University of Alberta

Asymmetric synthesis of carbocycles by intramolecular conjugate displacement and synthetic studies on sorbicillactone A

by

Dinesh T. Sreedharan

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

©Dinesh T. Sreedharan

Spring 2014

Edmonton, Alberta

Permission is hereby granted to the University of Alberta Libraries to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only. Where the thesis is converted to, or otherwise made available in digital form, the University of Alberta will advise potential users of the thesis of these terms.

The author reserves all other publication and other rights in association with the copyright in the thesis and, except as herein before provided, neither the thesis nor any substantial portion thereof may be printed or otherwise reproduced in any material form whatsoever without the author's prior written permission.
DEDICATED TO

MY SUPERVISOR PROF. D. L. J. CLIVE

MY PARENTS, MY WIFE MANJU

MY FAMILY, FRIENDS AND TEACHERS
ABSTRACT

The first chapter of this thesis describes an intramolecular conjugate displacement (ICD) for the asymmetric synthesis of carbocycles using a carbon nucleophile. The precursors for ICD were synthesized by Morita-Baylis-Hillman reaction between (5R)-5-(l-menthyl)-2(5H)-furanone and aldehydes, which carry a geminal phenylthio groups in the γ or δ position. Acetylation of the resulting hydroxyl group, followed by oxidation of the phenylthio groups to phenylsulfonyl groups gave the desired ICD precursor which, on treatment with a base, underwent ring closure by intramolecular conjugate displacement. Hydrogenation, DIBAL-H reduction and desulfonylation releases an optically pure carbocycle.

The second chapter describes studies aimed at the synthesis of the bioactive marine alkaloid sorbicillactone A. During this project, much of the carbon skeleton of sorbicillactone A was assembled, and studies to finish the total synthesis are in progress. The key reactions involved in this project are radical-mediated cyclization to synthesize the bicyclic core, 1,4 addition of a phenyldimethylsilyl unit, followed by trapping of the intermediate with methyl iodide and, finally, a one pot process for ketal protection and iodolactonization. After the successful installation of nitrogen at C-3, current research is directed at the installation of a methyl group at the same C-3 position.
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisor, Dr. D. L. J. Clive, for his superb guidance and constant encouragement during the course of my Ph.D. program, and for his assistance during the preparation of this Thesis.

Many thanks to all group members, past and present, for their assistance and useful discussions pertaining to my research and for making the research laboratories an enjoyable workplace.

My thanks are also extended to the support staff of the department (IR, MS, NMR, elemental analysis laboratories, glass blowing, electronic, machine and chemical shops), especially to Dr. R. McDonald for the X-ray measurements and to Dr. A. Morales-Izquierdo for mass spectrometry measurements and for invaluable discussions.

Many thanks to all my teachers for their constant support and encouragement. My thanks to all the members of Edmonton Super Team and Edmonton Cosmopolitans Community Services Foundation for their excellent support during my Ph. D. program.

Finally I would like to thank my parents, my wife, brother, sister and all my family members and friends for their priceless support and encouragement.
# TABLE OF CONTENTS

Chapter 1 ........................................................................................................................................... 01

1. Introduction ....................................................................................................................................... 02

   1.1. General ......................................................................................................................................... 02

   1.2. Asymmetric synthesis of carbocycles ....................................................................................... 02

      1.2.1. Method of MacMillan and co-workers ............................................................................. 02

      1.2.2. Method of Hong and co-workers ...................................................................................... 03

      1.2.3. Method of Panek and co-workers ...................................................................................... 06

      1.2.4. Method of Trost and co-workers ...................................................................................... 07

   1.3. Intermolecular and intramolecular conjugate displacement .............................................. 08

      1.3.1. Intermolecular conjugate displacement .......................................................................... 09

      1.3.2. Intramolecular conjugate displacement .......................................................................... 12

2. Results and Discussion .................................................................................................................... 25

   2.1. Synthesis of chiral lactones ..................................................................................................... 26

   2.2. Synthesis of aldehydes for coupling ....................................................................................... 29

   2.3. Condensation of the chiral lactones with the aldehydes and synthesis of ICD precursors ................................................................................................................................. 35

   2.4. Ring closure by intramolecular conjugate displacement ......................................................... 41

   2.5. Stereochemistry of ICD adducts ............................................................................................. 47

   2.6. Removal of the chiral auxiliary ............................................................................................... 50

3. Conclusion .......................................................................................................................................... 55

4. Experimental ....................................................................................................................................... 56
LIST OF FIGURES

Chapter 1

Figure 1. ORTEP diagram of compound 32.5c. .................................................. 40
Figure 2. ORTEP diagram of compound 32.5g. .................................................. 48
Figure 3. ORTEP diagram of compound 32.1l ................................................... 50
Figure 4. ORTEP diagram of compound 32.5i. ................................................... 52
Figure 5. ORTEP diagram of compound 32.5k. ................................................... 54

Chapter 2

Figure 1. ORTEP diagram of compound 16.1 ...................................................... 180
Figure 2. ORTEP diagram of compound 17.2 ...................................................... 183
Figure 3. ORTEP diagram of compound 19.1a ................................................... 185
Figure 4. ORTEP diagram of compound 23.1a ................................................... 189
Figure 5. ORTEP diagram of compound 23.1b ................................................... 190
Figure 6. ORTEP diagram of compound 28.2 ...................................................... 195
Figure 7. ORTEP diagram of compound 35.1 ...................................................... 202
LIST OF SCHEMES

Chapter 1

Scheme 1 .............................................................................................................03
Scheme 2 .............................................................................................................04
Scheme 3 .............................................................................................................05
Scheme 4 .............................................................................................................06
Scheme 5 .............................................................................................................07
Scheme 6 .............................................................................................................08
Scheme 7 .............................................................................................................09
Scheme 8 ............................................................................................................10
Scheme 9 .........................................................................................................11
Scheme 10 .........................................................................................................12
Scheme 11 .........................................................................................................13
Scheme 12 .........................................................................................................13
Scheme 13 .........................................................................................................14
Scheme 14 .........................................................................................................15
Scheme 15 .........................................................................................................16
Scheme 16 .........................................................................................................17
Scheme 17 .........................................................................................................17
Scheme 18 .........................................................................................................18
Scheme 19 .........................................................................................................19
Scheme 20 .........................................................................................................20
<table>
<thead>
<tr>
<th>Scheme</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 21</td>
<td>21</td>
</tr>
<tr>
<td>Scheme 22</td>
<td>22</td>
</tr>
<tr>
<td>Scheme 23</td>
<td>22</td>
</tr>
<tr>
<td>Scheme 24</td>
<td>23</td>
</tr>
<tr>
<td>Scheme 25</td>
<td>24</td>
</tr>
<tr>
<td>Scheme 26</td>
<td>25</td>
</tr>
<tr>
<td>Scheme 27</td>
<td>26</td>
</tr>
<tr>
<td>Scheme 28</td>
<td>26</td>
</tr>
<tr>
<td>Scheme 29</td>
<td>27</td>
</tr>
<tr>
<td>Scheme 30</td>
<td>28</td>
</tr>
<tr>
<td>Scheme 31</td>
<td>29</td>
</tr>
<tr>
<td>Scheme 32</td>
<td>30</td>
</tr>
<tr>
<td>Scheme 33</td>
<td>30</td>
</tr>
<tr>
<td>Scheme 34</td>
<td>31</td>
</tr>
<tr>
<td>Scheme 35</td>
<td>32</td>
</tr>
<tr>
<td>Scheme 36</td>
<td>33</td>
</tr>
<tr>
<td>Scheme 37</td>
<td>33</td>
</tr>
<tr>
<td>Scheme 38</td>
<td>34</td>
</tr>
<tr>
<td>Scheme 39</td>
<td>34</td>
</tr>
<tr>
<td>Scheme 40 (part 1)</td>
<td>37</td>
</tr>
<tr>
<td>Scheme 40 (part 2)</td>
<td>38</td>
</tr>
<tr>
<td>Scheme 40 (part 3)</td>
<td>39</td>
</tr>
<tr>
<td>Scheme 41</td>
<td>39</td>
</tr>
</tbody>
</table>
Scheme 42 ......................................................................................................................... 41
Scheme 43 (part 1) ............................................................................................................ 42
Scheme 43 (part 2) ............................................................................................................ 43
Scheme 44 ......................................................................................................................... 45
Scheme 45 ......................................................................................................................... 46
Scheme 46 ......................................................................................................................... 46
Scheme 47 ......................................................................................................................... 47
Scheme 48 ......................................................................................................................... 51
Scheme 49 ......................................................................................................................... 53

Chapter 2

Scheme 1 ......................................................................................................................... 160
Scheme 2 ......................................................................................................................... 161
Scheme 3 ......................................................................................................................... 161
Scheme 4 ......................................................................................................................... 162
Scheme 5 ......................................................................................................................... 165
Scheme 6 ......................................................................................................................... 167
Scheme 7 ......................................................................................................................... 168
Scheme 8 ......................................................................................................................... 170
Scheme 9 ......................................................................................................................... 171
Scheme 10 ....................................................................................................................... 172
Scheme 11 ....................................................................................................................... 173
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic ring</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting materials</td>
</tr>
<tr>
<td>Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>Bu-t</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>CD</td>
<td>circular dichroism</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzyloxy carbonyl</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylidine acetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>$N,N'$-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>concentration that gives 50% inhibition of an enzyme</td>
</tr>
<tr>
<td>ICD</td>
<td>intramolecular conjugate displacement</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>MCPBA</td>
<td>m-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration is the lowest concentration of a drug in mg/mL that inhibits the visible growth of a strain of bacteria</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td>1-methylpyrrolidin-2-one</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oak Ridge Thermal Ellipsoid Plot</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Pmb</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase transfer catalyst</td>
</tr>
<tr>
<td>pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>rr</td>
<td>regioisomer ratio</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SOMO</td>
<td>singly occupied molecular orbital</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-tetramethylpiperidin-1-yl)oxy</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMM</td>
<td>trimethylenemethane</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl</td>
</tr>
<tr>
<td>TsOH</td>
<td>$p$-toluenesulfonic acid</td>
</tr>
</tbody>
</table>
Chapter 1

Asymmetric synthesis of carbocycles: use of intramolecular conjugate displacement
1. Introduction

1.1 General

In this chapter of my thesis, I will describe a new method for making optically pure carbocycles using a process that I call intramolecular conjugate displacement (ICD). In the review section I will cover a few of the recent literature reports for the synthesis of optically pure carbocycles and will also give the background to the development of the ICD reaction. The preparation of single enantiomers is now a fundamental aspect of organic synthesis, and the asymmetric ICD process is a new contribution in this respect.

1.2 Asymmetric synthesis of carbocycles

In order to indicate the types of approach that are available for the asymmetric synthesis of optically pure carbocycles, I have selected a four examples from the recent literature to represent enantioselective and diastereoselective methods.

1.2.1 Method of MacMillan and co-workers

Recently, MacMillan and co-workers reported a method for the synthesis of carbocycles and heterocycles from unactivated aldehyde-olefin precursors, achieved via enantioselective SOMO-catalysis.

---

Their protocol involves a carbonyl-ene cyclization via an enamine radical cation (Scheme 1).

![Scheme 1](image)

The enamine radical cation adds stereoselectively from the unshielded face to the pendent olefin. MacMillan and his group have synthesized five-membered as well as six-membered heterocycles and carbocycles through this approach with $ee \ 85\text{-}99\%$ and $dr > 20\text{:}1$.\(^1\)

1.2.2 Method of Hong and co-workers\(^2\)

Hong and co-workers developed\(^2\) a method for the enantioselective synthesis of cyclohepta[b]indoles. Their approach involves an organocatalytic Michael addition, followed by double Friedel-Crafts alkylation (Scheme 2).
Hong’s group was able to synthesize cyclohepta[b]indoles in yields up to 72% and stereoselectivity up to 96% ee. The stereochemical rationale for this reaction (Scheme 3) is initial nucleophilic attack of indole malononitrile 2.1 on the iminium derivative of the α,β-unsaturated aldehyde 3.1, which occurs from the less hindered Re face to give the product 2.3. Subsequent treatment of 2.3 with 2.4 provides the cation 3.2. This prefers the stabilized π-π stacking and half-chair cycloheptane conformer 3.2, to afford the cyclohepta[b]indole 2.5 as the major isomer.²
Scheme 3
1.2.3 Method of Panek and co-workers

Panek and co-workers reported an organosilane-directed alkyne-alkene reductive coupling, followed by intramolecular alkylation, [3+2] annulation or Sakurai-like homodimerization, to synthesize a range of carbocyclic ring systems. One representative example from their work is shown in Scheme 4. The diastereoselectivity of the [3+2] annulation reaction (see 4.6→4.7→4.5) is attributed to the stereocontrolling effect of the chiral center carrying the silyl group.

Scheme 4
1.2.4 Method of Trost and co-workers

Trost and co-workers reported an enantioselective synthesis of carbocycles by an asymmetric trimethylenemethane cycloaddition. Their protocol involves an enantioselective [3+2] cycloaddition of trimethylenemethane with electron deficient olefins, using a pyrrolidine phosphoramidite ligand (5.3). Steric factors of the ligand system control the enantioselectivity.

The catalytic cycle for the trimethylenemethane (TMM) reaction of silyl allylic acetate (5.2) involves the generation of zwitterionic Pd-TMM intermediate (6.1) by a metal-promoted ionization of the allylic acetate, followed by desilylation. Addition of the nucleophilic Pd-TMM complex to the olefin 6.2 gives the intermediate 6.3. The collapse of this intermediate via an intramolecular
attack of the soft carbon nucleophile onto the π-allylpalladium affords the desired product 6.4 (Scheme 6).  

\[
\begin{align*}
\text{TMS} & \quad \text{5.2} \\
\text{5.2} & \quad \text{5.1} \\
\text{6.1} & \quad \text{6.2} \\
\text{6.2} & \quad \text{6.3} \\
\text{6.3} & \quad \text{6.4} \\
\text{6.4} & \quad \text{Scheme 6}
\end{align*}
\]

### 1.3 Intermolecular and Intramolecular Conjugate Displacement

Seebach and co-workers reported\(^5\) that the presence of an electron-withdrawing group (EWG) at C-2 of an allylic system carrying a leaving group at C-3 increases the rate of S\(_N\)2' displacement; such systems were investigated by Lawton and co-workers\(^6\) for cross-linking various chains.
Although, much research has been conducted on *intermolecular* versions of these $S_N2'$ reactions using this EWG-activated allylic theme, the intramolecular version of this process was not widely appreciated and only a few examples of protein cross linking and synthesis of macrocycles had been reported. The general utility in complex molecule synthesis does not appear to have been appreciated. In the past few years, research from this laboratory has demonstrated the usefulness of this intramolecular reaction using carbon, nitrogen and sulphur nucleophiles, and the method has also been applied in the construction of the core structures of several complex natural products. The starting materials for these reactions are usually derived from Morita-Baylis-Hillman alcohols.

### 1.3.1 Intermolecular conjugate displacement

The type of reaction represented in Scheme 7, is formally a hybrid of the classical Michael addition and an $S_N2'$ displacement. Seebach and co-workers in 1981 reported an early example of this type (Scheme 8).
Reaction of the 2-nitroallyl pivaloate \(8.1\) with Grignard reagents or organolithium reagents gave the product \(8.2\). From the results obtained, Seebach concluded that the reactivity of the substrate \(8.1\) was higher in the presence of the pivaloyloxy group (leaving group) than in its absence. The product \(8.2\), which is a Michael acceptor, is less reactive than the starting material \(8.1\), and was isolated and then subjected to a classical Michael addition to get the product \(8.3\).\(^{6a,b}\)

The fact that a Michael acceptor with an allylic leaving group is more reactive than one without the leaving group, was used in this laboratory during the synthesis of the marine natural product marinopyrrole B \((9.6)\).\(^{15}\) The extra reactivity allowed an alkylation to be done that was unsuccessful with less reactive reagents (Scheme 9).
Reaction of 9.1 with ethyl bromopyruvate 9.2, did not give any of the desired product (9.3). However, on treatment of 9.1 with the allylic acetate 9.4 and K₂CO₃ in refluxing MeCN, the desired conjugate displacement occurred and 9.5 was obtained in 95% yield. Cleavage of the terminal double bond by ozonolysis gave 9.3, which was then converted to marinopyrrole B.

Ramachandran and co-workers reported an enantioselective Sₘ₂' displacement for the synthesis of glutamic acid derivatives under phase transfer catalyst (PTC) conditions between benzophenone imine 10.1 and Morita-Baylis-Hillman acetate 10.2. Catalyst 10.3, derived from cinchonidine, was used as a PTC catalyst and the products were isolated with 80-97% ee (Scheme 10).
Intermolecular reactions using Morita-Baylis-Hillman adducts have been extensively reviewed; therefore, the rest of my introduction deals mainly with the intramolecular version.

1.3.2 **Intramolecular conjugate displacement (ICD)**

1.3.2.1 **ICD reactions reported by other groups**

The Foucaud group reported one of the early examples of ICD reactions in 1989 and 1994, during their synthesis of cyclophanes and cryptophanes, using nitrogen nucleophiles. The reaction between Morita-Baylis-Hillman adduct 11.1 and ammonia gave the desired intramolecular conjugate displacement product 11.2 (Scheme 11).
Kaye's group in 1990 reported\textsuperscript{18} the synthesis of indolizines from 2-pyridyl derivatives via an addition-elimination process using nitrogen as the nucleophile. But the mechanism proposed by Kaye's group contravenes Baldwin's rules for ring closure (5-\textit{endo-trig}, disfavored, Scheme 12). In contrast, when Drewes and co-workers heated the imidazole substrate 13.1 in THF (Scheme 13), they isolated only the allylic rearrangement product 13.3, and none of the ICD product 13.2 was obtained.
In a similar kind of experiment, Lee and co-workers observed\textsuperscript{19} that allylic rearrangement could occur at a lower temperature than ring closure. Treatment of 14.1 in refluxing xylene (~140 °C) gave only 14.3, which is a rearrangement product, whereas when the temperature was raised to 258 °C, the product isolated was the cyclized one 14.2 (Scheme 14).

Therefore, for those substrates in which the ICD reactions are disfavored by Baldwin's rules, the products are possibly formed by an allylic rearrangement followed by an S\textsubscript{N}2 displacement.
Lee and co-workers have reported\textsuperscript{20} the use of an iminophosphorane unit as a nucleophile for ICD reactions and they synthesized several 1,2-dihydroquinoline derivatives with such nucleophiles. Iminophosphoranes \textbf{15.2} were prepared by reaction between Morita-Baylis-Hillman acetates \textbf{15.1} and (EtO)\textsubscript{3}P. Refluxing of a solution of \textbf{15.2} in toluene gave the dihydroquinoline \textbf{15.3} (Scheme 15). When the electron-withdrawing group was CO\textsubscript{2}Me or COMe, a combination of aza-Wittig reaction and allylic shift occurred, resulting in the formation of \textbf{15.5}.
In 1994, Tokoroyama and co-workers studied the effect of oxy-substituents at C-1 for altering the diastereoselectivity of cyclization of compound 16.1. In their studies the carbocycles were formed via an intramolecular conjugate displacement promoted by a Lewis acid. During these ICD reactions, they isolated 3-4 diastereomers (depending on the substrate) but there was no correlation between the stereochemistry of the cyclized product and the stereochemistry of the C-1 substituent.
Use of oxygen as a nucleophile for what we would call an ICD reaction can be seen during conversion of erinacine P to erinacine B by Sassa and co-workers.²²a Treatment of erinacine P with Et₃N-LiBr resulted in the 1,4-addition of the hydroxyl group to the enal and elimination of acetate to give erinasine B. Nakada's group also used the same transformation during their enantioselective synthesis of (−)-erinacine B.²²b
Whitham's group observed a radical mediated process that can be classified as an ICD during their studies on radical induced cyclisation of allylic sulfones containing an electron-withdrawing group β to a sulfone group. Heating TolSO₂Na in aqueous acetic acid produces the sulfone radical which then attacks the substrate 18.1 to give 18.2.

![Scheme 18](image)

1.3.2.2 ICD reaction - prior work from the Clive group

The concept of ICD reactions emerged in this group during the total synthesis₁²₉,₁⁴₉ of the marine alkaloid halichlorine (Scheme 19) as a method of forming a ring, and only later were the related literature precedents found in the earlier work of Lawton⁶,⁸ and Foucauld.⁹ Treatment of 19.1 with Meerwein's salt resulted in the opening of the lactam and subsequent treatment of the resulting amine with Na₂CO₃ gave the tricyclic core structure 19.3 of halichlorine. This substance was then elaborated into the natural product.
The previous group members Dr. M. Yu and Dr. Z. Li generalized this methodology and showed that bicyclic amines with nitrogen at the bridgehead could be readily synthesized by ICD reaction in excellent yields.\textsuperscript{12b} The precursors for these ICD reactions were synthesized either by Morita-Baylis-Hillman reaction or by condensation of aldehydes with selenium-stabilized carbanions followed by oxidation and acetylation (Scheme 20). They also showed that the ICD reaction occurred with preservation of stereochemistry $\alpha$ to the nitrogen ($20.5 \rightarrow 20.6$).
Encouraged by the very high yields of this ICD reaction, Dr. Yu also tried to synthesize compound 21.2 via an 5-endo-trig cyclization, which is disfavored by Baldwin's rules. However, no desired product was found and, instead, the reaction gave the amide 21.3 by attack of nitrogen on the methyl ester (Scheme 21).\textsuperscript{12b} It should be pointed out that intermolecular conjugate addition, followed by cyclization via an $S_N2$ displacement could have generated 21.2. It is not clear why attack by nitrogen on the CO$_2$Me group was preferred over attack at the acetate carbonyl. In any event, the experimental observations indicate that ICD reactions are unfavorable when the ring that would be formed is five-membered, in accord with Baldwin's rules.
Dr. Z. Chen took advantage of this fact by introducing an unsaturated electrophile X=Y, which could easily be attacked by the nitrogen to generate a nucleophilic species N-X-Y− which, in turn can, undergo the ICD reaction by a 7-endo-dig pathway without violating Baldwin's rules. Examination of several potential electrophiles (PhNCO, PhNCS, SO₂, BnN=CH₂, (Cl₃C)₂C=NMe, CO₂, CS₂, H₂NCN), showed that CS₂ is satisfactory and gave the desired products. During these reactions, in some cases Dr. Chen observed the formation of a 5-membered side product as well (e.g. 22.5). The amount of side product depends on several factors: cyanide as the electron-withdrawing group increases the amount of 5-membered ring compared to a CO₂Me group. The amount of 5-membered ring formation was higher in acyclic precursors than in cyclic precursors in which the reacting arms are attached to an existing ring.
In 2007, Dr. Prabhudas developed the ICD reaction for the synthesis of carbocycles.\textsuperscript{11a} Later on, Dr. L. Wang conducted a detailed study on the all-carbon ICD reaction,\textsuperscript{11b} the results of which showed that ICD reactions occurred under mild conditions and could be used for the synthesis six-, seven- and eight-membered carbocycles. Dr. Wang's results (Scheme 23) also showed that ICD reactions are compatible with different electron withdrawing groups (-CO$_2$R, -SO$_2$Ph, -CN), and also with different acidifying groups (-CO$_2$R, -NO$_2$, -COR, -SO$_2$Ph).
The synthetic potential of all-carbon ICD reactions was illustrated during synthetic studies on the complex natural products CP-225, 917 and CP-263, 114. The core structure of these natural products was synthesized in this laboratory by an all-carbon ICD process using 24.1 with DBU as a base (Scheme 24).

Dr. Wang studied the mechanism of these all-carbon-ICD reactions and proposed that they involve a stepwise pathway, at least in those cases where there is a poor leaving group. He also tried to trap the carbanionic intermediate by using protic solvents, but trapping proved impossible.

During work on my project on asymmetric synthesis of carbocycles using ICD, another group member, Dr. P. Cheng, was studying the synthesis of optically
pure cyclic amines using same principle. Dr. Cheng was able to prepare optically pure six- or seven-membered cyclic amines possessing a stereogenic center $\alpha$ to the nitrogen, by using a chiral auxiliary approach.\textsuperscript{12c} The chiral auxiliary can be removed at the end of the sequence by reduction with DIBAL-H so as to release an optically pure amine (Scheme 25).

\[
\begin{align*}
25.1 + 25.2 & \xrightarrow{\text{PhSeLi}} 25.3 \\
25.3 & \xrightarrow{\text{AcCl}} 25.4 \\
25.4 & \xrightarrow{\text{DIBAL-H}} 25.6
\end{align*}
\]

Scheme 25
2. **Results and Discussion**

After the successful implementation of intramolecular conjugate displacement (ICD) for the synthesis of carbocycles and heterocycles from this laboratory [see Scheme 26], the objective of my research was to develop this chemistry for the synthesis of optically pure carbocycles.

\[ \text{EWG = electron-withdrawing group, X = N, S, C.} \]

**Scheme 26**

The principle behind my project was to attach a chiral auxiliary at the proper position of the acceptor double bond, so that the ICD occurs from the less hindered face of the double bond as shown in Scheme 27.

As indicated in the Scheme, the starting chiral lactone **27.1**, undergoes an aldol reaction with aldehyde **27.2**, which carries a geminal phenylthio group, to give alcohols **27.3**. Acetylation of the hydroxyl group, followed by oxidative removal of selenium would give the ICD precursor **27.4**. Treatment of **27.4** with a base should result in the formation of optically pure **27.6** by an ICD pathway. Finally, removal of the chiral auxiliary and desulfonylation should afford the optically pure carbocycles.
2.1 Synthesis of chiral lactones

The chiral lactones used for this study are shown in Scheme 28.

The chiral lactones 25.1 and 27.1 were synthesized as described below. Photooxygenation of furfural (29.1), mediated by Rose Bengal in MeOH, gave the hydroxy lactone 29.2 by a Diels-Alder pathway. The racemic 29.2 was coupled
with L-menthol to give a diastereomeric mixture of 29.3 and 29.4 which, after recrystallization from hexane, gave the desired single isomer 25.1. Hydrogenation of lactone 25.1, followed by deprotonation and selenation with PhSeCl, gave the selenolactone 27.1, as the major isomer. The stereochemistry at C-2 was confirmed by Dr. Cheng using single crystal X-ray analysis.\textsuperscript{10b}

The chiral lactone 28.1 was prepared according to the literature method.\textsuperscript{26} Acid catalyzed reaction between glyoxylic acid (30.1), morpholine (30.3) and propionaldehyde (30.2) gave the methyl-substituted hydroxy lactone 30.4, which was then coupled with L-menthol to form 30.5 as a mixture of diastereomers. Recrystallization of 30.5 from hexane afforded the single isomer 28.1.
Racemic \( \gamma \)-butyrolactone 28.2 was prepared by phenylselenation of the parent lactone 31.4, using KHMDS and PhSeCl. The synthesis of 31.4 was carried out as described in the literature.\(^{27d}\) Reaction of (phenylthio)acetic acid with LDA and 2-butyloxirane, followed by treatment with \( \text{H}_2\text{SO}_4 \), gave \( \alpha \)-(phenylthio)-\( \gamma \)-butyrolactone 31.2. Oxidative elimination then produced the \( \alpha,\beta \)-unsaturated \( \gamma \)-butyrolactone 31.3, which was hydrogenated to give 31.4.

Both enantiomers of the lactone 31.4 are known\(^{27a-c}\) and the enantiomers of 25.1, 27.1 and 28.1 should be accessible by using D-menthol instead of L-menthol.
2.2 Synthesis of aldehydes for aldol reactions

The aldehydes 27.2, used for the aldol reactions are shown in Scheme 32.
Of these, 32.1, 32.3 and 32.6 are known and were made by literature methods,\textsuperscript{11b} as summarized in Scheme 33.
Synthesis of aldehyde 32.2 started (Scheme 34) from commercially available 3-chloropropionaldehyde diethyl acetal (34.1). Treatment of 34.1 with \( p-\text{FC}_6\text{H}_4\text{SH} \) and TFA resulted in acetal exchange with \( p-\text{FC}_6\text{H}_4\text{S} \)- groups to give 34.2. This was then subjected to nucleophilic displacement of the chlorine with cyanide, using \( \text{NaCN} \) in DMSO at 50 °C to release 34.3 in 61% yield over two steps. Reduction of the nitrile using DIBAL-H gave the desired aldehyde 32.2 in 72% yield.

![Scheme 34](image)

Aldehyde 32.4 was synthesized from commercial 2-(bromomethyl)-benzonitrile. DIBAL-H reduction of the nitrile group (Scheme 35) to the aldehyde level was done according to the literature procedure. The stipulated use of hydrobromic acid in the workup of this reaction is crucial to avoid loss of the benzylic bromine and to prevent the formation of side products. The aldehyde
was then protected as an acetal using \((\text{MeO})_3\text{CH}\) and a catalytic amount of \(\text{TsOH}.\text{H}_2\text{O}\) in methanol. The resulting bromo acetal 35.3 was then alkylated with the anion derived from bis(phenylthio)methane. Finally, acid hydrolysis of the acetal group gave the desired aldehyde 32.4.

![Scheme 35](image)

Aldehyde 32.5 was also prepared (Scheme 36) by following the same sequence as above.\(^{29,30}\) Commercially available 2-methyl-5-fluorobenzonitrile (36.1), was first subjected to radical bromination using \(N\)-bromosuccinimide and AIBN. Reduction of the nitrile group to an aldehyde, followed by acetal protection, gave 36.4. Displacement of bromide by the anion of bis(phenylthio)methane and subsequent deprotection of the acetal released aldehyde 32.5.
Scheme 36

Benzylic bromination of methyl o-methylbenzoate under standard conditions using bromine and light gave the geminal dibromide 37.2 (Scheme 37). Double nucleophilic displacement of bromine with PhSNa (generated from PhSH and NaH) in DMF, followed by reduction of the ester with DIBAL-H,
produced the alcohol 37.4 in 94% yield. Parikh-Doering oxidation then generated aldehyde 32.7 in 79% yield.

The mono(phenylthio) aldehyde 32.8 was prepared from phthalide (38.1). Ring opening of phthalide with PhSNa by a known procedure\textsuperscript{32} gave acid 38.2 in 78% yield (Scheme 38). Reduction of the acid to an alcohol with BH\textsubscript{3}.SMe\textsubscript{2},\textsuperscript{33} followed by oxidation using SO\textsubscript{3}.Py-DMSO, gave the desired aldehyde 32.8.

![Scheme 38](image)

Aldehyde 32.9 was made from aldehyde 32.7 by Wittig olefination with Ph\textsubscript{3}P=CH(OMe) and acid hydrolysis (Scheme 39).

![Scheme 39](image)
2.3 Condensation of the chiral lactones with the aldehydes and synthesis of the ICD precursors

After the synthesis of the starting materials (Scheme 28) the next step was to condense the aldehydes with the lactones. Of course, these steps were studied after each aldehyde became available, but it is convenient to deal with all the aldehyde preparations together, and to treat the subsequent steps in a similar way.

Two different procedures were used for condensing the aldehydes with the lactones. In the first approach the $\alpha,\beta$-unsaturated chiral lactone 25.1 was allowed to react with the aldehydes under conditions reported by Jauch, using lithium phenyl selenide.\(^{34}\) When Jauch attempted to do similar Morita-Baylis-Hillman reactions using standard conditions (catalytic DABCO) the desired product was not formed. But, by changing the nucleophile from DABCO to the more nucleophilic and less basic lithium phenyl selenide, he was able to carry out the reactions in good yield.\(^{34a}\)

During our studies (Scheme 40), we observed that the aromatic aldehydes (32.4, 32.5, 32.7 and 32.8) react efficiently by the Jauch method. In contrast, the aliphatic aldehydes (32.1, 32.2, 32.3 and 32.6) reacted smoothly with the anion generated by deprotonation of the selenium-containing lactones 28.2 and 27.1. The best conditions for deprotonation of the lactones involved adding a freshly prepared LDA solution slowly to a solution of the lactone in THF at $-78^\circ$C and stirring for another 1 h. Then a solution of the aldehyde was added dropwise. Reversing the order of addition, i.e. adding the lactones to the LDA or fast addition of LDA to the lactone resulted in extensive deselenation; however, the
optimized procedure gave yields close to 70% with the aliphatic aldehydes. In a few experiments the use of (Me$_3$Si)$_2$NK for deprotonation was also examined, but the yields were lower. During these aldol reactions, two diastereomers were separated; these are epimeric at the hydroxyl-bearing carbon. The fact that two diastereomers were formed is inconsequential, however.

Oxidative removal of selenium using MCPBA generated the required $\alpha,\beta$-unsaturated lactone and also converted the phenylthio groups to phenylsulfonyl groups. This feature makes the use of phenylthio groups in the starting aldehydes especially convenient because the presence of a very acidic hydrogen [e.g. as in CH(SO$_2$Ph)$_2$,] at an earlier stage would probably interfere in the reaction of the carbanion with the aldehyde and, in fact, such interference was observed with the malonate system CH(CO$_2$Me)$_2$ (see below, page 45).

In the following Schemes R*O = L-menthylxoy, X = SPh, Y = SePh, Z = SO$_2$Ph, Z' = SO$_2$C$_6$H$_4$F-$p$. 
Scheme 40 (part 1)
Scheme 40 (part 2)
Condensation of aldehydes by the Jauch method using lithium phenyl selenide (entries v, vi and viii) resulted in the isolation of only a single isomer. The stereochemistry of the product was determined by X-ray analysis of suitable crystals obtained by recrystallization of 32.5c (Figure 1). Jauch rationalized this outcome through the Zimmerman-Traxler model for the transition state in the aldol step (Scheme 41).
Figure 1. ORTEP diagram of compound 32.5c

The condensation of chiral lactone 28.1 (Scheme 42), in which the double bond carries a methyl substituent, was done as follows. Treatment of the lactone with LDA in THF at −78 °C for 1 h, followed by addition of an aldehyde, gave the desired alcohol as a mixture of diastereomers which are epimeric at the hydroxyl-bearing carbon. The reaction occurred at the α-position to the lactone carbonyl (Scheme 42).
The ICD precursors are prepared (Schemes 40 and 42) from the corresponding alcohols in very good yields, either by oxidation (MCPBA) followed by acetylation (AcCl, pyridine, DMAP) or by reversing the order of this sequence.

### 2.4 Ring closure by intramolecular conjugate displacement

After the synthesis of the ICD precursors, the next step was to carry out the key intramolecular conjugate displacement so as to form optically pure carbocycles. For this, we used Cs$_2$CO$_3$ as the base in THF at 0 °C to room
temperature (Scheme 43), as these conditions had previously been found to work well.\textsuperscript{11b}

\begin{itemize}
  \item[i] \(32.1c, 32.1c'\) \hspace{1cm} \(32.1l\) 82\%,\textsuperscript{a} 87\%\textsuperscript{b}
  \item[ii] \(32.2c, 32.2c'\) \hspace{1cm} \(32.2d\) 70\%,\textsuperscript{a} 78\%\textsuperscript{b}
  \item[iii] \(32.1f, 32.1h'\) \hspace{1cm} \(32.1m\) 88\%,\textsuperscript{a} 91\%\textsuperscript{b}
  \item[iv] \(32.2c, 32.3e'\) \hspace{1cm} \(32.3f\) 88\%,\textsuperscript{a} 90\%\textsuperscript{b}
  \item[v] \(32.4c\) \hspace{1cm} \(32.4d\) 95\%
\end{itemize}

\textsuperscript{a}Acetate derived from more polar alcohol; \textsuperscript{b}Acetate derived from less polar alcohol.

\textbf{Scheme 43} (part 1)
In those cases where we obtained two separable isomers of the ICD precursors (Scheme 43, entry i-iv), both gave the identical product. This indicates that attack of the intermediate carbanion on the β-carbon of the unsaturated lactone unit occurs smoothly both syn and anti to the acetate leaving group, and the stereochemistry at the newly-formed asymmetric center is not controlled by the stereochemistry of the acetoxy-bearing carbon.

Formation of six membered rings (Scheme 43, entry i and ii), irrespective of the nature of the acidifying groups (-SO₂Ph, -SO₂C₆H₄F-p), proceeded smoothly at 0 °C and gave the desired product in very good yields (70-87%) as a single isomer. It had previously been reported from this laboratory that p-
fluorophenyl sulfones are desulfonylated faster than phenyl sulfones, hence the use of the \( \text{SO}_2\text{C}_6\text{H}_4\text{F}-p \) group.

Changing the bulky \( \text{L-menthyloxy} \) group to butyl (Scheme 43, entry iii) produced a minor amount of a second isomer at 0 °C, but on decreasing the temperature to \(-15 \) °C, we solved this problem, and isolated only one isomer. Formation of a seven-membered ring (Scheme 43, entry iv) also proceeded smoothly to give the desired product in 90% yield as a single isomer. However, when we attempted to form an eight-membered ring (Scheme 43, entry vii), conjugate displacement did not occur and the main pathway appeared to be the result of elimination of acetate.

Seven-membered rings fused onto a benzene ring (Scheme 43, entries v and vi) are easily formed and very high yields were obtained. In these cases the carbanionic center was one carbon atom removed from the benzylic position. On the other hand, when the carbanionic center was benzylic (Scheme 43, entry vii), we did not isolate any of the expected ICD product; likewise, the corresponding experiment in the nitrogen series was also unsuccessful.\(^{10b}\) We suspected that possibly the bulk of the two sulfone groups was preventing cyclization and so we prepared the ICD precursor \( 32.8c \), which contains only one sulfone group. Unfortunately, treatment of \( 32.8c \) either with LDA or with \( \text{Cs}_2\text{CO}_3 \) did not give any ICD product (Scheme 44).
At this point, we thought that there might be some unfavorable factors (such as the accessible approach angle of the nucleophile) that prevents the formation of six-membered rings from the benzylic position. In order to test this we prepared the ICD precursors 32.9c and 32.9c' (Scheme 45); however these did not cyclize either. Therefore, we concluded that a nucleophilic benzylic position (either as a carbanion or as an aniline\textsuperscript{12c}) is not suitable for ICD reactions.
The possibility that other acidifying groups might not be subject to this restriction, was explored briefly, but our attempts to prepare the ICD precursor using the ester 40.1 or the malonate 40.2 (Scheme 46) were unsuccessful: with the ester, the initial adduct underwent spontaneous lactonization and with the malonate, the presence of the acidic hydrogen \([\text{CH(CO}_2\text{Me)}_2]\) prevented addition of the carbanion from 27.1 to the aldehyde, even when the carbanion was used in excess.

**Scheme 45**

**Scheme 46**
A limitation to the ICD process is that substitution at the carbon being attacked is not tolerated and we found that compounds 32.1k, 32.1k' and 32.5f failed to undergo the ICD ring closure (Scheme 47); they were recovered unchanged at room temperature, and the ICD pathway was not followed at a higher temperature.

![Scheme 47](image)

2.5 Stereochemistry of ICD adducts

The ICD ring closure always occurs from the opposite side to the chiral auxiliary in the all-carbon series. For the fluorine-substituted 7-membered ICD product 32.5g, the stereochemistry at the newly created stereogenic center was established by single crystal X-ray analysis (Figure 2).
Figure 2. ORTEP diagram of compound 32.5g

The coupling constant for the signal of the acetal hydrogen (O-CH-O) of 32.5g at δ 6.46 is < 1 Hz and the value for the same hydrogen (δ 6.53) of 32.4d is 1 Hz. This is possible only if the relevant dihedral angles in both these compounds at the newly-created asymmetric center are very similar. Therefore, by analogy, we assign the same stereochemistry to 32.4d. Similarly, for the 7-membered ICD product 32.3f, the acetal signal at δ 6.78 is a doublet with $J = 1.3$ Hz, a value consistent only with the indicated stereochemistry, and we conclude that in all these cases, ICD formation occurred from the opposite side to chiral auxiliary, as expected on the basis of steric considerations.
For the six-membered ICD products 32.1l, 32.2d and 32.1m, assignment of stereochemistry was important because in the nitrogen series, formation of a six-membered ring resulted in an anomalous stereochemistry.\textsuperscript{12c} In that case the nitrogen nucleophile approached from the same face as the auxiliary group – an unexpected outcome that was established by single crystal X-ray analysis of the ICD product.\textsuperscript{12c} But in my project, we were able to get satisfactory crystals of 32.1l (Figure 3), and X-ray analysis established the indicated geometry, \textit{i.e.}, the ICD pathway occurred from the opposite side to chiral auxiliary. The stereochemistry for the other two examples in which a six-membered ring (32.2d and 32.1m) is formed were assigned by analogy. Evidently, the factors responsible for the anomalous outcome in the nitrogen series for the production of a six-membered ring (nitrogen adds \textit{syn} to the R*O group) do not operate in the all-carbon ICD series or else the steric bulk of the two-sulfone groups prevents this unusual outcome.
2.6 Removal of the chiral auxiliary

In the nitrogen series, where the nucleophile for the ICD reaction is nitrogen, the chiral auxiliary was easily removed by DIBAL-H reduction, and the pure cyclic amines were obtained in good yields. But in the present project, this process was initially very troublesome. In order to study this step, we used 32.5g as a test case (Scheme 48). Treatment of with DIBAL-H opened the ring that had been formed by ICD, and the resulting product, on treatment with Na(Hg), undergoes mono-desulfonylation to give diol 32.5i. Single crystal X-ray analysis of this compound confirmed the structure (Figure 4).

