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Total Synthesis of the Ionophore Antibiotic CP-61,405 (Routiennocin).‡

David Díez-Martin, Nikesh R. Kotecha, Steven V. Ley,* Sergio Mantegani, J. Carlos Menéndez, Helen M. Organ and Andrew D. White
Department of Chemistry, Imperial College of Science, Technology and Medicine, London, SW7 2AY, UK.
Bernard J. Banks
Pfizer Central Research, Sandwich, Kent, CT13 9NJ, UK.

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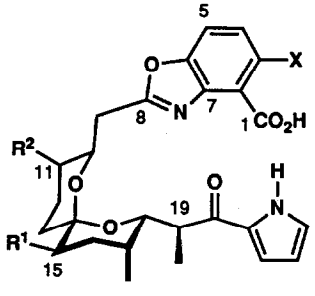
Abstract: The total synthesis of the spiroketal ionophore antibiotic routiennocin 1 (CP-61,405) employing π-allyltricarbonyl iron lactone complexes is described. These complexes were used as precursors for the preparation of substituted 2-phenylsulphonyl pyrans which, in turn, were coupled with iodoacetonides to afford spiroketals. Elaboration of the spiroketals by tetra-*n*-propylammonium perruthenate (TPAP) oxidation and coupling with 2-lithio-1-[β-(trimethylsilyl)ethoxymethyl] pyrrole followed by further oxidation, deprotection, oxidation and benzoxazole formation afforded the natural product. The preparation of the amino phenol fragment necessary for benzoxazole formation involved a novel amination procedure using benzeneselenenic anhydride and hexamethyldisilazane followed by samarium diiodide reduction.

CP-61,405 (Routiennocin)[1] **1** isolated from a microbial fermentation of *Streptomyces routiennii* Huang sp. nov. (ATCC 39446),[2] constituted a new member of a growing series of pyrrolylcarbonyl spiroketal ionophore antibiotics, the others of which are calcimycin (A-23187),[3] cezomycin,[4] X-14885A[5] and AC7230.[6]



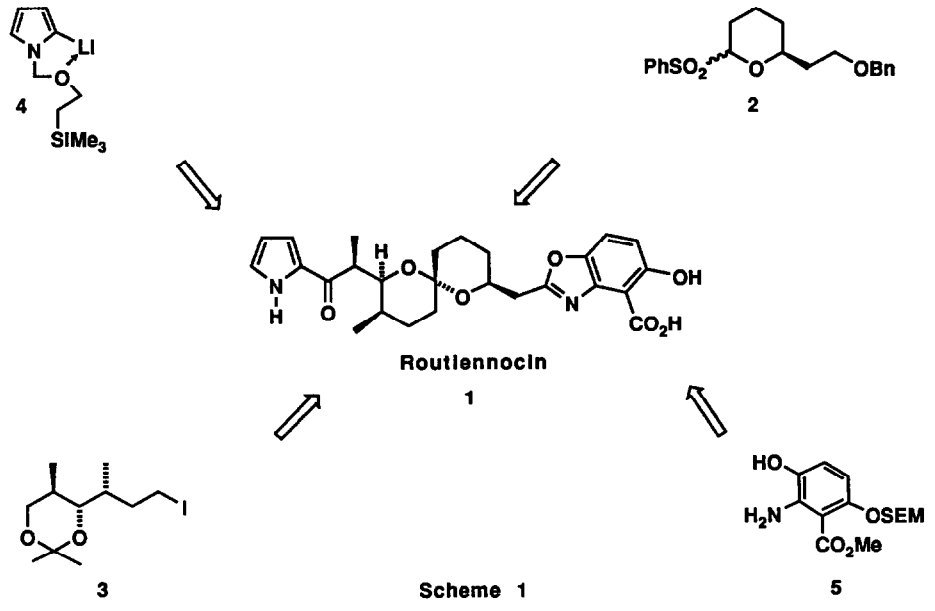
	R^1	R^2	X
Routiennocin	H	H	OH
Calcimycin	Me	Me	NHMe
Cezomycin	Me	Me	H
X-14885A	H	Me	OH
AC7230	Me	Me	OH

‡ *Dedicated to our friend and colleague Professor Charles Rees FRS on the occasion of his 65th birthday*

These compounds have the ability to form lipophilic complexes with high selectivity for various divalent cations such as Ca^{2+} and Mg^{2+} but, in some cases, will also bind monovalent ions like Li^+, Na^+, K^+ and Rb^+. As such, they are able to affect proton-cation exchange processes across biological membranes. Although their biological activity does not merit their development as commercial compounds, they are useful probes for cellular mechanisms owing to their ability to sequester calcium ions.[7]

