 1H, H\textsubscript{23}), 5.02 (app qu, \textsuperscript{1}H, H\textsubscript{26}), 4.47 (app qu, \textsuperscript{1}H, H\textsubscript{25}), 2.72 (ddd, J = 5.5, 8.8, 12.5 Hz, 1H, H\textsubscript{24}), 2.16 (s, 3H, CH\textsubscript{3}CO\textsubscript{2}), 2.08 (s, 3H, CH\textsubscript{3}CO\textsubscript{2}), 1.99 (ddd, J = 5.5, 10.5, 12.5 Hz, 1H, H\textsubscript{24}), 1.30 (d, J = 6.5 Hz, 3H, H\textsubscript{27}).
3,6-Dideoxy-D-xylo-hexitol (118):

This material was prepared using a modification of a procedure described by Pederson\textsuperscript{94}. Thus, 10.0 g (43.4 mmol) of the \(\gamma\)-lactone 117 was dissolved in THF (150 mL) and 3.10 g (142 mmol) of LiBH\(_4\) was added portionwise at 0\(^\circ\)C. After stirring for 30 minutes, the mixture was allowed to warm to room temperature and stirred a further 12 hours. It was then re-cooled to 0\(^\circ\)C and carefully quenched by addition of methanol. The mixture was stripped of solvent under reduced pressure and dissolved in methanol (100 mL) and an excess of Amberlite IR-120 resin in the H\(^+\) form was added (pH ~4). The resin was removed by filtration and the filtrate concentrated \textit{in vacuo}. Several co-evaporations were accomplished with a 3% acetic acid in methanol solution (3 X 60 mL). The resulting white solid could be recrystallized from ethanol yielding 6.26 g (96\%) of the tetrol 4 as white crystals melting at 95–96\(^\circ\)C (literature\textsuperscript{94}: 90\(^\circ\)C). \([\alpha]_D = +44^\circ\) (c = 2.0, H\(_2\)O) (literature\textsuperscript{94}: +52\(^\circ\)). \(^1\)H NMR (deuterium oxide, 300 MHz) \(\delta\): 3.62 - 3.72 (m, 1H, H\(_{23}\)), 3.46 - 3.53 (m, 2H, H\(_{25}\), H\(_{26}\)), 3.42 (dd, J = 3.9, 11.6 Hz, 1H, H\(_{22}\)), 3.30 (dd, J = 6.9, 11.6 Hz, 1H, H\(_{22}^\prime\)), 1.36 (d, J = 6.8 Hz, 1H, H\(_{24}\)), 1.34 (d, J = 5.9 Hz, 1H, H\(_{24}^\prime\)), 0.98 (d, J = 6.3 Hz, 3H, H\(_{27}\)). Anal. calcd. for C\(_6\)H\(_{14}\)O\(_4\): C, 47.98, H, 9.39; found: C, 47.62, H, 9.61.

1,4-Anhydro Diol 119:

The tetrol 118 (1.05 g, 6.99 mmol) was dissolved in pyridine (20 mL) at -10\(^\circ\)C containing p-toluenesulfonyl chloride (1.73 g, 0.07 mmol). After overnight
contact, water was added for 1 hour to destroy the excess sulfonyle chloride. The solution was subsequently stripped of solvent and the residue diluted with 100 mL of ethyl acetate. Washing the organic layer with 0.2N HCl, saturated aqueous NaHCO₃, and brine (50 mL of each) followed by drying over Na₂SO₄ and concentration in vacuo afforded 0.88 g (95%) of the 1,4-anhydro diol 119 as a colourless oil. ¹H NMR (300 MHz) δ: 4.34 - 4.37 (m, 1H, H₂₅), 3.84 - 3.92 (m, 1H, H₂₃), 3.90 (dd, A of AB, J = 2.6, 9.7 Hz, 1H, H₂₂), 3.72 (dd, B of AB, J = 3.5, 9.7 Hz, 1H, H₂₂), 3.75 - 3.79 (m, 1H, H₂₆), 2.29 (ddd, J = 5.9, 9.5, 15.4 Hz, 1H, H₂₄), 2.05 - 2.20 (br s, 2H, OH, exchangeable), 1.80 (ddd, J = 1.6, 4.1, 15.4 Hz, 1H, H₂₄), 1.28 (d, J = 6.4 Hz, 3H, H₂₇).

Acetylated 1,4-anhydro diol 120:

The 1,4-anhydro diol 119 (0.65 g, 4.42 mmol) and DMAP (0.12 g, 0.98 mmol) was dissolved in pyridine (10 mL) containing acetic anhydride (2.0 mL, 21 mmol) and the solution stirred at ambient temperature for 4 hours. Methanol (2.0 mL) was then added to destroy the excess acetic anhydride (1 hour). The solution was then stripped of solvent in vacuo and the remaining oil dissolved in 80 mL of ethyl acetate. The organic layer was extracted with 40 mL portions of 0.2N HCl, saturated aqueous NaHCO₃, and brine, dried over Na₂SO₄, and concentrated in vacuo to provide 0.94 g (88%) of the acetylated 1,4-anhydro compound 120 as a colourless oil. ¹H NMR (300 MHz) δ: 5.22 (m, 1H, H₂₃), 4.99 (qu, J = 6.5 Hz, 1H, H₂₆), 3.94 (ddd, J = 1.1, 2.2, 10.6 Hz, 1H, H₂₂), 3.87 (dd, J = 6.9, 14.5 Hz, 1H, H₂₅), 3.82 (dd, J = 4.9, 10.6 Hz, 1H, H₂₂), 2.37 (ddd, J = 7.6,
8.1, 10.2 Hz, 1H, H_{24}), 2.07 (s, 3H, CH_{3}CO_{2}), 2.04 (s, 3H, CH_{3}CO_{2}), 1.73 (ddd, J = 1.1, 3.1, 10.2 Hz, 1H, H_{24}), 1.22 (d, J = 6.5 Hz, H_{27}). MS (Cl ether) m/z: 217 (M^+1, 93%), 157 (M^+-59, 100%).

3,6-Dideoxy-1,2:4,5-di-O-isopropylidene-D-xylo-hexitol (121):

To 5.50 g (36.6 mmol) of the tetrol 118 was added 50 mL of a 30% 2,2-dimethoxypropane in benzene solution and 20 mg of TsOH. The initially heterogeneous mixture became, after overnight contact, homogeneous whereupon it was neutralized by addition of triethylamine and stripped of solvent in vacuo. The remaining oil was taken up in ether (100 mL) and washed successively with 60 mL portions of 0.2N HCl, saturated aqueous NaHCO_{3}, and brine. The ethereal layer was dried over Na_{2}SO_{4} and concentrated in vacuo to yield 7.33 g (87%) of the bis-acetonide 121 as a colourless oil which was used in the next step without purification. An analytical sample was obtained by SiO_{2} flash chromatography (6:4 ether/hexane). [α]_{D} = +11.2° (c = 1.0, CHCl_{3}). IR (thin film) ν: 2955, 2942, 2880, 1382, 1372, 1248, 1100, 1065 cm^{-1}. ^{1}H NMR (200 MHz) δ: 4.10 (app qu, 1H, H_{23}), 3.96 (dd, A of AB, J = 5.9, 8.1 Hz, 1H, H_{22}), 3.43 - 3.61 (m, 2H, H_{25}, H_{26}), 3.44 (dd, B of AB, J = 7.0, 8.1 Hz, 1H, H_{22}), 1.70 (ddd, J = 2.7, 7.2, 13.8 Hz, 1H, H_{24}), 1.50 (ddd, J = 5.5, 9.0, 13.8 Hz, 1H, H_{24}), 1.27 (s, 3H, (CH_{3})_{2}C(OR)_{2}), 1.25 (s, 3H, (CH_{3})_{2}C(OR)_{2}), 1.22 (s, 6H, 2 X (CH_{3})_{2}C(OR)_{2}), 1.13 (d, J = 5.7 Hz, 3H, H_{27}). ^{13}C NMR (50.4 MHz) δ: 108.5, 107.9 (2 X (CH_{3})C(OR)_{2}), 79.3, 76.9 (C_{25}, C_{26}), 73.7 (C_{23}), 69.7 (C_{22}), 36.7 (C_{24}), 27.0, 26.9, 26.7, 25.5 (2 X (CH_{3})_{2}C(OR)_{2}), 16.8 (C_{27}). MS (EI) m/z: 215 (M^+-15, 18%).
157 (M\(^+\)-73, 31\%). HRMS calcd. for C\(_{11}H_{19}O_4\) (M\(^+\)-CH\(_3\)): 215.1283; found: 215.1268.

**3,6-Dideoxy-4,5-O-isopropylidene-D-xylo-hexitol (122):**

**Procedure 1**

The bis-acetonide 121 (5.00 g, 21.7 mmol) was stirred in a 1.5% iodine/methanol (w/v) solution (100 mL) at room temperature until tlc (ethyl acetate) indicated complete consumption of the starting material. The reaction was quenched at this point by the addition of powdered sodium thiosulfate until the solution became colourless. The methanol was removed under reduced pressure and 100 mL of ethyl acetate was added to the residue. Undissolved material was removed by filtration. The filtrate was washed with 0.2N HCl, saturated aqueous NaHCO\(_3\), and brine (60 mL of each) and dried over Na\(_2\)SO\(_4\) and concentrated *in vacuo* to yield 2.61 g (63%) of 122 as a colourless oil. The filtered residue was dissolved in methanol and run through a pad of Celite. The solvent was removed *in vacuo* and the remaining powder was shown to be mostly starting material 121 (\(^1\)H NMR). Thus, it was reprocessed in the same manner as previously described (118 to 121 to 122) to afford another 0.56 g (14%) of 122 for a combined yield of 77%. This material was used without further purification.
Procedure 2:

To 3.00 g (13.0 mmol) of bis-acetonide 121 was added 20 mL of MeOH and 10 mg of TsOH and the mixture was stirred at room temperature until tlc (ethyl acetate) indicated complete consumption of the starting material. The reaction was then neutralized by the addition of a few drops of triethylamine and the solvent removed under reduced pressure. The oil was taken up in ethyl acetate (100 mL) and this solution was washed with saturated aqueous NaHCO₃ and brine (60 mL of each). The combined aqueous layers were extracted with 80 mL of ethyl acetate and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to yield 1.86 g (75%) of 122 as a colourless oil. This material was used without further purification. An analytical sample was obtained by SiO₂ flash chromatography (8:2 ethyl acetate/hexane). IR (thin film) ν: 3420, 2991, 2941, 1382, 1235, 1096 cm⁻¹. ¹H NMR (300 MHz) δ: 3.92 - 4.02 (m, 1H, H₂3), 3.77 (dd, A of AB, J = 2.6, 8.2 Hz, 1H, H₂2), 3.71 (dd, B of AB, J = 2.9, 8.2 Hz, 1H, H₂2'), 3.46 - 3.72 (m, 2H, H₂5, H₂6), 2.68 - 2.81 (br s, 2H, OH, exchangeable), 1.80 (ddd, J = 2.8, 8.2, 14.4 Hz, 1H, H₂4), 1.57 (ddd, J = 4.0, 8.1, 14.4 Hz, 1H, H₂₄'), 1.382 (s, 3H, (CH₃)₂C(OR)₂), 1.378 (s, 3H, (CH₃)₂C(OR)₂), 1.25 (d, J = 5.7 Hz, 3H, H₂₇). ¹³C NMR (50.4 MHz) δ: 108.2 ((CH₃)₂C(OR)₂), 79.3, 76.6 (C₂₅, C₂₆), 69.6 (C₂₃), 66.7 (C₂₂), 34.6 (C₂₄), 27.1, 27.0 ((CH₃)₂C(OR)₂), 16.8 (C₂₇). MS (El) m/z: 175 (M⁺-15, 23%), 115 (M⁺-75, 25%). HRMS calcd. for C₈H₁₅O₄ (M⁺-CH₃): 175.0971; found: 175.0968.
3,6-Dideoxy-5,6-isopropylidene-1-O-tosyl-D-xylo-hexitol (123):