Figure 3. ORTEP diagram of compound 32.11
Mechanistically, the formation of 32.5h (see Scheme 49) must have occurred by conjugate reduction of the unsaturated carbonyl system to generate an enolate equivalent (32.5n), which displaced the germinal bis(sulfone) unit to give 32.5o. An unsaturated lactone was reformed, and was then again reduced initially to lactol 32.5p and then to diol 32.5h. Periodic analysis of the DIBAL-H reduction mixture by HRMS revealed the generation of substances with molecular
formulas corresponding to the intermediates \textbf{32.5o} and \textbf{32.5p}. Situations in which displacements of the type \textbf{32.5n→32.5o} are observed must be rare as a search of the Reaxys database served to identify only a single close precedent.\textsuperscript{38}

Figure 4. ORTEP diagram of compound 32.5i
At this point we tried to remove the sulfone groups of 32.5g before reducing the lactone, but found that elimination of one of the sulfonyl groups occurred to give 32.5j (see Scheme 48); presumably, the electron-withdrawing sulfone groups acidified the allylic C-7 hydrogen sufficiently to permit elimination\(^3\) in the basic reaction medium.

Once these characteristics of 32.5g were established we found that stereoselective hydrogenation of 32.5g over Pearlman's catalyst gave the hydrogenated product 32.5k in quantitative yield (when we tried the hydrogenation with Pd-C and H\(_2\), the yield was either very low or no reaction occurred). The hydrogenation occurred from the less crowded face and the resulting stereochemistry was confirmed by single crystal X-ray analysis of 32.5k (Figure 5). DIBAL-H reduction of 32.5k, followed by desulfonylation, gave the desired optically pure carbocycle 32.5m in good yield.
Figure 4. ORTEP diagram of compound 32.5k
3 Conclusion

During this project, we were able to show that intramolecular conjugate displacement (ICD) can be successfully used for the synthesis of optically pure carbocycles. The precursors for the ICD reactions were made either by PhSeLi-mediated Morita-Baylis-Hillman condensation of chiral lactones with aldehydes or by an aldol reaction between selenium-containing chiral lactones with aldehydes. Both six-membered and seven-membered optically pure carbocycles were synthesized in good yield. A limitation is that the nucleophilic carbon atom must not be benzylic and the acceptor double bond should be unsubstituted. The method works well, especially for benzo-fused carbocycles, and either enantiomer is accessible because both enantiomers of the chiral auxiliary are readily available. The aldehyde components are made by simple reactions, at least in the examples we have studied. The stereochemistry of the key compounds was confirmed by NMR measurements and X-ray analysis. Our research, together with the prior work from this laboratory completes the study of the ionic ICD process.
4 EXPERIMENTAL SECTION

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N$_2$ that had been purified by passage through a column (3.5 x 42 cm) of R3-11 catalyst$^{40}$ and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in desiccators over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars.

Solvents used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator and the residue was then kept under oil pump vacuum.

Microliter syringes were washed with water and acetone using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,$^{41}$ followed by charring on a hot plate, or by examination
under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or cannula. Dry THF was distilled from sodium benzophenone ketyl. Dry Et$_3$N, i-Pr$_2$NH, CH$_2$Cl$_2$, and pyridine were distilled from CaH$_2$. All other solvents were used as purchased. Commercial (Aldrich) solutions of n-BuLi (in hexanes) were titrated and found to have the stated molarity.

FTIR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from specified solvent.

$^1$H Nuclear magnetic resonance spectra were recorded with Varian INOVA-300 (at 300 MHz), Varian INOVA-400 (at 400 MHz), Varian INOVA-500 (at 500 MHz) spectrometers in the specified deuterated solvent. $^{13}$C spectra were recorded with Varian INOVA-400 (at 100 MHz), Varian INOVA-500 (at 125 MHz). The symbols s, d, t, and q used for $^{13}$C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment.

Mass spectra were recorded with Agilent Technologies 6220 oaTOF or Agilent technologies 5975C MSD single quadrupole mass spectrometers. Low resolution LC-mass spectra were measured with an Agilent 1100MSD single quadrupole mass spectrometer with electrospray ionization.

Solvent mixtures specified as x% A-B indicate that X mL of A were mixed with (100-X) mL of B.
Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field $^1$H and $^{13}$C NMR spectra.

1-((3-Chloro-1-[(4-fluorophenyl)sulfanyl]propyl)sulfanyl)-4-fluorobenzene (34.2).

![Chemical structure of 1-(3-Chloro-1-[(4-fluorophenyl)sulfanyl]propyl)sulfanyl)-4-fluorobenzene (34.2).]

4-Fluorothiophenol (3.6 g, 28.15 mmol) and CF$_3$CO$_2$H (2.38 g, 21.11 mmol) were added to a stirred solution of 34.1 (1.17 g, 7.03 mmol) in CH$_2$Cl$_2$ (30 mL) at room temperature and stirring was continued for 24 h. The reaction mixture was quenched with water (20 mL) and extracted with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic extracts were washed with aqueous NaOH (10 w/v) 2 x 10 mL) and brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 8% Et$_2$O-hexane, gave 34.2 which was used directly for the next step.

4,4-Bis[(4-fluorophenyl)sulfanyl]butanenitrile (34.3).
A solution of \textbf{34.2} (2.13 g, 6.44 mmol) in DMSO (2.5 mL) was added to a stirred mixture of NaCN (1.58 g, 32.23 mmol) and Bu₄NI (475 mg, 1.28 mmol) in DMSO (25 mL), and the resulting mixture was stirred at 50 °C for 24 h, cooled to room temperature, diluted with water (20 mL) and extracted with Et₂O (2 x 100 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 20% Et₂O-hexane, gave \textbf{34.3} (1.37 g, 61% over two steps) as an oil: FTIR (CDCl₃, cast) 3094, 3067, 2856, 2248, 1589, 1489, 1443, 1420 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) δ 7.49-7.45 (m, 4 H), 7.07-7.02 (m, 4 H), 4.27 (t, \(J = 7.1\) Hz, 1 H), 2.68 (t, \(J = 7.1\) Hz, 2 H), 2.10 (q, \(J = 7.1\) Hz, 2 H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 163.1 (CF, d, \(^3\)JCF = 249.9 Hz), 136.1 (CCCF, d, \(^3\)JCF = 8.4 Hz), 127.5 (CCCCF, d, \(^4\)JCF = 3.5 Hz), 118.4 (s), 116.4 (CCF, d, \(^2\)JCF = 21.9 Hz), 58.5 (d), 31.0 (t), 15.2 (t); exact mass (electrospray) \(m/z\) calcd for C₁₀H₁₃F₂NNaS₂ (M + Na) 344.0350, found 344.0358.

**\textbf{4,4-Bis[(4-fluorophenyl)sulfanyl]butanal (32.2).}**
DIBAL-H (1 M in PhMe, 3.1 mL, 3.11 mmol) was added by syringe pump over 20 min to a stirred and cooled (-78 °C) solution of 34.3 (500 mg, 1.55 mmol) in CH₂Cl₂ (16 mL). After the addition, stirring at -78 °C was continued for 1 h and then the cold bath was replaced by an ice bath. Stirring at 0 °C was continued for 30 min and the mixture was quenched with water (0.56 mL, 31 mmol) and NaF (1.34 g, 31 mmol). The ice bath was removed, the mixture was diluted with Et₂O (50 mL), stirred vigorously for 1 h and then filtered through a pad of Celite (1 x 3 cm diameter) using Et₂O. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 15 cm), using 20% Et₂O-hexane, gave 32.2 (359 mg, 72%) as an oil: FTIR (CDCl₃, cast) 3067, 2927, 2849, 2726, 1724, 1589, 1490, 1443, 1443 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.80 (br s, 1 H), 7.49-7.45 (m, 4 H), 7.07-7.02 (m, 4 H), 4.30 (t, J = 6.8 Hz, 1 H), 2.83 (td, J = 7.1, 1.0 Hz, 2 H), 2.14 (q, J = 7.0 Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 200.6 (s), 162.9 (CF, ¹JCₜ = 249.0 Hz), 135.7 (CCCF, ³JCₜ = 8.3 Hz), 128.3 (CCCCF, ⁴JCₜ = 3.5 Hz), 116.2 (CCF, ²JCₜ = 21.9 Hz), 59.2 (d), 41.1 (t), 27.9 (t); exact mass (electrospray) m/z calcd for C₁₆H₁₄F₂NaOS₂ (M + Na) 347.0346, found 347.0346.
1-(Bromomethyl)-2-(dimethoxymethyl)benzene (35.3).

CH(OMe)₃ (2.54 mL, 23.23 mmol) was added to a solution of 35.2²⁸ (925 mg, 4.65 mmol) and TsOH·H₂O (88 mg, 0.46 mmol) in anhydrous MeOH (23 mL), and the mixture was heated at 50 °C for 12 h., cooled, and quenched with Et₃N (3 mL). The MeOH was evaporated under reduced pressure and the residue was diluted with water (20 mL) and extracted with Et₂O. The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 6% Et₂O-hexane, gave 35.3 (1.10 g, 100%) as a colorless oil: FTIR (CDCl₃, cast) 3064, 2991, 2953, 2904, 2829, 1488, 1455 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.60-7.56 (m, 1 H), 7.40-7.37 (m, 1 H), 7.34-7.30 (m, 2 H), 5.64 (s, 1 H), 4.69 (s, 2 H), 3.35 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 136.2 (s), 135.7 (s), 131.1 (d), 129.0 (d), 128.4 (d), 127.4 (d), 101.1 (d), 53.3 (q), 30.7 (t); exact mass (electrospray) m/z calcd for C₁₀H₁₃⁷⁹BrNaO₂ (M + Na) 266.9991, found 266.9989.

2-[2,2-Bis(phenylsulfanyl)ethyl]benzaldehyde (32.4).
BuLi (2.5 M in hexane, 0.63 mL, 1.57 mmol) was added dropwise to a stirred and cooled (0 °C) solution of (PhS)$_2$CH$_2$ (335 mg, 1.45 mmol) in THF (4 mL). Stirring at 0 °C was continued for 10 min and the mixture was then cooled to -78 °C. A solution of 35.3 (300 mg, 1.20 mmol) in THF (6 mL) was added rapidly in one portion and stirring at -78 °C was continued for 30 min and then at 0 °C (ice bath) for 10 min. Hydrochloric acid (4 M, 3 mL) was added, the cold bath was removed and stirring was continued for 3 h. The mixture was diluted with water (20 mL) and extracted with Et$_2$O (50 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 8% Et$_2$O-hexane, gave 32.4 (289 mg, 69%) as a colorless oil: FTIR (CDCl$_3$, cast) 3055, 2861, 2832, 2742, 1699, 1598, 1574, 1480, 1451 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.03 (br s, 1 H), 7.76 (dd, $J = 7.6$, 1.4 Hz, 1 H), 7.51 (td, $J = 7.5$, 1.5 Hz, 1 H), 7.41 (td, $J = 7.5$, 1.1 Hz, 1 H), 7.36-7.34 (m, 4 H), 7.31-7.24 (m, 7 H), 4.71 (t, $J = 7.5$ Hz, 1 H), 3.60 (d, $J = 7.5$ Hz, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 192.4 (d), 139.9 (s), 134.2 (s), 134.1 (d), 133.5 (d), 133.0 (d), 132.9 (d), 132.9 (d), 128.9 (d), 127.9 (d), 127.6 (d), 59.5 (d), 39.7 (t); exact mass (EI) $m/z$ calcd for C$_{21}$H$_{18}$OS$_2$ 350.0799, found 350.0796.
1-(Bromomethyl)-2-(dimethoxymethyl)-4-fluorobenzene (36.4).

CH(OMe)_3 (4.2 mL, 38.35 mmol) was added to a solution of 36.3\textsuperscript{29,30} (1.67 g, 7.67 mmol) and TsOH.H_2O (146 mg, 0.77 mmol) in anhydrous MeOH (30 mL) and the mixture was heated at 50 °C for 1 h. The reaction mixture quenched with Et\textsubscript{3}N (3 mL) and the MeOH was evaporated under reduced pressure. The residue was partitioned between water (20 mL) and Et\textsubscript{2}O (50 mL), and the organic phase was washed with brine, dried (MgSO\textsubscript{4}) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 5% Et\textsubscript{2}O-hexane, gave 36.4 (1.75 g, 86%) as a colorless oil: FTIR (CDCl\textsubscript{3}, cast) 3081, 2993, 2956, 2936, 2907, 2831, 1611, 1595, 1495, 1447, 1423 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.37-7.32 (m, 2 H), 7.01 (td, \( J = 8.2, 2.8 \text{ Hz}, 1 \text{ H} \)), 5.63 (s, 1 H), 4.64 (s, 2 H), 3.35 (s, 6 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 162.6 (CF, \( ^{1}J_{CF} = 248.5 \text{ Hz} \)), 139.0 (CCCF, \( ^{3}J_{CF} = 7.3 \text{ Hz} \)), 132.8 (CCCF, \( ^{3}J_{CF} = 8.3 \text{ Hz} \)), 131.6 (CCCCF, \( ^{4}J_{CF} = 3.6 \text{ Hz} \)), 115.8 (CCF, \( ^{2}J_{CF} = 21.7 \text{ Hz} \)), 114.9 (CCF, \( ^{2}J_{CF} = 23.4 \text{ Hz} \)), 99.9 (CF, \( ^{4}J_{CF} = 1.8 \text{ Hz} \)), 53.1 (q), 29.8 (t); exact mass (electrospray) \textit{m/z} calcd for C\textsubscript{10}H\textsubscript{12}\textsuperscript{79}BrFNaO\textsubscript{2} (M + Na) 284.9897, found 284.9896.

2-[2,2-Bis(phenylsulfanyl)ethyl]-5-fluorobenzaldehyde (32.5).
BuLi (2.5 M in hexane, 1.2 mL, 2.84 mmol) was added dropwise to a stirred and cooled (0 °C) solution of (PhS)_2CH_2 (660 mg, 2.84 mmol) in THF (20 mL). Stirring at 0 °C was continued for 10 min and the mixture was then cooled to -78 °C. A solution of 36.4 (630 mg, 2.36 mmol) in THF (6 mL) was added rapidly in one portion and stirring at -78 °C was continued for another 30 min and then at 0 °C (ice bath) for 10 min. Hydrochloric acid (4 M, 3 mL) was added, the cold bath was removed and stirring was continued for 3 h. The mixture was diluted with water (20 mL) and extracted with Et_2O (50 mL). The combined organic extracts were washed with brine, dried (MgSO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 10% Et_2O-hexane, gave 32.5 (839 mg, 96%) as a colorless oil: FTIR (CDCl_3, cast) 3059, 3019, 2866, 2736, 1695, 1609, 1582, 1494, 1479, 1439, 1419 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl_3) \(\delta\) 10.00 (d, \(J = 1.7\) Hz, 1 H), 7.49 (dd, \(J = 8.7, 2.8\) Hz, 1 H), 7.40-7.37 (m, 4 H), 7.32-7.29 (m, 7 H), 7.23 (td, \(J = 8.1, 2.8\) Hz, 1 H), 4.63 (t, \(J = 7.4\) Hz, 1 H), 3.58 (d, \(J = 7.4\) Hz, 2 H); \(^13\)C NMR (125 MHz, CDCl_3) \(\delta\) 190.5 (d), 161.9 (CF, \(^1J_{CF} = 248.7\) Hz), 135.8 (s), 135.8 (s), 135.8 (s), 134.6 (CCCF, \(^3J_{CF} = 7.3\) Hz), 133.9 (s), 133.0 (d), 129.0 (d), 128.0 (d), 120.6 (CCF, \(^2J_{CF} = 21.4\) Hz),
117.7 (CCF, $^2J_{CF} = 22.0$ Hz), 60.0 (s), 38.5 (t); exact mass (electrospray) $m/z$ calcd for $C_{21}H_{17}$FNaOS$_2$ (M + Na) 391.0597, found 391.0590.

5-Butyl-3-(phenylselanylo)xolan-2-one (28.2).

(Me$_3$Si)$_2$NK (0.5 M in PhMe, 1.29 mL, 0.65 mmol) was added dropwise to a stirred and cooled (-78 °C) solution 5-butyloxolan-2-one$^{27,43}$ (31.4) (92 mg, 0.64 mmol) in THF (4 mL). Stirring at -78 °C was continued for 45 min. Then a solution of PhSeCl (62 mg, 0.324 mmol) in THF (1 mL) was injected rapidly in ONE PORTION (this mode of addition is important) and stirring at -78 °C was continued for 20 min. Saturated aqueous NH$_4$Cl (ca 3 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 14% Et$_2$O-hexane, gave 28.2 as a mixture of diastereomers which was separated into three fractions (more polar, 24 mg, 25%; less polar, 28 mg, 29%; mixture, 20.2 mg, 21%). The more polar selenide had: FTIR (CDCl$_3$, cast) 3057, 2956, 2933, 2862, 1764, 1578, 1478, 1466, 1438 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67-7.65 (m,
2 H), 7.38-7.30 (m, 3 H), 4.41-4.35 (m, 1 H), 4.01 (t, J = 9.6 Hz, 1 H), 2.71 (ddd, J = 13.5, 9.4, 6.5 Hz, 1 H), 1.93 (ddd, J = 13.5, 9.8, 8.6 Hz, 1 H), 1.63-1.56 (m, 1 H), 1.49-1.42 (m, 1 H), 1.36-1.21 (m, 4 H), 0.87 (t, J = 7.0 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.8 (s), 135.6 (d), 129.3 (d), 128.8 (d), 127.1 (s), 79.3 (d), 37.6 (d), 36.0 (t), 35.1 (t), 27.1 (t), 22.3 (t), 13.8 (q); exact mass (electrospray) calcd for C$_{14}$H$_{18}$NaO$_2$Se (M + Na) 319.0375, found 319.0374.

The less polar selenide had: FTIR (CDCl$_3$, cast) 3057, 2956, 2932, 2862, 1770, 1578, 1478, 1467, 1438 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.69-7.67 (m, 2 H), 7.40-7.31 (m, 3 H), 4.35-4.29 (m, 1 H), 3.95 (dd, J = 7.8, 3.1 Hz, 1 H), 2.37-2.27 (m, 2 H), 1.73-1.66 (m, 1 H), 1.58-1.51 (m, 1 H), 1.42-1.26 (m, 4 H), 0.89 (t, J = 7.1 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.7 (s), 135.7 (d), 129.4 (d), 129.1 (d), 126.9 (s), 79.5 (d), 37.2 (d), 36.7 (t), 34.9 (t), 27.2 (t), 22.3 (t), 13.9 (q); exact mass (electrospray) m/z calcd for C$_{14}$H$_{18}$NaO$_2$Se (M + Na) 319.0375, found 319.0375.

(5R)-3-[1-Hydroxy-4,4-bis(phenylsulfanyl)butyl]-5-{{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-3-(phenylselenyl)oxolan-2-one (32.1a, 32.1a').

![Diagram](image-url)
A stock solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 0.75 mL, 1.89 mmol) was added to a stirred and cooled (-78 °C) solution of i-Pr₂NH (0.30 mL, 1.88 mmol) in THF (8 mL), and stirring was continued for 30 min at -78 °C. A portion (1.81 mL, 0.37 mmol LDA) of this stock solution was added dropwise (over ca 10 min, added manually by syringe) to a stirred and cooled (-78 °C) solution of lactone 27.1 (120 mg, 0.302 mmol) in THF (4 mL). Stirring at -78 °C was continued for 45 min and then HMPA (0.5 mL) was added dropwise. Stirring was continued for 5 min, and then a solution of aldehyde 32.1¹ᵇ (139 mg, 0.48 mmol) in THF (2 mL) was added at a fast dropwise rate. Stirring at -78 °C was continued for 20-30 min (TLC control, silica, Et₂O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH₄Cl (ca 3 mL) was added and the mixture was extracted with Et₂O. The combined organic extracts were dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 30% Et₂O-hexane, gave 32.1a and 32.1a' as separable isomers: more polar 32.1a (88 mg, 43%) and less polar 32.1a' (66 mg, 31%), each as an oil:

The more polar alcohol 32.1a had: FTIR (CDCl₃, cast) 3367, 3072, 3058, 2953, 2923, 2868, 1762, 1582, 1477, 1455, 1438 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.60-7.58 (m, 2 H), 7.49-7.44 (m, 4 H), 7.39-7.27 (m, 7 H), 7.25-7.21 (m, 2 H), 5.68 (d, J = 5.9 Hz, 1 H), 4.43 (t, J = 6.5 Hz, 1 H), 3.63-3.56 (m, 2 H), 2.91 (dd, J = 14.6, 6.4 Hz, 1 H), 2.60-2.50 (m, 1 H), 2.20-2.03 (m, 3 H), 2.02-1.93 (m, 2 H), 1.80-1.65 (m, 3 H), 1.56-1.48 (m, 1 H), 1.44-1.36 (m, 1 H), 1.31-1.21 (m, 1 H), 1.06-0.75 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 176.8 (s), 138.0 (d),
134.1 (s), 134.0 (s), 132.7 (d), 129.7 (d), 128.9 (d), 128.9 (d), 127.7 (d),
127.7 (d), 125.4 (s), 97.8 (d), 77.3 (d), 71.4 (d), 57.8 (d), 50.0 (s), 47.7 (d), 39.4
(t), 34.8 (t), 34.3 (t), 32.8 (t), 31.4 (d), 28.2 (t), 24.9 (d), 22.7 (t), 22.2 (q), 21.1
(q), 15.4 (q); exact mass (electrospray) calcd for C\textsubscript{36}H\textsubscript{44}NaO\textsubscript{4}S\textsubscript{2}\textsuperscript{78}Se (M + Na)
705.1755, found 705.1755.

The less polar alcohol 32.1\textsuperscript{a} had: FTIR (CDCl\textsubscript{3}, cast) 3495, 3057, 3018,
2953, 2923, 2868, 1763, 1582, 1476, 1454, 1438 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz,
CDCl\textsubscript{3}) \ensuremath{\delta} 7.65 (dd, \textit{J} = 8.1, 1.2 Hz, 2 H), 7.44-7.41 (m, 5 H), 7.34-7.26 (m, 8 H),
5.67 (dd, \textit{J} = 6.5, 1.3 Hz, 1 H), 4.40 (t, \textit{J} = 6.5 Hz, 1 H), 3.59-3.54 (m, 2 H), 2.86
(br s, 1 H), 2.71 (dd, \textit{J} = 15.3, 6.5 Hz, 1 H), 2.48-2.42 (m, 1 H), 2.17-2.07 (m, 2
H), 2.05-1.98 (m, 1 H), 1.91-1.81 (m, 2 H), 1.70-1.62 (m, 3 H), 1.43-1.34 (m, 1
H), 1.30-1.22 (m, 1 H), 1.06-0.76 (m, 12 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \ensuremath{\delta} 175.1
(s), 138.1 (d), 133.9 (s), 133.9 (s), 132.8 (d), 132.8 (d), 129.9 (d), 129.1 (d), 128.9
(d), 127.7 (d), 127.7 (d), 125.9 (s), 97.8 (d), 77.4 (d), 71.9 (d), 58.0 (d), 53.1 (s),
47.8 (d), 39.5 (t), 36.7 (t), 34.3 (t), 32.7 (t), 31.4 (d), 28.7 (t), 25.0 (d), 22.8 (t),
22.2 (q), 21.1 (q), 15.6 (q); exact mass (electrospray) \textit{m/z} calcd for
C\textsubscript{36}H\textsubscript{44}NaO\textsubscript{4}S\textsubscript{2}\textsuperscript{80}Se (M + Na) 707.1740, found 707.1727.

(5R)-3-[4,4-Bis(benzenesulfonyl)-1-hydroxybutyl]-5-[(1R,2S,5R)-5-
methyl-2-(propan-2-yl)cyclohexyl]oxy]-3-(pheylselanyl)-2,5-dihydrofuran-2-
one (32.1\textsubscript{b}, 32.1\textsubscript{b'}).
Use of 32.1a'

MCPBA (70%, 309 mg, 1.25 mmol) was added to a stirred and cooled (0 °C) solution of 32.1a' (43 mg, 0.062 mmol) in CH₂Cl₂ (4 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (2 mL) and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave 32.1b' (32.4 mg, 88%) as a colorless oil: FTIR (CDCl₃, cast) 3516, 3067, 2955, 2925, 2870, 1761, 1584, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.95-7.93 (m, 4 H), 7.71-7.67 (m, 2 H), 7.59-7.55 (m, 4 H), 6.96 (s, 1 H), 5.99 (s, 1 H), 4.77 (t, J = 5.6 Hz, 1 H), 4.52-4.50 (m, 1 H), 3.63 (td, J = 10.7, 4.3 Hz, 1 H), 2.68 (br s, 1 H), 2.35 (q, J = 6.5 Hz, 2 H), 2.17-2.07 (m, 3 H), 2.01-1.94 (m, 1 H), 1.69-1.64 (m, 2 H), 1.44-1.36 (m, 1 H), 1.28-1.22 (m, 1 H), 1.06-0.77 (m, 12 H); ¹³C NMR (175 MHz, CDCl₃) δ 170.2 (s), 143.9 (d), 139.0 (s), 137.7 (s), 137.7 (s), 134.7 (d), 134.6 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 99.4 (d), 82.7 (d), 79.4 (d), 66.6 (d), 47.7 (d), 40.4 (t), 34.2 (t), 32.3 (t),
31.5 (d), 25.3 (d), 23.1 (t), 22.2 (q), 21.9 (t), 20.9 (q), 15.8 (q); exact mass (electrospray) m/z calcd for C_{30}H_{38}NaO_8S_2 (M + Na) 613.1900, found 613.1892.

**Use of 32.1a**

MCPBA (70%, 382 mg, 1.55 mmol) was added to a stirred and cooled (0 °C) solution of 32.1a (53 mg, 0.077 mmol) in CH_2Cl_2 (4 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO_3 (2 mL) and saturated aqueous Na_2S_2O_3 (2 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave 32.1b (39.0 mg, 86%) as a colorless oil: FTIR (CDCl_3, cast) 3513, 3097, 3067, 2955, 2925, 2870, 1760, 1584, 1448 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl_3) \(\delta\) 7.95-7.94 (m, 4 H), 7.71-7.68 (m, 2 H), 7.57 (t, \(J = 7.6\) Hz, 4 H), 6.94 (t, \(J = 1.4\) Hz, 1 H), 5.99 (t, \(J = 1.1\) Hz, 1 H), 4.75 (t, \(J = 5.5\) Hz, 1 H), 4.50-4.48 (m, 1 H), 3.63 (td, \(J = 10.7, 4.3\) Hz, 1 H), 2.86 (br s, 1 H), 2.44-2.32 (m, 2 H), 2.17-2.07 (m, 3 H), 2.03-1.96 (m, 1 H), 1.70-1.64 (m, 2 H), 1.45-1.36 (m, 1 H), 1.28-1.23 (m, 1 H), 1.06-0.78 (m, 12 H); \(^{13}\)C NMR (125 MHz, CDCl_3) \(\delta\) 170.4 (s.), 143.5 (d), 138.8 (s), 137.7 (s), 137.7 (s), 134.6 (d), 134.6 (d), 129.6 (d), 129.6 (d), 129.1 (d), 129.1 (d), 99.4 (d), 82.7 (d), 79.5 (d), 66.4 (d), 47.7 (d), 40.4 (t), 34.2 (t), 32.4 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.2 (q), 22.0 (t), 20.9 (q), 15.8 (q); exact mass (electrospray) m/z calcd for C_{30}H_{38}NaO_8S_2 (M + Na) 613.1900, found 613.1891.
4,4-Bis(benzenesulfonyl)-1-[(5R)-5-([(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy)-2-oxo-2,5-dihydrofuran-3-yl]butyl acetate (32.1c, 32.1c').

Use of 32.1b'

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.1b' (32 mg, 0.05 mmol) in CH₂Cl₂ (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.02 mL, 0.27 mmol) and pyridine (0.04 mL, 0.37 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO₄ (2 mL) and water (5 mL), and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.1c' (31 mg, 91%) as a colorless foam: FTIR (neat) 3067, 2955, 2926, 2870, 1766, 1653, 1584, 1478, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.93-7.90 (m, 4 H), 7.71-7.68 (m, 2 H), 7.59-7.55 (m, 4 H), 6.94 (t, J = 1.2 Hz, 1 H), 6.00 (s, 1 H), 5.61-5.59 (m, 1 H), 4.50 (dd, J = 6.0, 5.0 Hz, 1 H), 3.61 (td, J = 10.7, 4.3 Hz, 1 H), 2.30-2.08 (m, 9 H), 1.69-1.63 (m, 2 H), 1.43-1.37 (m, 1 H),
1.27-1.21 (m, 1 H), 1.02-0.78 (m, 12 H); $^1$H NMR (100 MHz, CDCl$_3$) δ 169.9 (s), 168.9 (s), 145.4 (d), 137.9 (s), 137.9 (s), 136.1 (s), 134.9 (d), 134.9 (d), 129.8 (d), 129.9 (d), 129.4 (d), 99.3 (d), 82.9 (d), 79.5 (d), 67.5 (d), 47.9 (d), 40.7 (t), 34.4 (t), 31.7 (q), 30.5 (t), 25.4 (d), 23.3 (t), 22.4 (d), 21.2 (t), 21.1 (q), 21.1 (q), 15.9 (q); exact mass (electrospray) m/z calcd for C$_{32}$H$_{40}$NaO$_6$S$_2$ (M + Na) 655.2006, found 655.1999.

Use of 32.1b

DMAP (0.8 mg, 0.007 mmol) was added to a stirred solution of 32.1b (44 mg, 0.07 mmol) in CH$_2$Cl$_2$ (2 mL). The mixture was then cooled to 0 °C, and AcCl (0.026 mL, 0.37 mmol) and pyridine (0.042 mL, 0.52 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO$_4$ (2 mL) and water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.1c (42 mg, 90%) as a colorless foam: FTIR (neat) 3066, 2955, 2926, 2870, 1766, 1653, 1584, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.95-7.92 (m, 4 H), 7.71-7.68 (m, 2 H), 7.59-7.55 (m, 4 H), 6.90 (t, J = 1.1 Hz, 1 H), 5.97 (s, 1 H), 5.52-5.50 (m, 1 H), 4.51 (t, J = 5.4 Hz, 1 H), 3.63 (td, J = 10.7, 4.3 Hz, 1 H), 2.30-2.22 (m, 3 H), 2.16-2.10 (m, 6 H), 1.70-1.64 (m, 2 H), 1.44-1.37 (m, 1 H), 1.29-1.23 (m, 1 H), 1.06-0.78 (m, 12 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ
169.7 (s), 168.6 (s), 144.7 (d), 137.7 (s), 137.6 (s), 135.9 (s), 134.7 (d), 134.6 (d), 129.6 (d), 129.6 (d), 129.1 (d), 99.0 (d), 82.5 (d), 79.6 (d), 67.2 (d), 47.7 (d), 40.5 (t), 34.1 (t), 31.5 (q), 30.6 (t), 25.2 (d), 23.1 (t), 22.2 (d), 21.3 (t), 20.9 (q), 20.8 (q), 15.7 (q); exact mass (electrospray) m/z calcd for C_{32}H_{40}NaO_{9}S_{2} (M + Na) 655.2006, found 655.2001.

**(3R,3aR)-4,4-Bis(benzenesulfonyl)-3-\{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy\}-1,3,3a,4,5,6-hexahydro-2-benzofuran-1-one (32.1l).**

![Chemical Structure](image)

**Use of 32.1c’**

Cs$_2$CO$_3$ (77.3 mg, 0.23 mmol) was added to a stirred and cooled (0 °C) solution of 32.1c’ (30 mg, 0.047 mmol) in THF (3 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.1l (23.5 mg, 87%) as a single diastereoisomer.
Use of 32.1c

Cs$_2$CO$_3$ (61 mg, 0.19 mmol) was added to a stirred and cooled (0 °C) solution of 32.1c (24 mg, 0.037 mmol) in THF (3 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.1l (23.5 mg, 82%) as a single diastereoisomer: FTIR (neat) 3066, 2954, 2927, 2869, 1768, 1692, 1583, 1478, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.15-8.07 (m, 4 H), 7.76-7.70 (m, 2 H), 7.63-7.54 (m, 4 H), 6.84 (q, $J$ = 3.6 Hz, 1 H), 6.54 (d, $J$ = 4.5 Hz, 1 H), 3.78 (td, $J$ = 10.7, 4.1 Hz, 1 H), 3.25 (dt, $J$ = 7.6, 3.7 Hz, 1 H), 2.71-2.56 (m, 2 H), 2.44-2.37 (m, 1 H), 2.27-2.18 (m, 2 H), 1.91 (ddd, $J$ = 14.6, 9.0, 7.6 Hz, 1 H), 1.70-1.67 (m, 2 H), 1.44-1.35 (m, 2 H), 1.11-0.85 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.9 (s), 138.7 (s), 135.3 (s), 135.1 (d), 135.0 (d), 134.7 (d), 131.9 (d), 131.3 (d), 129.0 (d), 128.7 (d), 126.6 (s), 98.7 (d), 87.5 (s), 77.1 (d), 48.1 (d), 46.4 (d), 38.3 (t), 34.3 (t), 31.4 (d), 27.9 (t), 25.7 (d), 24.3 (t), 23.3 (t), 22.3 (q), 21.0 (q), 15.9 (q); exact mass (electrospray) $m/z$ calcd for C$_{30}$H$_{36}$NaO$_7$S$_2$ (M + Na) 595.1795, found 595.1788.

For X-ray analysis crystals of 32.1l were grown by slow vapor diffusion of hexanes into a solution of the compound in CH$_2$Cl$_2$: mp 210-212 °C.
A solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 2.58 mL, 6.45 mmol) was added to a stirred and cooled (-78 °C) solution of \( i-\text{Pr}_2\text{NH} \) (0.98 mL, 7 mmol) in THF (20 mL), and stirring was continued for 30 min at -78 °C. A portion (4.71 mL) of this stock solution was then taken up into a syringe and added dropwise (over ca 10 min, added manually by syringe) to a stirred and cooled (-78 °C) solution of lactone 27.1 (427 mg, 1.078 mmol) in THF (3 mL). Stirring at -78 °C was continued for 45 min and then HMPA (1 mL) was added dropwise. Stirring was continued for 5 min and then a solution of aldehyde 32.2 (524 mg, 1.61 mmol) in THF (2 mL) was added at a fast dropwise rate. Stirring at -78 °C was continued for 20-30 min (TLC control, disappearance of aldehyde monitored). Then saturated aqueous NH\(_4\)Cl (5 mL) was added and the mixture was extracted with Et\(_2\)O. The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 40% Et\(_2\)O-hexane gave two diastereoisomers which were partially separated.
[more polar isomer 32.2a (187 mg, 26%); less polar isomer 32.2a' (200 mg, 28%)] as oils. Neither isomer was pure and so the material was used without characterization for the next step.

\[
(5R)-3\{4,4\text{-Bis[(4-fluorobenzene)sulfonyl]-1-hydroxybutyl}\}-5\{[(1R,2S,5R)-5\text{-methyl-2-(propan-2-yl)cyclohexyl}oxy\}-2,5\text{-dihydrofuran-2-one (32.2b, 32.2b').}
\]

\[
\begin{array}{c}
\text{32.2a, 32.2a', } X' = \text{SC}_6\text{H}_4\text{F-}p \\
\text{32.2b, 32.2b', } Z' = \text{SO}_2\text{C}_6\text{H}_4\text{F-}p
\end{array}
\]

**Use of 32.2a'**

MCPBA (70%, 512 mg, 2.08 mmol) was added to a stirred and cooled (0 °C) solution of 32.2a' (100 mg, 0.14 mmol) in CH₂Cl₂ (5 mL). The ice bath was left in place but not recharged and stirring was continued for 4 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (2 mL), and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et₂O-hexane, gave 32.2b' (48 mg, 56%) as a colorless oil: FTIR (CDCl₃, cast) 3510, 3107, 2956, 2926, 2871, 1761, 1591, 1493, 1456, 1406 cm⁻¹;
Use of 32.2a

MCPBA (70%, 960 mg, 3.89 mmol) was added to a stirred and cooled (0 °C) solution of 32.2a (187 mg, 0.26 mmol) in CH₂Cl₂ (5 mL). The ice bath was left in place but not recharged and stirring was continued for 3 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (2 mL), extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% Et₂O-hexane, gave 32.2b (101 mg, 62%) as a colorless oil: FTIR (CDCl₃, cast) 3514, 3107, 2956, 2926, 2871, 1760, 1591, 1493, 1456, 1406 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.05-8.02 (m, 4 H), 7.32-7.28 (m, 4 H), 6.98 (t, J = 1.4 Hz, 1 H), 6.04 (t, J = 1.2 Hz, 1 H), 4.78 (t, J = 5.7 Hz, 1 H), 4.57 (dt, J = 8.6, 1.6 Hz, 1 H), 3.67 (dt, J = 10.7, 5.3 Hz, 1 H), 2.42-2.32 (m, 2 H), 2.23-2.02 (m, 4 H), 1.73-1.68 (m, 2 H),
1.45-1.40 (m, 1 H), 1.32-1.24 (m, 2 H), 1.07-0.81 (m, 12 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\) \(\delta\) 170.4 (s), 166.5 (CF, \(^1J_{CF} = 258.6\) Hz), 143.6 (d), 138.8 (s), 133.5 (s), 132.8 (CCCF, \(^3J_{CF} = 10.1\) Hz), 116.6 (CCF, \(^2J_{CF} = 23.0\) Hz), 99.4 (d), 82.9 (d), 79.6 (d), 66.4 (d), 47.7 (d), 40.4 (t), 34.2 (t), 32.4 (t), 31.5 (d), 25.3 (q), 23.1 (t), 20.9 (q), 15.8 (q); exact mass (electrospray) \(m/z\) calcd for C\(_{30}\)H\(_{36}\)F\(_2\)NaO\(_8\)S\(_2\) (M + Na) 649.1712, found 649.1710.

4,4-Bis[(4-fluorobenzene)sulfonyl]-1-[(5R)-5-[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy]-2-oxo-2,5-dihydrofuran-3-yl]butyl acetate (32.2c, 32.2c').

![Chemical structure]

Use of 32.2b'

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.2b' (50 mg, 0.079 mmol) in CH\(_2\)Cl\(_2\) (2 mL). The mixture was then cooled to 0 °C, and AcCl (0.028 mL, 0.39 mmol) and pyridine (0.046 mL, 0.55 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO\(_4\) (2 mL) and
water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave 32.2c$^\dagger$ (38 mg, 72%) as a colorless foam: FTIR (CDCl$_3$, cast) 3106, 2956, 2926, 2871, 1765, 1591, 1493, 1456, 1406 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.03-8.00 (m, 4 H), 7.32-7.28 (m, 4 H), 6.99 (t, $J = 1.3$ Hz, 1 H), 6.04 (s, 1 H), 5.66-5.63 (m, 1 H), 4.54 (dd, $J = 6.2$, 5.1 Hz, 1 H), 3.66 (td, $J = 10.7$, 4.3 Hz, 1 H), 2.35-2.09 (m, 9 H), 1.75-1.68 (m, 2 H), 1.46-1.44 (m, 1 H), 1.31-1.24 (m, 1 H), 1.06-0.81 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.7 (s), 168.8 (s), 166.5 (CF, $^1J_{CF} = 258.8$ Hz), 145.2 (d), 135.8 (s), 133.4 (CCF, $^2J_{CF} = 17.3$ Hz), 132.7 (CCCF, $^3J_{CF} = 10.2$ Hz), 116.6 (CCF, $^3J_{CF} = 23.9$ Hz), 99.1 (s), 82.8 (s), 79.4 (s), 67.1 (s), 47.7 (s), 40.4 (t), 34.2 (t), 31.5 (q), 30.3 (t), 25.2 (d), 23.1 (t), 22.2 (d), 21.1 (d), 20.9 (q), 20.9 (q), 15.7 (d); exact mass (electrospray) $m/z$ calcd for C$_{32}$H$_{38}$F$_2$NaO$_9$S$_2$ (M + Na) 691.1818, found 691.1809.