In addition to its antibiotic activity against Gram positive and anaerobic organisms, routiennocin is weakly effective against *Eimeria tenella* coccidia in poultry and induces a change in the proportion of fatty acids produced in the rumen of cattle by increasing the molar proportion of propionate in the rumen fluids.[8]

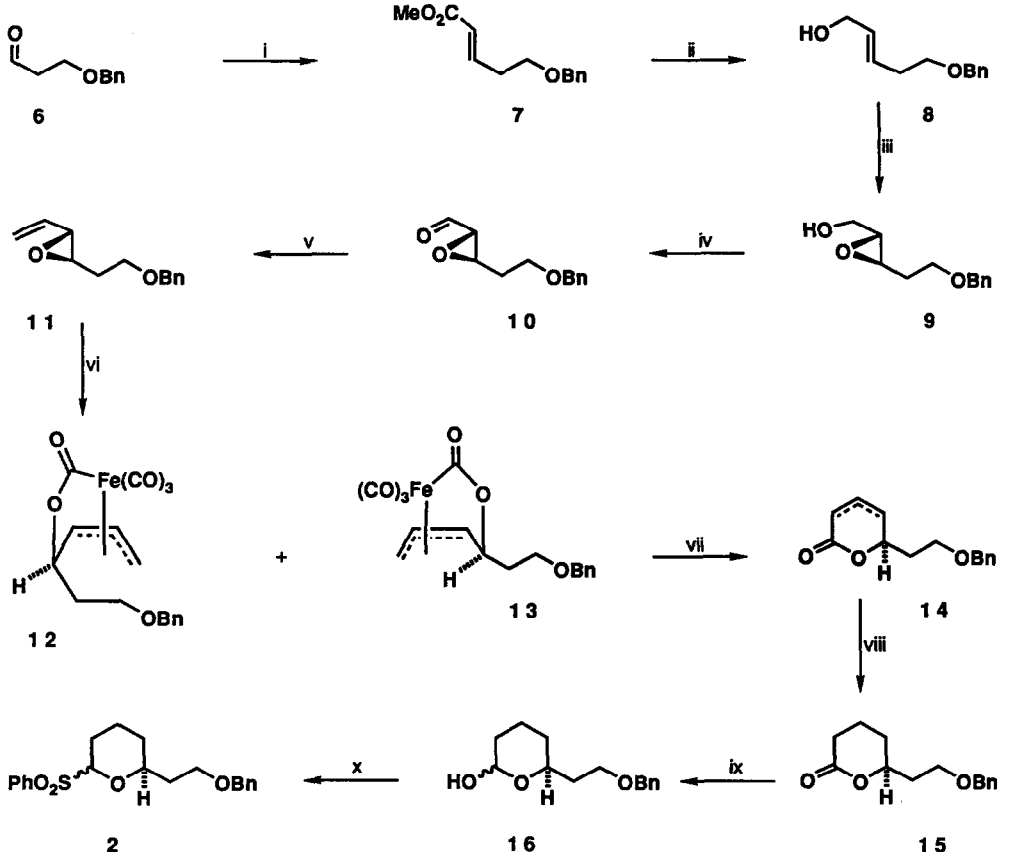
While there has been considerable effort towards the synthesis of calcimycin[9] and some structural analogues,[10] the other members of this series have received little attention. Here, we report in full on the total synthesis of **1** using methodology developed in our laboratories.[11] Our aim was to adopt a convergent strategy which would bring together four key components **2-5** as shown (Scheme 1).



Scheme 1

The choice of these coupling units was dictated by the wish to exploit further the use of 2-phenylsulphonyl pyrans in the preparation of spiroketals.[12] Furthermore this strategy allows us to examine a reverse coupling approach which is discussed later in the work. The other fragments proposed in the synthetic scheme make use of the 2-lithio-1-[β-(trimethylsilyl)ethoxymethyl] pyrrole **4** (2-lithio SEM-pyrrole) which we first introduced during our synthesis of indanomycin,[13] another pyrrolylcarbonyl containing ionophore antibiotic. The 1,2,3,4-tetra-substituted amino phenol derivative **5** exploits novel technology developed at Imperial College using benzeneselenenic anhydride and hexamethyldisilazane to oxidize phenols.[14]