p-Toluenesulfonyl chloride (3.16 g, 16.6 mmol) was added to 40 mL of a pyridine solution containing 2.62 g (13.8 mmol) of the diol 122 at -10°C. After 18 hours at this temperature, water (2.0 mL) was added and the solution stirred a further hour to destroy the excess sulfonyl chloride. The solution was concentrated in vacuo leaving a yellowish syrup which was dissolved in ethyl acetate (80 mL). The organic layer was washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (50 mL of each), and dried over Na₂SO₄ and treated with activated charcoal. Filtration and concentration in vacuo furnished 3.99 g (84%) of tosylated 123 as a colourless oil and of sufficient purity to be used directly in the next step. For analytical purposes, a sample was purified by radial chromatography (7:3 ether/hexane). \([\alpha]_D = +7.7^\circ\) (c = 1.0, CHCl₃). IR (thin film) \(\nu\): 3460, 2991, 2940, 1601, 1369, 1191, 1180, 1099 cm\(^{-1}\). \(^1\)H NMR (300 MHz) \(\delta\): 7.76 (d, J = 8.3 Hz, 2H, aromatic), 7.32 (d, J = 8.3 Hz, 2H, aromatic), 4.05 (dd, A of AB, J = 4.4, 8.6 Hz, 1H, H₂₂), 3.95 (dd, B of AB, J = 7.7, 8.6 Hz, 1H, H₂₂), 3.98 - 4.09 (m, 1H, H₂₃), 3.58 - 3.72 (m, 2H, H₂₅,H₂₆), 2.89 - 3.00 (br s, 1H, OH, exchangeable), 2.44 (s, 3H, PhCH₃), 1.71 (ddd, J = 2.0, 7.9, 14.5 Hz, 1H, H₂₄), 1.55 (ddd, J = 3.6, 4.9, 14.5 Hz, 1H, H₂₄), 1.34 (s, 3H, (CH₃)₂C(OR)₂), 1.33 (s, 3H, (CH₃)₂C(OR)₂), 1.22 (d, J = 5.7 Hz, 3H, H₂₇). \(^13\)C NMR (50.4 MHz) \(\delta\): 145.2, 132.6, 130.0, 128.0 (aromatic), 108.3 ((CH₃)₂C(OR)₂), 78.6, 76.5 (C₂₅,C₂₆), 73.2 (C₂₂), 66.9 (C₂₃), 34.3 (C₂₄), 27.0, 26.9 ((CH₃)₂C(OR)₂), 21.5 (PhCH₃), 16.7 (C₂₇). MS (EI) m/z: 329 (M⁺-15, 25%), 173 (M⁺-171, 10%). HRMS calcd. for C₁₅H₂₁O₆S (M⁺-CH₃): 329.1059; found: 329.1025.
3,6-Dideoxy-1-O-2,4,6-(triisopropylbenzene)sulfonyl-5,6-O-isopropyldiene-D-xylo-hexitol (124):  

The experimental procedure used to make the triisopropylbenzenesulfonated material 124 was the same as the procedure described above for the tosylated material 123 except that 2,4,6-triisopropylbenzenesulfonyl chloride was used instead of p-toluensulfonyl chloride and radial chromatography (1:1 ether/hexane) was required. Thus, 2.00 g (10.5 mmol) of diol 122 yielded 3.74 g (78%) of 124 as a colourless oil. $^1$H NMR (300 MHz) δ: 7.18 (s, 2H, aromatic), 4.13 (dd, A of AB, J = 4.8, 7.9 Hz, 1H, H$_{22}$), 3.96 (dd, B of AB, J = 7.9, 11.3 Hz, 1H, H$_{22}$), 4.08 - 4.14 (m, 1H, H$_{23}$), 3.70 - 3.79 (m, 2H, H$_{25}$, H$_{26}$), 2.90 (app qu, 3H, 3 X (CH$_3$)$_2$CHPh), 1.72 - 1.84 (m, 1H, H$_{24}$), 1.56 - 1.64 (m, 1H, H$_{24}$), 1.35 (s, 3H, (CH$_3$)$_2$C(OR)$_2$), 1.33 (s, 3H, (CH$_3$)$_2$C(OR)$_2$), 1.25 (d, J = 6.8 Hz, 12H, 2 X (CH$_3$)$_2$CHPh), 1.24 (d, J = 6.9 Hz, 6H, (CH$_3$)$_2$CHPh), 1.23 (d, J = 5.7 Hz, 3H, H$_{27}$). MS (EI) m/z: 441 (M$^+$-15, 5%), 267 (M$^+$-189, 16%). MS (Cl ether) m/z: 457 (M$^+$+1, 23%), 399 (M$^+$-57, 92%).

3,6-Dideoxy-1,2-epoxy-5,6-O-isopropyldiene-D-xylo-hexitol (125):

From 123:

The tosyl-protected material 123 (1.20 g, 3.48 mmol) was dissolved in 30 mL of methanol and a catalytic amount of K$_2$CO$_3$ (anhydrous, 0.30 g) was added. The reaction was stirred at 0°C for 2 hours whereupon it was diluted with
100 mL of ether. The ethereal layer was washed successively with 0.2N HCl, saturated aqueous NaHCO₃, and brine (40 mL of each), dried over Na₂SO₄, and concentrated in vacuo (bath temperature: 20°C) to yield a colourless oil. This oil contained the desired epoxide along with 6% epimeric C(23) epoxide. The presence of the diastereomeric epoxide was identified by gas chromatography (GC) (megabore vitreous silica bonded BP-5; ID: 0.22 mm, length: 10 m; column, injector, detector (FID) T: 100°, 200°, 250°C, respectively; the desired diastereomer eluted at 3.55 minutes versus 4.92 minutes for the epimeric C(23) diastereomer) and GC-MS. The C(23) undesired epimeric epoxide was readily removed by SiO₂ flash chromatography (3:7 ether/hexane) to yield 0.50 (83%) of homochiral epoxide 125 as a colourless oil. This material is slightly volatile and, thus, should not be exposed to reduced pressures for prolonged periods. Storage at -10°C is also recommended.

From 124:

The same experimental procedure as describe above for the conversion of 123 to 125 was used except that the sulfonate ester 124 was used. Thus, 0.92 g (2.01 mmol) of 10 yielded 0.18 g (52 %) of the epoxide 125. No epimeric C(23) epoxide was obtained. \([\alpha]D = +22.9^°\ (c = 2.4, \text{CHCl}_3)\). IR (thin film) \(\nu\): 2982, 2930, 2876, 1379, 1369, 1242, 1179, 1097 cm⁻¹. \(^1\text{H} NMR\ (300 \text{ MHz}) \delta:\)

3.71 - 3.75 (m, 2H, H₂₅, H₂₆), 3.06 (app sextet, 1H, H₂₃), 2.81 (dd, J = 4.0, 5.0 Hz, 1H, H₂₂), 2.50 (dd, J = 2.7, 5.0 Hz, 1H, H₂₂), 1.84 (ddd, J = 4.1, 8.0, 14.2 Hz, 1H, H₂₄), 1.57 (ddd, J = 3.7, 7.5 14.2 Hz, 1H, H₂₄), 1.40 (s, 3H, (CH₃)₂C(OR)₂), 1.37 (s, 3H, (CH₃)₂C(OR)₂), 1.27 (d, J = 5.7 Hz, 3H, H₂₇). \(^{13}\text{C} NMR\ (75.3 \text{ MHz}) \delta:\)
108.1 ((CH₃)₂C(OR)₂), 79.9, 76.9 (C₂⁵, C₂₆), 49.5 (C₂₃), 47.4 (C₂₂), 35.9 (C₂₄), 27.1, 27.0 ((CH₃)₂C(OR)₂), 17.1 (C₂₇), MS (EI) m/z: 157 (M⁺-15, 27%), 115 (M⁺-57, 16%). HRMS calcd. for C₈H₁₃O₃ (M⁺-CH₃): 157.0865; found: 157.0868.

**{(3R,5R,6R)-3-Hydroxy-5,6-O-isopropylidene-1,1-(propane-1',3'-dithio)-heptane (126):}**

1,3-Dithiane (0.78 g, 6.49 mmol) was dissolved in THF (20 mL) and cooled to -20°C at which point 4.33 mL (6.49 mmol) of nBuLi (1.5M in hexane) was added. This solution was stirred for 2 hours whereupon a solution of the epoxide 125 (0.86 g, 4.99 mmol) dissolved in 5 mL of THF was added via cannula. The mixture was stirred at -20°C a further 2 hours and then placed in a refrigerator at -10°C for 18 hours. At this point the reaction was quenched by the addition of saturated aqueous NH₄Cl (5 mL) and diluted with ethyl acetate (80 mL). The organic layer was washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (30 mL of each), dried over Na₂SO₄, and concentrated in vacuo to provide a yellow viscous oil. Purification by SiO₂ flash chromatography (7:3 ethyl acetate/hexane) yielded 0.69 g (47%) of the dithianyl derivative 126 as a colourless oil. [α]D = +12.2° (c = 1.0, CHCl₃). IR (thin film) ν: 3460, 2981, 2922, 2861, 1422, 1381, 1246, 1095 cm⁻¹. ¹H NMR (300 MHz) δ: 4.26 (dd, J = 5.3, 9.1 Hz, 1H, RCH(SR)₂), 4.15 - 4.26 (m, 1H, H₂₃), 3.74 - 3.82 (m, 2H, H₂₅, H₂₆), 2.79 - 3.00 (m, 4H, 2 X RCH₂ₛ), 2.07 - 2.19 (m, 2H, H₂₂), 1.83 - 2.00 (m, 2H, CH₂(CH₂ₛ)₂), 1.71 (ddd, J = 3.0, 8.2, 13.2 Hz, 1H, H₂₄), 1.62 (ddd, J = 3.3, 7.7, 13.2 Hz, 1H, H₂₄), 1.38 (s, 6H, (CH₃)₂C(OR)₂), 1.24 (d, J = 5.7 Hz, 1H, H₂₇). MS
(E) m/z: 292 (M⁺, 4%), 277 (M⁺-15, 13%), 274 (M⁺-18, 26%). HRMS calcd. for C₁₂H₂₁O₃S₂ (M⁺-CH₃): 277.0933; found: 277.0888.

