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UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

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) synthons 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) synthons 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 skilful 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.

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List of Abbreviations

Å ---------- Angström
Ac ---------- acetyl
Ac_2O ---------- acetic anhydride
ADEPT ---------- Auto DEPT
am ---------- amide
app ---------- apparent
aq ---------- aqueous
ar ---------- aromatic
Asp ---------- aspartic
atm ---------- atmosphere
BMS ---------- borane-methyl sulfide complex
Bn ---------- benzyl
BnTCA ---------- benzyl 2,2,2-trichloroacetimidate
bp ---------- boiling point
br ---------- broad
Bz ---------- benzoyl
cap ---------- capillary
CDI ---------- (N,N)-carbonylbis(imidazole)
α-CHY ---------- α-chymotrypsin
CI ---------- chemical ionization
cm ---------- centimetre
d ---------- doublet
dd ---------- doublet of doublets

ddd---------- doublet of doublets of doublets

de----------diastereomeric excess

DCC ----------dicyclohexylcarbodiimide

DEPT ----------distortionless enhanced polarization transfer

DIBAL ----------diisobutylaluminum hydride

DIEA ----------N,N-diisopropylethylamine

DMAP ---------- 4-dimethylaminopyridine

DME ----------1,2–dimethoxyethane

DMF----------N,N-dimethylformamide

2,2-DMP ---------- 2,2-dimethoxypropane

DMPM----------3,4-dimethoxyphenylmethyl

DMSO---------- dimethylsulfoxide

dt----------doublet of triplets

ECF ---------- ethyl chloroformate

EDC:1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

ee---------- enantiomeric excess

EI ---------- electron impact

eq----------equivalent

Et ----------ethyl

Et_2O---------- diethyl ether

EtOAc----------ethyl acetate

FAB ---------- fast atom bombardment

g ----------gram(s)

GAA----------glacial acetic acid

GC---------- 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-butydimethylsilyl

TBDPS ---------- tert-butyldiphenylsilyl

TBDPS-Cl ---------- tert-butyldiphenylsilyl chloride

tBuSH ---------- tert-butylthiol

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

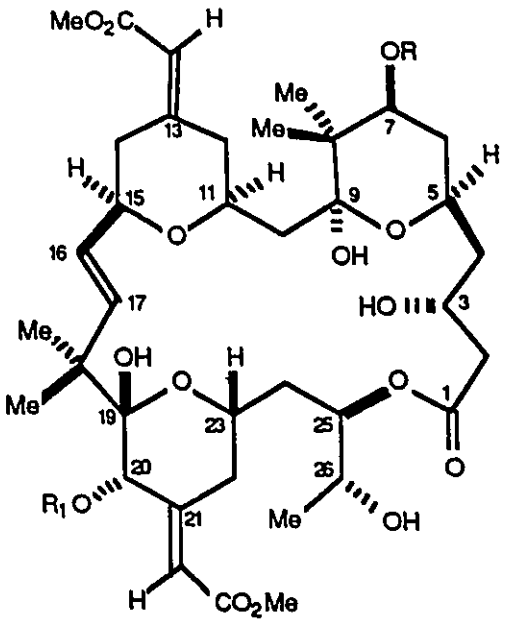
1.1 Isolation and Characterization

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[1]. 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*[2] and the cyclic peptide of the dolostatin 3 class from the shell-less mollusc *Dolabella auricularia*[3].

---

[1](a) G.R. Pettit, *Biosynthetic Products for Cancer Chemotherapy*, Vol. 1, Plenum Press, New York, 165 (1977). (b) G.R. Pettit, J.F. Day, J.L. Hartwell, and H.B. Wood, *Nature*, **227**, 962 (1970).
[2]G.R.Pettit, C.L. Herald, D.L. Doubek, D.L. Herald, E. Arnold, and J. Clardy, *J. Am.Chem. Soc.*, **104**, 6848 (1982).
[3]G.R. Pettit, Y. Kamano, P. Brown, D. Gust, M. Inoue, and C.L. Herald, *J. Am. Chem. Soc.*, **104**, 905 (1982).

Figure 1 — The Bryostatins



1 a R=$COCH_3$; R_1=(2E,4E)-octa-2,4-dienoyl (Bryostatin 1)
1 b R=$COCH_2CH(CH_3)_2$; R_1=$COCH_2CH_2CH_3$ (Bryostatin 4)
1 c R=$COCH_2CH_2CH_3$; R_1=$COCH_3$ (Bryostatin 6)
1 d R=R_1=$COCH_3$ (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[4], only 630 mg of bryostatin 1. In

[4]G.R. Pettit, Y. Kamano, R. Aoyagi, C.L. Herald, D.L. Doubek, J.M. Schmidt, and J.J. Rudloe, *Tetrahedron*, **41**, 985 (1985).

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 lymphocyctic 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-dienoate substituent. Three C(20) deoxy bryostatins have recently been

---

[5]J.M. Schmidt and G.R. Pettit, *Experientia*, **34**, 659 (1978)

[6] (a).G.R. Pettit, Y. Kamano, C.L. Herald, J.M. Schmidt, and C.G. Zubrod, *Pure Appl. Chem.*, **58**, 415 (1986). (b) C. Christophersen, *Acta Chem. Scand.*, **B39**, 517 (1985). (c) R.H. Morris, D.P. Abbott, E.C. Haderlie, *Intertidal Invertebrates of California*, Stanford University Press, Stanford, 96 (1980).

[7]G.R. Pettit,Y. Kamano, and C.L. Herald, *J. Org. Chem.*, **48**, 5354 (1983). G.R. Pettit, C.L. Herald, Y. Kamano, D. Gust, and R. Aoyagi, *J. Nat. Prod.*, **46**, 528.

[8] (a) G.R. Pettit, Y. Kamano, and C.L. Herald, *J. Org. Chem.*, **52**, 2848 (1987). (b) G.R. Pettit, J.E. Leet, C.L. Herald, Y.Kamano, F.E. Boettner, L. Baczynskyj, and R.A. Nieman, *J. Org. Chem.*, **52**, 2854 (1987). (c) G.R. Pettit, Y.Kamano, CIL. Herald, *J. Nat. Prod.*, **49**, 661 (1986). (d) G.R. Pettit, Y. Kamano, C.L. Herald, and M. Tozawa, *Can. J. Chem.*,**63**, 1204 (1984).

discovered[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[9]. Unlike phorbol esters (for instance, phorbol 12-myristate 13-acetate), bryostatins are not tumor promoters[10]. In addition, bryostatins have immunoenhancing properties on cytotoxic T lymphocytes[11] and inhibit RNA synthesis[12]. Like avermectins, bryostatins do not appear to have antibacterial properties typical of other macrolide antibiotics[13]. These promising biological activities have warranted pharmacological studies on the bryostatins. In this regard, they have currently reached Phase 2 of clinical trials.

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[9]A.S. Kraft, J.B. Smith, and R.L. Berkov, *Proc. Natl. Acad. Sci.*, USA, **83**,1334 (1986).
[10]H. Hennings, P.M. Blumberg, G.R. Pettit, C.L. Herald, R. Shores, and S. Yuspa, *Carcinogenesis* (London), **8**, 1343 (1987).
[11](a) G. Temm, G.R. Pettit, H. Takayama, J. Hu-Li, and M.V. Sitkorsky, *J. Immunol.*, **140**, 433 (1988). (b) A.D. Hess, M.K. Silanskis, A.H. Esa, G.R. Pettit, and W.S. May, *J. Immunol.*, **141**, 3263 (1988).
[12]A.S. Kraft, F.William, G.R. Pettit, and M.B. Lilly, *Canc. Res.*, **49**, 1287 (1989).
[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[14] who is near completion. Evans[15] is also engaged in the total synthesis. Partial syntheses have been accomplished by Thomas[16] who has synthesized the C(10)–C(16) fragment and Lavallée[17] and Garner[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.

---

[14](a) A.J. Duplantier, M.H. Natz, J.C. Roberts, R.P. Short, P. Somfai, and S. Masamune, *Tetrahedron Lett.*, **30**, 7357 (1989). (b) M.A. Blanchette, M.S. Natz, J.C. Roberts, P. Somfai, D.C. Whritenour, S. Masamune, M. Kageyama, and T. Tamura, *J. Org, Chem.*, **54**, 2817 (1989). (c) S. Masamune, *Pure Appl. Chem.*, **60**, 1587 (1988).

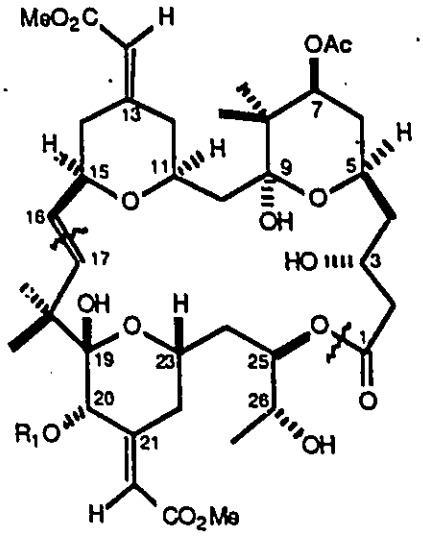
[15]D.A. Evans, E.M. Carreira, A.B. Charette, and J.A. Cauchet, Presented at the 196th National Meetings of the American Chemical Society, Los Angeles, CA, Sept. 25-30, 1988, ORGN 209.

[16]S.P. Munt and E.J. Thomas, *J. Chem. Soc.,Chem. Commun.*, 480 (1989).

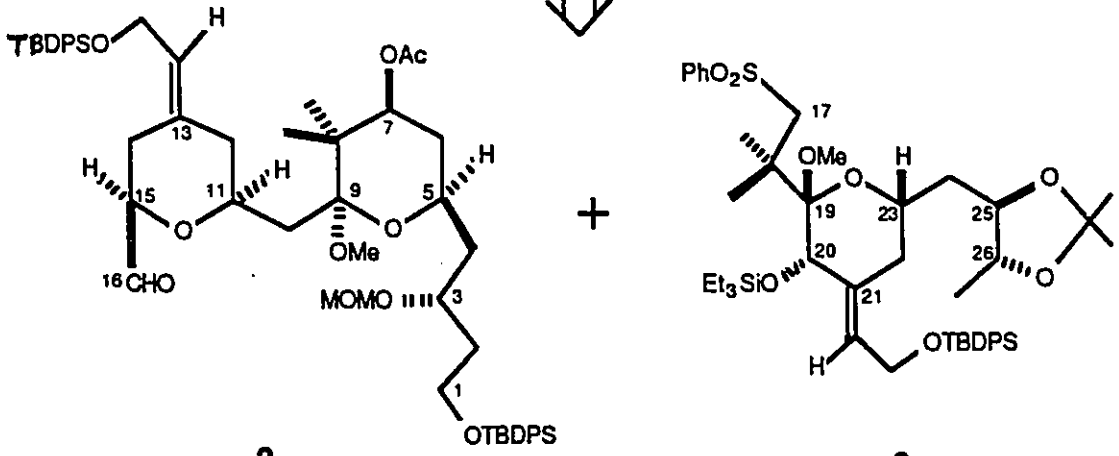
[17]P. Lavallée, R. Ruel, L. Grenier, and M. Bissonnette, *Tetrahedron Lett.*, **27**, 679 (1986).

[18](a) P. Garner and S. Ramakanth, *J. Org. Chem.*, **52**, 2629 (1987). (b) P. Garner and S. Ramakanth, Presented at the 18th Central Regional Meetings of the American Chemical Society, Bowling Green, OH, June 1-5, ORGN 317.

Figure 2 — Masamune's Retrosynthetic Analysis for 1



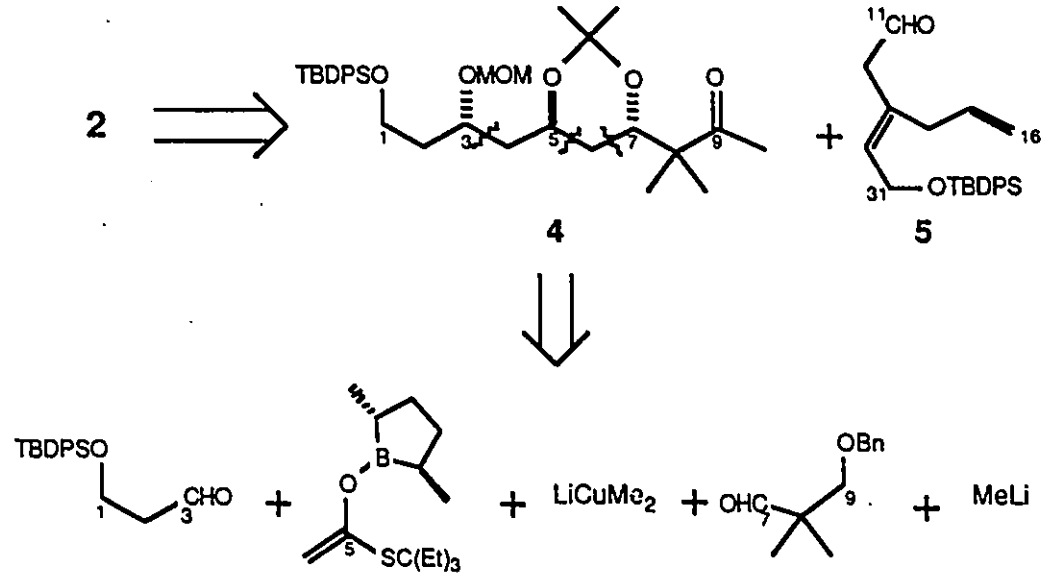
1 a R = (2E,4E)-octa-2,4-dienoyl (Bryostatin 1)



2 **3**

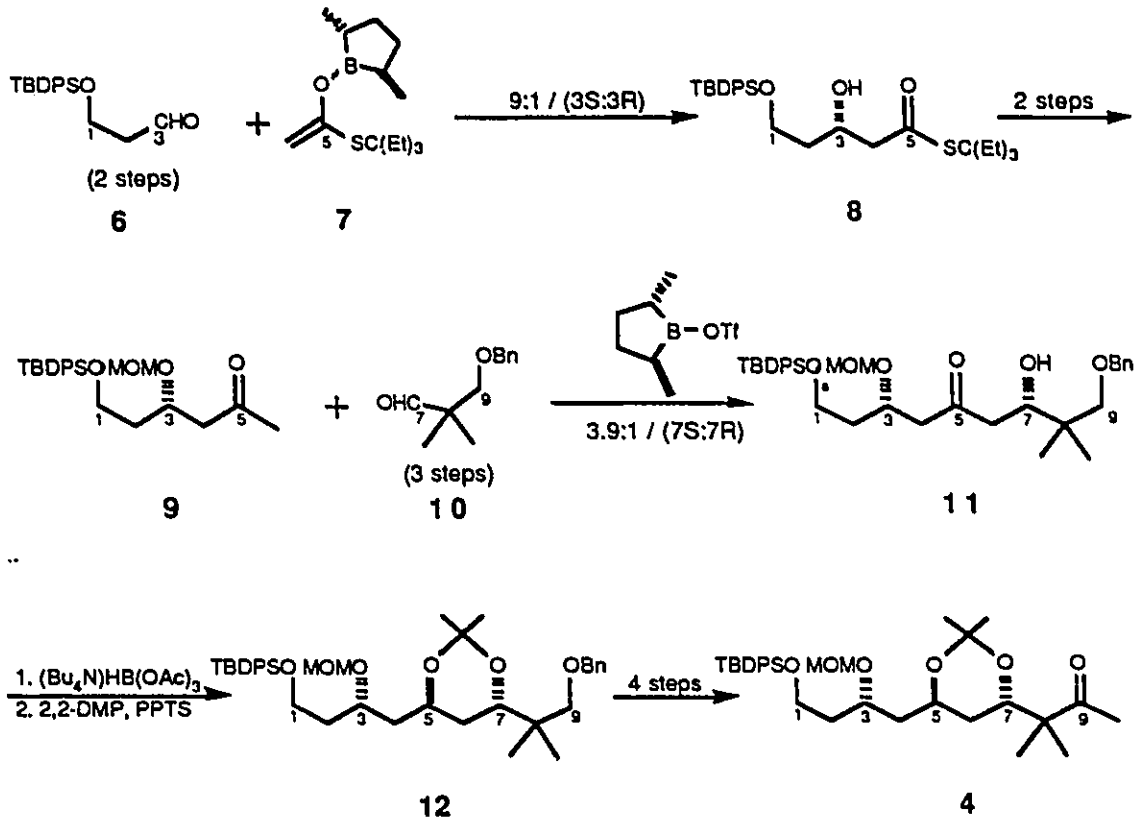
Dissection of **2** at the C(10)-C(11) bond revealed fragments **4** and **5** corresponding to the C(1)–C(10) and C(11)–C(16) segments of bryostatin 1 (Figure 3). The C(1)–C(10) intermediate **4** was further divided into 5 subunits.

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[19] reagent tetrabutylammonium triacetoxyborohydride (**11** to **12**) to relay the stereochemistry at C(7) to C(5).

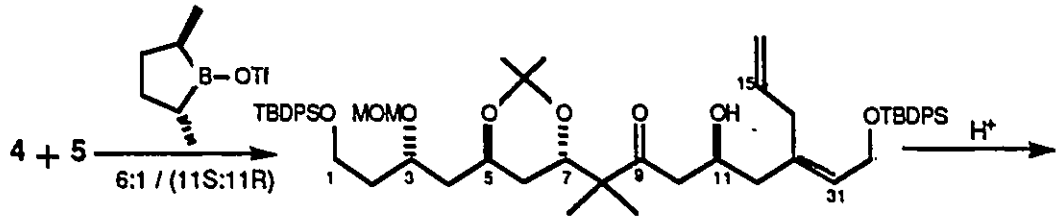


The 7-step synthesis of the achiral fragment **5** [C(10)–C(16)] was straightforward. The coupling of **4** and **5** was achieved with good stereocontrol (6:1) at C(11) again via a chiral-borolane mediated aldol reaction. The steps involved in the elaboration of **13** into the key intermediate **2**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

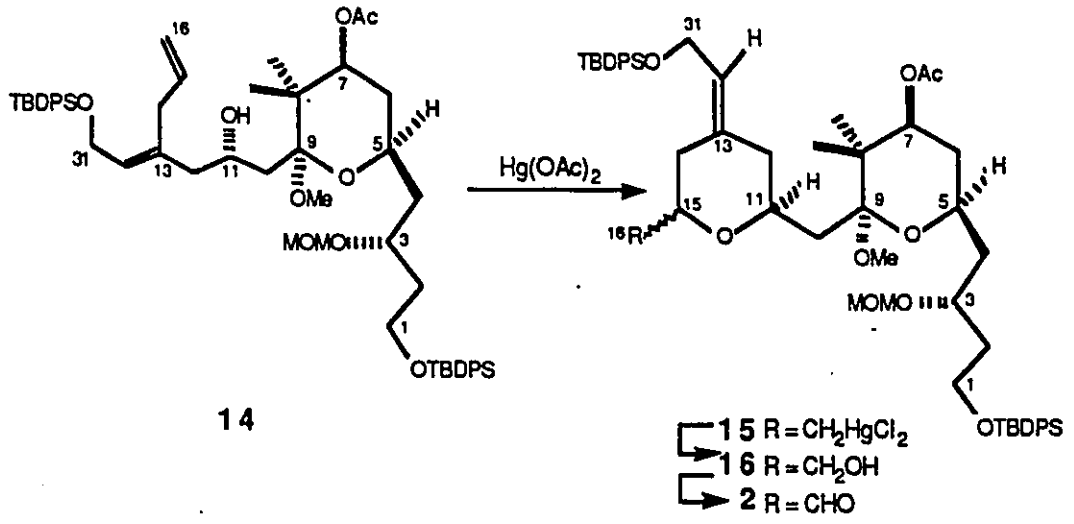
---

[19]D.A. Evans and K.T. Chapman, *Tetrahedron Lett.*, **27**, 5939 (1986). (b) D.A. Evans, K.T. Chapman, and E.M. Carreira, *J. Am Chem. Soc.*, **110**, 3560 (1988). (c) A.K. Saskena and P. Mangiaraina, *Tetrahedron Lett.*, **24**, 273 (1983).

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_2O_3 effected equilibration to a 9:1 equatorial/axial mixture of C(16) aldehydes.



13

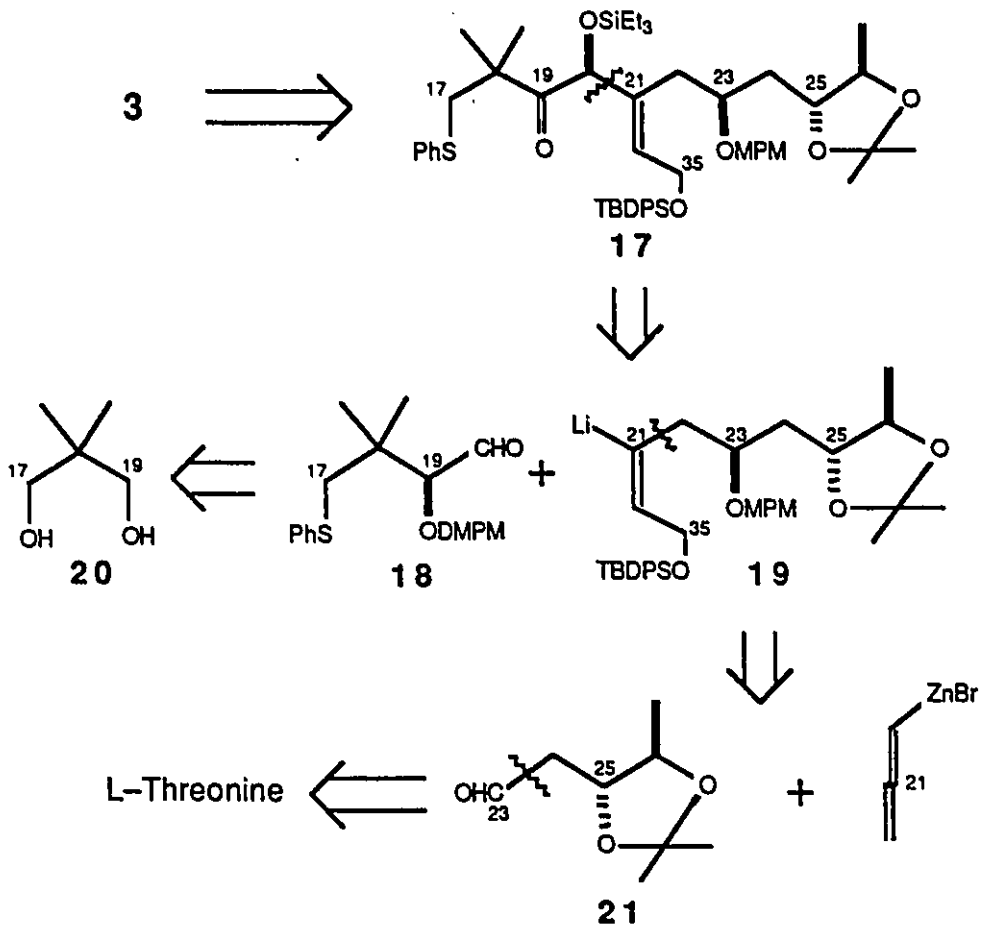


14

15 R = CH_2HgCl_2
16 R = CH_2OH
2 R = CHO

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.

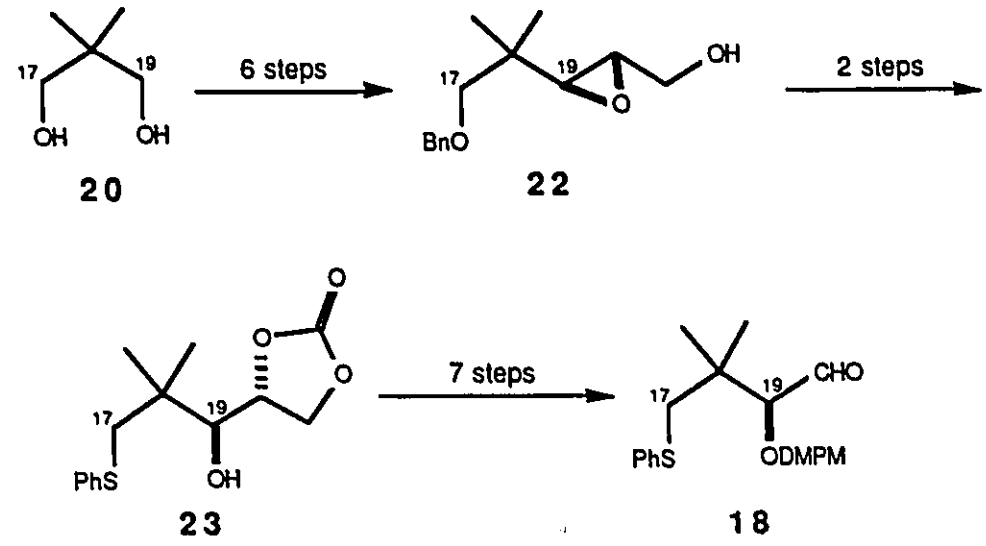
Figure 4 — Masamune's Retrosynthetic Analysis for **3**



Fragment **18** derived its chirality from a Sharpless epoxidation[20] of an allylic alcohol (**20** to **22**). Other important steps included selective epoxide ring opening[21] (**22** to **23**) and periodate cleavage (**23** to **18**). This somewhat

[20]T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham, and F.F. Walker, *J. Org. Chem.*, **47**, 1373 (1982).
[21]A. Pfenninger, *Synthesis*, **2**, 89 (1986).

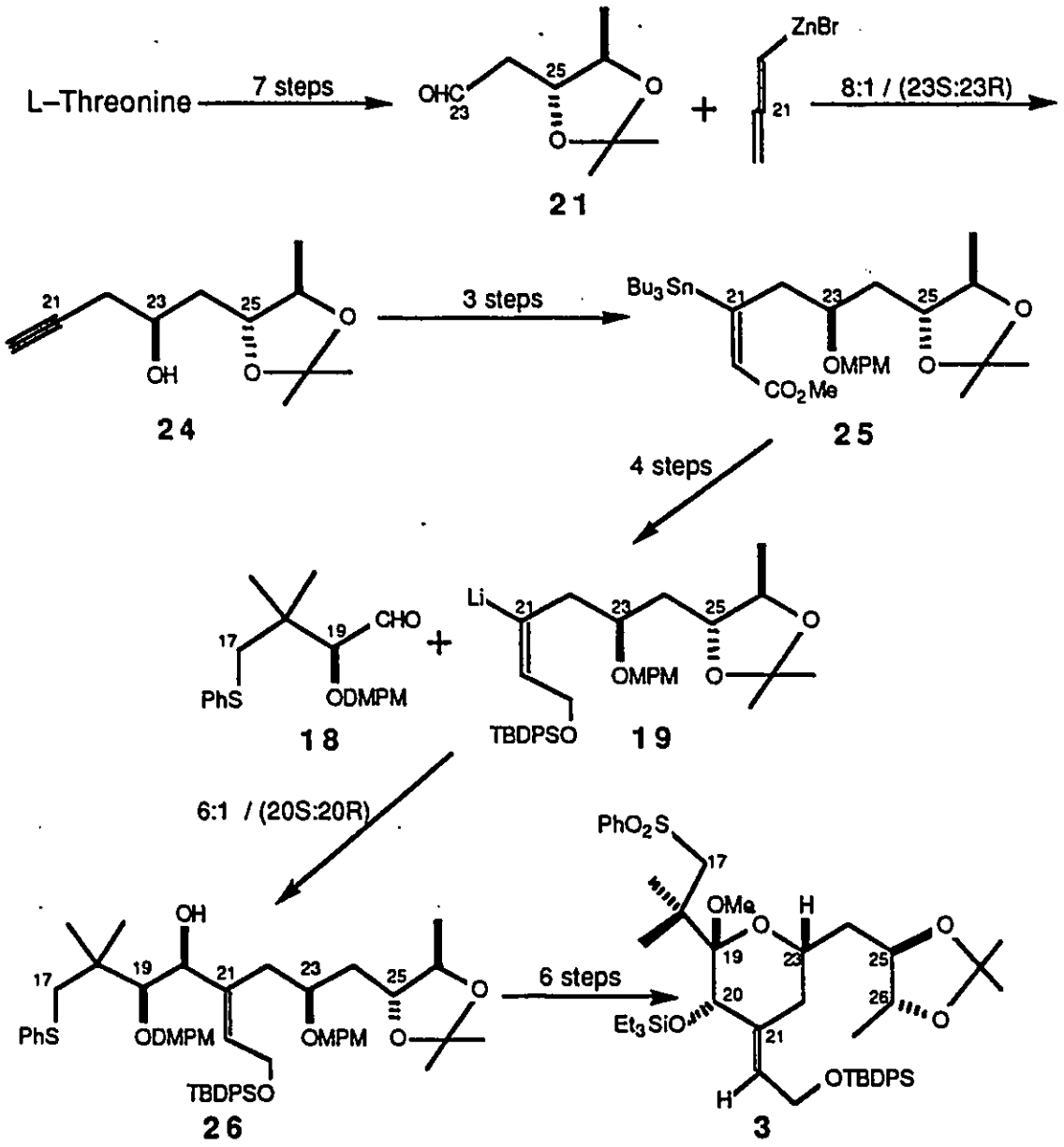
lengthy 15-step synthesis of the four carbon fragment **18** [C(17)–C(20)] is summarized below.



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[22] 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

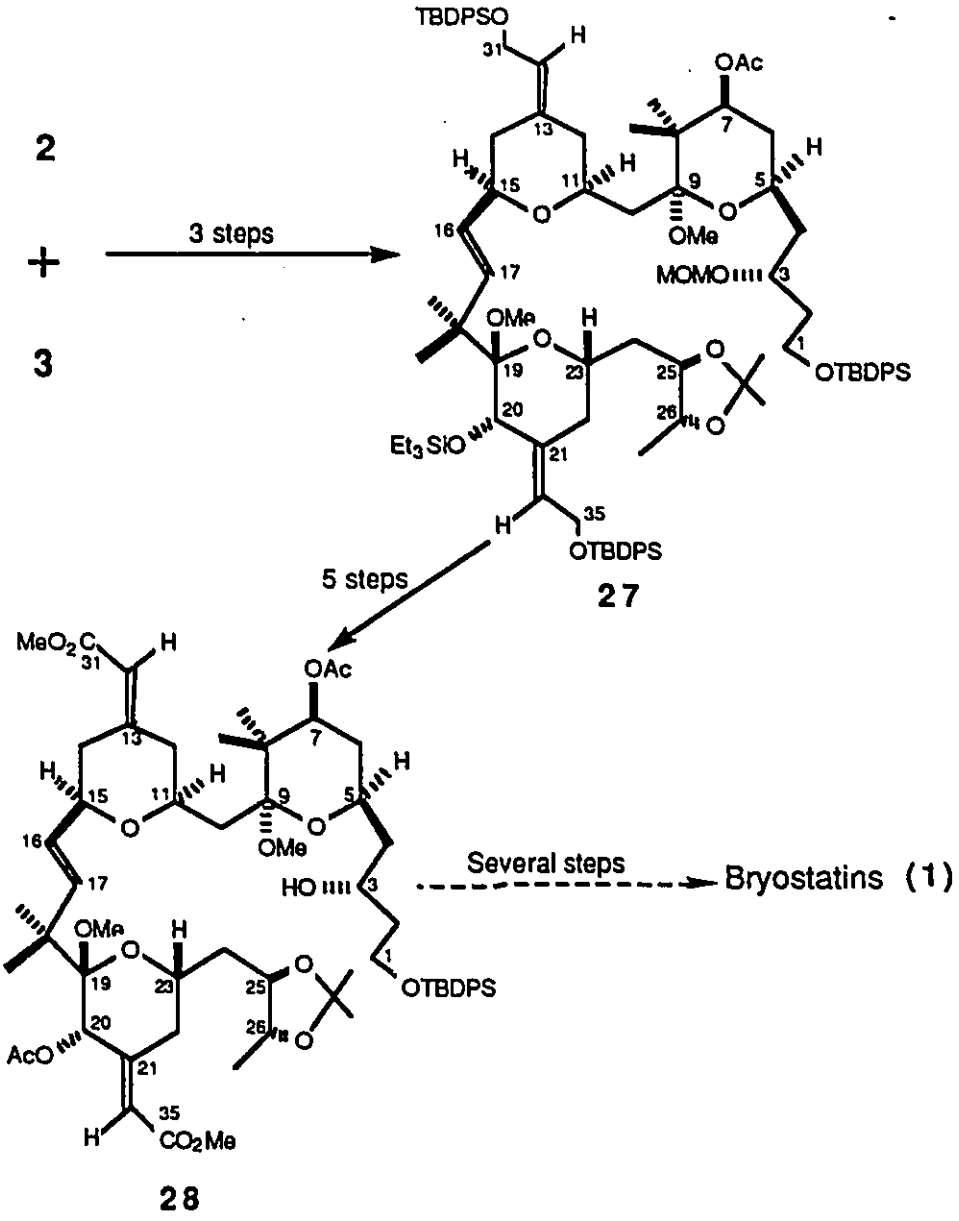
[22]E.Piers and H.E. Morton,*J. Org. Chem.*, 45, 4263 (1980).

converted to the major fragment **3** by a six step sequence of straightforward functional group interconversions.



Difficulties were encountered in the Julia-Lythgoe[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.

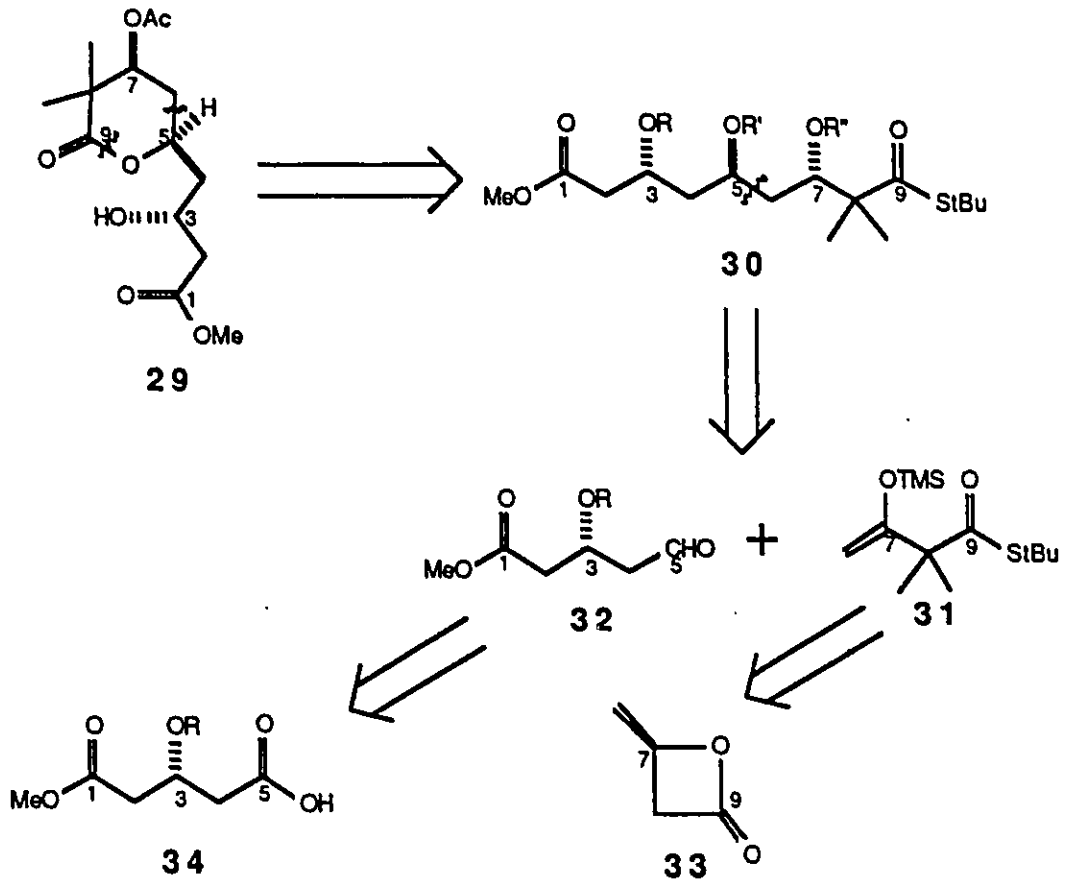
[23](a) P.J. Kocienski, B.Lythgoe, and I. Waterhouse, *J. Chem. Soc., PerkinTrans.*, **1**, 1045 (1980). (b) M. Julia and M. Paris, *Tetrahedron Lett.*, **14**, 4833 (1973).



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%).

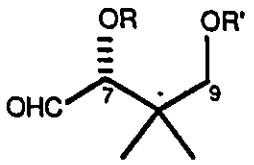
Figure 5 — Retrosynthetic Analysis for the C(1)–C(9) Subunit – Mukaiyama Condensation Approach



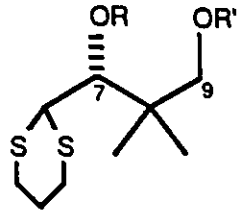
The use of **32** settles the stereochemical issue at C(3) of bryostatin. The synthetic plan was to employ this stereocentre to induce the desired configuration at C(5) upon addition of **31** via β-chelation. A Mukaiyama aldol condensation was viewed as the best method to accomplish this goal. Once 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[19]. 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**).