Although we investigated several routes to the sulphone fragment **2**, only two are reported here. Initially, we chose to adopt the use of π-allyltricarbonyliron lactone complexes[15] as we had successfully shown these to be attractive and novel precursors of tetrahydropyran derivatives.[16] Wittig reaction of the known aldehyde **6**[17] with the stabilized reagent carbomethoxymethylenetriphenylphosphorane gave the (*E*)-alkene **7**. This was converted to the corresponding allylic alcohol **8** by reduction with Dibal-H in toluene under standard conditions and then epoxidised using the Sharpless asymmetric procedure[18] with D-(-) diethyltartrate, titanium isopropoxide and t-butyl hydroperoxide to produce the epoxy alcohol **9**.[19] Compound **9** was further elaborated to the epoxy aldehyde **10** by oxidation with PDC[20] in CH_2Cl_2. This aldehyde was methylenated to give the vinyl epoxide **11** by reaction with methyltriphenylphosphonium bromide and potassium hexamethyldisilazide at -20°C.[21]

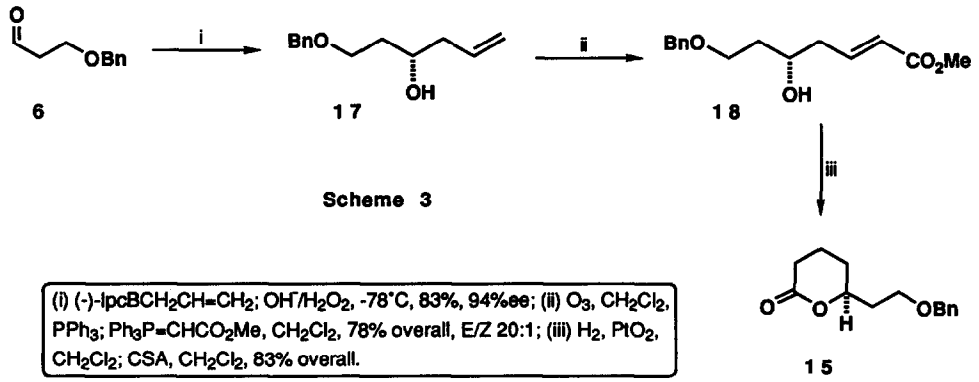


Scheme 2

(i) $MeO_2CCH{=}PPh_3$, CH_2Cl_2, RT, 5h, 81%; (ii) Dibal-H, PhMe, -78°C, 4h, 86%; (iii) D-(-)DET, $Ti(O^iPr)_4$, t-BuOOH, CH_2Cl_2, -25°C, 80%; (iv) PDC, CH_2Cl_2, RT, 12h, 86%; (v) $Ph_3PCH_3^+Br^-$, KHMDS, -20°C, 73%; (vi) $Fe_2(CO)_9$, THF, 6h, 72%; (vii) CO, Ph-H, 250 atm, 12h, 66%; (viii) H_2, PtO_2, AcOEt, RT, 75%; (ix) Dibal-H, PhMe, -78°C, 2h, 87%; (x) $PhSO_2H$, CSA, $CaCl_2$, CH_2Cl_2, RT, 5h, 72%.

Reaction of **11** with diironnonacarbonyl in THF[22] gave the *exo* and *endo* π-allyltricarbonyliron lactone complexes **12** and **13** in 72% yield. Although these complexes could be separated, we found it more convenient to carbonylate the mixture at 250atm and 90°C in benzene to afford the unsaturated lactones **14** (ratio α,β:β,γ 9:1, 66%). Similarly, these were not separated but were hydrogenated to a single lactone **15** using Adams' catalyst in ethyl acetate. The last steps for the preparation of the sulphone **2** were straightforward, involving the reduction of **15** with Dibal-H in toluene at -78°C to give an anomeric mixture of lactols **16**, followed by reaction with freshly prepared benzenesulphinic acid in CH_2Cl_2 containing calcium chloride under our previously reported conditions,[23] to give the crystalline sulphone **2** in 31% overall yield from the iron complexes (Scheme 2).

While this synthesis proceeded smoothly, we also developed an alternative sequence which led to the formation of the lactone **15** by a shorter route. Here, aldehyde **6** was treated with (-)allyl diisopinocampheyl borane[24] to give, after oxidative work-up, **17** in 83% yield and 94% ee.[25] Ozonolysis in CH_2Cl_2 at -78°C followed by reductive work-up, and one pot Wittig reaction with carbomethoxymethylenetriphenylphosphorane, furnished the unsaturated ester **18** (78%, *E/Z* 20:1). Hydrogenation of **18** employing platinum oxide as catalyst in CH_2Cl_2 produced an intermediate ester which was subsequently cyclized under acid catalysis to the previously synthesised lactone **15** in 83% overall yield (Scheme 3).