(3R,5R,6R)-3-Benzoyl-5,6-O-isopropylidene-1,1-(propane-1',3'-dithio)-heptane (127):

The alcohol 126 (0.61 g, 2.08 mmol) was dissolved in pyridine (10 mL) containing benzoyl chloride (1.21 mL, 10.4 mmol) and the mixture stirred at ambient temperature for 3 hours. Excess benzoyl chloride was destroyed by addition of water (1 mL) for 1 hour and the solvent removed in vacuo. The residue was diluted in 50 mL of ethyl acetate and washed successively with 30 mL portions of 0.2N HCl, saturated aqueous NaHCO₃, and brine. The organic layer was stripped of solvent in vacuo and the remaining oil further purified by radial chromatography (1:1 ether/hexane). This provided 0.61 g (74%) of benzoylated material 127 as a colourless oil. [α]D = +14.2° (c = 1.0, CHCl₃). IR (thin film) ν: 2933, 2860, 1718, 1452, 1318, 1270 cm⁻¹. ¹H NMR (300 MHz) δ: 8.03 - 8.11 (m, 2H, aromatic), 7.52 - 7.59 (m, 1H, aromatic), 7.40 - 7.47 (m, 2H, aromatic), 5.46 (app qu 1H, H₂₃), 4.11 (dd, J = 6.3, 8.1 Hz, 1H, RCH(SR)₂), 3.67 - 3.73 (m, 1H, H₂₅), 3.61 (dt, J = 3.0, 8.4 Hz, 1H, H₂₆), 2.60 - 3.06 (m, 4H, 2 X RCH₂S), 2.22 - 2.28 (m, 2H, H₂₂), 1.98 - 2.14 (m, 2H, CH₂(CH₂S)₂), 1.97 (ddd, J = 3.0, 6.3, 14.2 Hz, 1H, H₂₄), 1.84 (ddd, J = 6.4, 8.6, 14.2 Hz, 1H, H₂₄), 1.33 (s, 6H, (CH₃)₂C(OR)₂), 1.24 (d, J = 5.9 Hz, 3H, H₂₇). MS (El) m/z: 381 (M⁺-15, 9%), 274 (M⁺-122, 26%). MS (Cl ether) m/z: 397 (M⁺+1, 61%), 381 (M⁺-15, 11%), 339
(M+57, 75%). HRMS calcd. for C_{13}H_{22}O_{2}S_{2} (M+-PhCO_{2}H): 274.1063; found: 274.1066.
CHAPTER 6: MODEL STUDIES OF NUCLEOPHILIC ADDITIONS 
ONTO γ-LACTOL TEMPLATES

6.1 Introduction

From both synthetic and theoretical points of view, the relative asymmetric 
induction obtained in nucleophilic additions onto chiral aldehydes and ketones 
is of great importance. Intense interest and effort has been devoted to this 
subject since Cram's and Prelog's pioneering work on systematization 
of reactions of this type. Our synthetic efforts towards the synthesis of the C(17)–
C(27) fragment of bryostatins stimulated us to investigate a relatively unexplored 
facet of this topic; specifically, chelation and non-chelation controlled 
nucleophilic additions onto γ-lactol templates possessing α-chirality.

6.2 Goal

As discussed in Chapter 5.2 (Retrosynthetic Analysis), we envisioned that 
the stereochemistry at C(19) of the γ-lactol 115 should allow some degree of 
diastereofacial selectivity upon the addition of dithianyl fragment 127 to provide 
the desired C(19)-C(20)-anti diastereomer 130. This provides a potential 
handle for controlling the C(20) chirality of bryostatins. It is noteworthy that very

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101This work has appeared in part as "Controlled Diastereoselection in 2-Lithio-1,3-Dithiane 
Additions onto α-Substituted γ-Lactols. Model Studies Toward Bryostatins from (R)- 
little research has been published regarding the use of lactols in stereoselection\(^{105}\). Thus, the results obtained in this study may have general utility in asymmetric organic chemistry. To answer the questions posed regarding the nature of \(\gamma\)-lactol templates, we initiated a model study involving 2-lithio-1,3-dithiane additions onto various \(\gamma\)-lactols.

\[ \text{115} \quad \rightleftharpoons \quad \text{127} \]

\[ \text{130} \]

6.3 Predictions

Although little attention has been devoted to nucleophilic additions onto γ-lactol templates, it is possible to make some educated guesses. According to the Felkin-Anh modification of Cram's model\textsuperscript{106}, we speculated that the more polar and non-chelating C(19) silyloxy protecting group of the γ-lactol 115 will override the bulkier neopentyl group in its arrangement perpendicular to the carbonyl group in order to maximize the electronic effect (σ*–orbital energy). This should favour the formation of the C(19)-C(20)–anti product as pictured in Figure 24.

Clearly, attack of the incoming nucleophile along the Bürgi-Dünitz\textsuperscript{107} trajectory should occur from the less-hindered diastereotopic Si-face of the C(20) aldehyde (in the acyclic $\gamma$-hydroxy aldehyde form of the $\gamma$-lactol) as shown in Newman projection A. This would lead to the C(19)-C(20)—anti relationship which is what was desired for our proposed synthesis.

This situation may be contrasted to the one obtained for the unprotected C(19) hydroxyl. Under the basic conditions involved in this addition, the C(19) alkoxide will be formed. The metal cation (Li⁺ since nBuLi was used as base) should complex with the alkoxide and, presumably, the C(20) aldehyde to form a 5-membered chelate\textsuperscript{108} as shown in Figure 25. This should favour Re-face attack of the dithianyl nucleophile to afford the C(19)-C(20)-syn diol.

Figure 25 — Chelation Model (Anti-Cram) for Nucleophilic Addition Onto 76

Based upon these arguments, the α-substituted γ-lactols 115 and 76 should allow some degree of non-chelation and chelation control. They were, therefore, prepared, for a model study. The nucleophile chosen to mimic 127 was 2-lithio-1,3-dithiane.
6.4 Synthesis of γ-Lactol Templates 115 and 76

The synthesis of (2R)-[(tert-butyldimethylsilyl)oxy]pantolactol 115 was discussed in detail in Chapter 5.3. Briefly, it was obtained in 83% overall yield from (R)-pantolactone (67). Attempts to reduce 67 directly to (R)-pantolactol (76) under a similar set of conditions (DIBAL, THF or toluene) inevitably gave the triol as the primary product. Reduction with slightly acidic (H₂SO₄) sodium borohydride also yielded the triol as the major product. Finally, the controlled reduction to the lactol 76 was achieved using borane-tetrahydrofuran complex (BH₃-THF, THF, 0°C to 25°C, 12 hours). The yield was 83%, with only minimal amounts (<10%) of overreduced triol product being formed. The triol which was produced was readily removed by silica gel flash chromatography or by an aqueous extractive workup with the triol being extracted into the aqueous layer. This methodology was based upon work done by Perlin⁶⁴ regarding the reduction of various aldonolactones to aldoses.

6.5 Model Studies of 2-Lithio-1,3-Dithiane Additions Onto γ-Lactols 115 and 76

Work done by Corey and Seebach¹⁰⁹ and others⁹⁶ has demonstrated the versatility of the 1,3-dithiane group. For instance, lithiated 1,3-dithianes are good nucleophiles and allow the possibility of umpolung synthesis. Synthetic uses of this moiety have become ubiquitous in organic chemistry and there exists a

substantial body of knowledge regarding its chemistry. This information was beneficial for this model study.

Lithiation of 1,3-dithiane (nBuLi, THF, -20°C, 2 hours) using the standard procedure\textsuperscript{109} followed by the addition of either the α-protected lactol 115 or the α-unprotected lactol 76 afforded, after 18 hours, the adducts 131 and 132 and 133 and 134 in 73% and 71% yields, respectively.

\[ \begin{align*}
115 & \quad \text{OTBS} \\
17 & \quad \text{o} \\
20 & \quad \text{OH} \\
\downarrow & \quad \text{nBuLi, THF, -20°C, 73%}
\end{align*} \]

\[ \begin{align*}
131 & \quad \text{Anti: 96%} \\
132 & \quad \text{Syn: 4%}
\end{align*} \]

\[ \begin{align*}
76 & \quad \text{OTBS} \\
17 & \quad \text{o} \\
20 & \quad \text{OH} \\
\downarrow & \quad \text{nBuLi, THF, -20°C, 71%}
\end{align*} \]

\[ \begin{align*}
133 & \quad \text{Syn: 98%} \\
134 & \quad \text{Anti: 2%}
\end{align*} \]

The \(^1\text{H}\) NMR spectra of the crude adducts suggested that the diastereomeric excesses (de) for both these reactions were high (>90%). This was an extremely pleasing result to obtain. The key questions were to determine whether the predictions concerning the induced stereochemistry at C(20) were correct and the exact de.
Table 9 — Results for the Addition of 2-Lithio-1,3-Dithiane Onto 115 and 76

<table>
<thead>
<tr>
<th>γ-Lactol</th>
<th>Major Adduct</th>
<th>Yield</th>
<th>Anti/Syn Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>115</td>
<td>131</td>
<td>73%</td>
<td>96:4</td>
</tr>
<tr>
<td>71</td>
<td>133</td>
<td>71%</td>
<td>2:98</td>
</tr>
</tbody>
</table>

The first step was to deprotect the C(19) silyl ether of the diastereomeric diols 131 and 132. This was accomplished by acidic treatment in methanol to afford the triols 133 and 134 in quantitative yield (methanol, TsOH, 25°C). Comparison (tlc, 1H NMR, optical rotation) of triol 133 with triol 134 demonstrated that these compounds were, indeed, diastereomeric. Inferred from the discussion in Chapter 6.3, these triols were tentatively assigned as the C(19)-C(20)—anti (134) and C(19)-C(20)—syn (133) diastereomers. 1H NMR analysis of the crude spectra of these triols indicated 96:4 (de = 92%) and 2:98 (de = 96%) anti/syn ratios for the addition of 2-lithio-1,3-dithiane onto γ-lactols 115 and 76, respectively.

The last requirement for this model study was to determine the absolute configuration at C(20). To accomplish this goal, we chose to bind the C(19) and C(20) hydroxyls together by formation of their respective 1,3-dioxolane acetonides. It was expected that a 1H nuclear Overhauser effect (nOe) studies would then provide a definitive answer regarding the absolute stereochemistry C(20).

Thus, the anticipated syn-product (133) was subjected to standard acetonization conditions (2,2-dimethoxypropane, TsOH, benzene, 18 hours). An unusual and, at the time, disturbing result was that three products were obtained
in roughly equal amounts. Isolation of these compounds and mass spectroscopic analysis suggested that they were isomeric. The molecular weight was consistent with that expected for the desired 1,3-dioxolane product.

Inspection of the $^1$H NMR spectra provided the answer — all regioisomeric acetonides (135, 136, and 137) were formed. Equilibration to the thermodynamic 1,3-dioxolane acetonide (135) was apparently slow. Later experimentation demonstrated that this equilibration was significantly faster using acetone and a catalytic amount of TsOH. In this case, the 1,3-dioxolane compound 135 was formed as the exclusive product in only 3 hours at ambient temperature. Interestingly, Valverde$^{110}$ obtained a similar result (ie. formation of all 3 possible regiomeric acetonides when using 2,2-dimethoxypropane, TsOH and only the 1,3-dioxolane product when using acetone, TsOH) for the acetonization of a 4 carbon triol derived from L-tartaric acid.

Confirmation of the structure of the 5-membered acetonide (135) was obtained by acetylation of the primary hydroxyl at C(17) (92%, Ac$_2$O, pyridine, 4 hours). This resulted in the expected 0.5 ppm downfield shift of the C(17) methylene protons of 138, relative to those in 135. A $^1$H nOe study demonstrated that, for acetylated 1,3-dioxolane product 138, there was a 21% nOe difference enhancement between the proton on C(20) (dd at 4.14 ppm) and the gem-dimethyl protons (singlets at 0.96 and 0.99 ppm) as shown in Figure 26.
This nOe is only consistent with the proposed C(19)-C(20)–syn stereochemistry. No nOe would be expected for the C(19)-C(20)–anti configuration. The $^1$H NMR of 138 is given in Figure 27.

Figure 26 — Configuration at C(20) of Adduct 138 – $^1$H nOe Difference Results
Figure 27 — $^1$H NMR of 138
The identity of the 1,3-dioxane acetonide 136 was determined by comparison of the coupling pattern to that of the homologous benzylidenated triol. The pertinent $^1$H NMR data are given in Table 10. Briefly, upon treatment with a solution of benzaldehyde dimethyl acetal and a catalytic amount of TsOH in benzene for 1 hour at room temperature, the 6-membered benzylidene acetal 139 was formed (87% yield) between the C(17) and C(19) hydroxyls of the triol 133 and was the sole product obtained. The structure of 139 was confirmed by acetylation of the C(20) hydroxyl which formed the C(20) acetate 140 in 86% yield (Ac$_2$O, DMAP, pyridine, 25°C, 5 hours).