35

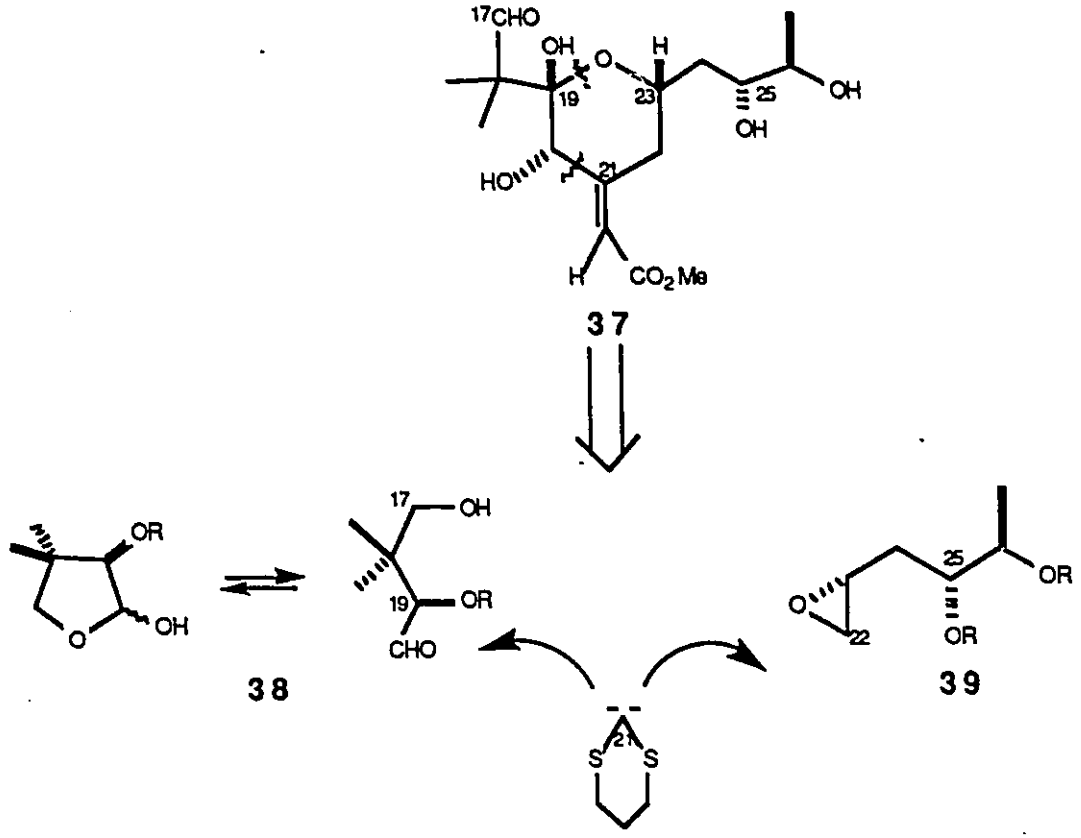


36

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.

Figure 6 — Retrosynthetic Analysis for the C(17)–C(27) Subunit – Chiron Approach



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[24]

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[25] 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[19], 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[26] 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

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[24]This work has appeared in part as "Chemoenzymatic Synthesis of a C_5-Chiral Building Block: A Substrate Modification Approach", R.Roy and A.W. Rey, *Tetrahedron Lett.*, **28**, 4935 (1987).
[25](a) S. Omura and H. Tanaka,*Macrolide Antibiotics: Chemistry, Biology and Practice*, S. Omura, ed., Academic Press, New York, 351 (1984) (b) D.W. Brooks, and J.T. Palmer, *Tetrahedron Lett.*, **24**, 3059 (1983).
[26]K.-M. Chen, G.E. Hardtman, K. Prasad, O. Repic, and M.J. Shapiro, *Tetrahedron Lett.*, **28**, 155 (1987).

reactions on β-alkoxy aldehydes[27] and the enantioselective reduction of 1,3-diketones[28].

The asymmetric synthetic opportunities provided by exploiting the chiral catalytic properties of enzymes is well-documented[29]. This area has witnessed explosive growth in the past decade. Enzymatic reactions — in both aqueous, and more recently, non-aqueous media[30] — have been added to the organic chemist's arsenal. An early example[31] was the α-chymotrypsin (α–CHY) mediated hydrolysis of dimethyl 3-hydroxyglutarate (**41**) to provide methyl hydrogen (3R)-hydroxyglutarate (**42a**).

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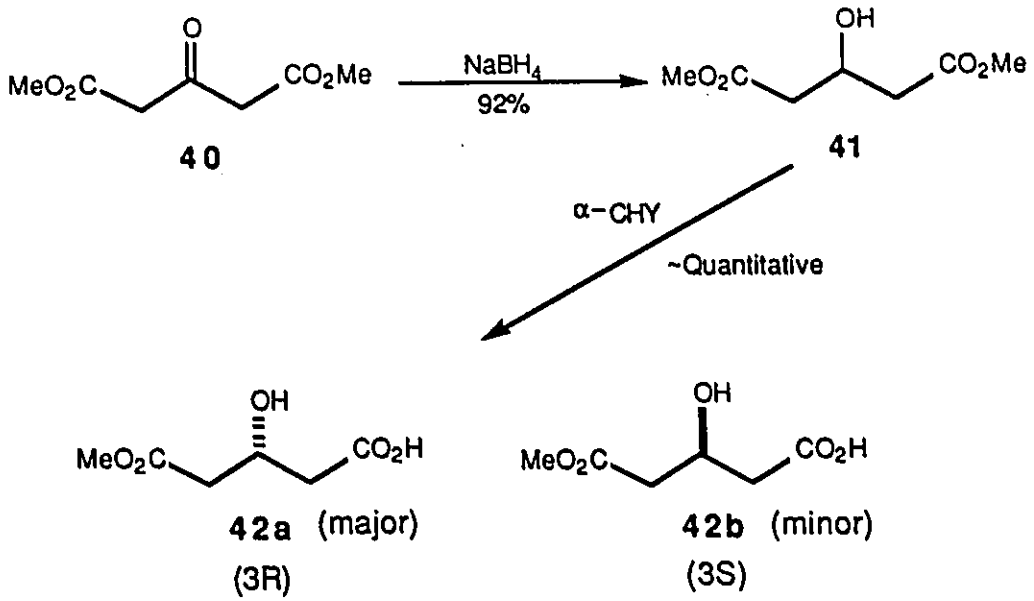
[27](a) Y. Ukaji, H. Kanda, K. Yamamoto, and T. Fujisawa, *Chem. Lett.*, 597 (1990). (b) S.D. Rychnovsky, *J. Org. Chem.*, **54**, 4982 (1989). (c) T. Nakata, T. Suenaga, and T. Oishi, *Tetrahedron Lett.*, **30**, 6525 (1989). (d) Y. Mori and M. Suzuki, *Tetrahedron Lett.*, **30**, 4383, 4387 (1989). (e) S.L. Schreiber, M.T. Goulet, and G. Schulte, *J. Am. Chem. Soc.*, **109**, 4718 (1987). (f) N.Ikeda, K. Omori, and H. Yamamoto, *Tetrahedron Lett.*, **27**, 1175 (1986). (g) S. Hanessian, S.P. Sahoo, and P.J. Murray, *Tetrahedron Lett.*, **26**, 5631 (1985). (h) T. Nakata, S. Nagao, and T. Oishi, *Tetrahedron Lett.*, **26**, 75 (1985). (i) M.T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984). (j) T. Nakata, S. Takao, M. Fukui, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, **24**, 3873 (1983). See also references cited therein.

[28]M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takayama, and R. Noyori, *J. Am. Chem. Soc.*, **110**, 629 (1988).

[29] (a) E.J. Toone, E.S. Simon, M.B. Bednarski, and G.M. Whitesides, *Tetrahedron*, **45**,5365 (1989). (b) A.J. Pratt, *Chem. in Britain*, **25**, 282 (1989). (c) J.B. Jones, *Tetrahedron*, **42**, 3351 (1986). (d) G.M. Whitesides and C.H. Wong, *Angew. Chem., Int. Ed. Engl.*, **24**, 617 (1985). (e) S. Butt and S.M. Roberts, *Nat. Prod Rep.*, 489 (1986).

[30](a) C.S. Chen and C.J. Sih, *Angew. Chem., Int. Ed. Engl.*, **28**, 1989, 695 (b) A.M. Klibanov, *Trends Biochem. Sci.*, **14**, 141 (1989). (c) J.S. Deetz and J.D. Rozzell, *Trends Biotechnol.*, **6**, 15 (1988). (d) A.M. Klibanov, *Chemtech*, ***16***, 354 (1986).

[31]S.G. Cohen and E. Khedouri, *J. Am. Chem. Soc.*, **83**, 4228 (1961).



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[25b], the lactone portion of mevinic acids[32], L-carnititine[33], and (R)-4-amino-3-hydroxybutanoic acid (GABOB)[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.

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[32](a) E. Baader, W. Bartman, G. Beck, A. Bergman, H.-W. Fehlbaber, H. Jendralla, K. Kesseler, R. Saric, H. Schüssler, V. Teets, M. Weber, and G. Wess, *Tetrahedron Lett.*, **29**, 2563 (1988). (b) L.K.-P. Lam and J.B. Jones, *Can. J. Chem.*, **66**, 1422 (1988). (c) T. Rosen and C.H. Heathcock, *Tetrahedron*, **42**, 4909 (1986).
[33]A.S. Gopanlan and C.J. Sih, *Tetrahedron Lett.*, **25**, 5235 (1984).

2.2 Background

The enzymatic reaction shown above was reported in 1961 by Cohen and Khedouri[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[34] for the same material prepared from completely resolved (+)-methyl hydrogen 3-acetoxyglutarate.

Heathcock (1984)[35], Brooks (1987)[36], Roy (1987)[24], Tamm (1987)[37], and Santaniello (1988)[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.

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[34]K. Serck-Hanssen, *Arkiv. Kemi.*, **10**, 135(1956).
[35]T. Rosen, M. Watanabe, and C. Heathcock, *J. Org. Chem.*, **49**, 3657 (1984).
[36]D.W. Brooks, R.P. Kellogg, and C.S. Cooper, *J. Org. Chem.*, **52**, 192 (1987).
[37]C. Tamm, P. Mohr, and L. Rösslein, *Helv. Chim. Acta*, **70**, 142 (1987).
[38]E. Santaniello, M. Chiarai, P. Ferraboschi, and S. Trave, *J. Org. Chem.*, **53**, 1567 (1988).

Table 1 — Summary of α-CHY-Mediated Hydrolysis of **41**

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

*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[39] have already led to striking improvements in similar situations. For instance, Jones[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[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_2HPO_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.

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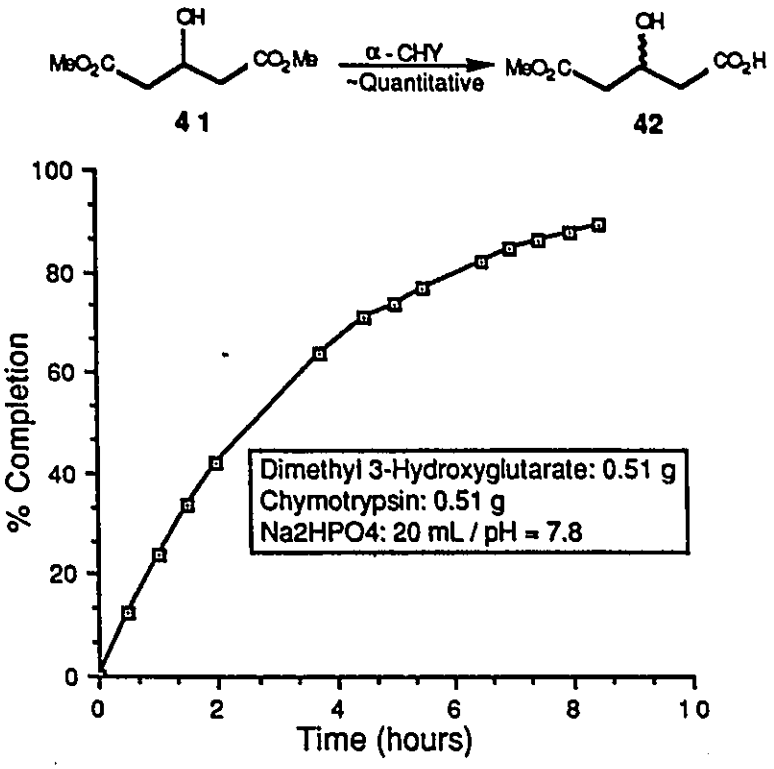
[39](a) A. Zaks and A.M. Klibanov, *J. Am. Chem. Soc.*, **108**, 2767 (1986). (b) B.-nan Zhou, A.S. Gopalan, F. Van Middlesworth, W.-R. Chieh, and C.J. Sih, *J. Am. Chem. Soc.*, **105**, 5925 (1983).
[40]L.K-P. Lam, R.A.H.F. Hui, and J.B. Jones, *J. Org. Chem.*, **51**, 2047 (1986).

Figure 7 — Rate of α-CHY-Mediated Hydrolysis of **41** – Percent Completion versus Reaction Time



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**

α-CHY: Subst (w/w)	pH	Solvent[a]	Yield[b]	ee[c]	Absolute Config.
1:2	6.7	A	100	66	R
1:5	7.0	A	92	64	R
1:2	7.0	A	86	60	R
1:1	7.0	A	95	67	R
1:5	7.8	A	83	59	R
1:2	7.8	A	99	65	R
1:1	7.8	A	61	65	R
1:2	7.8	B	100	57	R
2:1	7.0	C	67	64	R

[a]A = 0.01M Na_2HPO_4 buffer; B = A + 20% MeOH; C = PBS. Reactions performed at room temperature.

[b]Yields of isolated **42** based on recovered **41**.

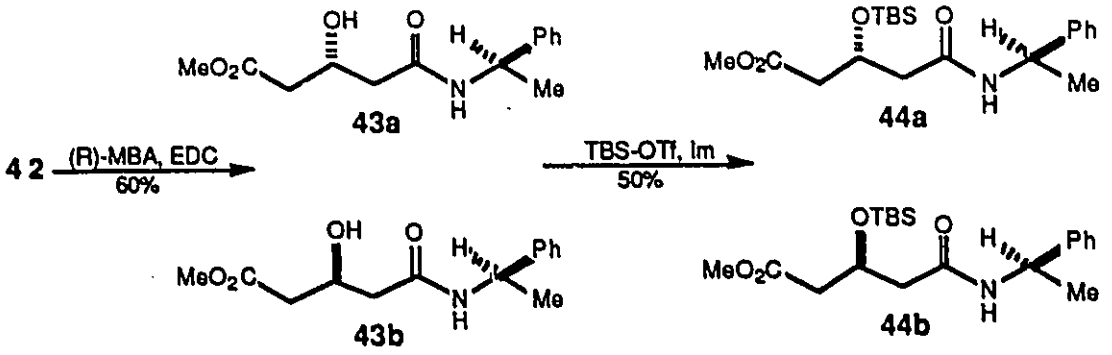
[c]Determined by GC and ^1H NMR analysis on **44**.

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 Na_2HPO_4 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, Tamm[37] 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, CH_2Cl_2) 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 ^1H 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_2CH_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° (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 ^1H 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**

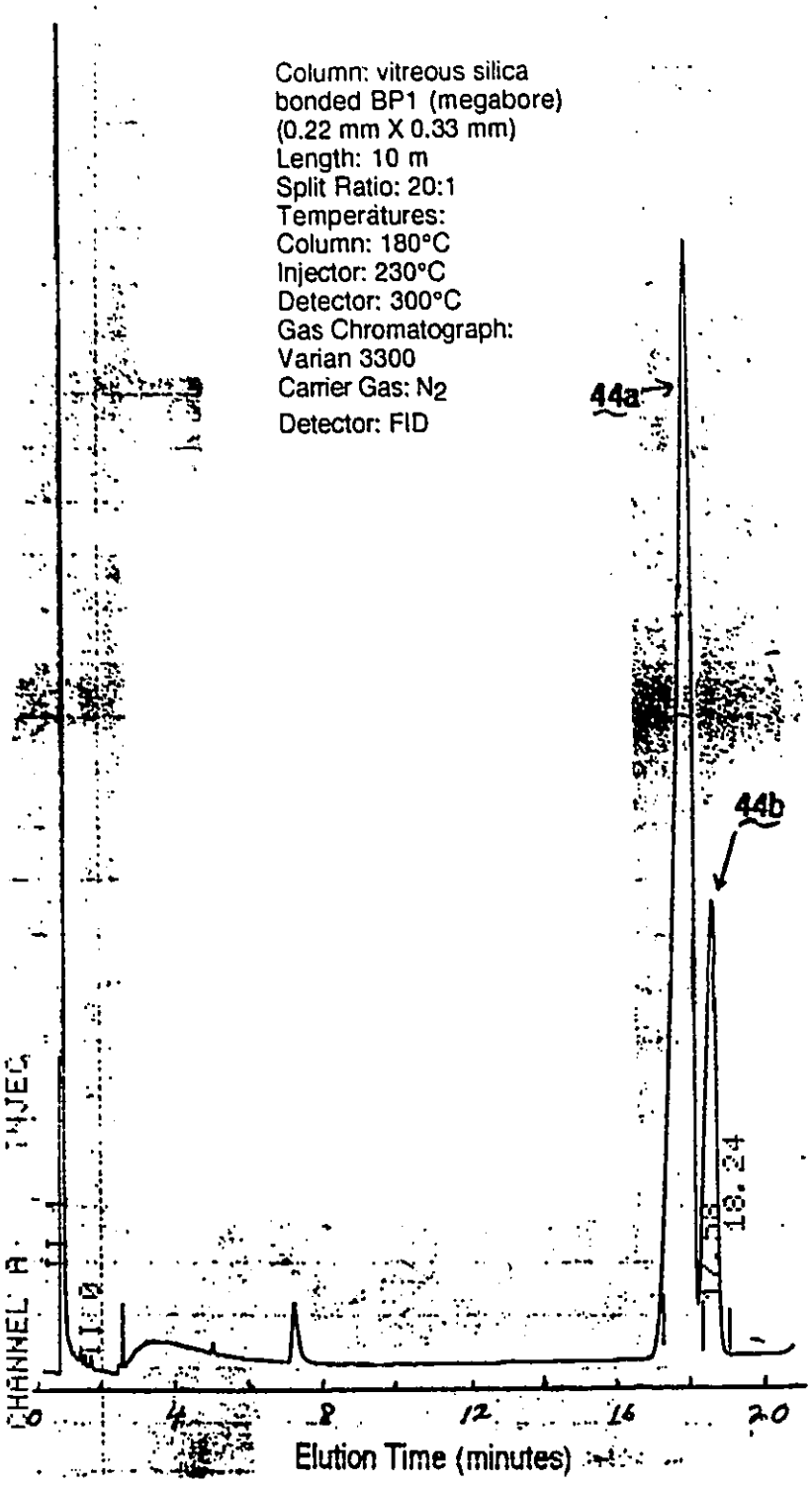
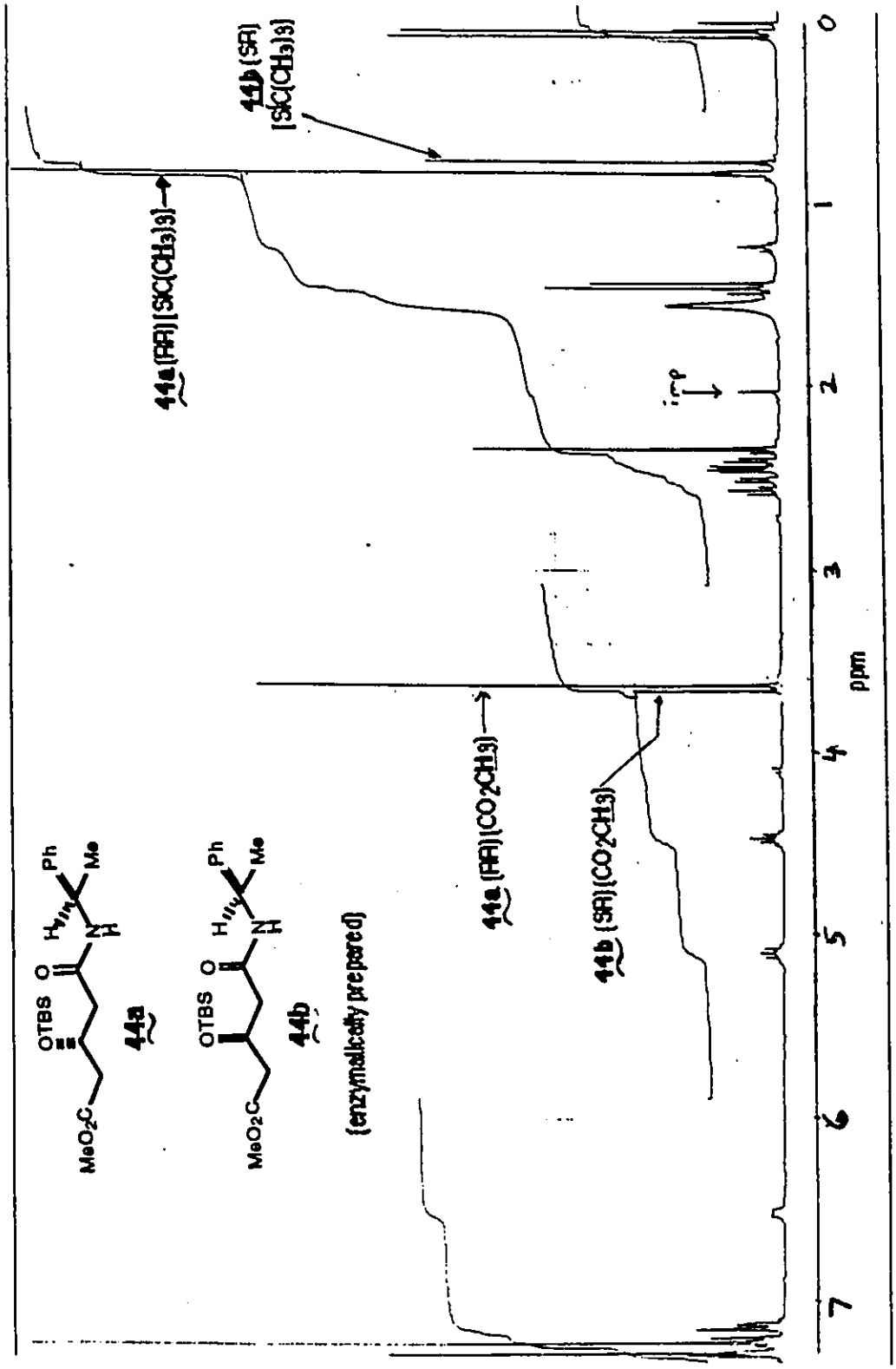


Figure 9 — ^{1}H NMR of **44a**, **44b**



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**

Group	Year	Reported ee (Absolute Config.)	Conditions		Reference
			pH	**41**:PLE Ratio[a]	
Tamm	1983	12% (S)	7.8	1.8:200	41
Jones	1986	nq[b]	7.0	1.0:400	40
Roy	1987	15% (S)	7.0	0.5:70	24
Tamm	1987	22% (S)	7.8	1.8:200	37
Santaniello	1988	30±5% (S)	7.0	0.5:130	38
Baader[c]	1988	76% (S)	7.0	nq[b]	32a
Jones	1989	16% (S)	7.0	1.0:400	42

[a]Grams of **41**:units of PLE.

[b]nq = not quoted.

[c]di-n-propyl-3-hydroxyglutarate used as substrate at 0°C.

2.6 Substrate Modification Approach

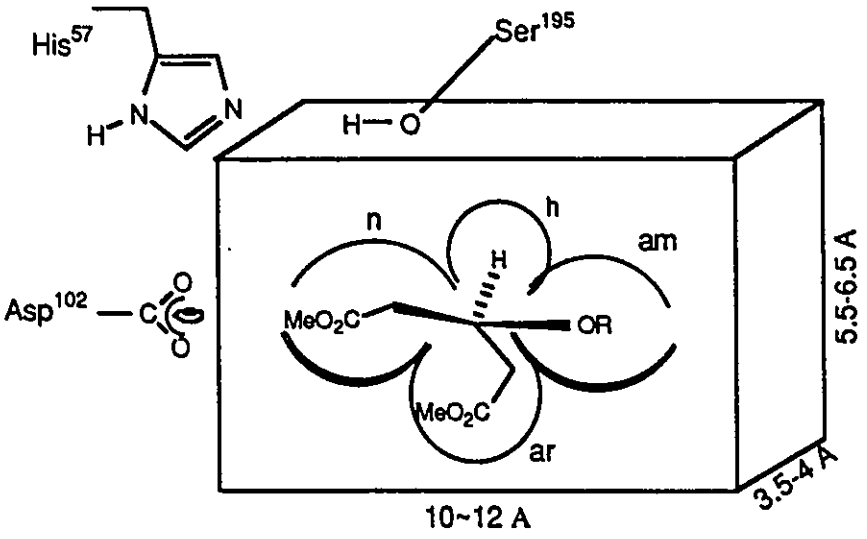
As discussed, it was hypothesized that two orientations of the substrate within the binding site of α-CHY were responsible for the lack of enantioselectivity. Therefore, the solution was realized by modification of the substrate in a logical manner in order to prevent the alternate mode of binding leading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

[41]P. Mohr, N. Waespe-Sarcevic, and C. Tamm, *Helv. Chim. Acta*, 66, 2501 (1983).
[42]L.K.-P. Lam, J.B. Jones, *Can. J. Chem.*, 66, 1422 (1988).

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[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



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

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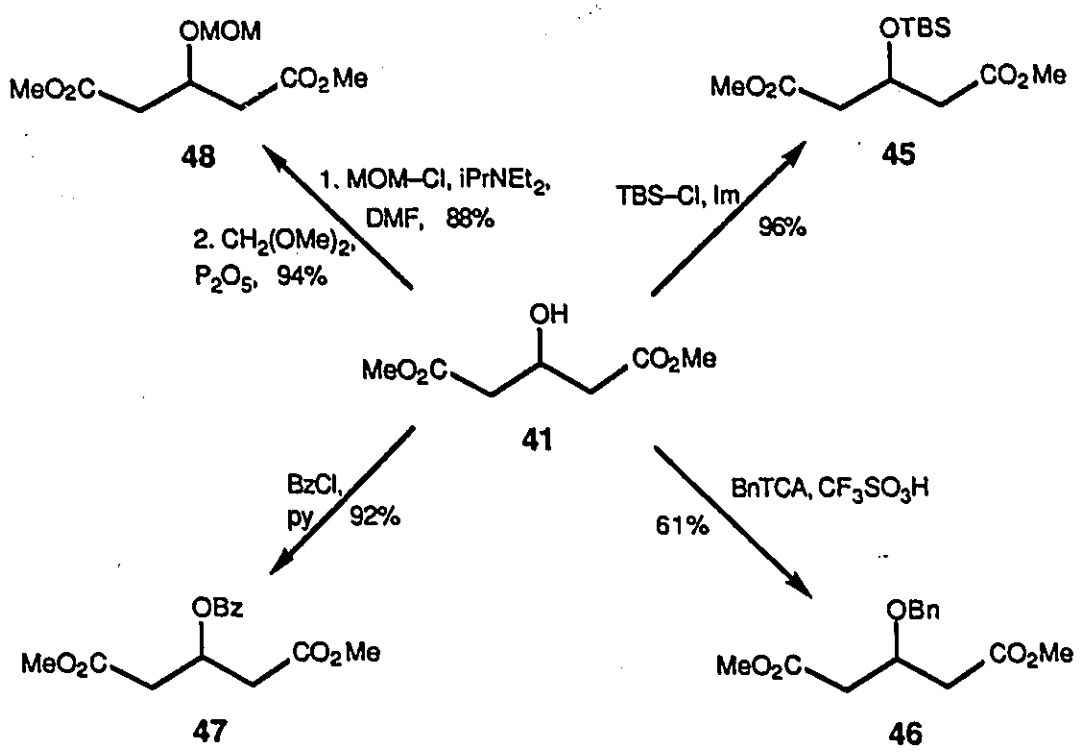
[43](a) V.T. D'Souza and M.L. Bender, *Acc. Chem. Res.*, **20**, 146 (1987). (b) D.M. Blow, *Acc. Chem. Res.*, **9**, 145 (1976). (c) S.G. Cohen, *Trans. N.Y. Acad. Sci.*, **31**, 705 (1969).

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[44] were unsuccessful. The benzyl group was incorporated by the use of the acid

[44]For instance, S. Czernecki, C. Georgoulis, and C. Provelegnhiou, *Tetrahedron Lett.*, **17**, 3535 (1976).

catalysed reaction of **41** with benzyl trichloroacetimidate in 61% yield. This methodology was developed by Bundle[45]. Treatment of **41** with chloromethyl methyl ether (MOM-Cl) under standard conditions[46] afforded the MOM ether **48** in good yield (88%). However, the less utilized procedure[47] with dimethoxymethane and P_2O_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.

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[45]T. Iversen and D.R. Bundle, *J. Chem. Soc., Chem. Commun.*, 1240 (1981)
[46]G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, **99**, 1275 (1977).
[47]K. Fugi, S. Nakano, and E. Fujita, *Synthesis*, 276 (1975).

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

Entry	CHY:Sub (w/w)	pH	Solvent[a]	Yield[b] (%)	ee[c] (%)	Absolute Config.
1	2:1(**45**)	7.8	A,B,C	~0	—	—
2	1:1 (**46**)	7.8	B	68	86	R
3	1:2 (**47**)	7.8	B[d]	42	86	R
4	1:1 (**47**)	7.8	B	86	94	R
5	1:2 (**47**)	7.8	B[e]	68	93	R
6	1:2 (**48**)	7.8	A[e]	100	90	R
7	1:2 (**48**)	7.0	A	95	95	R
8	1:1 (**48**)	7.8	A	100	95	R
9	2:1 (**48**)	7.8	A[d]	92	95	R

[a]A = 0.01M Na_2HPO_4 buffer; B = A + 20% 1,4-dioxane; C = A + 20% MeOH. Reactions performed at room temperature unless indicated otherwise.

[b]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.

[c]Determined by GC and/or ^{1}H-NMR analysis on **52**, **53**,and **54** (Chapter 2.9a).

[d]Accomplished at 36°C.

[e]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[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[38] Study: α-CHY–Mediated Hydrolyses

Substrate	α-CHY: Subst. (w/w)	pH	ee (%)	Absolute Config.
Dimethyl 3-acetoxy-glutarate	1:3	7.8	84	R
Diethyl 3-acetoxy-glutarate	1:3	7.8	95	R

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**

Substrate	PLE: Substrate Ratio[a]	pH	Solvent	Yield (%)	ee (%)	Absolute Config.
41	70:1	7.0	A	100	15	S
46	370:1	7.0	B	78	12	S
47	180:1	7.0	B	77	60	S
47	160:1	7.0	C	79	33	S
48	330:1	7.0	A	100	14	S

[a]units of PLE:mmol of substrate.

[b]A = 0.01M Na_2HPO_4 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 enantioselectivity 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[48]. The results presented in Table 6 are consistent with those obtained by Jones[42] and Santaniello[38] in subsequent studies. Their results are given in Table 7.

[48]For a recent review of PLE-mediated ester hydrolyses see: M. Ohno and M. Otsuka in *Organic Reactions*, Vol. 37, ed., A.S. Kende, John Wiley and Sons, New York, 1 (1989).

Table 7 — Results from Santaniello's[38] and Jones'[42] Studies on PLE-Mediated Hydrolyses

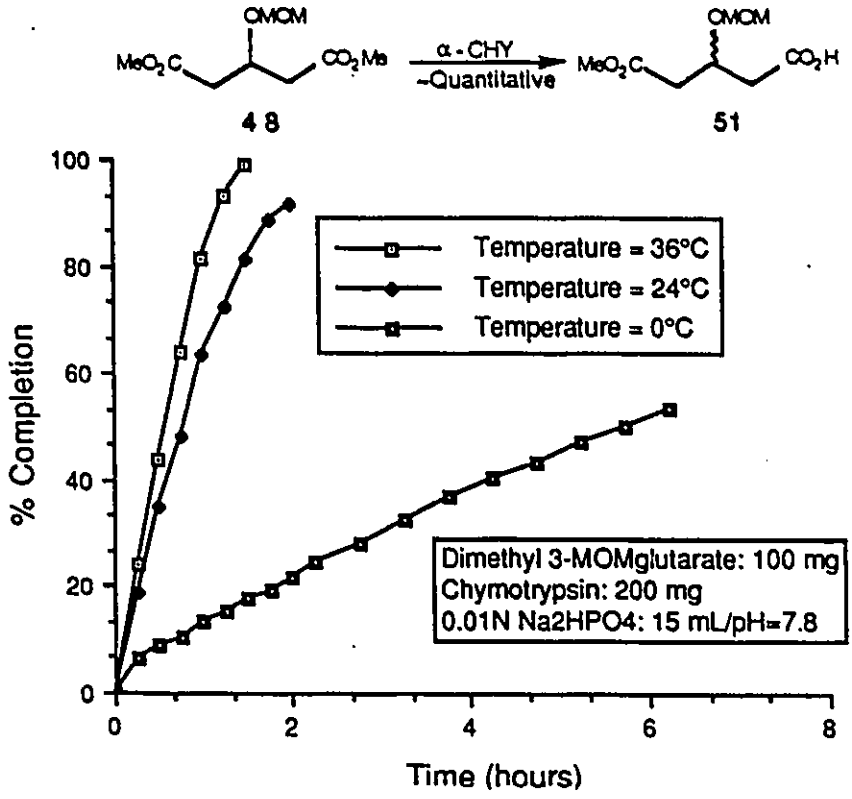
Substrate	PLE:Subst Ratio[a]	ee (%)	Absolute Conf.	Reference
Dimethyl 3-acetoxy glutarate	60:1	90	R	Santaniello[38]
Diethyl 3-acetoxy glutarate	60:1	83	R	Santaniello[38]
Dimethyl 3-methoxy-ethoxyglutarate	70:1	39	R	Jones[42]
Dimethyl 3-benzyl-oxyglutarate	70:1	40	S	Jones[42]

[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.

Figure 11 — Effect of Temperature Upon the Rate of the α-Chymotrypsin-Mediated Hydrolysis of **48**



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, Whitesides[49] formally published the methodology of enclosing enzymes in dialysis bags.

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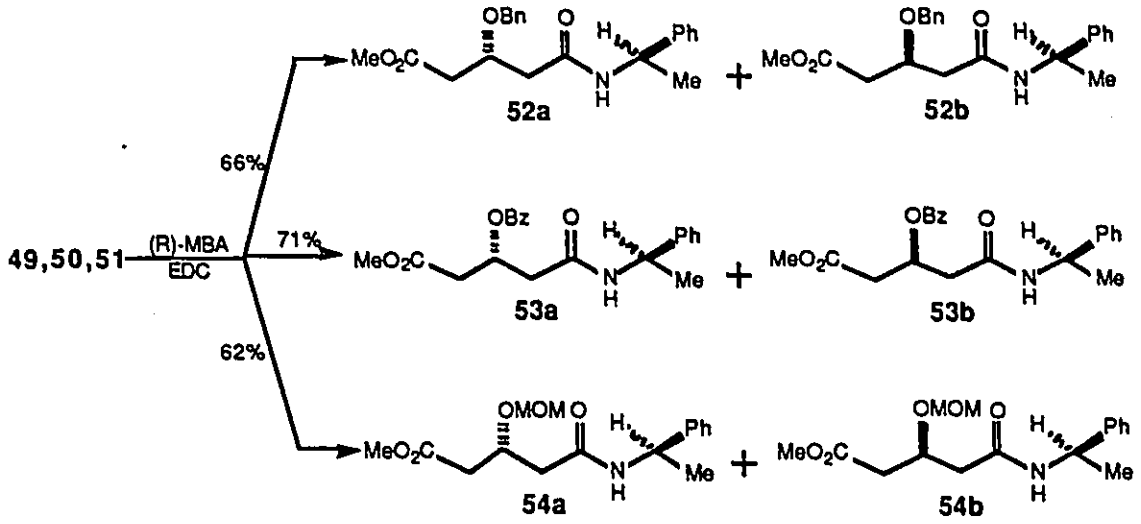
[49]M.D. Bednarski, H.K. Chenault, E.S. Simon, and G.M. Whitesides, *J. Am. Chem. Soc.*, **109**, 1283 (1987).

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**.

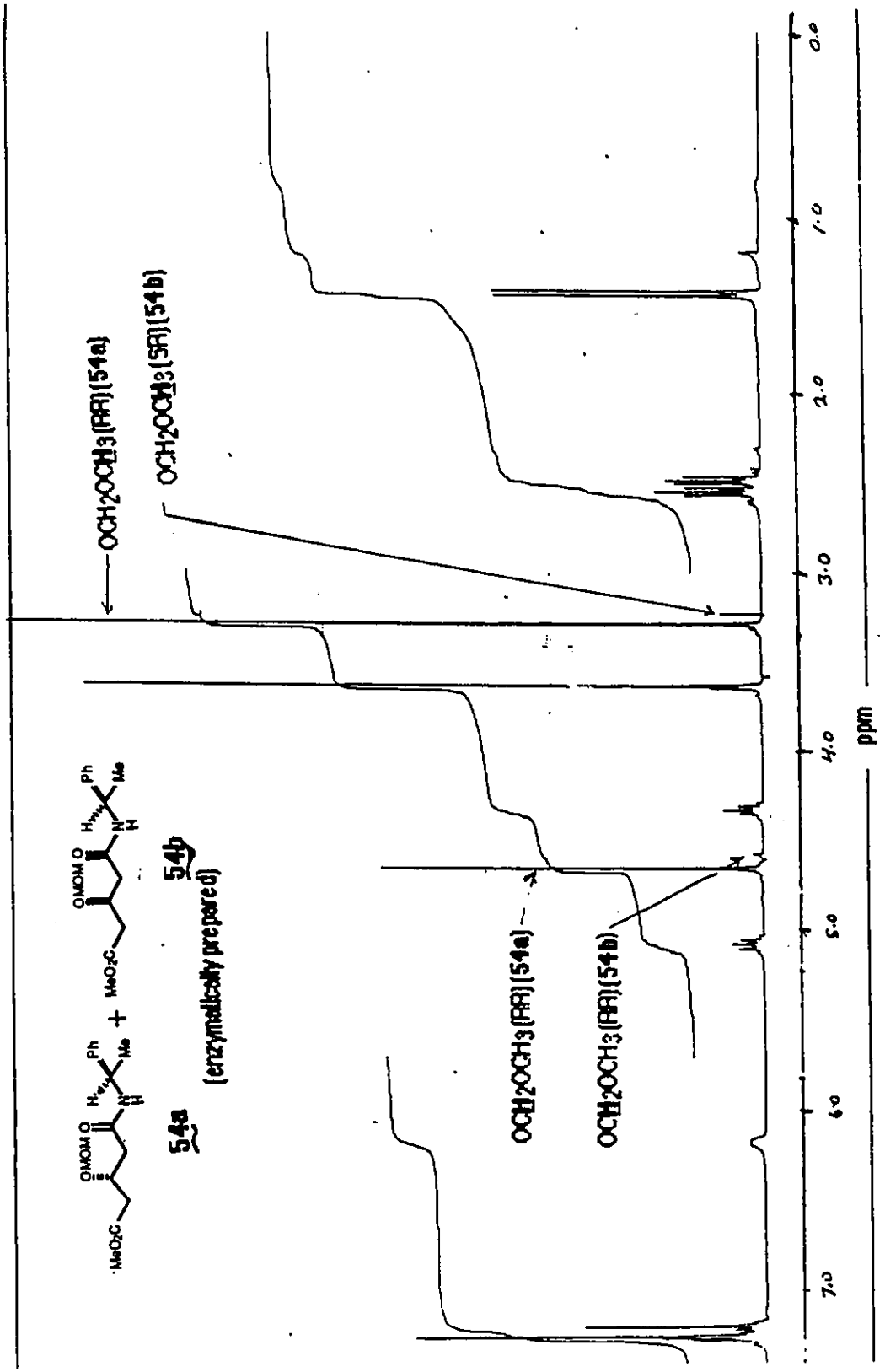


Fortunately, the ratio of amides **52**, **53**, and **54** could be conveniently determined by examination of the ^{1}H NMR spectrum (for an example see Figure 12; ^{1}H NMR of **54**) of the diastereomeric mixtures and/or capillary GC. These methods are summarized in Table 8. Exact GC conditions are given in the Experimental section (2.13).