6 17 18 15

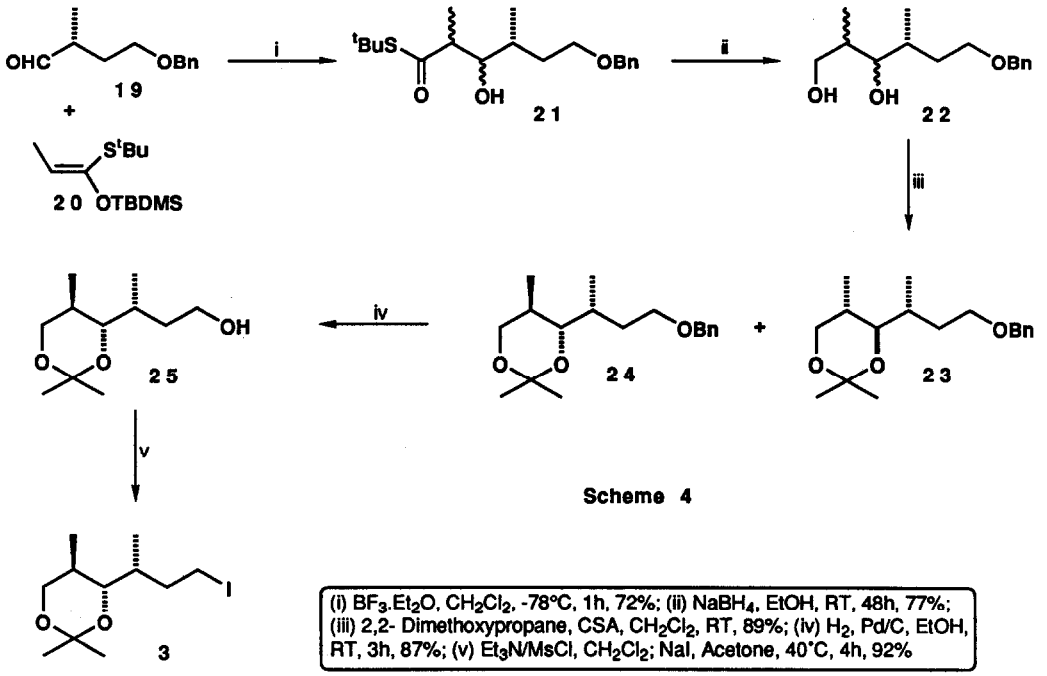
Scheme 3

(i) (-)-IpcBCH$_2$CH=CH$_2$; OH$^-$/H$_2$O$_2$, -78°C, 83%, 94%ee; (ii) O$_3$, CH_2Cl_2, PPh_3; Ph_3P=$CHCO_2Me$, CH_2Cl_2, 78% overall, E/Z 20:1; (iii) H_2, PtO_2, CH_2Cl_2; CSA, CH_2Cl_2, 83% overall.

The use of protecting groups other than benzyl was also investigated,[26] but were found to be less effective. An alternative approach towards the asymmetric synthesis of **15** using Enders' hydrazone alkylation methodology of a cyclopentanone derivative, followed by Baeyer-Villiger oxidation was also studied, but found to be unsatisfactory owing to poor enantioselectivity during the key alkylation reaction.

For the synthesis of the iodide coupling partner **3**, we again examined a number of routes. In the first of these, the aldehyde **19** obtained in six steps from *R*-(-)citronellene was reacted with the t-butyldimethylsilyl *Z*-ketene mono thioacetal **20** in the presence of $BF_3.OEt_2$ at -78°C, following the Gennari protocol.[27] All four possible aldol products were obtained contrary to expectations.[28] The two major diastereoisomers **21** (72%) were formed in a 70:30 ratio, as determined by high field NMR. These were separated from the minor diastereoisomers (12% combined yield). The major diastereoisomers **21** were reduced with sodium borohydride in ethanol to give the diols **22** which, again, were inseparable. Nevertheless, upon reaction with