**Use of 32.2b**

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.2b (35 mg, 0.05 mmol) in CH$_2$Cl$_2$ (2 mL). The solution was then cooled to 0 °C, and AcCl (0.019 mL, 0.28 mmol) and pyridine (0.031 mL, 0.39 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO$_4$ (2 mL) and water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic
extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave 32.2c (25 mg, 68%) as a colorless foam: FTIR (CDCl₃, cast) 3106, 2956, 2927, 1767, 1591, 1493, 1456, 1406 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.04-7.99 (m, 4 H), 7.31-7.27 (m, 4 H), 6.93 (t, J = 1.3 Hz, 1 H), 6.01 (t, J = 1.2 Hz, 1 H), 5.57-5.54 (m, 1 H), 4.54 (ddd, J = 6.5, 4.7, 2.0 Hz, 1 H), 3.67 (td, J = 10.7, 4.3 Hz, 1 H), 2.34-2.10 (m, 9 H), 1.70-1.67 (m, 2 H), 1.45-1.41 (m, 1 H), 1.31-1.25 (m, 1 H), 1.09-0.82 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 169.8 (s), 168.7 (s), 166.47 (CF, ¹JC = 258.7 Hz), 144.8 (d), 136.9 (s), 133.4 (CCCF, ³JC = 3.3 Hz), 132.8 (CCCF, ³JC = 5.2 Hz), 116.6 (CCF, ²JC = 22.9 Hz), 99.1 (d), 82.8 (d), 79.7 (d), 67.1 (d), 47.7 (d), 40.5 (t), 34.1 (t), 31.5 (t), 30.6 (t), 25.3 (d), 23.1 (t), 22.2 (d), 21.3 (t), 20.9 (q), 20.8 (q), 15.7 (q); exact mass (electrospray) m/z calcd for C₃₂H₃₈F₂NaO₉S₂ (M + Na) 691.1818, found 691.1804.

(3R,3aR)-4,4-Bis[(4-fluorobenzene)sulfonyl]-3-([(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy)-1,3,3a,4,5,6-hexahydro-2-benzofuran-1-one (32.2d).
Use of 32.2c'

Cs$_2$CO$_3$ (49 mg, 0.15 mmol) was added to a stirred and cooled (0 °C) solution of 32.2c' (20 mg, 0.03 mmol) in THF (2 mL). The ice bath was left in place but not recharged and stirring was continued for 3 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.2d (14 mg, 78%).

Use of 32.2c

Cs$_2$CO$_3$ (44 mg, 0.13 mmol) was added to a stirred and cooled (0 °C) solution of 32.2c (18 mg, 0.026 mmol) in THF (2 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.2d (11 mg, 70%): FTIR (CDCl$_3$, cast) 3106, 2955, 2927, 2870, 1769, 1692, 1590, 1493, 1456, 1406 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.17-8.08 (m, 4 H), 7.31-7.20 (m, 4 H), 6.88 (q, J = 3.7 Hz, 1 H), 6.47 (d, J = 4.5 Hz, 1 H), 3.76 (td, J = 10.7, 4.1 Hz, 1 H), 3.20 (dt, J = 7.7, 3.7 Hz, 1 H), 2.75-2.66 (m, 1 H), 2.57 (ddd, J = 14.6, 6.6, 2.1 Hz, 1 H), 2.49-2.42 (m, 1 H), 2.23-2.14 (m, 2 H), 1.91 (ddd, J = 14.7, 9.0, 7.3 Hz, 1 H), 1.71-1.67 (m, 2 H), 1.43-1.29 (m, 2 H), 1.08-0.82 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ
166.7 (CF, $^1J_{CF} = 258.3$ Hz), 165.7 (s), 135.01 (CCCF, $^3J_{CF} = 4.2$ Hz), 135.0 (s), 134.5 (d), 134.4 (d), 131.1 (CCCF, $^4J_{CF} = 3.4$ Hz), 126.5 (s), 116.5 (CCF, $^2J_{CF}, J = 22.7$ Hz), 116.2 (CCF, $^2J_{CF} = 22.8$ Hz), 98.5 (d), 87.8 (s), 76.5 (d), 48.2 (d), 46.5 (d), 38.4 (t), 34.3 (t), 31.4 (d), 28.0 (t), 25.8 (d), 24.3 (t), 23.3 (t), 22.4 (q), 21.1 (q), 16.0 (q); exact mass (electrospray) $m/z$ calcd for $C_{30}H_{34}F_2NaO_7S_2$ (M + Na) 631.1606, found 631.1600.

5-Butyl-3-[1-hydroxy-4,4-bis(phenylsulfanyl)butyl]-3-(phenylselanyl)-oxoan-2-one (32.1d, 32.1d').

A stock solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 0.63 mL, 1.59 mmol) was added to a stirred and cooled (-78 °C) solution of i-Pr$_2$NH (0.24 mL, 1.73 mmol) in THF (20 mL), and stirring was continued for 30 min at -78 °C. A portion (2.1 mL, 0.15 mmol LDA) of this stock solution was added dropwise (over ca 10 min, added manually by syringe) to a stirred and cooled (-78 °C) solution of lactone 28.2 (43 mg, 0.145 mmol) in THF (4 mL). Stirring at -78 °C was continued for 45 min and then HMPA (0.4 mL) was added dropwise. Stirring was continued for 5 min and then a solution of aldehyde
32.1 \textsuperscript{1}b (41.6 mg, 0.148 mmol) in THF (2 mL) was added at a fast dropwise rate. Stirring at -78 °C was continued for 20-30 min (TLC control, silica, Et\textsubscript{2}O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH\textsubscript{4}Cl (ca 3 mL) was added and the mixture was extracted with Et\textsubscript{2}O. The combined organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 30% Et\textsubscript{2}O-hexane, gave the less polar isomer 32.1d' (32 mg, 36%) and the more polar isomer 32.1d (26 mg, 32%) (57.6 mg in all, 68%) as oils.

The more polar alcohol 32.1d had: FTIR (CDCl\textsubscript{3}, cast) 3459, 3057, 2954, 2930, 2861, 1753, 1582, 1476, 1438 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.62-7.60 (m, 2 H), 7.50-7.46 (m, 4 H), 7.39 (ddt, \( J = 8.0, 6.9, 1.2 \) Hz, 1 H), 7.34-7.24 (m, 8 H), 4.48-4.40 (m, 2 H), 3.71 (dd, \( J = 10.7, 1.5 \) Hz, 1 H), 2.85 (dd, \( J = 14.4, 8.9 \) Hz, 1 H), 2.49 (dddd, \( J = 13.9, 10.2, 5.6, 1.8 \) Hz, 1 H), 2.18-2.11 (m, 2 H), 1.88-1.73 (m, 3 H), 1.66-1.58 (m, 1 H), 1.53-1.26 (m, 5 H), 0.90 (t, \( J = 7.1 \) Hz, 3 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 177.5 (s), 137.9 (d), 134.1 (s), 134.0 (s), 132.8 (d), 132.6 (d), 129.9 (d), 129.1 (d), 128.9 (d), 127.8 (d), 127.8 (d), 125.6 (s), 78.3 (d), 72.5 (d), 57.9 (d), 52.8 (s), 35.7 (t), 33.5 (t), 32.7 (t), 28.8 (t), 27.7 (t), 22.3 (t), 13.9 (q); exact mass (electrospray) calcd for C\textsubscript{30}H\textsubscript{34}NaO\textsubscript{3}S\textsubscript{2}\textsuperscript{78Se} (M + Na) 607.1021, found 607.1024.

The less polar alcohol 32.1d' had: FTIR (CDCl\textsubscript{3}, cast) 3477, 3057, 2955, 2931, 2861, 1753, 1582, 1476, 1438 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.66 (dt, \( J = 8.1, 1.5 \) Hz, 2 H), 7.51-7.41 (m, 5 H), 7.36-7.23 (m, 8 H), 4.44 (t, \( J = 6.5 \) Hz, 1 H), 4.39-4.34 (m, 1 H), 3.68 (dd, \( J = 9.9, 2.0 \) Hz, 1 H), 2.92 (br s, 1 H), 2.67 (dd, \( J = 8.0, 6.9 \) Hz, 1 H), 2.18-2.11 (m, 2 H), 1.88-1.73 (m, 3 H), 1.66-1.58 (m, 1 H), 1.53-1.26 (m, 5 H), 0.90 (t, \( J = 7.1 \) Hz, 3 H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 177.5 (s), 137.9 (d), 134.1 (s), 134.0 (s), 132.8 (d), 132.6 (d), 129.9 (d), 129.1 (d), 128.9 (d), 127.8 (d), 127.8 (d), 125.6 (s), 78.3 (d), 72.5 (d), 57.9 (d), 52.8 (s), 35.7 (t), 33.5 (t), 32.7 (t), 28.8 (t), 27.7 (t), 22.3 (t), 13.9 (q); exact mass (electrospray) calcd for C\textsubscript{30}H\textsubscript{34}NaO\textsubscript{3}S\textsubscript{2}\textsuperscript{78Se} (M + Na) 607.1021, found 607.1024.
= 14.8, 8.6 Hz, 1 H), 2.19-2.12 (m, 1 H), 1.98-1.85 (m, 3 H), 1.80-1.75 (m, 1 H), 1.65-1.58 (m, 1 H), 1.43-1.18 (m, 5 H), 0.88 (t, J = 7.1 Hz, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.6 (s), 138.0 (d), 133.9 (s), 133.9 (s), 132.8 (d), 132.8 (d), 129.9 (d), 128.9 (d), 128.9 (d), 127.8 (d), 127.7 (d), 126.0 (s), 78.2 (d), 72.9 (d), 58.0 (d), 55.4 (s), 35.6 (t), 35.3 (t), 32.8 (t), 29.4 (t), 27.4 (t), 22.3 (t), 13.9 (q); exact mass (electrospray) calcd for C\(_{30}\)H\(_{34}\)NaO\(_5\)S\(_2\)Se (M + Na) 607.1021, found 607.1024.

3-[4,4-Bis(benzenesulfonyl)-1-hydroxybutyl]-5-butyl-2,5-dihydrofuran-2-one (32.1e).

![Diagram](image)

32.1d, \(X = \text{SPh}\)  
32.1e, \(Z = \text{SO}_2\text{Ph}\)

Use of 32.1d

MCPBA (70%, 288 mg, 1.67 mmol) was added to a stirred and cooled (0 °C) solution of 32.1d (49 mg, 0.083 mmol) in CH\(_2\)Cl\(_2\) (4 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The mixture was quenched with a mixture of saturated aqueous NaHCO\(_3\) (2 mL) and saturated aqueous Na\(_2\)S\(_2\)O\(_3\) (2 mL), and extracted with CH\(_2\)Cl\(_2\). The combined organic extracts were washed with water and brine, dried (Na\(_2\)SO\(_4\)) and evaporated. Flash
chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave \textbf{32.1e} (34 mg, 84%) as a colorless oil: FTIR (CDCl$_3$, cast) 3513, 3067, 2957, 2931, 2872, 1745, 1584, 1479, 1448 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.96-7.94 (m, 4 H), 7.72-7.68 (m, 2 H), 7.57 (t, $J$ = 7.7 Hz, 4 H), 4.96-4.92 (m, 1 H), 4.81-4.78 (m, 1 H), 4.52-4.50 (m, 1 H), 2.91 (br s, 1 H), 2.36 (q, $J$ = 6.5 Hz, 2 H), 2.19-2.11 (m, 1 H), 2.06-1.96 (m, 1 H), 1.77-1.60 (m, 2 H), 1.45-1.33 (m, 4 H), 0.91 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.4 (s), 149.3 (d), 137.7 (s), 137.7 (s), 135.3 (s), 134.6 (d), 129.6 (d), 129.6 (d), 129.2 (d), 129.2 (d), 82.7 (d), 82.0 (d), 66.6 (d), 32.9 (t), 32.5 (t), 27.1 (t), 22.4 (t), 21.9 (t), 13.8 (q); exact mass (electrospray) \textit{m/z} calcd for C$_{24}$H$_{28}$NaO$_7$S$_2$ (M + Na) 515.1169, found 515.1164.

\textbf{4,4-Bis(benzenesulfonyl)-1-(5-butyl-2-oxo-2,5-dihydrofuran-3-yl)butyl acetate (32.1f).}

\begin{center}
\includegraphics[width=0.8\textwidth]{diagram}
\end{center}

\textbf{Use of 32.1e}

DMAP (1.1 mg, 0.01 mmol) was added to a stirred solution of \textbf{32.1e} (45 mg, 0.09 mmol) in CH$_2$Cl$_2$ (3 mL). The mixture was then cooled to 0 ℃ and
AcCl (0.033 mL, 0.46 mmol) and pyridine (0.051 mL, 0.64 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The mixture was quenched with saturated CuSO$_4$ (2 mL) and water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.1f (45 mg, 90%) as a colorless oil: FTIR (CDCl$_3$, cast) 3068, 2958, 2933, 2873, 1753, 1584, 1479, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.96-7.93 (m, 4 H), 7.72 (td, $J = 7.5, 0.7$ Hz, 2 H), 7.61-7.57 (m, 4 H), 7.25 (t, $J = 1.4$ Hz, 1 H), 5.58-5.56 (m, 1 H), 4.96 (t, $J = 6.5$ Hz, 1 H), 4.56 (t, $J = 5.4$ Hz, 1 H), 2.34-2.17 (m, 4 H), 2.11 (s, 3 H), 1.79-1.72 (m, 1 H), 1.69-1.62 (m, 1 H), 1.47-1.35 (m, 4 H), 0.93 (t, $J = 7.0$ Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.8 (s), 169.8 (s), 150.8 (d), 137.8 (s), 137.6 (s), 134.7 (d), 134.7 (d), 132.1 (s), 129.5 (d), 129.5 (d), 129.2 (d), 82.6 (d), 81.7 (d), 67.6 (d), 32.9 (t), 30.3 (t), 27.1 (t), 22.4 (t), 21.1 (t), 20.9 (q), 13.8 (q); exact mass (electrospray) $m/z$ calcd for C$_{26}$H$_{30}$NaO$_8$S$_2$ (M + Na) 557.1274, found 557.1268.

1-[5-Butyl-2-oxo-3-(phenylselanyl)oxolan-3-yl]-4,4-bis(phenyl-sulfanyl)butyl acetate (32.1g').
Use of 32.1d'

DMAP (1.1 mg, 0.01 mmol) was added to a stirred solution of 32.1d' (35 mg, 0.06 mmol) in CH₂Cl₂ (2 mL). The mixture was then cooled to 0 °C and AcCl (0.022 mL, 0.29 mmol) and pyridine (0.039 mL, 0.48 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated CuSO₄ (2 mL) and water (5 mL), and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% Et₂O-hexane, gave 32.1g' (32 mg, 86%) as a colorless oil: FTIR (CDCl₃, cast) 3058, 2956, 2932, 2861, 1761, 1582, 1477, 1439 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.65-7.63 (m, 2 H), 7.48-7.40 (m, 5 H), 5.26 (dd, J = 10.5, 2.6 Hz, 1 H), 4.38 (dd, J = 7.5, 6.1 Hz, 1 H), 4.28-4.23 (m, 1 H), 2.55 (dd, J = 14.7, 8.0 Hz, 1 H), 2.22-2.07 (m, 2 H), 2.01 (dd, J = 14.7, 6.7 Hz, 1 H), 1.95 (s, 3 H), 1.88-1.72 (m, 2 H), 1.51-1.43 (m, 1 H), 1.30-1.14 (m, 5 H), 0.85 (t, J = 7.1 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 174.8 (s), 170.2 (s), 138.0 (d), 133.6 (s), 133.5 (s), 133.2 (d), 133.0 (d), 129.9 (d), 129.3 (d), 128.9 (d), 127.9 (d), 127.9 (d), 126.2 (s), 78.1 (d), 74.8 (d),
57.5 (d), 53.2 (s), 37.3 (t), 35.4 (t), 31.9 (t), 28.6 (t), 27.2 (t), 22.3 (t), 20.7 (q),
13.8 (q); exact mass (electrospray) calcd for C_{32}H_{36}NaO_4S_2^{78}Se (M + Na)
649.1127, found 649.1133.

4,4-Bis(benzenesulfonyl)-1-(5-butyl-2-oxo-2,5-dihydrofuran-3-yl)butyl
acetate (32.1h').

![Diagram of chemical structures]

32.1g', X = SPh  
32.1h', Z = SO_2Ph

Use of 32.1g'

MCPBA (70%, 112 mg, 0.45 mmol) was added to a stirred and cooled (0
°C) solution of 32.1g' (19 mg, 0.030 mmol) in CH_2Cl_2 (4 mL). The ice bath was
left in place but not recharged and stirring was continued for 12 h. The reaction
mixture was quenched with a mixture of saturated aqueous NaHCO_3 (2 mL) and
saturated aqueous Na_2S_2O_3 (2 mL), and extracted with CH_2Cl_2. The combined
organic extracts were washed with water and brine, dried (Na_2SO_4) and
evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm),
using 50% EtOAc-hexane, gave 32.1h' (18 mg, 86%) as a colorless oil: FTIR
(CDCl_3, cast) 3069, 2958, 2932, 2873, 1753, 1584, 1448 cm^{-1}; ^1H NMR (500
MHz, CDCl_3) δ 7.95-7.91 (m, 4 H), 7.72-7.68 (m, 2 H), 7.59-7.56 (m, 4 H), 7.24
(t, J = 1.4 Hz, 1 H), 5.56-5.54 (m, 1 H), 4.94 (ddt, J = 7.4, 5.6, 1.7 Hz, 1 H), 4.52 (td, J = 5.5, 3.5 Hz, 1 H), 2.31-2.17 (m, 4 H), 2.10 (s, 3 H), 1.76-1.60 (m, 2 H), 1.46-1.33 (m, 4 H), 0.92 (t, J = 7.1 Hz, 3 H); 13C NMR (125 MHz, CDCl₃) δ 170.8 (s), 169.8 (s), 150.7 (d), 137.7 (s), 137.6 (s), 134.7 (d), 134.6 (d), 132.2 (s), 129.6 (d), 129.5 (d), 129.2 (d), 82.6 (d), 81.6 (d), 67.6 (d), 32.9 (t), 30.4 (t), 27.1 (t), 22.4 (t), 21.1 (t), 20.9 (q), 13.8 (q); exact mass (electrospray) m/z calcd for C₂₆H₃₀NaO₈S₂ (M + Na) 557.1274, found 557.1280.

(3S,3aR)-rel-4,4-Bis(benzenesulfonyl)-3-butyl-1,3,3a,4,5,6-hexahydro-2-benzofuran-1-one (32.1m).

![Chemical structure](image)

32.1f, 32.1h’  
32.1m, Z = SO₂Ph

Use of 32.1h’

Cs₂CO₃ (115 mg, 0.36 mmol) was tipped into a stirred and cooled (-15 °C) solution of 32.1h’ (38 mg, 0.034 mmol) in dry THF (2 mL), and stirring at -15 °C was continued for 2 h. The mixture was quenched with saturated aqueous NH₄Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash
chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1m** (30 mg, 91%).

**Use of 32.1f**

Cs₂CO₃ (91.5 mg, 0.28 mmol) was added to a stirred and cooled (0 °C) solution of **32.1f** (30 mg, 0.056 mmol) in THF (2 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH₄Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1m** (23 mg, 88%): FTIR (CDCl₃, cast) 3067, 3021, 2958, 2930, 2871, 1760, 1690, 1583, 1477, 1467, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, J = 7.6 Hz, 2 H), 7.89 (d, J = 7.7 Hz, 2 H), 7.76 (t, J = 7.5 Hz, 1 H), 7.71 (t, J = 7.5 Hz, 1 H), 7.63 (t, J = 7.9 Hz, 2 H), 7.56 (t, J = 7.9 Hz, 2 H), 6.75 (q, J = 3.3 Hz, 1 H), 4.93 (t, J = 8.3 Hz, 1 H), 3.61 (dq, J = 6.3, 3.1 Hz, 1 H), 2.49-2.35 (m, 4 H), 2.30-2.24 (m, 1 H), 1.68-1.60 (m, 1 H), 1.54-1.45 (m, 1 H), 1.44-1.25 (m, 3 H), 0.90 (t, J = 7.2 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 167.3 (s), 138.4 (s), 136.6 (s), 136.0 (d), 135.3 (d), 135.0 (d), 131.7 (d), 130.7 (d), 129.1 (d), 128.9 (d), 126.2 (s), 89.7 (s), 79.9 (d), 43.6 (d), 35.8 (t), 27.8 (t), 27.3 (t), 24.4 (t), 22.0 (t), 13.9 (q); exact mass (electrospray) m/z calcd for C₂₄H₂₆NaO₆S₂ (M + Na) 497.1063, found 497.1058.
A solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 0.15 mL, 0.38 mmol) was added to a stirred and cooled (-78 °C) solution of i-Pr$_2$NH (0.06 mL, 0.42 mmol) in THF (2 mL), and stirring was continued for 30 min at -78 °C. This LDA solution was then taken up into a syringe and added dropwise (over ca 10 min, added manually by syringe) to a stirred and cooled (-78 °C) solution of lactone 27.1 (120 mg, 0.30 mmol) in THF (2 mL). Stirring at -78 °C was continued for 45 min and then HMPA (0.4 mL) was added dropwise. Stirring was continued for 5 min and then a solution of aldehyde 32.3$^{11b}$ (165 mg, 0.55 mmol) in THF (1 mL) was added at a fast dropwise rate. Stirring at -78 °C was continued for 20-30 min (TLC control, silica, 40% Et$_2$O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH$_4$Cl (3 mL) was added and the mixture was extracted with Et$_2$O. The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 40% Et$_2$O-hexane, gave 32.3a, and 32.3a' (150 mg, 70%) as an
oil that was a mixture of diastereoisomers [more polar isomer 32.3a, 73 mg, 34%; less polar isomer 32.3a', 77 mg (not pure), ca 36%]. Only the more polar isomer 32.3a could be separated in pure form, and the crude less polar isomer 32.3a' (containing some 27.1) was acetylated and then purified.

The more polar alcohol 32.3a had: FTIR (CDCl₃, cast) 3457, 3073, 3058, 2951, 2923, 2868, 1763, 1582, 1477, 1455, 1438 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.63-7.61 (m, 2 H), 7.47-7.39 (m, 5 H), 7.34-7.27 (m, 8 H), 5.67 (d, J = 5.9 Hz, 1 H), 4.38 (t, J = 6.5 Hz, 1 H), 3.64 (dd, J = 10.4, 0.2 Hz, 1 H), 3.58 (td, J = 10.7, 4.1 Hz, 1 H), 2.88 (dd, J = 14.5, 6.4 Hz, 1 H), 2.51 (dtd, J = 14.0, 7.0, 2.7 Hz, 1 H), 2.20-2.11 (m, 2 H), 1.99-1.90 (m, 2 H), 1.85-1.75 (m, 2 H), 1.70-1.65 (m, 2 H), 1.60-1.51 (m, 2 H), 1.44-1.36 (m, 1 H), 1.30-1.19 (m, 2 H), 1.06-0.79 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 176.9 (s), 137.9 (d), 134.17 (s), 134.14 (s), 132.80 (d), 132.77 (d), 129.8 (d), 129.00 (d), 128.9 (d), 128.9 (d), 127.8 (d), 125.6 (s), 97.8 (d), 77.3 (d), 71.5 (d), 58.4 (d), 50.2 (q), 47.8 (t), 39.5 (t), 35.4 (t), 35.0 (t), 34.4 (t), 31.4 (s), 30.1 (t), 25.0 (d), 23.9 (t), 22.7 (t), 22.3 (q), 21.1 (q), 15.5 (q); exact mass (electrospray) m/z calcd for C₃₇H₄₆NaO₄S₂⁷⁸Se (M + Na) 719.1911, found 719.1901.

(5R)-3-[5,5-Bis(benzenesulfonyl)-1-hydroxypentyl]-5-{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.3b).
Use of 32.3a

MCPBA (70%, 232 mg, 0.94 mmol) was added to a stirred and cooled (0 °C) solution of 32.3a (33 mg, 0.047 mmol) in CH₂Cl₂ (3 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (2 mL), and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.3b (25.0 mg, 88%) as a colorless oil: FTIR (CDCl₃, cast) 3518, 3097, 2956, 2925, 2870, 1760, 1584, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.95 (d, J = 7.5 Hz, 4 H), 7.70 (t, J = 7.4 Hz, 2 H), 7.58 (t, J = 7.8 Hz, 4 H), 6.90 (t, J = 1.2 Hz, 1 H), 6.00 (s, 1 H), 4.47-4.44 (m, 2 H), 3.64 (td, J = 10.7, 4.3 Hz, 1 H), 2.61 (br s, 1 H), 2.23 (q, J = 6.6 Hz, 2 H), 2.14-2.08 (m, 2 H), 1.85-1.72 (m, 3 H), 1.69-1.60 (m, 3 H), 1.45-1.37 (m, 1 H), 1.28-1.23 (m, 1 H), 1.06-0.78 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.5 (s), 143.2 (d), 139.5 (s), 137.8 (s), 137.7 (s), 134.6 (d), 129.6 (d), 129.6 (d), 129.2 (d), 99.3 (d), 83.2 (d), 79.4 (d), 66.1 (d), 47.7 (d), 40.4 (t), 34.2 (t), 34.1 (t), 31.5 (d), 25.3 (d),
25.1 (t), 23.7 (t), 23.1 (t), 22.2 (q), 20.9 (q), 15.8 (q); exact mass (electrospray) 
$m/z$ calcd for $C_{31}H_{40}NaO_8S_2$ (M + Na) 627.2057, found 627.2049.

5,5-Bis(benzenesulfonyl)-1-[(5R)-5-{{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl}pentyl acetate (32.3c).

![Chemical Structure](image)

DMAP (1.3 mg, 0.01 mmol) was added to a stirred solution of crude 32.3b (65 mg, 0.107 mmol) in CH$_2$Cl$_2$ (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.038 mL, 0.53 mmol) and pyridine (0.069 mL, 0.72 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO$_4$ (2 mL) and water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.3c (64.6 mg, 93%) as a colorless foam: FTIR (CDCl$_3$, cast) 3067, 2955, 2926, 2870, 1766, 1584, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.95-7.93 (m, 4 H), 7.70 (td, $J = 7.5$, 0.5 Hz, 2 H), 7.60-7.56 (m, 4 H), 6.86 (t, $J =$
1.4 Hz, 1 H), 5.97 (t, J = 1.3 Hz, 1 H), 5.51-5.49 (m, 1 H), 4.39 (t, J = 5.7 Hz, 1 H), 3.63 (td, J = 10.7, 4.3 Hz, 1 H), 2.21-2.16 (m, 2 H), 2.14-2.09 (m, 5 H), 1.88-1.81 (m, 1 H), 1.77-1.63 (m, 5 H), 1.44-1.36 (m, 1 H), 1.28-1.21 (m, 1 H), 1.06-0.79 (m, 12 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 169.7 (s), 168.8 (s), 144.3 (d), 137.8 (s), 137.7 (s), 136.6 (s), 134.6 (d), 129.6 (d), 129.2 (d), 98.9 (d), 83.1 (d), 79.5 (d), 67.8 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.8 (t), 31.5 (d), 25.3 (d), 25.1 (t), 23.4 (t), 23.1 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.8 (q); exact mass (electrospray) \(m/z\) calcd for C\(_{33}\)H\(_{42}\)NaO\(_9\)S\(_2\) (M + Na) 669.2162, found 669.2154.

5,5-Bis(benzenesulfonyl)-1-[(5\(R\))-5-{{[(1\(R\),2\(S\),5\(R\))]methyl-2-(propan-2-yl)cyclohexyl}oxy}-2-oxo-3-(phenylselenyl)oxolan-3-yl]pentyl acetate (32.3d').

![Diagram](image)

32.3a' \rightarrow 32.3d', X = SPh

**Use of 32.3a'**

DMAP (1.37 mg, 0.01 mmol) was added to a stirred solution of 32.3a' (40 mg, 0.057 mmol) in CH\(_2\)Cl\(_2\) (3 mL). The mixture was then cooled to 0 °C, and Ac\(_2\)O (0.028 mL, 0.29 mmol) and Et\(_3\)N (0.048 mL, 0.343 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature.
The reaction mixture was quenched with saturated aqueous NH₄Cl (2 mL) and water (5 mL), and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% Et₂O-hexane, gave 32.3d' (35.4 mg, 84%) as a colorless oil: FTIR (CDCl₃, cast) 3058, 2952, 2924, 2868, 1766, 1746, 1582, 1477, 1455, 1438 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.66-7.64 (m, 2 H), 7.44-7.40 (m, 5 H), 7.35-7.27 (m, 8 H), 5.60 (dd, J = 6.5, 2.6 Hz, 1 H), 5.22 (dd, J = 9.7, 2.7 Hz, 1 H), 4.31 (t, J = 6.8 Hz, 1 H), 3.52 (td, J = 10.7, 4.2 Hz, 1 H), 2.67 (dd, J = 15.3, 6.5 Hz, 1 H), 2.32-2.25 (m, 1 H), 2.14-2.03 (m, 5 H), 1.89-1.76 (m, 2 H), 1.69-1.56 (m, 6 H), 1.40-1.34 (m, 1 H), 1.26-1.19 (m, 1 H), 1.04-0.78 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 173.4 (s), 170.2 (s), 138.2 (d), 134.1 (s), 134.2 (s), 132.8 (d), 132.8 (d), 129.8 (d), 129.0 (d), 128.9 (d), 128.9 (d), 127.7 (d), 127.7 (d), 126.3 (s), 97.8 (d), 77.5 (d), 74.6 (d), 58.1 (d), 51.1 (s), 47.7 (d), 39.5 (t), 38.0 (t), 35.6 (t), 34.3 (t), 31.4 (q), 30.4 (t), 24.9 (d), 23.6 (t), 22.8 (t), 22.3 (d), 21.1 (q), 20.9 (q), 15.6 (q); exact mass (electrospray) m/z calcd for C₃⁹H₄₈NaO₅S₂⁸₀Se (M + Na) 761.2018, found 761.2016.

5,5-Bis(benzenesulfonyl)-1-[(5R)-5-[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy]-2-oxo-2,5-dihydrofuran-3-yl]pentyl acetate (32.3e').
MCPBA (70%, 266 mg, 1.08 mmol) was added to a stirred and cooled (0 °C) solution of 32.3d' (40 mg, 0.054 mmol) in CH₂Cl₂ (3 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The mixture was quenched with a mixture of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (2 mL), and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave 32.3e' (28.9 mg, 83%) as a colorless foam: FTIR (CDCl₃, cast) 3096, 3067, 2955, 2926, 2870, 1766, 1584, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.94-7.92 (m, 4 H), 7.70 (tq, J = 7.5, 1.6 Hz, 2 H), 7.60-7.56 (m, 4 H), 6.92 (t, J = 1.3 Hz, 1 H), 6.01 (s, 1 H), 5.60-5.58 (m, 1 H), 4.40 (t, J = 5.7 Hz, 1 H), 3.62 (td, J = 10.7, 4.2 Hz, 1 H), 2.25-2.08 (m, 7 H), 1.87-1.75 (m, 2 H), 1.69-1.62 (m, 4 H), 1.44-1.36 (m, 1 H), 1.27-1.22 (m, 1 H), 1.06-0.78 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 169.7 (s), 168.9 (s), 144.9 (d), 137.8 (s), 137.7 (s), 136.3 (d), 134.6 (d), 129.6 (d), 129.2 (d), 99.0 (d), 83.0 (d), 79.2 (d), 67.9 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 31.4 (t), 25.2 (d), 25.1 (t), 23.1 (t), 23.1 (t), 22.2 (d), 20.9 (q), 20.9 (q), 15.7 (q); exact mass (electrospray) m/z calcd for C₃₃H₄₉NaO₉S₂ (M + Na) 669.2162, found 669.2153.
(3R,3aR)-4,4-Bis(benzenesulfonyl)-3-{{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-1H,3H,3aH,4H,5H,6H,7H-cyclohepta[cfuran-1-one (32.3f).

\[
\text{Use of 32.3e'}
\]

Cs\(_2\)CO\(_3\) (55 mg, 0.17 mmol) was added to a stirred and cooled (0 °C) solution of 32.3e' (22 mg, 0.034 mmol) in THF (2 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH\(_4\)Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na\(_2\)SO\(_4\)) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.3f (17.9 mg, 90%).

\[
\text{Use of 32.3c}
\]

Cs\(_2\)CO\(_3\) (121 mg, 0.37 mmol) was added to a stirred and cooled (0 °C) solution of 32.3c (48 mg, 0.074 mmol) in THF (4 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH\(_4\)Cl (2 mL) and extracted with EtOAc (20 mL).
mL). The combined organic extracts were washed with water and brine, dried \((\text{Na}_2\text{SO}_4)\) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave 32.3f (38 mg, 88%): FTIR (CDCl\(_3\), cast) 3066, 2955, 2927, 2870, 1766, 1682, 1583, 1448 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.16 (dd, \(J = 8.4, 1.0\) Hz, 2 H), 7.98-7.97 (m, 2 H), 7.76-7.69 (m, 2 H), 7.60 (dt, \(J = 11.4, 7.9\) Hz, 4 H), 6.78 (br signal including d, \(J = 1.3\) Hz, 2 H), 3.88 (t, \(J = 1.7\) Hz, 1 H), 3.74 (td, \(J = 10.7, 4.1\) Hz, 1 H), 2.45-2.32 (m, 1 H), 2.26-2.16 (m, 3 H), 2.13-2.07 (m, 1 H), 1.71-1.65 (m, 2 H), 1.45-1.37 (m, 1 H), 1.34-1.16 (m, 3 H), 1.09-0.82 (m, 12 H), 0.56-0.47 (m, 1 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.8 (s), 138.3 (d), 137.5 (s), 136.2 (s), 135.2 (d), 134.8 (d), 132.0 (d), 131.1 (d), 129.7 (d), 128.6 (d), 125.8 (s), 96.9 (d), 91.1 (s), 76.6 (d), 48.2 (d), 46.3 (d), 39.0 (t), 34.4 (t), 31.8 (t), 31.5 (t), 31.5 (d), 25.5 (d), 23.3 (t), 22.3 (q), 21.0 (q), 18.4 (t), 15.8 (q); exact mass (electrospray) \(m/z\) calcd for C\(_{31}\)H\(_{38}\)NaO\(_7\)S\(_2\) (M + Na) 609.1951, found 609.1942.

\((5R)-3-[(S)-(2-[2,2-Bis(phenylsulfonyl)ethyl]phenyl)(hydroxy)methyl]-5-[[1R,2S,5R]-5-methyl-2-(propan-2-yl)cyclohexyl]oxy]-2,5-dihydrofuran-2-one (32.4a).
BuLi (2.5 M in hexane, 0.941 mL, 0.255 mmol) was added dropwise to a stirred and cooled (-20 °C) solution of PhSeSePh (721 mg, 2.312 mmol) in THF (4 mL). After 10 min, the mixture was cooled to -45 °C, a mixture of 25.1 (275.0 mg, 1.156 mmol) and 32.4 (289 mg, 0.8257 mmol) in THF (9 mL) was added dropwise, and stirring was continued for 8 h at -45 °C. Then BnBr (0.28 mL, 2.312 mmol) and Bu$_4$NI (30.4 mg, 0.0825 mmol) were added and stirring was continued for another 8 h at -45 °C to -20 °C. The mixture was quenched with saturated aqueous NH$_4$Cl (3 mL) and extracted with Et$_2$O. The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:3 Et$_2$O-hexanes, gave 32.4a [(223 mg, 46 %, or 71% corrected for recovered 25.1 (85 mg)] as an oil: FTIR (CDCl$_3$, cast) 3439, 3059, 2955, 2925, 2897, 1765, 1582, 1480, 1450, 1439 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.44-7.25 (m, 14 H), 6.70 (t, $J$ = 1.4 Hz, 1 H), 5.99 (s, 1 H), 5.51 (s, 1 H), 4.62 (dd, $J$ = 7.8, 6.7 Hz, 1 H), 3.65 (td, $J$ = 10.7, 4.3 Hz, 1 H), 3.35-3.26 (m, 2 H), 2.98 (s, 1 H), 2.13-2.09 (m, 2 H), 1.72-1.65 (m, 2 H), 1.44-1.39 (m, 1 H), 1.31-1.24 (m, 1 H), 1.09-0.81 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.1 (s), 144.2 (d), 139.4 (s), 137.9 (s), 135.7 (s), 134.0 (s), 133.9 (s), 133.3 (d), 132.9 (d), 131.5 (d), 130.9 (d), 129.0 (d), 129.0 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.5 (d), 99.2 (d), 79.3 (d), 65.6 (d), 60.2 (d), 47.7 (d), 40.4 (t), 39.2 (t), 34.2 (t), 31.5 (d), 25.5 (d), 23.3 (s), 22.2 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) m/z calcd for C$_{35}$H$_{40}$NaO$_4$S$_2$ (M + Na) 611.2260, found 611.2258.
(5R)-3-[(S)-2-[2,2-Bis(benzenesulfonyl)ethyl]phenyl](hydroxy)-methyl]-5-[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy]-2,5-dihydrofuran-2-one (32.4b).

MCPBA (70%, 197 mg, 0.79 mmol) was added to a stirred and cooled (0 °C) solution of 32.4a (47 mg, 0.079 mmol) in CH₂Cl₂ (3 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (2 mL), and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et₂O-hexane, gave 32.4b (50 mg, 96%) as a colorless oil: FTIR (CDCl₃, cast) 3497, 3065, 2955, 2925, 2870, 1757, 1584, 1491, 1479, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.88-7.86 (m, 2 H), 7.75-7.73 (m, 2 H), 7.67-7.64 (m, 1 H), 7.61-7.57 (m, 1 H), 7.53-7.50 (m, 2 H), 7.45-7.42 (m, 2 H), 7.27-7.17 (m, 4 H), 7.07 (t, J = 1.5 Hz, 1 H), 6.05 (t, J = 1.4 Hz, 1 H), 5.89 (t, J = 1.7 Hz, 1 H), 5.40 (dd, J = 7.9, 4.2 Hz, 1 H), 3.87-3.74 (m, 2 H), 3.64 (td, J = 10.7, 4.2 Hz, 1 H), 3.08 (d, J = 3.8 Hz, 1 H), 2.14-2.03 (m, 2 H), 1.70-1.64 (m, 2 H), 1.42-1.35
(m, 1 H), 1.30-1.24 (m, 1 H), 1.05-0.76 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.9 (s), 143.9 (d), 1396 (s), 138.6 (s), 138.2 (s), 137.7 (s), 134.6 (d), 134.3 (d), 134.1 (s), 131.3 (d), 129.6 (d), 129.1 (d), 129.1 (d), 128.9 (d), 128.7 (d), 128.2 (d), 127.9 (d), 99.5 (d), 84.4 (d), 79.4 (d), 65.7 (d), 47.7 (d), 40.4 (t), 34.2 (t), 31.5 (d), 28.2 (t), 25.6 (d), 23.4 (t), 22.2 (q), 20.8 (q), 16.1 (q); exact mass (electrospray) $m/z$ calcd for C$_{35}$H$_{40}$NaO$_8$S$_2$ (M + Na) 675.2057, found 675.2049.

(S)-{2-[2,2-Bis(benzenesulfonyl)ethyl]phenyl}[(5R)-5-{{(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl}oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.4c).