Table 10 — Comparison of the $^1$H NMR data of 1,3-O-Isopropylidene (136) and 1,3-O-Benzylidene (139) Acetals

<table>
<thead>
<tr>
<th>Parent Triol</th>
<th>Acetal</th>
<th>Chemical Shift (ppm) Proton</th>
<th>Coupling (Hz) Proton</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H$_21$</td>
<td>H$_20$</td>
</tr>
<tr>
<td>C(19)-Dioxane</td>
<td>1,3-</td>
<td>4.12</td>
<td>3.60</td>
</tr>
<tr>
<td>C(20)-136</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>syn 133</td>
<td>Benzylidene</td>
<td>4.23</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td>139</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Exposing the expected C(19)-C(20)-anti triol (134) to the same acetonide forming conditions (2,2-dimethoxypropane, TsOH, benzene, 18 hours) as described previously for the triol 133 led to the isolation of two products in 31% and 59% yield based upon the initial amount of 133. A similar structure identification protocol to the one described above (1H NMR, MS, derivatization by acetylation) revealed that these products (141 and 142) were the 6- and 7-membered ring acetonides, respectively. No 1,3-dioxolane product was observed.
The explanation for the absence of the 5-membered ring acetonide is that this product would require both the gem-dimethyl and 1,3-dithiane substituents to reside on the same side of the 1,3-dioxolane ring. Inspection of Dreiding models illustrates that this situation is sterically demanding and, hence, this product is not formed. This offers further chemical evidence for the absolute stereochemistry at C(20).
The structure of the 1,3-dioxane acetonide 141 was determined by comparison of its coupling pattern and chemical shifts to the homologous 6-membered benzylidene acetal 143 (134, benzaldehyde dimethyl acetal, TsOH, benzene, 1 hour) which was prepared in 84% yield using standard methodology. Table 11 gives the relevant ¹H NMR data. Acetylation of the benzylidene acetal 143 (Ac₂O, DMAP, pyridine, 5 hours) formed the acetate 144 in 74% yield and demonstrated that the C(20) hydroxyl was, as predicted, free.

Table 11 — Comparison of the ¹H NMR data of 1,3-O-Isopropyldiene (141) and 1,3-O-Benzylidene (143) Acetals

<table>
<thead>
<tr>
<th>Parent Triol</th>
<th>Acetal</th>
<th>Chemical Shift (ppm) Proton</th>
<th>Coupling (Hz) Proton</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H₂₁</td>
<td>H₂₀</td>
</tr>
<tr>
<td>C(19)-</td>
<td>1,3-</td>
<td>4.52</td>
<td>3.82</td>
</tr>
<tr>
<td>C(20)-</td>
<td>Dioxane 141</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>anti</td>
<td>4.59</td>
<td>3.96</td>
</tr>
<tr>
<td></td>
<td>134 Benzylidene 143</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In terms of our synthetic efforts towards the C(17)–C(27) fragment of bryostatins, this model study had provided the desired information. The dithianyl fragment 127 should add onto the γ-lactol 115 to afford, with high diastereofacial selectivity (de~92%), the adduct 130. From a more theoretical and general perspective, the unexpectedly high de obtained for this addition suggests that long range 1,4-chelation as depicted in Figure 28 might reinforce the induction. In other words, the 1,2- and 1,4-induction effects are co-operating with each other to lead to increased levels of stereoselection (see ref. 89 and 105 for other examples). It may be conjectured that attack of the nucleophile from the Si-face of conformer A (Figure 24) leading to the C(19)-C(20)-anti relationship is further favoured (relative to B) since it permits chelation of the C(17) alkoxide with the released C(20) aldehyde as shown in Figure 28. A similar model was recently suggested by Suzuki\textsuperscript{105a} to account for high anti-selectivity for methyl lithium additions onto α-methyl γ-lactols.

Figure 28 — 1,4-Chelation Model for Nucleophilic Addition Onto 115
From a practical viewpoint, it may be noted that the addition reaction may be reiterative. For instance, the dithiane moiety of adducts 131, 132, 133 and 134 could be hydrolyzed to form the α-substituted δ-lactol. This is set-up for another 2-lithio-1,3-dithiane addition. Based upon Suzuki's work\textsuperscript{105a}, reasonable diastereofacial selectivities may still be expected.

Finally, Corey\textsuperscript{111} has recently reported useful methodology for inverting the stereochemistry of the α-hydroxyl on (R)-pantolactone. This procedure involves formation of the triflate ester on (R)-pantolactone. Displacement with potassium acetate and subsequent deacetylation yields (S)-pantolactone in 90% overall yield and 97% ee. Utilizing both enantiomers of pantolactone allows access to all possible diastereomeric adducts for this particular dithiane addition.

\section*{6.6 Allyltrimethylsilane Addition onto γ-Lactols 115 and 77}

The synthetic work regarding the 2-lithio-1,3-dithiane addition onto γ-lactols stimulated our interest in reactions of this type. One interesting and potentially useful result was the TiCl\textsubscript{4} and SnCl\textsubscript{4}-mediated addition of allyltrimethylsilane onto (R)-pantolactol.

A literature survey suggested that Lewis acid promoted additions of allyltrimethylsilane onto lactol templates\textsuperscript{112} generally affords, via an oxonium ion intermediate, 2-allyl substituted cyclic ethers. Indeed, the BF\textsubscript{3}-Et\textsubscript{2}O-mediated addition of allyltrimethylsilane onto the α-silyl ether γ-lactol 115 (115, BF\textsubscript{3}-Et\textsubscript{2}O, 

CH₂Cl₂, -78°C, 15 minutes then allyltrimethylsilane, 5 hours, 0°C) delivered exclusively the 2,3,4-trisubstituted tetrahydrofurans 145a and 145b in excellent yield (93%) and having a cis/trans ratio of 1:2.

We speculated that having the α-hydroxylation of the γ-lactol unprotected and the use of an exceptionally strong Lewis acid such as TiCl₄ or SnCl₄ should encourage the formation of the interesting acyclic adduct. These hypotheses were rewarded. The TiCl₄-mediated addition of allyltrimethylsilane onto the α-hydroxylation γ-lactol 76 (76, TiCl₄, CH₂Cl₂, -78°C, 15 minutes then allyltrimethylsilane, 30 minutes) provided the acyclic adduct 146 in 83% yield. No tetrahydrofuran product was detected. Perhaps of more significance, the diastereofacial selectivity of this transformation was impressive: within the limits of high field ¹H and ¹³C NMR analysis, the product was a single diastereomer (>99% de). The nucleophile attacked from the Re-face. The use of SnCl₄ as Lewis acid provided essentially the same result as TiCl₄; namely the triol 146 was obtained as the exclusive product in 81% yield.
The high diastereofacial selectivities for these Lewis acid mediated additions may be conveniently rationalized by 1,2-chelation controlled induction caused by the rigid 5-membered titanium- or tin-chelate as shown in Figure 29. The possibility of remote chelation from the γ-hydroxyl (Figure 29, conformer B) is very real. This tri-chelation would further hinder the Si-face and, thus, is consistent with the observed complete Re-face nucleophilic attack.
The use of TiCl$_4$ or SnCl$_4$ was not sufficient for exclusive formation of the acyclic product — the presence of an $\alpha$-hydroxylic was necessary. This was implied by the TiCl$_4$-mediated addition of allyltrimethylsilane onto the $\alpha$-silylated $\gamma$-lactol 115 (115, TiCl$_4$, CH$_2$Cl$_2$, -78°C, 15 minutes then allyltrimethylsilane, 1 hour) which afforded a 32% isolated yield of the acyclic adduct 146 (5.0:1 syn to anti) along with a 41% yield of the 2,3,4-trisubstituted tetrahydrofuran 145a and 145b.

The syn configuration of 146 was unambiguously established using an analogous ketalization methodology as for the triol adduct 133 (Chapter 6.5). In this case, there was a $^1$H NOE difference (ca. 12% enhancement) between the proton on C(4) (ddd at 3.95 ppm) and the gem-dimethyl protons (singlets at 0.90 and 0.94 ppm) of the 1,3-dioxolane acetonide 147 as illustrated in Figure 30. Again, this is only consistent with the C(4)-C(5)-syn geometry. The $^1$H NMR
spectrum of 147 is given in Figure 31. Further verification of the structure of 147 was obtained by formation of the C(7) acetate (85%, Ac₂O, pyridine) which resulted in the expected 0.5 ppm downfield shift for the C(7) methylene protons of 148 relative to those of 147.

Figure 30 — Configuration at C(4) of Adduct 147 — ¹H nOe Difference Results
Figure 31 — $^1$H NMR of 147
The generality of this type of Lewis acid mediated nucleophilic addition is worthy of further exploration. An illustration of the synthetic potential of this transformation is the addition of allyltrimethylsilane onto free 2-hydroxy sugars. For instance, the TiCl$_4$-mediated addition of allyltrimethylsilane onto the known D-xylose derivative (-)-3,5-di-O-benzyl-α-D-xylofuranose$^{113}$ (149, obtained in 4 steps from D-xylose) furnished, in 55% yield, the acyclic product 150 as the exclusive diastereomer formed. The identical result was obtained for the SnCl$_4$-mediated reaction except that the yield was higher (81%).

The C(4)-C(5)-syn geometry of 150 was established using the analogous methodology as used for the determination of the absolute configuration of 146. Specifically, the 1,3-dioxolane acetonide 151 was formed (89%, acetone, TsOH, 18 hours). In this case there was a $^1\text{H}$ nOe difference of 8% between the C(3) methylene protons and H$_5$ (Figure 32). This nOe difference is only consistent with the proposed C(4)-C(5)-syn stereochemistry. The assignments of the protons on 151 was aided by HOMCOR-NMR and their well-resolved coupling pattern. Additional evidence was obtained by acetylation (90%, Ac$_2$O, pyridine) of the C(7) hydroxyl on 151 which resulted in a 1.2 ppm downfield shift of H$_7$ on 152 (relative to 151).

Figure 32 — Configuration at C(4) of Adduct 151 — $^1\text{H}$ nOe Difference Results

Thus, this type of Sakurai reaction should enable quick access to acyclic polyoxygenated products having well-defined stereochemistries. Furthermore, both ends of the chain have well-differentiated functionality facilitating chain
extension. The opportunities provided by this methodology in regards to asymmetric organic synthesis are numerous. Applications include a novel route to the synthesis of higher 2-deoxy carbohydrates (ie. via ozonolysis of 150), related carbohydrate-like molecular assemblies, and various polyoxygenated natural products.

6.7 Conclusions

The model studies presented in Chapters 6.5 and 6.6 demonstrate the usefulness of using γ-lactol templates for the stereoselective addition of nucleophiles. Thus, 2-lithio-1,3-dithiane additions to α-substituted γ-lactols exhibit high diastereoselectivity in favour of the anti-diol (anti/syn = 96:4) in accord with non-chelation control when the α-position was protected as its tert-butyldimethylsilyl ether. The unprotected lactol provided the reversed syn-diol diastereoselectivity (anti/syn = 2:98) following chelation control addition. Furthermore, the TiCl₄-mediated additions of allyltrimethylsilane onto various α-hydroxy γ-lactols exhibited virtually perfect stereoselection towards the syn-diol product (chelation control). No tetrahydrofuran product was produced.

The higher than expected diastereofacial selectivity obtained for the α-substituted γ-lactol (115) was rationalized by invoking possible 1,4-chelation. This result is useful for our synthetic efforts towards the C(17)–C(27) fragments of bryostatin; specifically, for controlling the C(20) stereocentre.

Taken together, the results presented in this Chapter suggest that a promising and relatively unexploited area in asymmetric organic synthesis is the use of γ-lactols as chiral templates.
6.8 Experimental

The general comments regarding instruments and reagents made in the Experimental section of Chapter 2.13 are applicable here as well.