Table 8 — Enantiomeric Excess Determinations for **52**, **53**, and **54**

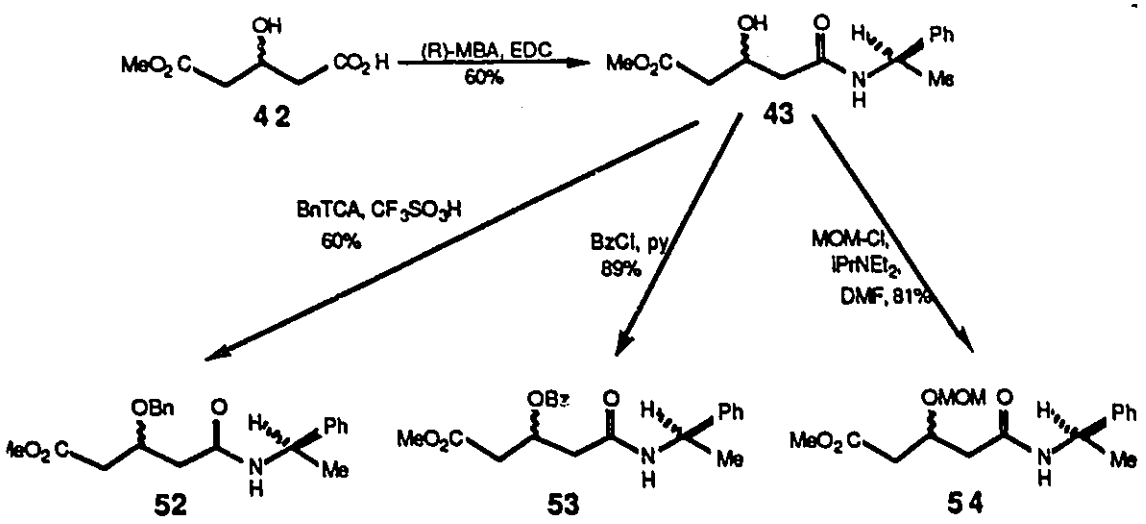
Diastereomeric Amides	Technique	Elution Time (minutes)	Chemical Shift (ppm)
52a	Cap. GC	23.0	—
52b		24.1	
52a	^{1}H NMR	—	3.65 (CO_2CH_3)
52b	(300 MHz)		3.67 (CO_2CH_3)
53a	Cap. GC	25.1	—
53b		25.9	
54a	^{1}H NMR	—	3.31
54b	(300 MHz)		(OCH_2OCH_3)
			3.26
			(OCH_2OCH_3)

Figure 12 — ^{1}H NMR Spectrum of **54**



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-hydroxyl 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[50]. Also, the optical purity of the (R)-MTPA used in this study had been established by measurement of its optical rotation.

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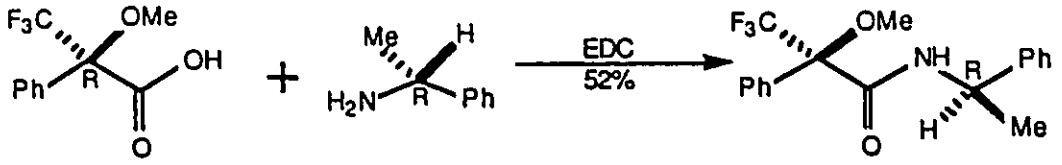
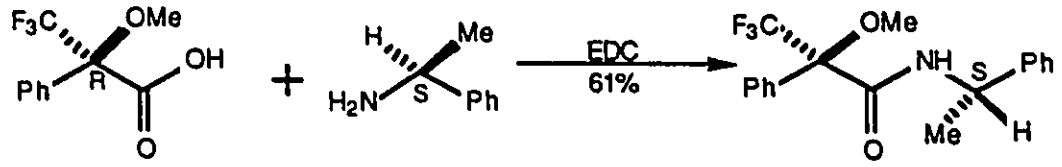
[50](a) J.A. Dale and H.S. Mosher, *J. Am. Chem. Soc.*, 95, 512 (1973).(b) G.R. Sullivan, J.A. Dale, and H.S. Mosher, *J. Org. Chem.*, 38, 2143 (1973).



55a



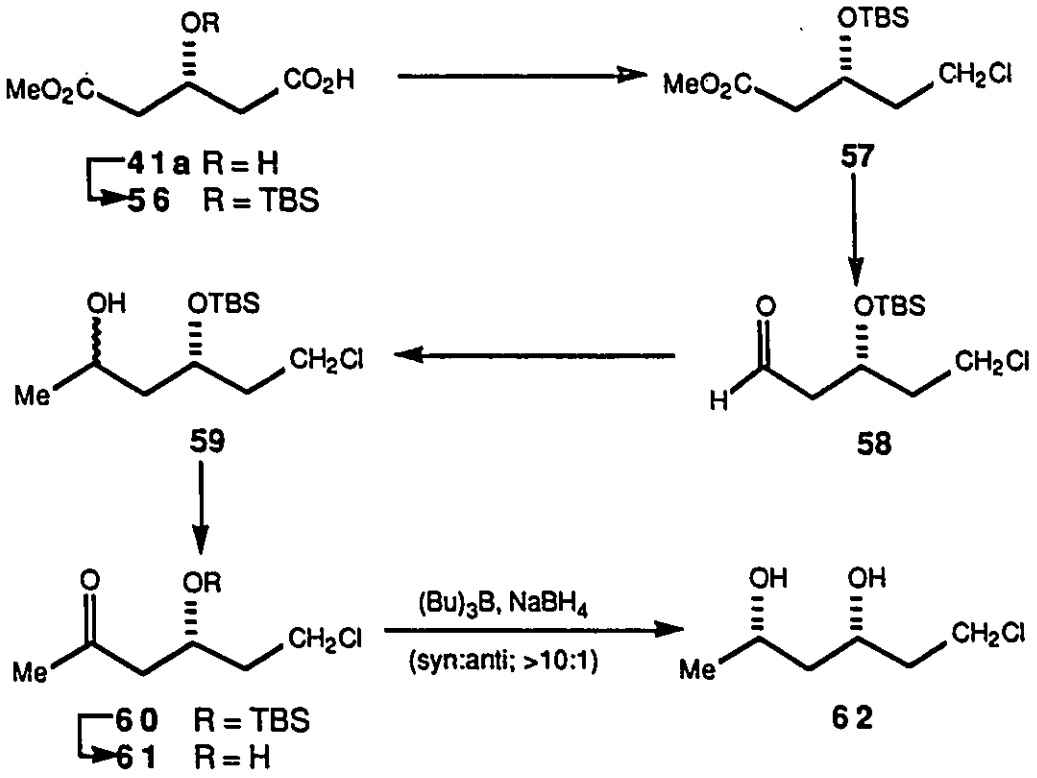
55b

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[51] as depicted below.



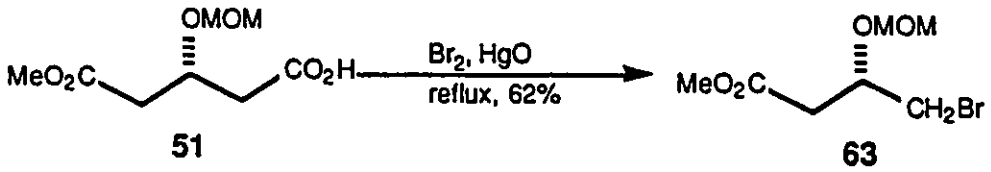
It is noteworthy to mention that, if desired, the absolute configuration at the C(3) position of the synthon **51** can be changed from R to S by two reasonably facile methods. Thus, selective reduction of the methyl ester of **51** followed by lactonization and ring opening by sodium methoxide, would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

[51] L. Rösslein and C.Tamm, *Helv. Chim. Acta*, 71, 47 (1988).

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[52] reaction (after suitable protection of the C(5) carboxylic acid).

2.11 Conversion to a Chiral C_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[53] rearrangement (62%, **51**, Br_2, HgO, CCl_4, reflux 1.5 hours). This C_4-synthon represents an excellent starting material for compounds such as the unnatural isomers of GABOB [(S)-4-amino-3-hydroxybutanoic acid] and carnitine[33].



51 **63**

[52](a) D.L. Hughes, R.A. Reamer, J.J. Bergan, and E.J.J. Grabowski, *J. Am. Chem. Soc.*, **110**, 6487 (1988). (b) O. Mitsunobu, *Synthesis*, 1 (1981).
[53]S.J. Cristol and W.C. Firth Jr., *J. Org. Chem.*, 26, 280 (1961).

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 (EI-MS 70 eV; CI-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 (^{1}H NMR) were taken in deuterochloroform ($CDCl_3$) 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 (^{13}C NMR) spectra were recorded in $CDCl_3$ 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 F_{254} precoated silica gel plates of 0.25 mm thickness and visualized by means of U.V., I_2 or by charring. Preparative layer chromatography was done on PSC-Fertig platten Kieselgel 60 F_{254} 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 chromatotrography 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 (NEt_3), 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 acid[54]. 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

[54]W.G. Kofron and L.M. Baclawski, *J. Org. Chem.*, 41, 1879 (1976).

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[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-12O 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[31]: 138-140°C at 8 Torr) gave 46.5 g (92%) of the alcohol **41** as a colourless oil. IR (thin film) υ: 3505, 2962, 1740,1441, 998 cm^{-1}. ^1H NMR (300 MHz) δ: 4.42 - 4.50 (app qu, 1H, H_3), 3.70 (s, 6H, 2 X CO_2CH_3), 3.32 - 3.43 (br s, 1H, OH, exchangeable), 2.55 (d, J = 6.3 Hz,

4H, 2 X CH_2). ^{13}C NMR (50.4 MHz) δ: 172.0 (CO_2CH_3), 64.3 (C_3), 51.4 (CO_2CH_3), 40.3 (CH_2).

3-Hydroxypentanedioic 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 Na_2HPO_4 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 Na_2SO_4 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 Na_2SO_4 and concentrated *in vacuo* to afford a yellowish oil. Purification by SiO_2 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 ($CHCl_3$) υ: 3490, 2982, 1733, 1718, 1439, 1422, 1269, 1178 cm^{-1}. ^1H NMR (300 MHz) δ: 4.46 (qu, J = 6.2 Hz, 1H, H_3), 3.71 (s, 3H, CO_2CH_3), 2.60 (d, J = 6.2 Hz, 2H, RCH_2R), 2.57 (d, J = 6.2 Hz, 2H, RCH_2R).

(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 $NaHCO_3$, and brine (30 mL portions), dried over

Na_2SO_4, 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, H_3), 3.69 (s, 3H, CO_2CH_3), 2.38 - 2.55 (m, 4H, H_2, H_4), 1.47 (1.48) (d, J = 6.9 Hz, 3H, CH_3CH).

(3R,S,1'R)-N-(1'-Phenylethyl)-3-[(tert-butyldimethylsilyl)oxy]-4-carbomethyoxybutanamide (44)[55]:

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 $NaHCO_3$, and brine (20 mL of each), dried over Na_2SO_4, 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) υ: 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, H_3), 3.65 (3.68) (s, 3H, CO_2CH_3), 2.55 (dd, A of ABX, J = 5.1, 15.0 (5.2, 15.0) Hz, 1H, H_2), 2.48 (2.59) (d, J = 1.8 (6.1) Hz, 1H (2H), H_4), 2.45 (d, J =

[55] ^1H NMR spectrum identical to the one described by Heathcock (ref. 32c).

2.4 Hz, 1H, $H_{4'}$), 2.39 (2.40) (dd, B of ABX, J = 5.2, 15.0 (4.9, 15.0) Hz, 1H, $H_{2'}$); 1.47 (1.50) (d, J = 6.7 (6.8) Hz, $CHCH_3$), 0.85 (0.79) (s, 9H, $C(CH_3)_3$), 0.10, 0.07 (0.06, 0.02) (s, 6H, $Si(CH_3)_2$). 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[35]. 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 Na_2SO_4 and the

solvent was removed *in vacuo*. The yellow oil was purified by SiO_2 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, H_3), 3.65 (s, 6H, 2 X CO_2CH_3), 2.53 (d, J = 6.1 Hz, 4H, 2 X CH_2), 0.84 (s, 9H, $C(CH_3)_3$), 0.08 (s, 6H, 2 X $SiCH_3$).

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 cyclohexane-dichloromethane (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 $NaHCO_3$ (50 mL) and once with brine (50 mL) and dried over Na_2SO_4. Concentration *in vacuo* yielded a reddish oil which was purified by SiO_2 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, OCH_2Ph), 4.31 (app qu, 1H, H_3) 3.66 (s, 6H, 2 X CO_2CH_3), 2.68 (dd, A of ABX, J = 6.8, 15.5 Hz, 2H, H_2, H_4), 2.60 (dd, B of ABX, J = 5.8, 15.5 Hz, 2H, $H_{2'}$, $H_{4'}$).

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[56] ^1H 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 $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, 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) υ: 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, H_3), 3.67 (s, 6H, 2 X CO_2CH_3), 2.84 (d, J = 6.3 Hz, 4H, 2 X CH_2). ^{13}C NMR (50.4 MHz) δ: 170.4 (2 X CO_2CH_3), 166.0 ($PhCO_2$), 133.3,129.9, 128.5 (aromatic), 67.5 (C_3), 51.8 (2 X CO_2CH_3), 38.1 (2 X CH_2). MS (EI) m/z: 175 (M^+-105, 9%), 159 (M^+-121, 9%). MS (CI ether) m/z: 281 (M^++1, 59%), 249 (M^+-31, 16%). HRMS calcd. for $C_7H_{11}O_5$ (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 $NaHCO_3$, and once with brine (50 mL portions). It was then dried over Na_2SO_4 and concentrated *in vacuo* to yield a pale yellow oil. Purification by SiO_2 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 Na_2CO_3 at 0°C and extracted with ether (3 x 80 mL). The combined ethereal extracts were washed with brine (100 mL) and dried over Na_2SO_4. 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) υ: 2961, 1742,1442, 1155, 1042 cm^{-1}. ^1H NMR (300 MHz) δ: 4.67 (s, 2H, OCH_2O), 4.40 (app qu, 1H, H_3), 3.68 (s, 6H, 2 X CO_2CH_3), 3.33 (s, 3H, OCH_3), 2.69 (dd, A of ABX, J = 6.8, 14.8 Hz, 2H, H_2, H_4), 2.62 (dd, B of ABX, J = 5.8, 14.8 Hz, 2H, $H_{2'}$, $H_{4'}$). ^{13}C NMR (50.4 MHz) δ: 171.2 (2 X CO_2CH_3), 96.4 (OCH_2O), 71.3 (C_3), 55.4 (OCH_3),

51.4 (2 X CO_2CH_3), 39.5 (2 X CH_2). MS (EI) m/z: 189 (M^+-31,12%), 175 (M^+-45, 2%). HRMS calcd. for $C_8H_{13}O_5$ (M^+-CH_3O): 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-Benzyloxypentanedioic acid monomethyl ester (49)[56]:

IR (thin film) υ: 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, OCH_2Ph), 4.32 (app qu, 1H, H_3), 3.70 (s, 3H, CO_2CH_3), 2.69 (d, J = 6.0 Hz, 2H, H_2, H_4), 2.68 (d, J = 6.0 Hz, 2H, $H_{2'}$, $H_{4'}$).

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

IR (thin film) υ: 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, H_3), 3.62 (s, 3H, CO_2CH_3), 2.82 - 2.90 (m,

4H, H_2, H_4). ^{13}C NMR (50.4 MHz) δ: 175.5 (CO_2H), 170.5 (CO_2CH_3), 165.5 ($PhCO_2$), 133.2, 129.6, 129.6, 128.3 (aromatic), 67.1 (C_3), 51.7 (CO_2CH_3), 37.8 (C_2, C_4). MS (CI ether) m/z : 267 (M^++1, 63%), 235 (M^+-31, 4%), 145 (M^+-121, 30 %). Anal. calcd. for $C_{13}H_{14}O_6$: C, 58.65, H, 5.30; found: C, 58.51, H, 5.21.

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

$[\alpha]_D$ = -3.3°. IR (thin film) υ: 3150, 2961, 1734, 1442, 1152, 1103 cm^{-1}. ^1H NMR (300 MHz) δ: 11.1 (br s, 1H, COOH, exchangeable), 4.68 (s, 2H, OCH_2O), 4.40 (app qu, 1H, H_3), 3.68 (s, 3H, CO_2CH_3), 3.34 (s, 3H, OCH_3), 2.58 - 2.75 (m, 4H, 2 X CH_2). ^{13}C NMR (50.4 MHz) δ: 176.5 (CO_2H), 171.4 (CO_2CH_3), 96.4 (OCH_2O), 71.2 (C_3), 55.5 (OCH_3), 51.6 (CO_2CH_3), 39.5, 39.4 (C_2, C_4). MS (EI) m/z: 175 (M^+-31, 4%). MS (CI ether) m/z: 207 (M^++1, 15%), 175 (M^+-31, 100%); Anal. calcd. for $C_8H_{14}O_6$: C, 46.60, H, 6.85; found: C, 47.08, H, 6.91.

(3R,S,1'R)-N-(1'-Phenylethyl)-3-protected-4-carbomethoxybutanamides (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'-Phenylethlethyl)-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) δ: 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_2Ph), 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_2CH_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) υ: 3310, 2962, 2938, 1745, 1733, 1658, 1549, 1441, 1279. ^{1}H NMR (300 MHz) δ: 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_2CH_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 (CI 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) υ: 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, OCH_2O), 4.36 (app qu, 1H, H_3), 3.66 (3.67) (s, 3H, CO_2CH_3), 3.31 (3.26) (s, 3H, OCH_3), 2.56 (app d of t, 4H, H_2, H_4), 1.47 (d, J = 6.9 Hz, 3H, CH_3CH). ^{13}C NMR (50.4 MHz) δ: 171.5 (CO_2CH_3), 169.1 (CONH), 143.3, 128.7, 127.4, 126.2 (aromatic), 96.7 (OCH_2O), 72.3 (C_3), 55.7 (OCH_3), 51.7 (CO_2CH_3), 48.6 ($CHCH_3$), 41.9, 39.3 (C_2, C_4), 21.7 (CH_3CH). 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 $C_{14}H_{18}O_4N$ (M^+-CH_2OCH_3): 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-benzyloxy-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 ^{1}H 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 $NaHCO_3$, and brine (20 mL of each). The organic layer was dried over Na_2SO_4 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, OCH_3), 1.49 (d, J = 6.9, 3H, CH_3CH). 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, OCH_3), 1.53 (d, J = 6.9 Hz, 1H, CH_3CH).

^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 $NaHCO_3$ 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 $NaHCO_3$ and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford a yellowish oil. Purification by SiO_2 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, OCH_2O), 4.68 (d, B of AB, J = 7.1 Hz, 1H, OCH_2O), 4.18 (app qu, 1H, H_3) 3.69 (s, 3H, CO_2CH_3), 3.55 (s, 1H, RCH_2Br), 3.53 (d, J = 0.8 Hz, RCH_2'Br), 3.38 (s, 3H, OCH_3), 2.75 (dd, A of ABX, J = 5.2, 16.1 Hz, 1H, H_2), 2.67 (dd, B of ABX, J = 7.4, 16.1 Hz, 1H, H_2'). GC-MS (EI) m/z: 211, 209 (M^+-31, 3%), 181, 179 (M^+-61, 9%), 147 (M^+-95 (CH_2Br), 18%).

CHAPTER 3: WITTIG AND DIANION APPROACHS 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[57] to assemble the desired C(5)–C(9) δ-lactone. The required 6-*Endo-Trig* ring closure will be, hopefully, preferred relative to the also favoured 5-*Exo-Trig* cyclization mode[57a]. The chiral Wittig precursor could be obtained by straightforward transformations of chiral building blocks **51** and **67**.

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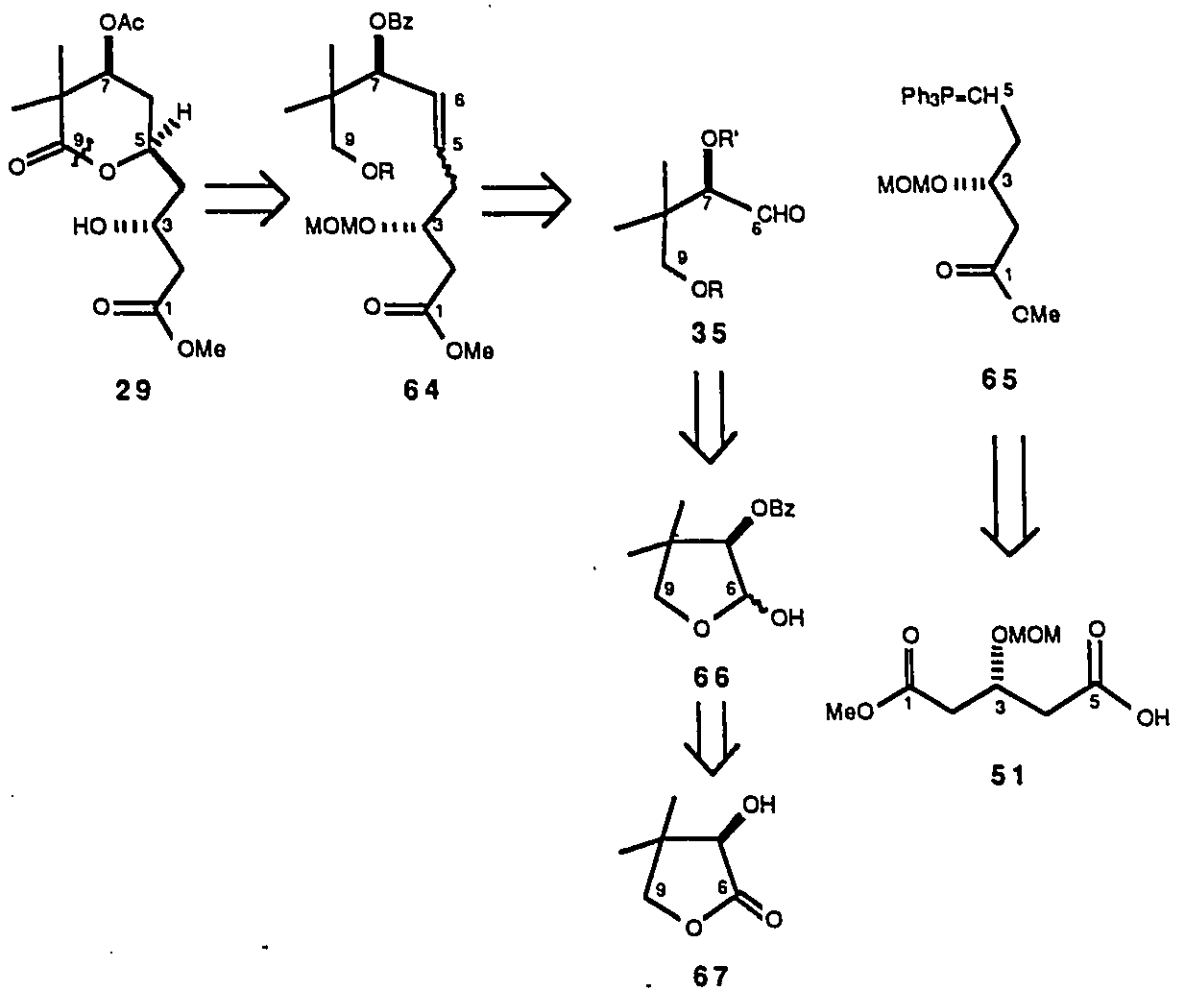
[57]For leading references, see: (a) B.B. Snider and M.I. Johnston, *Tetrahedron Lett.*, **26**, 5497 (1985). (b) P.A. Bartlett and J. Myerson, *Tetrahedron*, **40**,2317 (1984). (c) A.R. Chamberlin, M. Desube, P. Dussault, and M.C. McMills, *J. Am Chem. Soc.*, **105**, 5819 (1983). (d) Y. Tamaru, M. Mizutani, Y. Furukawa, S. Kawamura, Z. Yoshida, K. Yanagi, and M. Minobe, *J. Am. Chem. Soc.*, **106**, 1079 (1984). For references on Baldwins rules, see (e) J.E. Baldwin and M.J. Lusch, *Tetrahedron*, **38**, 2939 (1982). (f) J.E. Baldwin, R.C. Thomas, L.I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).

Figure 13 — Retrosynthetic Analysis for C(1)–C(9) Subunit — Wittig Approach



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[58] which demonstrates that variations in the reaction conditions can be made to encourage the formation of the desired trans-olefin.

The (R)-benzoylpantolactol was prepared in a two-step sequence from the commercially available (R)-pantolactone (**67**). Thus, **67** was benzoylated in near-quantitative yield (95%) using standard methodology (BzCl, pyridine, 25°C, 15 hours) to afford the α-benzoylated 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).

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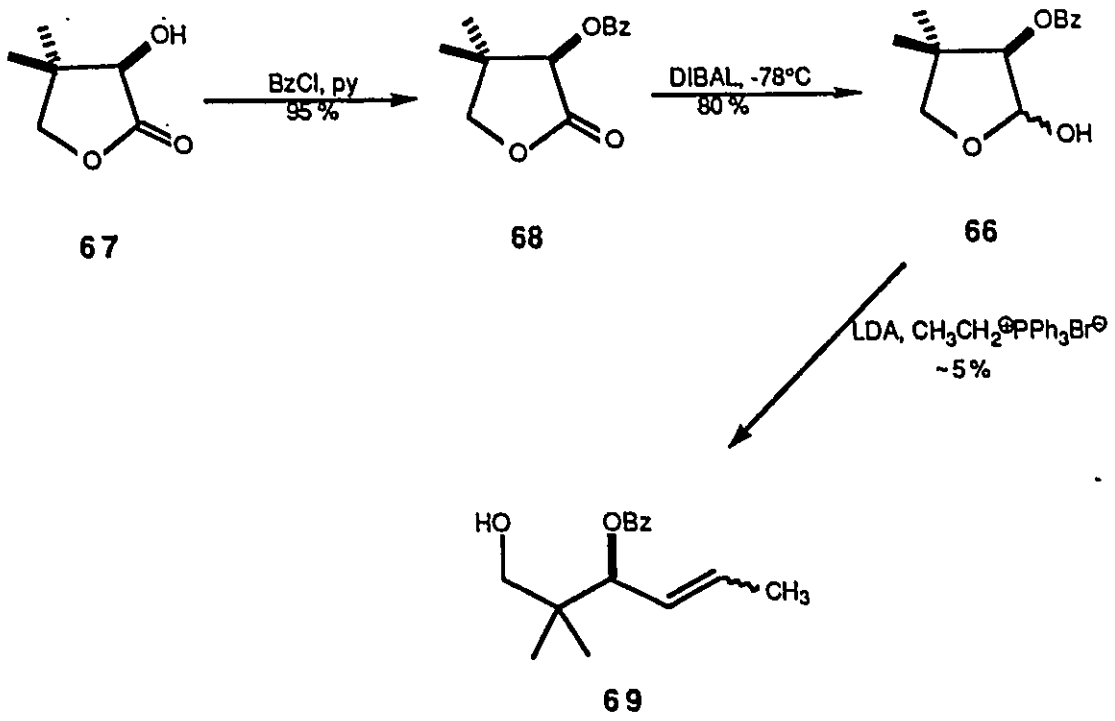
[58]B.E. Maryanoff and A.B. Reitz, *Chem. Rev.*, **89**, 863 (1989) and references cited therein.



Wittig olefination of **66** with ethylenetriphenylphorphorane 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 α-benzoyl substituents combined with the favourable five-membered ring entropy conspired to drive the equilibrium constant far towards the closed γ-lactol form of **66**. Thus, the external phosphorane was not exposed to the γ-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[59]. On the other hand, there are cases where this type of reaction failed (for example, in Fuchs'[60] synthetic efforts towards the quassinoid bruceantin). Clearly, the nature of the γ-lactol has substantial influence on the success of the Wittig reaction[61]. Taken together, the results from the model study discouraged us from attempting the addition of phosphorane **65** directly onto **66**.

Opening of the benzoylated γ-lactone **68** using technology developed by Wessel[62] or Weinreb[63] 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-butyldimethylsilyl 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.

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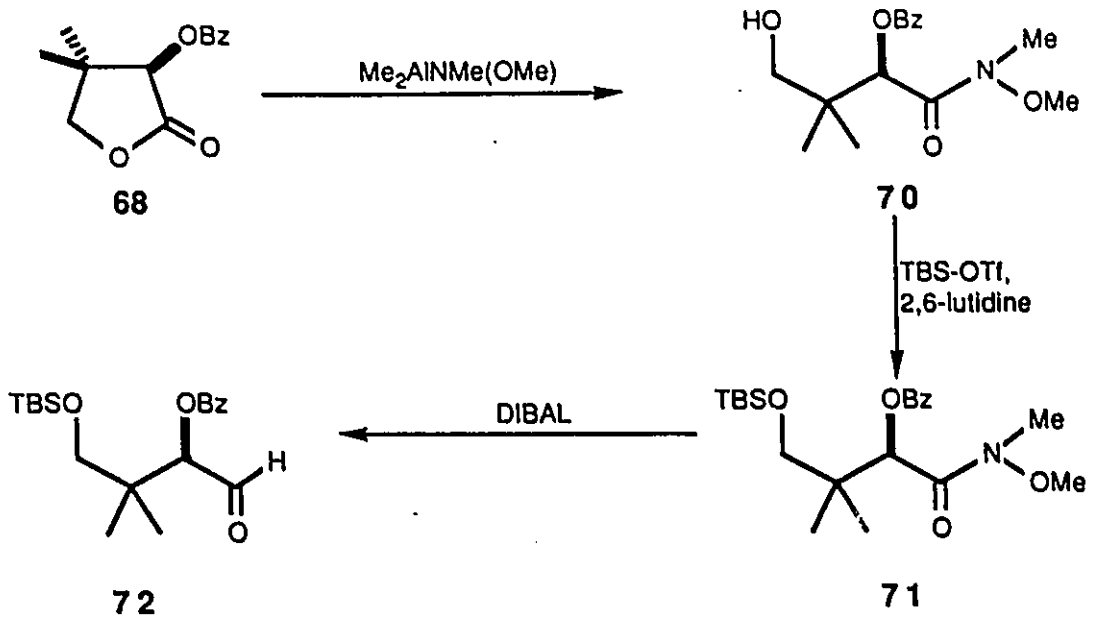
[59]For instance: (a) T. Ibuka, N. Akimoto, M. Tanaka, S. Nishi, and Y. Yamamoto,, *J. Org. Chem.*, **54**, 4055 (1989). (b) E.W. Yankee, U. Axen, and G. L. Bundy, *J. Am.Chem. Soc.*, **96**, 5865 (1974).
[60]S.N. Suyawanshi and P.L. Fuchs, *J. Org. Chem.*, **51**, 902 (1986).
[61]P. Fuchs, private communication.
[62]H.P. Wessel, *J. Carbohyd. Chem.*, **8**, 443 (1989).
[63]A. Basha, M. Lipton, and S.M. Weinreb, *Tetrahedron Lett.*, **18**, 4171 (1977).

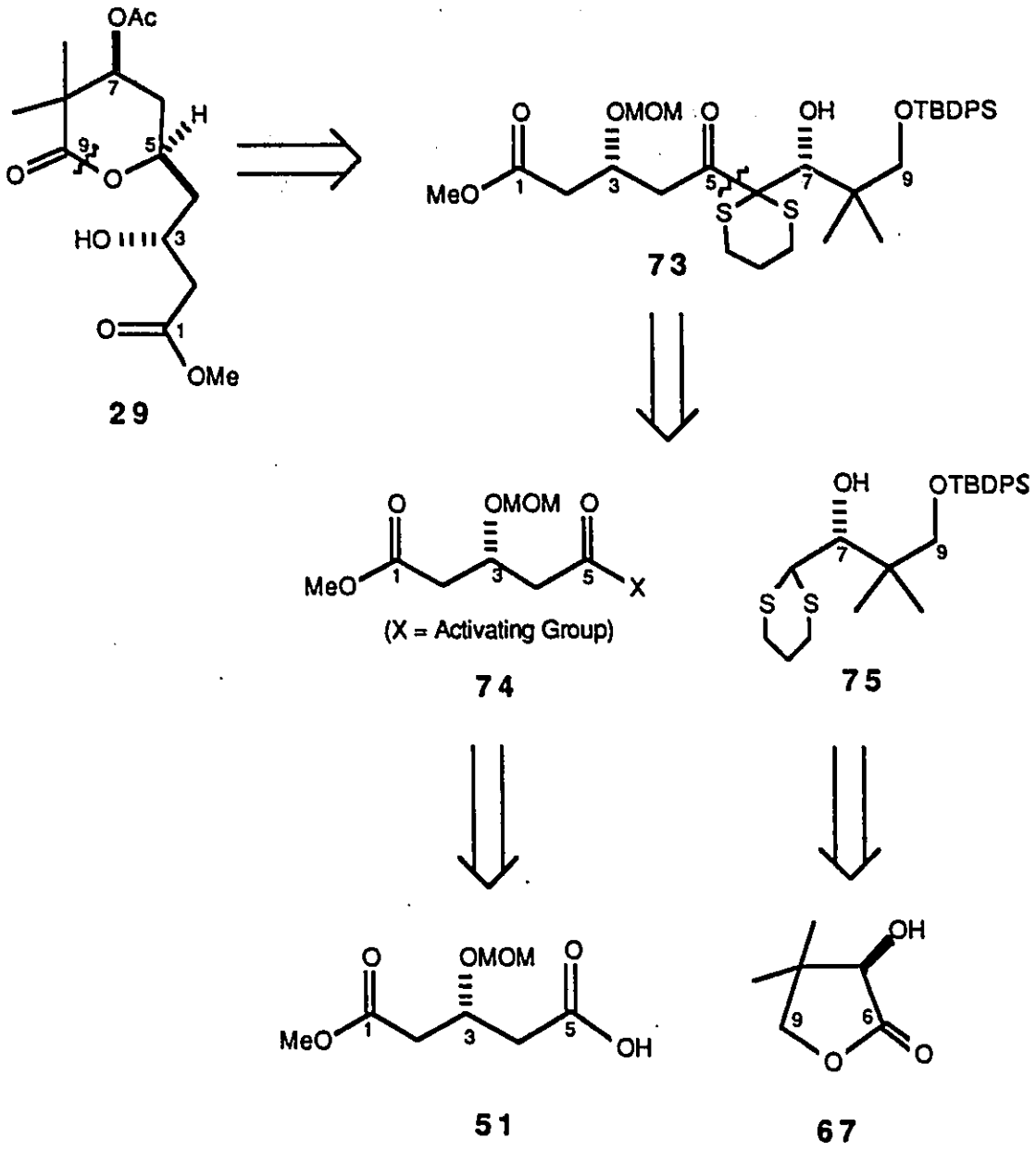


However, while this avenue was being explored, a more appealing route to the C(1)–C(9) fragment became apparent and the Wittig olefination approach was discontinued.

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[19]. The C(5)–C(9) δ-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_4 and C_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[64] in 83% yield (BH_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_3·Et_2O, CH_2Cl_2, 25°C, hours). The primary hydroxyl [C(9) of bryostatin] was then selectively protected as its tert-butyldiphenylsilyl ether (75%, TBDPSCl, DMAP, imidazole, DMF, 25°C, 6 hours) using technology developed by

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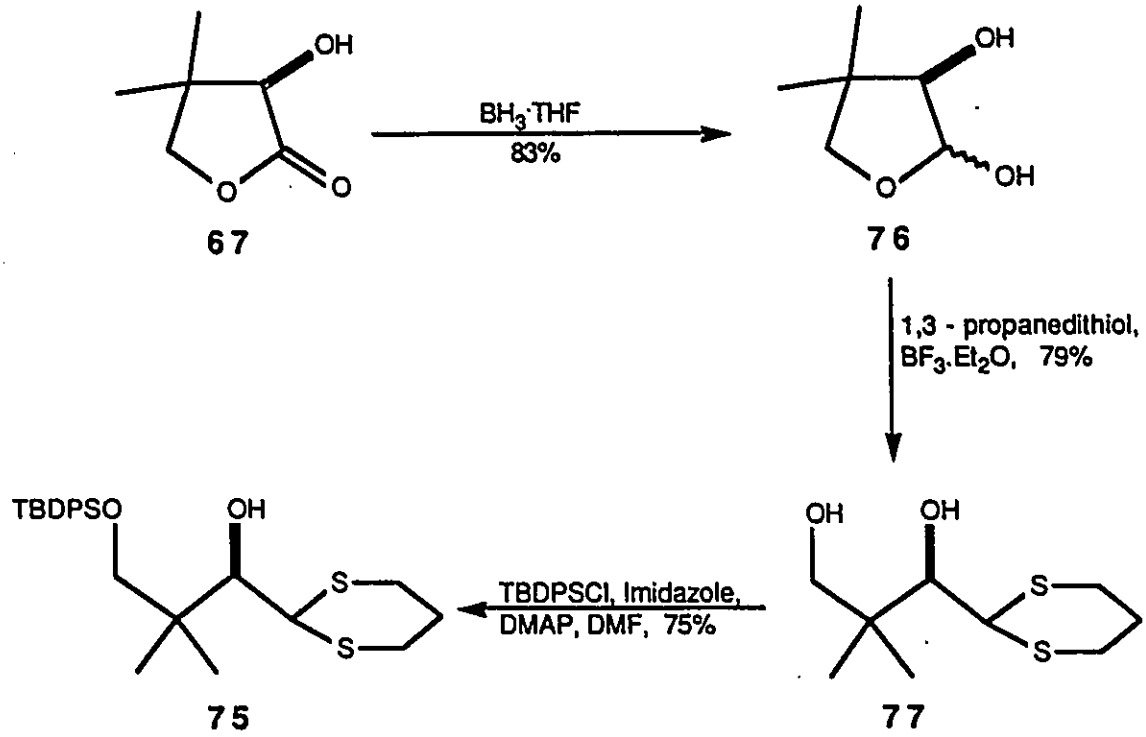
[64]S.S. Bhattacharjee, J.A. Schwarcz, and A.S. Perlin, *Carbohyd. Res.*, **42**, 259 (1979).