![Chemical Structure](image)

32.4b 32.4c, Z = SO$_2$Ph

DMAP (1.8 mg, 0.015 mmol) was added to a stirred solution of 32.4b (50 mg, 0.09 mmol) in CH$_2$Cl$_2$ (2 mL). The mixture was then cooled to 0 °C, and AcCl (0.033 mL, 0.46 mmol) and pyridine (0.049 mL, 0.61 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO$_4$ (2 mL) and water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic
extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et$_2$O-hexane, gave 32.4c (49 mg, 93%) as a colorless foam: FTIR (CDCl$_3$, cast) 3065, 2955, 2926, 2870, 1764, 1585, 1493, 1480, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.96-7.89 (m, 3 H), 7.61-7.58 (m, 2 H), 7.49-7.46 (m, 4 H), 7.42 (dd, $J$ = 7.6, 1.1 Hz, 1 H), 7.28-7.18 (m, 3 H), 7.13 (t, $J$ = 1.4 Hz, 1 H), 6.82 (t, $J$ = 1.7 Hz, 1 H), 6.21 (t, $J$ = 5.8 Hz, 1 H), 6.03 (t, $J$ = 1.4 Hz, 1 H), 4.05 (dd, $J$ = 15.8, 5.7 Hz, 1 H), 3.88 (dd, $J$ = 15.8, 5.9 Hz, 1 H), 3.63 (td, $J$ = 10.6, 4.3 Hz, 1 H), 2.13-2.03 (m, 5 H), 1.69-1.64 (m, 2 H), 1.42-1.36 (m, 1 H), 1.32-1.20 (m, 2 H), 1.03-0.76 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.4 (s), 168.6 (s), 144.4 (d), 138.3 (s), 138.1 (s), 137.1 (s), 135.2 (s), 134.3 (s), 134.1 (d), 134.1 (d), 133.4 (d), 128.7 (d), 128.7 (d), 128.6 (d), 128.2 (d), 127.6 (d), 99.2 (d), 81.6 (d), 79.4 (d), 67.2 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (d), 28.7 (t), 25.4 (d), 23.3 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) $m/z$ calcd for C$_{37}$H$_{42}$NaO$_8$S$_2$ (M + Na) 717.2162, found 717.2150.

(6R,7R)-8,8-Bis(benzenesulfonyl)-6-{{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyloxy]-5-oxatricyclo[8.4.0.0$^{3,7}$]tetradeca-1(14),2,10,12-tetraen-4-one (32.4d).
Cs₂CO₃ (56.3 mg, 0.17 mmol) was added to a stirred and cooled (0 °C) solution of 32.4c (26 mg, 0.035 mmol) in THF (1.5 mL). The ice bath was left in place but not recharged and stirring was continued for 1 h, by which time the temperature had reached 5 °C. The mixture was quenched with saturated aqueous NH₄Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et₂O-hexane, gave 32.4d (21 mg, 95%) whose ¹H NMR spectrum indicated the presence of ca 2% of an impurity: FTIR (CDCl₃, cast) 3065, 2955, 2926, 2869, 1769, 1660, 1583, 1478, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.17-8.08 (m, 3 H), 7.76 (tt, J = 7.5, 1.4 Hz, 1 H), 7.70-7.53 (m, 6 H), 7.33-7.26 (m, 2 H), 7.10 (td, J = 7.4, 1.6 Hz, 1 H), 6.98-6.95 (m, 1 H), 6.54 (d, J = 1.1 Hz, 1 H), 3.68-3.62 (m, 2 H), 3.53 (d, J = 14.9 Hz, 1 H), 3.05 (d, J = 14.9 Hz, 1 H), 2.05-1.96 (m, 2 H), 1.67-1.61 (m, 3 H), 1.35-1.28 (m, 1 H), 1.18-1.12 (m, 1 H), 1.05-0.72 (m, 11 H), 0.52 (q, J = 11.7 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 168.6 (s), 137.5 (s), 137.2 (s), 136.8 (d), 135.7 (s), 135.1 (d), 134.9 (d), 133.7 (s), 133.1 (d), 132.2 (d), 132.1 (d), 130.2 (d), 129.2 (d), 129.1 (d), 128.8 (s), 128.7 (d), 127.8 (d), 102.8 (s), 96.6 (d), 76.1 (d), 48.8 (d), 47.7 (d), 38.4 (t), 37.7 (t), 34.4 (t), 31.3 (d), 25.3 (d), 23.1 (t), 22.3 (q), 20.9 (q), 15.7 (q); exact mass (electrospray) m/z calcd for C₃₅H₃₈NaO₇S₂ (M + Na) 657.1951, found 657.1949.
(4R)-2-[(S)-2-[2,2-Bis(phenylsulfanyl)ethyl]-5-fluorophenyl]-
(hydroxy)methyl]-4-[[1R,2S,5R]-5-methyl-2-(propan-2-yl)cyclohexyl]oxy)-
cyclopent-2-en-1-one (32.5a).

BuLi (2.5 M in hexane, 0.17 mL, 0.42 mmol) was added dropwise to a
stirred and cooled (-20 °C) solution of PhSeSePh (130.6 mg, 0.42 mmol) in THF
(6 mL). After 10 min, the mixture was cooled to -60 °C and a mixture of 25.1
(166 mg, 0.697 mmol) and 32.5 (385 mg, 1.05 mmol) in THF (6 mL) was added
dropwise. Stirring was continued for 8 h, during which time the temperature of
the cold bath rose to -20 °C. The reaction mixture was then quenched with
saturated aqueous NH₄Cl (3 mL) and extracted with Et₂O. The combined organic
extracts were washed with brine, dried (MgSO₄) and evaporated. Flash
chromatography of the residue over silica gel (2 x 15 cm), using 30% Et₂O-
hexanes, gave 32.5a (371 mg, 88%) as an oil: FTIR (CDCl₃, cast) 3460, 3060,
2955, 2925, 2870, 1766, 161, 1590, 1497, 1479, 1455, 1439 cm⁻¹; ¹H NMR (500
MHz, CDCl₃) δ 7.45-7.43 (m, 2 H), 7.37-7.20 (m, 9 H), 7.10 (dd, J = 9.8, 2.7 Hz,
1 H), 6.97 (td, J = 8.2, 2.7 Hz, 1 H), 6.66 (s, 1 H), 6.00 (s, 1 H), 5.43 (s, 1 H), 4.53
(t, J = 7.2 Hz, 1 H), 3.66 (td, J = 10.7, 4.2 Hz, 1 H), 3.24 (dd, J = 7.0, 5.0 Hz, 2
H), 3.08 (d, J = 2.8 Hz, 1 H), 2.14-2.07 (m, 2 H), 1.70 (dq, J = 10.0, 3.5 Hz, 2 H), 1.45-1.40 (m, 1 H), 1.32-1.26 (m, 1 H), 1.06-0.79 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.0 (s), 162.1 (CF, $^1J_{CF}$ = 246.6 Hz), 144.4 (d), 140.2 (s), 140.1 (s), 138.9 (s), 133.9 (s), 133.8 (s), 133.3 (d), 133.2 (d), 133.1 (d), 133.0 (d), 131.3 (s), 131.2 (s), 129.1 (d), 129.1 (d), 128.2 (CCCF, $^3J_{CF}$ = 7.1 Hz), 115.4 (CCF, $^2J_{CF}$ = 21.3 Hz), 114.1 (CCF, $^2J_{CF}$ = 22.5 Hz), 99.2 (d), 79.4 (d), 65.2 (d), 60.4 (d), 47.7 (d), 40.3 (t), 38.5 (t), 34.2 (t), 31.5 (d), 25.5 (d), 23.3 (t), 22.2 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) $m/z$ calc'd for C$_{35}$H$_{39}$FNaO$_4$S$_2$ (M + Na) 629.2166, found 629.2163.

(S)-(2-[2,2-Bis(phenylsulfanyl)ethyl]-5-fluorophenyl)[(5R)-5-{{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.5b).

![Diagram of 32.5a and 32.5b](image)

DMAP (5.5 mg, 0.045 mmol) was added to a stirred solution of 32.5a (274 mg, 0.45 mmol) in CH$_2$Cl$_2$ (5 mL). The mixture was then cooled to 0 °C, and AcCl (0.19 mL, 2.71 mmol) and pyridine (0.29 mL, 3.61 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was
continued for 3 h, during which time the cold bath reached room temperature.
The reaction mixture was quenched with saturated aqueous CuSO₄ (5 mL) and
water (5 mL), and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic
extracts were washed with brine, dried (MgSO₄) and evaporated. Flash
chromatography of the residue over silica gel (1 x 15 cm), using 40% Et₂O-
hexane, gave **32.5b** (292 mg, 99%) as a colorless foam: FTIR (CDCl₃, cast) 3060,
2956, 2925, 2870, 1774, 1592, 1500, 1479, 1456, 1439 cm⁻¹; ¹H NMR (500
MHz, CDCl₃) δ 7.47-7.45 (m, 2 H), 7.39-7.37 (m, 2 H), 7.29-7.23 (m, 7 H), 7.02-
6.94 (m, 2 H), 6.65 (t, J = 1.4 Hz, 1 H), 6.42 (d, J = 1.2 Hz, 1 H), 5.95 (t, J = 1.1
Hz, 1 H), 4.88 (t, J = 7.3 Hz, 1 H), 3.60 (td, J = 10.7, 4.2 Hz, 1 H), 3.27 (d, J = 7.4
Hz, 2 H), 2.11-2.03 (m, 5 H), 1.69-1.63 (m, 2 H), 1.41-1.36 (m, 1 H), 1.26-1.20
(m, 1 H), 1.04-0.77 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 169.0 (s), 167.9 (s),
162.0 (CF, ¹JC = 246.6 Hz), 145.9 (d), 137.0 (s), 137.0 (s), 136.5 (s), 134.0 (s),
133.8 (d), 133.7 (d), 133.7 (s), 133.4 (d), 132.7 (d), 131.9 (s), 131.9 (s), 129.0 (d),
128.9 (d), 128.0 (d), 127.7 (d), 115.7 (CCF, ²JC = 21.1 Hz), 114.5 (CCF, ²JC =
22.7 Hz), 98.6 (d), 79.4 (d), 66.0 (d), 58.0 (d), 47.7 (d), 40.4 (t), 38.7 (t), 34.2 (t),
31.5 (q), 25.4 (d), 23.3 (t), 22.2 (d), 20.8 (q), 20.8 (q), 15.9 (q); exact mass
(electrospray) m/z calcd for C₇₁H₄₁FNaO₅S₂ (M + Na) 671.2272, found 671.2261.

**(S)-(2-[2,2-Bis(benzenesulfonyl)ethyl]-5-fluorophenyl)\{(5R)-5-\-
\{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy\}-2-oxo-2,5-dihydro-
furan-3-yl\}methy acetate (32.5c).**
MCPBA (70%, 1.37 g, 5.54 mmol) was added to a stirred and cooled (0 °C) solution of \textbf{32.5b} (360 mg, 0.55 mmol) in CH$_2$Cl$_2$ (8 mL). The ice bath was left in place but not recharged and stirring was continued for 7 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO$_3$ (2 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (2 mL), and extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 60% Et$_2$O-hexane, gave \textbf{32.5c} (383 mg, 96%) as a solid: FTIR (CDCl$_3$, cast) 3066, 2956, 2927, 2871, 1764, 1613, 1593, 1502, 1479, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.95-7.91 (m, 4 H), 7.62 (td, $J = 7.5, 0.9$ Hz, 2 H), 7.52-7.48 (m, 4 H), 7.43 (dd, $J = 8.6, 5.7$ Hz, 1 H), 7.18 (t, $J = 1.4$ Hz, 1 H), 6.98-6.90 (m, 2 H), 6.81 (d, $J = 1.5$ Hz, 1 H), 6.19 (t, $J = 5.7$ Hz, 1 H), 6.05 (s, 1 H), 4.00 (dd, $J = 15.9, 5.7$ Hz, 1 H), 3.88 (dd, $J = 15.9, 5.7$ Hz, 1 H), 3.64 (td, $J = 10.7, 4.2$ Hz, 1 H), 2.13-2.03 (m, 5 H), 1.70-1.65 (m, 2 H), 1.42-1.37 (m, 1 H), 1.31-1.25 (m, 1 H), 1.07-0.77 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.4 (s), 168.6 (s), 162.3 (CF, $^1$J$_{CF} = 247.3$ Hz), 144.7 (d), 138.1 (s), 138.0 (s), 137.6 (s), 137.5 (s), 136.7 (s), 135.4 (d), 135.4 (d), 134.2 (d), 130.3 (s), 130.3 (s), 129.8 (d), 129.7 (d), 128.8 (d), 128.8 (d), 115.9 (CCF, $^2$J$_{CF} = 21.0$ Hz), 114.2 (CCF, $^2$J$_{CF} = 22.7$ Hz),
99.3 (d), 81.5 (d), 79.6 (d), 67.0 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 28.1 (t),
25.5 (d), 23.4 (t), 22.2 (d), 20.9 (q), 20.8 (q), 16.0 (q); exact mass (electrospray)

\[ m/z \text{ calcld for } C_{37}H_{41}FNaO_9S_2 (M + Na) 735.2068, \text{ found } 735.2057. \]

**(6R,7R)-8,8-Bis(benzenesulfonyl)-13-fluoro-6-[(1R,2S,5R)-5-methyl-2-(propan-2-yl)-cyclohexyl]oxy]-5-oxatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,10,12-tetraen-4-one (32.5g).**

Cs\(_2\)CO\(_3\) (876 mg, 2.69 mmol) was added to a stirred and cooled (0 °C)
solution of **32.5c** (383 mg, 0.54 mmol) in THF (10 mL) and stirring at 0 °C was
continued for 20 min. The cold bath was removed and stirring was continued for
1 h. The mixture was quenched with saturated aqueous NH\(_4\)Cl (2 mL) and
extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic extracts were washed
with water and brine, dried (Na\(_2\)SO\(_4\)) and evaporated. Flash chromatography of
the residue over silica gel (1 x 15 cm), using 60% Et\(_2\)O-hexane, gave **32.5g** (348
mg, 99%) as a solid: mp 135-137 °C; FTIR (CDCl\(_3\), cast) 3069, 2955, 2927,
2869, 1770, 1668, 1581, 1502, 1494, 1479, 1448 cm\(^{-1}\); \(^1\)H NMR (500 MHz,
CDCl\(_3\)) \(\delta\) 8.14-8.12 (m, 2 H), 8.07-8.05 (m, 2 H), 7.75 (tt, \(J = 7.5, 1.4 \) Hz, 1 H),
7.67 (tt, J = 7.5, 1.4 Hz, 1 H), 7.62-7.59 (m, 3 H), 7.56-7.53 (m, 2 H), 7.00-6.94 (m, 2 H), 6.79 (td, J = 8.3, 2.7 Hz, 1 H), 6.46 (d, J = 1.0 Hz, 1 H), 3.63-3.58 (m, 2 H), 3.45 (d, J = 15.0 Hz, 1 H), 3.04 (d, J = 15.0 Hz, 1 H), 1.98-1.92 (m, 2 H), 1.65-1.58 (m, 2 H), 1.33-1.25 (m, 1 H), 1.15-1.09 (m, 1 H), 1.02-0.73 (m, 11 H), 0.44 (q, J = 11.7 Hz, 1 H); 13C NMR (125 MHz, CDCl3) δ 168.3 (s), 161.9 (CF, 1J CF = 249.0 Hz), 137.5 (s), 137.0 (s), 135.6 (d), 135.2 (d), 135.1 (d), 134.9 (d), 134.8 (d), 132.2 (d), 132.1 (d), 130.2 (s), 129.5 (s), 129.3 (d), 128.8 (d), 116.5 (CCF, 2J CF = 22.1 Hz), 116.1 (CCF, 2J CF = 21.4 Hz), 102.7 (s), 96.5 (d), 76.0 (d), 48.8 (d), 47.7 (d), 38.3 (t), 37.0 (t), 34.4 (t), 31.3 (t), 25.4 (d), 23.2 (t), 22.3 (q), 20.9 (q), 15.7 (q); exact mass (electrospray) m/z calcd for C35H37FNaO7S2 (M + Na) 675.1857, found 675.1854.

(2Z)-2-((2-[2,2-Bis(benzenesulfonyl)ethyl]-5-fluorophenyl)methyl)but-2-ene-1,4-diol (32.5h).

\[\text{32.5g} \rightarrow \text{32.5h}, Z = \text{SO}_2\text{Ph}\]

DIBAL-H (1 M solution in PhMe, 0.61 mL, 0.61 mmol) was added by syringe pump over 20 min to a stirred and cooled (-78 °C) solution of 32.5g (40 mg, 0.061 mmol) in PhMe. After the addition, stirring at -78 °C was continued.
for 1 h. The cold bath was replaced by an ice bath and stirring at 0 °C was continued for 1 h. Finally the ice bath was removed and stirring was continued for 2 h. The reaction mixture was quenched with water (1.226 mmol, 0.022 mL) and NaF^{2-} (51 mg, 1.2 mmol), diluted with Et₂O (50 mL), stirred vigorously for 1 h at room temperature, and then filtered through a pad of Celite (1 x 1 cm), using Et₂O as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 80% EtOAc-hexane, gave 32.5h (21 mg, 68%) as an oil: FTIR (CDCl₃, cast) 3524, 3378, 3069, 2858, 2926, 2855, 1588, 1498, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.82 (dd, J = 8.4, 1.1 Hz, 4 H), 7.67-7.64 (m, 2 H), 7.52-7.49 (m, 4 H), 7.23 (dd, J = 8.5, 5.8 Hz, 1 H), 6.84-6.79 (m, 2 H), 5.28 (t, J = 6.8 Hz, 1 H), 5.10 (t, J = 6.3 Hz, 1 H), 4.18 (d, J = 6.7 Hz, 2 H), 4.13 (s, 2 H), 3.59 (d, J = 6.3 Hz, 2 H), 3.51 (s, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 162.1 (CF, ¹JCₐ₇ = 246.8 Hz), 141.7 (s), 139.5 (s), 139.4 (s), 138.1 (s), 134.6 (d), 133.0 (d), 129.7 (s), 129.7 (s), 129.4 (d), 129.1 (d), 128.7 (d), 117.4 (CCF, ²JCₐ₇ = 21.3 Hz), 113.7 (CCF, ²JCₐ₇ = 21.2 Hz), 83.7 (d), 60.5 (t), 58.4 (t), 37.9 (t), 28.4 (t); exact mass (electrospray) m/z calcd for C₂₅H₂₅FNaO₆S₂ (M + Na) 527.0969, found 527.0958.

\( (2Z)-2-((2-[2-(Benzenesulfonyl)ethyl]-5-fluorophenyl)methyl)but-2-ene-1,4-diol \) (32.5i).
6% Na(Hg) (80 mg) was added to a stirred and cooled (0 °C) solution of 32.5h (5 mg, 0.009 mmol) and Na₂HPO₄ (14 mg, 0.099 mmol) in MeOH (2 mL). Stirring at 0 °C was continued for 30 min. The ice bath was removed and stirring was continued for 2 h. The reaction mixture was quenched with water (2 mL) and the MeOH was evaporated under reduced pressure. The residue was extracted with EtOAc (20 mL) and the combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 100% EtOAc, gave 32.5i (2.3 mg, 64%) as a solid: FTIR (CDCl₃, cast) 3415, 3064, 2926, 2855, 1611, 1590, 1499, 1477 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.94 (dt, J = 8.3, 1.6 Hz, 2 H), 7.68 (tt, J = 7.5, 1.5 Hz, 1 H), 7.60-7.57 (m, 2 H), 7.04 (dd, J = 8.3, 5.8 Hz, 1 H), 6.89-6.84 (m, 2 H), 5.30 (t, J = 6.8 Hz, 1 H), 4.21 (d, J = 6.9 Hz, 2 H), 4.16 (s, 2 H), 3.48 (s, 2 H), 3.32-3.28 (m, 2 H), 3.03 (dt, J = 7.9, 4.2 Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 161.7 (CF, ¹J CF = 246.1 Hz), 141.7 (s), 139.2 (s), 139.1 (s), 138.9 (s), 134.0 (d), 132.0 (s), 132.0 (s), 131.0 (d), 130.9 (d), 129.5 (d), 128.5 (d), 128.0 (d), 117.9 (CCF, ²J CF = 21.2 Hz), 114.0 (CCF, ²J CF = 21.1 Hz), 60.4 (t), 58.4 (t), 56.9 (t), 38.4 (t), 24.5 (t); exact mass (electrospray) m/z calcd for C₁₉H₂₁FNaO₄S (M + Na) 387.1037, found 387.1028.
For X-ray analysis crystals of 32.5i were grown by slow vapor diffusion of hexanes into a solution of the compound in Et₂O.

\[(6R)-8-(\text{Benzenesulfonyl})-13\text{-fluoro-6-}[(1R,2S,5R)-5\text{-methyl-2-}(\text{propan-2-yl})\text{cyclohexyl}]\text{oxy}-5\text{-oxatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,7,10,12-pentaen-4-one (32.5j).}\]

6% Na(Hg) (100 mg) and Na₂HPO₄ (37 mg, 0.026 mmol) were added to a stirred and cooled (0 °C) solution of 32.5g (17 mg, 0.026 mmol) in MeOH (1 mL), and stirring at 0 °C was continued for 30 min. The ice bath was removed and stirring was continued for 2 h. The mixture was quenched with water (2 mL) and the MeOH was evaporated under reduced pressure. The residue was extracted with EtOAc (10 mL) and the organic layer was washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 80% EtOAc, gave 32.5j (6 mg, 45%) as an oil: FTIR (CDCl₃, cast) 3065, 2955, 2925, 2869, 1776, 1644, 1613, 1571, 1494, 1448 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) δ 8.05 (s, 1 H), 8.01 (d, \(J = 7.2\) Hz, 2 H), 7.61 (t, \(J =\)
7.4 Hz, 1 H), 7.53 (t, \( J = 7.7 \) Hz, 2 H), 7.17 (dd, \( J = 8.8, 2.6 \) Hz, 1 H), 7.07 (td, \( J = 8.2, 2.7 \) Hz, 1 H), 6.95 (s, 1 H), 6.70 (dd, \( J = 8.4, 5.2 \) Hz, 1 H), 3.77 (td, \( J = 10.7, 4.2 \) Hz, 1 H), 3.69 (d, \( J = 15.0 \) Hz, 1 H), 3.13 (d, \( J = 14.8 \) Hz, 1 H), 2.47 (d, \( J = 13.8 \) Hz, 1 H), 2.00-1.94 (m, 1 H), 1.67-1.63 (m, 2 H), 1.41-1.38 (m, 1 H), 1.24-1.20 (m, 1 H), 1.08-0.77 (m, 12 H); \( ^{13} \)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 168.3 (s), 161.6 (CF, \( ^{1}J_{CF} = 246.3 \) Hz), 142.4 (d), 140.1 (s), 140.0 (s), 135.0 (s), 134.9 (s), 134.0 (d), 131.6 (s), 130.4 (d), 130.3 (d), 129.3 (d), 128.9 (s), 128.4 (d), 125.3 (d), 120.6 (CCF, \( ^{2}J_{CF} = 21.8 \) Hz), 116.7 (CCF, \( ^{2}J_{CF} = 21.9 \) Hz), 96.4 (d), 77.9 (d), 48.0 (d), 38.8 (t), 34.3 (t), 34.1 (t), 31.6 (d), 25.3 (d), 23.3 (t), 22.3 (q), 21.0 (q), 15.6 (q); exact mass (electrospray) \( m/z \) calcd for C\(_{29}\)H\(_{31}\)NaO\(_{5}\)S (M + Na) 533.1768, found 533.1767.

\[(3S,6R,7R)-8,8\text{-Bis(benzenesulfonyl)}-13\text{-fluoro-6-}[(1R,2S,5R)-5\text{-methyl-2-(propan-2-yl)cyclohexyl]oxy}-5\text{-oxatricyclo}[8.4.0.0^{3,7}]\text{tetradeca-1(14),10,12-trien-4-one (32.5k).}\]

\[
\begin{align*}
32.5g & \rightarrow 32.5k, Z = \text{SO}_2\text{Ph} \\
10\% \text{ Pd(OH)}_2\text{-charcoal (50 mg) was added to a solution of 32.5g (100 mg, 0.153 mmol) in EtOAc (10 mL) and AcOH (1 mL). The mixture was}
\end{align*}
\]
hydrogenated in a Parr apparatus (50 psi) at room temperature for 36 h and then filtered through a pad of Celite, using EtOAc (50 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 80% EtOAc-hexane, gave 32.5k (100 mg, 100%): FTIR (CDCl$_3$, cast) 3067, 2955, 2927, 2870, 1790, 1613, 1595, 1583, 1498, 1447 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.24 (d, $J = 7.5$ Hz, 2 H), 7.97 (d, $J = 7.4$ Hz, 2 H), 7.75 (t, $J = 7.5$ Hz, 1 H), 7.69 (t, $J = 7.5$ Hz, 1 H), 7.62 (t, $J = 7.9$ Hz, 2 H), 7.57 (t, $J = 7.8$ Hz, 2 H), 6.91 (dd, $J = 8.7$, 2.5 Hz, 1 H), 6.58 (s, 1 H), 6.54 (td, $J = 8.4$, 2.6 Hz, 1 H), 6.42 (dd, $J = 8.3$, 5.6 Hz, 1 H), 3.75 (d, $J = 16.3$ Hz, 1 H), 3.53 (td, $J = 10.7$, 4.0 Hz, 1 H), 3.38 (t, $J = 13.0$ Hz, 1 H), 3.31-3.25 (m, 1 H), 3.18-3.11 (m, 2 H), 3.04 (d, $J = 9.2$ Hz, 1 H), 2.00-1.93 (m, 2 H), 1.65-1.60 (m, 2 H), 1.34-1.21 (m, 1 H), 1.15-1.10 (m, 1 H), 0.99-0.75 (m, 11 H), 0.56 (q, $J = 11.7$ Hz, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.3 (s), 162.3 (CF, $^1$J$_{CF} = 248.2$ Hz), 141.3 (s), 141.2 (s), 137.6 (s), 136.8 (s), 135.2 (d), 135.1 (d), 132.8 (d), 132.4 (d), 132.3 (d), 131.8 (d), 129.6 (d), 128.6 (d), 126.6 (s), 126.6 (s), 115.1 (CCF, $^2$J$_{CF} = 21.8$ Hz), 113.3 (CCF, $^2$J$_{CF} = 21.2$ Hz), 97.6 (d), 87.9 (s), 76.2 (d), 48.3 (d), 47.9 (d), 41.8 (d), 38.9 (t), 35.3 (t), 34.4 (t), 31.3 (d), 30.4 (t), 25.5 (d), 22.8 (t), 22.2 (q), 21.1 (q), 15.3 (q); exact mass (electrospray) m/z calcd for C$_{35}$H$_{39}$FNaO$_7$S$_2$ (M + Na) 677.2013, found 677.2008.

(7R,8S)-6,6-Bis(benzenesulfonyl)-2-fluoro-8-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-7-yl)methanol (32.5l).
DIBAL-H (1 M in PhMe, 1.5 mL, 1.53 mmol) was added manually dropwise over 5 min. by syringe to a stirred and cooled (0 °C) solution of **32.5k** (50 mg, 0.076 mmol) in PhMe (4 mL). After the addition stirring at 0 °C was continued for 1 h. The cold bath was removed and stirring was continued for 8 h. The mixture was quenched with MeOH (0.052 mL, 1.52 mmol), water (0.028 mL, 1.52 mmol) and NaF^42 (64 mg, 1.52 mmol). The mixture was diluted with EtOAc (20 mL), stirred vigorously at room temperature for 1 h, and then filtered through a pad of Celite, using Et2O as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 80% EtOAc-hexane, gave **32.5l** (32 mg, 82%) as an oil: FTIR (CDCl3, cast) 3354, 3103, 3068, 2928, 1613, 1584, 1502, 1477, 1448 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl3) \(\delta\) 8.05 (d, \(J = 7.7\) Hz, 2 H), 7.72-7.68 (m, 3 H), 7.62 (tt, \(J = 7.5, 1.1\) Hz, 1 H), 7.57 (t, \(J = 7.9\) Hz, 2 H), 7.40 (t, \(J = 8.0\) Hz, 2 H), 6.75 (dd, \(J = 9.5, 2.7\) Hz, 1 H), 6.60 (td, \(J = 8.2, 2.6\) Hz, 1 H), 6.36 (s, 1 H), 4.31 (dd, \(J = 12.0, 4.1\) Hz, 1 H), 4.23-4.18 (m, 1 H), 3.89 (d, \(J = 16.4\) Hz, 1 H), 3.74-3.69 (m, 1 H), 3.60-3.56 (m, 1 H), 3.46 (dd, \(J = 16.6, 11.5\) Hz, 1 H), 3.38-3.30 (m, 2 H), 3.19 (br s, 1 H), 2.42-2.34 (m, 3 H); \(^13\)C NMR (125 MHz, CDCl3) \(\delta\) 162.0 (CF, \(^1J_{CF} = 247.3\) Hz), 142.6 (s), 142.5 (s), 138.5 (s), 137.1 (s), 134.9 (d), 134.7 (d), 134.6 (d), 134.4 (d), 132.0 (d), 131.5 (d),
128.9 (d), 128.2 (d), 126.6 (s), 116.3 (CCF, $^{2}J_{CF} = 21.1$ Hz), 112.6 (CCF, $^{2}J_{CF} = 21.1$ Hz), 97.8 (s), 64.9 (t), 59.4 (t), 45.7 (d), 39.5 (d), 36.2 (t), 33.2 (t); exact mass (electrospray) $m/z$ calcd for C$_{25}$H$_{25}$FNaO$_{6}$S$_{2}$ (M + Na) 527.0969, found 527.0965.

[(7R,8S)-2-Fluoro-8-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-benzo[7]-annulen-7-yl]methanol (32.5m).

6% Na(Hg) (300 mg) and Na$_{2}$HPO$_{4}$ (56 mg, 0.396 mmol) were added to a stirred and cooled (0 °C) solution of 32.5l (20 mg, 0.039 mmol) in MeOH (5 mL), and stirring at 0 °C was continued for 30 min. The ice bath was removed and stirring was continued for 2 h. The mixture was quenched with water (2 mL) and the MeOH was evaporated under reduced pressure. The residue was extracted with EtOAc (20 mL) and the combined organic extracts were washed with water and brine, dried (Na$_{2}$SO$_{4}$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 100% EtOAc, gave 32.5m (7 mg, 79%) as an oil: FTIR (CDCl$_{3}$, cast) 3315, 2926, 2881, 1611, 1592, 1498, 1443, 1422 cm$^{-1}$; $^{1}$H NMR (500 MHz, CDCl$_{3}$) $\delta$ 7.02 (dd, $J = 8.1, 5.9$ Hz, 1 H), 6.82-6.76 (m, 2 H),
3.70-3.64 (m, 2 H), 3.42 (dd, J = 10.9, 4.6 Hz, 1 H), 3.31 (dd, J = 10.6, 8.6 Hz, 1 H), 2.89-2.85 (m, 2 H), 2.82-2.72 (m, 2 H), 2.33-2.29 (m, 1 H), 2.11-2.05 (m, 1 H), 1.76-1.71 (m, 1 H), 1.53-1.44 (m, 1 H), 1.26 (s, 1 H), 0.89-0.86 (m, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.2 (CF, $^1$J$_{CF}$ = 243.5 Hz), 141.0 (CCCF, $^1$J$_{CF}$ = 7.9 Hz), 138.1 (CCCF, $^4$J$_{CF}$ = 3.3 Hz), 130.0 (CCCF, $^3$J$_{CF}$ = 8.0 Hz), 116.5 (CCF, $^2$J$_{CF}$ = 20.9 Hz), 112.6 (CCF, $^2$J$_{CF}$ = 20.5 Hz), 66.6 (t), 62.4 (t), 47.4 (d), 39.5 (d), 38.3 (t), 34.1 (t), 26.4 (t); exact mass (electrospray) m/z calcd for C$_{13}$H$_{17}$FNaO$_2$ (M + Na) 247.1105, found 247.1102.

(5R)-3-[1-Hydroxy-4,4-bis(phenylsulfanyl)butyl]-4-methyl-5-
{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.1i, 32.1i').

BuLi (2.5 M in hexanes, 0.38 mL, 0.95 mmol) was added to a stirred and cooled (-78 °C) solution of i-Pr$_2$NH (0.15 mL, 1.11 mmol) in THF (3 mL), and stirring was continued for 30 min at -78 °C. A solution of 28.1$^{2b}$ (200 mg, 0.79 mmol) in THF (2 mL) was then added dropwise and stirring at -78 °C was continued for 50 min. A solution of aldehyde 32.1$^{1b}$ (274 mg, 0.95 mmol) in
THF (2 mL) was added at a fast dropwise rate and stirring at -78 °C was continued for 30 min. Saturated aqueous NH₄Cl (ca 3 mL) was added and the mixture was extracted with Et₂O. The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% Et₂O-hexane, gave an oil, which was separated into three fractions: less polar alcohol 32.1i' (41 mg, 10 %), more polar alcohol 32.1i (52 mg, 12%), and a mixture of both isomers (172 mg, 40%).

The more polar alcohol 32.1i had: FTIR (CDCl₃, cast) 3476, 3058, 2954, 2923, 2869, 1756, 1686, 1583, 1480, 1455, 1439 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.48-7.46 (m, 4 H), 7.33-7.26 (m, 6 H), 5.63 (s, 1 H), 4.46-4.41 (m, 2 H), 3.61 (td, J = 10.7, 4.3 Hz, 1 H), 2.84 (d, J = 9.1 Hz, 1 H), 2.15-1.81 (m, 9 H), 1.70-1.64 (m, 2 H), 1.44-1.39 (m, 1 H), 1.27-1.21 (m, 1 H), 1.03-0.78 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3 (s), 155.6 (s), 133.9 (s), 133.9 (s), 132.9 (d), 132.9 (d), 130.2 (s), 129.0 (d), 129.0 (d), 127.9 (d), 127.9 (d), 100.8 (d), 79.6 (d), 66.4 (d), 58.0 (d), 47.8 (d), 40.5 (t), 34.2 (t), 33.8 (t), 31.7 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.3 (q), 20.9 (q), 15.8 (q), 11.5 (q); exact mass (electrospray) m/z calcd for C₃₁H₄₀NaO₄S₂ (M + Na) 563.2260, found 563.2251.

The less polar alcohol 32.1i' had: FTIR (CDCl₃, cast) 3477, 3058, 2954, 2923, 2869, 1755, 1687, 1583, 1480, 1455, 1439 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.50-7.48 (m, 4 H), 7.36-7.29 (m, 6 H), 5.68 (s, 1 H), 4.49-4.44 (m, 2 H), 3.64 (td, J = 10.7, 4.3 Hz, 1 H), 2.84 (d, J = 9.2 Hz, 1 H), 2.18-1.88 (m, 9 H), 1.73-1.67 (m, 2 H), 1.46-1.41 (m, 1 H), 1.30-1.25 (m, 1 H), 1.08-0.82 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 171.4 (s), 155.6 (s), 133.9 (s), 133.9 (s), 132.9 (d),
132.9 (d), 130.3 (s), 129.0 (d), 127.9 (d), 127.9 (d), 101.1 (d), 79.8 (d), 66.6 (d), 58.1 (d), 47.7 (d), 40.6 (t), 34.2 (t), 33.9 (t), 31.8 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.3 (q), 20.9 (q), 15.8 (q), 11.6 (q); exact mass (electrospray) m/z calcd for C_{31}H_{40}NaO_{4}S_{2} (M + Na) 563.2260, found 563.2255.

(5R)-3-[4,4-Bis(benzenesulfonyl)-1-hydroxybutyl]-4-methyl-5-
{(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl}oxy]-2,5-dihydrofuran-2-
one (32.1j, 32.1j').

MCPBA (70%, 1.18 g, 4.77 mmol) was added to a stirred and cooled (0 °C) solution of a mixture of 32.1i and 32.1i' (172 mg, 0.318 mmol) in CH$_2$Cl$_2$ (4 mL). The ice bath was removed and stirring was continued for 3 h. The mixture was quenched with a mixture of saturated aqueous NaHCO$_3$ (3 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (3 mL), and extracted with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 80% Et$_2$O-hexane, gave a separable mixture of isomers (140 mg, 73%):
more polar sulfone alcohol 32.1j (74 mg, 39%) and the less polar sulfone alcohol 32.1j' (66 mg, 34%).

The more polar alcohol 32.1j had: FTIR (CDCl₃, cast) 3517, 3065, 2955, 2924, 2870, 1753, 1687, 1585, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.97-7.94 (m, 4 H), 7.70 (t, J = 7.5 Hz, 2 H), 7.58 (t, J = 7.9 Hz, 4 H), 5.69 (s, 1 H), 4.65 (t, J = 5.8 Hz, 1 H), 4.48 (td, J = 8.4, 3.8 Hz, 1 H), 3.61 (td, J = 10.7, 4.3 Hz, 1 H), 2.89 (d, J = 8.2 Hz, 1 H), 2.46-2.25 (m, 2 H), 2.14-1.91 (m, 7 H), 1.70-1.64 (m, 2 H), 1.44-1.38 (m, 1 H), 1.27-1.21 (m, 1 H), 1.06-0.78 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3 (s), 156.3 (s), 137.9 (s), 137.7 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.5 (d), 129.2 (d), 129.2 (d), 101.0 (d), 82.8 (d), 79.8 (d), 66.3 (d), 47.8 (d), 40.5 (t), 34.2 (t), 33.8 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.3 (t), 22.3 (q), 20.9 (q), 15.8 (q), 11.6 (q); exact mass (electrospray) m/z calcd for C₃₁H₄₀NaO₈S₂ (M + Na) 627.2057, found 627.2050.

The less polar alcohol 32.1j' had: FTIR (CDCl₃, cast) 3514, 3066, 2955, 2924, 2870, 1754, 1686, 1585, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.98-7.94 (m, 4 H), 7.72-7.68 (m, 2 H), 7.60-7.56 (m, 4 H), 5.69 (s, 1 H), 4.66 (t, J = 5.8 Hz, 1 H), 4.47 (td, J = 9.0, 3.9 Hz, 1 H), 3.61 (td, J = 10.7, 4.3 Hz, 1 H), 2.85 (d, J = 8.6 Hz, 1 H), 2.39 (ddt, J = 15.2, 9.2, 5.8 Hz, 1 H), 2.29 (ddt, J = 15.3, 9.0, 6.3 Hz, 1 H), 2.14-1.91 (m, 7 H), 1.70-1.64 (m, 2 H), 1.45-1.36 (m, 1 H), 1.28-1.22 (m, 1 H), 1.06-0.76 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3 (s), 156.3 (s), 137.9 (s), 137.7 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 101.2 (d), 82.8 (d), 79.9 (d), 66.5 (d), 47.7 (d), 40.6 (t), 34.2 (t), 34.1 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.4 (t), 22.3 (q), 21.0 (q), 15.7 (q), 11.7 (q); exact
mass (electrospray) m/z calcd for C_{31}H_{40}NaO_{8}S_{2} (M + Na) 627.2057, found 627.2050.

4,4'-Bis(benzenesulfonyl)-1-[(5R)-4-methyl-5-[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy]-2-oxo-2,5-dihydrofuran-3-yl]butyl acetate (32.1k, 32.1k').

32.1j, 32.1j', Z = SO_{2}Ph

32.1k, 32.1k'

Use of 32.1j'

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.1j' (12 mg, 0.0198 mmol) in CH_{2}Cl_{2} (1 mL). The mixture was then cooled to 0 °C, and AcCl (8.5 µL, 0.11 mmol) and pyridine (0.0128 mL, 0.16 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO_{4} (2 mL) and water (5 mL), and extracted with CH_{2}Cl_{2} (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO_{4}) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 80% Et_{2}O-hexane, gave 32.1k' (10.1 mg, 79%) as a colorless foam: FTIR (CDCl_{3}, cast)
3065, 3023, 2955, 2925, 2870, 1760, 1670, 1584, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.99-7.97 (m, 4 H), 7.76-7.73 (m, 2 H), 7.62 (t, J = 7.8 Hz, 4 H), 5.72 (s, 1 H), 5.58 (dd, J = 8.9, 4.5 Hz, 1 H), 4.54 (t, J = 5.8 Hz, 1 H), 3.64 (td, J = 10.6, 4.2 Hz, 1 H), 2.46-2.39 (m, 1 H), 2.29-2.10 (m, 11 H), 1.73-1.69 (m, 2 H), 1.48-1.42 (m, 1 H), 1.32-1.26 (m, 1 H), 1.10-0.84 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.2 (s), 169.4 (s), 159.5 (s), 137.8 (s), 137.6 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 126.8 (s), 100.6 (d), 82.6 (d), 79.8 (d), 66.6 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 30.1 (t), 25.1 (d), 23.1 (t), 22.3 (d), 21.6 (t), 20.9 (q), 20.8 (q), 15.7 (q), 12 (q); exact mass (electrospray) m/z calcd for C₃₃H₄₂NaO₉S₂ (M + Na) 669.2162, found 669.2156.