(R)-[(tert-Butyldimethylsilyl)oxy]pantolactone (114):

To 40 mL of dichloromethane was added 2.00 g (15.4 mmol) of (R)-(−)-pantolactone (67, dried using Dean-Stark apparatus, benzene) followed by 2.69 mL (19.3 mmol) of triethylamine, 2.79 g (18.5 mmol) of tert-butyldimethylsilyl chloride and 0.39 g (3.2 mmol) of DMAP. After stirring for 1 day at ambient temperature, the mixture was diluted with ether (100 mL) and washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (50 mL of each). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The white amorphous residue was recrystallized in hexane yielding 3.76 g (95%) of the silyl ether 114 as white needles melting at 95.6-96.3°C. [α]D = +33.8° (c = 1.0, CHCl₃). IR (CH₂Cl₂) ν: 3050, 2959, 2858, 2302, 1791, 1252, 1132 cm⁻¹. ¹H NMR (300 MHz) δ: 3.97 (d, A of AB, J = 8.9 Hz, 1H, H₁₇), 3.97 (s, 1H, H₁₉), 3.86 (d, B of AB, J = 8.9 Hz, 1H, H₁₇), 1.12 (s, 3H, gem CH₃), 1.03 (s, 3H, gem CH₃), 0.91 (s, 9H, C(CH₃)₃), 0.18 (s, 3H, SiCH₃), 0.11 (s, 3H, SiCH₃). ¹³C NMR (50.4 MHz) δ: 176.9 (RCO₂R), 76.5 (C₁₉), 75.5 (C₁₇), 40.7 (C₁₈), 25.4 (C(CH₃)₃), 22.7, 18.8 (gem CH₃’s), 18.0 (SiC(CH₃)₃), -4.8, -5.7 (Si(CH₃)₂). MS (EI) m/z: 187 (M⁺-57, 20%), 143 (M⁺-101, 35%). HRMS calcd. for C₈H₁₅O₃Si (M⁺-C(CH₃)₃): 187.0791; found: 187.0796.
(R)-[(tert-Butyldimethylsilyl)oxy]pantolactol (115):

The silylated γ-lactone 114 (1.91 g, 7.81 mmol) was dissolved in 30 mL of THF and cooled to -78°C. Diisobutylaluminum hydride (1.0M in THF, 10.9 mL, 10.9 mmol) was added over a 15 minute period via a pressure-equalizing addition funnel. This mixture was stirred for 3 hours and then quenched by addition of Glauber's salt (Na₂SO₄·10H₂O, ~2 g). After warming to ambient temperature, the Glauber's salt was removed by filtration under suction. The filter cake was returned to the flask and refluxed with 50 mL of ethyl acetate (5 minutes), and filtered. This procedure was repeated with another 50 mL portion of ethyl acetate. The combined filtrates were washed with 0.2N HCl (2 X 50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL), dried over Na₂SO₄, and concentrated in vacuo to yield a white amorphous solid. Purification by SiO₂ flash chromatography (2:8 ether/hexane) and recrystallization from hexane afforded 1.67 g (87%) of the silylated γ-lactol 115 as white needles melting at 48.5-51.5°C. When different, the data for the minor anomer (2.3:1 anomeric ratio) is given in brackets. [α]D = -13.3° (c = 2.0, CHCl₃). IR (CH₂Cl₂) ν: 3591, 3050, 2959, 2931, 2859, 1472, 1256, 1048 cm⁻¹. ¹H NMR (300 MHz) δ: 5.12 (app t, 1H, H₂₀), (5.35) (dd, J = 4.2, 9.8 Hz, 1H, H₂₀), (3.82) (d, J = 9.8 Hz, 1H, H₁₉), 3.76 (d, A of AB, J = 8.2 Hz, 1H, H₁₇), 3.64 (s, 1H, H₁₉), 3.63 (d, B of AB, J = 8.2 Hz, 1H, H₁₇), (3.60) (s, 2H, H₁₇), 1.03 (s, 3H, gem CH₃), 0.97 (s, 3H, gem CH₃), 0.88 (0.92) (s, 9H, C(CH₃)₃), 0.07, 0.05 (0.10, 0.08) (s, 6H, Si(CH₃)₂). ¹³C NMR (50.4 MHz) δ: 98.0 (104.6) (C₂₀), 79.2 (85.5) (C₁₉), 76.3 (78.4) (C₁₇), 42.0 (42.1) (C₁₈), 25.6 (C(CH₃)₃), 25.4, 19.9 (23.6, 19.9) (gem CH₃'s), 18.0 (17.9) (SiC(CH₃)₃), -5.4 (-4.8) (Si(CH₃)₂). MS (Cl ether) m/z: 247 (M⁺+1, 1%), 229 ((M⁺+1)-18,
100%), 189 (M+-57, 23%). Anal. calcd. for C_{12}H_{26}O_{3}Si: C, 58.49, H, 10.63, Si, 11.40; found: C, 58.45, H, 10.59, Si, 11.33.

**(R)-(-)-Pantolactol (76):**

Over a period of 1 hour, borane-tetrahydrofuran complex (1.0M in THF, 232 mL, 232 mmol) was added to (R)-(-)-pantolactone (67) (6.00 g, 46.1 mmol, dried using Dean-Stark apparatus, benzene) in 100 mL of THF at 0°C. After stirring for 12 hours at ambient temperature, the reaction was quenched by careful addition of water until the evolution of hydrogen had ceased. The solvent was then removed *in vacuo* leaving a colourless syrup. Several co-evaporations with 60 mL of a 2% acetic acid in methanol solution were accomplished followed by SiO₂ flash chromatography (7:3 ether/hexane). This yielded 5.00 (82%) of the hydroxy γ-lactol 76 as a colourless oil. When different, the data for the minor anomer (1.4:1 anomeric ratio) is given in brackets. \([\alpha]_D = -2.7^\circ (c = 2.2, \text{CHCl}_3).\) IR (thin film) ν: 3395, 2971, 2881, 1471, 1382, 1031 cm⁻¹. ¹H NMR (200 MHz) δ: 5.41 - 5.47 (5.21 - 5.26) (m, 1H, H₂O), (3.82) (d, A of AB, J = 8.4 Hz, 1H, H₁₇), (3.73) (d, B of AB, J = 8.4 Hz, 1H, H₁₇), 3.66 (d, A of AB, J = 8.1 Hz, 1H, H₁₇), 3.62 - 3.69 (m, 1H, H₁₉), 3.45 (d, B of AB, J = 8.1 Hz, 1H, H₁₇), 2.85 - 2.91 (2.51 - 2.61) (br s, 1H, OH, exchangeable), 1.06, 1.04 (1.10, 106) (s, 6H, gem CH₃'s). ¹³C NMR (50.4 MHz) δ: 97.5 (103.4) (C₂₀), 78.2 (84.1) (C₁₉), 77.2 (78.5) (C₁₇), 41.5 (41.6) (C₁₈), 25.4, 19.5 (23.7, 19.3) (gem CH₃'s). MS (Cl ether) m/z: 133 (M⁺+1, 15%), 131 (M⁺-1, 18%), 115 ((M⁺+1)-18, 96%). Anal. calcd. for C₆H₁₂O₃: C, 54.53, H, 9.15; found: C, 54.34, H, 8.97.
(2R,3R)-2,5-Dihydroxy-4,4-dimethyl-3-[(tert-butyldimethylsilyl)oxy]-1,1'-(propane-1',3'-dithio)-pentane (131):

To 1,3-dithiane (1.26 g, 10.5 mmol, purified by vacuum sublimation) in 30 mL of THF at -20°C was added nBuLi (1.5M in hexane, 7.00 mL, 10.5 mmol) and the solution was stirred for 2 hours whereupon a solution of the silylated γ-lactol 115 (1.03 g, 4.18 mmol) in THF (5 mL) was added via cannula. The mixture was stirred a further 2 hours and then placed in the refrigerator (-10°C) for 18 hours whereupon it was quenched by addition of 2 mL of saturated aqueous NH₄Cl and allowed to warm to room temperature. The solution was then diluted with ethyl acetate (80 mL) and extracted with 0.2N HCl (30 mL), saturated aqueous NaHCO₃ (30 mL), and brine (30 mL), dried over Na₂SO₄, and concentrated in vacuo to provide a syrup. Further purification by SiO₂ flash chromatography (4:6 ether/hexane) yielded 1.12 g (73%) of the diastereomeric diol adducts 131 and 132 (131:132, 96:4). Both were obtained as colourless syrups. The following data are for the major C(19)-C(20)-anti diastereomer (131). [α]D = -6.2° (c = 1.8, CHCl₃). ¹H NMR (300 MHz) δ: 4.30 (d, J = 5.9 Hz, 1H, H₂₁), 3.90 (dd, J = 5.1, 5.9 Hz, 1H, H₂₀), 3.84 (d, J = 5.1 Hz, 1H, H₁₉), 3.61 (d, A of AB, J = 11.3 Hz, 1H, H₁₇), 3.35 (d, B of AB, J = 11.3 Hz, 1H, H₁₇), 2.66 - 2.96 (m, 4H, CH₂(CH₂S)₂), 2.41 - 3.00 (br s, 2H, OH, exchangeable), 1.88 - 2.16 (m, 2H, CH₂(CH₂S)₂), 1.04, 0.93 (s, 6H, gem CH₃'s), 0.92 (s, 9H, C(CH₃)₃), 0.18, 0.11 (s, 6H, Si(CH₃)₂). MS (Cl ether) m/z: 367 (M⁺+1, 1%), 329 (M⁺-37, 83%).
(2S,3R)-2,3,5-Trihydroxy-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (133):

This material was prepared using a similar procedure to the one described above for the conversion of 115 to 131 and 132. Thus, 0.44 g (3.33 mmol) of the 2-hydroxy γ-lactol 76 when treated with 2-lithio-1,3-dithiane (11.7 mmol) yielded, after purification by SiO₂ flash chromatography (6:4 ether/hexane), 0.60 g (71%) of the diastereomeric triol adducts 133 and 134 (133:134, 98:2). Both were obtained as a white solid. The melting point of the syn-triol 133 was 63.0-64.5°C. The following data are for the major C(19)-
C(20)—syn diastereomer (133). [α]₀ = -36.4° (c = 2.5, CHCl₃). ¹H NMR (300 MHz) δ: 4.04 (d, J = 8.8 Hz, 1H, H₂₁), 3.93 (d, J = 8.8 Hz, 1H, H₂₀), 3.79 (s, 1H, H₁₉), 3.63 (d, A of AB, J = 11.4 Hz, 1H, H₁₇), 3.34 (d, B of AB, J = 11.4 Hz, 1H, H₁₇), 2.71 - 3.00 (br s, 3H, OH, exchangeable), 2.62 - 2.93 (m, 4H, CH₂(CH₂S)₂), 1.99 - 2.07 (m, 2H, CH₂(CH₂S)₂), 1.00, 0.95 (s, 6H, gem CH₃'s). MS (Cl ether) m/z: 253 (M⁺+1, 92%), 235 ((M⁺+1)-18, 73%), 149 (M⁺-103, 68%), 133 (M⁺-119, 64%).

(2R,3R)-2,3,5-Trihydroxy-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (134):

The silyl ether 131 (0.96 g, 2.62 mmol) was dissolved in methanol (30 mL) and a catalytic amount of TsOH (~10 mg) was added and the solution was stirred at ambient temperature for 5 hours. At this point, tlc (ether) indicated the
reaction to be complete and it was subsequently processed by addition of an excess of Dowex 1-X8 resin in the -OH form, filtration, and removal of solvent in vacuo to yield a resinous material. This was further purified by SiO₂ flash chromatography (7:3 ether/hexane) to provide a quantitative yield (0.66 g) of the C(19)-C(20)-anti triol adduct 134 as a solid melting at 108.0-109.1°C. [α]D = -33.3° (c = 2.5, CHCl₃). ¹H NMR (300 MHz) δ: 4.55 (d, J = 2.7 Hz, 1H, H₂₁), 3.93 (dd, J = 2.7, 8.4 Hz, 1H, H₂₀), 3.58 (d, J = 8.4 Hz, 1H, H₁₉), 3.54 (d, A of AB, J = 11.3 Hz, 1H, H₁₇), 3.45 (d, B of AB, J = 11.3 Hz, 1H, H₁₇'), 2.86 - 3.01 (m, 4H, CH₂(CH₂S)₂), 2.52 - 2.79 (br s, 3H, OH, exchangeable), 1.85 - 2.14 (m, 2H, CH₂(CH₂S)₂), 1.04, 0.93 (s, 6H, gem CH₃'s). MS (EI) m/z: 149 (M⁺-103, 6%). MS (Cl ether) m/z: 253 (M⁺+1, 24%), 235 ((M⁺+1)-18, 11%), 149 (M⁺-103, 20%), 133 (M⁺-119, 27%).