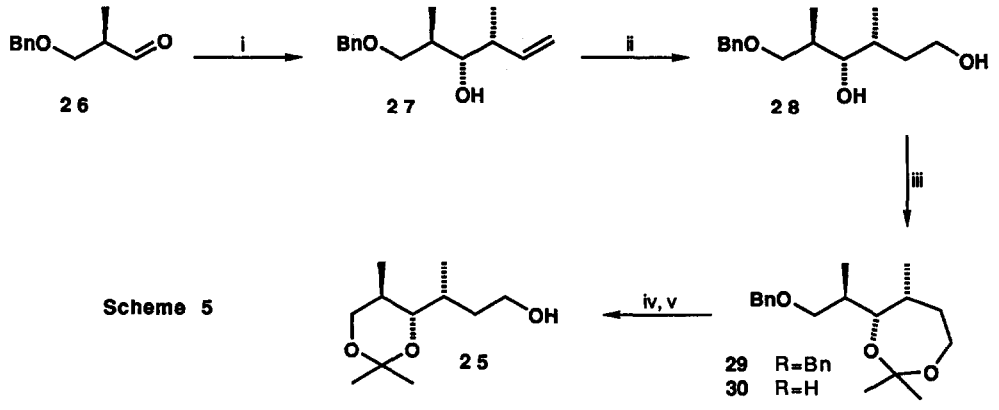
2,2-dimethoxypropane and catalytic camphor sulphonic acid (CSA), **22** gave the separable acetonides **23** and **24**. Proof of structure of the various products of these reactions followed from detailed NMR experiments and x-ray crystal structure determination of later derivatives[29] which are not reported here. The results of the aldol coupling can be summarised as producing a 2,3-*anti* to *syn* ratio of 6.4:1 and within the major *anti*-diastereoisomers a Cram/*anti*-Cram ratio of 2.3:1. Compound **24** obtained by this sequence was deprotected by hydrogenolysis under the normal conditions (H_2,Pd/C) to give the alcohol **25**. This was further transformed to the desired iodide **3** by iodide displacement of an intermediate mesylate under standard conditions (Scheme 4). These rather unsatisfactory ratios led us to develop a new route.



Scheme 4

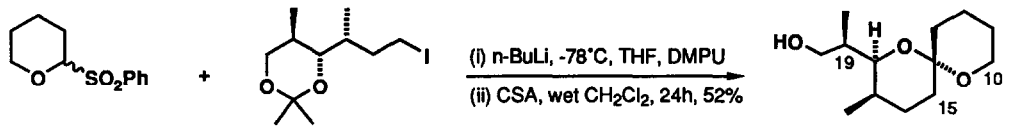
(i) $BF_3.Et_2O$, CH_2Cl_2, -78°C, 1h, 72%; (ii) $NaBH_4$, EtOH, RT, 48h, 77%; (iii) 2,2- Dimethoxypropane, CSA, CH_2Cl_2, RT, 89%; (iv) H_2, Pd/C, EtOH, RT, 3h, 87%; (v) Et_3N/MsCl, CH_2Cl_2; NaI, Acetone, 40°C, 4h, 92%

A much better synthesis of the alcohol **25** in high overall yield on a multi-gram scale, was achieved from the known aldehyde **26**.[30] This was reacted with (-)-B-methoxydiisopinocampheyl borane and (*Z*)-butene at -90°C under the Brown conditions[31] to afford alkenol **27**. The reaction proceeded with high stereoselectivity (9:1). Hydroboration of **27** with 9-BBN and work-up with alkaline hydrogen peroxide furnished an intermediate diol **28**, which was immediately treated with 2,2-dimethoxypropane and catalytic CSA to give the seven membered ring acetonide **29** (96%). Deprotection of **29** by hydrogenolysis in ethanol using Pd/C as catalyst gave alcohol **30**, which underwent ketal exchange to the required more thermodynamically stable six membered ring acetonide **25** upon stirring at room temperature with a trace of CSA and anhydrous copper sulphate. This pleasing rearrangement reaction under mild conditions also plays a role in a later reverse coupling strategy, and may well have application in other syntheses.[32] This synthesis from **26** proceeds in an excellent 44% overall yield (Scheme 5).



(i) (*Z*)-Butene, (-)-IpcBOMe, OH^-/H_2O_2; -90°C, 72%; (ii) 9-BBN,THF, OH^-/H_2O_2, 65°C, 2h, 92%; (iii) 2,2- Dimethoxypropane, CSA, CH_2Cl_2, RT, 5h, 96%; (iv) H_2, Pd/C, EtOH, RT, 12h, 82%; (v) Acetone, CSA, $CuSO_4$, RT, 10h, 84%.