Hanessian[65]. This provided the α-hydroxy dithianyl synthon **75** in 49% overall yield from (R)-pantolactone.



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) succinimidyl ester[66]. This was accomplished by activating the C(5) carboxylic acid with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) followed by

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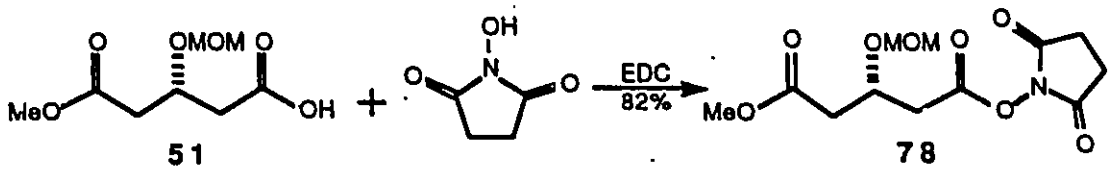
[65](a) S. Hanessian and P. Lavallée, *Can. J. Chem.*, **53** 2975 (1975). (b) S. Hanessian and P. Lavallée, *Can. J. Chem.*, **55**, 562 (1977).
[66]G.W. Anderson, J.E. Zimmerman, and F.M.Callahan, *J. Am. Chem. Soc.*, **86**, 1839 (1964).

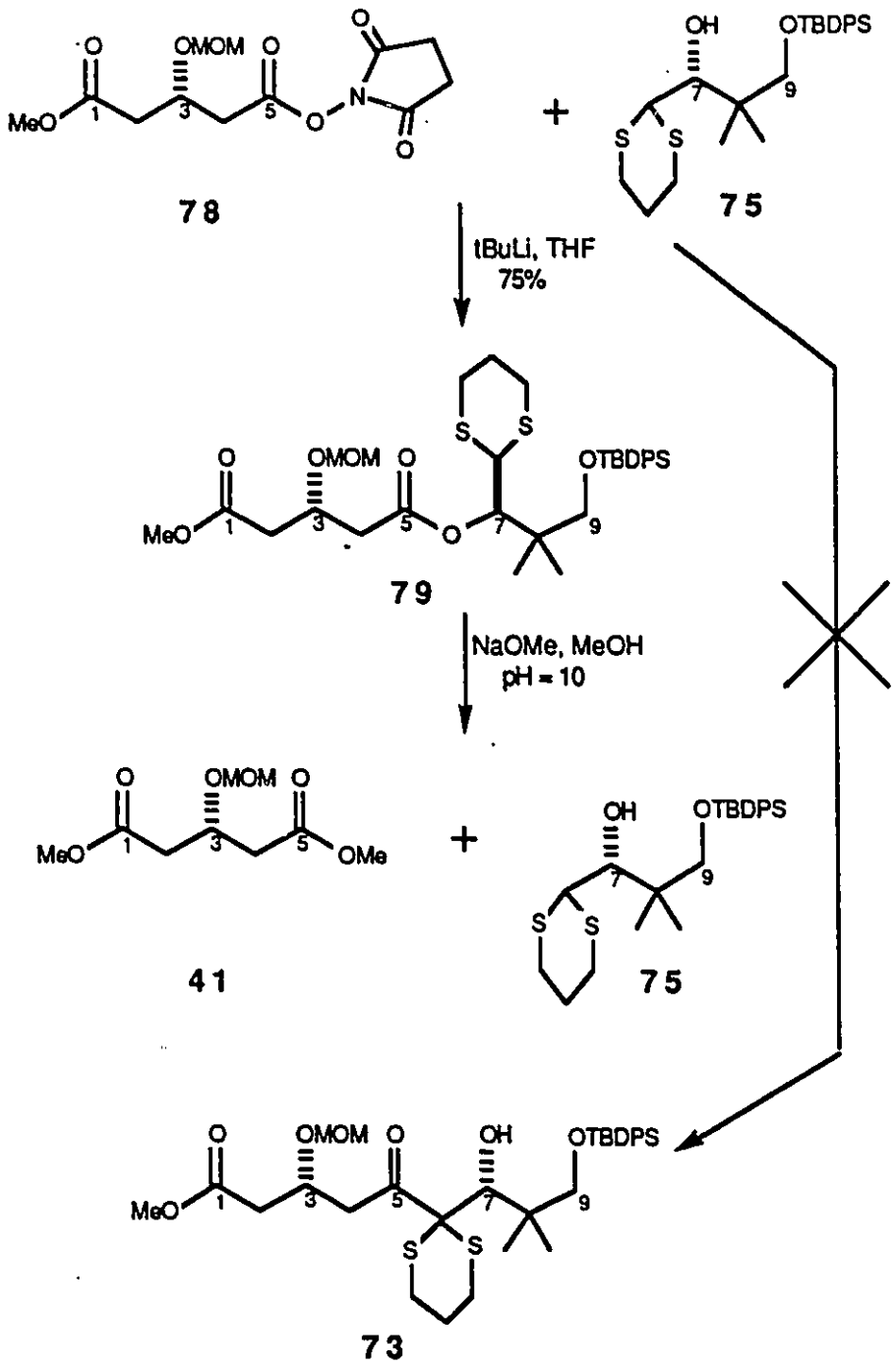
esterification with N-hydroxysuccinimide (EDC, N-hydroxysuccinimide, tBuOH, 2 hours). The yield of the succininidyl ester **78** was 82%.



51 **78**

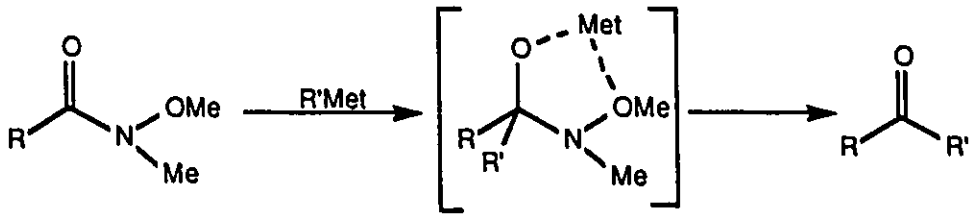
3.6 Addition of 75 Onto C(5)-Activated Ester 78

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 (^{1}H 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
tBuLi, THF
75%
79
NaOMe, MeOH
pH = 10
41
75
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_2Cl_2, 25°C, 16 hours). The yield of **80** was 62%.

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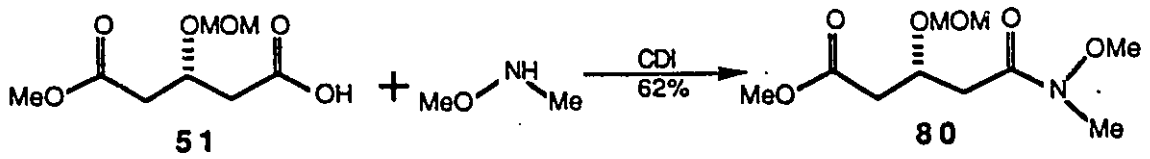
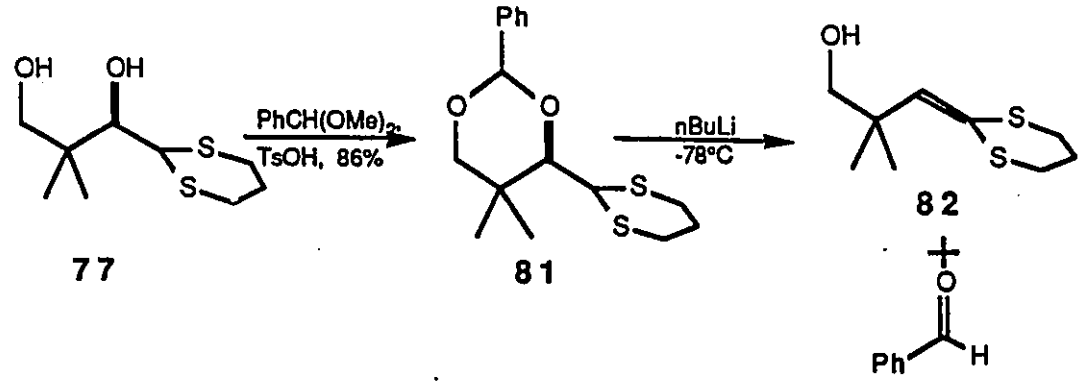
[67](a) T.A. Oster and T.M. Harris, *Tetrahedron Lett.*, **24**, 1851 (1983). (b) P.D. Theisen and C.H. Heathcock, *J. Org. Chem.*, **53**, 2374 (1988). (c) S. Nahm and S.M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).



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 dianion of **75** was not formed.

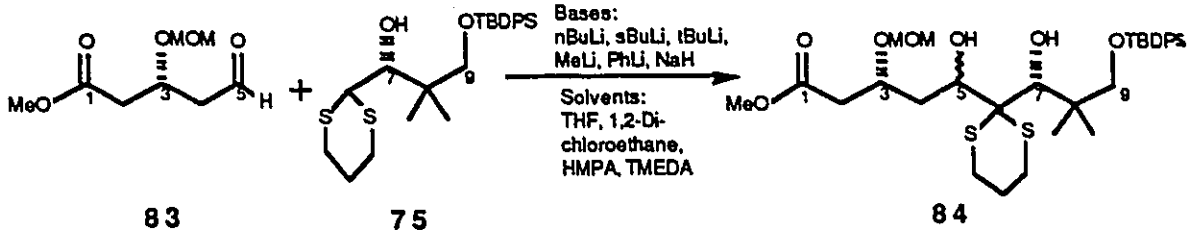
Protection of both hydroxyls on the 1,3-propanedithioacetal **77** represented another method for preventing O-acylation to occur. Thus, the benzylidene acetal was formed in 86% yield using standard methodology (benzaldehyde dimethyl acetal, TsOH, benzene, 25°C, 2 hours).



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).



83 **75** **84**

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,

[68]D. Seebach and E.J. Corey, *J. Org. Chem.*, **40**, 231 (1975).

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_2O and MeOD were made. This resulted in no deuterium incorporation (^1H 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 $BF_3{\cdot}Et_2O$ to afford the diethylthioacetal diol **85** in 61% yield (EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25°C, 16 hours).

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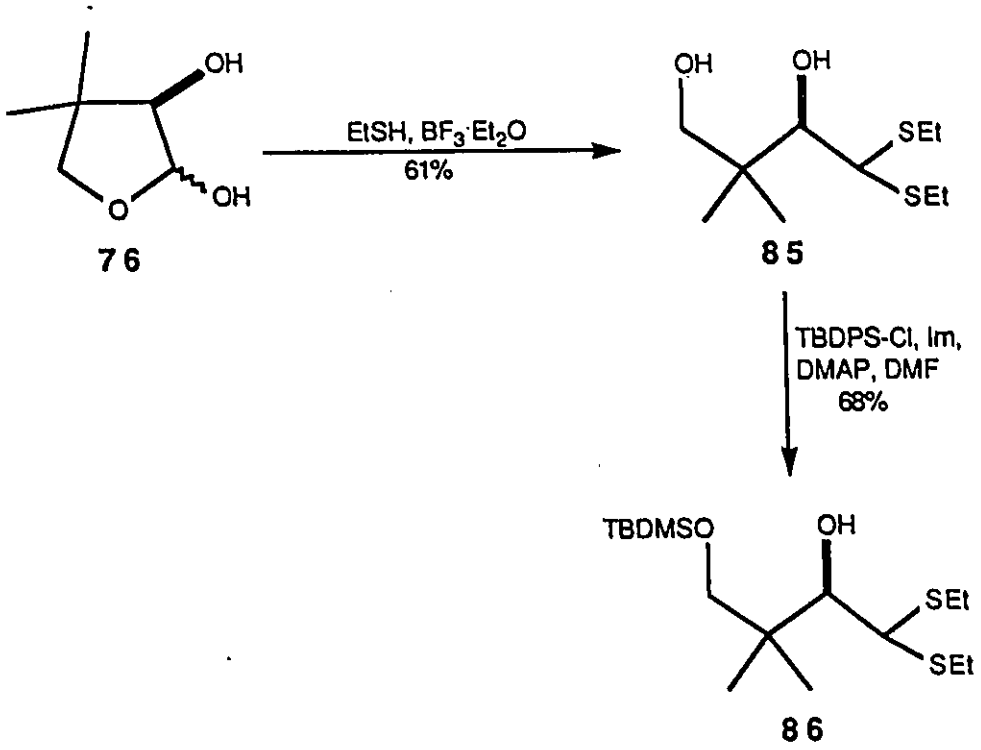
[69]M. Kinoshita, M. Taniguchi, M. Morioka, H. Takami, and Y. Mizusawa, *Bull. Chem. Soc. Jpn.*, **61**, 2147 (1988).

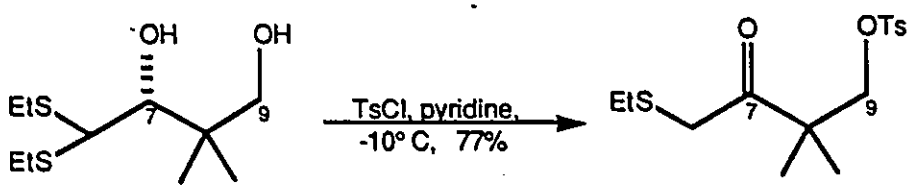


76 **85** **86**

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 (TBDPSCl, 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, $CHCl_3$, 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 benzylidene acetal on **85** (using the same procedure as for the conversion of **77** to **81**). Reductive benzylidene-ring opening[70] would then provide the desired primary benzyl ether. This sequence was prevented by difficulties encountered in formation of the benzylidene 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.



85 **87**

Recent literature[71] suggests that C-alkylation with dianions derived from α-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.

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[70](a) S. Takano, M.A. Akiyama, S. Sato, and K. Ogasawara, Chem. Lett., 1593 (1983). (b) J. Gelas in "*Advances in Carbohydrate Chemistry*", Vol. 39, ed. R.S. Tipson and D. Horton, Academic Press, New York, 71 (1981) and references cited therein.

[71]For example: (a) T. Nakata, T. Suenaga, and T. Oishi, *Tetrahedron Lett.*, **30**, 6525 (1989). (b) G. Solladie and J. Hutt, *Tetrahedron Lett.*, **28**, 797 (1987).

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 $NaHCO_3$ (100 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* leaving a white amorphous residue. This was recrystallized from hexane yielding 12.0 g (95%) of the benzoylated γ-lactone **68** as white needles melting at 51.1–52.2°C. $[\alpha]_D$ = +3.2° (c = 1.5, $CHCl_3$). IR (CH_2Cl_2) υ: 3018, 2962, 1788, 1728, 1267, 1118, 1013 cm^{-1}. ^1H NMR (300 MHz) δ: 7.43 - 8.10 (m, 5H, aromatic), 5.60 (s, 1H, H_7), 4.12 (d, A of AB, J = 9.1 Hz, 1H, H_9), 4.08 (d, B of AB, J = 9.1 Hz, 1H, $H_{9'}$), 1.26 (s, 3H, gem CH_3), 1.21 (s, 3H, gem CH_3). ^{13}C NMR (50.4 MHz) δ: 172.4 (RCO_2R), 165.3 ($PhCO_2R$), 138.7, 129.9, 128.6, 128.5 (aromatic), 76.0 (C_9), 75.2 (C_7), 40.2 (C_8), 22.6 (gem CH_3), 19.6 (gem CH_3). MS (EI) 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 benzoylated 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 ($Na_2SO_4 \cdot 10H_2O$, ~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 $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield a white amorphous solid. Purification by SiO_2 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 anomeric ratio) is given in brackets. $[\alpha]_D$ = +30.1° (c = 1.0 in $CHCl_3$). IR (CH_2Cl_2) υ: 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, H_6), (5.66 - 5.75, m, 1H, H_6), 5.02 - 5.04 (m, 1H, H_7), 3.97 (d, A of AB, J = 8.6 Hz, 1H, H_9), 3.79 (d, B of AB, J = 8.6 Hz, 1H, $H_{9'}$), (3.93) (d, A of AB, J = 8.3 Hz, 1H, H_9), (3.62) (d, B of AB, J = 8.3 Hz, 1H, $H_{9'}$), 1.29 (s, 3H, gem CH_3), 1.14 (s, 3H, gem CH_3), (1.12) (s, 3H, gem CH_3), (1.16) (s, 3H, gem CH_3). ^{13}C NMR (75.4 MHz) δ: 166.0 ($PhCO_2R$), 133.2, 129.6, 129.5, 128.4 (133.2, 129.7, 129.5, 128.4) (aromatic), 102.8 (97.0) (C_6), 86.0 (79.8) (C_7), 79.3, 77.3 (C_9), 41.7 (40.9) (C_8), 24.7, 20.8 (25.8, 20.4) (gem CH_3's).

MS (CI ether) m/z: 237 (M^++1, 12%), 235 (M^+-1, 30%), 219 ((M^++1)-18, 100%). Anal. calcd. for $C_{13}H_{16}O_4$: 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 Na_2SO_4, and concentrated *in vacuo* to yield an oil which was of sufficient purity (tlc, ^{1}H 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) υ: 3481, 3256, 2962, 2939, 2884, 1472, 1411, 1281, 1179, 1170, 1081, 1050 cm^{-1}. ^{1}H NMR (300 MHz) δ: 4.25 (d, J = 3.4 Hz, 1H, H_6), 3.71 (dd, J = 3.4, 4.5 Hz, 1H, H_7), 3.56 (dd, J = 4.8, 11.0 Hz, 1H, H_9), 3.49 (dd, J = 4.5, 11.0 Hz, 1H, $H_{9'}$), 3.04 (d, J = 4.5, 1H, R_2CHOH), 2.76 - 2.94 (m, 4H, $CH_2(CH_2S)$, 2.56 (app t, J = 6.0 Hz, 1H, RCH_2OH), 1.88 - 2.10 (m, 2H, $CH_2(CH_2S)_2$), 1.02 (s, 6H, gem CH_3's). ^{13}C NMR (50.4 MHz) δ: 80.4 (C_6), 71.4 (C_9), 49.9 (C_7), 39.7 (C_8), 30.0 ($CH_2(CH_2S)$, 29.0 ($CH_2(CH_2S)$, 25.3 ($CH_2(CH_2S)_2$), 22.6, 20.0 (gem CH_3's). MS (EI) 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), 0.2N 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_9), 3.41 (d, J = 4.9 Hz, 1H, OH, exchangeable), 3.40 (d, B of AB, J = 9.8 Hz, 1H, $H_{9'}$), 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). ^{13}C 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 ($CH_2(\mathbf{C}H_2S)$), 29.7 ($CH_2(\mathbf{C}H_2S)$), 26.7 ($C(\mathbf{C}H_3)_3$), 25.5 ($\mathbf{C}H_2(CH_2S)_2$), 22.1, 20.5 (gem CH_3's), 19.0 ($\mathbf{C}(CH_3)_3$). MS (CI 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 $NaHCO_3$, and brine (50 mL portions). The organic layer was dried over Na_2SO_4 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. $[\alpha]_D$ = -6.6° (c = 2.0, $CHCl_3$). IR thin film) υ: 2959, 1820, 1789, 1739, 1441, 1370, 1210, 1033 cm^{-1}. ^1H NMR (200 MHz) δ 4.59 (s, 2H, OCH_2O), 4.33 (app qu, 1H, H_3) 3.58 (s, 3H, CO_2CH_3), 3.25 (s, 3H, OCH_3), 2.87 (d, J = 6.3 Hz, 2H, H_4), 2.73 (s, 4H, 2 X $N(CO)CH_2R$), 2.70 (dd, A of ABX, J = 9.2, 16.1 Hz, 1H, H_2), 2.58 (dd, B of ABX, J = 5.7, 16.1 Hz, 1H, $H_{2'}$). ^{13}C NMR (50.4 MHz) δ: 170.9 (CO_2CH_3), 169.2 (2 X NCOR), 166.0 (CO_2N), 96.7 (OCH_2O), 70.9 (C_3), 55.6 (OCH_3), 51.6 (CO_2CH_3), 39.2 (C_2), 36.6 (C_4), 25.3 (2 X $NCOCH_2R$). 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 NH_4Cl 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 $NaHCO_3$, and brine (30 mL of each), dried over Na_2SO_4, 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, $RCO_2CHR'_2$), 4.44 (d, J = 3.0 Hz, 1H, $RCH(SR')_2$), 4.72 (d, A of AB, J = 6.9 Hz, 1H, OCH_2O), 4.61 (d, B of AB, J = 6.9 Hz, 1H, OCH_2O), 4.37 - 4.45 (m, 1H, H_3), 3.67 (s, 3H, CO_2CH_3), 3.40 (d, A of AB, J = 10.0 Hz, 1H, RCH_2OSi), 3.36 (d, B of AB, J = 10.0 Hz, 1H, RCH'_2OSi), 3.34 (s, 3H, CH_2OCH_3), 2.52 - 2.84 (m, 8H, $CH_2(CH_2S)_2$, H_2, H_4), 1.64 - 2.04 (m, 2H, $CH_2(CH_2S)_2$), 1.07 (s, 9H, $C(CH_3)_3$), 1.02, 0.96 (s, 6H, gem CH_3's). MS (CI 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 N_2 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 $NaHCO_3$ (1 X 30 mL), and brine (1 X 30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* . Purification by SiO_2 flash chromatography (ether) yielded 412 mg (62%) of the N-methoxy-N-methylamide **80** as a colourless oil. IR (thin film) υ: 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, OCH_2O), 4.63 (d, B of AB, J = 6.9 Hz, 1H, OCH_2O), 4.42 (app qu, 1H, H_3), 3.65 (s, 3H, CO_2CH_3), 3.64 (s, 3H, $NOCH_3$), 3.30 (s, 3H, OCH_3), 3.13 (s, 3H, NCH_3), 2.88 (dd, A of ABX, J = 6.9, 15.8 Hz, 1H, H_2), 2.64 (d, J = 5.8 Hz, 1H, H_4), 2.63 (d, J = 6.4 Hz, 1H, $H_{4'}$), 2.59 (dd, B of ABX, J = 6.2, 15.8 Hz, 1H, $H_{2'}$). 182.2 ($CONR_2$), 171.6 ($CONR_2$), 96.7 (OCH_2O), 71.6 (C_3), 61.2 ($NOCH_3$), 55.5 (CH_2OCH_3), 51.5 (CO_2CH_3), 40.0 (C_2), 37.2 (C_4), 32.0 (NCH_3). MS (EI) m/z: 218 (M^+-31, 3%), 189 (M^+-60, 17%). MS (EI ether) m/z: 250 (M^++1, 5%), 247 (M^+-2, 50%), 218 (M^+-31, 100%). HRMS calcd. for $C_8H_{13}O_5$ [M^+-$N(OCH_3)CH_3$)]: 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 $NaHCO_3$, and brine (40 mL portions). The organic layer was dried over Na_2SO_4 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, PhC**H**), 4.33 (d, J = 5.2 Hz, 1H, H_6), 3.72 (d, J = 5.1 Hz, 1H, H_7), 3.66 (d, A of AB, J = 11.1 Hz, 1H, H_9), 3.58 (d, B of AB, J = 11.2 Hz, 1H, $H_{9'}$), 2.82 - 2.99 (m, 4H, $CH_2(CH_2S)_2$), 1.80 - 2.18 (m, 2H, $CH_2(CH_2S)_2$), 1.28, 0.95 (s, 6H, gem CH_3's). MS (CI 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 Na_2SO_4, 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, H_6), 3.65 (dd, J = 3.7, 4.2 Hz, 1H, H_7), 3.54 (d, A of AB, J = 9.8 Hz, 1H, H_9), 3.48 (d, B of AB, J = 9.8 Hz, 1H, $H_{9'}$), 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 SCH_2CH_3), 1.27 (t, J = 7.5 Hz, 6H, 2 X SCH_2CH_3), 1.01 (s, 6H, gem CH_3's). MS (CI ether) m/z: 239 (M^++1, 8%), 177 (M^+-61, 100%).

(2R)-2-Hydroxy-3,3-dimethyl-4-[(tert-butyldiphenylsilyl)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 diethyldithioacetal 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, H_6), 3.94 (dd, J = 2.8, 4.5 Hz, 1H, H_7), 3.69 (d, A of AB, J = 9.7 Hz, 1H, H_9), 3.38 (d, B of AB, J = 9.7 Hz, 1H, $H_{9'}$), 3.36 (d, J = 4.5 Hz, 1H, OH, exchangeable), 2.61 - 2.76 (m, 4H, 2 X SCH_2CH_3), 1.24 (t, J = 7.4 Hz, 3H, SCH_2CH_3), 1.23 (t, J = 7.4 Hz, 3H, SCH_2CH_3), 1.05 (s, 9H, $C(CH_3)_3$), 1.01, 0.98 (s, 6H, gem CH_3's). MS (CI 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 thioacetal 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 $NaHCO_3$, and brine (30 mL of each). The ethereal layer was dried over Na_2SO_4 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) υ: 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, H_9), 3.34 (s, 2H, H_6), 2.47 (q, J = 7.4 Hz, 2H, SCH_2CH_3), 2.44 (s, 3H, $PhCH_3$), 1.21 (s, 6H, gem CH_3's), 1.20 (s, 3H, SCH_2CH_3). ^{13}C NMR (50.4 MHz) δ: 206.7 (C_7), 145.1, 132.4,129.9, 128.0 (aromatic), 75.2 (C_9), 47.2 (C_8), 36.5 (C_6), 25.8 (SCH_2CH_3), 21.9 (gem CH_3's), 21.4 ($PhCH_3$), 13.8 (SCH_2CH_3). MS (EI) m/z: 330 (M^+,18%), 227 (M^+-103, 8%), 209 (M^+-121, 24%). HRMS calcd. for $C_{15}H_{22}O_4S_2$ (M^+): 330.0957; found: 330.0939.

CHAPTER 4: SYNTHESIS OF THE C(1)–C(9) FRAGMENT OF BRYOSTATIN BY LEWIS ACID MEDIATED ALDOL COUPLING[72]

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)-methoxymethoxyglutarate (**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 one[14], 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 C_5 chiral building block **83**, obtained from **51** in high enantiomeric excess (ee) by use of immobilized α-chymotrypsin[24] (α-CHY) (Chapter 2), could induce its chirality from C(3) to C(5) upon addition of the C_4 synthon **31** through

[72]This 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).

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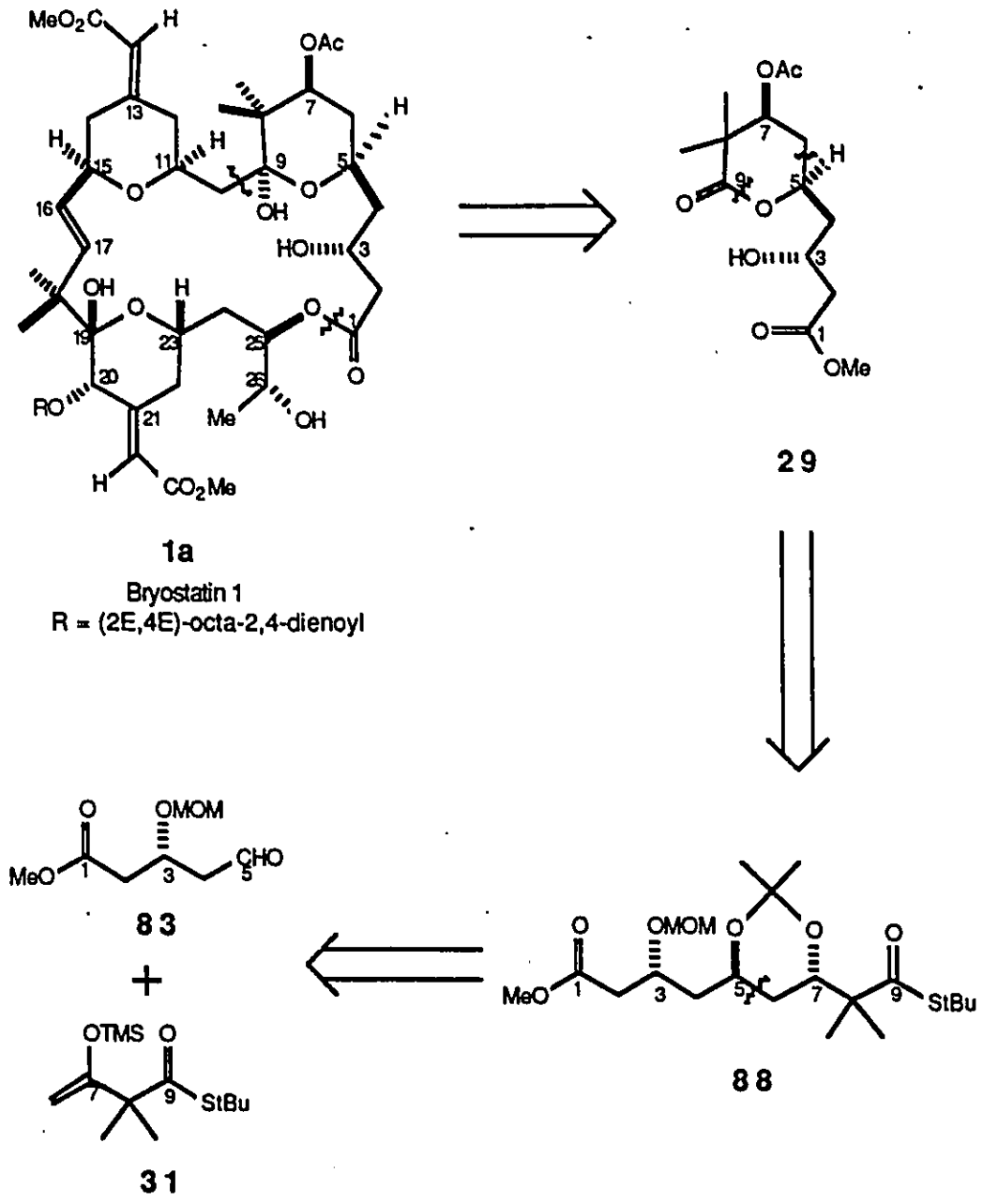
[73]See for examples: (a) M.T. Reetz and A.J. Jung, *J. Am. Chem. Soc.*, **105**, 4833 (1983). (b) M.T. Reetz, K. Kesseler, and A.J. Jung. *Tetrahedron Lett.*, **25**, 729 (1984). (c) S.J. Danishefsky, S.L. De Ninno, S.-H. Chen, L. Boisvert, and M. Barbachyn, *J. Am. Chem. Soc.*, **111**, 5810 (1989). (d) T.M. Wilson, P. Kocienski, K. Jarowicki, K. Isaac, P.M. Hitchcock, A. Faller, and S.F. Campbell, *Tetrahedron*, **46**, 1767 (1990).

[74](a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.*, 1011 (1973). (b) T. Kobayashi, T. Mukaiyama, *Chem. Lett.*, 1805 (1986). (c) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).

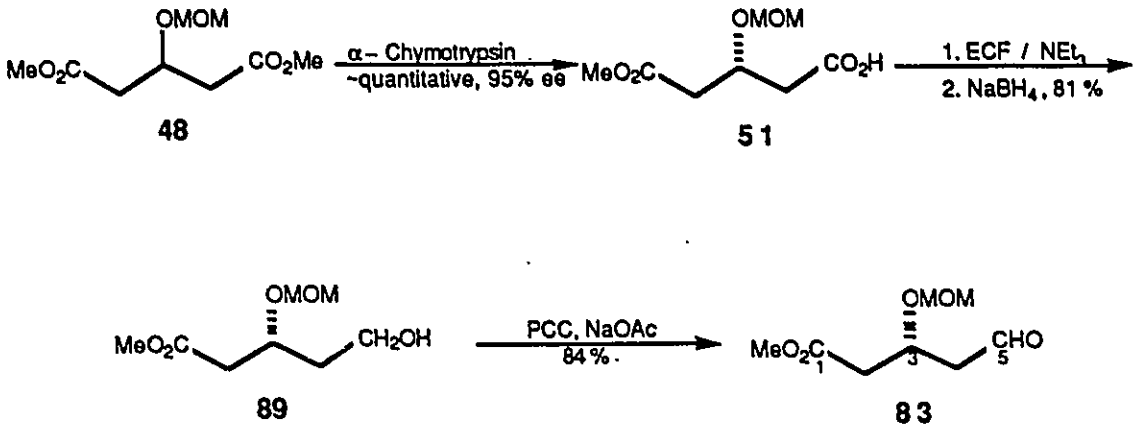
[75](a) S. Masamune, S. Kamata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975). (b) S. Masamune, *Aldrichimica Acta*, **11**, 23 (1978).

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



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.



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 synthesis[24].

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[76] and Guibe[77].

Fujisawa's method[76] employs N,N-dimethylchloromethyleniminium chloride for the chemoselective conversion of the carboxylic acid into the carboxymethyleniminum chloride which is subsequently reduced *in situ* by lithium tri(tert-butoxy)aluminum hydride (oxalyl chloride, DMF, pyridine, CuI, $LiAlH(OBu^t)_3$, 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 <u>not</u> improve the yields. Moreover, scale-up (5 mmol of **51**) gave even poorer results (<30%).

Guibe's[77] methodology was tried as well. Briefly, this method relies upon the formation of an acid chloride (oxalyl chloride, CH_2Cl_2, 0°C, 1 hour) and, without isolation, the subsequent palladium-catalysed reduction with tributyltin hydride [$Pd(PPh_3)_4$ (10^{-2} equiv), Bu_3SnH, benzene, 25°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.

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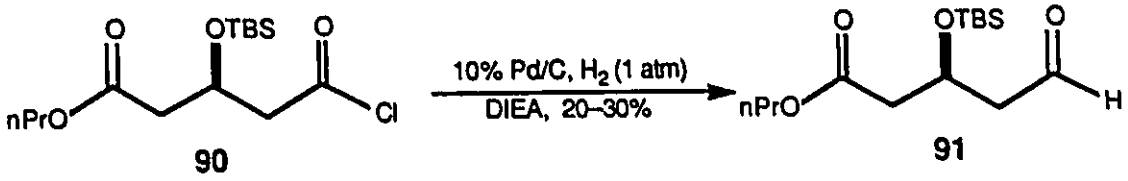
[76]T. Fujisawa, T. Mori, S. Tsuge, and T. Sato, *Tetrahedron Lett.*, 24, 1543 (1983).
[77]P. Four and F. Guibe, *J. Org. Chem.*, 46, 4439 (1981).

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



90 **91**

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 ($NaBH_3CN$) 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 $NaBH_3CN$ does not reduce aldehydes at neutral pH's[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

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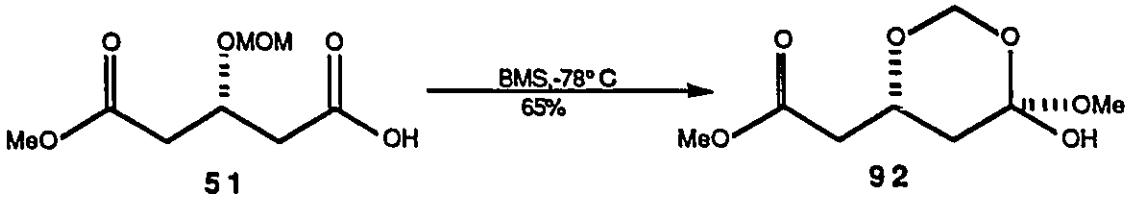
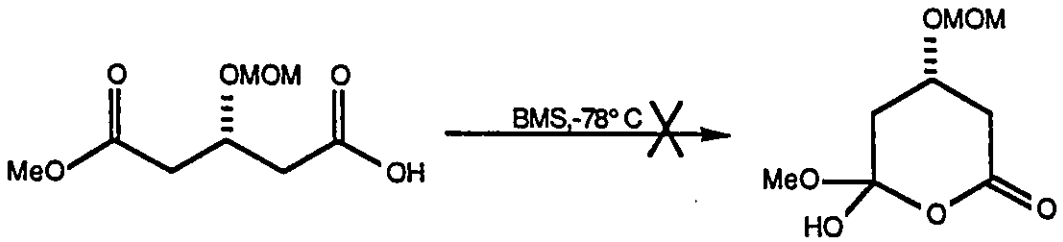
[78]E. Mosettig and R. Mozinzo, *Org. Reactions*, 4, 362 (1948).
[79]C.F. Lane, *Synthesis*, 135 (1975).

chemoselective reducing agent borane-methyl sulfide complex (BMS)[80]. 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.



51 **92**

Another plausible alternative for the structure of **92** is **93**.



51 **93**

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

[80]H.C. Brown and Y.M. Choi, *Synthesis*, 439 (1981).

(OCH_2OCH_3) and methoxy protons (OCH_2OCH_3) on the MOM group at ~4.6 ppm and ~3.3 ppm, respectively, were absent. Likewise, the ^{13}C NMR shifts at ~96.0 ppm (OCH_2O) and ~55.5 ppm (OCH_2OCH_3) 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: CO_2CH_3, 3.71 ppm; ^{13}C NMR: CO_2CH_3, 171.1 ppm and CO_2CH_3, 51.9 ppm).

A seldom used procedure developed in 1964 by workers at Bristol-Myers[81] 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, NEt_3, THF, 0°C, 1 hour) and, without isolation, borohydride reduction ($NaBH_4$, 7 equiv). This two-step, one-pot, reaction provided **89** in 81% yield.