**Acetonide Formation on (2S,3R)-2,3,5-Trihydroxy-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (133):**

Triol 133 (0.89 g, 3.53 mmol) was dissolved in 10 mL of a 40% 2,2-dimethoxypropane in benzene solution containing a catalytic amount of TsOH (~15mg) and the solution was stirred at ambient temperature. After overnight contact, the reaction was neutralized by addition of triethylamine and stripped of solvent in vacuo. The residue was diluted in ethyl acetate (40 mL) and washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (30 mL portions). Drying over Na₂SO₄ and concentration in vacuo afforded a colourless oil. Purification by preparative TLC (1:1 ether/hexane) yielded three products: 0.13 g (13%) of
135, 0.43 g (42%) of 136, and 0.31 g (30%) of 137 (5-, 6-, and 7-membered ring acetonides, respectively) as colourless oils. The separation procedure used was preparative TLC (1:1 ether/hexane) (order of polarity: 137>135>136; r'f's: 0.33, 0.38, 0.50, respectively). Submitting triol 133 to the acetonide forming conditions of acetone and a catalytic amount of TsOH afforded the thermodynamic 1,3-dioxolane acetonide 135 as the exclusive product. Thus, 55.6 mg (0.221 mmol) of the triol 133 was dissolved in reagent grade acetone (5 mL) containing TsOH (~10 mg) and the solution was stirred at ambient temperature for 3 hours. The reaction was quenched and processed in the same manner as described above yielding, after purification, 54.6 mg (85%) of the 1,3-dioxolane acetal 135 as the exclusive product.

(2S,3R)-5-Hydroxy-2,3-O-isopropylidene-4,4-dimethyl-1,1-(propane-1',3'-dithio)pentane (135):

$^1$H NMR (300 MHz) δ: 4.12 (d, J = 4.6 Hz, 1H, H$_{21}$), 4.12 (s, 1H, H$_{19}$), 4.11 (d, J = 4.6 Hz, 1H, H$_{20}$), 3.47 (d, A of AB, J = 11.2 Hz, 1H, H$_{17}$), 3.42 (d, B of AB, J = 11.2 Hz, 1H, H$_{17'}$), 2.77 - 3.00 (m, 4H, CH$_2$(CH$_2$S)$_2$), 1.95 - 2.20 (br s, 1H, OH, exchangeable), 1.92 - 2.17 (m, 2H, CH$_2$(CH$_2$S)$_2$), 1.46, 1.40 (s, 6H, (RO)$_2$C(CH$_3$)$_3$), 0.98, 0.93 (s, 6H, gem CH$_3$'s). MS (Cl ether) m/z : 293 (M$^+$+1, 53%), 275 ((M$^+$+1)-18, 1%), 235 ((M$^+$+1)-58, 58%).
(2S,3R)-2-hydroxy-3,5-O-isopropylidene-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (136):

$^1$H NMR (300 MHz) $\delta$: 4.12 (d, $J = 6.6$ Hz, 1H, H$_{21}$), 3.93 (s, 1H, H$_{19}$), 3.80 (d, $J = 6.6$ Hz, 1H, H$_{20}$), 3.65 (d, A of AB, 1H, $J = 11.4$ Hz, H$_{17}$), 3.27 (d, B of AB, $J = 11.4$ Hz, 1H, H$_{17}$), 2.85 - 3.00 (br s; 1H, OH, exchangeable), 2.71 - 2.88 (m, 4H, CH$_2$(CH$_2$S)$_2$), 1.83 - 2.16 (m, 2H, CH$_2$(CH$_2$S)$_2$), 1.47, 1.42 (s, 6H, (RO)$_2$C(CH$_3$)$_2$), 1.12, 0.78 (s, 6H, gem CH$_3$'s). MS (Cl ether) m/z: 293 (M$^{+}$+1, 80%), 275 ((M$^{+}$+1)-18, 2%), 235 ((M$^{+}$+1)-58, 100%).

(2S,3R)-3-Hydroxy-2,5-O-isopropylidene-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (137):

$^1$H NMR (300 MHz) $\delta$: 4.38 (d, $J = 10.2$ Hz, 1H, H$_{21}$), 3.98 (d, $J = 10.2$ Hz, 1H, H$_{20}$), 3.55 (s, 1H, H$_{19}$), 3.66 (d, A of AB, $J = 12.5$ Hz, 1H, H$_{17}$), 2.96 (d, B of AB, $J = 12.5$ Hz, 1H, H$_{17}$), 2.82 - 2.87 (m, 4H, CH$_2$(CH$_2$S)$_2$), 2.41 - 2.60 (br s, 1H, OH, exchangeable), 1.79 - 2.10 (m, 2H, CH$_2$(CH$_2$S)$_2$), 1.41, 1.38 (s, 6H, (RO)$_2$C(CH$_3$)$_2$), 0.99, 0.87 (s, 6H, gem CH$_3$'s). MS (Cl ether) m/z: 293 (M$^{+}$+1, 96%), 275 ((M$^{+}$+1)-18, 6%), 235 ((M$^{+}$+1)-58, 95%).
Acetonide Formation on (2R,3R)-2,3,5-Trihydroxy-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (134):

The acetonides on the C(19)-C(20)-anti triol 134 were prepared in a similar manner to the one described above for the conversion of 133 to 135, 136, and 137. Thus, 155 mg, (0.613 mmol) of triol 134 yielded two products. They were identified as the 6-membered (141) and 7-membered (142) ring acetonides (141 less polar than 142; r f's: 0.50 and 0.41, respectively). The yields for 141 and 142 were 59% and 31%, respectively and both products were obtained as colourless oils.

(2R,3R)-2-Hydroxy-3,5-O-isopropyldiene-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (141):

$^1$H NMR (300 MHz) $\delta$: 4.52 (d, J = 1.9 Hz, 1H, H$_{21}$), 3.82 (dd, J = 1.9, 8.9 Hz, 1H, H$_{20}$), 3.70 (d, J = 8.9 Hz, 1H, H$_{19}$), 3.56 (d, A of AB, J = 11.6 Hz, 1H, H$_{17}$), 3.20 (d, B of AB, J = 11.6 Hz, 1H, H$_{17}$), 2.79 - 3.02 (m, 4H, CH$_2$(CH$_2$S)), 1.96 - 2.41 (br s, 1H, OH, exchangeable), 1.81 - 2.16 (m, 2H, CH$_2$(CH$_2$S)$_2$), 1.39, 1.36 (s, 6H, (RO)$_2$C(CH$_3$)$_2$), 1.07, 0.92 (s, 6H, gem CH$_3$'s). MS (Cl ether) m/z: 293 (M$^+$+1, 15%), 275 ((M$^+$+1)-18, 1%), 235 ((M$^+$+1)-58, 52%).
(2R,3R)-3-Hydroxy-2,5-O-isopropyldene-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (142):

$^1$H NMR (300 MHz) $\delta$: 4.45 (d, J = 2.7 Hz, 1H, H$_{21}$), 3.97 (dd, J = 2.7, 9.2 Hz, 1H, H$_{20}$) 3.56 (d, A of AB, J = 12.5 Hz, 1H, H$_{17}$), 3.35 (dd, J = 5.6, 9.2 Hz, 1H, H$_{19}$), 3.04 (d, B of AB, J = 12.5 Hz, 1H, H$_{17}$), 2.81 - 3.01 (m, 4H, CH$_2$(CH$_2$S)$_2$), 2.19 (d, J = 5.6 Hz, 1H, OH, exchangeable), 1.91 - 2.15 (m, 2H, CH$_2$(CH$_2$S)$_2$), 1.39, 1.35 (s, 6H, (RO)$_2$C(CH$_3$)$_2$), 0.98 (s, 6H, gem CH$_3$'s). MS (Cl ether) m/z: 293 (M$^+$+1, 35%), 275 ((M$^+$+1)-18, 3%), 235 ((M$^+$+1)-58, 95%).

(2S,3R)-5-Acetoxy-2,3-O-isopropyldene-4,4-dimethyl-1,1-(propane-1',3'-dithio)pentane (138):

To the acetonide alcohol 135 (52.5 mg, 0.180 mmol) in 5.0 mL of pyridine was added 1.0 mL of acetic anhydride and the solution stirred at room temperature for 4 hours. At this point, 1.0 mL of methanol was added for 1 hour to destroy the excess acetic anhydride and the solution then stripped of solvent in vacuo. The remaining oil was dissolved in 50 mL of ethyl acetate and washed with 30 mL portions of 0.2N HCl, saturated aqueous NaHCO$_3$, and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. Further purification by preparative TLC (2:8 ether/hexane) afforded 55.2 mg (92%) of the acetate 138 as a colourless oil. $^1$H NMR (300 MHz) $\delta$: 4.14 (dd, J = 3.2, 7.5 Hz, 1H, H$_{20}$), 4.06 (d, J = 3.2 Hz, 1H, H$_{19}$), 4.05 (d, J = 7.5 Hz, 1H, H$_{21}$), 3.97 (d, A of AB, J = 11.0 Hz, 1H, H$_{17}$), 3.86 (d, B of AB, J = 11.0 Hz, 1H, H$_{17}$), 2.71 - 3.01 (m,
4H, CH₂(CH₂S)₂), 2.08 (s, 3H, CH₃CO₂R), 1.91 - 2.16 (m, 2H, CH₂(CH₂S)₂),
1.45; 1.37 (s, 6H, (RO)₂C(CH₃)₂), 0.99, 0.96 (s, 6H, gem CH₃'s). MS (EI) m/z:
334 (M⁺, 3%), 319 (M⁺-15, 1%), 215 (M⁺-119, 22%). MS (Cl ether) m/z: 335
(M⁺+1, 45%), 276 ((M⁺+1)-59, 100%). HRMS calcd. for C₁₅H₂₆O₄S₂ (M⁺):
334.1272; found: 334.1267.