Use of 32.1j

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.1j (12 mg, 0.0198 mmol) in CH₂Cl₂ (1 mL). The mixture was then cooled to 0 °C, and AcCl (8.5 µL, 0.11 mmol) and pyridine (0.0128 mL, 0.16 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO₄ (2 mL) and water (5 mL), and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 80% Et₂O-hexane, gave 32.1k (10.3 mg, 81%) as a colorless foam: FTIR (CDCl₃, cast) 3067, 3025, 2955, 2925, 2870, 1761, 1690, 1584, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.99-7.97 (m, 4 H), 7.76-7.73 (m, 2 H), 7.62 (t, J = 7.8 Hz, 4 H), 5.72 (s, 1 H), 5.58 (dd, J = 8.9, 4.5 Hz, 1 H), 4.54 (t, J = 5.8 Hz, 1 H), 3.64 (td, J = 10.6, 4.2 Hz, 1 H), 2.46-2.39 (m, 1 H), 2.29-2.10 (m, 11 H), 1.73-1.69 (m, 2 H), 1.48-1.42 (m, 1 H), 1.32-1.26 (m, 1 H), 1.10-0.84 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.2 (s), 169.4 (s), 159.5 (s), 137.8 (s), 137.6 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 126.8 (s), 100.6 (d), 82.6 (d), 79.8 (d), 66.6 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 30.1 (t), 25.1 (d), 23.1 (t), 22.3 (d), 21.6 (t), 20.9 (q), 20.8 (q), 15.7 (q), 12 (q); exact mass (electrospray) m/z calcd for C₃₃H₄₂NaO₉S₂ (M + Na) 669.2162, found 669.2156.
CDCl$_3$) δ 7.95-7.93 (m, 4 H), 7.70 (t, $J = 7.5$ Hz, 2 H), 7.58 (t, $J = 7.6$ Hz, 4 H), 5.66 (s, 1 H), 5.55 (dt, $J = 8.8$, 4.5 Hz, 1 H), 4.53 (t, $J = 5.8$ Hz, 1 H), 3.61 (td, $J = 10.7$, 4.3 Hz, 1 H), 2.34-2.04 (m, 12 H), 1.69-1.65 (m, 2 H), 1.44-1.37 (m, 1 H), 1.29-1.23 (m, 1 H), 1.07-0.80 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.1 (s), 169.4 (s), 158.9 (s), 137.8 (s), 137.6 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 127.0 (s), 100.6 (d), 82.5 (d), 80.0 (d), 66.6 (d), 47.7 (d), 40.6 (t), 34.2 (t), 31.5 (q), 30.1 (t), 25.2 (d), 23.1 (t), 22.3 (d), 21.6 (t), 20.9 (q), 20.8 (q), 15.8 (q), 11.8 (q); exact mass (electrospray) m/z calcd for C$_{33}$H$_{42}$NaO$_9$S$_2$ (M + Na) 669.2162, found 669.2150.

(5R)-3-((2-[2,2-Bis(phenylsulfanyl)ethyl]-5-fluorophenyl)(hydroxy)-methyl)-4-methyl-5-([(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy)-2,5-dihydrofuran-2-one (32.5d).

BuLi (2.5 M in hexanes, 0.46 mL, 1.14 mmol) was added to a stirred and cooled (-78 °C) solution of i-Pr$_2$NH (0.18 mL, 1.30 mmol) in THF (5 mL), and stirring was continued for 30 min. A solution of 28.1 (273 mg, 1.08 mmol) in
THF (3 mL) was then added dropwise and stirring at -78 °C was continued for 50 min. A solution of aldehyde **32.5** (200 mg, 0.54 mmol) in THF (2 mL) was added at a fast dropwise rate and stirring at -78 °C was continued for 30 min. Then saturated aqueous NH₄Cl (ca 5 mL) was added and the mixture was extracted with Et₂O. The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% Et₂O-hexane, gave crude **32.5d** (171 mg, 51%) which could not be purified by flash chromatography and was used directly for next step.

$$(5R)-3-((2-\{2,2-Bis(benzenesulfonyl)ethyl\}-5-fluorophenyl)(hydroxy)-methyl)-4-methyl-5-\{(\{1R,2S,5R\}-5-methyl-2-(propan-2-yl)cyclohexyl\}oxy\}-2,5$-dihydrofuran-2-one (32.5e).$$

MCPBA (70%, 465 mg, 1.88 mmol) was added to a stirred and cooled (0 °C) solution of crude **32.5d** (117 mg, ca 0.188 mmol) in CH₂Cl₂ (5 mL). The ice bath was removed and stirring was continued for 4 h. The mixture was quenched with a mixture of saturated aqueous NaHCO₃ (3 mL) and saturated aqueous
Na$_2$S$_2$O$_3$ (3 mL), and extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et$_2$O-hexane, gave 32.5e (81 mg, 63%) as an inseparable mixture of diastereomers: FTIR (CDCl$_3$, cast) 3502, 3066, 3021, 2956, 2924, 2871, 1749, 1689, 1613, 1592, 1501, 1499, 1479, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.86-7.83 (m, 2 H), 7.77-7.73 (m, 2 H), 7.66-7.61 (m, 2 H), 7.52-7.46 (m, 4 H), 7.30-7.26 (m, 1 H), 6.96-6.88 (m, 2 H), 5.96 (s, 1 H), 5.80 (s, 1 H), 5.55 (t, J = 6.1 Hz, 1 H), 3.95 (dd, J = 15.8, 6.1 Hz, 1 H), 3.75 (dd, J = 15.8, 6.2 Hz, 1 H), 3.67 (td, J = 10.7, 4.3 Hz, 1 H), 3.61 (s, 1 H), 2.15-2.04 (m, 5 H), 1.73-1.69 (m, 2 H), 1.47-1.26 (m, 2 H), 1.12-0.82 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.6 (s), 162.2 (CF, $^1$J$_{CF}$ = 247.6 Hz), 157.6 (s), 141.6 (s), 141.6 (s), 138.4 (s), 138.2 (s), 134.4 (d), 134.4 (d), 133.5 (d), 133.5 (d), 129.9 (s), 129.9 (d), 129.2 (d), 129.2 (d), 129.0 (d), 129.0 (d), 128.8 (s), 115.5 (CCF, $^2$J$_{CF}$ = 21.3 Hz), 114.6 (CCF, $^2$J$_{CF}$ = 22.5 Hz), 101.3 (d), 83.7 (d), 79.8 (d), 66.1 (d), 47.7 (d), 40.4 (t), 34.2 (t), 31.5 (d), 27.7 (t), 25.4 (d), 23.3 (t), 22.3 (q), 20.8 (q), 15.9 (q), 12 (q); exact mass (electrospray) m/z calcd for C$_{36}$H$_{41}$FNaO$_8$S$_2$ (M + Na) 707.2119, found 707.2111.

{(2-[2,2-Bis(benzenesulfonyl)ethyl]-5-fluorophenyl)[(5R)-4-methyl-5-{{(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl}oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.5f).
DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.5e (13.5 mg, 0.0197 mmol) in CH₂Cl₂ (1 mL). The mixture was then cooled to 0 °C, and AcCl (0.0084 mL, 0.11 mmol) and pyridine (0.0128 mL, 0.16 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO₄ (2 mL) and water (5 mL), and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% Et₂O-hexane, gave 32.5f (12.7 mg, 89%) as a colorless foam: FTIR (CDCl₃, cast) 3068, 2956, 2926, 2871, 1759, 1685, 1613, 1592, 1501, 1448 cm⁻¹;¹H NMR (500 MHz, CDCl₃) δ 7.92-7.89 (m, 3 H), 7.63-7.35 (m, 7 H), 7.01 (dd, J = 9.6, 2.7 Hz, 1 H), 6.91-6.84 (m, 2 H), 6.16-6.11 (m, 1 H), 5.70 (s, 1 H), 3.93 (d, J = 6.1 Hz, 2 H), 3.61 (td, J = 10.7, 4.3 Hz, 1 H), 2.34-2.01 (m, 9 H), 1.71-1.65 (m, 2 H), 1.43-1.39 (m, 1 H), 1.31-1.24 (m, 1 H), 1.05-0.73 (m, 12 H);¹³C NMR (125 MHz, CDCl₃) δ 169.6 (s), 169.2 (s), 162.2 (CF, ¹JCF = 247.1 Hz), 157.4 (s), 138.4 (s), 138.2 (s), 134.8 (d), 134.8 (d), 134.1 (d), 129.6 (d), 128.8 (d), 127.4 (s), 115.7 (CCF, ²JCF = 21.3 Hz),
114.8 (CCF, $^2J_{CF} = 22.5$ Hz), 101.1 (d), 81.6 (d), 79.9 (d), 68.1 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 27.8 (t), 25.4 (d), 23.3 (t), 22.3 (d), 20.9 (q), 20.8 (q), 15.9 (q), 12.5 (q); exact mass (electrospray) $m/z$ calcd for C$_{38}$H$_{43}$FNaO$_9$S$_2$ (M + Na) 749.2225, found 749.2218.

$^{(5R)}$-3-[1-Hydroxy-6,6-bis(phenylsulfanyl)hexyl]-5-[[($R,2S,5R$)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy]-3-(phenylselanyl)oxolan-2-one (32.6a, 32.6a').

![Reaction Scheme](image)

A solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 0.625 mL, 1.57 mmol) was added to a stirred and cooled (-78 °C) solution of i-Pr$_2$NH (0.25 mL, 1.76 mmol) in THF (5 mL), and stirring was continued for 30 min at -78 °C. A portion (1.18 mL, 0.32 mmol) of this stock solution was then taken up into a syringe and added manually dropwise over ca 10 min, to a stirred and cooled (-78 °C) solution of lactone 27.1 (100 mg, 0.25 mmol) in THF (2 mL). Stirring at -78 °C was continued for 45 min and then HMPA (0.5 mL) was added dropwise. Stirring was continued for 5 min and then a solution of aldehyde 32.6$^{11b}$ (127 mg, 0.55 mmol) in THF (2 mL) was added at a fast dropwise rate.
Stirring at -78 °C was continued for 20-30 min (TLC control, silica, Et₂O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH₄Cl (3 mL) was added and the mixture were extracted with Et₂O. The combined organic extracts were washed with brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 30% Et₂O-hexane, gave 32.6a (more polar isomer, 98 mg, 55%) and 32.6a' (less polar isomer, 40 mg, 22%) as oils.

The more polar alcohol 32.6a had: FTIR (CDCl₃, cast) 3452, 3073, 3058, 2949, 2925, 2866, 1764, 1582, 1478, 1455, 1438 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.64-7.62 (m, 2 H), 7.47-7.43 (m, 5 H), 7.40-7.37 (m, 1 H), 7.33-7.26 (m, 7 H), 5.67 (d, J = 5.8 Hz, 1 H), 4.39 (t, J = 6.6 Hz, 1 H), 3.65 (dd, J = 10.1, 3.9 Hz, 1 H), 3.58 (td, J = 10.7, 4.1 Hz, 1 H), 2.88 (dd, J = 14.6, 6.4 Hz, 1 H), 2.54-2.47 (m, 1 H), 2.17-2.10 (m, 2 H), 1.95-1.92 (m, 2 H), 1.87-1.83 (m, 2 H), 1.70-1.56 (m, 5 H), 1.51-1.35 (m, 3 H), 1.30-0.80 (m, 13 H); ¹³C NMR (100 MHz, CDCl₃) δ 177.2 (s), 138.2 (d), 134.6 (s), 134.5 (s), 133.0 (d), 132.9 (d), 130.0 (d), 129.2 (d), 129.2 (d), 129.1 (d), 129.1 (d), 127.9 (s), 127.9 (d), 127.9 (d), 125.9 (d), 98.1 (d), 71.8 (d), 58.6 (d), 50.5 (s), 48.0 (d), 39.7 (t), 36.0 (t), 35.2 (t), 34.6 (t), 31.7 (d), 30.7 (t), 27.0 (t), 26.0 (t), 25.2 (d), 23.0 (t), 22.5 (d), 21.4 (t), 15.7 (q); exact mass (electrospray) m/z calcd for C₃₈H₄₈NaO₂S₂Se (M + Na) 735.2051, found 735.2050.

The less polar alcohol 32.6a' had: FTIR (CDCl₃, cast) 3500, 3073, 3058, 2951, 2925, 2867, 1764, 1582, 1477, 1455, 1438 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.65 (dd, J = 8.1, 1.2 Hz, 2 H), 7.43-7.23 (m, 13 H), 5.66 (dd, J = 6.3,
1.2 Hz, 1 H), 4.34 (t, J = 6.7 Hz, 1 H), 3.59-3.54 (m, 2 H), 2.81 (s, 1 H), 2.70 (dd, 
J = 15.3, 6.5 Hz, 1 H), 2.46-2.39 (m, 1 H), 2.11-2.07 (m, 1 H), 1.98 (dd, J = 15.3, 
1.5 Hz, 1 H), 1.82-1.78 (m, 2 H), 1.69-1.65 (m, 2 H), 1.60-1.46 (m, 4 H), 1.43-
1.34 (m, 1 H), 1.30-1.21 (m, 3 H), 1.03-0.77 (m, 12 H); \(^{13}\)C NMR (100 MHz, 
CDCl\(_3\)) δ 175.1 (s), 138.1 (d), 134.2 (s), 132.7 (d), 129.9 (d), 129.1 (d), 128.8 (d), 
127.6 (d), 125.8 (s), 97.7 (d), 77.3 (d), 71.9 (d), 58.2 (d), 53.4 (s), 47.8 (d), 39.5 
t), 36.6 (t), 35.6 (t), 34.3 (t), 31.4 (d), 31.1 (t), 26.9 (t), 26.0 (t), 25.0 (d), 22.8 (t), 
22.3 (q), 21.1 (q), 15.6 (q); exact mass (electrospray) m/z calcd for 
C\(_{38}\)H\(_{48}\)NaO\(_4\)S\(_2\)Se (M + Na) 735.2051, found 735.2047.

\((5R)-3-[6,6-\text{Bis(benzenesulfonyl)}-1-\text{hydroxyhexyl}]5-\text{[(1R,2S,5R)-5-}
\text{methyl-2-(propan-2-yl)cyclohexyl}oxy]-2,5-\text{dihydrofuran-2-one (32.6b,}
32.6b').

![Diagram](image)

32.6a, 32.6a', X = SPh

32.6b, 32.6b', Z = SO\(_2\)Ph

Use of 32.6a'

MCPBA (70%, 276 mg, 1.12 mmol) was added to a stirred and cooled (0 °C) solution of 32.6a' (40 mg, 0.056 mmol) in CH\(_2\)Cl\(_2\) (4 mL). The ice bath was left in place but not recharged and stirring was continued for 3 h. The reaction
mixture was quenched with a mixture of saturated aqueous NaHCO$_3$ (2 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (2 mL), and extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave 32.6b' (29.7 mg, 86%) as a colorless oil: FTIR (CHCl$_3$, cast) 3525, 3020, 2953, 2925, 2869, 2848, 1761, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.95 (d, $J$ = 7.7 Hz, 4 H), 7.70 (t, $J$ = 7.5 Hz, 2 H), 7.58 (t, $J$ = 7.9 Hz, 4 H), 6.91 (t, $J$ = 1.3 Hz, 1 H), 6.01 (s, 1 H), 4.46 (dd, $J$ = 8.4, 3.5 Hz, 1 H), 4.39 (t, $J$ = 5.6 Hz, 1 H), 3.64 (td, $J$ = 10.7, 4.2 Hz, 1 H), 2.41 (br s, 1 H), 2.19-2.07 (m, 4 H), 1.76-1.55 (m, 6 H), 1.49-1.32 (m, 3 H), 1.29-1.23 (m, 1 H), 1.07-0.80 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.4 (s), 143.2 (d), 139.9 (s), 137.8 (s), 134.6 (d), 129.6 (d), 129.1 (d), 99.2 (d), 83.5 (d), 79.2 (d), 66.7 (d), 47.7 (d), 40.4 (t), 34.4 (t), 34.2 (t), 31.5 (d), 27.6 (t), 25.4 (t), 25.3 (d), 24.5 (t), 23.1 (t), 22.2 (q), 20.9 (q), 15.8 (q); exact mass (electrospray) $m/z$ calcd for C$_{32}$H$_{42}$NaO$_8$S$_2$ (M + Na) 641.2213, found 641.2206.

**Use of 32.6a**

MCPBA (70%, 678 mg, 2.75 mmol) was added to a stirred and cooled (0 °C) solution of 32.6a (98 mg, 0.14 mmol) in CH$_2$Cl$_2$ (5 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO$_3$ (2 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (2 mL), and extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and...
evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave 32.6b (74 mg, 88%) as a colorless oil: FTIR (CHCl₃, cast) 3526, 3065, 2954, 2869, 2848, 1761, 1455, 1448, 1438 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.96-7.93 (m, 4 H), 7.71-7.68 (m, 2 H), 7.59-7.55 (m, 4 H), 6.88 (t, J = 1.4 Hz, 1 H), 5.99 (t, J = 1.2 Hz, 1 H), 4.44-4.43 (m, 1 H), 4.39 (t, J = 5.6 Hz, 1 H), 3.63 (td, J = 10.7, 4.3 Hz, 1 H), 2.58 (br s, 1 H), 2.18-2.07 (m, 4 H), 1.74-1.56 (m, 6 H), 1.49-1.34 (m, 3 H), 1.28-1.23 (m, 1 H), 1.06-0.82 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.5 (s), 143.0 (d), 139.7 (s), 137.8 (s), 134.6 (d), 129.6 (d), 129.1 (s), 99.3 (d), 83.5 (d), 79.4 (d), 66.4 (d), 47.7 (d), 40.4 (t), 34.4 (t), 34.2 (t), 31.5 (d), 27.6 (t), 25.4 (t), 25.3 (d), 24.5 (t), 23.2 (t), 22.2 (q), 20.9 (q), 15.8 (q); exact mass (electrospray) m/z calcd for C₃₂H₄₂NaO₈S₂ (M + Na) 641.2213, found 641.2204.

6,6-Bis(benzenesulfonyl)-1-[(5R)-5-[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy]-2-oxo-2,5-dihydrofuran-3-yl]hexyl acetate (32.6c, 32.6c').

![diagram](image-url)
Use of 32.6b'

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.6b' (27 mg, 0.044 mmol) in CH₂Cl₂ (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.016 mL, 0.22 mmol) and pyridine (0.28 mL, 0.35 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO₄ (2 mL) and water (5 mL), and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave 32.6c' (25.8 mg, 90%) as a colorless foam: FTIR (CHCl₃, cast) 3065, 2954, 2926, 2870, 1766, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.95-7.93 (m, 4 H), 7.72-7.69 (m, 2 H), 7.60-7.56 (m, 4 H), 6.91 (t, J = 1.3 Hz, 1 H), 6.01 (s, 1 H), 5.60-5.58 (m, 1 H), 4.35 (t, J = 5.6 Hz, 1 H), 3.62 (td, J = 10.7, 4.3 Hz, 1 H), 2.17-2.09 (m, 7 H), 1.85-1.64 (m, 4 H), 1.62-1.55 (m, 2 H), 1.44-1.37 (m, 1 H), 1.31-1.22 (m, 3 H), 1.06-0.79 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 169.7 (s), 168.9 (s), 144.5 (d), 137.9 (s), 137.8 (s), 136.8 (s), 134.6 (d), 129.6 (d), 129.1 (d), 98.9 (d), 83.6 (d), 79.2 (d), 68.2 (d), 47.7 (d), 40.5 (t), 34.2 (t), 32.0 (t), 31.5 (q), 27.7 (t), 25.4 (t), 25.2 (d), 24.4 (t), 23.1 (t), 22.2 (q), 20.9 (q), 20.9 (q), 15.7 (q); exact mass (electrospray) m/z calcd for C₃₄H₄₅NaO₇S₂ (M + Na) 683.2319, found 683.2312.
Use of 32.6b

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.6b (57 mg, 0.092 mmol) in CH₂Cl₂ (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.033 mL, 0.46 mmol) and pyridine (0.060 mL, 0.74 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was then quenched with saturated aqueous CuSO₄ (2 mL) and water (5 mL), and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave 32.6c (55 mg, 91%) as a colorless foam: FTIR (neat) 3096, 3067, 2954, 2926, 2870, 1767, 1448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.96-7.94 (m, 4 H), 7.72-7.68 (m, 2 H), 7.59-7.56 (m, 4 H), 6.85 (t, J = 1.4 Hz, 1 H), 5.97 (t, J = 1.4 Hz, 1 H), 5.51 (td, J = 5.6, 2.6, 1.5 Hz, 1 H), 4.36 (t, J = 5.6 Hz, 1 H), 3.63 (td, J = 10.7, 4.3 Hz, 1 H), 2.16-2.07 (m, 7 H), 1.84-1.54 (m, 6 H), 1.44-1.22 (m, 4 H), 1.06-0.80 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 169.8 (s), 168.9 (s), 144.0 (d), 137.9 (s), 137.8 (s), 137.0 (s), 134.6 (d), 129.6 (d), 129.6 (d), 129.1 (d), 129.1 (d), 98.9 (d), 83.6 (d), 79.5 (d), 68.2 (d), 47.7 (d), 40.5 (t), 34.2 (t), 32.3 (t), 31.5 (q), 27.7 (t), 25.4 (t), 25.4 (d), 24.6 (t), 23.2 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) m/z calcd for C₃₅H₄₄NaO₉S₂ (M + Na) 683.2319, found 683.2310.

Methyl 2-[bis(phenylsulfanyl)methyl]benzoate (37.3).
NaH (60%, 1.58 g, 39.32 mmol) was added slowly to a stirred and cooled (0 °C) solution of PhSH (3.9 mL, 38.04 mmol) in DMF (60 mL). Stirring was continued for 10 min, a solution of 37.2 (4.68 g, 15.21 mmol) in DMF (10 mL) was then added, and stirring was continued for 12 h. The mixture was quenched with hydrochloric acid (1 M, 5 mL) and extracted with Et₂O (2 x 100 mL). The combined organic extracts were washed with aqueous NaOH (10%, 20 mL) to remove unreacted PhSH, and the organic phase was washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 5% Et₂O-hexane, gave 37.3 (3.5 g, 65%) as an oil: FTIR (cast film) 3057, 3019, 2948, 2926, 1715, 1598, 1581, 1480, 1438 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.87-7.83 (m, 2 H), 7.47 (ddddd, J = 7.9, 7.4, 1.5, 0.4 Hz, 1 H), 7.39-7.36 (m, 4 H), 7.30-7.21 (m, 7 H), 7.06 (s, 1 H), 3.82 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 167.4 (s), 141.2 (s), 134.4 (d), 132.4 (d), 132.3 (d), 130.4 (d), 129.7 (d), 128.8 (d), 128.1 (s), 127.6 (d), 127.6 (d), 54.7 (q), 52.2 (d); exact mass (electrospray) m/z calcd for C₂₁H₁₈NaO₂S₂ (M + Na) 389.0640, found 389.0642.

(2-[Bis(phenylsulfanyl)methyl]phenyl)methanol (37.4).
DIBAL-H (1 M solution in PhMe, 24.6 mL, 24.6 mmol) was added by syringe pump over 20 min to a stirred and cooled (-78 °C) solution of 37.3 (3.49 g, 9.85 mmol) in CH₂Cl₂ (100 mL). After the addition stirring at -78 °C was continued for 1 h and then the cold bath was replaced by an ice bath and stirring was continued for 1 h. The reaction was quenched with water (3.5 mL, 197 mmol) and NaF₂ (8.27 g, 197 mmol) at 0 °C, diluted with Et₂O (100 mL), stirred vigorously for 1 h at room temperature, and filtered through a pad of Celite using Et₂O. Evaporation of the filtrate and flash chromatography of the residue over silica gel (4 x 15 cm), using 40% Et₂O-hexane, gave 37.4 (3.13 g, 94%) as an oil: FTIR (neat) 3396, 3059, 3016, 3003, 2922, 2883, 1602, 1582, 1480, 1452, 1439 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.68 (m, 1 H), 7.40-7.22 (m, 13 H), 5.94 (s, 1 H), 4.66 (s, 2 H), 1.70 (br s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.0 (s), 137.4 (s), 134.2 (s), 132.8 (d), 129.1 (d), 129.0 (d), 128.9 (d), 128.6 (d), 128.3 (d), 128.0 (d), 63.4 (t), 56.8 (d); exact mass (electrospray) m/z calcd for C₂₀H₁₈NaOS₂ (M + Na) 361.0691, found 361.0697.

2-[Bis(phenylsulfanyl)methyl]benzaldehyde (32.7).
Et$_3$N (4.2 mL, 30 mmol) and DMSO (4.2 mL, 60 mmol) were added to a stirred and cooled (0 °C) solution of 37.4 (1.01 g, 3 mmol) in CH$_2$Cl$_2$ (30 mL). Stirring was continued for 5 min and then SO$_3$-py (1.4 g, 9 mmol) was added and stirring was continued for 12 h, the ice bath being left in place but not recharged. The reaction mixture was quenched with water (5 mL) and extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 20% Et$_2$O-hexane, gave 32.7 (798 mg, 79%) as an oil: FTIR (CHCl$_3$, cast) 3057, 3017, 2834, 2745, 1696, 1597, 1581, 1573, 1480, 1449, 1438 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.12 (s, 1 H), 7.85 (d, $J = 7.7$ Hz, 1 H), 7.71 (dd, $J = 7.6$, 1.5 Hz, 1 H), 7.55-7.51 (m, 1 H), 7.43 (td, $J = 7.5$, 1.2 Hz, 1 H), 7.39-7.35 (m, 4 H), 7.24-7.21 (m, 6 H), 6.97 (s, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 192.7 (d), 141.5 (s), 134.1 (d), 134.0 (s), 133.9 (d), 132.6 (d), 132.3 (s), 129.9 (d), 128.9 (d), 128.3 (d), 127.9 (d), 54.1 (d); exact mass (electrospray) m/z calcd for C$_{20}$H$_{16}$NaOS$_2$ (M + Na) 359.0535, found 359.0538.
BuLi (2.5 M in hexane, 0.52 mL, 1.29 mmol) was added dropwise to a stirred and cooled (-20 °C) solution of PhSeSePh (367 mg, 1.17 mmol) in THF (5 mL). After 10 min, the mixture was cooled to -45 °C, a mixture of 25.1 (140 mg, 0.59 mmol) and 32.7 (198 mg, 0.59 mmol) in THF (4 mL) was added dropwise, and stirring was continued for 8 h at -45 °C. Then BnBr (0.18 mL, 1.47 mmol) and Bu₄NI (217 mg, 0.589 mmol) were added and stirring was continued for 8 h at -45 °C to -20 °C. The mixture was quenched with saturated aqueous NH₄Cl (5 mL) and extracted with Et₂O (2 x 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 40% Et₂O-hexanes, gave 32.7a [183 mg, 55 %, 83% after correction for recovered 25.1 (75 mg)]: FTIR (CHCl₃, cast) 3423, 3060, 3020, 2955, 2925, 2869, 1766, 1582, 1480, 1453, 1439 cm⁻¹; ′H NMR (400 MHz, CDCl₃) δ 7.70 (d, J = 6.2 Hz, 1 H), 7.43-7.22 (m, 13 H), 6.71 (dd, J = 1.6, 1.3 Hz, 1 H), 5.90 (s, 1 H), 5.88 (t, J = 1.2 Hz, 1 H), 5.79 (s, 1 H), 3.60 (td, J
= 10.7, 4.3 Hz, 1 H), 2.09-2.04 (m, 2 H), 1.69-1.61 (m, 2 H), 1.34-1.18 (m, 2 H),
1.02-0.75 (m, 13 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.3 (s), 145.2 (d), 138.4 (s), 137.2 (s), 134.1 (s), 133.6 (s), 133.2 (d), 132.8 (d), 129.3 (d), 128.9 (d), 128.9 (d), 128.5 (d), 128.0 (d), 99.4 (d), 79.3 (d), 66.1 (d), 47.7 (d),
40.4 (t), 34.2 (t), 31.4 (d), 25.3 (d), 23.1 (t), 22.2 (d), 20.8 (q), 15.8 (q); exact
mass (electrospray) $m/z$ calcd for C$_{34}$H$_{38}$NaO$_4$S$_2$ (M + Na) 597.2104, found
597.2102.

(S)-(2-[Bis(phenylsulfanyl)methyl]phenyl)[(5R)-5-([(1R,2S,5R)-5-]

methyl-2-(propan-2-yl)cyclohexyl]oxy)-2-oxo-2,5-dihydrofuran-3-yl]methyl
acetate (32.7b).

![Chemical Structure](32.7a.png) → ![Chemical Structure](32.7b.png)

$^{32.7a}$, X = SPh

DMAP (0.5 mg, 0.005 mmol) was added to a stirred solution of $^{32.7a}$ (28
mg, 0.049 mmol) in CH$_2$Cl$_2$ (2 mL). The mixture was then cooled to 0 °C, and
AcCl (0.0104 mL, 0.146 mmol) and pyridine (0.0196 mL, 0.24 mmol) were added
sequentially. The ice bath was left in place but not recharged and stirring was
continued for 3 h, during which time the cold bath reached room temperature.
The reaction mixture was then quenched with saturated aqueous CuSO$_4$ (2 mL)
and water (2 mL), and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et$_2$O-hexane, gave **32.7b** (23 mg, 76%): FTIR (CHCl$_3$, cast) 3060, 3022, 2955, 2924, 2869, 1774, 1745, 1582, 1481, 1454, 1439 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.75-7.73 (m, 1 H), 7.38-7.21 (m, 13 H), 6.94 (s, 1 H), 6.65 (t, $J = 1.4$ Hz, 1 H), 5.96 (s, 1 H), 5.87 (t, $J = 1.1$ Hz, 1 H), 3.59 (td, $J = 10.7$, 4.3 Hz, 1 H), 2.07-1.99 (m, 5 H), 1.67-1.60 (m, 2 H), 1.39-1.33 (m, 1 H), 1.22-1.15 (m, 1 H), 1.01-0.69 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.4 (s), 168.4 (s), 146.7 (d), 137.1 (s), 136.3 (s), 134.1 (s), 133.8 (s), 133.4 (s), 132.7 (d), 132.4 (d), 129.6 (d), 129.2 (d), 128.9 (d), 128.9 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.7 (d), 98.7 (d), 79.0 (d), 66.3 (d), 55.9 (d), 47.7 (d), 40.4 (t), 34.2 (t), 31.4 (q), 25.2 (d), 23.1 (t), 22.2 (d), 20.8 (q), 15.7 (q); exact mass (electrospray) $m/z$ calcd for $C_{36}H_{46}NaO_5S_2$ (M + Na) 639.2209, found 639.2214.

(S)-(2-[Bis(benzenesulfonyl)methyl]phenyl][(5R)-5-{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.7c).

![Chemical Structure](image-url)

32.7b, X = SPh

32.7c, Z = SO$_2$Ph
MCPBA (70%, 58 mg, 0.26 mmol) was added to a stirred and cooled (0 °C) solution of 32.7b (16 mg, 0.026 mmol) in CH\(_2\)Cl\(_2\) (3 mL). The ice bath was left in place but not recharged and stirring was continued for 6 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO\(_3\) (2 mL) and saturated aqueous Na\(_2\)S\(_2\)O\(_3\) (2 mL), and extracted with CH\(_2\)Cl\(_2\) (2 x 10 mL). The combined organic extracts were washed with water and brine, dried (Na\(_2\)SO\(_4\)) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave 32.7c (14 mg, 82%) as a colorless oil: FTIR (CHCl\(_3\), cast) 3067, 3024, 2955, 2926, 2870, 1768, 1584, 1478, 1446 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.92-7.79 (m, 5 H), 7.65-7.60 (m, 2 H), 7.52-7.44 (m, 6 H), 7.34-7.30 (m, 1 H), 6.86 (t, \(J = 1.4\) Hz, 1 H), 6.68 (s, 1 H), 6.43 (s, 1 H), 6.01 (t, \(J = 1.2\) Hz, 1 H), 3.62 (td, \(J = 10.7, 4.3\) Hz, 1 H), 2.13-2.07 (m, 5 H), 1.67-1.61 (m, 2 H), 1.40-1.35 (m, 1 H), 1.26-1.19 (m, 1 H), 1.00-0.74 (m, 12 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 169.6 (s), 168.4 (s), 146.7 (d), 138.2 (s), 137.6 (s), 137.6 (s), 136.1 (s), 134.6 (d), 134.4 (d), 133.7 (d), 131.6 (d), 130.8 (d), 130.2 (d), 130.1 (d), 130.0 (d), 129.8 (d), 129.1 (d), 128.9 (d), 128.8 (d), 128.8 (d), 128.3 (d), 124.0 (s), 99.1 (d), 82.6 (d), 79.5 (d), 65.7 (d), 47.7 (d), 40.6 (t), 34.1 (t), 31.4 (q), 30.9 (d), 25.2 (d), 23.1 (t), 22.2 (q), 20.9 (q), 15.8 (q); exact mass (electrospray) \(m/z\) calcd for C\(_{36}\)H\(_{40}\)NaO\(_5\)S\(_2\) (M + Na) 703.2006, found 703.2001.

2-[(Phenyl-sulfanyl)methyl]benzaldehyde (32.8).
Et$_3$N (2.16 mL, 15.5 mmol) and DMSO (2.2 mL, 31.04 mmol) were added to a stirred and cooled (0 °C) solution of **38.3** (388 mg, 1.55 mmol) in CH$_2$Cl$_2$ (11 mL). Stirring was continued for 5 min and then SO$_3$.py (988 mg, 6.21 mmol) was added. Stirring was continued for 12 h, the ice bath being left in place but not recharged. The reaction mixture was then quenched with water (5 mL) and extracted with CH$_2$Cl$_2$ (2 x 20 mL), and the combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 15% Et$_2$O-hexane, gave **32.8** (343 mg, 89%) as an oil: FTIR (CDCl$_3$, cast) 3059, 3019, 2932, 2836, 2744, 1696, 1598, 1575, 1481, 1451, 1439, 1402 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 10.23 (s, 1 H), 7.85-7.83 (m, 1 H), 7.49-7.41 (m, 2 H), 7.34-7.21 (m, 6 H), 4.53 (s, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 192.0 (d), 139.8 (s), 135.3 (s), 133.7 (s), 133.6 (d), 132.8 (d), 131.3 (d), 131.2 (d), 128.9 (d), 127.8 (d), 127.1 (d), 36.3 (t); exact mass (EI) $m/z$ calcd for C$_{14}$H$_{12}$OS (M) 228.0608, found 228.0610.
(5R)-3-[(S)-Hydroxy([2-[(phenylsulfanyl)methyl]phenyl)methyl]-5-\{[(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy\}-2,5-dihydrofuran-2-one (32.8a).

BuLi (2.5 M in hexane, 80 µL, 0.20 mmol) was added dropwise to a stirred and cooled (-20 °C) solution of PhSeSePh (63 mg, 0.20 mmol) in THF (2 mL). After 10 min, the mixture was cooled to -45 °C, a mixture of 25.1 (78 mg, 0.33 mmol) and 32.8 (90 mg, 0.39 mmol) in THF (2 mL) was added dropwise, and stirring was continued for 8 h at -45 °C. Then BnBr (44 µL, 0.36 mmol) and Bu₄NI (12 mg, 0.036 mmol) were added and stirring was continued for 8 h at -45 °C to -20 °C. The mixture was quenched with saturated aqueous NH₄Cl (5 mL) and extracted with Et₂O (2 x 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 40% Et₂O-hexanes, gave 32.8a [78 mg, 56%, 87% after correction for recovered 25.1 (32 mg)]: FTIR (microscope) 3452, 3060, 2954, 2924, 2869, 1768, 1584, 1481, 1454, 1439 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, J = 7.7, 1.2 Hz, 1 H), 7.34-7.17 (m, 8 H), 6.88 (t, J = 1.5 Hz, 1 H), 6.02 (t, J = 1.3 Hz, 1 H), 5.93 (s, 1 H), 4.36 (d, J = 12.6 Hz, 1 H), 4.15 (d, J =
12.7 Hz, 1 H), 3.64 (td, J = 10.7, 4.3 Hz, 1 H), 3.16 (s, 1 H), 2.14-2.04 (m, 2 H), 1.70-1.63 (m, 2 H), 1.44-1.21 (m, 2 H), 1.07-0.76 (m, 12 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.2 (s), 144.5 (d), 139.2 (s), 138.3 (s), 135.2 (s), 134.7 (s), 130.9 (d), 130.8 (d), 129.0 (d), 128.5 (d), 128.2 (d), 127.6 (d), 127.1 (d), 99.3 (d), 79.2 (d), 65.8 (d), 47.7 (d), 40.4 (t), 37.1 (t), 34.2 (t), 31.5 (d), 25.5 (d), 23.3 (t), 22.2 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) \(m/z\) calcd for \(\text{C}_{28}\text{H}_{34}\text{NaO}_4\text{S} (\text{M} + \text{Na})\) 489.207, found 489.2070.

\((S)-(5R)-5-\{(1R,2S,5R)-5\text{-methyl-2-(propan-2-yl)cyclohexyl}oxy\}-2-\text{oxo-2,5-dihydrofuran-3-yl}\{2-\{(\text{phenylsulfanyl})\text{methyl}\}\text{phenyl}\})\text{methyl acetate (32.8b).}

\[\text{\includegraphics{32.8a}}\rightarrow\text{\includegraphics{32.8b}, }X = \text{SPh}\]

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.8a (20 mg, 0.043 mmol) in CH\(_2\)Cl\(_2\) (2 mL). The mixture was then cooled to 0 °C, and AcCl (9.1 µL, 0.13 mmol) and pyridine (21 µL, 0.25 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous CuSO\(_4\) (2 mL) and
water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et$_2$O-hexane, gave 32.8b (21 mg, 96%) as a colorless oil: FTIR (CHCl$_3$, cast) 3060, 2955, 2925, 2869, 1771, 1748, 1659, 1600, 1584, 1481, 1455, 1439 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41 (dd, $J = 7.6$, 1.1 Hz, 1 H), 7.36-7.18 (m, 8 H), 6.94 (t, $J = 1.3$ Hz, 1 H), 6.83 (t, $J = 1.4$ Hz, 1 H), 6.03 (t, $J = 1.2$ Hz, 1 H), 4.36 (d, $J = 13.0$ Hz, 1 H), 4.31 (d, $J = 13.0$ Hz, 1 H), 3.64 (td, $J = 10.7$, 4.2 Hz, 1 H), 2.12-2.03 (m, 5 H), 1.69-1.62 (m, 2 H), 1.43-1.36 (m, 1 H), 1.26-1.20 (m, 1 H), 1.02-0.73 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.5 (s), 168.6 (s), 146.0 (d), 137.0 (s), 135.8 (s), 135.3 (s), 135.0 (s), 130.7 (d), 130.4 (d), 128.9 (d), 128.9 (d), 128.1 (d), 127.9 (d), 126.6 (d), 98.7 (d), 79.0 (d), 66.4 (d), 47.8 (d), 40.4 (t), 36.7 (t), 34.2 (t), 31.5 (q), 25.4 (d), 23.3 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) $m/z$ calcd for C$_{30}$H$_{36}$NaO$_5$S (M + Na) 531.2175, found 531.2172.