Pyridinium chlorochromate oxidation[82] (PCC, 4Å molecular sieves, CH_2Cl_2, 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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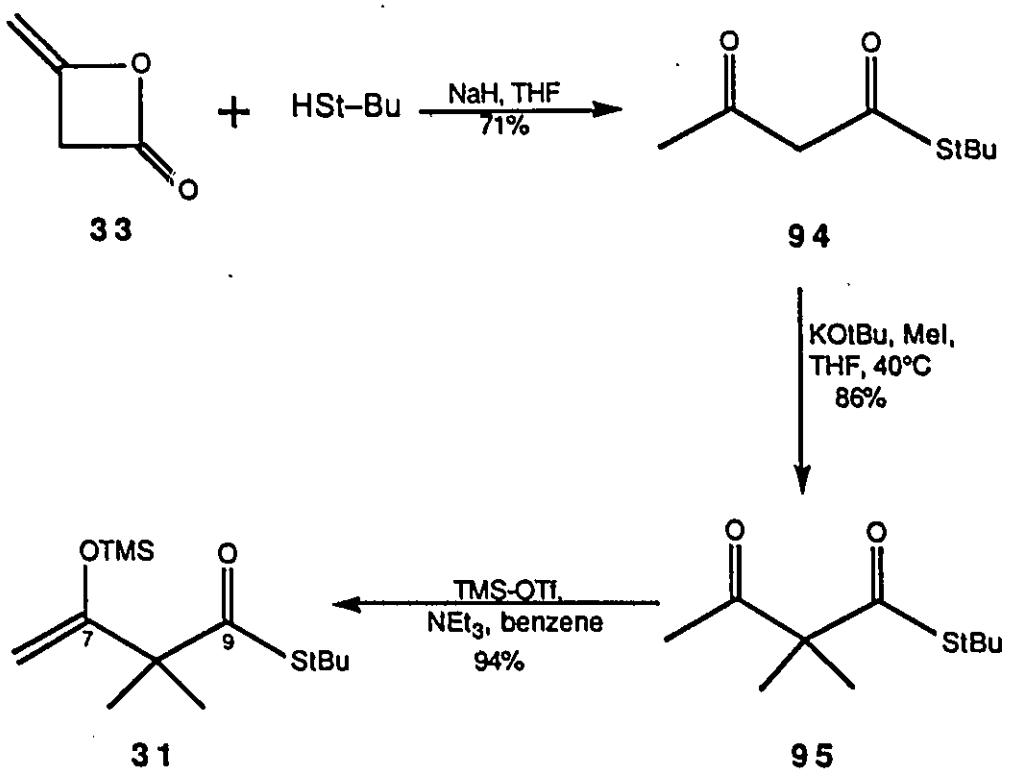
[81](a) Y.G. Perron, L.B. Crast, J.M. Essery, R.R. Fraser, J.C. Godfrey, C.T. Holdrege, W.F. Minor, M.E. Newbert, R.A. Partyka, and L.C. Cheney, *J. Med. Chem.*, 7, 483 (1964). (b) W.M. Braun, R.A. Braun, H.R. Crissman, M. Opperman, and R.M. Adams, *J. Org. Chem.*, 36, 2388 (1971). (c) G. Sabbioni and J.B. Jones, *J. Org. Chem.*, 52, 4565 (1987).

[82]E.J. Corey and J.W. Suggs, *Tetrahedron Lett*, 2647 (1975).



Briefly, using a procedure developed by Ley[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[84] involving the alkylation of various

[83]C.M.J. Fox and S.V. Ley, *Organic Syntheses*, **66**, 108 (1987).
[84]W.B. Renfrow and A. Renfrow, *J. Am. Chem. Soc.*, **68**, 1801 (1946).

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, NEt_3, benzene, 5°C to 25°C, 4 hours) of **95**[85]. 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 C_4 and C_5 Synthons 31 and 83

The key condensation of the C_4 and C_5 synthons was accomplished as shown on the next page.

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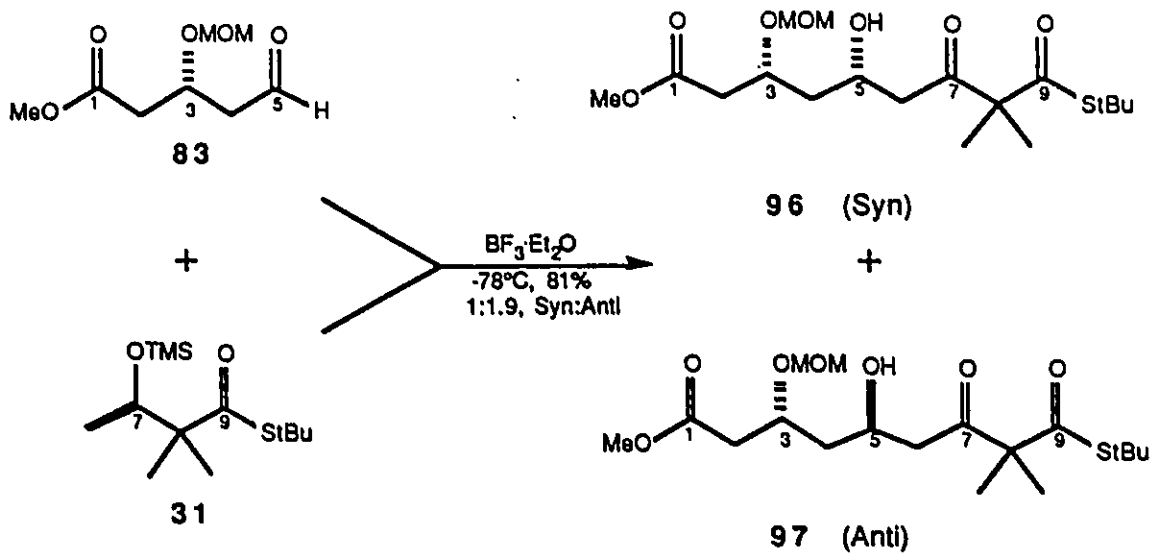
[85](a) G. Simchem and W.Kober, *Synthesis*, 259 (1979). (b) H. Emde, A. Gotz, K. Hoffman, and G. Simchen, *Liebigs Ann. Chem.*, 1643 (1981). (c) E.J. Corey, H. Cho, C. Rucker, and D.H. Hua, *Tetrahedron Lett.*, 22, 3455 (1981), (d) A.P. Kozikowski, T.R. Nieduzak, T. Konoike, and J.P. Springer, *J. Am. Chem. Soc.*, 109, 5167 (1987).

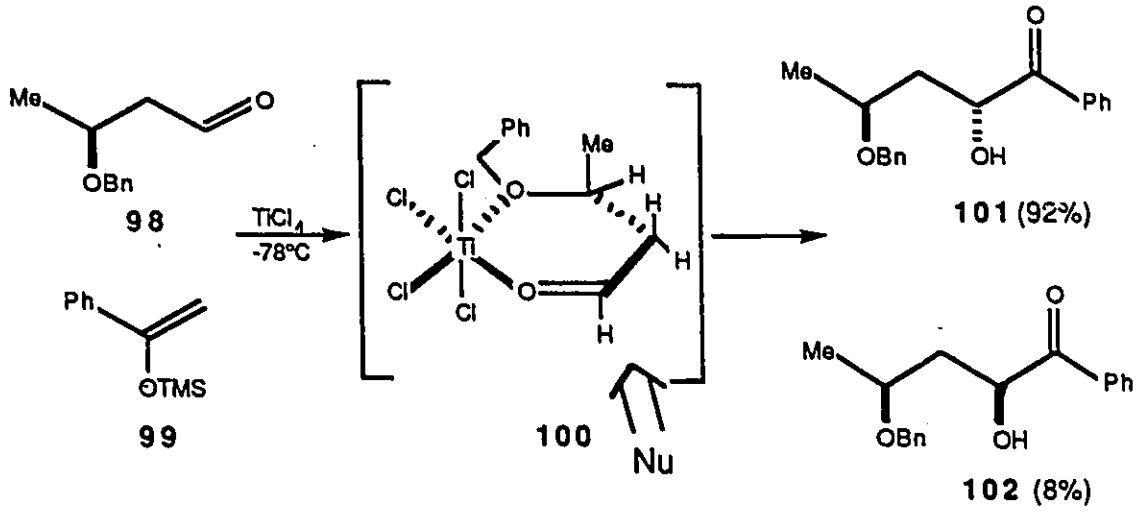


Initially, a direct aldol condensation between the lithium enolate derived from **95** and the β-alkoxyaldehyde **83** was attempted (**95**, LDA, $CeCl_3$, THF, -20°C, 30 minutes then **83**, -78°C, 1 hour). This afforded the diastereomeric aldol products **96** and **97** in 62% yield without significant diastereoselection (1.05:1; determined by ^1H NMR spectroscopy). Addition of $CeCl_3$ 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

[86]T. Imamato, T. Kusumoto, and M. Yokoyama, *Tetrahedron Lett.*, 24, 5233 (1983).

high diastereofacial selectivity towards the desired anti stereoisomer (**97**) under Ti(IV) or Sn(IV) tetrachloride chelation control addition. For instance, Reetz[73a] obtains impressive diastereoselectivity (92:8 anti to syn) for the $TiCl_4$ catalysed addition of the enol silane derived from acetophenone (**99**) onto the β-benzyloxyaldehyde **98**.



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[87] of intermediate **100**. Considerable evidence supports this model[88].

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

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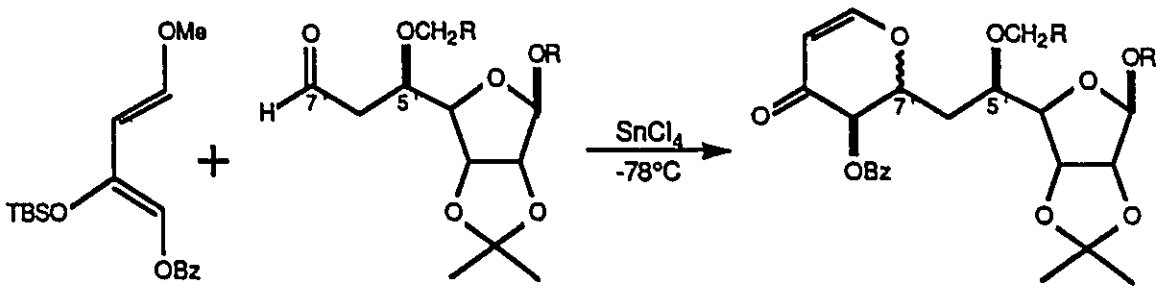
[87]G.E. Keck and S. Castellino, *J. Am. Chem. Soc.*, **108**, 3847 (1986).

[88]For a comprehensive discussion of stereoselectivity in the addition of organotitanium reagents to carbonyl compounds see: (a) M.T. Reetz 'Organotitanium Reagents in Organic Synthesis', Springer-Verlan, Berlin, 123-189 (1986). (b) C.H. Heathcock, S.K. Davidsen, K.T. Hug, and L.A. Flippin, *J. Org. Chem.*, **51**, 3027 (1986).

condensation. For instance, Danishefsky[73c] reported in his tunicamycin synthesis improved anti selectivity when a MOM ether was in the β-position of the chiral aldehyde **101**.

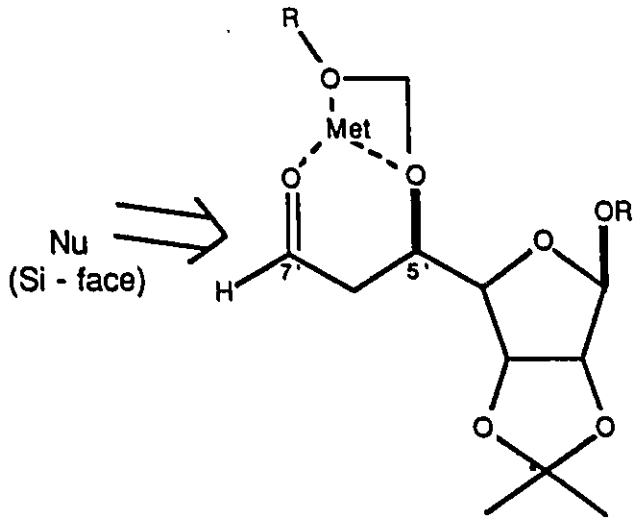


103 **104** **105**

	C(5')-C(7')–relationship (anti / syn)
R = Ph	0:1
R = OCH_2Ph	1:2
R = OMe	3:1

To rationalize these results, Danishefsky postulates a cage–type chelate as shown is Figure 16. The explanation for the C(5') benzyloxy 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 diastereochemical 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.

Figure 16 — Danishefsky's Proposed Cage–Type Chelate



104

A most interesting and, at the time, disturbing result was that the $SnCl_4$-mediated addition of **31** onto **83** (**83**, $SnCl_4$, CH_2Cl_2, -78°C, 15 minutes then **31**, -78°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 $TiCl_4$, but the MOM protecting group was also lost. Although **96** and **97** were obtained as an inseparable mixture of diastereomers, their stereochemical 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[89]. 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 ($BF_3 \cdot Et_2O$) 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 $BF_3 \cdot Et_2O$ catalysed aldol condensation would simulate C(3) chelation control.

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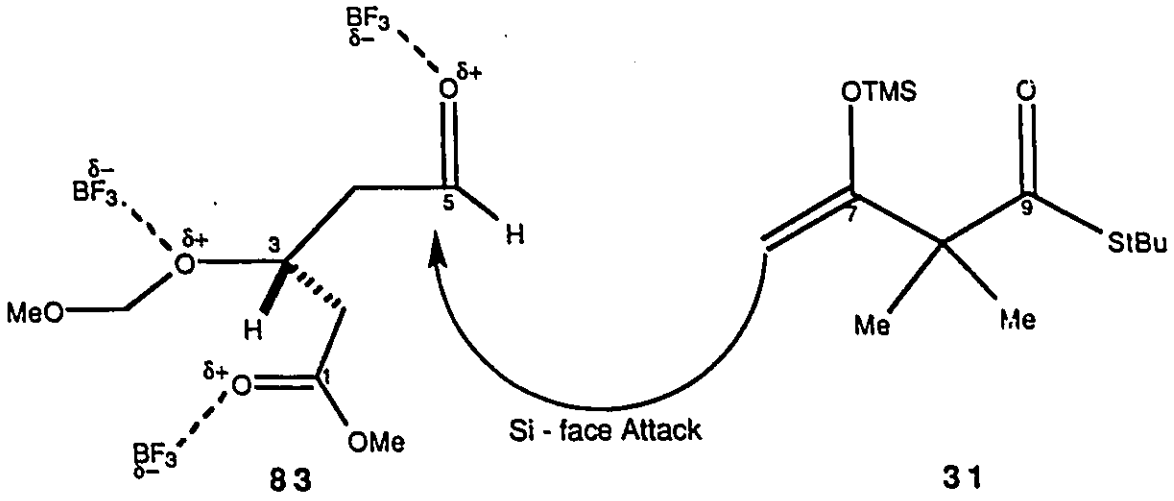
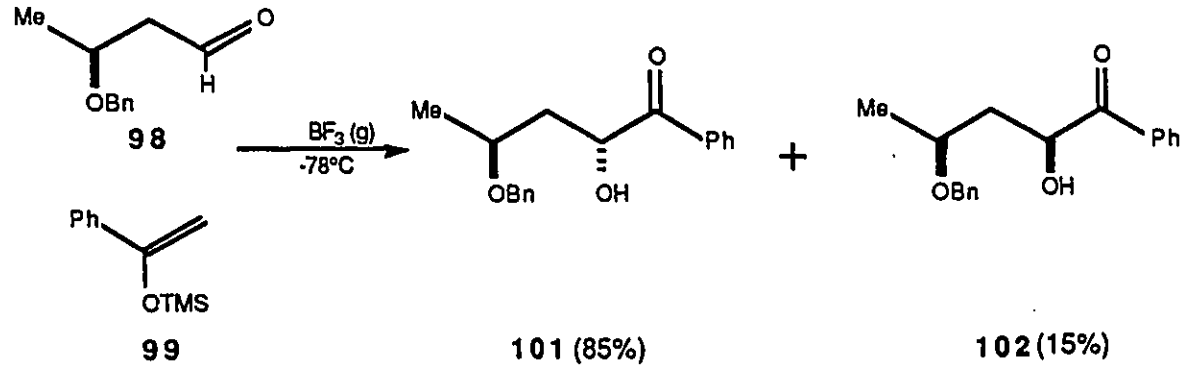
[89](a) K. Tomooka, T. Okinaga, K. Suzuki, and G.-i. Tsuchihashi, *Tetrahedron Lett.*, **30**, 1563 (1989). (b) T. Kunz and H.-U. Reissig, *Agnew. Chem., Int. Ed. Engl.*, **27**, 268. (c) T. Poll, J.O. Metter, and G. Helmchen, *Angew . Chem., Int. Ed. Engl.*, **24**, 112 (1985). (d) R. Frenette, M. Kakushima, R. Zamboni, R.N. Young, and T.R. Verhoeven, *J. Org. Chem.*, **52**, 304 (1987).

Figure 17 — $BF_3{\cdot}Et_2O$ Electrostatic Repulsion Model



A model of this type was proposed by Reetz[73b] to accommodate the observations shown below.

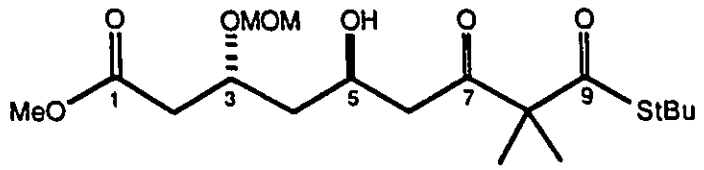


These postulates were duly rewarded since the $BF_3{\cdot}Et_2O$ catalysed aldol condensation of **31** with **83** (**83**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78°C, 15 minutes then **31**, -78°C, 1 hour) provided a 81% yield of the aldol products **96** and **97** with improved diastereoselectivity (anti: syn, 1.9:1).

As mentioned, the diastereomers **96** and **97** were not separable chromatographically. The diastereomeric ratio was assessed by integration of the ^1H 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):

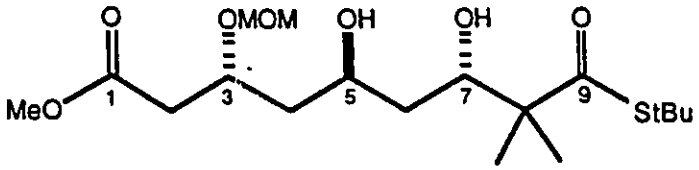
The β-hydroxy ketones **96** and **97** were subjected to the directed reduction method of Evans and Saskena[19] ($Me_4NHB(OAc)_3$, MeCN, HOAc, -40°C, 9 hours) to afford the desired C(5)-C(7)–anti diol **107** and its C(5)-C(7)–epimeric diastereomer **106** in 84% combined yield.



\+ C(5) – epimer

97 **96**

$Me_4NBH(OAc)_3$, CH_3CN, HOAc, -40° C, 84%



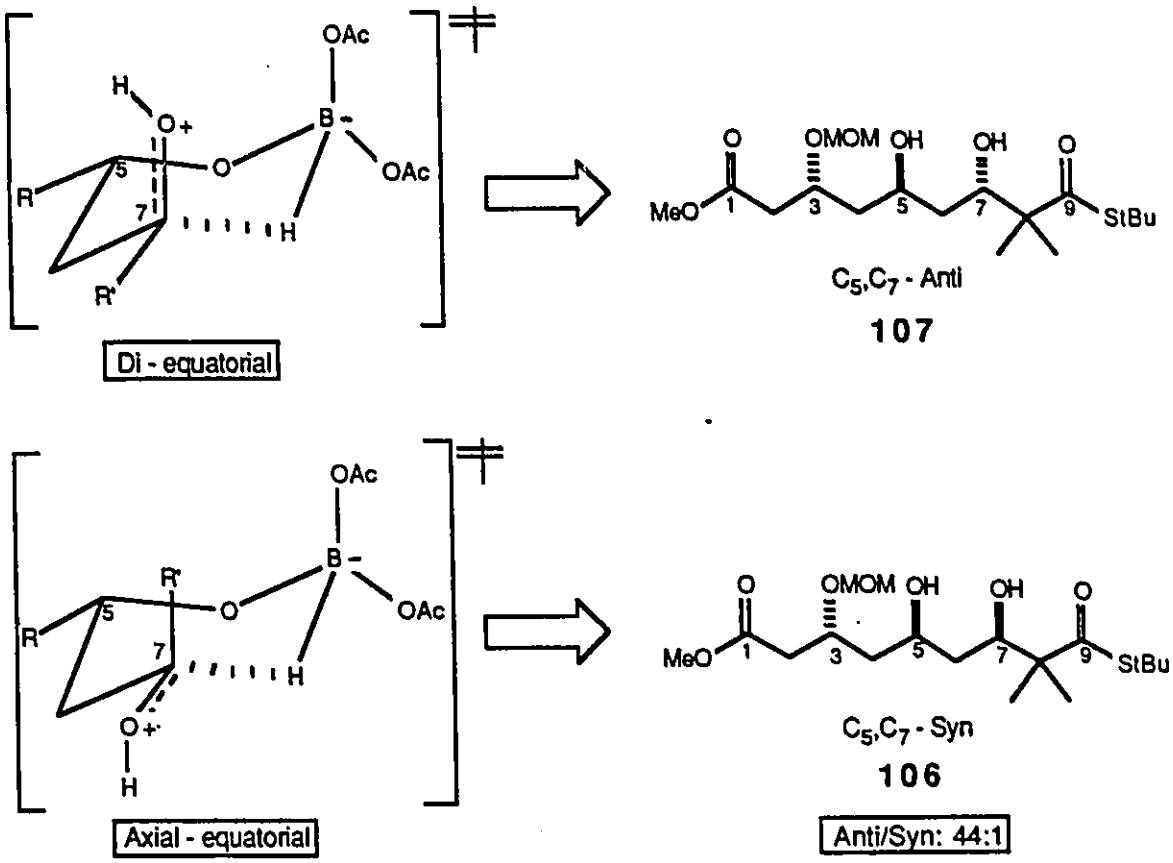
\+ C(5),C(7) – epimer

107 **106**

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[19]. Briefly, ligand exchange between the C(5) hydroxyl and the labile borohydride ligands affords the intermediate substrate-bound alkoxydiacetoxy 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.

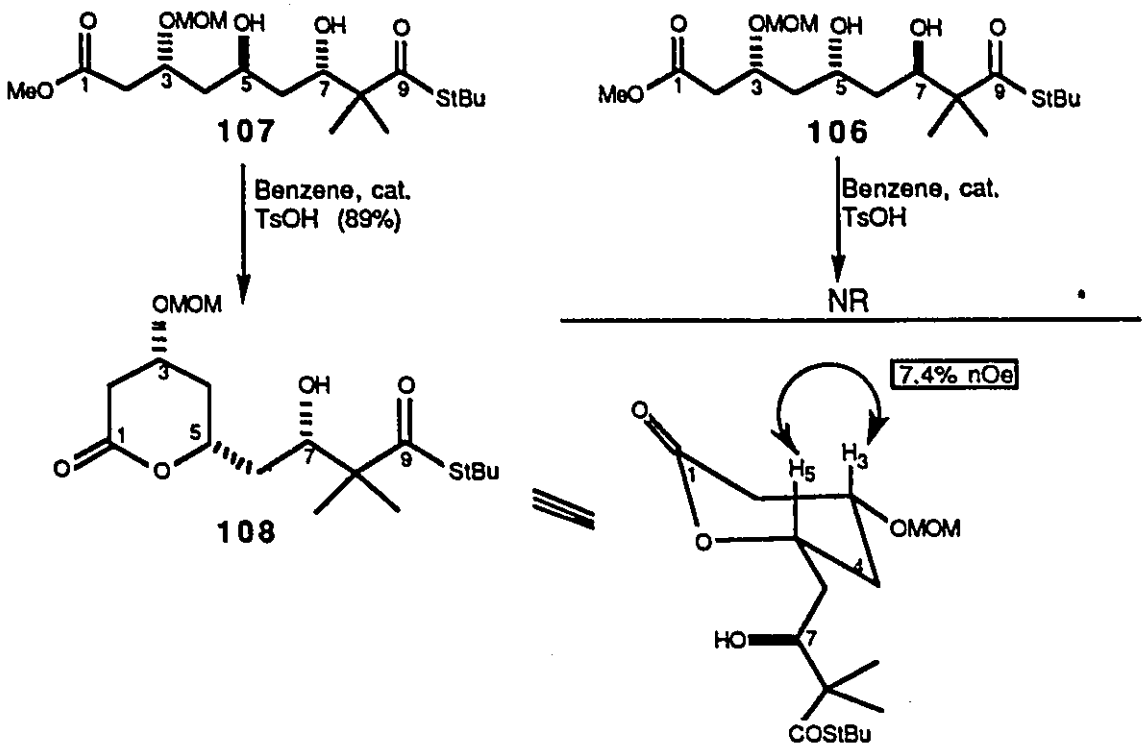
Figure 18 — Transition State for β-Hydroxy Ketone Reduction



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**.



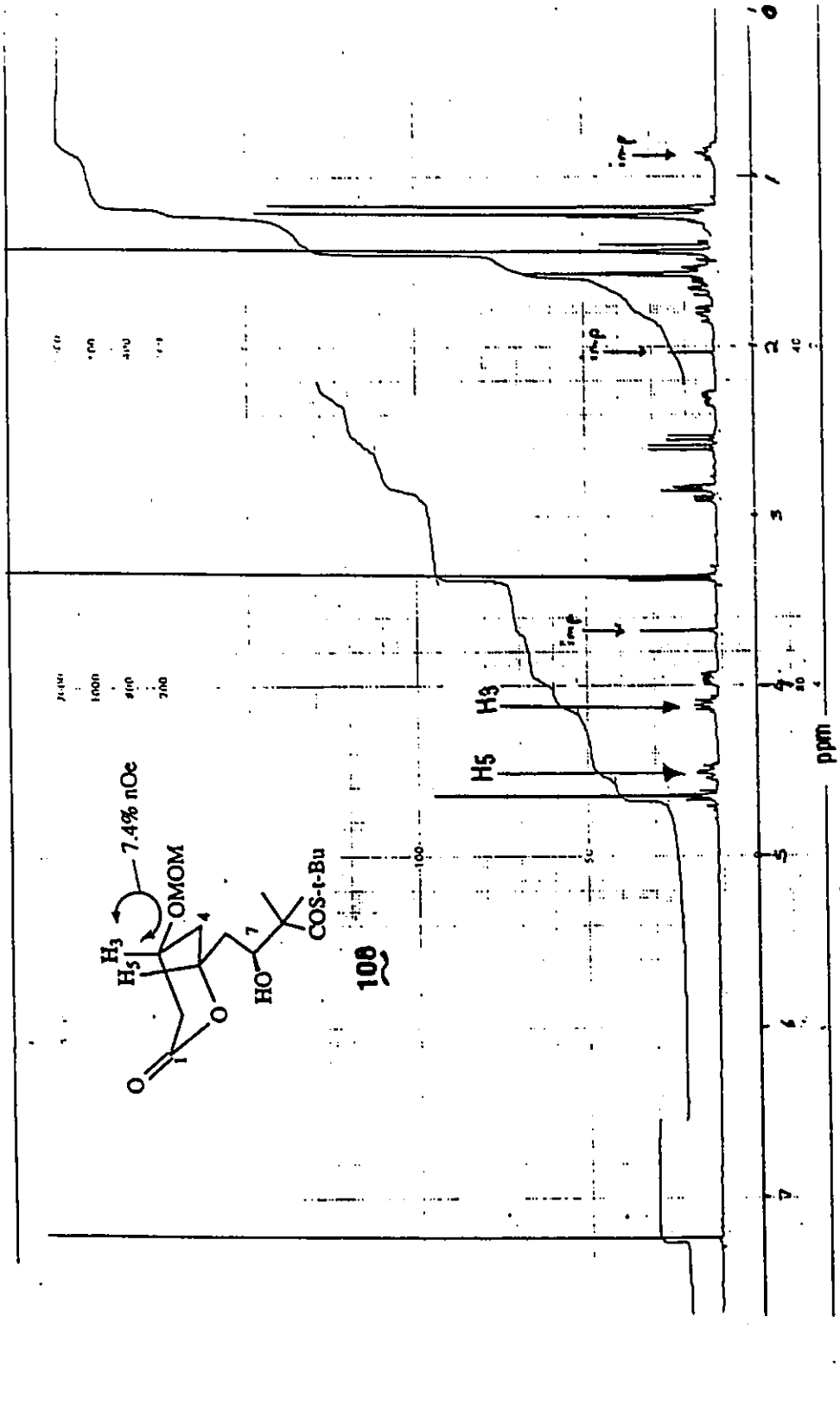
This reactivity difference may be rationalized as follows. The δ-lactone **108** is formed from **107** since it allows the substituents at C(3) and C(5) to adopt the diequatorial relationship in the chair form. This may be contrasted to the less thermodynamically favourable situation for **106**; the 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[90] neatly employed this phenomena in his synthetic efforts towards FK-506.

The identification of the δ-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_2CH_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

[90]S.J. Danishefsky and A. Villalobos, *J. Org. Chem.*, **54**, 15 (1989). For the formulation and another application of the concept of end-group differentiation by diastereoselective lactonization see: T.R. Hoye, D.R. Peck, and T.A. Swanson, *J. Am. Chem. Soc.*, **106**, 2738 (1984).

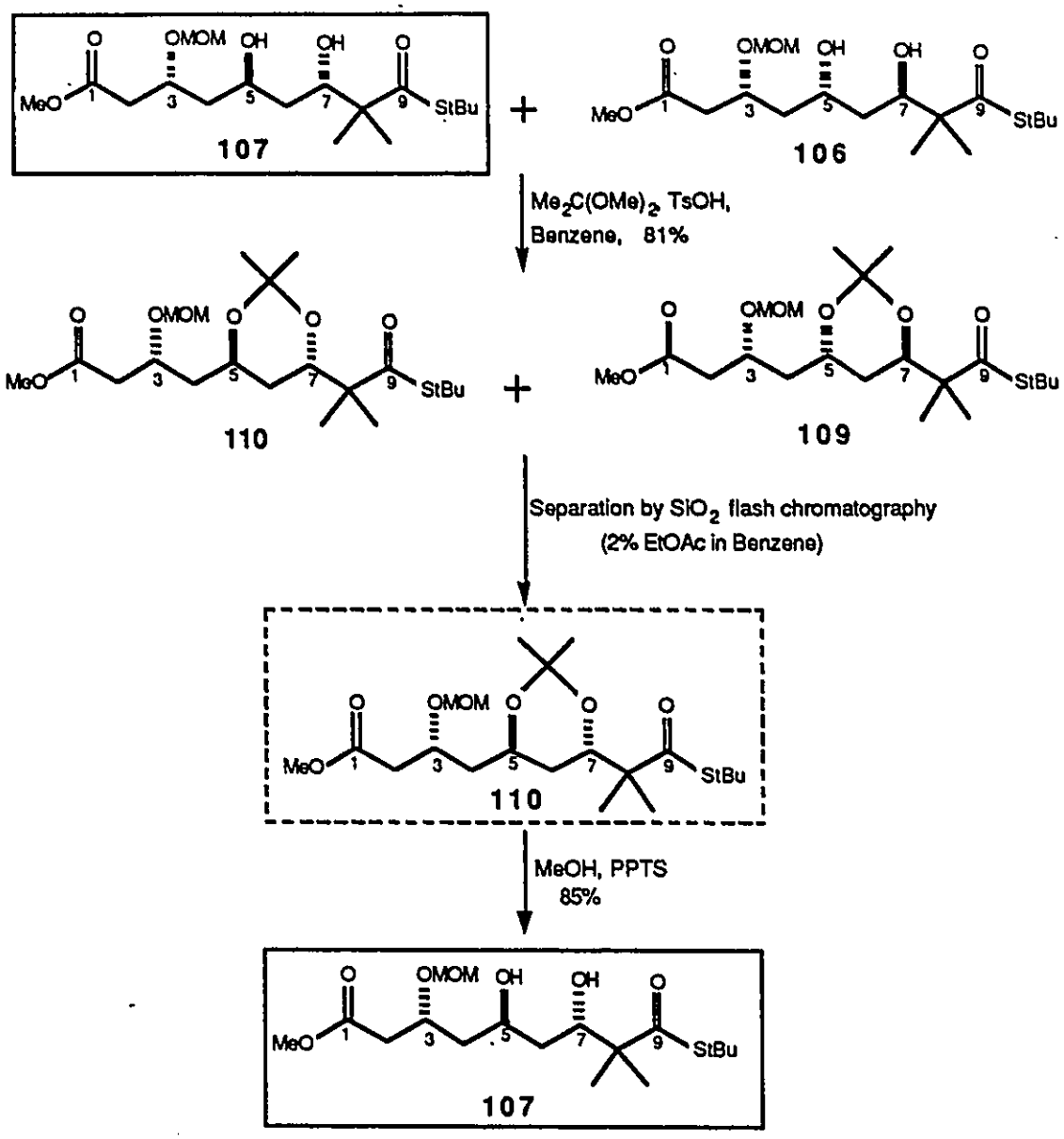
Figure 19 — ^{1}H NMR Spectrum of **108**



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% ^1H 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 β-hydroxy ketone reduction. The absolute stereochemistries at C(3), C(5), and C(7) were established by ^1H 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[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** [$(\alpha)_D$ = -19.4° (c=1.0, $CHCl_3$)] constitutes an appropriate intermediate for further synthetic elaboration of the bryostatin molecule. Structurally, it is closely related to Masamune's[14] C(1)–C(9) synthon **12** [(α) = -12.8° (c=0.80, $CHCl_3$); 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 ^1H NMR spectrum for **110** is given is Figure 20.

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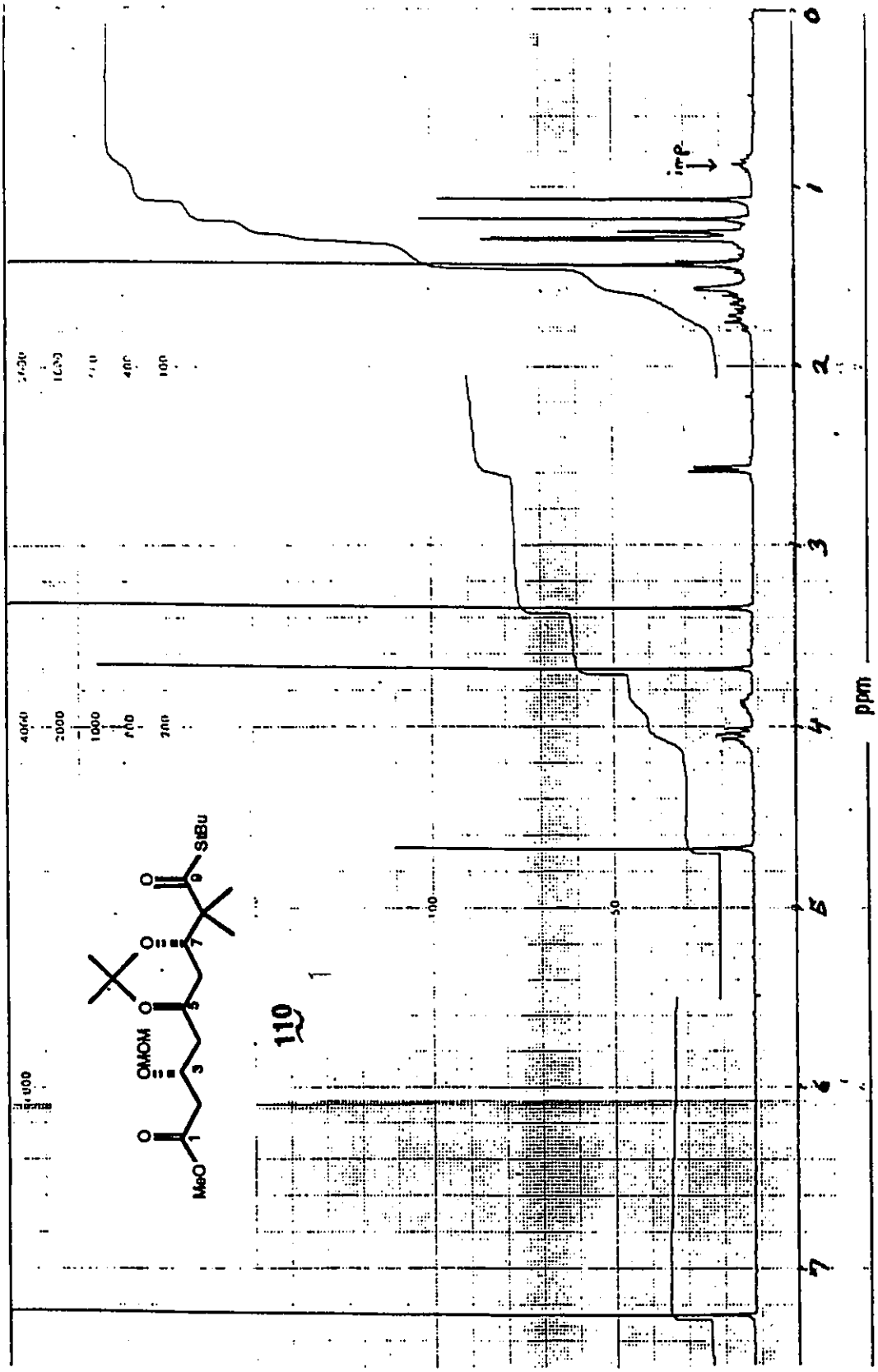
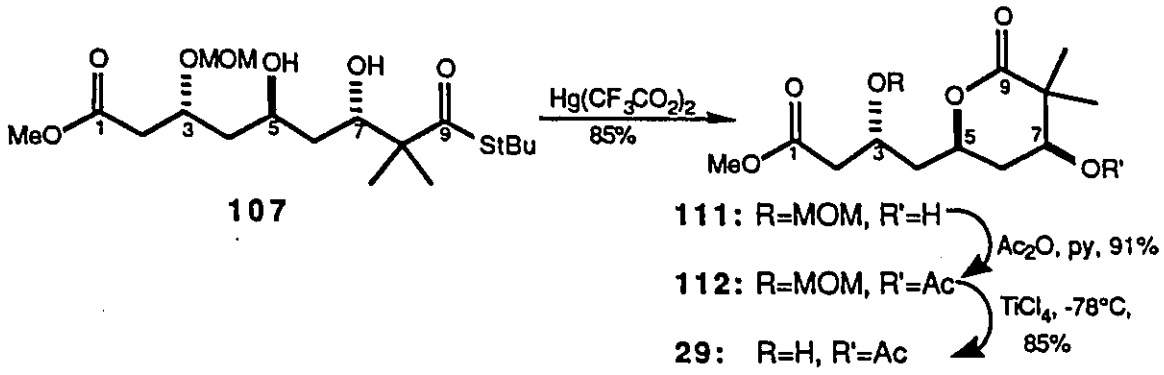
[91]S.D. Rychnovsky and D.J. Skalitzky, *Tetrahedron Lett.*, **31**, 945 (1990).

Figure 20 — ^{1}H NMR Spectrum of **110**



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[75]. Thus, treatment of the anti-diol **107** with mercury trifluoroacetate [$Hg(CF_3CO_2)_2$, 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.



107

The structure of **111** was confirmed by spectral analysis. For example, ^1H NMR revealed the loss of the tert-butylthiol group by the disappearance of the resonance for the $C(CH_3)_3$ 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 β-lactones occurs at ~1810 cm^{-1} whereas **111** had a carbonyl stretching frequency at 1721 cm^{-1} (consistent with δ-lactones). The assignments of the protons in the ^1H NMR spectrum were ascertained by HOMCOR– and NOESY– ^1H NMR experiments.

Bryostatin 1 (**1a**) has the C(7) hydroxyl protected as its acetate. Thus, the δ-lactone **111** was acetylated using standard methodology (Ac_2O, pyridine, 6 hours) to provide the C(7) acetate **112** in excellent yield (91%).