(2S,3R)-3,5-O-Benzylidene-(2S)-hydroxy-4,4-dimethyl-1,1-
(propane-1',3'-dithio)-pentane (139):

To the C(19)-C(20)-syn triol 133 (98.5 mg, 0.39 mmol) in benzene (10
mL) was added 234 µL (1.56 mmol) of benzaldehyde dimethyl acetal and a
catalytic amount of TsOH (~10 mg). After stirring 1 hour at ambient temperature,
it was neutralized with triethylamine and the cf solvent removed in vacuo. The
residue was diluted in ethyl acetate (40 mL) and washed successively with 0.2N
HCl, saturated aqueous NaHCO₃, and brine (30 mL of each), dried over
Na₂SO₄, and concentrated under reduced pressure. The oil was further purified
by radial chromatography (2:8 ether/hexane) providing 115 mg (87%) of
benzylidenated material 139 as a colourless oil. ¹H NMR (300 MHz) δ: 7.33 -
7.53 (m, 5H, aromatic), 5.63 (s, 1H, (RO)₂CHPh), 4.23 (d, J = 6.6 Hz, 1H, H₂₁),
3.95 (s, 1H, H₁₉), 3.90 (d, J = 6.6 Hz, 1H, H₂₀), 3.73 (d, A of AB, J = 11.1 Hz, 1H,
H₁₇), 3.66 (d, B of AB, J = 11.1 Hz, 1H, H₁₇'), 2.80 - 3.02 (br s, 1H, OH,
exchangeable), 2.74 - 2.91 (m, 4H, CH₂(CH₂S)₂), 1.84 - 2.15 (m, 2H,
CH₂(CH₂S)₂), 1.25, 0.85 (s, 6H, gem CH₃'s). MS (Cl ether) m/z: 341 (M⁺+1,
79%), 323 ((M⁺+1)-18, 4%), 235 ((M⁺+1)-106, 59%).
(2S,3R)-Acetoxy-3,5-O-benzylidene-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (140):

The alcohol 139 (61.2 mg, 0.180 mmol) was stirred at room temperature in pyridine (5.0 mL) containing acetic anhydride (1.0 mL) and DMAP (8.2 mg, 0.067 mmol). After 5 hours, the excess acetic anhydride was quenched by addition of methanol (1 mL) for 1 hour and the solution was concentrated under reduced pressure. The remaining syrup was taken up in ethyl acetate (30 mL) and washed with 0.2N HCl, saturated aqueous NaHCO₃, and brine (20 mL of each). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. Further purification was accomplished by radial chromatography (1:9 ether/hexane) to yield 59.3 mg (86%) of the acetate 140 as a colourless oil. ¹H NMR (300 MHz) δ: 7.32 - 7.52 (m, 5H aromatic), 5.60 (dd, J = 1.3, 10.1 Hz, 1H, H₂₀), 5.48 (s, 1H, (RO₂)₂CHPh), 4.35 (d, J = 1.3 Hz, 1H, H₂₁), 3.91 (d, J = 10.1 Hz, 1H, H₁₉), 3.70 (d, A of AB, J = 10.7 Hz, 1H, H₁₇), 3.63 (d, B of AB, J = 10.7 Hz, 1H, H₁₇). 2.88 - 3.00 (m, 2H, CH₂(CH₂S)₂), 2.48 - 2.63 (m, 2H, CH₂(CH₂S)₂), 2.11 (s, 3H, CH₃CO₂R), 1.96 - 2.10 (m, 2H, CH₂(CH₂S)₂), 1.15, 0.91 (s, 6H, gem CH₃'s).

(2R,3R)-3,5-O-Benzylidene-2-hydroxy-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (143):

This material was prepared and purified in the same manner as described above for the conversion of 133 to 139. Thus, 81.2 mg (0.322 mmol) of the
C(19)-C(20)-anti triol 134 yielded 91.9 mg (84%) of benzylidenated material 143 as a colourless oil. $^1$H NMR (300 MHz) $\delta$: 7.33 - 7.49 (m, 5H, aromatic), 5.44 (s, 1H, (RO)$_2$CHPh), 4.59 (d, J = 1.8 Hz, 1H, H$_{21}$), 3.96 (dd, J = 1.8, 9.0 Hz, 1H, H$_{20}$), 3.74 (d, J = 9.0 Hz, 1H, H$_{19}$), 3.65 (d, A of AB, J = 11.3 Hz, 1H, H$_{17}$), 3.60 (d, B of AB, J = 11.3 Hz, 1H, H$_{17}$), 2.81 - 2.99 (m, 4H, CH$_2$(CH$_2$S)$_2$), 1.80 - 2.16 (m, 2H, CH$_2$(CH$_2$S)$_2$), 1.51 - 1.80 (br s, 1H, OH, exchangeable), 1.21, 0.97 (s, 6H, gem CH$_3$'s). MS (Cl ether) m/z: 341 (M$^+$+1, 37%), 323 ((M$^+$+1)-18, 3%), 235 ((M$^+$+1)-106, 23%).

(2R,3R)-Acetoxy-3,5-O-benzyldiene-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (144):

This material was prepared and purified in the same manner as described above for the conversion of 139 to 140. Thus, 42.0 mg (0.123 mmol) of the alcohol 143 yielded 34.6 mg (74%) of the acetate 144 as a colourless oil. $^1$H NMR (300 MHz) $\delta$: 7.35 - 7.50 (m, 5H, aromatic), 5.47 (s, 1H, (RO)$_2$CHPh), 5.44 (dd, J = 2.2, 9.2 Hz, 1H, H$_{20}$), 4.55 (d, J = 2.2 Hz, 1H, H$_{21}$), 3.74 (d, J = 9.2 Hz, 1H, H$_{19}$), 3.61 (s, 2H, H$_{17}$), 2.76 - 2.98 (m, 4H, CH$_2$(CH$_2$S)$_2$), 2.14 (s, 3H, CH$_3$CO$_2$R), 1.85 - 2.12 (m, 2H, CH$_2$(CH$_2$S)$_2$), 1.18, 0.78 (s, 6H, gem CH$_3$'s).
(2R,3R)-2-Allyl-4,4-dimethyl-3-
[(tert-butyldimethylsilyl)oxy]tetrahydrofuran (145a) and (2S,3R)-2-
Allyl-4,4-dimethyl-3-[(tert-butyldimethylsilyl)oxy]tetrahydrofuran
(145b):

The α-silylated γ-lactol 115 (150 mg, 0.609 mmol) was dissolved in 20
mL of dichloromethane and cooled to -78°C and BF₃·Et₂O (150 µL, 1.22 mmol)
was added. The solution was stirred at this temperature for 15 minutes at which
point allyltrimethylsilane (193 µL, 1.21 mmol) was added and the dry-
ice/acetone bath removed and replaced by an ice-bath. After stirring 5 hours at
0°C, the mixture was quenched by addition of saturated aqueous NaHCO₃ (5
mL) and allowed to warm to ambient temperature. It was diluted with an
additional 20 mL of dichloromethane and, subsequently, extracted with
saturated aqueous NaHCO₃ (20 mL) and brine (20 mL). The organic layer was
dried over Na₂SO₄ and concentrated in vacuo to deliver 153 mg (93%) of a 2:1
cis/trans mixture of 2,3,4-trisubstituted tetrahydrofurans 145a and 145b as a
colourless oil and of sufficient purity (tlc, ¹H NMR) for characterization. When
different, the spectral data for the minor cis isomer (145a) is given in brackets.
IR (thin film) ν: 2961, 2938, 2862, 1466, 1473, 1260, 1190, 840, 788 cm⁻¹. ¹H
NMR (200 MHz) δ: 5.79 - 5.87 (m, 1H, H₂), 5.04 - 5.14 (m, 2H, H₁), 3.66 - 3.70 (m,
1H, H₃), 3.53 (s, 2H, H₇), 3.44 (3.61) (d, J = 6.1 (7.8) Hz, 1H, H₅), 2.41 - 2.46 (m,
1H, H₃), 2.18 - 2.25 (m, 1H, H₃), 0.99, 0.96 (1.02) (s, 6H, gem CH₃'s), 0.88 (0.91)
s, 9H, Si(CH₃)₃), 0.050, 0.041 (s, 6H, Si(CH₃)₂). ¹³C NMR (50.4 MHz) δ:
(136.6) 135.3 (C₂), 116.9 (116.2) (C₁), 84.4 (81.9) (C₅), 83.0 (80.5) (C₄), 78.9
(77.6) (C₃), 43.6) 41.9 (C₂), 37.9 (35.2) (C₁), 25.8) 25.7 (C(CH₃)₃), 25.4) 25.0
(gem CH₃), 20.4) 20.1 (gem CH₃), 18.1) 17.9 (SiC(CH₃)₃), -4.4) -4.5
\((\text{Si(CH}_3)_2)\). MS (El) \(m/z\): 229 (M\(^+\)-41, 17\%), 213 (M\(^+\)-57, 23\%). MS (Cl ether) \(m/z\): 271 (M\(^+\)+1, 8\%), 229 (M\(^+\)-41, 100\%), 213 (M\(^+\)-57, 25\%). HRMS calcd. for C\(_{11}\)H\(_{21}\)O\(_2\)Si (M\(^+\)-C(CH\(_3\))\(_3\)): 213.1311; found: 213.1315.

\((4R,5R)-4,5,7\)-Trihydroxy-6,6-dimethyl-1-heptene (146):

The \(\gamma\)-lactol 76 (225 mg, 1.70 mmol) was dissolved in 20 mL of dichloromethane and cooled to -78°C whereupon 0.59 mL (4.25 mmol) of TiCl\(_4\) was added. After stirring 15 minutes, 0.62 mL (3.91 mmol) of allyltrimethylsilane was added. The reaction was quenched after 30 minutes by the addition of 3 mL of saturated aqueous NaHCO\(_3\) and allowed to warm to ambient temperature. The mixture was then diluted with 60 mL of dichloromethane and washed with saturated aqueous NaHCO\(_3\) (2 \times 30 mL) and brine (30 mL), dried over Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo}. The residual oil was purified by SiO\(_2\) flash chromatography (2:8 methanol/chloroform) to yield 247 mg (83\%) of the allyl triol 146 as a colourless oil. \([\alpha]_D = -9.0^\circ\) (c = 1.0, CHCl\(_3\)). IR (thin film) \(\nu\): 3380, 3082, 2962, 1646, 1479, 1398, 1049, 920 cm\(^{-1}\). \(^1\)H NMR (300 MHz) \(\delta\): 5.75 - 5.87 (m, 1H, H\(_2\)), 5.10 - 5.18 (m, 2H, H\(_1\)), 3.88 (dd, 1H, J = 6.0, 7.9 Hz, H\(_4\)), 3.65 (d, A of AB, J = 11.1 Hz, 1H, H\(_7\)), 3.30 (d, B of AB, J = 11.1 Hz, 1H, H\(_7\)), 3.19 (s, 1H, H\(_5\)), 2.21 - 2.46 (m, 2H, H\(_3\)), 2.10 - 2.40 (br s, 3H, OH, exchangeable), 0.96, 0.91 (s, 6H, gem CH\(_3\)'s). \(^1\)C NMR (50.4 MHz) \(\delta\): 135.0 (C\(_2\)), 118.2 (C\(_1\)), 78.5 (C\(_5\)), 68.0 (C\(_4\)), 67.9 (C\(_7\)), 39.8 (C\(_3\)), 39.0 (C\(_6\)), 24.1, 20.6 (gem CH\(_3\)'s). MS (Cl ether) \(m/z\): 175 (M\(^+\)+1, 100\%), 157 ((M\(^+\)+1)-18, 73\%). Anal calcd. for C\(_9\)H\(_{18}\)O\(_3\)·\(\text{1/3H}_2\)O: C, 59.97, H, 10.44; found: C, 60.33, H, 10.42.
(4R,5R)-7-Hydroxy-4,5-O-isopropylidene-6,6-dimethyl-1-heptene (147):

The allyl triol 146, (0.18 g, 1.05 mmol) was dissolved in 20 mL of acetone containing a catalytic amount of TsOH (15 mg). After stirring overnight at room temperature, the reaction was neutralized by the addition of triethylamine and the solvent removed under reduced pressure. The residue was diluted in ether (50 mL) and washed with 0.2N HCl (30 mL), saturated aqueous NaHCO₃ (30 mL), and brine (30 mL), dried over Na₂SO₄, and concentrated in vacuo. The oil was purified by SiO₂ flash chromatography (4:6 ether/hexane) to provide 0.17 g (76%) of the acetonide 147 as a colourless oil. [α]₀ = +24.2° (c = 1.0, CHCl₃).

¹H NMR (300 MHz) δ: 5.83 - 5.94 (m, 1H, H₂), 5.07 - 5.13 (m, 2H, H₁), 3.95 (dd, J = 3.3, 7.6, 7.9 Hz, 1H, H₄), 3.67 (d, J = 7.9 Hz, 1H, H₅), 3.44 (s, 2H, H₇), 2.38 - 2.42 (m, 1H, H₃), 2.24 - 2.32 (m, 1H, 1H₃), 1.80 - 2.10 (br s, 1H, OH, exchangeable), 1.38, 1.37 (s, 6H, (RO)₂C(CH₃)₂), 0.94, 0.90 (s, 6H, gem CH₃'s).