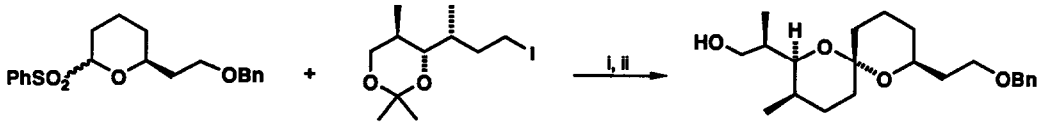
With two of the key fragments **2** and **3** in hand, we were now in a position to study their coupling to give the inherent central spiroketal portion of **1**. Prior to examining the real system, we investigated coupling of the iodide **3** with the simple 2-phenylsulphonylpyran **31** to test the feasibility of spiroketal production and define appropriate reaction conditions. We found that the anion derived from **31**, by treatment with n-butyllithium at -78°C in THF containing 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidone[33] (DMPU), reacted smoothly with **3** and, after treatment with CSA in wet CH_2Cl_2, a good yield (52%) of the required spiroketal product **32** was obtained (Scheme 6). The stereochemistry of the central asymmetric carbon of **32** is governed by the anomeric effect.



31 **3** **Scheme 6** **32**

This result confirmed our previous observations on the power of these sulphones as precursors of spiroketals for natural product synthesis.[34] Following this reaction, the coupling of real partners for the synthesis of **1** was undertaken.

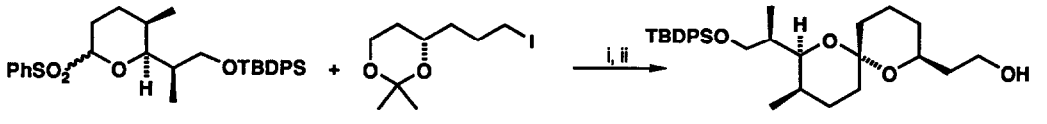
Under similar reaction conditions the sulphone **2** was deprotonated at -78°C to give a deep yellow solution and reacted with iodide **3** to give, after spirocyclization, the spiroketal **33** as the only isolable product in 68% yield (Scheme 7).



2 3 33

Scheme 7 (i) n-BuLi, -78°C, THF, DMPU; (ii) CSA, wet CH_2Cl_2,12h, 68%

The spiroketal alcohol **33** contains all the stereogenic centres required for the preparation of **1** and also contains suitable functionality for elaboration to the natural product. However, to exemplify further the versatility of this sulphone based methodology, we have investigated a reverse coupling strategy which first required the preparation of the alternative partners **34** and **35** which, we believed, could be coupled to give **36** (Scheme 8).