The final step in the synthesis of the target δ-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 δ-lactone **112** was subjected to the conditions discovered above ($TiCl_4$, CH_2Cl_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 δ-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 ^1H 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)

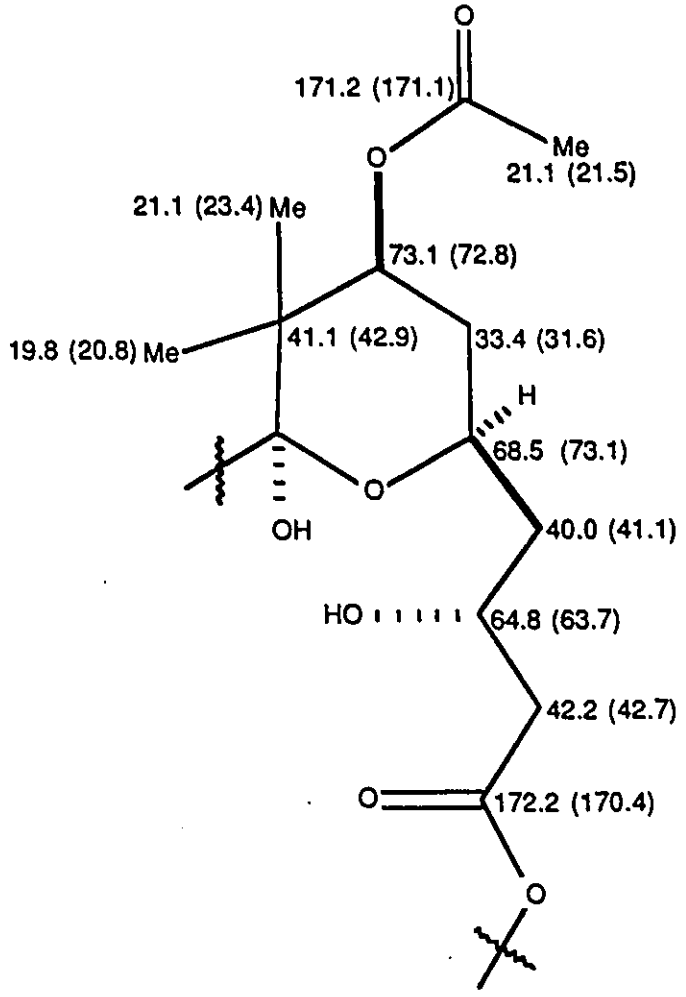
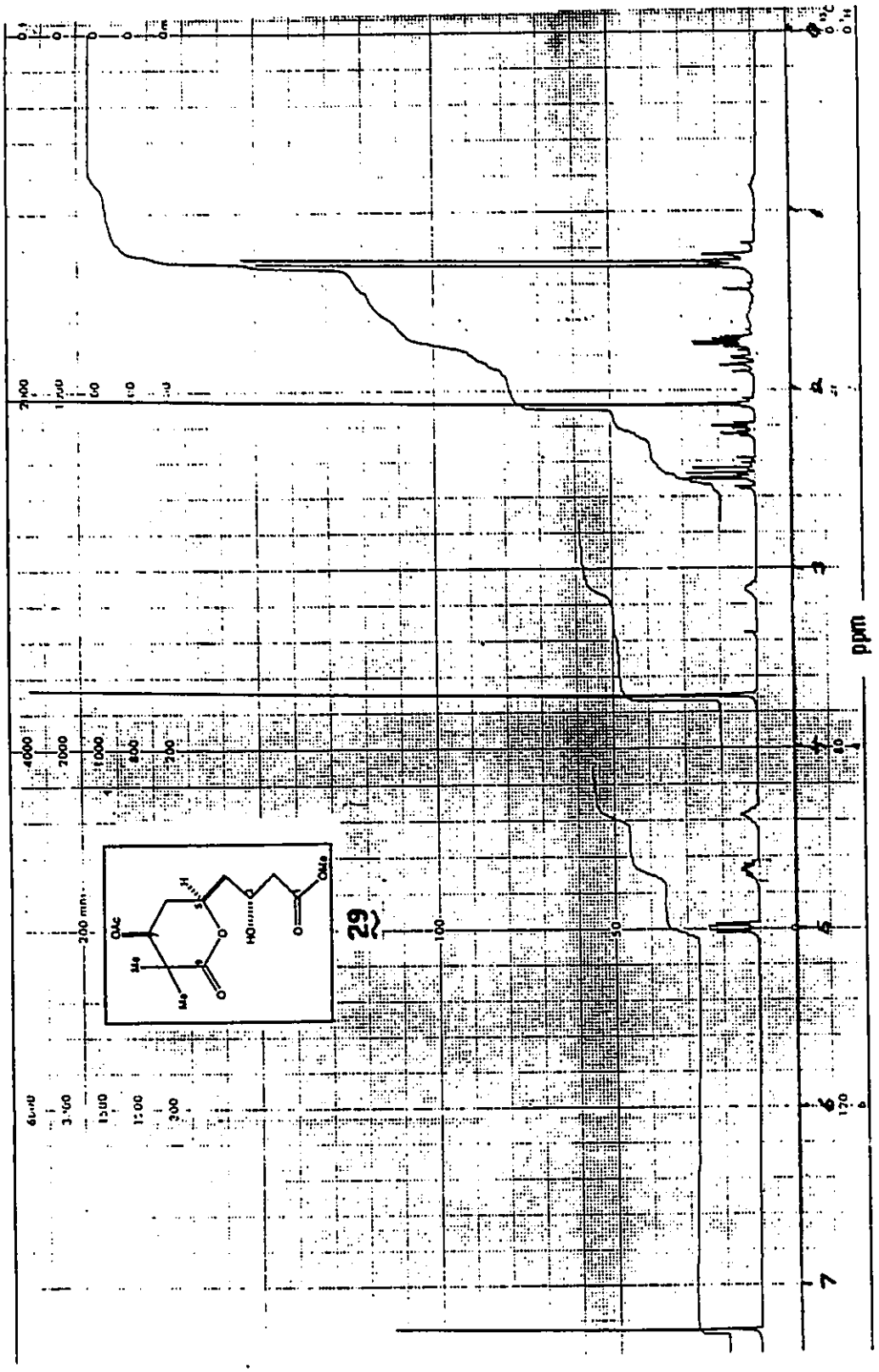


Figure 22 — ^{1}H NMR spectrum of **29**



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 Na_2HPO_4 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 Na_2SO_4 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 SiO_2 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° (c = 3, $CHCl_3$). IR (thin film) υ: 3150, 2961, 1734, 1442, 1152, 1103 cm^{-1}. ^1H NMR (300 MHz) δ: 11.1 (br s, 1H, COOH, exchangeable), 4.68 (s, 2H, OCH_2O), 4.40 (app qu, 1H, H_3), 3.68 (s, 3H, CO_2CH_3), 3.34 (s, 3H, OCH_3), 2.58 - 2.75 (m, 4H, 2 X CH_2). ^{13}C NMR (50.4 MHz) δ: 176.5 (CO_2H), 171.4 (CO_2CH_3), 96.4 (OCH_2O), 71.2 (C_3), 55.5 (OCH_3), 51.6 (CO_2CH_3), 39.5, 39.4 (C_2, C_4). MS (EI) m/z: 175 (M^+-31, 4%). MS (CI ether) m/z: 207 (M^++1, 15%), 175 (M^+-31, 100%); Anal. calcd. for $C_8H_{14}O_6$: C, 46.60, H, 6.85; found: C, 47.08, H, 6.91.

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 SiO_2 flash chomatography (1:1 ether/hexane) to afford 0.33 g (65%) of the hemi-orthoester **92** as the major product. IR (thin film) υ: 3462, 2941, 2921, 1741, 1441, 1285, 1168, 1151, 1098 cm^{-1}. ^1H NMR (300 MHz) δ (major diastereomer): 5.253 (s, 1H,

OCH_2O), 5.250 (s, 1H, OCH_2O), 4.42 - 4.51 (m, 1H, H_3), 3.71 (s, 3H, CO_2CH_3) 3.46 (s, 3H, OCH_3), 3.32 (br s, 1H, OH, exchangeable), 2.59 (d. J = 6.0, 2H, H_2), 2.56 (d, J = 6.3, 2H, H_4). ^{13}C NMR (50.4 MHz) δ: 172.0 (C_5), 171.1 (CO_2CH_3), 90.6 (OCH_2O), 64.6 (C_3), 57.8 (OCH_3), 51.9 (CO_2CH_3), 40.7, 40.4 (C_2, C_4). MS (EI) m/z: 143 (M^+-63, 3%), 127 (M^+-79, 2%), 100 (M^+-106, 10%). MS (CI ether) m/z: 207 (M^++1, 4%), 189 ((M^++1)-18, 9%), 175 (M^+-31, 100%). Anal. calcd. for $C_8H_{14}O_6$: 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 $NaBH_4$ (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 NH_4Cl (50 mL) and transferred to a separatory funnel charged with 150 mL of ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The combined aqueous layers were re-extracted with an equal volume of ethyl acetate and subsequently dried over Na_2SO_4 and the solvent removed *in vacuo* to yield a colourless oil. Purification by SiO_2 flash chromatography (7:3 ethyl acetate/hexane) afforded 2.27 g (81%) of the alcohol **89** as a colourless oil. $[\alpha]_D$ = +14.2° (c = 1.0, $CHCl_3$). IR (thin film) υ: 3450, 2960, 1740, 1442, 1153, 1103 cm^{-1}. ^1H NMR (300 MHz) δ: 4.72 (d, A of

AB, J = 6.9 Hz, 1H, OCH_2O), 4.64 (d, B of AB, J = 6.9 Hz, 1H, OCH_2O), 4.12 - 4.30 (m, 1H, H_3), 3.72-3.82 (m, 2H, H_5), 3.70 (s, 3H, CO_2CH_3), 3.37 (s, 3H, OCH_3), 2.66 (dd, A of ABX, J = 7.0, 15.5 Hz, 1H, H_2), 2.51 (dd, B of ABX, J = 5.7, 15.5 Hz, 1H, $H_{2'}$), 2.25 (b, 1H, OH, exchangeable), 1.79 - 1.98 (m, 2H, H_4). ^{13}C NMR (50.4 MHz) δ: 171.8 (CO_2CH_3), 96.3 (OCH_2O), 72.9 (C_3), 58.8 (C_5), 55.4 (OCH_3), 51.3 (CO_2CH_3), 40.0 (C_2), 37.1 (C_4). MS (EI) m/z: 161 (M^+-31,3%). MS (CI 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 $C_8H_{16}O_5$: 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 SiO_2 and the solvent removed *in vacuo* to provide a colourless oil. The oil was purified by SiO_2 flash chromatography (7:3 ether/hexane) to deliver 1.66 g of aldehyde **83** (84%). $[\alpha]_D$ = +4.9° (c = 1.5, $CHCl_3$). IR (thin film) υ: 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, OCH_2O), 4.65 (d, B of AB, J = 7.1 Hz, 1H, OCH_2O), 4.49 (app qu, 1H, H_3), 3.68

(s, 3H, CO_2CH_3), 3.32 (s, 3H, OCH_3), 2.72 - 2.81 (m, 2H, H_4), 2.69 (dd, A of ABX, J = 6.9, 15.7 Hz, 1H, H_2), 2.57 (dd, B of ABX, J = 5.9, 15.7 Hz, 1H, $H_{2'}$). ^{13}C NMR (50.4 MHz) δ: 200.4 (CHO), 171.2 (CO_2CH_3), 96.5 (OCH_2O), 69.9 (C_3), 55.6 (OCH_3), 51.6 (CO_2CH_3), 48.6 (C_4), 39.6 (C_2). MS (EI) m/z : 175 (M^+-15, 1%), 159 (M^+-31, 1%), 145 (M^+-45, 4%). MS (CI ether) m/z: 191 (M^++1, 3%), 159 (M^+-31, 100%). Anal. calcd. for $C_8H_{14}O_5.{}^1/_2H_2O$: C, 48.24, H, 7.59; found: C, 48.50, H, 7.05. HRMS (recorded on a Kratos Concept 2H mass spectrometer) calcd. for $C_7H_{11}O_5$ (M^+-CH_3): 175.0606; found: 175.0602.

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

This material was prepared according to the method of Ley[83]. 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 NH_4Cl (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 $NaHCO_3$, 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 Na_2SO_4 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) υ: 1712, 1676, 1621 cm^{-1}. ^1H NMR (200 MHz) δ: 3.57 (s, 2H, CH_2), 2.26 (s, 3H, CH_3CO), 1.48 (s, 9H, $C(CH_3)_3$); 15% in enol-form: 5.33 (s, 1H, C=CH), 1.90 (s, 3H, $CH_3C(OH)=C$), 1.48 (s, 9H, $C(CH_3)_3$).

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 NH_4Cl (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 $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 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) υ: 2973, 1722, 1675, 1461, 1368, 948 cm^{-1}. ^1H NMR (200 MHz) δ: 2.16 (s, 3H, CH_3CO), 1.48 (s, 9H, $C(CH_3)_3$), 1.37 (s, 6H, gem CH_3's). ^{13}C NMR (50.4 MHz) δ:

205.6 (C=O), 201.8 ((C=O)S), 63.9 ($C(CH_3)_3$), 48.0 (C_8), 29.4 ($C(CH_3)_3$), 25.5 (CH_3CO), 21.8 (gem CH_3's). MS (EI) m/z: 202 (M^+, 1%), 160 (M^+-42, 2%), 146 (M^+-56, 30%). MS (CI ether) m/z: 203 (M^++1, 100%). HRMS calcd. for $C_9H_{10}O_2S$ (M^+-$(CH_3)_2C=CH_2$): 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 $NaHCO_3$. 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 $NaHCO_3$, and brine. Drying over Na_2SO_4 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) υ: 2970, 1685, 1628, 1258, 1171, 1022 cm^{-1}. ^1H NMR (200 MHz) δ: 4.26 (d, A of AB, J = 2.0 Hz, 1H, $H_2C=C$), 4.11 (d, B of AB, J = 2.0 Hz, 1H, $H_2C=C$), 1.41 (s,

9H, $C(CH_3)_3$), 1.27 (s, 6H, gem CH_3's), 0.19 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (50.4 MHz) δ: 204.3 ((C=O)S), 161.8 (C=CH-O), 88.8 (CH_2=C), 56.0 ($C(CH_3)_3$), 46.8 (C_8), 29.7 ($C(CH_3)_3$), 23.9 (gem CH_3's), -0.25 ($Si(CH_3)_3$). MS (EI) m/z: 217 (M^+- 57, 22%). HRMS calcd. for $C_9H_{17}O_2SSi$ (M^+- $C(CH_3)_3$): 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 NH_4Cl 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 $NaHCO_3$ (20 mL) and brine (20 mL) was accomplished. The ethereal layer was dried over Na_2SO_4 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 $NaHCO_3$ and warmed to ambient temperature. The mixture was then diluted with 50 mL of dichloromethane and washed with saturated aqueous $NaHCO_3$ and brine (130 mL of each). The organic layer was dried over Na_2SO_4 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 ($TiCl_4$, $SnCl_4$, $ZnBr_2$, ZnI_2, $MgCl_2$). The experimental protocol was identical. When data for the minor, and undesired, (3R, 5S)- diastereomer (**96**) differs, it appears in brackets. IR (thin film) υ: 3470, 2962, 2935, 1739, 1668, 1368, 1151, 1102, 1038 cm^{-1}. ^1H NMR (300 MHz) δ: 4.60 - 4.70 (m, 2H, OCH_2O), 4.10 - 4.32 (m, 2H, H_3, H_5), 3.66 (s, 3H, CO_2CH_3), 3.37 (3.33) (s, 3H, OCH_3), 3.25 (br s, 1H, OH, exchangeable), 2.51 - 2.66 (m, 4H, H_2, H_6), 1.72 - 1.90 (m, 1H, H_4), 1.45 - 1.70 (m, 1H, $H_{4'}$), 1.44 (s, 9H, $C(CH_3)_3$), 1.36 (s, 3H, gem CH_3), 1.35 (s, 3H, gem

CH_3). ^{13}C NMR (50.4 MHz) δ: 208.5 (C=O), 201.7 ((C=O)S), 171.7 (CO_2CH_3), 96.9 (96.1) (OCH_2O), 72.4 (73.0) (C_3), 64.1 (65.4) (C_5), 63.9 ($C(CH_3)_3$), 55.7 (55.6) (OCH_3), 51.4 (CO_2CH_3), 48.4 (C_8), 45.1 (45.0) (C_6), 41.6, 40.5 (40.9, 39.7) (C_2, C4), 29.5 ($C(CH_3)_3$), 22.0 (gem CH_3), 21.8 (gem CH_3). MS (CI ether) m/z: 361 (M^+-31, 6%), 343 (M^+-49, 5%), 313 (M^+-79, 43%). Anal. calcd. for $C_{18}H_{32}O_7S$: 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-dimethylnonanoic 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 $NaHCO_3$ (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 $NaHCO_3$ (40 mL). The aqueous layer was back extracted four times with 30 mL portions of dichloromethane and the combined organic layers were dried over Na_2SO_4 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) υ: 3468, 2960, 2938, 1742, 1669, 1368, 1153, 1103 cm^{-1}. ^{1}H NMR (300 MHz) δ: 4.64 - 4.73 (m, 2H , OCH_2O), 4.12 - 4.20 (m, 1H, H_3), 3.91 - 4.00 (m, 2H, H_5, H_7), 3.67 (s, 3H, CO_2CH_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) δ: 208.7 ((C=O)S), 171.8 ($\mathbf{C}O_2CH_3$), 97.1 (96.1) (OCH_2O), 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 ($\mathbf{C}(CH_3)_3$), 51.7 ($CO_2\mathbf{C}H_3$), 47.6 (C_8), 41.9, 40.4, 37.9 (41.8, 40.1) (C_2, C_4, C_6), 29.6 ($C(\mathbf{C}H_3)_3$), 22.3 (22.0) (gem CH_3), 20.9 (gem CH_3). MS (CI 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-Butylthioate-5,7-O-isopropylidene-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 $NaHCO_3$ (30 mL) and brine (30 mL). The ethereal layer was dried over Na_2SO_4 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 SiO_2 flash chromatography (3.5% ethyl acetate in benzene and 120:1 SiO_2 (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)]. $[\alpha]_D$ = -19.4° (c = 1.0, $CHCl_3$). IR (thin film) υ: 2950, 1745, 1675, 1382, 1228, 1141, 949 cm^{-1}. ^1H NMR (300 MHz) δ: 4.65 (s, 2H, OCH_2O), 3.96 - 4.10 (m, 1H, H_3), 4.02 (dd, J = 6.5, 9.7 Hz, 1H, H_7), 3.78 - 3.90 (m, 1H, H_5), 3.67 (s, 3H, CO_2CH_3), 3.33 (s, 3H, OCH_3), 2.57 (d, J = 5.5 Hz, 1H, H_2), 2.56 (d, J = 6.4 Hz, 1H, $H_{2'}$), 1.50 - 1.88 (m, 4H, H_4, H_6), 1.42 (s, 9H, $C(CH_3)_3$), 1.28 (s, 3H, $(CH_3)_2C(OR)_2$), 1.27 (s, 3H, $(CH_3)_2C(OR)_2$), 1.17 (s, 3H, gem CH_3), 1.06 (s, 3H, gem CH_3). ^{13}C NMR (50.4 MHz) δ: 206.1 ((C=O)S), 172.1 ($\mathbf{C}O_2CH_3$), 100.6 ($(CH_3)_2\mathbf{C}(OR)_2$), 97.2 (OCH_2O), 73.2 (C_3), 70.8 (C_7), 63.4 (C_5), 55.6 (OCH_3), 53.4 ($\mathbf{C}(CH_3)_3$), 51.5 ($CO_2\mathbf{C}H_3$), 47.1 (C_8), 41.4, 41.1 (C_2, C_6), 33.2 (C_4), 29.6 ($C(\mathbf{C}H_3)_3$), 24.3 ($(\mathbf{C}H_3)_2C(OR)_2$, 24.0 ($(CH_3)_2C(OR)_2$), 20.1 (gem CH_3), 20.0 (gem CH_3). MS (CI

ether) m/z: 435 (M^++1, 1%), 403 (M^+-31, 6%), 377 (M^+-57, 69%). Anal. calcd. for $C_{21}H_{38}O_7S$: 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 $NaHCO_3$ and extracted with 100 mL of ether. The ethereal layer was washed with brine (30 mL) and dried over Na_2SO_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**. $[\alpha]_D$ = -1.5° (c = 1.0, $CHCl_3$). IR (thin film) υ : 3468, 2960, 2938, 1742, 1669, 1368, 1153, 1103 cm^{-1}. ^1H NMR (300 MHz) δ: 4.73 (d, A of AB, J = 6.8 Hz, 1H, OCH_2O), 4.63 (d, B of AB, J = 6.8 Hz, 1H, OCH_2O), 4.12 - 4.20 (m, 1H, H_3), 4.01 - 4.11 (m, 1H, H_5), 3.98 (dd, J = 6.5, 6.6 Hz, 1H, H_7), 3.67 (s, 3H, CO_2CH_3), 3.38 (s, 3H, OCH_3), 2.65 (dd, A of ABX, J = 7.2, 15.5 Hz, 1H, H_2), 2.52 (dd, B of ABX, J = 5.5, 15.5 Hz, 1H, $H_{2'}$), 1.48-1.90 (m, 4H, H_4, H_6), 1.44 (s, 9H, $C(CH_3)_3$), 1.19 (s, 6H, gem CH_3's). ^{13}C NMR (50.4 MHz) δ: 208.7 ((C=O)S), 171.8 ($\mathbf{C}O_2CH_3$), 97.1 (OCH_2O), 73.7, 73.2 (C_3, C_7), 65.1 (C_5), 55.9 (OCH_3), 54.2 ($\mathbf{C}(CH_3)_3$), 51.7 ($CO_2\mathbf{C}H_3$), 47.6 (C_8), 41.9, 40,4, 37.9 (C_2, C_4, C_6), 29.6 ($C(\mathbf{C}H_3)_3$), 22.3 (gem CH_3), 20.9 (gem CH_3). MS (CI 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-Butylthioate-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. $[\alpha]_D$ = -24.1° (c = 0.50, $CHCl_3$). IR (thin film) υ: 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, H_5), 4.12 (app qu, 1H, H_3), 3.96 (dd, J = 6.6, 11.4 Hz, 1H, H_7), 3.35 (s, 3H, OCH_3), 2.87 (dd, A of ABX, J = 6.0, 17.1 Hz, 1H, H_2), 2.57 (dd, B of ABX, J = 7.0, 17.1 Hz, 1H, $H_{2'}$), 1.52 - 1.88 (m, 4H, H_4, H_6), 1.44 (s, 9H, $C(CH_3)_3$), 1.22 (s, 3H, gem CH_3), 1.18 (s, 3H, gem CH_3). ^{13}C NMR δ: 209.2 ((C=O)S), 170.6 (RCO_2R'), 95.2 (OCH_2O), 73.7, 72.6 (C_3, C_7), 69.0 (C_5), 55.5 (OCH_3), 53.8 ($C(CH_3)_3$), 47.9 (C_8), 37.6, 37.1, 36.2 (C_2, C_4, C_6), 29.6 ($C(CH_3)_3$), 23.3 (gem CH_3), 20.3 (gem CH_3). MS (CI 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° (c = 0.50, $CHCl_3$). IR (thin film) υ: 3450, 2961, 2938, 1727, 1441, 1392, 1268, 1155, 1032 cm^{-1}. ^1H NMR (300 MHz) δ: 4.70 (d, A of AB, J = 6.8 Hz, 1H, OCH_2O), 4.68 (d, B of AB, J = 6.8 Hz, 1H, OCH_2O), 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_2CH_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_2R'), 171.5 (CO_2CH_3), 97.0 (OCH_2O), 72.8, 71.6, 71.5 (C_3, C_5, C_7), 55.7 (OCH_3), 51.6 (CO_2CH_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 (CI 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-6,8-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 $NaHCO_3$, and brine. The ethereal layer was then dried over Na_2SO_4 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**. $[\alpha]_D$ = +45° (c = 0.50, $CHCl_3$). IR (thin film) υ: 2930, 1740, 1375, 1238, 1155, 1032 cm^{-1}. ^1H NMR (300 MHz) δ: 4.97 (dd, J = 4.3, 10.4 Hz, 1H, H_7), 4.68 (s, 2H, OCH_2O), 4.50 - 4.61 (m, 1H, H_5), 4.25 (app qu, 1H, H_3), 3.67 (s, 3H, CO_2CH_3), 3.34 (s, 3H, OCH_3), 2.62 (dd, A of ABX, J = 5.86, 15.2 Hz, 1H, H_2), 2.55 (dd, B of ABX, J = 5.92, 15.2 Hz, 1H, H_2), 2.03 - 2.12 (m, 1H, H_4), 2.08 (s, 3H, CH_3CO_2), 1.70 - 1.82 (m, 3H, H_4, H_6), 1.29 (s, 3H, gem CH_3), 1.27 (s, 3H, gem CH_3). ^{13}C NMR (50.4 MHz) δ: 175.7 (RCO_2R'), 171.3 (CH_3CO_2), 170.4 (CO_2CH_3), 96.9 (OCH_2O), 73.0, 72.6, 71.4 (C_3, C_5, C_7), 55.7 (OCH_3), 51.6 (CO_2CH_3), 42.9 (C_8), 42.0, 40.4 (C_2, C_4), 31.6 (C_6), 23.4 (gem CH_3), 21.5 (CH_3CO_2), 20.8 (gem CH_3). MS (EI) m/z: 315 (M^+-31, 1%). MS (CI ether) m/z: 347 (M^++1, 10%), 315 (M^+-31, 100%). Anal. calcd. for $C_{16}H_{26}O_8$: 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 $TiCl_4$ was added. After stirring for 30 minutes, the reaction was quenched by addition of 5 mL of saturated aqueous $NaHCO_3$ and allowed to warm to ambient temperature. Dichloromethane (25 mL) was added and the solution washed with saturated aqueous $NaHCO_3$ and brine (15 mL of each), dried over Na_2SO_4, 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. $[\alpha]_D$ = +42° (c = 0.50, $CHCl_3$). IR (thin film) υ: 3460, 2930, 2860, 1740, 1735, 1466, 1240, 1160 cm^{-1}. ^{1}H NMR (300 MHz) δ: 4.98 (dd, J = 4.3, 10.4 Hz, 1H, H_7), 4.62 - 4.73 (m, 1H, H_5), 4.32 - 4.43 (m, 1H, H_3), 3.70 (s, 3H, CO_2CH_3), 3.08 - 3.18 (br s, 1H, OH, exchangeable), 2.51 (dd, A of ABX, J = 3.5, 16.7 Hz, 1H, H_2), 2.42 (dd, B of ABX, J = 8.7, 16.7 Hz, 1H, $H_{2'}$), 2.18-2.28 (m, 1H, H_4), 2.07 (s, 3H, CH_3CO_2), 1.68-1.92 (m, 3H, $H_{4'}$, H_6), 1.30 (s, 3H, gem CH_3), 1.27 (s, 3H, gem CH_3). ^{13}C NMR (50.4 MHz) δ: 175.8 (RCO_2R'), 173.1 ($CH_3\mathbf{C}O_2$), 170.4 ($\mathbf{C}O_2CH_3$), 73.1, 72.8 (C_5, C_7), 63.7 (C_3), 51.8 ($CO_2\mathbf{C}H_3$), 42.9 (C_8), 42.7, 41.1 (C_2, C_4), 31.5 (C_6), 23.4 (gem CH_3), 21.5 ($\mathbf{C}H_3CO_2$), 20.8 (gem CH_3). MS (CI ether) m/z: 303 (M^++1, 100%), 271 (M^+-31, 2%), 243 (M^+-59, 5%). Anal. calcd. for $C_{14}H_{22}O_7$: 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[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[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

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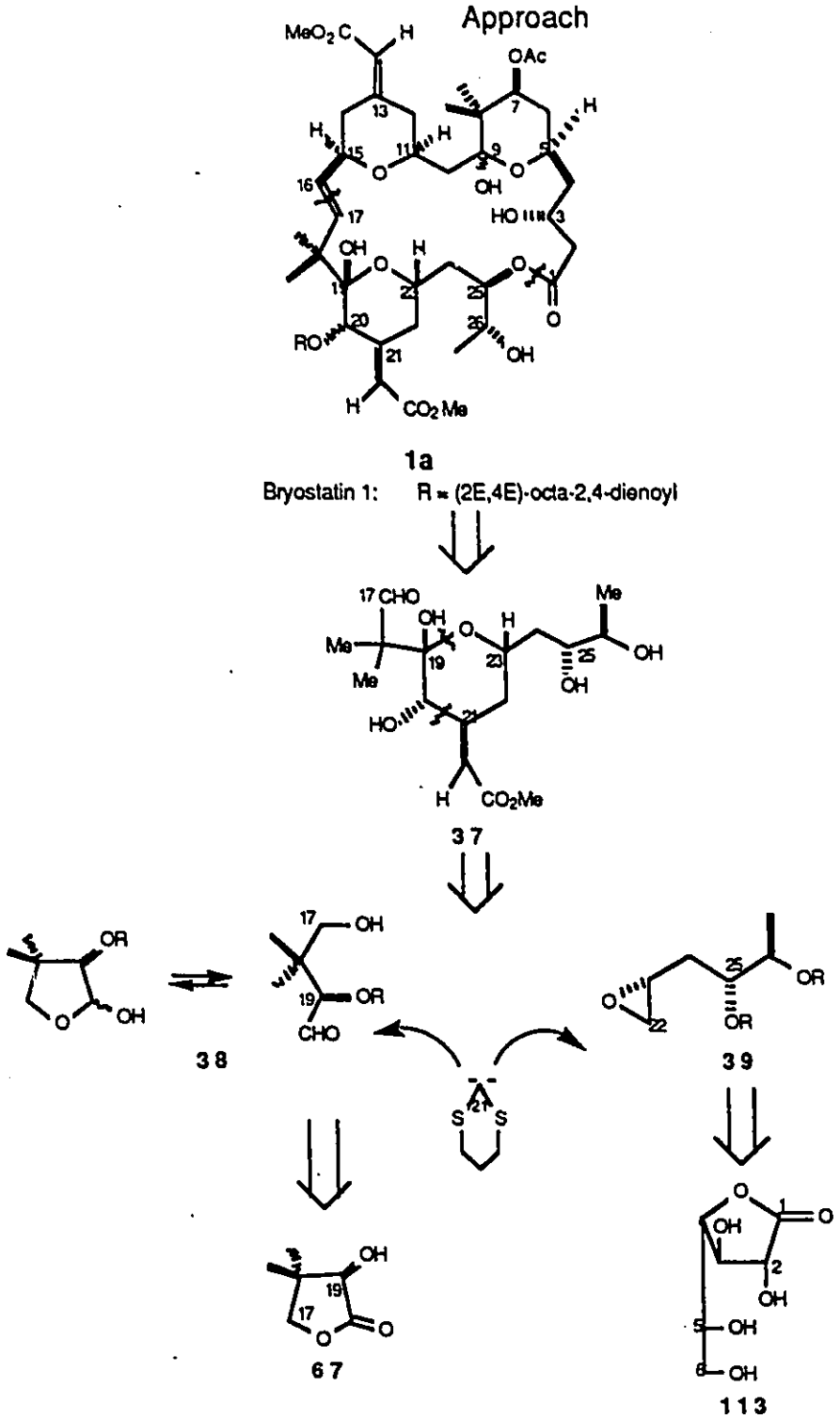
[92]This work has appeared in part as "Enantiospecific Synthesis of the C-17–C-20 and C-21–C-27 Synthons of the Antineoplastic Macrolide Bryostatins", R. Roy, A.W. Rey, R. Molino, and M. Charron, *J. Chem. Soc., Chem. Comm.*, 1308 (1989).

[93](a) S. Hanessian in "The Chiron Approach", ed. J.E. Baldwin, Pergamon Press, Oxford (1983). (b) B. Fraser-Reid and R.C. Anderson, *Forstschr. Chem. Org. Naturst..*, **39**, 1 (1980). (c) B. Fraser-Reid, *Acc. Chem. Res.*, **104**, 367 (1982). (d) T.D. Inch, *Tetrahedron*, **40**, 3161 (1984) and references cited therein.

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[17] 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[94] 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

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[94]K. Bock, I. Lundt, and C. Pedersen, *Acta Chem. Scand.*, **B35**, 155 (1981).

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2-lithio-1,3-dithiane addition. In effect, the dithiane group acted as a linchpin[95] to connect synthons **38** and **39**. The dithiane moiety could then be unmasked by hydrolysis[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[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%, TBDMSCl, DMAP, NEt_3, CH_2Cl_2, 24 hours). DIBAL reduction[97] of this α-silylated γ-lactone formed the γ-lactol **115** [87%, DIBAL, THF, -78°C, 3 hours; $(\alpha)_D$ = -13.3° (c=2.0, $CHCl_3$)]. When this reduction was attempted in toluene, overreduction occurred

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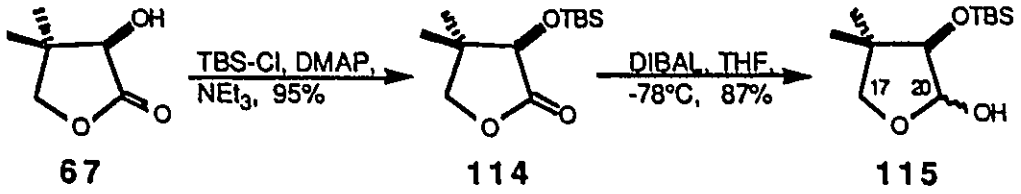
[95]For a similar strategy see: B.H. Lipshutz, H. Kotsuki, and W. Lew, *Tetrahedron Lett.*, **27**, 4825 (1986).
[96]P.C. Bulman Page, M.B. van Niel, and J.C. Prodger, *Tetrahedron*, **45**, 7643 (1989) and references cited therein.
[97]E. Winterfeldt, *Synthesis*, 617 (1975) and references cited therein.

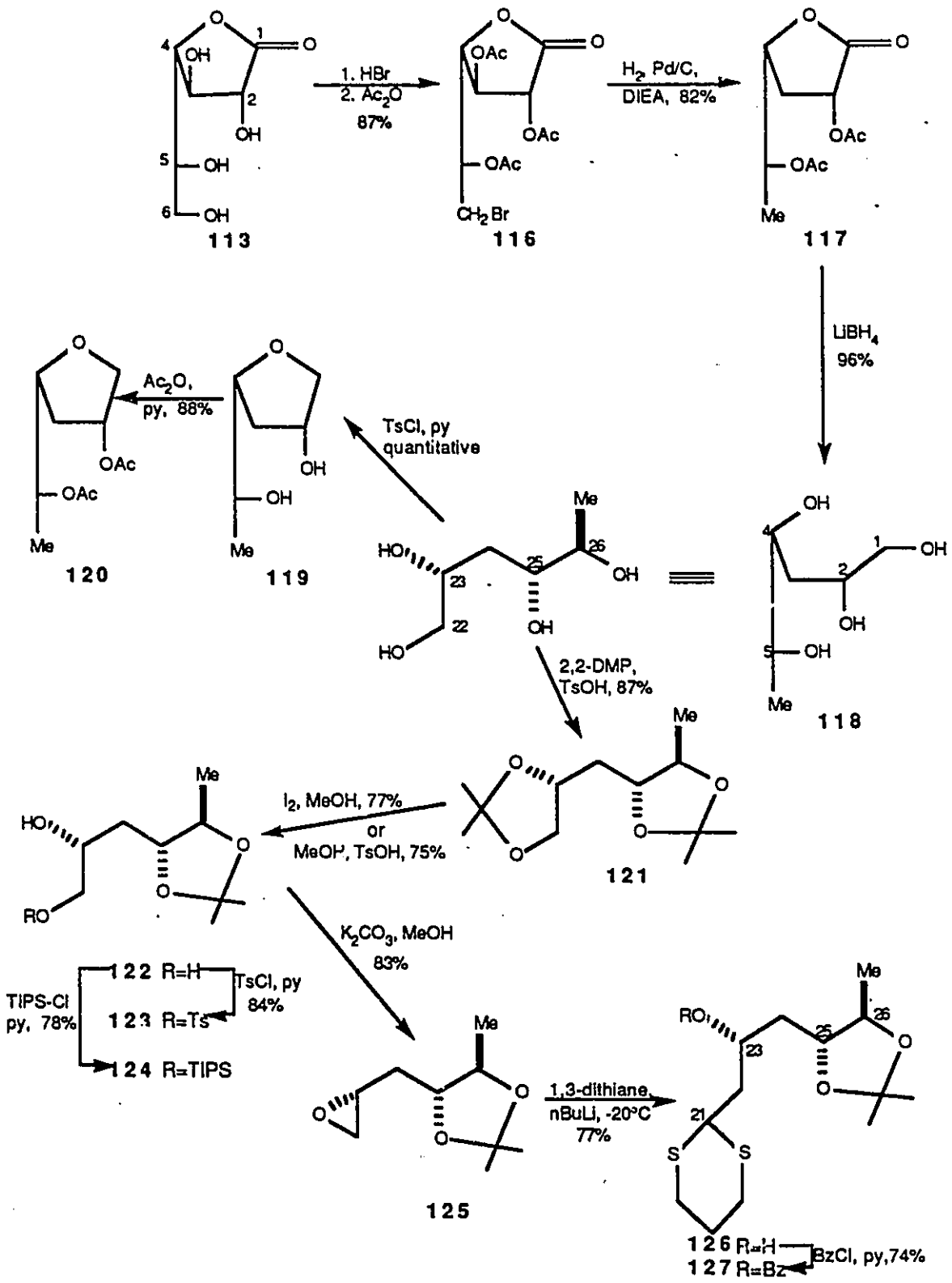
to a large extent. These simple transformations furnished the desired C(17)–C(20) synthon.



67 114 115

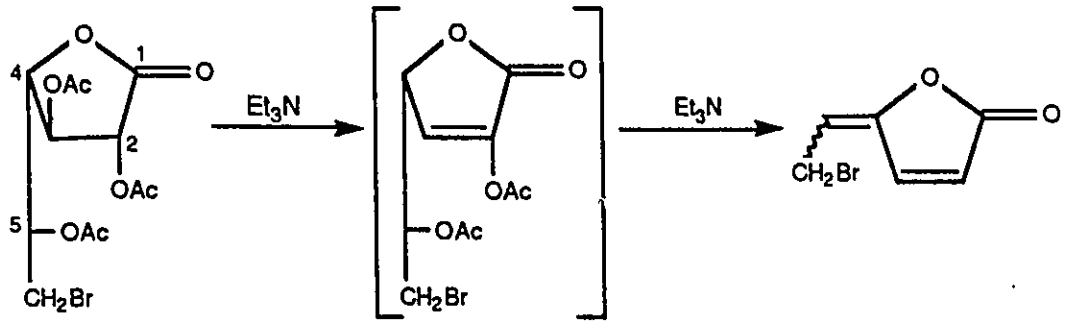
5.4 Synthesis of the C(21)–C(27) Synthon (127)

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[94].