(S)-(2-[(Benzenesulfonyl)methyl]phenyl)[(5R)-5-[((1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy]-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.8c).
MCPBA (70%, 102 mg, 0.41 mmol) was added to a stirred and cooled (0 °C) solution of 32.8b (21 mg, 0.041 mmol) in CH₂Cl₂ (3 mL). The ice bath was left in place but not recharged and stirring was continued for 4 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (2 mL), and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et₂O-hexane, gave 32.8c (22 mg, 100%) as a colorless oil: FTIR (CH₂Cl₂, cast) 3065, 2955, 2926, 2870, 1768, 1585, 1496, 1448 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.88-7.85 (m, 2 H), 7.67-7.52 (m, 4 H), 7.41 (td, J = 7.6, 1.4 Hz, 1 H), 7.31 (td, J = 7.5, 1.4 Hz, 1 H), 7.21 (dd, J = 7.8, 1.3 Hz, 1 H), 6.93 (t, J = 1.4 Hz, 1 H), 6.78 (t, J = 1.4 Hz, 1 H), 6.04 (t, J = 1.3 Hz, 1 H), 4.69 (d, J = 14.1 Hz, 1 H), 4.62 (d, J = 14.1 Hz, 1 H), 3.61 (td, J = 10.7, 4.3 Hz, 1 H), 2.12-2.01 (m, 5 H), 1.68-1.60 (m, 2 H), 1.43-1.32 (m, 1 H), 1.26-1.19 (m, 1 H), 1.01-0.70 (m, 12 H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8 (s), 168.8 (s), 145.1 (d), 139.1 (s), 137.0 (s), 136.8 (s), 133.8 (d), 133.0 (d), 129.5 (d), 129.2 (d), 129.1 (d), 129.0 (d), 128.4 (d), 126.4 (s), 99.2 (d), 79.2 (d), 66.7 (d), 59.4 (t), 47.7 (d), 40.6 (t), 34.2 (t), 31.4 (q), 25.3 (d), 23.2 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.8 (q); exact
mass (electrospray) $m/z$ calcd for $C_{30}H_{36}NaO_7S$ (M + Na) 563.2074, found 563.2074.

2-{2-[Bis(phenylsulfanyl)methyl]phenyl}acetaldehyde (32.9).

(Me$_3$Si)$_2$NNa (1 M in THF, 7.13 mL, 7.13 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of (methoxy-methyl)triphenylphosphonium chloride (3.26 g, 9.5 mmol) in THF (20 mL). The resulting slurry was stirred for 90 min at -78 °C and then a solution of 32.7 (798 mg, 2.38 mmol) was added dropwise over 5 min. The cold bath was left in place but not recharged and stirring was continued for 12 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (ca 10 mL) and extracted with Et$_2$O. The combined organic extracts were washed with brine (20 mL), dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 5% Et$_2$O-hexane, gave 39.1, which was used for the next step.

Hydrochloric acid (4 M, 4 mL) was added to a solution of 39.1 in THF (15 mL) and the mixture was refluxed at 66 °C for 3 h, cooled, quenched with
saturated aqueous NaHCO₃ (ca 5 mL), diluted with water (20 mL) and extracted with Et₂O (50 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 10% Et₂O-hexane, gave 32.9 (464 mg, 56% over two steps) as an oil: FTIR (CDCl₃, cast) 3058, 3019, 2822, 2724, 1721, 1581, 1480, 1448, 1438, 1415 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.53 (t, J = 2.3 Hz, 1 H), 7.71 (d, J = 6.9 Hz, 1 H), 7.37-7.24 (m, 12 H), 7.15 (dd, J = 7.2, 1.8 Hz, 1 H), 5.54 (s, 1 H), 3.71 (d, J = 1.9 Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 199.0 (d), 138.5 (s), 133.9 (s), 133.0 (d), 131.2 (d), 129.7 (s), 129.5 (d), 129.0 (d), 128.5 (d), 128.2 (d), 128.2 (d), 57.9 (d), 47.9 (t); exact mass (electrospray) m/z calcd for C₂₁H₁₈NaOS₂ (M + Na) 373.0691, found 373.0695.

(4R)-2-(2-(2-[Bis(benzenesulfonyl)methyl]phenyl)-1-hydroxyethyl)-4-{{(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl}oxy}-2-(phenylselanyl)-cyclopentan-1-one (32.9a, 32.9a').

(Me₃Si)₂NK (0.5 M in PhMe, 0.92 mL, 0.46 mmol) was added dropwise (over ca 10 min) to a stirred and cooled (−78 °C) solution of lactone 27.1 (166 mg,
0.42 mmol) in THF (5 mL). Stirring at -78 °C was continued for 45 min and then a solution of aldehyde 32.9 (165 mg, 0.47 mmol) in THF (2 mL) was added. Stirring at -78 °C was continued for 20-30 min (TLC control, silica, 40% Et₂O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH₄Cl (3 mL) was added and the mixture was extracted with Et₂O. The combined organic extracts were dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 40% Et₂O-hexane gave 32.9a and 32.9a' as an oil. This mixture of diastereoisomers was used directly for next step.

\[(4R)-2-[2-\{2-[\text{Bis(benzenesulfonyl)methyl} phenyl]-1\text{-hydroxyethyl}\}-4-\{[(1R,2S,5R)-5\text{-methyl}-2\text{-propan-2-yl} cINDOW \text{cyclohexyl}oxy\}cycinpent-2\text{-en-1-one} \] (32.9b, 32.9b').

\[32.9a, 32.9a', X = SPh \quad 32.9b, 32.9b', Z = \text{SO}_2\text{Ph} \]

MCPBA (70%, 1.27 g, 5.1 mmol) was added to a stirred and cooled (0 °C) solution of 32.9a and 32.9a' (192 mg, 0.26 mmol) in CH₂Cl₂ (5 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (2 mL) and extracted with CH₂Cl₂. The
combined organic extracts were washed with water and brine, dried (Na$_2$SO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et$_2$O-hexane, gave a mixture of diastereomers which was separated into three fractions (more polar, 13 mg, 5%; less polar, 10 mg, 4%; mixture, 73 mg, 27%). The more polar alcohol 32.9b had: FTIR (CDCl$_3$, cast) 3508, 3067, 2954, 2928, 2871, 1754, 1584, 1493, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.99 (dd, $J = 7.9, 1.3$ Hz, 1 H), 7.84-7.78 (m, 4 H), 7.66-7.62 (m, 2 H), 7.47 (t, $J = 7.5$ Hz, 4 H), 7.38 (td, $J = 7.5, 1.4$ Hz, 1 H), 7.31 (td, $J = 7.6, 1.3$ Hz, 1 H), 7.15 (dd, $J = 7.6, 1.3$ Hz, 1 H), 6.95 (t, $J = 1.4$ Hz, 1 H), 6.31 (s, 1 H), 6.02 (t, $J = 1.4$ Hz, 1 H), 4.60-4.58 (m, 1 H), 3.65 (td, $J = 10.7, 4.3$ Hz, 1 H), 2.77 (dd, $J = 14.5, 2.6$ Hz, 1 H), 2.42 (dd, $J = 14.5, 9.0$ Hz, 1 H), 2.16-2.10 (m, 2 H), 1.71-1.66 (m, 2 H), 1.41-1.37 (m, 1 H), 1.30-1.21 (m, 2 H), 1.05-0.82 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.1 (s), 143.8 (s), 139.1 (s), 139.0 (s), 138.5 (s), 138.0 (s), 134.7 (s), 134.5 (s), 131.8 (s), 131.5 (s), 130.9 (s), 130.0 (s), 129.6 (s), 128.9 (s), 128.9 (s), 127.6 (s), 124.6 (s), 99.4 (s), 82.7 (s), 79.3 (s), 68.6 (s), 47.8 (s), 40.4 (s), 39.0 (s), 34.2 (s), 31.6 (s), 25.4 (s), 23.2 (s), 22.3 (s), 21.0 (s), 15.9 (q); exact mass (electrospray) $m/z$ calcd for C$_{35}$H$_{40}$NaO$_8$S$_2$ (M + Na) 675.2057, found 675.2046.

The less polar alcohol 32.9b' had: FTIR (CDCl$_3$, cast) 3503, 3067, 2955, 2928, 2870, 1753, 1599, 1584, 1493, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.99-7.94 (m, 1 H), 7.85-7.77 (m, 4 H), 7.66-7.57 (m, 3 H), 7.49-7.28 (m, 5 H), 7.14 (dd, $J = 7.6, 1.3$ Hz, 1 H), 6.96 (t, $J = 1.4$ Hz, 1 H), 6.39 (s, 1 H), 6.00 (s, 1 H), 4.61-4.59 (m, 1 H), 3.66 (td, $J = 10.7, 4.3$ Hz, 1 H), 2.84 (dd, $J = 14.5, 2.7$ Hz,
1.08-0.81 (m, 12 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) \(^{13}\)C NMR (CDCl\(_3\), 126 MHz) \(\delta\) 170.1 (s), 144.1 (d), 139.1 (s), 139.0 (s), 138.5 (s), 137.9 (s), 135.4 (d), 134.6 (d), 134.5 (d), 133.7 (d), 131.7 (d), 131.5 (d), 130.8 (d), 130.0 (d), 129.6 (d), 128.9 (d), 128.9 (d), 128.8 (d), 128.3 (d), 127.5 (d), 124.6 (s), 99.3 (d), 82.7 (d), 79.2 (d), 68.6 (d), 47.8 (d), 40.3 (d), 38.5 (d), 34.2 (d), 31.5 (d), 25.4 (d), 23.2 (t), 22.2 (q), 20.9 (q), 15.9 (q); exact mass (electrospray) \(m/z\) calcd for C\(_{35}\)H\(_{40}\)NaO\(_8\)S\(_2\) (M + Na) 675.2057, found 675.2058.

(1\(S\))-2-\{2-[Bis(benzenesulfonyl)methyl]phenyl\}-1-\{(3\(R\))-3-{[(1\(R\),2\(S\),5\(R\))-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-5-oxocyclopent-1-en-1-yl\}ethyl acetate (32.9\(c\), 32.9\(c'\)).

![Chemical diagram]

32.9\(b\), 32.9\(b'\) 32.9\(c\), 32.9\(c'\) \(Z = SO_2Ph\)

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of 32.9\(b\) and 32.9\(b'\) (73 mg, 0.11 mmol) in CH\(_2\)Cl\(_2\) (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.048 mL, 0.67 mmol) and pyridine (0.072 mL, 0.89 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature.
The reaction mixture was quenched with saturated aqueous CuSO$_4$ (2 mL) and water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave as a mixture of diastereomers which was separated into two fractions (less polar, 22 mg, 28%; mixture, 42 mg, 55%). The less polar isomer **32.9c** had: FTIR (CDCl$_3$, cast) 3066, 2954, 2928, 2870, 1758, 1748, 1584, 1491, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.16 (dd, $J = 7.8$, 1.3 Hz, 1 H), 7.94 (dd, $J = 8.3$, 1.0 Hz, 2 H), 7.71-7.64 (m, 3 H), 7.59-7.49 (m, 3 H), 7.40-7.28 (m, 4 H), 6.98 (dd, $J = 7.5$, 1.3 Hz, 1 H), 6.81 (t, $J = 0.9$ Hz, 1 H), 6.35 (s, 1 H), 5.86 (s, 1 H), 5.62 (t, $J = 7.3$ Hz, 1 H), 3.61 (td, $J = 10.7$, 4.3 Hz, 1 H), 2.87 (dd, $J = 14.3$, 7.3 Hz, 1 H), 2.50 (dd, $J = 14.3$, 7.4 Hz, 1 H), 2.12-2.04 (m, 5 H), 1.68-1.64 (m, 2 H), 1.41-1.34 (m, 1 H), 1.25-1.19 (m, 1 H), 1.00-0.75 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.2 (s), 169.2 (s), 147.0 (d), 138.7 (s), 138.1 (s), 137.7 (s), 134.5 (d), 134.4 (d), 134.1 (s), 132.0 (d), 131.2 (d), 130.5 (d), 129.9 (d), 129.6 (d), 128.9 (d), 128.8 (d), 127.7 (d), 124.4 (s), 99.1 (d), 82.0 (d), 79.8 (d), 69.3 (d), 47.7 (d), 40.4 (t), 35.0 (t), 34.1 (t), 31.5 (q), 25.4 (d), 23.1 (t), 22.2 (d), 20.9 (q), 20.9 (q), 15.9 (q); exact mass (electrospray) $m/z$ calcd for C$_{37}$H$_{42}$NaO$_9$S$_2$ (M + Na) 717.2162, found 717.2162.

The mixture of isomers (containing mainly the more polar) **32.9c** had: FTIR (CDCl$_3$, cast) 3067, 2955, 2928, 2870, 1807, 1758, 1748, 1584, 1492, 1448 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.15-7.97 (m, 3 H), 7.75-7.64 (m, 3 H), 7.62-7.31 (m, 7 H), 7.03-6.99 (m, 1 H), 6.85-6.83 (m, 1 H), 6.42-6.39 (m, 1 H), 5.99-
5.90 (m, 1 H), 5.73-5.65 (m, 1 H), 3.67-3.57 (m, 1 H), 2.91 (dd, $J = 14.2, 7.6$ Hz, 1 H), 2.64-2.51 (m, 1 H), 2.15-2.04 (m, 5 H), 1.72-1.66 (m, 2 H), 1.45-1.37 (m, 1 H), 1.29-1.20 (m, 1 H), 1.06-0.78 (m, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.2 (s), 169.3 (s), 147.5 (d), 139.0 (s), 138.8 (s), 138.1 (s), 137.8 (s), 137.7 (s), 137.5 (s), 135.4 (d), 134.6 (d), 134.5 (d), 134.5 (d), 134.4 (d), 134.2 (d), 133.9 (s), 132.0 (d), 131.9 (d), 131.3 (d), 131.3 (d), 130.8 (d), 130.5 (d), 130.5 (d), 130.0 (d), 129.9 (d), 129.9 (d), 129.7 (d), 129.7 (d), 129.6 (d), 128.9 (d), 128.9 (d), 128.9 (d), 128.8 (d), 128.8 (d), 128.7 (d), 128.7 (d), 128.7 (d), 128.7 (d), 128.7 (d), 127.7 (d), 127.7 (d), 124.4 (s), 124.4 (s), 99.1 (d), 98.7 (d), 82.1 (d), 82.0 (d), 79.8 (d), 78.5 (d), 69.4 (d), 69.4 (d), 47.7 (d), 47.7 (d), 40.5 (t), 40.1 (t), 35.0 (t), 34.9 (t), 34.2 (t), 34.2 (t), 31.5 (q), 31.5 (q), 25.4 (d), 25.3 (d), 23.1 (t), 22.2 (t), 22.2 (d), 21.0 (q), 21.0 (q), 20.9 (q), 20.9 (q), 15.9 (q); exact mass (electrospray) $m/z$ calcd for $C_{37}H_{42}NaO_{9}S_{2}$ (M + Na) 717.2162, found 717.2163.
References


(40) An American supplier of this BASF catalyst is Research Catalysts, Inc., P.O. Box 981014, Houston, Texas 77098.

(41) Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (985 mL) and concentrated sulfuric acid (15 mL).

Chapter 2

Studies towards the total synthesis of the marine alkaloid

sorbicillactone A
1. **Introduction**

1.1 **Isolation of sorbicillin**

Sorbicillin (1.1) is a hexaketide isolated in 1948 by Cram and Tishler of Merck & Co. from the fungus *Pencillium notatum*.\(^{1a,b}\) In 1953 Arima and co-workers in Japan reported isolation of this compound from *Penicillium chrysogenum*.\(^2\) For several decades this remained the only example of a hexaketide in which cyclization had taken place on the carboxylate terminus (see later, Scheme 5).\(^3\)

\[
\begin{align*}
\text{OH} & \quad \text{Me} \\
\text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{O} \\
\text{HO} & \quad \text{Me}
\end{align*}
\]

Scheme 1

There are a number of natural products evidently derived from sorbicillin or by related biosynthetic pathways. All of these compounds can be categorized into monomeric, dimeric, trimeric, or polycyclic sorbicillinoids, vertinolides or nitrogen-containing sorbicillinoids.\(^3\) The structures of several of these compounds are shown in Scheme 2.
Sorbicillactone A (3.1) and its 2',3'-dihydro analogue, sorbicillactone B (3.2) are the first nitrogen-containing sorbicillinoids.
1.2 Isolation and structure determination of sorbicillactone A

In the search for new bioactive compounds from marine sponges and their associated microorganisms, Bringmann and co-workers in 2003 isolated novel alkaloids sorbicillactone A and sorbicillactone B.\textsuperscript{4a,b} These compounds are produced by a saltwater culture of a \textit{Pencillium chrysogenum} strain isolated from the Mediterranean sponge \textit{Ircinia fasciculate}.

For investigation of the secondary metabolic profile, the fungus was propagated as a 10-L culture in a saline medium for 14 days. After this period, both the mycelium and culture broth were extracted with organic solvents, and the extracts were subjected to detailed chromatographic analysis. Two metabolites were identified as meleagrine (\textit{4.1}) and roquefortine C (\textit{4.2}) by comparing their UV spectra with a commercially available natural product database.\textsuperscript{4a,b}

![Scheme 4](image-url)
Besides these known compounds several other peaks were detected in the chromatograms. The most prominent of these peaks were thoroughly investigated using HPLC-NMR, and the evidence indicated the presence of a sorbyl residue (4.3). The UV spectrum of the compound containing this residue showed some similarity to the spectra of the so-called bisorbicillinoids (e.g. 2.2). But HPLC-MS showed a molecular mass of 417 which was too low for the compound to belong to the bisorbicillinoids, and did not fit any of the few known monomeric sorbicillin-derived natural products.4,6a,b

Bringmann and coworkers isolated the new compounds by preparative HPLC on an RP-18 phase column and obtained 6 mg of the compound.4a,b Extensive 2D-NMR and mass spectrometry measurements were carried out in Bringmann's group and allowed the structure of the new compounds to be identified as sorbicillactone A (3.1) and sorbicillactone B (3.2). The absolute configuration of the compounds was elucidated by quantum mechanical calculation of circular dichroism (CD) spectra and comparison with experimental measurements.

1.3 Biosynthesis of sorbicillactone A

There is little biosynthetic work published, but the general belief is that sorbicillactone A and sorbicillactone B are derived as shown in Scheme 5. After optimizing the growth conditions of the fungus Penicillium chrysogenum for the production of sorbicillactone A, Bringmann and co-workers carried out labeling experiments to study the biosynthesis of this molecule, the results of which are
discussed below, using the non-systematic skeletal numbering of his original publications.\textsuperscript{4a}

Feeding experiment performed in Brigmann's group with \([^{13}\text{C}_2]\)-acetate showed high incorporation of \(^{13}\text{C}\) in all position of the six membered ring and the sorbyl chain, but no labeling at all at C-9, C-10 and C-11, nor at the methyl carbons C-7 and C-8. This observation firmly established the polyketide origin of this family of compounds. Administration of \([^{13}\text{C}_3]\)-L-alanine to the fungus resulted in a significantly higher concentration of \(^{13}\text{C}\) at the C-9, C-10 and C-11 positions. These results clearly indicated that the C\textsubscript{3} unit forming the lactone ring is derived directly from alanine (possibly activated by Schiff base formation with pyridoxal phosphate). Feeding of \([\text{methyl}^{13}\text{C}]\)-L-methionine led to a significant increase in the relative intensity of the C-7 and C-8 signals in the \(^{13}\text{C}\) NMR spectrum of sorbicillactone A, which showed that the methyl carbons C-7 and C-8 are incorporated, presumably by methyl transfer from S-adenosylmethionine. But the fumaryl residue showed a weaker labeling pattern in all the above feeding experiments. Also, the labeling pattern of the amidic side chain was found to be non-symmetric, which clearly indicated that this residue, at least partially, was derived from an unsymmetrical compound. Furthermore, feeding of \([^{13}\text{C}_4]\)-fumaric acid did not result in labeling of the fumaryl side chain and this fact indicated that fumaric acid itself is not the biosynthetic precursor of this side chain; however, it may be formed from a biosynthetic equivalent of fumaric acid. Results from the Abe group\textsuperscript{7} and the Bringmann group\textsuperscript{4a,b} showed the carbon skeleton of sorbicillactone A is derived from a sorbicillinol unit (5.2). Based on
these feeding experiments, Bringmann and co-workers proposed the biosynthetic route to sorbicillactone A outlined in Scheme 5.

Scheme 5
1.4 Biological properties and biotechnological production of sorbicillactone A

The novel structural features of sorbicillactone A and sorbicillactone B made them attractive candidates for biological studies.$^{3,4a,b}$

Bringmann and co-workers studied the biological properties of both sorbicillactone A and sorbicillactone B. Sorbicillactone A showed significant cytotoxic/cytostatic activity against murine leukemic lymphoblast L5178y cells with an IC$_{50}$ value of 2.2 µg/mL. But against rat pheochromocytoma PC12 cells, human T lymphocyte H9 cells and human cervix carcinoma HeLa S3 cells its IC$_{50}$ value was > 10 µg/mL. On the other hand, the structurally related sorbicillactone B exhibited a significantly lower activity than sorbicillactone A with IC$_{50}$ values > 10 µg/mL for L5178y, PC13 and HeLa cells.

Besides its cytotoxicity, sorbicillactone A also showed high anti-HIV activity. In the concentration range between 0.3-3.0 mg/mL, sorbicillactone A protected human T lymphocytes (H9 cells) against the cytopathic effect of HIV-1 and inhibited the expression of viral proteins.$^{8,9}$ Results obtained from Bringmann's group on the effect of sorbicillactone A on calcium ion concentration in primary neurons after stimulation with serotonin showed that sorbicillactone A can be considered as a promising neuroprotective compound. Overall, the biological properties of sorbicillactone A include selective anti-leukemia activity without showing significant cytotoxicity, and also antiviral as well as neuroprotective properties. It could, therefore, be a potential new lead structure in medicinal chemistry.$^{4a,b}$
The initial amount of sorbicillactone A produced was approximately 4 mg/L (range 2-6 mg/L).\(^\text{10}\) In order to increase the yield and to adapt the production to amounts sufficient for preclinical and clinical studies, the Bringmann group in 2007 developed an efficient process for the biotechnological large scale production of sorbicillactone A. By this procedure they were able to isolate 100 g of pure sorbicillactone A for ongoing preclinical studies on this potential antitumor drug.\(^\text{10}\)

1.5 Synthetic studies of sorbicillactone A reported in the literature

1.5.1 Harned's synthesis of racemic sorbicillactone A

So far, there is only one total synthesis of sorbicillactone A (racemic) reported in the literature by Harned's group in 2011.\(^\text{11}\)
The synthetic plan used by Harned's group is depicted in Scheme 6, in which the sorbyl side chain was installed at a late stage through the use of a bicyclic intermediate similar to 6.1. The key bond formation, C3-C3a, was established through an intramolecular conjugate displacement of activated (by “Z-group”) dienone 6.2 which, in turn, can be synthesized from 6.3. Based on this strategy, phenol 6.4 was chosen as the starting material.

**Scheme 7**
The synthesis in Harned's group began with commercially available 2-
methylresorcinol (7.1). Vilsmeier-Haack reaction to introduce a formyl group
adjacent to one hydroxyl, selective O-benzylation and methylation of both
hydroxyl groups, followed by aldehyde reduction and exhaustive hydrogenolysis
resulted in the formation of 6.4 from 7.1. Oxidative dearomatization of 6.4
produced quinol 6.3 in 80% yield. Acylation of the quinol using a malonic acid
monoester then produced dienone 7.2. Harned's group used a malonic acid unit as
an activating group for a Michael addition and also as a masked amine group that
could be revealed later through a Curtius rearrangement. Malonate 7.2 was
cyclized to provide bicyclic lactone 7.3 in the presence of Cs$_2$CO$_3$.

The critical alkylation of the bicyclic lactone was carried out by using
MeI, but the desired isomer [7.4a, with an exo methyl group at C-3] for the
synthesis of sorbicillactone A was obtained only in poor yield. Very recently,
Harned has reported an explanation for this unusual stereochemical outcome.$^{12}$
According to his explanation, alkylation involving methyl iodide proceeds from
the concave (endo) face of the bicyclo[4.3.0]nonene ring system, whereas carbon-
based electrophiles larger than methyl iodide approach from the convex (exo) face
(Scheme 8). Computational studies, using M06-2X and B3LYP methods, have
revealed that the observed stereoselectivity is due to a subtle energetic difference
between a staggered transition state with less torsional strain and an unfavorable
steric interaction with the cyclohexenone ring.$^{12}$
When the electrophile approaches from the *endo* face, the dihedral angle between Ca-Cb-Cc-Cd is \( \sim 75^\circ \), whereas for *exo* approach this angle is only \( 15^\circ \). Compression of this dihedral angle creates a torsional strain in the system for the *exo* approach. Therefore, the small electrophile methyl iodide approaches from the *endo* face. On the other hand, in the case of larger electrophiles steric hindrance experienced from the cyclohexenone ring in approach from the *endo* face is severe, and outweighs the unfavorable factors that otherwise impede approach from the *exo* face.

To finish the synthesis of sorbicillactone A, Harned and co-workers converted the *tert*-butyl ester in **7.4a** into acyl azide **9.1**. Curtius rearrangement of **9.1**, followed by acylation of the resulting amine, gave amide **9.2**, which was then subjected to C-acylation at C-4 to produce compound **9.3**. Finally, cleavage of the methyl ether and *tert*-butyl ester completed the total synthesis of sorbicillactone A (**3.1**). Even though Harned's group was able to finish the synthesis of racemic sorbicillactone A, their product was stated to be impure and the yield in the last two last steps was only 12%. As indicated above, the yield of the desired isomer in the critical methylation was 15%.
1.5.2 The Clive synthesis of optically pure bicyclic γ-lactones

In 2010, Clive and Sunasee described a desymmetrization process whereby the symmetrical dienone 10.1 was converted into optically pure lactone 10.5 using a free radical cyclization (Scheme 10).\textsuperscript{13} The product had the absolute configuration corresponding to that of the core of sorbicillactone A.

Scheme 9
In this desymmetrization strategy stereoinduction occurs via a covalently bonded chiral sugar moiety. In the presence of NIS, the tertiary alcohol 10.1 reacted with glycal 11.1 to provide a single iodo-ether 11.2, which underwent stannane-mediated radical cyclization to gave the cyclized product 11.3 as a single isomer. Acid hydrolysis of 11.3 released the diol 11.4; this was then cleaved by treatment with Pb(OAc)$_4$ in the presence of Na$_2$CO$_3$ to dialdehyde 11.5. The dialdehyde was subjected to acid hydrolysis with dilute H$_2$SO$_4$, followed by Jones oxidation of the resulting crude product, to give lactone 10.5 as a single isomer.$^{13}$
Apart from this work and that of the Harned group, there have been no reports on synthetic activity in this field, although the synthesis of a compound called (±)-fumimycin (12.9) that has some resemblance to sorbicillactone A was reported by Bräse and co-workers in 2010.14
1.5.3 Total synthesis of fumimycin

Both sorbicillactone A and fumimycin possess a six-membered ring fused to a five-membered lactone as a skeleton and have an α-trisubstituted amine linked to a fumaric acid moiety. The total synthesis of fumimycin by the Bräse group is summarized in Scheme 12.\textsuperscript{14}

The Bräse group started their synthesis with vanillin (12.1), which was first allylated, then subjected to Dakin oxidation, followed by Friedel-Crafts acylation and silylation to give ketone 12.2. The ketone was then subjected to oxime formation, diphenylphosphinic amide formation and selective 1,2-addition with MeMgBr to provide phosphinic amide 12.3. Thermal lactonization of 12.3, followed by Claisen rearrangement and subsequent isomerization of the terminal double bond, gave olefin 12.4 (trans/cis 10:1). The isomers were separated by column chromatography. Cleavage of the methyl ether and selective silylation of the hydroxyl group, followed by deprotection of the amide, gave amine 12.6. Finally, acylation of the amine, using acid chloride 12.7, and cleavage of the silyl ether and \textit{tert}-butyl ester completed the total synthesis of fumimycin (12.9).
Scheme 12
2. Results and Discussion

The aim of my project was to make racemic sorbicillactone A from racemic 10.5, and then to apply the same route to optically pure 10.5, which can be synthesized as shown in Scheme 11, and thus achieve the synthesis of (-)-sorbicillactone A.

2.1 Retrosynthetic analysis of sorbicillactone A

![Scheme 13](image-url)
In principle, sorbicillactone A can be synthesized from 13.2 by attaching the side chains by N-acylation and an aldol reaction. Compound 13.2, in turn, should be available from 13.3 by α-amination followed by α-alkylation. Functional group manipulation of 10.5 can give 13.3. The core 10.5 is the result of a radical cyclization of compound 13.4, which can be synthesized from 10.1 by O-acylation. The dienone 10.1 has been prepared from p-cresol (13.5).

2.2 Synthetic studies towards sorbicillactone A

Our synthetic studies towards sorbicillactone A began with commercially available p-cresol (13.5). Oxidation with Oxone in the presence of NaHCO₃ in MeCN-H₂O, using a procedure developed by Carreño and co-workers,¹⁵ gave cyclohexadienone 10.1 in 64% yield. Acylation of the hydroxyl group of 10.1 with bromoacetyl bromide produced 14.1 in 76% (crude yield), which was then subjected to Finkelstein reaction with NaI to give the iodo-ester 13.4. This underwent radical cyclization under stannane-mediated conditions, giving the cyclized product 10.5 (racemic) in 84% yield.
After the synthesis of the bicyclic core, we studied the installation of the methyl group at C-6. The first approach was to try metal-halogen exchange chemistry. Bromination of 10.5, using Br₂ and Et₃N, gave the desired bromo compound 15.1 (Scheme 15), but all attempts to replace the halogen by a methyl unit failed to give the desired product 15.3. As this outcome might be due to the presence of acidic hydrogens in the molecule, we protected the ketone as the cyclic ketal 15.2, using 1,2-bis(trimethylsiloxy)ethane and Me₃SiOSO₂CF₃. However, subsequent attempts at methylation (15.2→15.4) again failed.
At this point, we reacted the bicyclic ketal 15.2 with LDA or KHMDS and MeI to study the stereochemical outcome of alkylation at C-3 (Scheme 16).

The desired C-3 methylated bicyclic lactone 16.1 was obtained in 70% yield as a single isomer. Moreover, X-ray crystallographic analysis of 16.1
(Figure 1) showed that the stereochemistry obtained at C-3 was opposite to that observed by Harned and co-workers.\textsuperscript{11} In our case the alkylation at C-3 occurs from the more accessible \textit{exo} face. From this experiment, it is clear that in order to get the proper stereochemistry of sorbicillactone A at C-3, the nitrogen unit must be installed before the methyl unit.

![Figure 1. ORTEP diagram of compound 16.1](image)

Our second approach was to do a conjugate addition on the bicyclic lactone \textbf{10.5}, using a phenyldimethylsilyl cuprate, and then to quench the intermediate \textbf{17.1} with methyl iodide so as to form compound \textbf{17.2}. The silicon
group would then be replaced by a hydroxyl group via a Fleming-Tamao oxidation\textsuperscript{16} to afford \textbf{17.3} (Scheme 17).

![Scheme 17](image)

In order to achieve the synthesis of compound \textbf{17.2}, we first treated the bicyclic lactone \textbf{10.5} with PhMe\textsubscript{2}SiLi and CuI, followed by MeI. The desired product was obtained in very low yield, but we were able to isolate an inseparable mixture of the two silanes \textbf{18.1} in 40% yield. The isomers \textbf{18.1} were separable after protecting the ketone as the cyclic ketals \textbf{18.2} (Scheme 18).
Fortunately, by changing the source of copper from CuI to CuCN, we were able to synthesize the desired bicyclic lactone 17.2 in 80% yield as a single isomer (Scheme 19). X-ray crystallographic analysis of 17.2 showed that both substituents at C-6 and C-7 are equatorial (Figure 2).
After the synthesis of silyl bicyclic lactone 17.2, the next step was to replace the silyl group by a hydroxyl group via a Fleming-Tamao oxidation. Fleming and co-workers reported that the presence of a ketone group can be problematic for this step, and so we first tried to protect the ketone in 17.2 as a cyclic ketal 19.1 (Scheme 19).

Figure 2. ORTEP diagram of compound 17.2
Scheme 19

The protected cyclic ketal was isolated in low yield (30%) as a mixture of C-6 isomers (19.1a and 19.1b), because both the ketone 17.2 and the ketal 19.1 can undergo epimerization at position C-6 under the reaction conditions. However, it is not clear whether epimerization occurs before protection or afterwards. The more polar isomer 19.1a was separated partially from the other isomer and X-ray crystallographic analysis of this compound showed that the C-6 methyl is equatorial (Figure 3).
The next step was to replace the silicon group by a hydroxyl. First we tried the oxidation on the model compound 18.2, using KBr, NaOAc, AcOH and AcOOH, the conditions reported by Fleming and co-workers. During this reaction three different spots were detected on the thin layer chromatograms. HRMS of material extracted from these spots showed masses 251.0889 (C_{11}H_{16}NaO_{5}), 309.0941 (C_{13}H_{18}NaO_{7}) and 313.0046 (C_{11}H_{15}^{79}BrNaO_{4}), which could be, respectively, 20.1, 20.2 and 20.3.
Later, we tried oxidation of silicon in **17.2** using different procedures (Scheme 21) reported in the literature, but none gave the desired product (**17.3**).

At this stage, an extensive literature survey showed that aryltrimethylsilanes can be iodinated using a silver salt and a source of iodine (either ICl or I₂). Encouraged by these reports, we tried the iodination of **17.2** using ICl (Scheme 22), and the product **22.1** was isolated in 72% yield. The product contains a minor amount of another compound that has the same mass as **22.1**; it might be the other isomer at C-6.
Encouraged by this result, we next tried the same chemistry on protected ketal 19.1a, and were able to isolate the product 23.1b in 82% yield. The stereochemistry of the product was later confirmed by combining the results of NMR and by X-ray analysis. From these results, a new one-pot procedure was developed for the protection of the ketone carbonyl and for the desilylative iodination of bicyclic lactone 17.2 (Scheme 23) to give the isomers 23.1a and 23.1b.
Reaction of 17.2 with 1,2-bis(trimethylsilyloxy)ethane and Me₃SiOSO₂CF₃ at -78 °C for 4 h resulted in protection of the ketone as well as opening of the bicyclic lactone, which, on subsequent reaction with ICl at -30 °C for 15 min (monitoring by low resolution mass spectrometry) gave the desired products 23.1a and 23.1b, epimeric at C-6. X-ray crystallographic structures were obtained for both isomers, establishing that iodine is equatorial whereas the methyl is equatorial in the more polar isomer 23.1a and axial in less polar isomer 23.1b (Figures 4 and 5).
Figure 4. ORTEP diagram of compound 23.1a
In the meantime, we also studied the installation of the side chains at C-3 of 17.2. Reaction of 17.2 with LDA, followed by addition of 2,4,6-(i-Pr)$_3$C$_6$H$_2$SO$_2$N$_3$ (trisyl azide) and then quenching with Me$_3$SiCl,$^{19}$ gave the desired isomer 24.1, the presence of which was confirmed by high resolution mass spectrometry. Compound 24.1 was then subjected to alkylation using LDA and MeI, but unfortunately no desired product 24.2 was obtained (Scheme 24).
One product from this reaction was isolated. It had a mass of 410.1751 corresponding to the formula C$_{21}$H$_{29}$NNaO$_4$Si. The infrared spectrum showed a broad band at 3373 cm$^{-1}$, which might indicate the presence of an N-H bond. By comparing these observations with literature observations on the behavior of azido lactones, the structure 25.5 was assigned for this compound (Scheme 25).
After the successful synthesis of iodo-lactone 23.1, our next objective was to replace the iodine moiety by a hydroxyl group. This was done by using a standard two-step free radical method where Bu$_3$SnH and AIBN were added in portions alternating with portions of TEMPO. The labile N-O bond of the TEMPO adduct 26.1, was then cleaved with Zn in AcOH to give the hydroxy-lactones 26.2a (less polar alcohol) and 26.2b (more polar alcohol), which were separated.
Next, we decided to oxidize the hydroxyl group to a ketone and protect it as a ketal, so that the global deprotection of both ketals at a later stage could give the core bicyclic structure of sorbicillactone A. The oxidation of both alcohols 26.2a and 26.2b under Swern conditions proceeded smoothly to give the desired ketones 27.1a (from less polar alcohol) and 27.1b (from more polar alcohol). Unfortunately, attempts to protect the ketone did not give an acceptable yield (under various conditions) of the desired product 27.2 (Scheme 27).
Therefore, we decided to continue the synthesis with hydroxy-lactone 26.2. To this end, the hydroxyl group was first protected as a TBDMS-ether 28.1a (less polar isomer) and 28.1b (more polar isomer), and the subsequent experiments were done using the less polar isomer 28.1a.

Treatment of 28.1a with LDA, trisyl azide and subsequent quenching with Me₃SiCl gave the desired azide 28.2 (Scheme 28). The stereochemistry of 28.2 was confirmed by single crystal X-ray analysis (Figure 6) which indicated that the azide approached the substrate from the more accessible \textit{exo} face, as expected.
Scheme 28

Figure 6. ORTEP diagram of compound 28.2
Our next plan was to install the fumaryl unit present on the nitrogen and then carry out the alkylation at C-3. To do this, the azide 28.2 was first reduced to amine 29.1 by hydrogenation using Pearlman's catalyst and hydrogen. Coupling of the crude amine with acid 29.2 using DCC and DMAP gave the desired product 29.3 in 61% yield.

Scheme 29

However, attempted alkylation of 29.3 (LDA, MeI or LiHMDS, MeI) met with no success. Protection of the nitrogen with Boc₂O and pyridine gave 30.2 (Scheme 30), but subsequent alkylation (LiHMDS, MeI) also did not work (no starting material was recovered, and only a complex mixture formed). We suspected that the unsaturated ester moiety should not be present for this alkylation reaction.
Therefore, we next protected the amine 29.1, using Boc₂O and NaHCO₃ to give mono nitrogen-protected amide 31.1 (when we used Boc₂O and pyridine to carry out the mono protection, we did not get any of the desired product 31.1, and obtained instead 31.2 as the main product). Attempted alkylation of 31.1 (LDA, MeI or KHMDs, MeI or LDA, BuLi, MeI²³) also did not give any desired product 31.3, the starting material being partially recovered.

Amine 29.1 was then doubly protected using Boc₂O and pyridine to obtain compound 31.4, which also failed to undergo alkylation (LDA, MeI or or LDA, BuLi, MeI, LiCl²³).
Next, the amine was protected as its bis-PMB derivative, using $\text{K}_2\text{CO}_3$ and PMB-Br in MeCN. The desired product (32.1) was isolated in 68% yield, but all attempted alkylation conditions we applied to 32.1 (Scheme 32) failed to give the desired product (32.2) and only a complex mixture was formed.
Amine 29.1 was then converted to the imine 33.1 by heating with benzophenone imine in PhMe at 100 °C. Various alkylation conditions (see Scheme 33) were tried in order to alkylate imine 33.1, but none of them was successful and the product 33.2 was not detected (by low resolution mass spectral measurements).

From all these experiments, we concluded that the α-hydrogen in these substrates may not be easily accessible under normal deprotonation conditions.
By increasing the acidity of the \(\alpha\)-hydrogen, it might be possible to effect deprotonation and, in order to increase the acidity, we converted the azide 28.2 into the corresponding nitro compound by a procedure reported by Corey and co-workers.\(^\text{24}\) Treatment of the azide with \(\text{Ph}_3\text{P}\), followed by ozone, gave the desired nitro compound 34.1 in 62% yield. Alkylation of 34.1 using \(\text{Cs}_2\text{CO}_3\) and MeI in MeCN did not give any of the desired product 34.2, but two products were isolated which, according to high resolution mass spectrometry, had masses of 408.1813 \((\text{C}_{18}\text{H}_{31}\text{NNaO}_6\text{Si})\) and 438.1919 \((\text{C}_{19}\text{H}_{33}\text{NNaO}_7\text{Si})\). By comparing this observation with a literature report\(^\text{25}\) on the behavior of nitro lactones we suspect that 34.5 and 34.4 are possible structures for these compounds.
Because of the failure to install the methyl unit via an electrophilic route, our next attempt was to examine nucleophilic addition at C-3 for installing the methyl unit. For this purpose the amine 29.1 was first converted to the corresponding oxime 35.1 by reaction with Na₂WO₄, 30% H₂O₂ in EtOH. The desired product 35.1 was isolated in 72% yield (Scheme 35). The stereochemistry of the oxime was confirmed by single crystal X-ray analysis (Figure 7).
To improve the reactivity of oxime 35.1 towards nucleophilic addition, an electron withdrawing group needs to be installed at nitrogen. To do this, we tried to convert the oxime 35.1 into the phosphinic amide 36.1 using Ph₂PCl and
Et$_3$N.$^{14}$ But none of the desired product was isolated and, instead, we got product \textbf{36.2} (Scheme 36).