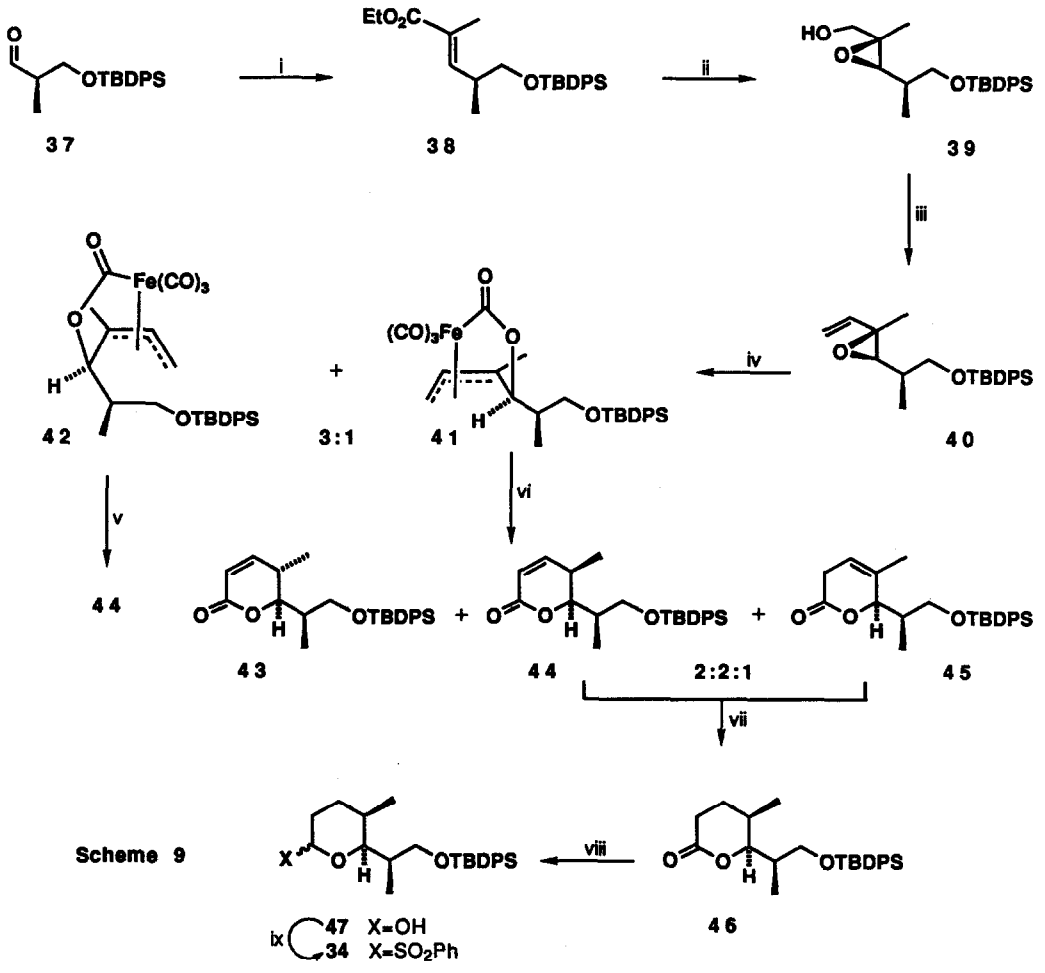


34 35 36

Scheme 8 (i) n-BuLi, -78°C, THF, DMPU; (ii) CSA, wet CH_2Cl_2,16h, 64%

Compound **36**, in turn, should be readily transformed to the spiroketal alcohol **33** obtained above, therefore providing a link between the two routes. Accordingly, we chose to adopt the use of iron carbonyl chemistry for the first approach to the preparation of the 2-phenylsulphonylpyran **34**.

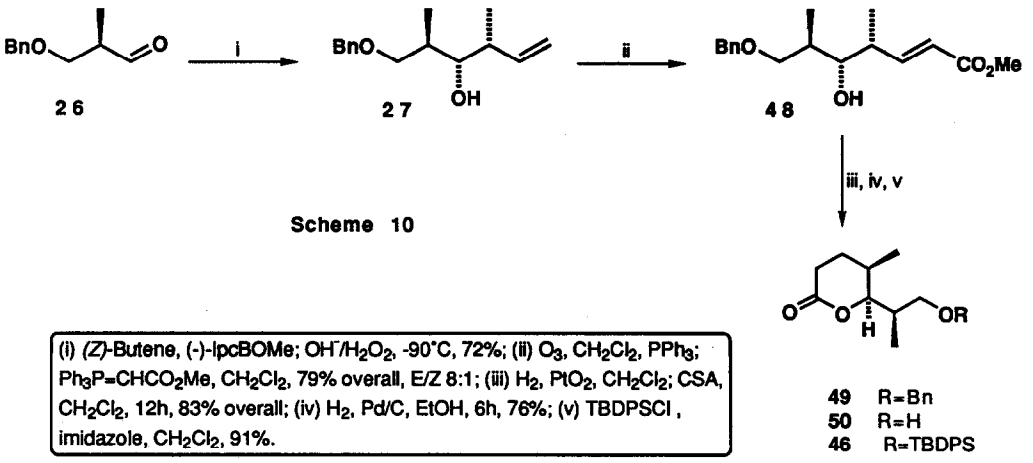
The known aldehyde **37**[30] was reacted with ethoxycarbonylethylidenetriphenylphosphorane to give the (*E*)-alkene **38** in excellent yield. This was converted by Dibal-H reduction at -78°C to the intermediate allylic alcohol, which was oxidised under the Sharpless non-catalytic epoxidation conditions, using D(-) diethyltartrate as the chiral auxiliary, to the epoxy alcohol **39**[35] in 93% overall yield. Conversion to the vinyl epoxide **40** was achieved by oxidation using the Swern conditions[36] followed by Wittig methylenation as before. Compound **40** was then reacted with diironnonacarbonyl in THF to give a 65% yield of the separable diastereomeric iron lactone complexes **41** and **42** in a 1:3 ratio. After separation by flash column chromatography, these complexes were individually carbonylated at high pressure to afford δ-lactones. **42**, upon treatment with carbon monoxide at 90°C and 240atm in benzene for three days gave the unsaturated lactone **44** in an excellent 98% yield. Under the same conditions complex **41** afforded three lactones **43**, **44** and **45** in essentially quantitative yield and a 2:2:1 ratio; the two required lactones **44** and **45** were readily separated from the undesired isomer **43**. Hydrogenation of pure **44**, or the mixture of **44** and **45**, using platinum oxide as catalyst, gave a single saturated lactone **46**. Proof of the structure of **46** follows from detailed NMR studies and coupling constant comparison with predicted values generated by computer modelling using the Macromodel program[37] and also by other later experiments. Lastly, **46** was converted to the required pyran sulphone **34** by reduction with Dibal-H to afford the intermediate lactols **47** which, on treatment with benzenesulphinic acid, gave **34** in excellent yield. The structure of **34** was additionally confirmed by single crystal x-ray studies.[38] The overall yields of **34** from the iron complexes **41** and **42** were 61% and 82% respectively (Scheme 9)