1. HBr
2. Ac2O
87%
H2, Pd/C,
DIEA, 82%
LiBH4
96%
Ac2O,
py, 88%
TsCl, py
quantitative
2,2-DMP,
TsOH, 87%
I2, MeOH, 77%
or
MeOH, TsOH, 75%
K2CO3, MeOH
83%
TIPS-Cl
py, 78%
TsCl, py
84%
1,3-dithiane,
nBuLi, -20°C
77%
BzCl, py,74%
113
116
117
118
119
120
121
122 R=H
123 R=Ts
124 R=TIPS
125
126 R=H
127 R=Bz

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; literature[94]: 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 precedent[94] 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.



116 **128** **129**

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 $LiAlH_4$. Isolation of the tetrol **118** was also troublesome, presumably due to stable aluminate complex formation. This difficulty was overcome by use of $LiBH_4$ followed by cation exchange resin treatment ($LiBH_4$, THF, 0°C,14 hours) to afford improved yields (96%) of the known[94,98] 3,6-dideoxy-D-xylo-hexitol (**118**) (mp: 95-96°C; literature[94]: 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%, Ac_2O, 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

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[98]O. Westphal and L. Lüderitz, *Angew. Chem.*, **72**, 881 (1960).

been expected. Also, the ^1H 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_2CO_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_2CO_3, methanol, 0°C, 4 hours) provided a 52% yield of the epoxide **125** as the only diastereomer [ie. no

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[99]W.A. Szarek, A. Zamojski, K.N. Tiwari, and E.R. Ison, *Tetrahedron Lett.*, **27**, 3827 (1985).

epimeric C(23) epoxide was noted[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, $[\alpha]_D$ = +23° (c=2.4, $CHCl_3$)].

Regioselective epoxide ring opening was then achieved by the addition of 2-lithio-1,3-dithiane[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

[100]For a similar example see: S. Hanessian and P.J. Murray, *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[18a] has noted that stabilized phosphonium ylides undergo accelerated Wittig reactions with α-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[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[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[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[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 $NaHCO_3$ (2 X 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_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[94]: 98-100°C). $[\alpha]_D$ = -10.0° (c = 2.5, $CHCl_3$) (literature[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[94]. Thus, 300 mL of ethyl acetate was added to 3.50 g of 5% palladium on carbon. In a well-vented fumehood, 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_2SO_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[94]: 86–87°C). $[\alpha]_D$ = -22.0° (c = 1.0, $CHCl_3$) (literature[94]: -22.8°). ^1H NMR (300 MHz) δ: 5.49 (dd, J = 8.9, 10.5 Hz, 1H, H_{23}), 5.02 (app qu, 1H, H_{26}), 4.47 (app qu, 1H, H_{25}), 2.72 (ddd, J = 5.5, 8.8, 12.5 Hz, 1H, H_{24}), 2.16 (s, 3H, CH_3CO_2), 2.08 (s, 3H, CH_3CO_2), 1.99 (ddd, J = 5.5, 10.5, 12.5 Hz, 1H, $H_{24'}$), 1.30 (d, J = 6.5 Hz, 3H, H_{27}).

3,6-Dideoxy-D-xylo-hexitol (118):

This material was prepared using a modification of a procedure described by Pederson[94]. Thus, 10.0 g (43.4 mmol) of the γ-lactone **117** was dissolved in THF (150 mL) and 3.10 g (142 mmol) of $LiBH_4$ was added portionwise at 0°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°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 *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°C (literature[94]: 90°C). $[\alpha]_D$ = +44° (c = 2.0, H_2O) (literature[94]: +52°). ^1H NMR (deuterium oxide, 300 MHz) δ: 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, $H_{22'}$), 1.36 (d, J = 6.8 Hz, 1H, H_{24}), 1.34 (d, J = 5.9 Hz, 1H, $H_{24'}$), 0.98 (d, J = 6.3 Hz, 3H, H_{27}). Anal. calcd. for $C_6H_{14}O_4$: 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°C containing p-toluenesulfonyl chloride (1.73 g, 0.07 mmol). After overnight

contact, water was added for 1 hour to destroy the excess sulfonyl 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 $NaHCO_3$, and brine (50 mL of each) followed by drying over Na_2SO_4 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, H_{25}), 3.84 - 3.92 (m, 1H, H_{23}), 3.90 (dd, A of AB, J = 2.6, 9.7 Hz, 1H, H_{22}), 3.72 (dd, B of AB, J = 3.5, 9.7 Hz, 1H, $H_{22'}$), 3.75 - 3.79 (m, 1H, H_{26}), 2.29 (ddd, J = 5.9, 9.5, 15.4 Hz, 1H, H_{24}), 2.05 - 2.20 (br s, 2H, OH, exchangeable), 1.80 (ddd, J = 1.6, 4.1, 15.4 Hz, 1H, $H_{24'}$), 1.28 (d, J = 6.4 Hz, 3H, H_{27}).

Acetylated 1,4-anhydro diol 120 :

The 1,4-anyhdro 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 $NaHCO_3$, and brine, dried over Na_2SO_4, 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, H_{23}), 4.99 (qu, J = 6.5 Hz, 1H, H_{26}), 3.94 (ddd, J = 1.1, 2.2, 10.6 Hz, 1H, H_{22}), 3.87 (dd, J = 6.9, 14.5 Hz, 1H, H_{25}), 3.82 (dd, J = 4.9, 10.6 Hz, 1H, $H_{22'}$), 2.37 (ddd, J = 7.6,

8.1, 10.2 Hz, 1H, H_{24}), 2.07 (s, 3H, CH_3CO_2), 2.04 (s, 3H, CH_3CO_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 (CI 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_2SO_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). $[\alpha]_D$ = +11.2° (c = 1.0, $CHCl_3$). IR (thin film) υ: 2955, 2942, 2880, 1382, 1372, 1248, 1100, 1065 cm^{-1}. ^1H 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, $(CH_3)_2C(OR)_2$), 1.25 (s, 3H, $(CH_3)_2C(OR)_2$), 1.22 (s, 6H, 2 X $(CH_3)_2C(OR)_2$), 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 $(CH_3)_2C(OR)_2$), 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_2SO_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 $NaHCO_3$ 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 Na_2SO_4 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 SiO_2 flash chromatography (8:2 ethyl acetate/hexane). IR (thin film) υ: 3420, 2991, 2941, 1382, 1235, 1096 cm^{-1}. ^1H NMR (300 MHz) δ: 3.92 - 4.02 (m, 1H, H_{23}), 3.77 (dd, A of AB, J = 2.6, 8.2 Hz, 1H, H_{22}), 3.71 (dd, B of AB, J = 2.9, 8.2 Hz, 1H, $H_{22'}$), 3.46 - 3.72 (m, 2H, H_{25}, H_{26}), 2.68 - 2.81 (br s, 2H, OH, exchangeable), 1.80 (ddd, J = 2.8, 8.2, 14.4 Hz, 1H, H_{24}), 1.57 (ddd, J = 4.0, 8.1, 14.4 Hz, 1H, $H_{24'}$), 1.382 (s, 3H, $(CH_3)_2C(OR)_2$), 1.378 (s, 3H, $(CH_3)_2)C(OR)_2$), 1.25 (d, J = 5.7 Hz, 3H, H_{27}). ^{13}C NMR (50.4 MHz) δ: 108.2 ($(CH_3)_2\mathbf{C}(OR)_2$), 79.3, 76.6 (C_{25}, C_{26}), 69.6 (C_{23}), 66.7 (C_{22}), 34.6 (C_{24}), 27.1, 27.0 ($(\mathbf{C}H_3)_2C(OR)_2$), 16.8 (C_{27}). MS (EI) m/z: 175 (M^+-15, 23%), 115 (M^+-75, 25%). HRMS calcd. for $C_8H_{15}O_4$ (M^+-CH_3): 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 $NaHCO_3$, and brine (50 mL of each), and dried over Na_2SO_4 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° (c = 1.0, $CHCl_3$). IR (thin film) υ: 3460, 2991, 2940, 1601, 1369, 1191, 1180, 1099 cm^{-1}. ^1H NMR (300 MHz) δ: 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, H_{22}), 3.95 (dd, B of AB, J = 7.7, 8.6 Hz, 1H, $H_{22'}$), 3.98 - 4.09 (m, 1H, H_{23}), 3.58 - 3.72 (m, 2H, H_{25},H_{26}), 2.89 - 3.00 (br s, 1H, OH, exchangeable), 2.44 (s, 3H, PhCH_3), 1.71 (ddd, J = 2.0, 7.9, 14.5 Hz, 1H, H_{24}), 1.55 (ddd, J = 3.6, 4.9, 14.5 Hz, 1H, $H_{24'}$), 1.34 (s, 3H, $(CH_3)_2C(OR)_2$), 1.33 (s, 3H, $(CH_3)_2C(OR)_2$), 1.22 (d, J = 5.7 Hz, 3H, H_{27}). ^{13}C NMR (50.4 MHz) δ: 145.2, 132.6, 130.0, 128.0 (aromatic), 108.3 ($(CH_3)_2$**C**$(OR)_2$), 78.6, 76.5 (C_{25},C_{26}), 73.2 (C_{22}), 66.9 (C_{23}), 34.3 (C_{24}), 27.0, 26.9 ($(CH_3)_2C(OR)_2$), 21.5 (PhCH_3), 16.7 (C_{27}). MS (EI) m/z: 329 (M^+-15, 25%), 173 (M^+-171, 10%). HRMS calcd. for $C_{15}H_{21}O_6S$ (M^+-CH_3): 329.1059; found; 329.1025.

3,6-Dideoxy-1-O-2,4,6-(triisopropylbenezene)sulfonyl-5,6-O-isopropylidene-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-toluenesulfonyl 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 $(CH_3)_2CHPh$), 1.72 - 1.84 (m, 1H, H_{24}), 1.56 - 1.64 (m, 1H, $H_{24'}$), 1.35 (s, 3H, $(CH_3)_2C(OR)_2$), 1.33 (s, 3H, $(CH_3)_2C(OR)_2$), 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 (CI ether) m/z: 457 (M^++1, 23%), 399 (M^+-57, 92%).

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

<u>From 123:</u>

The tosyl-protected material **123** (1.20 g, 3.48 mmol) was dissolved in 30 mL of methanol and a catalytic amount of K_2CO_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 $NaHCO_3$, and brine (40 mL of each), dried over Na_2SO_4, 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 SiO_2 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, $CHCl_3$). IR (thin film) υ: 2982, 2930, 2876, 1379, 1369, 1242, 1179, 1097 cm^{-1}. ^1H NMR (300 MHz) δ: 3.71 - 3.75 (m, 2H, H_{25}, H_{26}), 3.06 (app sextet, 1H, H_{23}), 2.81 (dd, J = 4.0, 5.0 Hz, 1H, H_{22}), 2.50 (dd, J = 2.7, 5.0 Hz, 1H, $H_{22'}$), 1.84 (ddd, J = 4.1, 8.0, 14.2 Hz, 1H, H_{24}), 1.57 (ddd, J = 3.7, 7.5 14.2 Hz, 1H, H_{24}), 1.40 (s, 3H, $(CH_3)_2C(OR)_2$), 1.37 (s, 3H, $(CH_3)_2C(OR)_2$), 1.27 (d, J = 5.7 Hz, 3H, H_{27}). ^{13}C NMR (75.3 MHz) δ:

108.1 ($(CH_3)_2C(OR)_2$), 79.9, 76.9 (C_{25}, C_{26}), 49.5 (C_{23}), 47.4 (C_{22}), 35.9 (C_{24}), 27.1, 27.0 ($(CH_3)_2C(OR)_2$), 17.1 (C_{27}), MS (EI) m/z: 157 (M^+-15, 27%), 115 (M^+-57, 16%). HRMS calcd. for $C_8H_{13}O_3$ (M^+-CH_3): 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 NH_4Cl (5 mL) and diluted with ethyl acetate (80 mL). The organic layer was washed with 0.2N HCl, saturated aqueous $NaHCO_3$, and brine (30 mL of each), dried over Na_2SO_4, and concentrated *in vacuo* to provide a yellow viscous oil. Purification by SiO_2 flash chromatography (7:3 ethyl acetate/hexane) yielded 0.69 g (47%) of the dithianyl derivative **126** as a colourless oil. $[\alpha]_D$ = +12.2° (c = 1.0, $CHCl_3$). IR (thin film) υ: 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, H_{23}), 3.74 - 3.82 (m, 2H, H_{25}, H_{26}), 2.79 - 3.00 (m, 4H, 2 X RCH_2S), 2.07 - 2.19 (m, 2H, H_{22}), 1.83 - 2.00 (m, 2H, $CH_2(CH_2S)_2$), 1.71 (ddd, J = 3.0, 8.2, 13.2 Hz, 1H, H_{24}), 1.62 (ddd, J = 3.3, 7.7, 13.2 Hz, 1H, $H_{24'}$), 1.38 (s, 6H, $(CH_3)_2C(OR)_2$), 1.24 (d, J = 5.7 Hz, 1H, H_{27}). MS

(EI) m/z: 292 (M^+ , 4%), 277 (M^+-15, 13%), 274 (M^+-18, 26%). HRMS calcd. for $C_{12}H_{21}O_3S_2$ (M^+-CH_3): 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 $NaHCO_3$, 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. $[\alpha]_D$ = +14.2° (c = 1.0, $CHCl_3$). IR (thin film) υ: 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, H_{23}), 4.11 (dd, J = 6.3, 8.1 Hz, 1H, $RCH(SR)_2$), 3.67 - 3.73 (m, 1H, H_{25}), 3.61 (dt, J = 3.0, 8.4 Hz, 1H, H_{26}), 2.60 - 3.06 (m, 4H, 2 X RCH_2S), 2.22 - 2.28 (m, 2H, H_{22}), 1.98 - 2.14 (m, 2H, $CH_2(CH_2S)_2$), 1.97 (ddd, J = 3.0, 6.3, 14.2 Hz, 1H, H_{24}), 1.84 (ddd, J = 6.4, 8.6, 14.2 Hz, 1H, $H_{24'}$), 1.33 (s, 6H, $(CH_3)_2C(OR)_2$), 1.24 (d, J = 5.9 Hz, 3H, H_{27}). MS (EI) m/z: 381 (M^+-15, 9%), 274 (M^+-122, 26%). MS (CI ether) m/z: 397 (M^++1, 61%), 381 (M^+-15, 11%), 339

(M^+-57, 75%). HRMS calcd. for $C_{13}H_{22}O_2S_2$ (M^+-$PhCO_2H$): 274.1063; found: 274.1066.

CHAPTER 6: MODEL STUDIES OF NUCLEOPHILIC ADDITIONS ONTO γ-LACTOL TEMPLATES[101]

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[102] since Cram's[103] and Prelog's[104] 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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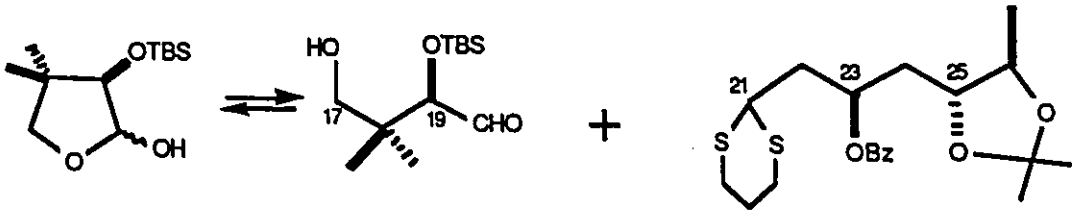
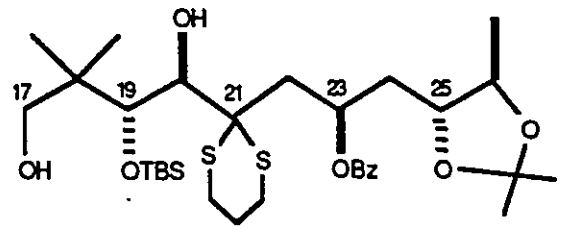
[101]This work has appeared in part as "Controlled Diastereoselection in 2-Lithio-1,3-Dithiane Additions onto α-Substituted γ-Lactols. Model Studies Toward Bryostatins from (R)-Pantolactone", R. Roy and A.W. Rey, *Canadian Journal of Chemistry*, in press (1990).
[102](a) E.P. Lodge and C.H. Heathcock, *J. Am. Chem. Soc.*, **109**, 3353 (1987). (b) E.L. Eliel in "Asymmetric Synthesis" Vol. 2A, ed. J.D. Morrison, Academic Press, New York, 125 (1983).
[103]D.J. Cram and F.A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 3210 (1952).
[104]V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

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 γ-lactol templates, we initiated a model study involving 2-lithio-1,3-dithiane additions onto various γ-lactols.



115 127



130

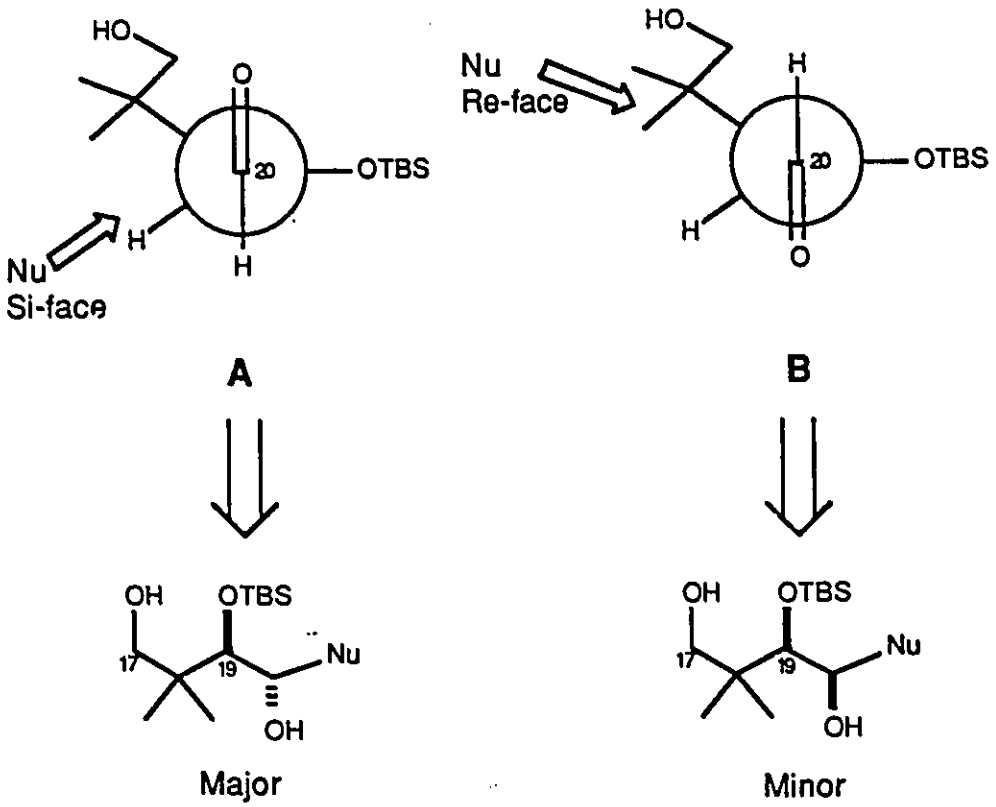
[105](a) K. Tamooka, T. Okinaga, K. Suzuki, and G.-i. Tsuchihashi, *Tetrahedron Lett.*, **30**, 1563 (1989). (b) C. Brückner, H. Lorey, and H.-U. Reissig, *Angew. Chem., Int. Ed. Engl.*, **25**, 556 (1986). (c) M. Cornia, G. Casiraghi, and L. Zetta, *Tetrahedron*, **46**, 3071 (1990) and references cited therein.

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[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.

[106](a) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 9, 2201 (1968). (b) M. Chérest and H. Felkin, *Tetrahedron Lett.*, 9, 2205 (1968).

Figure 24 — Felkin-Ahn / Cram Model for Nucleophilic Addition Onto **115**



Clearly, attack of the incoming nucleophile along the Bürgi-Dünitz[107] trajectory should occur from the less-hindered diastereotopic Si-face of the C(20) aldehyde (in the acyclic γ-hydroxy aldehyde form of the γ-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.

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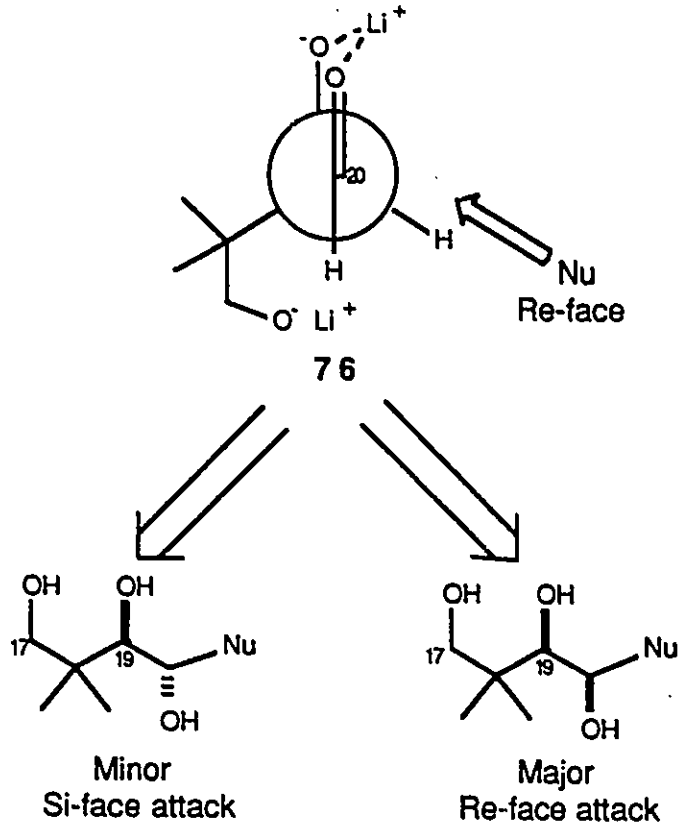
[107](a) H.B. Bürgi, J.D. Dünitz, J.M. Lehn, and G. Wipff, *Tetrahedron*, **30**, 1563 (1974). (b) H.B. Bürgi, J.M. Lehn, and G. Wipff, *J. Am . Chem. Soc.*, **96**, 1956 (1974). (c) H.B. Bürgi, J.D. Dunitz, and E. Shefter, *J. Am. Chem. Soc.*, **95**, 5065 (1973).

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[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.

[108]M.T. Reetz, *Agnew . Chem. , Int. Ed. Engl.*, 23, 556 (1984) and references cited therein.

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 (H_2SO_4) sodium borohydride also yielded the triol as the major product. Finally, the controlled reduction to the lactol **76** was achieved using borane-tetrahydrofuran complex (BH_3·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 Perlin[64] 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 Seebach[109] and others[96] 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

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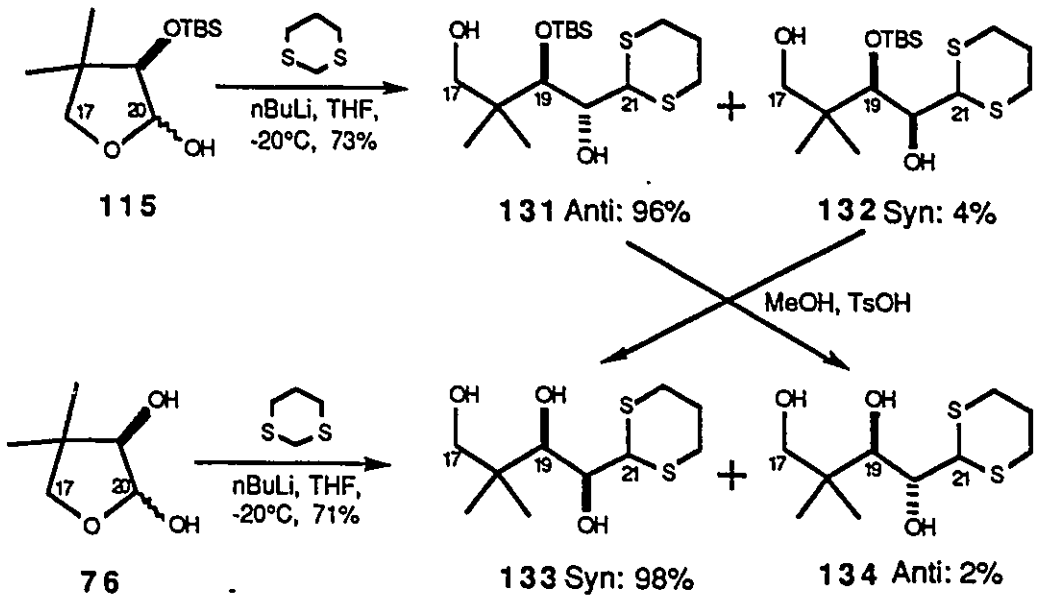
[109]D. Seebach and E.J. Corey, *J. Org. Chem.*, **40**, 231 (1975). (b) B. Grobel and D. Seebach, *Synthesis*, 357 (1977).

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[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.



The ^{1}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**

γ-Lactol	Major Adduct	Yield	Anti/Syn Ratio
115	**131**	73%	96:4
71	**133**	71%	2:98

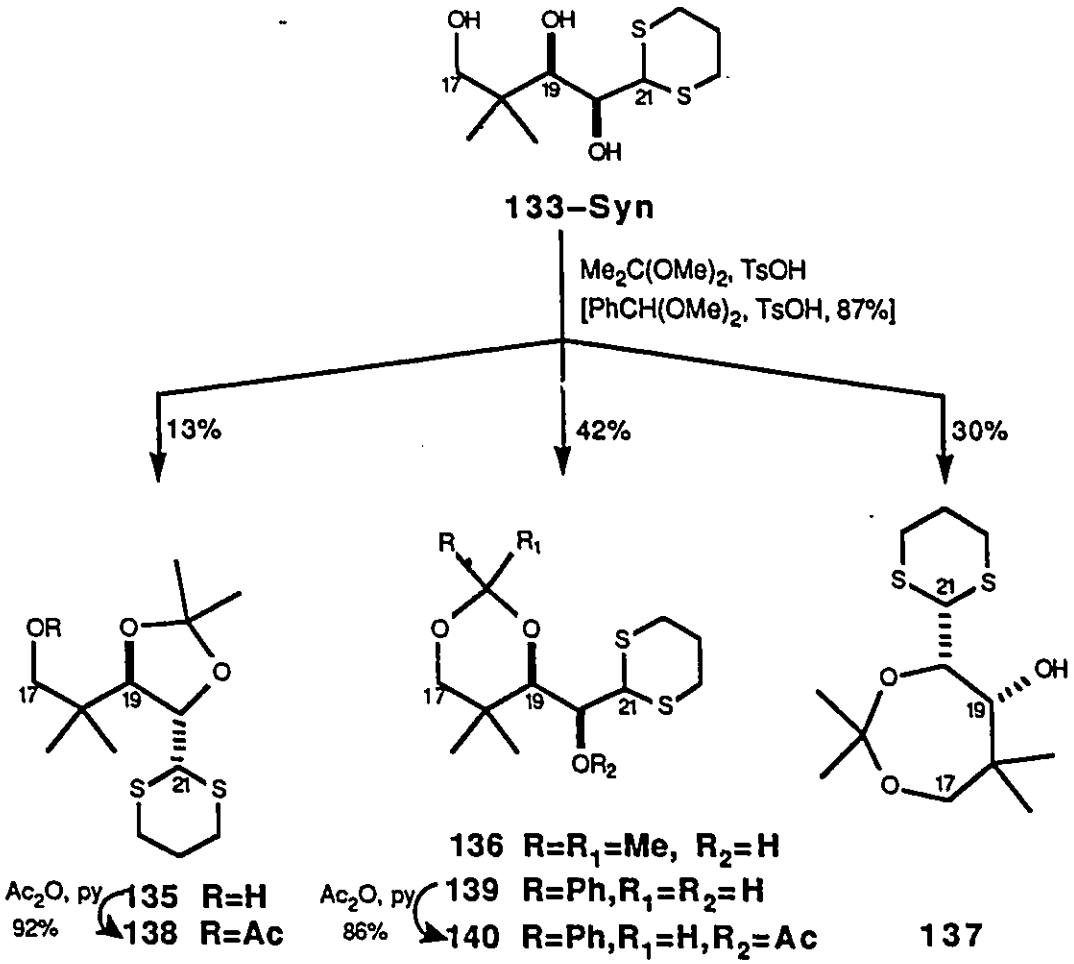
The first step was to deprotect the C(19) silyl ether of the diastereomeric diols **131** and **132**. This was accomplished by acidic treatment in methanol to afford the triols **133** and **134** in quantitative yield (methanol, TsOH, 25°C). Comparison (tlc, ^{1}H NMR, optical rotation) of triol **133** 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. ^{1}H 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 ^{1}H 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 ^1H 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 equililbration 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.

[110]S. Valverde, B. HHerradon, and M. Martin-Lomas, *Tetrahedron Lett.*, 26, 3731 (1985).



Confirmation of the structure of the 5-membered acetonide (**135**) was obtained by acetylation of the primary hydroxyl at C(17) (92%, Ac_2O, 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 ^1H 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

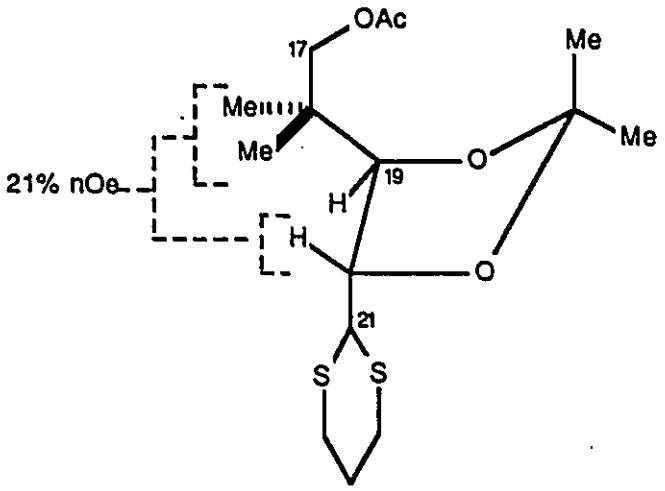
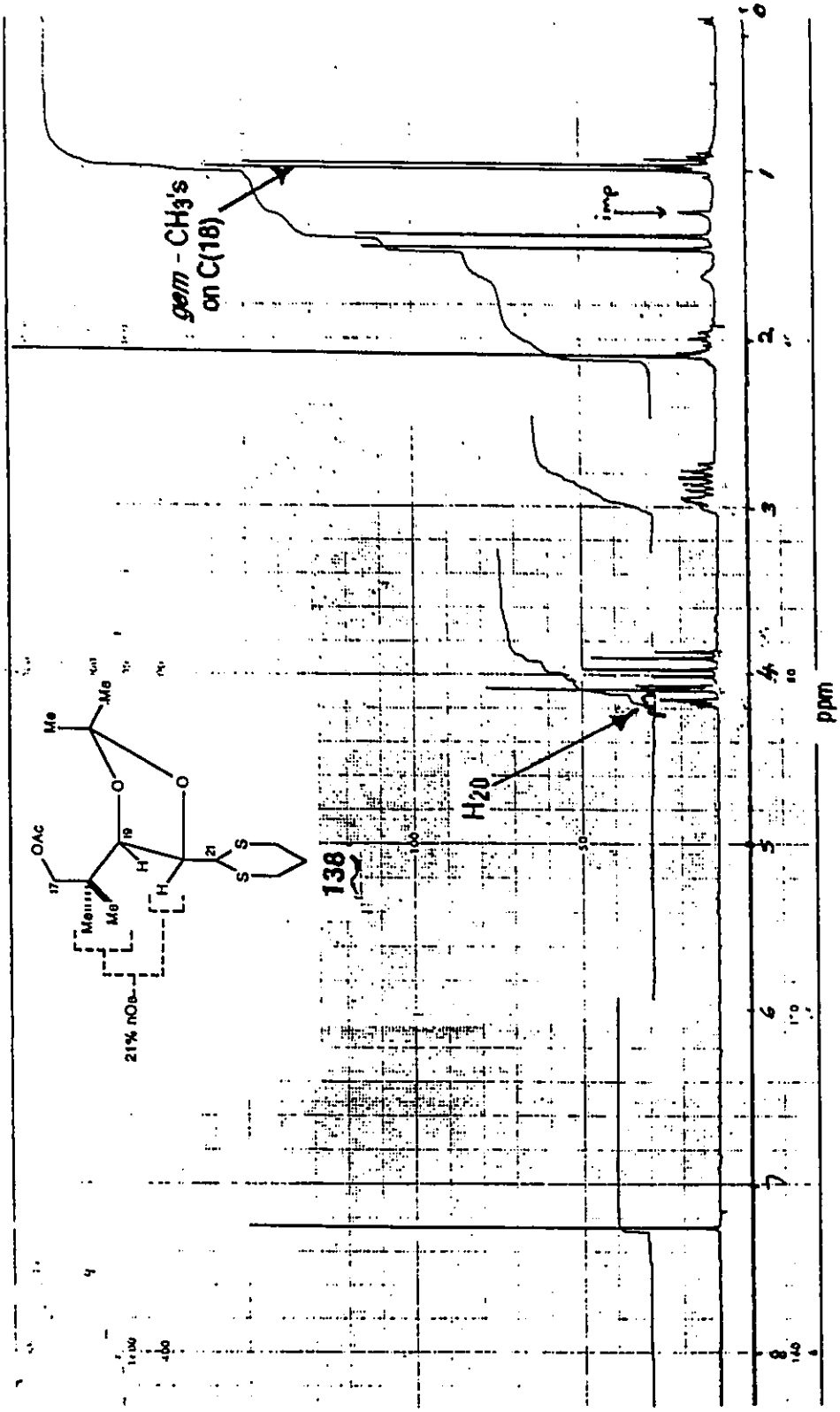


Figure 27 — ^{1}H NMR of **138**

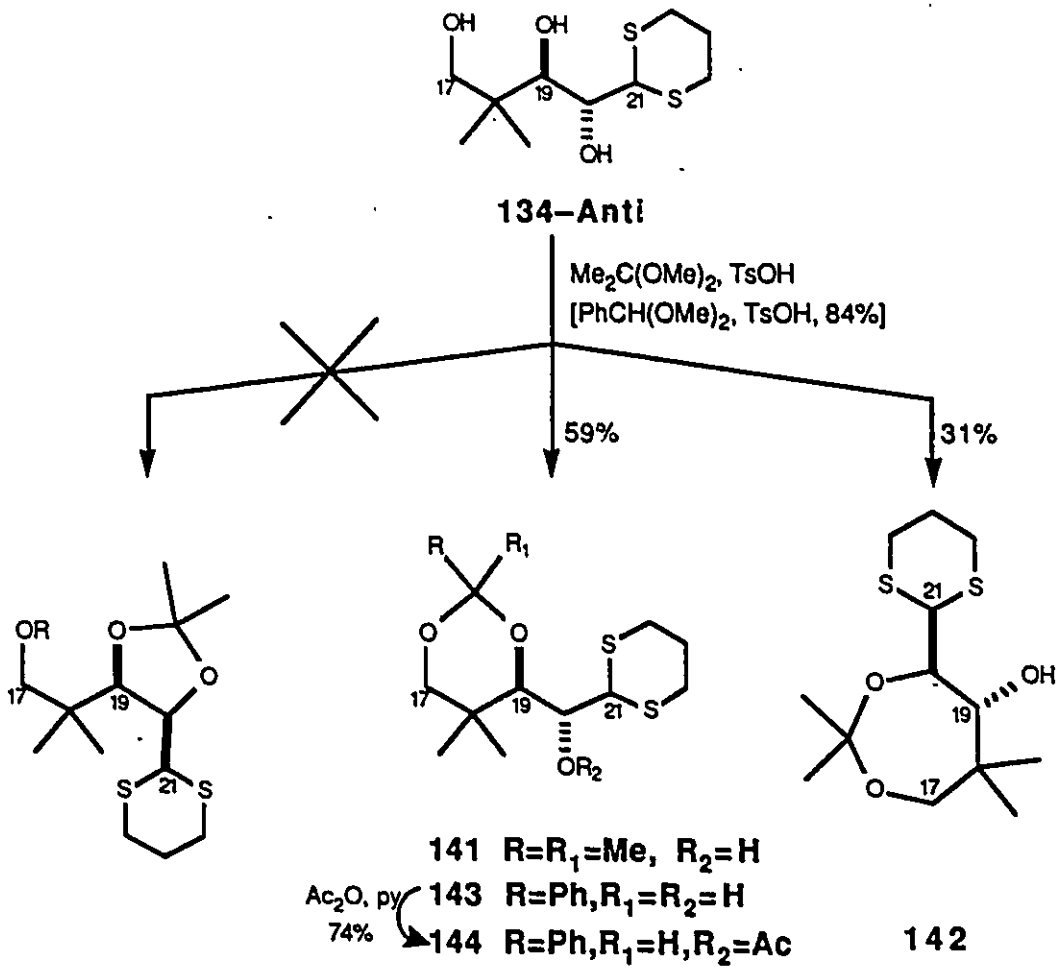


The identity of the 1,3-dioxane acetonide **136** was determined by comparison of the coupling pattern to that of the homologous benzylidenated triol. The pertinent ^1H NMR data are given in Table 10. Briefly, upon treatment with a solution of benzaldehyde dimethyl acetal and a catalytic amount of TsOH 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_2O, DMAP, pyridine, 25°C, 5 hours).

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

Parent Triol	Acetal	Chemical Shift (ppm) Proton			Coupling (Hz) Proton		
		H_{21}	H_{20}	H_{19}	H_{21}	H_{20}	H_{19}
C(19)–C(20)-syn **133**	1,3-Dioxane **136**	4.12	3.80	3.93	$J_{20,21}$ = 6.6	$J_{20,21}$ = 6.6 $J_{19,20}$ = 0.0	$J_{19,20}$ = 0.0
	Benzylidene **139**	4.23	3.90	3.95	$J_{20,21}$ = 6.6	$J_{20,21}$ = 6.6 $J_{19,20}$ = 0.0	$J_{19,20}$ = 0.0

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 (^{1}H 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).