¹³C NMR (50.4 MHz) δ: 134.5 (C₂), 117 (C₁), 108.2 ((RO)₂C(CH₃)₂), 86.1 (C₅), 76.6 (C₄), 71.6 (C₇), 39.2 (C₃), 36.5 (C₆), 27.1, 27.0 ((RO)₂C(CH₃)₂), 21.9, 18.9 (gem CH₃'s). MS (Cl ether) m/z: 215 (M⁺+1, 77%), 199 (M⁺-15, 31%). HRMS calcd. for C₁₁H₁₉O₃ (M⁺-CH₃): 199.1335; found: 199.1307.
(4R,5R)-7-Acetoxy-4,5-O-isopropyldene-6,6-dimethyl-1-heptene (148):

This material was prepared in the same manner as previously described for the conversions of 135 to 138 except that the material was purified by preparative TLC (2:8 ether/hexane). Thus, 45.2 mg (0.21 mmol) of the alcohol 147 yielded 46.0 mg (85%) of the acetate 148 as a colourless oil. $^1$H NMR (300 MHz) $\delta$: 5.88 - 5.99 (m, 1H, H$_2$), 5.04 - 5.13 (m, 2H, H$_1$), 3.94 (ddd, J = 3.6, 7.5, 7.7 Hz, 1H, H$_4$), 3.93 (d, A of AB, J = 10.9 Hz, 1H, H$_7$), 3.86 (d, B of AB, J = 10.9 Hz, 1H, H$_7$), 3.62 (d, J = 7.7 Hz, 1H, H$_5$), 2.15 - 2.45 (m, 2H, H$_3$), 2.05 (s, 3H, CH$_3$CO$_2$R), 1.34 (s, 6H, (RO)$_2$C(CH$_3$)$_2$), 0.95, 0.91 (s, 6H, gem CH$_3$'s). MS (Cl ether) m/z: 257 (M$^+$+1, 52%), 241 (M$^+$-15, 9%), 199 ((M$^+$+1)-58, 100%).

(4R,5S,6R,7R)-6,8-Dibenzyloxy 4,5,7-trihydroxy-1-octene (150):

To a stirred solution of (+)-3,5-di-O-benzyl-α-D-xylofuranose 157 (111 mg, 0.337 mmol) in dichloromethane (15 mL) at -78°C was added 138 μL (1.18 mmol) of SnCl$_4$. After stirring 10 minutes, allyltrimethylsilane (188 μL, 1.0 mmol) was added. The reaction was stirred a further 20 minutes whereupon it was quenched by addition of 5 mL of saturated aqueous Na$_2$HCO$_3$ and allowed to warm to room temperature. The reaction was then diluted with ethyl acetate (70 mL) and extracted with saturated aqueous NaHCO$_3$ (30 mL) and brine (30 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residual white solid was purified by preparative TLC (0.5/9.5
methanol/chloroform) to yield 98.1 mg (78%) of allyl triol 158 as a white powder. In another experiment, TiCl₄ was used instead of SnCl₄. The procedure was identical except that the reaction time was 5 minutes (versus 20 minutes) and the yield of 158 was 55%. [α]D = +0.8° (c = 1.0, CHCl₃). IR (thin film) ν: 3408, 2926, 1641, 1498, 1452, 1209, 1095, 1029 cm⁻¹. ¹H NMR (300 MHz) δ: 7.25 - 7.38 (m, 10H, aromatics), 5.71 - 5.86 (m, 1H, H₂), 5.06 - 5.14 (m, 2H, H₁), 4.61 (d, A of AB, J = 11.3 Hz, 1H, CH₂Ph), 4.57 (d, B of AB, J = 11.3 Hz, 1H, CH₂Ph), 4.54 (d, A of AB, J = 11.9 Hz, 1H, CH₂Ph), 4.49 (d, B of AB, J = 11.9 Hz, 1H, CH₂Ph), 4.05 - 4.11 (m, 1H, H₅), 3.86 (dd, J = 1.5, 5.4, 6.7 Hz, H₇), 3.60 - 3.65 (m, 2H, H₄, H₆), 3.58 (dd, A of ABX, J = 6.7, 9.5 Hz, 1H, H₈), 3.49 (dd, B of ABX, J = 5.4, 9.5, 1H, H₈), 2.43 - 2.94 (br s, 3H, OH, exchangeable), 2.20 - 2.78 (m, 2H, H₃). ¹³C NMR (50.4 MHz) δ: 137.7, 137.6 (aromatic), 134.9 (C₂), 128.7, 128.6, 128.4, 128.3, 126.0 (aromatic), 117.7 (C₁), 78.9 (C₆), 74.1, 73.4 (2 X CH₂Ph), 71.1 (C₇), 70.8, 69.1, 69.0 (C₄, C₅, C₇), 38.1 (C₃). MS (Cl ether) m/z: 373 (M⁺+1, 100%), 355 ((M⁺) -18, 16%). Anal calcd. for C₂₂H₂₆O₅: C, 70.94, H, 7.58; found: C, 70.81, H, 7.61.

(4R,5S,6R,7R)-6,8-Dibenzyl oxy-4,5-O-isopropylidene-7-hydroxy-1-octene (151):

The allyl triol 150 (346 mg, 0.929 mmol) was dissolved in acetone (20 mL) containing a catalytic quantity of TsOH (15 mg). It was stirred overnight at room temperature whereupon it was neutralized by the addition of triethylamine and the solvent removed under reduced pressure. The residue was diluted in ether (50 mL) and extracted with 0.2N HCl, saturated aqueous NaHCO₃, and brine (30
mL of each). The ethereal layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative TLC to afford 340 mg (89%) of the acetonide 151 as a colourless oil. IR (thin film) ν: 3472, 2993, 2936, 2862, 1500, 1382, 1362, 1255, 1219, 1029 cm⁻¹. ¹H NMR (300 MHz) δ: 7.25 - 7.38 (m, 10H, aromatic), 5.70 - 5.81 (m, 1H, H₂), 5.04 - 5.12 (m, 2H, H₁), 4.68 (d, A of AB, J = 11.4 Hz, 1H, CH₂Ph), 4.62 (d, B of AB, J = 11.4 Hz, 1H, CH₂Ph), 4.50 (s, 2H, CH₂Ph), 4.00 - 4.06 (m, 1H, H₇), 3.91 - 3.99 (m, 1H, H₄), 3.85 (dd, J = 4.0, 8.2 Hz, 1H, H₅), 3.60 (dd, J = 3.2, 4.0 Hz, 1H, H₆), 3.54 (dd, A of ABX, J = 5.8, 9.5 Hz, 1H, H₇), 3.50 (dd, B of ABX, J = 6.1, 9.5 Hz, 1H, H₈), 2.20 - 2.37 (m, 2H, H₉), 1.38 (s, 3H, (RO)₂C(CH₃)₂), 1.36 (s, 3H, (RO)₂C(CH₃)₃), 1.63 - 1.80 (s, OH, 1H, exchangeable). ¹³C NMR (50.4 MHz) δ: 138.0, 137.9 (aromatic), 134.0 (C₂), 128.5, 128.4, 128.1, 128.0, 127.9 (aromatic), 117.6 (C₁), 108.7 ((RO)₂C(CH₃)₂), 80.9 (C₆), 76.7, 76.1 (C₄, C₅), 74.3, 73.4 (2 × CH₂Ph), 70.9 (C₈), 70.6 (C₇), 36.9 (C₃), 27.1 ((RO)₂C(CH₃)₂), 26.7 ((RO)₂C(CH₃)₃). MS (CI ether) m/z: 413 (M⁺+1, 100%), 381 (M⁺-31, 11%). Anal. calcd. for C₂₅H₃₂O₅: C, 72.79, H, 7.82; found: C, 72.48, H, 7.58.

(4R,5R,6R,7R)-7-Acetoxy-6,8-dibenzyloxy-4,5-O-isopropylidene-1-octene (152):

This material was prepared in the same manner as previously described for the conversion of 135 to 138 except that this material was purified by preparative TLC (1:9 ethyl acetate/hexane). Thus, 55.1 mg (0.113 mmol) of the alcohol 151 yielded, after purification, 54.5 mg (90%) of the acetate 152 as a colourless oil. IR (thin film) ν: 2937, 2860, 1745, 1456, 1372, 1240, 1075 cm⁻¹. ¹H NMR (300
MHz) δ: 7.23 - 7.35 (m, 10H, aromatic), 5.57 - 5.58 (m, 1H, H2), 5.25 - 5.30 (m, 1H, H7), 4.98 - 5.05 (m, 2H, H1), 4.72 (d, A of AB, J = 11.7 Hz, 1H, CH2Ph), 4.58 (d, B of AB, J = 11.7 Hz, 1H, CH2Ph), 4.55 (d, A of AB, J = 12.0 Hz, 1H, CH2Ph), 4.43 (d, B of AB, J = 12.0 Hz, 1H, CH2Ph), 3.88 - 3.94 (m, 1H, H4), 3.63 - 3.75 (m, 4H, H5, H6, H8), 2.04 - 2.20 (m, 2H, H3), 2.02 (s, 3H, CH3CO2R), 1.34 (s, 3H, (RO)2C(CH3)2), 1.29 (s, 3H, (RO)2C(CH3)2). MS (Cl ether) m/z: 455 (M+1, 100%), 397 (M+-57, 83%).
APPENDIX A

Claims to Original Research

1. The strategy involving the modification of substrates in a controlled manner based upon the enzymatic binding site (substrate modification approach) was used to improve the enantioselectivity of α-chymotrypsin-mediated hydrolyses of protected 3-hydroxyglutarate substrates.

2. The expedient synthesis of gram quantities of (3R)-methoxymethoxypentadioic acid, monomethyl ester (51) of sufficient optical purity (ee = 95%) for chemoenzymatic synthesis was accomplished via the immobilized α-chymotrypsin-mediated hydrolysis of dimethyl 3-methoxymethoxy-glutarate 48. This trifunctionalized 5-carbon compound represents a versatile chiral building block.

3. The stereocontrolled and practical synthesis of the C(1)–C(9) segment of bryostatins in forms suitable for synthetic elaboration (110) and structure/activity studies (29) was achieved. The pivotal step utilized a diastereoselective Mukaiyama aldol condensation of a diketene derived silylenol ether [C(6)–C(9)] with an enzymatically derived β-alkoxyaldehyde [C(1)–C(5)]. Other key stereocontrol elements included a highly selective chelated β-hydroxy ketone reduction and regioselective mercury assisted lactonization.

4. The chiron strategy was used for the practical enantioselective synthesis of (3R,5R,6R)-3-benzoyl-5,6-O-isopropylidene-1,1-(propane-1',3'-dithio)-heptane (127) which represents the C(21)–C(27) synthon of bryostatins.
5. The conversion of (R)-pantolactone into the C(17)–C(20) synthon of bryostatins (115) was accomplished. Model reactions of 115 with 2-lithio-1,3-dithiane exhibited high diastereoselectivity in favour of the anti-diol in accord with non-chelation addition (anti/syn = 96:4). The unprotected lactol (R)-pantolactol (76) provided the reversed syn-diol diastereoselectivity (anti/syn = 2:98) following chelation (anti-Cram) addition. These results suggest that the coupling of 127 with 115 should proceed with high stereocontrol towards the desired diastereomer 130.

6. The potential utility of α-hydroxylated γ-lactols as chiral templates for Lewis acid mediated alkylations using silylated nucleophiles was explored. For instance, the TiCl₄-mediated addition of allyltrimethylsilane onto (R)-pantolactol (76) afforded the acyclic adduct (4R,5R)-4,5,7-trihydroxy-6,6-dimethyl-1-heptene (146) in 83% yield and as the exclusive product. The syn-configuration is consistent with 1,2-chelation control addition.
APPENDIX B

Publications from Thesis:

Papers


Conference Presentations


Syntèse Chimio - Enzymatique Du Fragment C(1)–C(9) des Bryostatins. R. Roy and A.W. Rey. Presented at the 58th Congrès de l'ACFAS, Quebec City, PQ, May 1990.