![Scheme 36]

Therefore, we decided to protect the oxime as its O-acetate and then try the nucleophilic addition. With this idea in mind, we made the protected oxime \textbf{37.1} by treating \textbf{35.1} with AcCl, DMAP and pyridine. Unfortunately, attempted addition of Me$_2$Zn to \textbf{37.1} also did not give any of the expected product \textbf{37.2} (Scheme 37). Low-resolution mass spectrometric analysis showed that the OAc group was attacked by the nucleophile instead of the ketimine moiety.
Our next plan was to add an allyl group to the oxime and later convert this group into the required methyl unit. In 1996, Hanessian and co-workers reported a zinc-mediated alkylation of oximes in aqueous media.\textsuperscript{27} Ritson and co-workers in 2004, reported an indium mediated alkylation of oxime ethers as well.\textsuperscript{28} In order to try these two procedures in our synthesis, we made the benzyl oxime ether \textbf{38.1} by reacting oxime \textbf{35.1} with BnBr and Ag\textsubscript{2}O in DMF. But, we were not able to isolate any of the desired alkylated product \textbf{38.3}, under the Hanessian or Ritson conditions.
2.2.1 Further plans for the installation of methyl unit

When we tried the alkylation on the nitro compound (34.1) using MeI (see Scheme 34), the methyl unit went onto the oxygen instead of the α-position (C-3). Therefore, if we use use allyl bromide instead of methyl iodide we may be able to get the O-allylated compound 39.1, which on heating may undergo a rearrangement to give the desired C-allylated product 39.2 (see Scheme 39).
We may also try to follow the same principle that Harned and co-workers used:\textsuperscript{11} Install an electron-withdrawing group such as an ester at C-3 and do the alkylation at this position. The ester group can then be converted to an amine by a Curtius rearrangement (Scheme 40). In our series, unlike the system used by Harned, alkylation occurs from the \textit{exo} face.
Scheme 40
3. CONCLUSION

During this project, most of the carbon skeleton present in sorbicillactone A was assembled. The core bicyclic unit was generated through a stannane-mediated radical cyclization. A new one-pot approach for protection and iodolactonization was developed that allowed us to protect the ketone carbonyl and install the required C-7 hydroxyl. The stereochemistry of key compounds was confirmed by X-ray analysis. A number of different alkylation procedures were tried to install the methyl unit at C-3, but further work on this step is required and is now in progress.
4. **Experimental**

**General Procedures.** Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N$_2$ that had been purified by passage through a column (3.5 x 42 cm) of R3-11 catalyst$^{29}$ and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in desiccators over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or N$_2$), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,$^{30}$ followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).
Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or by cannula. Dry THF was distilled from sodium benzophenone ketyl. Dry Et₃N, i-Pr₂NH, CH₂Cl₂, and pyridine were distilled from CaH₂. All other solvents were used as purchased. Commercial (Aldrich) solutions of n-BuLi (in hexanes) were titrated and found to have the stated molarity.

FTIR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from specified solvent.

¹H nuclear magnetic resonance spectra were recorded with Varian INOVA-300 (at 300 MHz), Varian INOVA-400 (at 400 MHz), or Varian INOVA-500 (at 500 MHz) spectrometers in the specified deuterated solvent. ¹³C spectra were recorded with Varian INOVA-400 (at 100 MHz) or Varian INOVA-500 (at 125 MHz) spectrometers. The symbols s, d, t, and q used for ¹³C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on APT experiments.

Mass spectra were recorded with Agilent Technologies 6220 oaTOF, Agilent technologies 5975C MSD single quadrupole mass spectrometers. Low resolution LC-mass spectra were measured with an Agilent 1100MSD single quadrupole mass spectrometer with electrospray ionization.

Solvent mixtures specified as x% A-B indicate that X mL of A were mixed with (100-X) mL of B.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ¹H and ¹³C NMR spectra.
4-Hydroxy-4-methylcyclohexa-2,5-dien-1-one (10.1).

An intimate mixture of Oxone (284.5 g, corresponding to 1.87 mol of KHSO₅) and NaHCO₃ (116.5 g, 1.39 mol) was added in portions over 30 min to a vigorously stirred solution of p-cresol (10 g, 92.47 mmol) in a mixture of MeCN (100 mL) and water (400 mL) contained in a 1-L three-necked flask. Two necks of the flask were fitted with septa, each pierced by a needle attached to a cut-off plastic syringe attached to a balloon. Once the addition was over the third neck was also fitted with a balloon in the same way. The progress of the reaction was monitored by TLC (silica, 50% EtOAc-hexane) and, when the reaction was over (usually 1 h), the mixture was diluted with water. Then Na₂S₂O₃ (73.05 g, 924.7 mmol) was added with stirring, and stirring was continued overnight. The mixture was extracted with EtOAc and the combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (6 x 15 cm), using 50% EtOAc-hexane, gave 10.1 (7.34 g, 64%) as a solid: FTIR (microscope) 3389, 3044, 2979, 2931, 1667, 1637, 1622 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.43 (s, 3 H), 3.33 (s, 1 H), 6.15 (d, J = 10.2 Hz, 2 H), 6.88 (d, J = 10.1 Hz, 2 H); ¹³C NMR (CDCl₃, 125 MHz) δ 26.7 (q), 67.1
(s), 126.8 (d), 152.8 (d), 185.8 (s); exact mass (electrospray) m/z calcd for C₇H₈NaO₂ (M + Na) 147.0412, found 147.0417.

1-Methyl-4-oxocyclohexa-2,5-dien-1-yl 2-bromoacetate (14.1).

![Chemical structure](image)

1.1

1.1

10.1

DMAP (974 mg, 7.98 mmol) and then pyridine (16.13 mL, 199.9 mmol) were added to a stirred and cooled (0 °C) solution of 10.1 (4.95 g, 39.9 mmol) in CH₂Cl₂. Neat BrCH₂COBr (10.4 mL, 119.7 mmol) was added by syringe pump over 15 min. The ice bath was removed and stirring was continued for 1 h. The mixture was quenched with saturated aqueous CuSO₄ and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 40% EtOAc-hexane, gave crude 14.1 (7.42 g, ca 76%) as a solid, which was used directly without characterization.

1-Methyl-4-oxocyclohexa-2,5-dien-1-yl 2-iodoacetate (13.4).
NaI (15.1 g, 100.86 mmol) was added to a solution of 14.1 (6.18 g, 25.22 mmol) in reagent grade acetone (150 mL). The mixture was stirred and refluxed for 6 h, cooled to room temperature and evaporated. The residue was filtered through a pad of Celite, using EtOAc, and the filtrate was washed with water and brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 20% EtOAc-hexane, gave 13.4 (5.44 g, 74%) as a solid: FTIR (microscope) 3048, 2984, 2933, 2869, 1736, 1666, 1630, 1609 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 1.58 (s, 3 H), 3.66 (s, 2 H), 6.26 (d, $J = 10.2$ Hz, 2 H), 6.88 (d, $J = 10.2$ Hz, 2 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 26.0 (q), 75.5 (t), 128.7 (d), 147.8 (d), 167.3 (s), 184.7 (s); exact mass (electrospray) $m/z$ calcd for C$_9$H$_9$INaO$_3$ (M + Na) 314.948, found 314.9489.

(3aR,7aS)-rel-7a-Methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2,5-dione (10.5).
A solution of Bu₃SnH (3.23 mL, 12.18 mmol) and AIBN (181 mg, 1.11 mmol) in dry PhH (80 mL) was added by syringe pump over 8 h to a refluxing solution of 13.4 (3.23 g, 11.07 mmol) in PhH (553 mL) contained in a 1-L round-bottomed flask (N₂ atmosphere). After the addition refluxing was continued overnight. The solution was cooled and evaporated and the residue was taken up in the minimum amount of CH₂Cl₂ and applied to the top of a chromatography column (3 x 15 cm) made up with flash chromatography silica gel-10% KF and 40% EtOAc-hexane. Development of the column with 40% EtOAc-hexane gave 10.5 (1.54 g, 84%) as a solid: FTIR (microscope) 3039, 2979, 2932, 2869, 1790, 1684, 1627, 1419 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.67 (s, 3 H), 2.40 (dd, J = 17.5, 11.7 Hz, 1 H), 2.59 (ddd, J = 17.3, 3.1, 0.9 Hz, 1 H), 2.69 (ddd, J = 17.4, 10.6, 6.9 Hz, 2 H), 2.88-2.94 (m, 1 H), 6.06 (d, J = 10.3 Hz, 1 H), 6.63 (dd, J = 10.3, 1.9 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ 24.2 (q), 34.7 (t), 36.8 (t), 40.9 (d), 81.5 (s), 129.2 (d), 146.5 (d), 173.7 (s), 195.0 (s); exact mass (electrospray) m/z calcd for C₉H₁₀NaO₃ (M + Na) 189.0522, found 189.0518.

(3aR,7aS)-rel-6-Bromo-7a-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2,5-dione (15.1).
A solution of Br$_2$ (41 µL, 0.80 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise over 5 min to a stirred and cooled (0 °C) solution of 10.5 (121 mg, 0.73 mmol) in CH$_2$Cl$_2$ (8 mL). Stirring at 0 °C was continued for 30 min and then Et$_3$N (0.51 mL, 3.64 mmol) was added at a fast dropwise rate, the ice bath was removed and stirring was continued for 1 h. The mixture was quenched with dilute hydrochloric acid (1 M, 10 mL) and extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et$_2$O-hexane, gave 15.1 (153.4 mg, 86%) as a solid: FTIR (cast film) 3041, 2980, 2931, 2869, 1781, 1700, 1611, 1417 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.70 (s, 3 H), 2.43 (dd, $J = 17.5$, 11.4 Hz, 1 H), 2.72-2.85 (m, 3 H), 2.89-3.01 (m, 1 H), 7.11 (s, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 24.2 (q), 34.5 (t), 36.8 (t), 40.9 (d), 83.2 (s), 125.2 (s), 146.9 (d), 173.1 (s), 187.3 (s); exact mass (electrospray) m/z calcd for C$_9$H$_9$BrNaO$_3$ (M + Na) 266.9627, found 266.9625.

(3aR,7aS)-rel-6-Bromo-7a-methyl-3,3a,4,7a-tetrahydro-2H-spiro[1-benzofuran-5,2'-(1,3)dioxolan]-2-one (15.2).
Me$_3$SiOSO$_2$CF$_3$ (20.37 µL, 0.1125 mmol) and 1,2-bis(trimethylsiloxy)ethane (0.18 mL, 0.75 mmol) were added dropwise in that order to a stirred and cooled (-78 °C) solution of 15.1 (23 mg, 0.09 mmol) in CH$_2$Cl$_2$ (1 mL). The cold bath was left in place but not recharged and stirring was continued for 5 h. At this point the $^1$H NMR spectrum of a worked-up sample showed that the reaction was complete. The solvent was evaporated and the residue in a little CH$_2$Cl$_2$ was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with hexane. Development of the column with 40% EtOAc-hexane gave 15.2 (18 mg, 66%) as a solid: FTIR (cast film) 2975, 2895, 1774, 1701, 1642, 1474, 1429 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.51 (s, 3 H), 2.03-2.13 (m, 2 H), 2.61-2.71 (m, 2 H), 2.85-2.91 (m, 1 H), 3.98-4.04 (m, 2 H), 4.17-4.27 (m, 2 H), 6.22 (s, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 25.2 (q), 33.7 (t), 34.9 (t), 38.7 (d), 66.0 (t), 66.3 (t), 83.45 (s), 103.7 (s), 129.2 (s), 134.5 (d), 174.9 (s); exact mass (electrospray) $m/z$ calcd for C$_{11}$H$_{13}$BrNaO$_4$ (M + Na) 310.9889, found 310.9884.
(3R,3aR,7aS)-rel-6-Bromo-3,7a-dimethyl-3,3a,4,7a-tetrahydro-2H-
spiro[1-benzofuran-5,2′-[1,3]dioxolan]-2-one (16.1). 

Use of (Me₃Si)₃NK

(Me₃Si)₃NK (0.5 M in PhMe, 0.12 mL, 0.06 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of 15.2 (15 mg, 0.05 mmol) in THF (1 mL). Stirring was continued for 50 min and then MeI (4.84 µL, 0.08 mmol) was added and stirring at -78 °C was continued for 20 min. The reaction flask was then transferred to an ice bath, stirring was continued for 10 min, the mixture was quenched with saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. The residue, in a little CH₂Cl₂, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with hexane. Development of the column with 20% EtOAc-hexane gave 16.1 (11 mg, 70%) as a solid:
Use of LDA

A stock solution of LDA was prepared by addition of BuLi (2.5 M in hexane, 0.27 mL, 0.67 mmol) to a stirred and cooled (-78 °C) solution of i-Pr₂NH (78.8 µL, 0.78 mmol) in THF (5 mL). Stirring was continued for 30 min. A portion (0.53 mL, 0.12 mmol LDA) of this stock solution was taken up into a syringe and added dropwise to a stirred and cooled (-78 °C) solution of 15.2 (15 mg, 0.05 mmol) in THF (1 mL). Stirring was continued for 50 min and then MeI (6.46 µL, 0.01 mmol) was added and stirring at -78 °C was continued for 30 min. The reaction flask was then transferred to an ice bath, stirring was continued for 15 min, the mixture was quenched with saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. The residue, in the minimum amount of CH₂Cl₂, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with hexane. Development of the column with 20% EtOAc-hexane gave 16.1 (11 mg, 70%) as a solid: FTIR (cast film) 2977, 2932, 2895, 1777, 1641, 1456, 1434 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.23 (d, J = 7.0 Hz, 3 H), 1.51 (s, 3 H), 2.12-2.21 (m, 3 H), 3.08-3.15 (m, 1 H), 3.97 (td, J = 7.5, 6.3 Hz, 1 H), 4.06 (ddd, J = 7.3, 6.3, 4.4 Hz, 1 H), 4.19 (td, J = 7.4, 6.4 Hz, 1 H), 4.27 (ddd, J = 7.6, 6.4, 4.4 Hz, 1 H), 6.20 (d, J = 1.3 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.2 (q), 24.6 (q), 32.8 (t), 37.8 (d), 47.6 (d), 66.2 (t), 66.2 (t), 81.8 (s), 103.5 (s), 128.0 (s), 135.3 (d), 177.8 (s); exact mass (electrospray) m/z calcd for C₁₂H₁₅⁷⁹BrNaO₄ (M + Na) 325.0046, found 325.0041.
(1S,7R)-rel-1-Methyl-3,10-dioxatricyclo[5.3.0.0^{2,4}]decane-5,9-dione (i).

Aqueous KOH (1 M, 92 µL, 0.092 mmol) and H_{2}O_{2} (30%, 0.26 mL, 2.3 mmol) were added in that order to a stirred and cooled (-10 °C, Haake immersion cooler in a bath of aqueous ethylene glycol) solution of 10.5 (83 mg, 0.50 mmol) in MeOH (3 mL). Stirring at -10 °C was continued overnight and then the MeOH was evaporated at room temperature. The residue was extracted with CH_{2}Cl_{2} and the combined organic extracts were washed with water and brine, dried (MgSO_{4}) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 40% EtOAc-hexane, gave epoxide i as two separable diastereomers. The less polar isomer (32 mg, 35%) had: FTIR (cast film) 3479, 2979, 2954, 2932, 1772, 1731, 1682, 1419, 1379 cm^{-1}; ^{1}H NMR (CDCl_{3}, 500 MHz) δ 1.80 (s, 3 H), 2.21 (ddd, J = 14.3, 3.1, 0.9 Hz, 1 H), 2.29 (dd, J = 17.9, 10.9 Hz, 1 H), 2.74 (dd, J = 17.9, 9.4 Hz, 1 H), 2.79-2.85 (m, 1 H), 3.05 (dd, J = 14.3, 4.8 Hz, 1 H), 3.41 (dd, J = 3.6, 0.8 Hz, 1 H), 3.58 (dd, J = 3.6, 1.9 Hz, 1 H); ^{13}C NMR (CDCl_{3}, 125 MHz) δ 23.9 (s), 33.4 (t), 34.4 (t), 43.1 (d), 55.3 (d), 62.0 (d), 80.0 (s), 173.3
(s), 204.0 (s); exact mass (electrospray) \( m/z \) calcd for \( \text{C}_9\text{H}_{10}\text{NaO}_4 \) (M + Na) 205.0471, found 205.0466.

The more polar isomer (34 mg, 37%) had: FTIR (cast film) 3421, 2984, 2936, 1780, 1724 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 1.55 (s, 3 H), 2.45 (dd, \( J = 16.0, 8.3 \) Hz, 1 H), 2.62-2.68 (m, 1 H), 2.71-2.87 (m, 3 H), 3.48 (dd, \( J = 4.3, 0.5 \) Hz, 1 H), 3.66 (dd, \( J = 4.3, 1.0 \) Hz, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 23.9 (q), 37.1 (t), 37.4 (t), 39.4 (d), 56.2 (d), 62.4 (d), 81.9 (s), 174.1 (s), 203.4 (s); exact mass (electrospray) \( m/z \) calcd for \( \text{C}_9\text{H}_{10}\text{NaO}_4 \) (M + Na) 205.0471, found 205.0466.

\((3\text{aR},7\text{aS})\)-rel-7-[Dimethyl(phenyl)silyl]-7a-methyloctahydro-1-benzo-furan-2,5-dione (18.1).

\begin{align*}
\text{PhMe}_2\text{SiCuLi} &
\end{align*}

A solution of PhMe\(_2\)SiCuLi was prepared as follows:\(^\text{16}\)

Lithium wire (97 mg, 13.92 mmol) was cut into small pieces (1-2 mm long) that were allowed to drop into a beaker of dry hexane. The pieces were removed with tweezers, blotted with filter paper and transferred to a pear-shaped flask containing THF (4 mL) (Ar atmosphere). The contents of the flask were
cooled (0 °C) and stirred while PhMe$_2$SiCl (1 mL, 5.95 mmol) was added dropwise. Stirring was continued for 4 h, by which time a deep red color had formed, to give a 1 M solution of PhMe$_2$SiLi.

In another flask dry HMPA (0.98 mL) was added to a stirred mixture of CuI (295 mg, 1.54 mmol) and THF (8 mL) and the mixture was cooled (-78 °C). The solution of PhMe$_2$SiLi (3.1 mL, 3.1 mmol) was taken up into a syringe and added dropwise with stirring to the CuI mixture. After the addition, stirring at -78 °C was continued for 10 min, and at 0 °C (ice bath) for 1 h. The mixture was then recooled to -78 °C, and a solution of 10.5 (234 mg, 1.41 mmol) in THF (3 mL) was added dropwise over 5 min. The cold bath was left in place but not recharged and stirring was continued for 50 min. The mixture was recooled to -78 °C and MeI (0.44 mL, 7.04 mmol) was added. Stirring was continued at -78 °C for 20 min and at 0 °C (ice bath) for 2 h. The mixture was filtered through a pad of Celite using Et$_2$O as a rinse. The filtrate was washed with dilute hydrochloric acid (1 M), water and brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave an inseparable mixture of the two silanes 18.1 (171 mg, 40%). Only a trace of the C-methylated silane was isolated, but this compound could be made as described below. Compounds 18.1 had: FTIR (cast film) 2963, 1770, 1717, 1427 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.43-0.49 (m, 6 H), 1.49-1.46 (m, 3 H), 2.10-2.21 (m, 2 H), 2.26-2.58 (m, 5 H), 2.72-2.91 (m, 2 H), 7.35-7.39 (m, 3 H), 7.49-7.51 (m, 1 H), 7.54-7.56 (m, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -3.8 (q), -3.4 (q), -2.3 (q), -2.2 (q), 24.8 (q), 29.5 (q), 31.6 (t), 32.5 (t), 34.9 (t), 35.4 (t), 37.1 (t), 37.5 (t),
39.8 (t), 41.1 (d), 41.4 (t), 41.5 (d), 86.9 (s), 87.7 (s), 128.1 (d), 128.1 (d), 129.6 (d), 129.6 (d), 134.0 (d), 134.1 (d), 136.5 (s), 136.9 (s), 174.6 (s), 174.7 (s), 209.6 (s), 210.1 (s); exact mass (electrospray) $m/z$ calcd for $C_{17}H_{22}NaO_3Si (M + Na)$ 325.123, found 325.1225.

$\text{(3aR,6S,7R,7aS)-rel-7-[Dimethyl(phenyl)silyl]-6,7a-dimethylocta}$-
hydro-1-benzofuran-2,5-dione (17.2).

A solution of PhMe$_2$SiCuLi was prepared as follows.$^{16}$

Lithium wire (387 mg, 55.76 mmol) was cut into small pieces (1-2 mm long) that were allowed to drop into a beaker of dry hexane. The pieces were removed with tweezers, blotted with filter paper and transferred to a pear-shaped flask containing THF (16 mL) (Ar atmosphere). The contents of the flask were cooled (0 °C) and stirred while PhMe$_2$SiCl (4 mL, 23.82 mmol) was added dropwise. Stirring was continued for 4 h, by which time a deep red color had formed, to give a 1 M solution of PhMe$_2$SiLi.

In another flask dry HMPA (3.6 mL) was added to a stirred mixture of CuCN (808.4 mg, 9.02 mmol) and THF (36 mL) and the mixture was cooled (0
°C). The solution of PhMe$_2$SiLi (18.1 mL, 18.1 mmol) was taken up into a syringe and added dropwise over ca 5 min to the CuCN mixture. After the addition, stirring at 0 °C was continued for 1 h, and the mixture was then cooled to -78 °C. A solution of 10.5 (1.5 g, 9.03 mmol) in THF (5 mL) was added dropwise over 5 min. After this addition the temperature was allowed to rise over ca 2 h to -20 °C (by not recharging the cold bath). At this point, examination of the mixture by TLC (silica, 40% EtOAc-hexane, developed three times) showed that all 10.5 had reacted. The mixture was cooled to -50 °C and HMPA (5 mL) was added, followed by MeI (5.6 mL, 90.26 mmol). Stirring was continued without recharging the cold bath so that the temperature rose to 0 °C over 2 h. The mixture was quenched with saturated aqueous NH$_4$Cl and extracted with Et$_2$O. The combined organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 40% EtOAc-hexane, gave 17.2 (2.26 g, 80%) as a solid: FTIR (cast film) 2973, 1771, 1714, 1488, 1458, 1427 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.47 (s, 3 H), 0.51 (s, 3 H), 1.03 (d, $J$ = 7.2 Hz, 3 H), 1.56 (s, 3 H), 2.08 (dd, $J$ = 16.5, 8.3 Hz, 1 H), 2.17 (dd, $J$ = 18.0, 4.9 Hz, 1 H), 2.38-2.47 (m, 3 H), 2.68-2.74 (m, 1 H), 2.84 (dd, $J$ = 18.0, 8.9 Hz, 1 H), 7.33-7.37 (m, 1 H), 7.54-7.56 (m, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -1.9 (q), -0.1 (q), 18.4 (q), 30.7 (q), 35.6 (t), 40.0 (t), 40.7 (d), 41.0 (d), 42.1 (d), 87.9 (s), 128.0 (d), 129.3 (d), 134.1 (d), 138.1 (s), 174.7 (s), 212.2 (s); exact mass (electrospray) $m/z$ calcd for C$_{18}$H$_{24}$NaO$_3$Si (M + Na) 339.1387, found 339.1378.
(3aR,7R,7aS)-rel-7-[Dimethyl(phenyl)silyl]-7a-methylhexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (18.2a) and (3aR,7S,7aS)-rel-7-[Dimethyl(phenyl)silyl]-7a-methylhexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (18.2b).

Ethylene glycol (0.63 mL, 11.32 mmol), camphorsulfonic acid (26 mg, 0.11 mmol) and MeC(OMe)_3 (0.62 mL, 5.66 mmol) were added in that order to a stirred solution of 18.1 (171 mg, 0.57 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 4 h (TLC monitoring, silica, 40% EtOAc-hexane), at which point the reaction was complete. The mixture was quenched with saturated aqueous NaHCO_3, and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (MgSO_4) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 40% EtOAc-hexane, gave 18.2-more polar (39 mg, 20%) and 18.2-less polar (31 mg, 16%), both as oils. We did not assign stereochemistry to the individual isomers. The less polar isomer had: FTIR (cast film) 2954, 2892, 1769, 1447, 1428 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 500 MHz) \(\delta\) 0.40 (s, 3 H), 0.44 (s, 3 H), 1.46-1.49 (m, 4 H), 1.64-
1.69 (m, 2 H), 1.79-1.88 (m, 2 H), 2.38-2.46 (m, 2 H), 3.12-3.11 (m, 1 H), 3.68-3.73 (m, 1 H), 3.81-3.92 (m, 3 H), 7.34-7.36 (m, 3 H), 7.49-7.51 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ -3.5 (q), -1.8 (q), 23.3 (q), 29.4 (d), 32.9 (t), 32.9 (t), 33.9 (t), 43.8 (d), 63.9 (t), 64.4 (t), 86.9 (s), 107.5 (s), 127.8 (d), 129.1 (d), 133.9 (d), 137.8 (s), 176.2 (s); exact mass (electrospray) $m/z$ calcd for C$_{19}$H$_{26}$NaO$_4$Si (M + Na) 369.1493, found 369.1487.

The more polar isomer: FTIR (cast film) 2956, 2887, 1770, 1452, 1428 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 0.39 (s, 3 H), 0.47 (s, 3 H), 1.24 (s, 3 H), 1.43-1.48 (m, 1 H), 1.53-1.62 (m, 3 H), 1.80 (ddd, $J = 13.8$, 6.4, 2.4 Hz, 1 H), 2.18 (dd, $J = 17.6$, 1.8 Hz, 1 H), 2.42 (dddd, $J = 11.0$, 7.7, 6.3, 1.6 Hz, 1 H), 2.83 (dd, $J = 17.6$, 7.7 Hz, 1 H), 3.80-3.82 (m, 1 H), 3.87-3.92 (m, 3 H), 7.34-7.36 (m, 3 H), 7.55-7.57 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ -2.7 (q), -1.6 (q), 27.7 (q), 31.3 (d), 32.0 (t), 36.9 (t), 41.6 (d), 64.3 (t), 86.9 (s), 107.5 (s), 127.9 (d), 129.1 (d), 134.0 (d), 138.7 (s), 176.4 (s); exact mass (electrospray) $m/z$ calcd for C$_{19}$H$_{26}$NaO$_4$Si (M + Na) 369.1493, found 369.1488.

(3aR,6S,7R,7aS)-rel-7-[Dimethyl(phenyl)silyl]-6,7a-dimethylhexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (19.1a) and (3aR,6R,7R,7aS)-rel-7-[Dimethyl-(phenyl)silyl]-6,7a-dimethylhexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (19.1b).
Ethylene glycol (0.22 mL, 4.01 mmol), camphorsulfonic acid (9.3 mg, 0.04 mmol) and HC(OMe), (0.22 mL, 2.01 mmol) were added to a stirred solution of 17.2 (single isomer, 63 mg, 0.21 mmol) in CH₂Cl₂ (1 mL) and stirring was continued for 24 h, by which time all 17.2 had reacted (TLC monitoring, silica, 15% EtOAc-hexane). The mixture was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃. The organic phase was washed with water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 15% EtOAc-hexane, gave the more polar isomer (19.1a) (13 mg, 18%) and the less polar isomer (19.1b) (9 mg, 12%), as solids. The more polar isomer was pure and the stereochemistry was established by single crystal X-ray analysis. The less polar isomer was contaminated by some of the more polar and its ¹H NMR spectrum was too complicated to be informative. The more polar isomer had: FTIR (cast film) 2975, 2882, 1771, 1462, 1427 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.42 (s, 3 H), 0.50 (s, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.27 (s, 3 H), 1.55-1.70 (m, 4 H), 2.03 (dd, J = 11.3, 7.4 Hz, 1 H), 2.29 (d, J = 17.6 Hz, 1 H), 2.90 (dd, J = 17.6, 7.4 Hz, 1 H), 3.80-3.84 (m, 1 H), 3.90-3.97 (m, 4 H), 7.38-7.39 (m, 3 H), 7.59-7.61 (m, 2 H); ¹³C NMR (CDCl₃, 125 MHz) δ -2.8 (q), -1.3
(q), 11.7 (q), 27.9 (q), 31.3 (d), 32.0 (t), 36.4 (t), 40.8 (d), 49.7 (d), 64.8 (t), 65.3 (t), 87.5 (s), 108.8 (s), 127.9 (d), 129.0 (d), 133.9 (d), 138.9 (s), 176.6 (s); exact mass (electrospray) m/z calcd for C_{20}H_{28}NaO_{4}Si (M + Na) 383.1649, found 383.1644.

\((3R,3aR,7R,7aS)-rel-3-Azido-7-[dimethyl(phenyl)silyl]-6,7a-dimethyl-hexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one\) (24.1).

A stock solution of LDA was prepared by addition of BuLi (2.5 M in hexane, 0.45 mL, 1.13 mmol) to a stirred and cooled (-78 °C) solution of \(i\)-Pr\{_2\}NH (0.18 mL, 1.23 mmol) in THF (2 mL). Stirring was continued for 30 min. A portion (0.263 mL, 0.43 mmol LDA) of this stock solution was taken up into a syringe and added dropwise to a stirred and cooled (-78 °C) solution of 17.2 (C-6 isomer mixture, 37 mg, 0.10 mmol) in THF (1 mL). Stirring was continued for 50 min and HMPA (0.1 mL), followed by a solution of 2,4,6-(\(i\)-Pr)\{_3\}\)C\{_6\}H\{_2\}SO\{_2\}N\{_3\} (38.1 mg, 1.12 mmol) in THF (1 mL), was added dropwise and stirring at -78 °C was continued for 2 h. Me\{_3\}SiCl (65.17 µL, 0.51 mmol) was added and stirring was
continued overnight, the cold bath being left in place but not recharged. The mixture was quenched with pH 7 buffer and the organic phase was extracted with Et₂O. The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 10% EtOAc-hexane), gave 24.1 (27 mg, 66%) as a mixture of isomers: exact mass (electrospray) m/z calcd for C₂₀H₂₇N₃NaO₄Si (M + Na) 424.1663, found 424.1655.

(3aR,6S,7aS)-rel-7-Iodo-6,7a-dimethylhexahydro-2H-spiro[1-benzo-furan-5,2'-[1,3]dioxolan]-2-one (23.1b).

![Image](19.1a) → ![Image](23.1b)

ICl (1 M in CH₂Cl₂, 27 µL, 0.027 mmol) was added dropwise to a stirred and cooled (0 °C) solution of 19.1a (10 mg, 0.027 mmol) in Et₂O (1 mL). After 1 h, examination of the mixture by TLC (silica, 30% EtOAc-hexane) showed that some 19.1a remained and so more ICl (1 M in CH₂Cl₂, 14 µL, 0.014 mmol) was added. Stirring was continued at 0 °C for 30 min, by which time reaction was complete, and the mixture was then filtered through a pad of Celite, using Et₂O as
a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6 x 7 cm), using 60% Et₂O-hexane, gave 23.1b (8 mg, 82%) as an oil: FTIR (cast film) 2983, 2943, 2893, 1778, 1721, 1682 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.26 (d, J = 7.5 Hz, 3 H), 1.71 (s, 3 H), 1.78-1.81 (m, 1 H), 2.19 (dd, J = 15.0, 6.4 Hz, 1 H), 2.24-2.30 (m, 1 H), 2.50 (dd, J = 17.8, 8.8 Hz, 1 H), 2.82 (dddd, J = 12.7, 8.6, 6.4, 2.2 Hz, 1 H), 3.33 (dd, J = 17.8, 12.6 Hz, 1 H), 3.91-4.03 (m, 1 H), 4.84 (d, J = 4.7 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ 14.7 (q), 28.2 (t), 28.7 (q), 33.9 (t), 39.5 (d), 40.5 (d), 46.3 (d), 64.2 (t), 64.7 (t), 84.6 (s), 109.1 (s), 174.8 (s); exact mass (electrospray) m/z calcd for C₁₂H₁₇INO₄ (M + Na) 375.0064, found 375.0057.

\[(3aR,7S,7aS)-rel-6,7a-Dimethyl-7-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]hexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (26.1).\]

\[23.1a, 23.1b \quad 26.1\]

Solutions of Bu₃SnH (4.68 mL, 17.66 mmol) in PhMe (10 mL) and of TEMPO (4.13 g, 26.49 mmol in PhMe (10 mL) were prepared. An aliquot (3.3 mL) of the stannane solution was added by syringe over 2 min to a refluxing
solution of 23.1a and 23.1b (mixture of C-6 isomers) (1.55 g, 4.41 mmol) in PhMe (26.4 mL) and then an aliquot (6.7 mL) of the TEMPO solution was added over 2 min. The remaining stannane and TEMPO solutions were then added sequentially, each in three equal portions, over the next 60 min, i.e. 20 min, 40 min and 60 min after the first addition of TEMPO. Refluxing was continued for an additional 30 min and the solvent was then evaporated. Flash chromatography of the residue over flash chromatography silica gel-10% KF (2 x 15 cm), using 40% EtOAc-hexane, gave 26.1 as a mixture of isomers (1.17 g, 70%) as a solid, which was used for the next step without separation.

\[(3aR,6S,7S,7aS)-rel-7-Iodo-6,7a-dimethyloctahydro-1-benzofuran-2,5-dione \text{(22.1)}.\]

ICl (1 M in CH₂Cl₂, 63.2 µL, 0.06 mmol) was added to a stirred and cooled (-78 °C) solution of 17.2 (10 mg, 0.03 mmol) in Et₂O (1 mL). No reaction was observed (TLC) after 1 h and so the mixture was allowed to warm to -20 °C over ca 30 min, at which point some reaction occurred (TLC). The mixture was
allowed to warm to 0 °C. More ICl (1 M in CH2Cl2, 31 µL, 0.031 mmol) was added and the mixture was maintained at 0 °C for 15 min. The mixture was quenched with saturated aqueous Na2S2O3 and extracted with Et2O. The combined organic extracts were washed with water and brine, dried (MgSO4) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 60% Et2O-hexane, gave 22.1 (7 mg, 72%) as a single isomer: FTIR (cast film) 2978, 2932, 2893, 1773, 1721, 1682, 1454, 1426 cm\(^{-1}\); \(^1\)H NMR (CDCl3, 500 MHz) \(\delta\) 1.39 (d, \(J = 6.9\) Hz, 3 H), 1.80 (s, 3 H), 2.48-2.67 (m, 3 H), 2.72-2.77 (m, 1 H), 2.89-3.00 (m, 2 H), 4.37 (d, \(J = 12.2\) Hz, 1 H); \(^{13}\)C NMR (CDCl3, 125 MHz) \(\delta\) 18.3 (q), 26.8 (q), 35.6 (t), 38.8 (d), 39.3 (d), 40.5 (t), 49.8 (d), 85.0 (s), 172.8 (s), 205.3 (s); exact mass (electrospray) \(m/z\) calcd for C10H13INaO3 (M + Na) 330.9802, found 330.9795.

\((3aR,6R,7S,7aS)-rel-7-Iodo-6,7a-dimethylhexahydro-2H-spiro[1-benzofuran-5,2'\-[1,3]dioxolan]-2-one\) (23.1a) and \((3aR,6S,7S,7aS)-rel-7-Iodo-6,7a-dimethylhexahydro-2H-spiro[1-benzofuran-5,2'\-[1,3]dioxolan]-2-one\) (23.1b).
1,2-Bis(trimethylsilyloxy)ethane (4.5 mL, 18.56 mmol) and Me₃SiOSO₂CF₃ (1.12 mL, 6.19 mmol) were added dropwise to a stirred and cooled (-78 °C) solution of 17.2 (1.96 g, 6.19 mmol) in CH₂Cl₂ (37 mL). The cold bath was left in place but not recharged and stirring was continued for 4 h, by which time the temperature had risen to room temperature and all of 17.2 had reacted (monitoring by low resolution mass spectrometry). The mixture was then cooled to -30 °C and ICl (1 M solution in CH₂Cl₂, 12.3 mL, 12.38 mmol) was added at a fast dropwise rate. Stirring was continued for 10 min (monitoring by low resolution mass spectrometry) and the mixture was quenched with saturated aqueous Na₂S₂O₃ and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 80% Et₂O-hexane, gave 23.1a and 23.1b which were separated into three fractions: the less polar isomer 23.1b (348 mg, 16%), the more polar isomer 23.1a (305 mg, 14%) and a mixture of the two (915 mg, 42%), all as solids. The more polar isomer 23.1a had: FTIR (cast film) 2983, 2937, 2898 1782, 1766, 1458, 1435 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.17 (d, J = 6.6 Hz, 3 H), 1.75 (s, 3 H), 1.82 (dd, J = 14.9, 6.3 Hz, 1 H), 1.94 (dd, J = 14.9, 2.0 Hz, 1 H), 2.10 (dd, J = 12.9, 6.6 Hz, 1 H), 2.43 (dd, J = 17.5, 8.4 Hz, 1 H), 2.79 (dddd, J = 13.3, 8.4, 6.4, 1.9 Hz, 1 H), 3.20 (dd, J = 17.6, 13.4 Hz, 1 H), 3.94-4.05 (m, 4 H), 4.40 (d, J = 12.8 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ 17.6 (q), 25.6 (q), 32.1 (t), 33.2 (t), 40.3 (d), 44.7 (d), 44.9 (d), 65.0 (t), 65.6 (t), 85.6 (s), 108.1 (s), 174.8 (s); exact mass (electrospray) m/z calcd for C₁₂H₁₇INaO₄ (M + Na) 375.0064, found 375.0057.
The less polar isomer 23.1b had: FTIR (cast film) 2983, 2943, 2893, 1778, 1721, 1682 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 1.26 (d, \(J = 7.5\) Hz, 3 H), 1.71 (s, 3 H), 1.78-1.81 (m, 1 H), 2.19 (dd, \(J = 15.0, 6.4\) Hz, 1 H), 2.24-2.30 (m, 1 H), 2.50 (dd, \(J = 17.8, 8.8\) Hz, 1 H), 2.82 (dddd, \(J = 12.7, 8.6, 6.4, 2.2\) Hz, 1 H), 3.33 (dd, \(J = 17.8, 12.6\) Hz, 1 H), 3.91-4.03 (m, 1 H), 4.84 (d, \(J = 4.7\) Hz, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 14.7 (q), 28.2 (t), 28.7 (q), 33.9 (t), 39.5 (d), 40.5 (d), 46.3 (d), 64.2 (t), 64.7 (t), 84.6 (s), 109.1 (s), 174.8 (s); exact mass (electrospray) \(m/z\) calcd for C\(_{12}\)H\(_{17}\)INaO\(_4\) (M + Na) 375.0064, found 375.0054.

\((3aR,6S,7S,7aS)-rel-7\)-Hydroxy-6,7a-dimethylhexahydro-2\(H\)-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (26.2a) and \(3aR,6R,7S,7aS\)-rel-7-Hydroxy-6,7a-dimethyl-hexahydro-2\(H\)-spiro[1-benzofuran-5,2'-[1,3]dioxol- lan]-2-one (26.2b).

```
\[
\text{Water (50 mL), AcOH (41.5 mL) and Zn powder (60.1 g, 921.2 mmol)}
\]
```

```
\[
\text{were added to a stirred solution of 26.1 (1.75 g, 4.60 mmol) in THF (100 mL).}
\]
```

The mixture was stirred and heated at 50 °C in a flask fitted with a reflux
condenser. Heating was continued for 6 h and the mixture was cooled and filtered through a pad of Celite, using EtOAc as a rinse. The filtrate was washed with saturated aqueous NaHCO₃, water and brine. The combined organic extracts were dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% EtOAc-hexane, gave 26.2b (more polar) (423 mg, 38%) and 26.1a (less polar) (356 mg, 32%) as solids. The more polar isomer (26.2b) had: FTIR (cast film) 3466, 2980, 2941, 2893, 1765, 1458, 1437 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.05 (d, J = 6.6 Hz, 3 H), 1.51 (s, 3 H), 1.75-1.80 (m, 1 H), 1.89-1.95 (m, 2 H), 2.12 (d, J = 4.0 Hz, 1 H), 2.50 (dd, J = 17.2, 8.7 Hz, 1 H), 2.56-2.62 (m, 1 H), 3.09 (t, J = 8.6 Hz, 1 H), 3.78 (dd, J = 11.4, 4.0 Hz, 1 H), 3.97-4.05 (m, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ 9.2 (q), 18.0 (q), 32.2 (t), 34.2 (t), 40.6 (d), 42.4 (d), 65.0 (t), 65.5 (t), 75.5 (d), 88.2 (s), 110.1 (s), 176.0 (s); exact mass (electrospray) m/z calcd for C₁₂H₁₈NaO₅ (M + Na) 265.1046, found 265.1043.