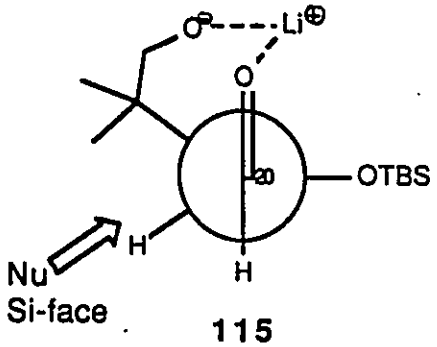
The structure of the 1,3-dioxane acetonide **141** was determined by comparison of its coupling pattern and chemical shifts to the homologous 6-membered benzylidene acetal **143** (**134**, benzaldehyde dimethyl acetal, TsOH, benzene, 1 hour) which was prepared in 84% yield using standard methodology. Table 11 gives the relevant ^1H NMR data. Acetylation of the benzylidene acetal **143** (Ac_2O, 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-Isopropylidene (**141**) and 1,3-O-Benzylidene (**143**) Acetals

Parent Triol	Acetal	Chemical Shift (ppm) Proton			Coupling (Hz) Proton		
		H_{21}	H_{20}	H_{19}	H_{21}	H_{20}	H_{19}
C(19)–C(20)-anti **134**	1,3–Dioxane **141**	4.52	3.82	3.70	$J_{20,21}$ = 1.9	$J_{20,21}$ = 1.9 $J_{19,20}$ = 8.9	$J_{19,20}$ = 8.9
	Benzylidene **143**	4.59	3.96	3.74	$J_{20,21}$ = 1.8	$J_{20,21}$ =1.8 $J_{19,20}$ = 9.0	$J_{19,20}$ =9.0

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[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**



115

From a practical viewpoint, it may be noted that that 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[105a], reasonable diastereofacial selectivities may still be expected.

Finally, Corey[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.

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 $TiCl_4$- and $SnCl_4$-mediated addition of allyltrimethylsilane onto (R)-pantolactol.

A literature survey suggested that Lewis acid promoted additions of allyltrimethylsilane onto lactol templates[112] generally affords, via an oxonium ion intermediate, 2-allyl substituted cyclic ethers. Indeed, the $BF_3{\cdot}Et_2O$-mediated addition of allyltrimethylsilane onto the α-silyl ether γ-lactol **115** (**115**, $BF_3{\cdot}Et_2O$,

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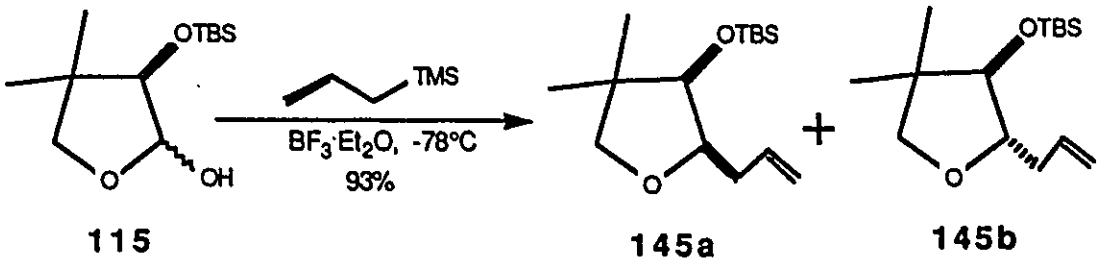
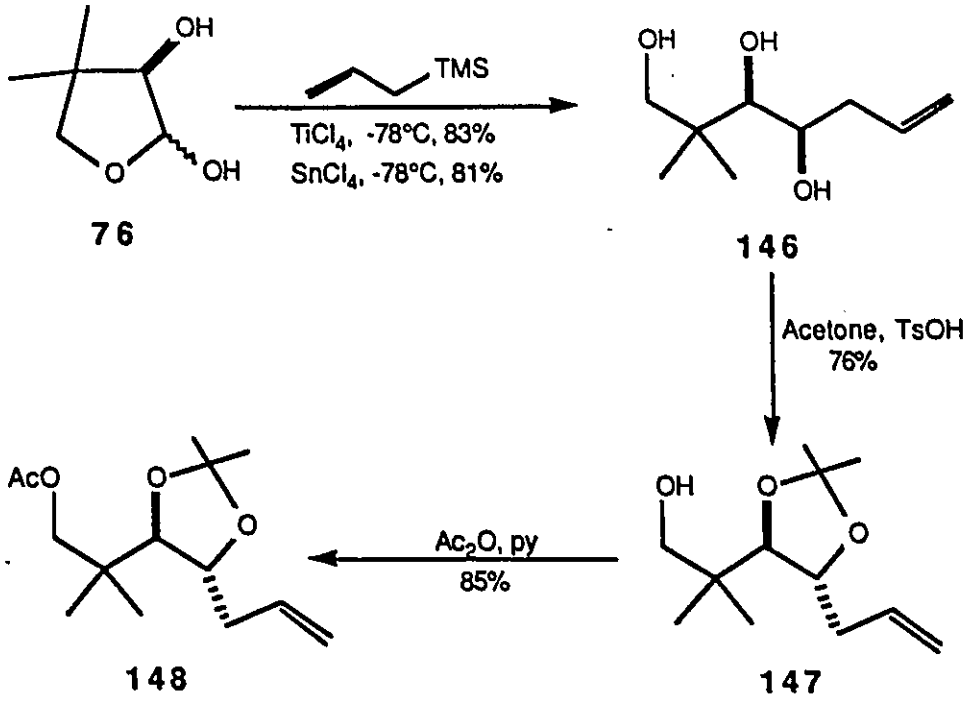
[111]E.J. Corey and H.-C. Huang, *Tetrahedron Lett.*, **30**, 5235 (1989).
[112](a) A. Schmitt and H.-U.Reissig, *Synlett*, **1**, 40 (1990). (b) I. Fleming, J. Dunoguès, and R. Smithers in *Organic Reactions*, Vol. 37, ed. A.S. Kende, John Wiley and Sons, New York, 57 (1989) and references cited therein.

CH_2Cl_2, -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.



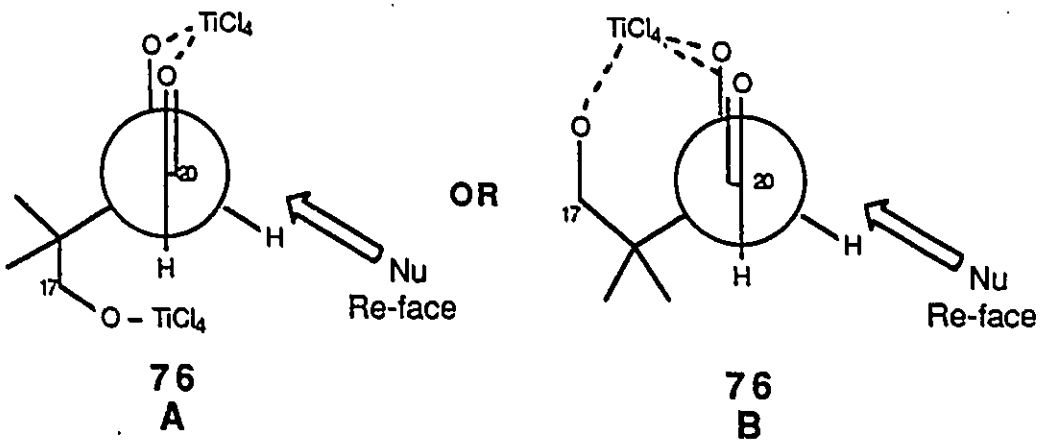
115 **145a** **145b**

We speculated that having the α-hydroxyl of the γ-lactol unprotected and the use of an exceptionally strong Lewis acid such as $TiCl_4$ or $SnCl_4$ should encourage the formation of the interesting acyclic adduct. These hypotheses were rewarded. The $TiCl_4$-mediated addition of allyltrimethylsilane onto the α-hydroxl γ-lactol **76** (**76**, $TiCl_4$, CH_2Cl_2, -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 ^{13}C NMR analysis, the product was a single diastereomer (>99% de). The nucleophile attacked from the Re-face. The use of $SnCl_4$ as Lewis acid provided essentially the same result as $TiCl_4$; 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.

Figure 29 — Model for $TiCl_4$-Mediated Nucleophilic Additions Onto **76**



76
A

1,2-chelation

76
B

1,2- plus 1,4-chelation

The use of $TiCl_4$ or $SnCl_4$ was <u>not</u> sufficient for exclusive formation of the acyclic product — the presence of an α-hydroxyl was necessary. This was implied by the $TiCl_4$-mediated addition of allyltrimethylsilane onto the α-silylated γ-lactol **115** (**115**, $TiCl_4$, CH_2Cl_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 tetrahydrofurans **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 ^1H 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 ^1H 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%, Ac_2O, 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

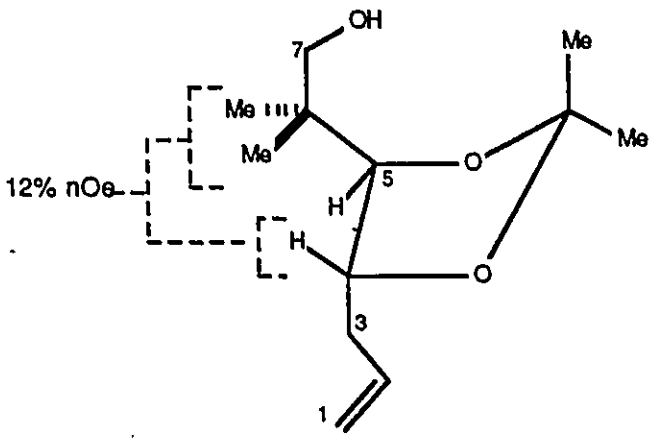
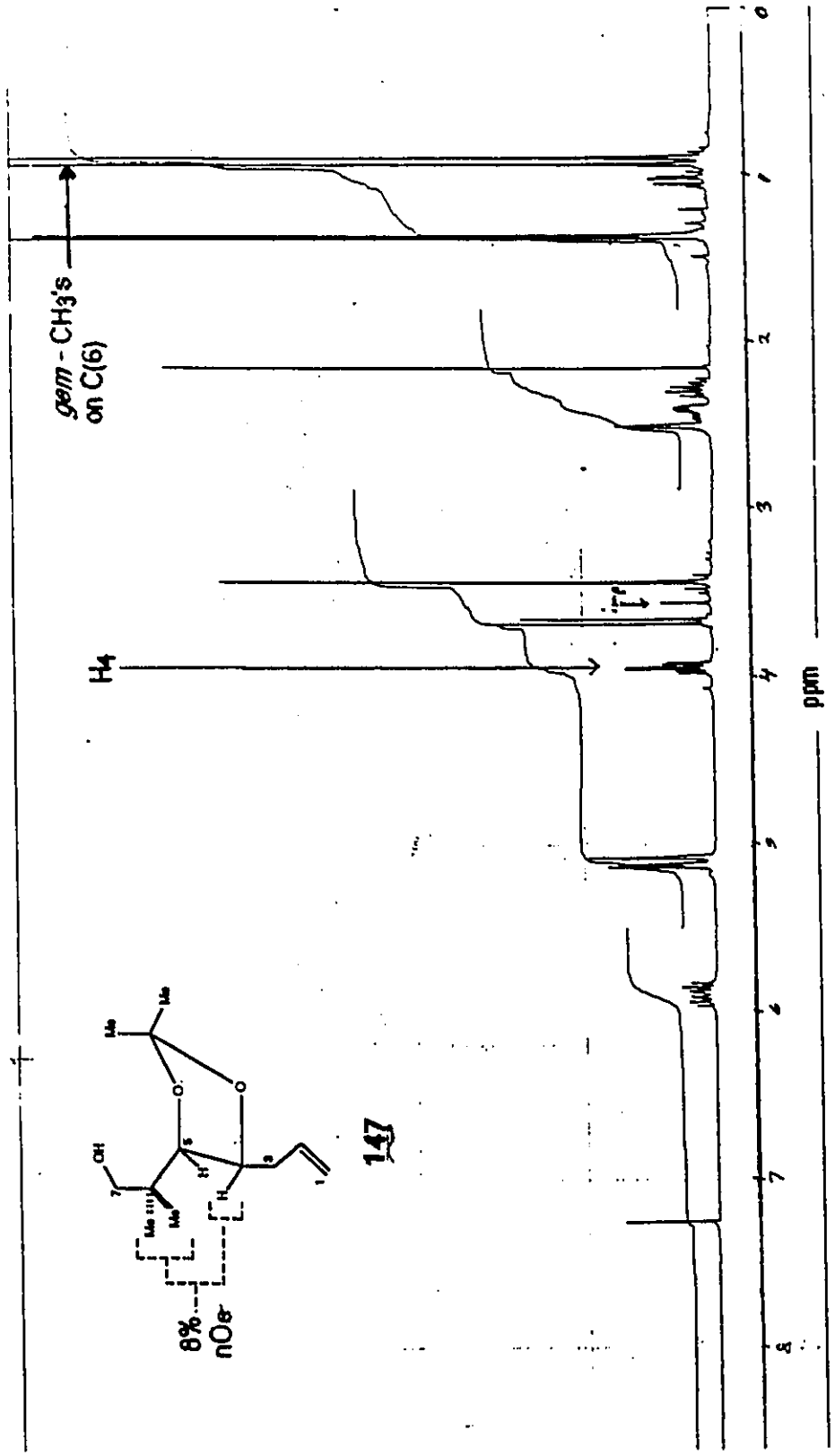
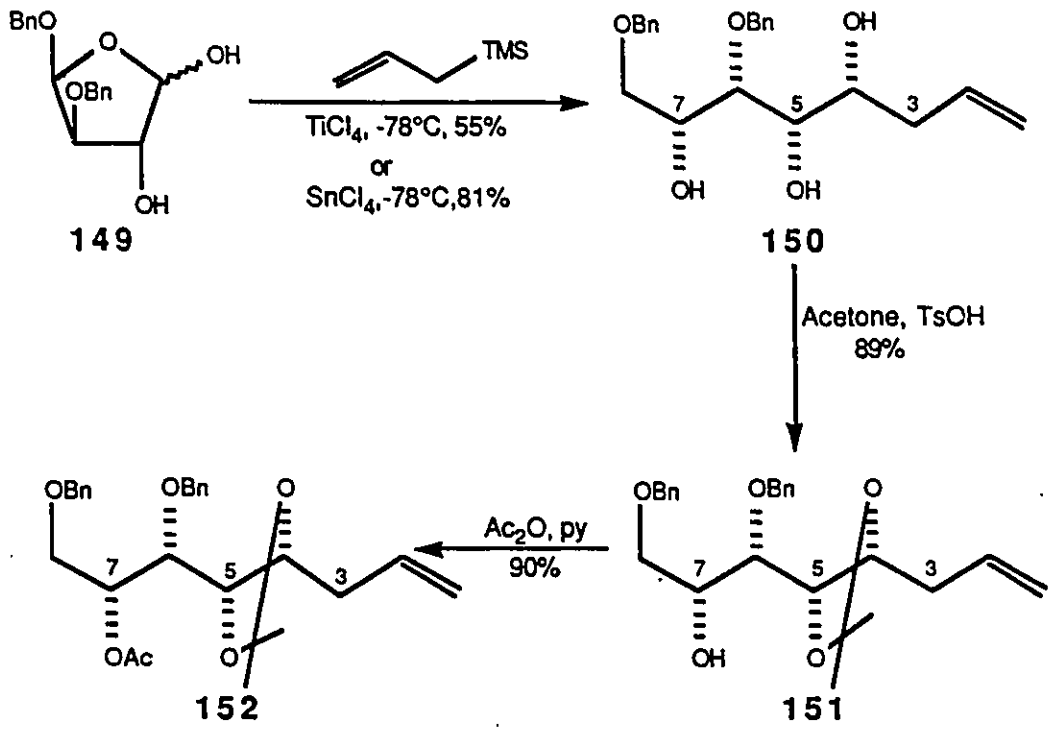


Figure 31 — ^{1}H NMR of **147**



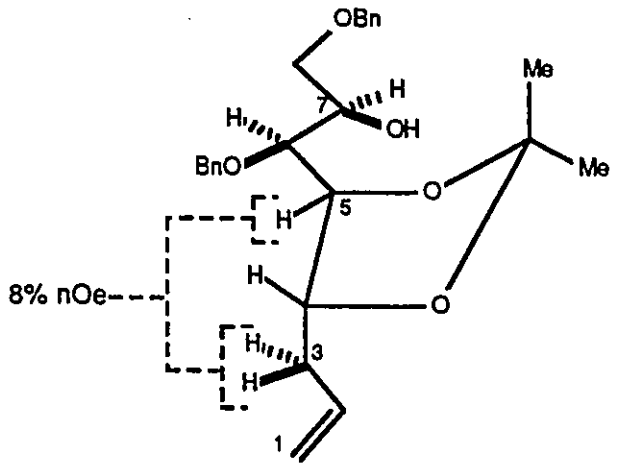
The generality of this type of Lewis acid mediated nucleophilic addition is worthy of further exploration. An illustration of the synthetic potential of this transformation is the addition of allyltrimethylsilane onto free 2-hydroxy sugars. For instance, the $TiCl_4$-mediated addition of allyltrimethylsilane 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%).



[113]F. Matsuda and S. Terashima, *Tetrahedron*, **44**, 4721 (1988).

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 ^1H 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_2O, 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** – ^1H nOe Difference Results



Thus, this type of Sakürai 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 $TiCl_4$-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 $NaHCO_3$, and brine (50 mL of each). The organic layer was dried over Na_2SO_4 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. $[\alpha]_D$ = +33.8° (c = 1.0, $CHCl_3$). IR (CH_2Cl_2) υ: 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, H_{17}), 3.97 (s, 1H, H_{19}), 3.86 (d, B of AB, J = 8.9 Hz, 1H, $H_{17'}$), 1.12 (s, 3H, gem CH_3), 1.03 (s, 3H, gem CH_3), 0.91 (s, 9H, $C(CH_3)_3$), 0.18 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$). ^{13}C NMR (50.4 MHz) δ: 176.9 (RCO_2R), 76.5 (C_{19}), 75.5 (C_{17}), 40.7 (C_{18}), 25.4 ($C(CH_3)_3$), 22.7, 18.8 (gem CH_3's), 18.0 ($SiC(CH_3)_3$), -4.8, -5.7 ($Si(CH_3)_2$). MS (EI) m/z: 187 (M^+-57, 20%), 143 (M^+-101, 35%). HRMS calcd. for $C_8H_{15}O_3Si$ (M^+-$C(CH_3)_3$): 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 ($Na_2SO_4 \cdot 10H_2O$, ~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 $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield a white amorphous solid. Purification by SiO_2 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. $[\alpha]_D$ = -13.3° (c = 2.0, $CHCl_3$). IR (CH_2Cl_2) υ: 3591, 3050, 2959, 2931, 2859, 1472, 1256, 1048 cm^{-1}. ^1H NMR (300 MHz) δ: 5.12 (app t, 1H, H_{20}), (5.35) (dd, J = 4.2, 9.8 Hz, 1H, H_{20}), (3.82) (d, J = 9.8 Hz, 1H, H_{19}), 3.76 (d, A of AB, J = 8.2 Hz, 1H, H_{17}), 3.64 (s, 1H, H_{19}), 3.63 (d, B of AB, J = 8.2 Hz, 1H, $H_{17'}$), (3.60) (s, 2H, H_{17}), 1.03 (s, 3H, gem CH_3), 0.97 (s, 3H, gem CH_3), 0.88 (0.92) (s, 9H, $C(CH_3)_3$), 0.07, 0.05 (0.10, 0.08) (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (50.4 MHz) δ: 98.0 (104.6) (C_{20}), 79.2 (85.5) (C_{19}), 76.3 (78.4) (C_{17}), 42.0 (42.1) (C_{18}), 25.6 ($C(CH_3)_3$), 25.4, 19.9 (23.6, 19.9) (gem CH_3's), 18.0 (17.9) ($SiC(CH_3)_3$), -5.4 (-4.8) ($Si(CH_3)_2$). MS (CI ether) m/z: 247 (M^++1, 1%), 229 ((M^++1)-18,

100%), 189 (M^+-57, 23%). Anal. calcd. for $C_{12}H_{26}O_3Si$: 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 SiO_2 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° (c = 2.2, $CHCl_3$). IR (thin film) υ: 3395, 2971, 2881, 1471, 1382, 1031 cm^{-1}. ^1H NMR (200 MHz) δ: 5.41 - 5.47 (5.21 - 5.26) (m, 1H, H_{20}), (3.82) (d, A of AB, J = 8.4 Hz, 1H, H_{17}), (3.73) (d, B of AB, J = 8.4 Hz, 1H, $H_{17'}$), 3.66 (d, A of AB, J = 8.1Hz, 1H, H_{17}), 3.62 - 3.69 (m, 1H, H_{19}), 3.45 (d, B of AB, J = 8.1 Hz, 1H, $H_{17'}$), 2.85 - 2.91 (2.51 - 2.61) (br s, 1H, OH, exchangeable), 1.06, 1.04 (1.10, 106) (s, 6H, gem CH_3's). ^{13}C NMR (50.4 MHz) δ: 97.5 (103.4) (C_{20}), 78.2 (84.1) (C_{19}), 77.2 (78.5) (C_{17}),41.5 (41.6) (C_{18}), 25.4, 19.5 (23.7, 19.3) (gem CH_3's). MS (CI ether) m/z: 133 (M^++1, 15%), 131 (M^+-1, 18%), 115 ((M^++1)-18, 96%). Anal. calcd. for $C_6H_{12}O_3$: 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 NH_4Cl 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 $NaHCO_3$ (30 mL), and brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide a syrup. Further purification by SiO_2 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**). $[\alpha]_D$ = -6.2° (c = 1.8, $CHCl_3$). ^1H NMR (300 MHz) δ: 4.30 (d, J = 5.9 Hz, 1H, H_{21}), 3.90 (dd, J = 5.1, 5.9 Hz, 1H, H_{20}), 3.84 (d, J = 5.1 Hz, 1H, H_{19}), 3.61 (d, A of AB, J = 11.3 Hz, 1H, H_{17}), 3.35 (d, B of AB, J = 11.3 Hz, 1H, $H_{17'}$), 2.66 - 2.96 (m, 4H, $CH_2(CH_2S)_2$), 2.41 - 3.00 (br s, 2H, OH, exchangeable), 1.88 - 2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.04, 0.93 (s, 6H, gem CH_3's), 0.92 (s, 9H, $C(CH_3)_3$), 0.18, 0.11 (s, 6H, $Si(CH_3)_2$). MS (CI 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 SiO_2 flash chromatography (6:4 ether/hexane), 0.60 g (71%) of the diastereomeric triol adduct s **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**). $[\alpha]_D$ = -36.4° (c = 2.5, $CHCl_3$). ^1H NMR (300 MHz) δ: 4.04 (d, J = 8.8 Hz, 1H, H_{21}), 3.93 (d, J = 8.8 Hz, 1H, H_{20}), 3.79 (s, 1H, H_{19}), 3.63 (d, A of AB, J = 11.4 Hz, 1H, H_{17}), 3.34 (d, B of AB, J = 11.4 Hz, 1H, $H_{17'}$), 2.71 - 3.00 (br s, 3H, OH, exchangeable), 2.62 - 2.93 (m, 4H, $CH_2(CH_2S)_2$), 1.99 - 2.07 (m, 2H, $CH_2(CH_2S)_2$), 1.00, 0.95 (s, 6H, gem CH_3's). MS (CI 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 SiO_2 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 meltling at 108.0-109.1°C. $[\alpha]_D$ = -33.3° (c = 2.5, $CHCl_3$). ^1H NMR (300 MHz) δ: 4.55 (d, J = 2.7 Hz, 1H, H_{21}), 3.93 (dd, J = 2.7, 8.4 Hz, 1H, H_{20}), 3.58 (d, J = 8.4 Hz, 1H, H_{19}), 3.54 (d, A of AB, J = 11.3 Hz, 1H, H_{17}), 3.45 (d, B of AB, J = 11.3 Hz, 1H, $H_{17'}$), 2.86 - 3.01 (m, 4H, $CH_2(CH_2S)_2$), 2.52 - 2.79 (br s, 3H, OH, exchangeable), 1.85 - 2.14 (m, 2H, $CH_2(CH_2S)_2$), 1.04, 0.93 (s, 6H, gem CH_3's). MS (EI) m/z: 149 (M^+-103, 6%). MS (CI 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 $NaHCO_3$, and brine (30 mL portions). Drying over Na_2SO_4 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**; rf'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, $CH_2(CH_2S)_2$), 1.95 - 2.20 (br s, 1H, OH, exchangeable), 1.92 - 2.17 (m, 2H, $CH_2(CH_2S)_2$), 1.46, 1.40 (s, 6H, $(RO)_2C(CH_3)_3$), 0.98, 0.93 (s, 6H, gem CH_3's). MS (CI 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) δ: 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, $CH_2(CH_2S)_2$), 1.83 - 2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.47, 1.42 (s, 6H, $(RO)_2C(CH_3)_2$), 1.12, 0.78 (s, 6H, gem CH_3's). MS (CI 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) δ: 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, $CH_2(CH_2S)_2$), 2.41 - 2.60 (br s, 1H, OH, exchangeable), 1.79 - 2.10 (m, 2H, $CH_2(CH_2S)_2$),1.41, 1.38 (s, 6H, $(RO)_2C(CH_3)_2$), 0.99, 0.87 (s, 6H, gem CH_3's). MS (CI 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**; rf'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-Hyroxy-3,5-O-isopropylidene-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (141):

^{1}H NMR (300 MHz) δ: 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, $CH_2(CH_2S)$), 1.96 - 2.41 (br s, 1H, OH, exchangeable), 1.81 - 2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.39, 1.36 (s, 6H, $(RO)_2C(CH_3)_2$). 1.07, 0.92 (s, 6H, gem CH_3's). MS (CI ether) m/z: 293 (M^++1, 15%), 275 ((M^++1)-18, 1%), 235 ((M^++1)-58, 52%).

(2R,3R)-3-Hydroxy-2,5-O-isopropylidene-4,4-dimethyl-1,1-(propane-1',3'-dithio)-pentane (142):

^{1}H NMR (300 MHz) δ: 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, $CH_2(CH_2S)_2$), 2.19 (d, J = 5.6 Hz, 1H, OH, exchangeable), 1.91 - 2.15 (m, 2H, $CH_2(CH_2S)_2$), 1.39, 1.35 (s, 6H, $(RO)_2C(CH_3)_2$), 0.98 (s, 6H, gem CH_3's). MS (CI ether) m/z: 293 (M^++1, 35%), 275 ((M^++1)-18, 3%), 235 ((M^++1)-58, 95%).

(2S,3R)-5-Acetoxy-2,3-O-isopropylidene-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_2SO_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) δ: 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, $CH_2(CH_2S)_2$), 2.08 (s, 3H, CH_3CO_2R), 1.91 - 2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.45, 1.37 (s, 6H, $(RO)_2C(CH_3)_2$), 0.99, 0.96 (s, 6H, gem CH_3's). MS (EI) m/z: 334 (M^+, 3%), 319 (M^+-15, 1%), 215 (M^+-119, 22%). MS (CI ether) m/z: 335 (M^++1, 45%), 276 ((M^++1)-59, 100%). HRMS calcd. for $C_{15}H_{26}O_4S_2$ (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 of solvent removed *in vacuo* . The residue was diluted in ethyl acetate (40 mL) and washed successively with 0.2N HCl, saturated aqueous $NaHCO_3$, and brine (30 mL of each), dried over Na_2SO_4, 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, H_{21}), 3.95 (s, 1H, H_{19}), 3.90 (d, J = 6.6 Hz, 1H, H_{20}), 3.73 (d, A of AB, J = 11.1 Hz, 1H, H_{17}), 3.66 (d, B of AB, J = 11.1 Hz, 1H, $H_{17'}$), 2.80 - 3.02 (br s, 1H, OH, exchangeable), 2.74 - 2.91 (m, 4H, $CH_2(CH_2S)_2$), 1.84 - 2.15 (m, 2H, $CH_2(CH_2S)_2$), 1.25, 0.85 (s, 6H, gem CH_3's). MS (CI 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 $NaHCO_3$, and brine (20 mL of each). The organic layer was dried over Na_2SO_4 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, H_{20}), 5.48 (s, 1H, $(RO)_2CHPh$), 4.35 (d, J = 1.3 Hz, 1H, H_{21}), 3.91 (d, J = 10.1 Hz, 1H, H_{19}), 3.70 (d, A of AB, J = 10.7 Hz, 1H, H_{17}), 3.63 (d, B of AB, J = 10.7 Hz, 1H, $H_{17'}$). 2.88 - 3.00 (m, 2H, $CH_2(CH_2S)_2$), 2.48 - 2.63 (m, 2H, $CH_2(CH_2S)_2$), 2.11 (s, 3H, CH_3CO_2R), 1.96 - 2.10 (m, 2H, $CH_2(CH_2S)_2$), 1.15, 0.91 (s, 6H, gem CH_3'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) δ: 7.33 - 7.49 (m, 5H, aromatic), 5.44 (s, 1H, $(RO)_2CHPh$), 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, $CH_2(CH_2S)_2$), 1.80 - 2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.51 - 1.80 (br s, 1H, OH, exchangeable), 1.21, 0.97 (s, 6H, gem CH_3's). MS (CI ether) m/z: 341 (M^++1, 37%), 323 ((M^++1)-18, 3%), 235 ((M^++1)-106, 23%).

(2R,3R)-Acetoxy-3,5-O-benzylidene-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) δ: 7.35 - 7.50 (m, 5H, aromatic), 5.47 (s, 1H, $(RO)_2CHPh$), 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, $CH_2(CH_2S)_2$), 2.14 (s, 3H, CH_3CO_2R), 1.85 - 2.12 (m, 2H, $CH_2(CH_2S)_2$), 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 $BF_3{\cdot}Et_2O$ (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 $NaHCO_3$ (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 $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 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) υ: 2961, 2938, 2862, 1466, 1473, 1260, 1190, 840, 788 cm^{-1}. ^1H NMR (200 MHz) δ: 5.79 - 5.87 (m, 1H, H_2), 5.04 - 5.14 (m, 2H, H_1), 3.66 - 3.70 (m, 1H, H_3), 3.53 (s, 2H, H_7), 3.44 (3.61) (d, J = 6.1 (7.8) Hz, 1H, H_5), 2.41 - 2.46 (m, 1H, H_3), 2.18 - 2.25 (m, 1H, H_3'), 0.99,.0.96 (1.02) (s, 6H, gem CH_3's), 0.88 (0.91) (s, 9H, $SiC(CH_3)_3$), 0.050, 0.041 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (50.4 MHz) δ: (136.6) 135.3 (C_2), 116.9 (116.2) (C_1), 84.4 (81.9) (C_5), 83.0 (80.5) (C_4), 78.9 (77.6) (C_3), (43.6) 41.9 (C_2), 37.9 (35.2) (C_1), (25.8) 25.7 ($C(CH_3)_3$), (25.4) 25.0 (gem CH_3), (20.4) 20.1 (gem CH_3), (18.1) 17.9 ($SiC(CH_3)_3$), (-4.4) -4.5

($Si(CH_3)_2$). MS (EI) m/z: 229 (M^+-41, 17%), 213 (M^+-57, 23%). MS (CI ether) m/z: 271 (M^++1, 8%), 229 (M^+-41, 100%), 213 (M^+-57, 25%). HRMS calcd. for $C_{11}H_{21}O_2Si$ (M^+-$C(CH_3)_3$): 213.1311; found: 213.1315.

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

The γ-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 X 30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated *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° (c = 1.0, $CHCl_3$). IR (thin film) υ: 3380, 3082, 2962, 1646, 1479, 1398, 1049, 920 cm^{-1}. ^1H NMR (300 MHz) δ: 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). ^{13}C NMR (50.4 MHz) δ: 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 (CI ether) m/z: 175 (M^++1, 100%), 157 ((M^++1)-18, 73%). Anal calcd. for $C_9H_{18}O_3 \cdot 1/3H_2O$: 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 $NaHCO_3$ (30 mL), and brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The oil was purified by SiO_2 flash chromatography (4:6 ether/hexane) to provide 0.17 g (76%) of the acetonide **147** as a colourless oil. $[\alpha]_D$ = +24.2° (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz) δ: 5.83 - 5.94 (m, 1H, H_2), 5.07 - 5.13 (m, 2H, H_1), 3.95 (ddd, J = 3.3, 7.6, 7.9 Hz, 1H, H_4), 3.67 (d, J = 7.9 Hz, 1H, H_5), 3.44 (s, 2H, H_7), 2.38 - 2.42 (m, 1H, H_3), 2.24 - 2.32 (m, 1H, $1H_{3'}$), 1.80 - 2.10 (br s, 1H, OH, exchangeable), 1.38, 1.37 (s, 6H, $(RO)_2C(CH_3)_2$), 0.94, 0.90 (s, 6H, gem CH_3's). ^{13}C NMR (50.4 MHz) δ: 134.5 (C_2), 117 (C_1), 108.2 ($(RO)_2C(CH_3)_2$), 86.1 (C_5), 76.6 (C_4), 71.6 (C_7), 39.2 (C_3),36.5 (C_6), 27.1, 27.0 ($(RO)_2C(CH_3)_2$), 21.9, 18.9 (gem CH_3's). MS (CI ether) m/z: 215 (M^++1, 77%), 199 (M^+-15, 31%). HRMS calcd. for $C_{11}H_{19}O_3$ (M^+-CH_3): 199.1335; found: 199.1307.

(4R,5R)-7-Acetoxy-4,5-O-Isopropylidene-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) δ: 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_3CO_2R), 1.34 (s, 6H, $(RO)_2C(CH_3)_2$), 0.95, 0.91 (s, 6H, gem CH_3's). MS (CI 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 $NaHCO_3$ 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_2SO_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, $TiCl_4$ was used instead of $SnCl_4$. The procedure was identical except that the reaction time was 5 minutes (versus 20 minutes) and the yield of **158** was 55%. $[\alpha]_D$ = +0.8° (c = 1.0, $CHCl_3$). IR (thin film) υ: 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, H_2), 5.06 - 5.14 (m, 2H, H_1), 4.61 (d, A of AB, J = 11.3 Hz, 1H, CH_2Ph), 4.57 (d, B of AB, J = 11.3 Hz, 1H, CH_2Ph), 4.54 (d, A of AB, J = 11.9 Hz, 1H, CH_2Ph), 4.49 (d, B of AB, J = 11.9 Hz, 1H, CH_2Ph), 4.05 - 4.11 (m, 1H, H_5), 3.86 (ddd, J = 1.5, 5.4, 6.7 Hz, H_7), 3.60 - 3.65 (m, 2H, H_4, H_6), 3.58 (dd, A of ABX, J = 6.7, 9.5 Hz, 1H, H_8), 3.49 (dd, B of ABX, J = 5.4, 9.5, 1H, $H_{8'}$), 2.43 - 2.94 (br s, 3H, OH, exchangeable), 2.20 - 2.78 (m, 2H, H_3). ^{13}C NMR (50.4 MHz) δ: 137.7, 137.6 (aromatic), 134.9 (C_2), 128.7, 128.6, 128.4, 128.3, 128.0 (aromatic), 117.7 (C_1), 78.9 (C_6), 74.1, 73.4 (2 X CH_2Ph). 71.1 (C_8), 70.8, 69.1, 69.0 (C_4, C_5, C_7), 38.1 (C_3). MS (CI ether) m/z: 373 (M^++1, 100%), 355 ((M+1) -18, 16%). Anal calcd. for $C_{22}H_{28}O_5$: C, 70.94, H, 7.58; found: C, 70.81, H, 7.61.

(4R,5S,6R,7R)-6,8-Dibenzyloxy-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 $NaHCO_3$, and brine (30

mL of each). The ethereal layer was dried over Na_2SO_4 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) υ: 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, H_2), 5.04 - 5.12 (m, 2H, H_1), 4.68 (d, A of AB, J = 11.4 Hz, 1H, CH_2Ph), 4.62 (d, B of AB, J = 11.4 Hz, 1H, CH_2Ph), 4.50 (s, 2H, CH_2Ph), 4.00 - 4.06 (m, 1H, H_7), 3.91 - 3.99 (m, 1H, H_4), 3.85 (dd, J = 4.0, 8.2 Hz, 1H, H_5), 3.60 (dd, J = 3.2, 4.0 Hz, 1H, H_6), 3.54 (dd, A of ABX, J = 5.8, 9.5 Hz, 1H, H_8), 3.50 (dd, B of ABX, J = 6.1, 9.5 Hz, 1H, $H_{8'}$), 2.20 - 2.37 (m, 2H, H_3), 1.38 (s, 3H, $(RO)_2C(CH_3)_2$), 1.36 (s, 3H, $(RO)_2C(CH_3)_3$), 1.63 - 1.80 (s, OH, 1H, exchangeable). ^{13}C NMR (50.4 MHz) δ: 138.0, 137.9 (aromatic), 134.0 (C_2), 128.5, 128.4, 128.1, 128.0, 127.9 (aromatic), 117.6 (C_1), 108.7 ($(RO)_2C(CH_3)_2$), 80.9 (C_6), 76.7, 76.1 (C_4, C_5), 74.3, 73.4 (2 X CH_2Ph), 70.9 (C_8), 70.6 (C_7), 36.9 (C_3), 27.1 ($(RO)_2C(CH_3)_2$), 26.7 ($(RO)_2C(CH_3)_2$). MS (CI ether) m/z: 413 (M^++1, 100%), 381 (M^+-31, 11%). Anal. calcd. for $C_{25}H_{32}O_5$: 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) υ: 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, H_2), 5.25 - 5.30 (m, 1H, H_7), 4.98 - 5.05 (m, 2H, H_1), 4.72 (d, A of AB, J = 11.7 Hz, 1H, CH_2Ph), 4.58 (d, B of AB, J = 11.7 Hz, 1H, CH_2Ph), 4.55 (d, A of AB, J = 12.0 Hz, 1H, CH_2Ph), 4.43 (d, B of AB, J = 12.0 Hz, 1H, CH_2Ph), 3.88 - 3.94 (m, 1H, H_4), 3.63 - 3.75 (m, 4H, H_5, H_6, H_8), 2.04 - 2.20 (m, 2H, H_3), 2.02 (s, 3H, CH_3CO_2R), 1.34 (s, 3H, $(RO)_2C(CH_3)_2$), 1.29 (s, 3H, $(RO)_2C(CH_3)_2$). MS (CI 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 $TiCl_4$-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

R. Roy and A.W. Rey, A Direct Convergent Chemoenzymatic Synthesis of the C(1)–C(9) Fragment of Bryostatin. Unusual Diastereoselectivitiy During a Mukaiyama Aldol Condensation, *Synlett*, **1**, 448 (1990).

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