The less polar isomer (26.2a) had: FTIR (cast film) 3465, 2976, 2938, 2888, 1776, 1458, 1430 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.09 (d, J = 6.5 Hz, 3 H), 1.26-1.34 (m, 1 H), 1.57 (s, 3 H), 1.67 (d, J = 11.7 Hz, 1 H), 1.93 (ddd, J = 12.6, 9.7, 6.7 Hz, 2 H), 2.25 (d, J = 17.3 Hz, 1 H), 2.45 (dt, J = 11.9, 6.6 Hz, 1 H), 3.00 (dd, J = 17.3, 6.7 Hz, 1 H), 3.45 (t, J = 11.5 Hz, 1 H), 3.94-4.03 (m, 4 H); ¹³C NMR (CDCl₃, 125 MHz) δ 9.5 (q), 23.1 (q), 37.4 (t), 37.6 (t), 37.7 (d), 42.4 (d), 65.1 (t), 65.5 (t), 77.5 (d), 86.0 (s), 108.4 (s), 175.2 (s); exact mass (electrospray) m/z calcd for C₁₂H₁₈NaO₅ (M + Na) 265.1046, found 265.1042.
DMSO (0.11 mL, 1.54 mmol) was added to a stirred and cooled (-78 °C) solution of (COCl)$_2$ (0.11 mL, 1.25 mmol) in CH$_2$Cl$_2$ (2 mL). The mixture was stirred for 30 min and then a solution of 26.2b (69 mg, 0.28 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise over ca 2 min. Stirring at -78 °C was continued for 45 min and then Et$_3$N (0.32 mL, 2.26 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued for 4 h, during which time the mixture attained room temperature. The mixture was quenched with saturated aqueous NH$_4$Cl and extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with water and brine, dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 60% EtOAc-hexane, gave 27.1b (64 mg, 93%) as an oil: FTIR (cast film) 2986, 2943, 2894, 1787, 1729, 1453 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 1.13 (d, $J = 6.6$ Hz, 3 H), 1.51 (s, 3 H), 1.76 (dd, $J = 14.1, 11.3$ Hz, 1 H), 2.18 (dd, $J = 14.1, 7.0$ Hz, 1 H), 2.40 (dd, $J = 17.4, 0.9$ Hz, 1 H), 2.57-2.62 (m, 1 H), 2.97 (dd, $J = 17.4, 7.1$ Hz, 1
H), 3.17 (q, J = 6.6 Hz, 1 H), 3.93-4.07 (m, 4 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ
6.7 (q), 20.2 (q), 36.0 (t), 38.2 (t), 38.4 (d), 50.4 (d), 65.7 (t), 65.8 (t), 84.5 (s),
109.2 (s), 175.2 (s), 202.1 (s); exact mass (electrospray) m/z calcd for C$_{12}$H$_{16}$NaO$_5$
(M + Na) 263.089, found 263.0885.

(3aR,6S,7aS)-rel-6,7a-Dimethylhexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2,7-dione (27.1a).

DMSO (52.8 µL, 0.74 mmol) was added to a stirred and cooled (-78 °C)
solution of (COCl)$_2$ (57 µL, 0.65 mmol) in CH$_2$Cl$_2$ (1 mL). The mixture was
stirred for 30 min and then a solution of 26.2a (36 mg, 0.15 mmol) in CH$_2$Cl$_2$ (1
mL) was added dropwise over ca 1 min. Stirring at -78 °C was continued for 45
min and then Et$_3$N (0.16 mL, 1.17 mmol) was added dropwise. The cold bath was
left in place but not recharged and stirring was continued for 4 h, during which
time the mixture attained room temperature. The mixture was quenched with
saturated aqueous NH$_4$Cl and extracted with CH$_2$Cl$_2$. The combined organic
extracts were washed with water and brine, dried (MgSO$_4$) and evaporated. Flash
chromatography of the residue over silica gel (0.8 x 15 cm), using 60% EtOAc-hexane, gave 27.1a (32 mg, 89%) as an oil: FTIR (cast film) 2987, 2941, 2897, 1784, 1731, 1455 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.12 (d, J = 6.5 Hz, 3 H), 1.69 (s, 3 H), 2.12 (dd, J = 15.0, 2.2 Hz, 1 H), 2.21 (dd, J = 14.9, 6.0 Hz, 1 H), 2.47 (dd, J = 17.2, 8.0 Hz, 1 H), 2.77 (ddddd, J = 12.6, 8.1, 5.9, 2.2 Hz, 1 H), 2.93 (dd, J = 17.2, 12.7 Hz, 1 H), 3.10 (q, J = 6.5 Hz, 1 H), 3.98-4.08 (m, 4 H); ¹³C NMR (CDCl₃, 125 MHz) δ 6.5 (q), 22.4 (q), 32.8 (t), 32.9 (t), 41.5 (d), 51.2 (d), 65.3 (t), 66.1 (t), 87.3 (s), 111.5 (s), 174.3 (s), 204.1 (s); exact mass (electrospray) m/z calcd for C₁₁₂H₆₁NaO₅ (M + Na) 263.089, found 263.0885.

(3'aR,7'aS)-rel-6',7'a-Dimethylhexahydrodispiro[1,3-dioxolan-2,5']-[1]benzofuran-7',2''-[1,3]dioxolan]-2'-one (27.2).

![](image)

HC(OMe)₃ (0.27 mL, 2.5 mmol), ethylene glycol (0.14 mL, 2.5 mmol) and TsOH.H₂O (2 mg) were added to a stirred solution of 27.1a (20 mg, 0.08 mmol) in CH₂Cl₂ (1 mL). Stirring was continued for 2 h, at which point analysis of a sample by LC-MS showed only a weak signal for 27.2. The mixture was refluxed
overnight, cooled, quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 50% Et₂O-hexane, gave 27.2 (5 mg, 22%) as an oil, which was a single isomer (¹H and ¹³C NMR). We did not establish the stereochemistry of the C-6 methyl group: FTIR (cast film) 2985, 2949, 2895, 1776 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.98 (d, J = 6.7 Hz, 3 H), 1.56 (s, 3 H), 1.82 (dd, J = 14.8, 6.3 Hz, 1 H), 2.05 (dd, J = 14.9, 2.8 Hz, 1 H), 2.26 (q, J = 6.7 Hz, 1 H), 2.38 (dd, J = 17.1, 9.4 Hz, 1 H), 2.57 (dddd, J = 12.5, 9.4, 6.4, 3.0 Hz, 1 H), 3.25-3.15 (m, 1 H), 3.84-4.20 (m, 8 H); ¹³C NMR (CDCl₃, 125 MHz) δ 5.8 (q), 21.3 (q), 32.3 (t), 33.4 (t), 41.5 (d), 44.1 (d), 64.1 (t), 65.6 (t), 66.0 (t), 68.0 (t), 87.6 (s), 109.7 (s), 111.3 (s), 176.5 (s); exact mass (electrospray) m/z calcd for C₁₄H₂₃NaO₆ (M + Na) 307.1152, found 307.1146.

(3aR,6S,7S,7aS)-rel-7-[(tert-Butyldimethylsilyl)oxy]-6,7a-dimethyl-hexahydro-2H-spiro[1-benzofuran-5,2’-[1,3]dioxolan]-2-one (28.1a)
t-BuMe₂SiCl (1.52 g, 10.08 mmol), imidazole (1.03 g, 15.12 mmol) and DMAP (15 mg, 0.13 mmol) were added in that order to a stirred solution of 26.2a (305 mg, 1.26 mmol) in DMF (5 mL). The mixture was heated at 50 °C for 16 h (N₂ atmosphere), at which point not all 26.2a had reacted (TLC, silica, 80% Et₂O-hexane). t-BuMe₂SiCl (569 mg, 3.78 mmol) and imidazole (428 mg, 6.3 mmol) were added and stirring at 70 °C was continued for 1 h, by which time reaction was complete (TLC). The mixture was cooled and diluted with Et₂O. The organic phase was washed with saturated aqueous NH₄Cl, water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et₂O-hexane, gave 28.1a (403 mg, 90%) as a solid: FTIR (cast film) 2936, 2954, 2887, 2857, 1772, 1473, 1463 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.07 (s, 3 H), 0.16 (s, 3 H), 0.91-0.94 (m, 12 H), 1.43 (s, 1 H), 1.71 (dd, J = 14.7, 6.3 Hz, 1 H), 1.80-1.89 (m, 2 H), 2.41 (dd, J = 17.2, 8.7 Hz, 1 H), 2.51 (dddd, J = 12.8, 8.6, 6.3, 2.2 Hz, 1 H), 3.05 (dd, J = 17.2, 12.8 Hz, 1 H), 3.68 (d, J = 11.4 Hz, 1 H), 3.90-4.00 (m, 4 H); ¹³C NMR (CDCl₃, 125 MHz) δ -4.7 (q), -4.1 (q), 9.9 (q), 18.3 (q), 18.5 (s), 26.1 (q), 32.1 (t), 34.1 (t), 41.0 (d), 43.9 (d), 64.8 (t), 65.5 (t), 76.5 (d), 88.3 (s), 110.3 (s), 176.0 (s); exact mass (electrospray) m/z calcd for C₁₈H₃₂NaO₅Si (M + Na) 379.1911, found 379.1903.

(3aR,6R,7S,7aS)-rel-7-[(tert-Butyldimethylsilyl)oxy]-6,7a-dimethyl-hexahydro-2H-spiro[1-benzofuran-5,2’-[1,3]dioxolan]-2-one (28.1b).
t-BuMe₂SiCl (2.95 g, 19.58 mmol), imidazole (1.33 g, 19.58 mmol) and DMAP (20 mg, 0.16 mmol) were added in that order to a stirred solution of 26.2b (316 mg, 1.31 mmol) in DMF (2 mL). The mixture was heated at 70 °C for 48 h (N₂ atmosphere), cooled and diluted with Et₂O. The organic phase was washed with saturated aqueous NH₄Cl, water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et₂O-hexane, gave 28.1b (429 mg, 92%) as a solid: FTIR (cast film) 2956, 2933, 2886, 2858, 1777 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 0.98 (d, J = 7.3 Hz, 3 H), 1.48 (s, 3 H), 1.67 (dd, J = 13.4, 10.9 Hz, 1 H), 2.00 (dd, J = 13.4, 7.2 Hz, 1 H), 2.21-2.16 (m, 1 H), 2.29 (dd, J = 17.3, 5.5 Hz, 1 H), 2.39-2.34 (m, 1 H), 2.82 (dd, J = 17.3, 8.7 Hz, 1 H), 3.62 (d, J = 5.2 Hz, 1 H), 3.96-3.91 (m, 4 H); ¹³C NMR (CDCl₃, 125 MHz) δ -4.3 (q), -4.1 (q), 12.0 (q), 18.2 (s), 24.8 (q), 26.0 (q), 37.2 (t), 37.4 (d), 38.1 (t), 44.5 (d), 64.4 (t), 65.6 (t), 79.4 (d), 86.1 (s), 109.0 (s), 176.4 (s); exact mass (electrospray) m/z calcd for C₁₈H₃₂NaO₅Si (M + Na) 379.1911, found 379.1914.
BuLi (2.5 M in hexane, 0.61 mL, 1.53 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of i-Pr₂NH (0.25 mL, 1.79 mmol) in THF (4 mL). Stirring was continued for 30 min and the resulting solution was taken up into a syringe and added dropwise over ca 5 min to a stirred and cooled (-78 °C) solution of 28.1a (455 mg, 1.28 mmol) in THF (6 mL). Stirring was continued for 1 h at -78 °C and then HMPA (0.6 mL) was added, followed by solid trisyl azide (791 mg, 2.56 mmol). Stirring was continued for 30 min at -78 °C and then neat Me₃SiCl (0.65 mL, 5.11 mmol) was injected. Stirring was continued for 4 h, the cold bath being left in place but not recharged, so that the mixture attained room temperature. The mixture was quenched with pH 7 buffer and extracted with Et₂O. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 30% Et₂O-hexane, gave 28.2 (398 mg, 79%) as a solid: FTIR (cast film) 2956, 2931, 2888, 2858, 2113, 1785, 1473, 1463 cm⁻¹; ¹H NMR
(CDCl₃, 500 MHz) δ 0.06 (s, 3 H), 0.14 (s, 3 H), 0.89-0.94 (m, 12 H), 1.45 (s, 3 H), 1.72 (dd, J = 15.0, 6.0 Hz, 1 H), 1.80-1.86 (m, 1 H), 2.00 (d, J = 14.8 Hz, 1 H), 2.28 (dd, J = 12.3, 5.6 Hz, 1 H), 3.57 (d, J = 11.3 Hz, 1 H), 3.91-4.04 (m, 4 H), 4.77 (d, J = 12.5 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ -4.6 (q), -4.1 (q), 9.8 (q), 18.3 (q), 18.5 (s), 26.1 (q), 30.6 (t), 44.0 (d), 47.4 (d), 60.8 (d), 65.0 (t), 65.5 (t), 77.1 (d), 86.2 (s), 109.9 (s), 172.3 (s); exact mass (electrospray) m/z calcd for C₁₈H₃₁N₃NaO₅Si (M + Na) 420.1925, found 420.1923. Recrystallization of a sample from Et₂O-hexane by diffusion of hexane into an ether solution gave crystals suitable for X-ray analysis.

(3R,3aR,6S,7S,7aS)-rel-3-Amino-7-[(tert-Butyldimethylsilyl)oxy]-6,7a-dimethylhexa-hydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (29.1).

Pearlman’s reagent [Pd(OH)₂, 4 mg] was added to a solution of 28.2 (40 mg, 0.10 mmol) in THF (1 mL) and the mixture was stirred under an atmosphere of H₂ (balloon). Stirring was continued for 1.5 h, by which time all 28.2 had reacted (TLC, silica, 50% EtOAc-hexane). The mixture was filtered through a
pad of Celite, using EtOAc as a rinse. Evaporation of the filtrate gave 29.1, which was kept under oil pump vacuum and used directly in the next step.

**tert-Butyl (2E)-3-\{((3R,3aR,6S,7S,7aS)-rel-7-[(tert-butyldimethylsilyl)-oxy]-6,7a-dimethyl-2-oxohexahydro-2H-spiro[1-benzofuran-5,2’-[1,3]dioxolan-3-yl]carbamoyl}prop-2-enoate** (29.3).

![Chemical Structures](image)

DCC (101.3 mg, 0.45 mmol) and DMAP (19.9 mg, 0.16 mmol) were added to a stirred and cooled solution of crude 29.1 (from 0.16 mmol azide 28.2) and acid 29.2 (56.3 mg, 0.33 mmol) in CH₂Cl₂ (2 mL). After 5 min the ice bath was removed and stirring was continued for 3 h, by which time all the amine had reacted (TLC, silica, 50% Et₂O-hexane). The mixture was diluted with Et₂O and washed with saturated aqueous NaHCO₃, water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 30% Et₂O-hexane, gave 29.3 (52 mg, 61%) as a solid: FTIR (cast film) 3368, 2979, 2956, 2932, 2888, 2858, 1763, 1719, 1684, 1528, 1473, 1462 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.07 (s, 3 H), 0.14 (s, 3 H), 0.92-0.97 (m, 12 H), 1.47-
1.51 (m, 12 H), 1.61-1.65 (m, 1 H), 1.84 (dd, $J = 11.3, 6.6$ Hz, 1 H), 2.15 (d, $J = 14.9$ Hz, 1 H), 2.40 (dd, $J = 12.3, 6.3$ Hz, 1 H), 3.71 (d, $J = 11.3$ Hz, 1 H), 3.85 (q, $J = 7.2$ Hz, 1 H), 3.98-4.2 (m, 1 H), 4.06-4.10 (m, 1 H), 4.16-4.20 (m, 1 H), 5.43 (dd, $J = 12.4, 7.9$ Hz, 1 H), 6.05-6.11 (m, 1 H), 6.78 (q, $J = 16.6$ Hz, 2 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ -4.6 (q), -4.1 (q), 9.7 (q), 18.5 (s), 18.7 (q), 26.1 (q), 28.0 (q), 30.1 (t), 43.9 (d), 48.8 (d), 53.0 (d), 65.0 (t), 65.2 (t), 77.3 (d), 81.8 (s), 86.6 (s), 109.5 (s), 133.4 (d), 134.2 (d), 164.3 (s), 164.3 (s), 174.0 (s); exact mass (electrospray) $m/z$ calcd for C$_{26}$H$_{43}$NNaO$_8$Si (M + Na) 548.3, found 548.3.

**tert-Butyl** $\quad$ (2E)-4-{$\{(3R,3aR,6S,7S,7aS)-rel-7-[(tert-butylidimethylsilyl)oxy]-6,7a-dimethyl-2-oxohexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolane]-3-yl][$(tert-butoxy)carbonyl]$amino}-4-oxobut-2-enoate (30.2).

[Diagram of 29.3 and 30.2]

Pyridine (33.8 $\mu$L, 0.42 mmol), DMAP (ca 1 mg) and Boc$_2$O (96.2 $\mu$L, 0.42 mmol) were added in that order to a stirred and cooled (0 °C) solution of 29.3 (22 mg, 0.042 mmol) in MeCN (1 mL). After the addition the cold bath was removed and stirring was continued overnight. The mixture was quenched with
saturated aqueous CuSO₄ and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 20% Et₂O-hexane, gave 30.2 (22 mg, 86%) as a solid: FTIR (cast film) 2980, 2936, 2888, 2858, 1784, 1742, 1720, 1687, 1473, 1461 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.08 (s, 3 H), 0.16 (s, 3 H), 0.90-0.95 (m, 12 H), 1.49-1.55 (m, 22 H), 1.80-1.84 (m, 2 H), 2.84-2.95 (m, 1 H), 3.69 (d, J = 11.4 Hz, 1 H), 3.83 (q, J = 7.2 Hz, 1 H), 3.94-4.10 (m, 3 H), 5.95-6.03 (m, 1 H), 6.59-6.64 (m, 1 H), 7.50-7.56 (m, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ -4.6 (q), -4.0 (q), 9.7 (q), 18.5 (s), 18.8 (q), 26.1 (q), 27.9 (q), 28.0 (q), 30.1 (t), 43.8 (d), 65.0 (t), 65.2 (t), 77.5 (d), 81.7 (s), 85.8 (s), 86.3 (s), 109.4 (s), 132.2 (d), 136.1 (d), 164.4 (d); exact mass (electrospray) m/z calcd for C₃₁H₅₁NNaO₁₀Si (M + Na) 648.3174, found 648.3178.

**tert-Butyl N-[(3R,3aR,6S,7S,7aS)-rel-7-[(tert-butyldimethylsilyl)oxy]-6,7a-dimethyl-2-oxohexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-3-yl]carbamate (31.1).**

![Chemical structure of 29.1](image1.png) ![Chemical structure of 31.1](image2.png)
Boc₂O (58.8 mg, 0.27 mmol) and solid NaHCO₃ (18.1 mg, 0.21 mmol) were added to a stirred and cooled (0 °C) solution of 29.1 [from azide 28.2 (43 mg, 0.108 mmol)] in a mixture of MeCN (1.2 mL) and water (0.4 mL). The cooling bath was left in place but not recharged and stirring was continued for 3 h, by which time the mixture had reached room temperature. The mixture was quenched with saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 20% EtOAc-hexane, gave 31.1 (43.6 mg, 86% over two steps) as a solid:

FTIR (cast film) 3352, 2979, 2954, 2931, 2888, 2858, 1783, 1718, 1520, 1473, 1462 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.05 (s, 3 H), 0.13 (s, 3 H), 0.92-0.94 (m, 12 H), 1.45 (s, 12 H), 1.57-1.65 (m, 1 H), 1.83 (dq, J = 11.4, 6.5 Hz, 1 H), 2.10 (d, J = 14.4 Hz, 1 H), 2.33-2.38 (m, 1 H), 3.67 (d, J = 10.7 Hz, 1 H), 3.85 (q, J = 7.1 Hz, 1 H), 3.97-4.12 (m, 3 H), 4.80 (d, J = 8.0 Hz, 1 H), 4.99 (t, J = 8.9 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ -4.6 (q), -4.1 (q), 9.7 (q), 18.5 (s), 18.7 (q), 26.1 (q), 28.2 (q), 30.0 (t), 43.9 (d), 48.3 (d), 53.8 (d), 64.9 (t), 65.1 (t), 80.2 (s), 77.3 (d), 85.8 (d), 109.6 (s), 155.4 (s), 174.3 (s); exact mass (electrospray) m/z calcd for C₂₃H₄₁NNaO₇Si (M + Na) 494.2545, found 494.2543.

DMAP (1 mg), pyridine (8.5 µL, 0.11 mmol) and Boc₂O (23.1 mg, 0.11 mmol) were added to a stirred and cooled (0 °C) solution of **31.1** (10 mg, 0.02 mmol) in MeCN (0.5 mL). After 5 min, the ice bath was removed and stirring was continued for 1 h. The mixture was quenched with saturated aqueous CuSO₄ and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine, dried (MgSO₄) and evaporated. The residue, in a little CH₂Cl₂, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with CH₂Cl₂. Development of the column with 20% Et₂O-hexane gave **31.4** (10.5 mg, 86%) as a solid: FTIR (cast film) 2980, 2937, 2888, 2858, 1787, 1759, 1740, 1705, 1473, 1461 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.06 (s, 3 H), 0.16 (s, 3 H), 0.91-0.94 (m, 12 H), 1.48-1.55 (m, 21 H), 1.61 (dd, J = 14.9, 6.8 Hz, 1 H), 1.79-1.90 (m, 2 H), 2.92-2.96 (m, 1 H), 3.67 (d, J = 11.4 Hz, 1 H), 3.81-3.86 (m, 1 H), 3.93-4.00 (m, 1 H), 4.04-4.08 (m, 1 H), 5.64 (d, J = 12.1 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ -4.7 (q), -4.0 (q), 9.7 (q), 18.5 (s), 18.7 (q), 26.2 (q), 28.0 (q), 30.2 (t), 43.8 (d), 44.2 (d), 58.3 (t), 64.9 (t), 65.1 (t), 77.4 (d), 83.7 (s), 85.5 (s), 109.6 (s), 172.3 (s); exact mass (electrospray) m/z calcd for C₂₈H₄₉NNaO₉Si (M + Na) 594.3069, found 594.3091.
(3R,3aR,6S,7S,7aS)-rel-3-{Bis[(4-methoxyphenyl)methyl]amino}-7-
[(tert-butyldimethylsilyl)oxy]-6,7a-dimethylhexahydro-2H-spiro[1-benzo-
furan-5,2'-[1,3]dioxolan]-2-one (32.1).

K₂CO₃ (35.5 mg, 0.26 mmol) and PmbBr (18.5 µL, 0.13 mmol) were
added to a stirred solution of 29.1 [from azide 28.2 (17 mg, 0.048 mmol)] in
MeCN (0.5 mL), and stirring was continued overnight. The mixture was
quenched with water and extracted with CH₂Cl₂. The combined organic extracts
were washed with brine, dried (MgSO₄) and evaporated. The residue, in a little
CH₂Cl₂, was applied directly to the top of a flash chromatography silica gel
column made up in a Pasteur pipette (0.6 x 7 cm) with CH₂Cl₂. Development of
the column with 20% EtOAc-hexane gave 32.1 (17.7 mg, 68%) as a solid: FTIR
(cast film) 2953, 2933, 2901, 2856, 1763, 1612, 1586, 1512, 1463, 1442 cm⁻¹; ¹H
NMR (CDCl₃, 500 MHz) δ 0.08 (s, 3 H), 0.19 (s, 3 H), 0.83 (d, J = 6.6 Hz, 3 H),
0.93 (s, 9 H), 1.40 (s, 3 H), 1.56 (dd, J = 14.5, 6.9 Hz, 1 H), 1.74 (dq, J = 11.8, 6.1
Hz, 1 H), 1.88 (dd, J = 14.5, 1.1 Hz, 1 H), 2.34-2.37 (m, 1 H), 2.86 (q, J = 7.3 Hz,
1 H), 3.40 (dt, J = 7.9, 5.8 Hz, 1 H), 3.47 (d, J = 11.4 Hz, 1 H), 3.68-3.75 (m, 3
H), 3.81-3.88 (m, 9 H), 4.13 (d, J = 12.2 Hz, 1 H), 6.86-6.88 (m, 4 H), 7.27 (dd, J = 10.8, 2.2 Hz, 4 H); 13C NMR (CDCl3, 125 MHz) δ -4.6 (q), -4.0 (q), 9.7 (q), 18.51 (s), 19.1 (q), 26.1 (q), 30.5 (t), 43.9 (d), 44.6 (d), 54.1 (t), 55.3 (d), 61.4 (d), 64.8 (t), 64.8 (t), 77.6 (d), 85.3 (s), 109.8 (s), 113.7 (d), 130.1 (d), 131.9 (s), 158.8 (s), 175.1 (s); exact mass (electrospray) m/z calcd for C34H49NNaO7Si (M + Na) 634.3171, found 634.3171.

(3R,3aR,6S,7S,7aS)-rel-7-[(tert-Butyldimethylsilyl)oxy]-3-[(diphenylmethylidene)amino]-6,7a-dimethylhexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (33.1).

Benzophenone imine (12.6 µL, 0.076 mmol) was added to a solution of 29.1 [from azide 28.2 (20 mg, 0.05 mmol)] in PhMe (0.5 mL) and the mixture was heated at 100 °C for 6 h (TLC monitoring, silica, 50% EtOAc-hexane), by which time all 29.1 had reacted. The solvent was evaporated and the residue, in a little CH2Cl2, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with CH2Cl2. Development of
the column with 50% EtOAc-hexane gave **33.1** (19.9 mg, 74%) as a solid: FTIR (cast film) 2954, 2930, 2888, 2857, 1776, 1622, 1598, 1576, 1472, 1446, 1463 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) -0.00 (s, 3 H), 0.12 (s, 3 H), 0.79 (d, \(J = 6.6\) Hz, 3 H), 0.89-0.92 (m, 9 H), 1.51 (s, 3 H), 1.67-1.68 (m, 2 H), 1.76 (dd, \(J = 11.4, 6.6\) Hz, 1 H), 3.00 (ddd, \(J = 11.5, 4.8, 3.3\) Hz, 1 H), 3.36-3.42 (m, 2 H), 3.45-3.55 (m, 1 H), 3.71 (td, \(J = 7.4, 6.3\) Hz, 1 H), 3.79 (ddd, \(J = 7.5, 6.5, 5.0\) Hz, 1 H), 4.79 (d, \(J = 11.5\) Hz, 1 H), 7.31-7.36 (m, 2 H), 7.38-7.42 (m, 3 H), 7.45-7.48 (m, 3 H), 7.62-7.64 (m, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) -4.8 (q), -4.1 (q), 9.7 (q), 18.5 (q), 28.2 (q), 30.9 (t), 43.9 (d), 49.6 (d), 64.8 (d), 64.8 (t), 65.3 (t), 77.2 (d), 86.2 (s), 109.8 (s), 128.1 (d), 128.2 (d), 128.6 (d), 129.1 (d), 129.2 (d), 130.5 (d), 135.9 (s), 139.5 (s), 173.7 (s), 174.0 (s); exact mass (electrospray) \(m/z\) calcd for C\(_{31}\)H\(_{41}\)NNaO\(_5\)Si (M + Na) 558.2646, found 558.2643.

\((3R,3aR,6S,7S,7aS)-\text{rel-7-[(tert-butyldimethylsilyl)oxy]-6,7a-dimethyl-3-nitrohexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one}\) (**34.1**).
Ozonized oxygen was passed into cooled (-78 °C) \( \text{CH}_2\text{Cl}_2 \) (3.4 mL) until the solution became blue.

\( \text{Ph}_3\text{P} \) (9 mg, 0.03 mmol) was added to a stirred solution of 28.2 (10 mg, 0.025 mmol) and stirring was continued for 4 h. The resulting mixture was then transferred by syringe to the above stirred and cooled (-78 °C) saturated solution of \( \text{O}_3 \) in \( \text{CH}_2\text{Cl}_2 \). Stirring at -78 °C was continued for 30 min and then Ar was bubbled through the solution until the blue color was discharged. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.6 x 7 cm), using 30% EtOAc-hexane, gave 34.1 (6.2 mg, 62%) as an oil: FTIR (cast film) 2982, 2956, 2931, 2889, 2858, 1794, 1564 cm\(^{-1}\); \(^1\)H NMR (\( \text{CDCl}_3 \), 500 MHz) \( \delta \) 0.07 (s, 3 H), 0.14 (s, 3 H), 0.95-0.92 (m, 12 H), 1.57 (s, 3 H), 1.88-1.77 (m, 2 H), 1.96 (dd, \( J = 15.2, 1.8 \) Hz, 1 H), 3.28 (ddd, \( J = 12.6, 5.9, 1.8 \) Hz, 1 H), 3.47 (d, \( J = 11.3 \) Hz, 1 H), 4.06-3.94 (m, 4 H), 6.02 (d, \( J = 12.6 \) Hz, 1 H); \(^{13}\)C NMR (\( \text{CDCl}_3 \), 125 MHz) \( \delta \) -4.6 (q), -4.2 (q), 9.7 (q), 18.0 (q), 18.4 (s), 26.0 (q), 30.4 (t), 43.9 (d), 46.8 (d), 65.1 (t), 65.6 (t), 77.6 (d), 85.8 (d), 86.9 (s), 109.3 (s), 164.9 (s); exact mass (electrospray) \( m/z \) calcd for \( \text{C}_{18}\text{H}_{31}\text{NNaO}_7\text{Si} \) (M + Na) 424.1762, found 424.1755.

\((3E,3aR,6S,7S,7aS)-\text{rel}-7-[(\text{tert}-\text{butyldimethylsilyl})\text{oxy}]\text{-3-(hydroxy-imino)}\text{-6,7a-dimethylhexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one}\) (35.1).
\( \text{Na}_2\text{WO}_4\cdot2\text{H}_2\text{O} \) (24 mg, 0.072 mmol) and then \( \text{H}_2\text{O}_2 \) (30%, 0.5 mL, 5.8 mmol) were added to a stirred solution of 29.1 [from azide 28.2 (20 mg, 0.050 mmol)] in absolute EtOH (0.5 mL). Stirring was continued for 4 h, by which time all 29.1 had reacted (TLC monitoring, silica, 1:1 EtOAc-hexane). The mixture was quenched with saturated aqueous \( \text{NH}_4\text{Cl} \) and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous \( \text{NaHSO}_3 \) and brine, dried (\( \text{MgSO}_4 \)) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 30% EtOAc-hexane, gave 35.1 (15 mg, 72%) as a solid: FTIR (cast film) 3298, 2955, 2931, 2887, 2858, 1777 \text{ cm}^{-1}; \text{^1}H \text{ NMR (CDCl}_3, 500 \text{ MHz}) \delta 0.09 (s, 3 H), 0.17 (s, 3 H), 0.96-0.92 (m, 12 H), 1.45 (s, 3 H), 1.97-1.87 (m, 2 H), 2.60 (dd, \text{J} = 14.3, 4.3 \text{ Hz}, 1 \text{ H}), 3.21 (dd, \text{J} = 6.7, 4.4 \text{ Hz}, 1 \text{ H}), 3.61 (d, \text{J} = 8.8 \text{ Hz}, 1 \text{ H}), 3.96-3.87 (m, 4 H), 9.17 (s, 1 \text{ H}); \text{^13C NMR (CDCl}_3, 125 \text{ MHz}) \delta -4.6 (q), -4.2 (q), 10.9 (q), 18.3 (s), 20.8 (q), 26.0 (q), 30.4 (t), 43.2 (d), 44.0 (d), 64.6 (t), 65.5 (t), 78.1 (d), 85.9 (s), 108.8 (s), 150.2 (s), 164.9 (s); exact mass (electrospray) \text{m/z} \text{ calcd for C}_{18}\text{H}_{34}\text{NNaO}_6\text{Si} (\text{M} + \text{Na}) 408.1813, \text{found 408.1808}. \text{Recrystallization of a sample from Et}_2\text{O-hexane by diffusion of hexane into an ether solution gave crystals suitable for X-ray analysis.}
(6S,7S,7aS)-rel-7-[(tert-butyldimethylsilyl)oxy]-3-[(diphenylphosphoryl)amino]-6,7a-dimethyl-4,6,7,7a-tetrahydro-2H-spiro[1-benzofuran-5,2’-[1,3]dioxolan]-2-one (36.2).

Et₃N (5.2 µL, 0.037 mmol) was added dropwise to a stirred and cooled (-50 °C) solution of 35.1 (12 mg, 0.0312 mmol) in CH₂Cl₂ (0.5 mL). After 5 min neat Ph₂PCl (6.7 µL, 0.037 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued for 4 h, by which time the mixture had reached room temperature. The mixture was quenched with water and extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 40% EtOAc-hexane, gave 36.2 (12 mg, 67%) as an oil: FTIR (cast film) 3240, 3060, 2981, 2956, 2930, 2886, 2857, 1759, 1694, 1471, 1462, 1439 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.05 (s, 3 H), 0.17 (s, 3 H), 0.92-0.88 (m, 12 H), 1.23 (s, 3 H), 1.75 (d, J = 14.3 Hz, 1 H), 3.34 (d, J = 10.8 Hz, 1 H), 3.51 (d, J = 14.3 Hz, 1 H), 3.51 (d, J = 10.8 Hz, 1 H), 3.86-3.80 (m, 2 H), 3.98-3.89 (m, 2 H), 5.37 (d, J = 10.4 Hz, 1 H), 7.51-7.45 (m, 4 H), 7.58-7.53
(m, 2 H), 7.81-7.76 (m, 2 H), 7.90-7.85 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ - 4.6 (q), -3.9 (q), 9.9 (q), 17.8 (q), 18.4 (s), 26.1 (q), 34.4 (t), 44.1 (d), 65.3 (t), 65.3 (t), 78.4 (d), 88.1 (s), 109.3 (s), 122.9 (s), 128.9 (s), 128.9 (s), 129.0 (s), 130.1 (s), 131.0 (s), 131.2 (s), 131.5 (d), 131.6 (d), 132.1 (d), 132.2 (d), 132.6 (d), 132.7 (d), 137.6 (s), 169.9 (s), 170.0 (s); exact mass (electrospray) $m/z$ calcd for C$_{30}$H$_{40}$NNaO$_6$PSi (M + Na) 592.2255, found 592.2255.

$[(3E,3aR,6S,7S,7aS)-7-[(\text{tert-butyldimethylsilyl})\text{oxy}]\text{-}6,7a\text{-dimethyl-2-oxohexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-3-ylidene}]{\text{amino}}$ acetate (37.1).

![Diagram](image)

DMAP (1 mg), pyridine (10 $\mu$L, 0.0124 mmol) and AcCl (14.8 $\mu$L, 0.207 mmol) were added in that order to a stirred and cooled (0 °C) solution of 35.1 (16 mg, 0.0415 mmol) in CH$_2$Cl$_2$ (1 mL), and stirring was continued for 20 min. The cold bath was removed and stirring was continued for 1.5 h. The mixture was quenched with saturated aqueous CuSO$_4$ and extracted with CH$_2$Cl$_2$ and the combined organic extracts were dried (MgSO$_4$) and evaporated. Flash
chromatography of the residue over silica gel (0.6 x 7 cm), using 30% EtOAc-hexane, gave 37.1 (16 mg, 90%) as oil: FTIR (cast film) 2955, 2933, 2887, 2858, 1797 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.10 (s, 3 H), 0.16 (s, 3 H), 0.96-0.88 (m, 12 H), 1.47 (s, 3 H), 1.95-1.90 (m, 1 H), 2.02 (dd, J = 13.8, 6.4 Hz, 1 H), 2.35 (s, 3 H), 2.54 (dd, J = 14.2, 2.5 Hz, 1 H), 3.26 (dd, J = 5.9, 2.9 Hz, 1 H), 3.61 (d, J = 7.6 Hz, 1 H), 3.97-3.83 (m, 4 H); ¹³C NMR (CDCl₃, 125 MHz) δ -4.6 (q), -4.3 (q), 11.2 (q), 18.2 (s), 19.5 (q), 21.4 (q), 25.9 (q), 31.5 (t), 44.5 (d), 44.6 (d), 64.9 (t), 65.6 (t), 78.1 (d), 85.5 (s), 108.6 (s), 155.7 (s), 162.9 (s), 169.2 (s); exact mass (electrospray) m/z calcd for C₂₀H₃₃NNaO₇Si (M + Na) 450.1918, found 450.1916.

(3E,3aR,6S,7S,7aS)-3-[(Benzyloxy)imino]-7-[(tert-butyldimethylsilyl)-oxy]-6,7a-dimethylhexahydro-2H-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (38.1).

Bu₄NI (9.5 mg, 0.026 mmol), BnBr (4.6 µL, 0.039 mmol) and Ag₂O (Aldrich, 12 mg, 0.052 mmol) were added in that order to a stirred and cooled (0 °C) solution of 35.1 (10 mg, 0.026 mmol) in dry DMF (0.4 mL). Stirring was
continued for 10 min, the cold bath was removed and stirring was continued for 20 min. At this point, examination by TLC (silica, 40% EtOAc-hexane) showed that all 35.1 had reacted. The mixture was filtered through a plug of Celite in a Pasteur pipette, using Et₂O as a rinse. The ether phase was washed with saturated aqueous Na₂S₂O₃ and brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 10% Et₂O-hexane, gave 38.1 (9.5 mg, 78%) as a solid: FTIR (cast film) 2955, 2931, 2885, 2858, 1779, 1642, 1472, 1456 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.09 (s, 3 H), 0.16 (s, 3 H), 0.94-0.90 (m, 12 H), 1.42 (s, 3 H), 1.90-1.85 (m, 2 H), 2.40 (dd, J = 14.1, 4.3 Hz, 1 H), 3.16 (dd, J = 6.7, 4.2 Hz, 1 H), 3.62-3.55 (m, 2 H), 3.81-3.71 (m, 3 H), 5.31 (s, 1 H), 7.39-7.34 (m, 5 H); ¹³C NMR (CDCl₃, 125 MHz) δ -4.6 (q), -4.2 (q), 11.2 (q), 18.3 (s), 21.5 (q), 26.0 (s), 30.6 (t), 43.2 (d), 44.2 (d), 64.5 (t), 65.3 (t), 78.0 (d), 78.7 (t), 85.1 (s), 108.8 (s), 128.6 (d), 128.6 (d), 128.7 (d), 136.2 (s), 149.6 (s), 164.6 (s); exact mass (electrospray) m/z calcd for C₂₅H₃₇NNaO₆Si (M + Na) 498.2282, found 498.2283.
References


(8) Bringmann, G.; Lang, G.; Mühlbacher, J.; Steffens, S.; Rytik, P. G.;
Hentschel, U.; Morschhäuser, J.; Brun, R. In Marine Molecular
Biotechnology, Müller, W. E. G. Ed.; Sponges (Porifera); Springer:

(9) Bringmann, G.; Lang, G.; Mühlbacher, J.; Schaumann, K.; Steffens, S.;

(10) Bringmann, G.; Gulder, T. A. M.; Lang, G.; Schmitt, S.; Stöhr, R.; Wiese,

4489.


2006, 45, 2737-2741.

(16) Fleming, I.; Hennig, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. J.

(17) (a) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.;
Andersson, P. G.; Ito, Y. J. Am. Chem. Soc. 1993, 115, 6487-6498. (b)


(29) An American supplier of this BASF catalyst is Research Catalysts, Inc., P.O. Box 981014, Houston, Texas 77098.
(30) Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (985 mL) and concentrated sulfuric acid (15 mL).