Scheme 9

(i) $EtO_2CC(CH_3)=PPh_3$, CH_2Cl_2, RT, 5h, 95%; (ii) Dibal-H, PhMe, -78°C, 30min; $Ti(O^iPr)_4$, D-(-) DET, CH_2Cl_2, t-BuOOH, -25°C, 93% overall; (iii) Me_2SO, $(COCl)_2$, CH_2Cl_2, -78°C, 30min, Et_3N; $Ph_3PCH_3^+Br^-$, KHMDS, -20°C, 85% overall; (iv) $Fe_2(CO)_9$, THF, 8h, 65%; (v) CO (240atm), PhH, 90°C, 3 days, 98%; (vi) same as (v),100%; (vii) H_2, PtO_2, EtOAc, 12h, 95%; (viii) Dibal-H, PhMe, -78°C, 1h, 96%; (ix) $PhSO_2H$, CSA, CH_2Cl_2, RT, 20h, 92%.

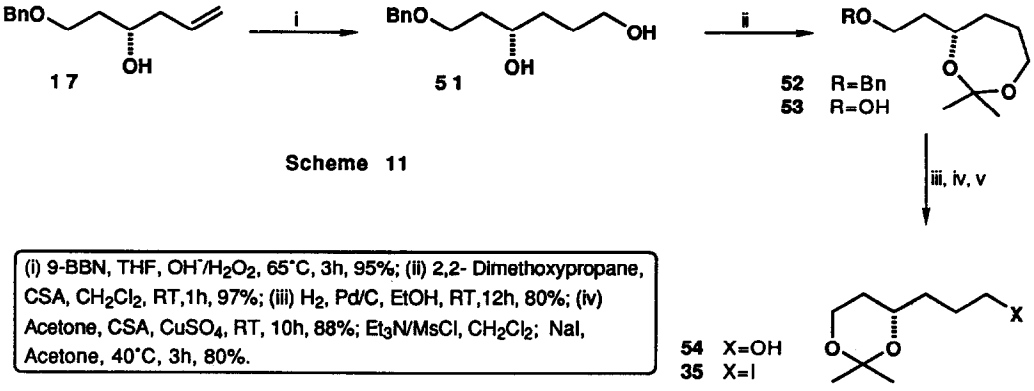
An alternative route to **34**, which we were able to operate on a larger scale, employed the aldehyde **26** used earlier (scheme 5) as the starting material. Once again, under the Brown conditions of (-)-B-methoxy-diisopinocampheyl borane and (Z)-butene at -90°C, **26** afforded the alkenol **27** with excellent stereoselectivity. This was transformed to the unsaturated ester **48** by standard ozonolysis and one pot Wittig coupling with carbomethoxytriphenylphosphorane to afford an 8:1 mixture of *E/Z* isomers in 79% overall yield. These were further transformed to the lactone **49** by hydrogenation of the double bond followed by lactonisation with catalytic camphor sulphonic acid in CH_2Cl_2 over 12 hours (Scheme 10). Following deprotection of the benzyl ether by hydrogenolysis, **49** was converted to **50** which, after silylation afforded the lactone **46** synthesised earlier (*vide supra*).



Scheme 10

(i) (*Z*)-Butene, (-)-IpcBOMe; OH^-/H_2O_2, -90°C, 72%; (ii) O_3, CH_2Cl_2, PPh_3; $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 79% overall, E/Z 8:1; (iii) H_2, PtO_2, CH_2Cl_2; CSA, CH_2Cl_2, 12h, 83% overall; (iv) H_2, Pd/C, EtOH, 6h, 76%; (v) TBDPSCl, imidazole, CH_2Cl_2, 91%.

For the preparation of the iodide **35**, required in this alternative coupling approach, we used a similar strategy to the previous sequence to maximise the use of common precursors. Thus the same alkenol **17** used in Scheme 3 was subjected to hydroboration to give the diol **51** using 9-BBN under the usual conditions. This was then protected with 2,2-dimethoxypropane and CSA to afford the seven membered ring acetal **52**. Following removal of the benzyl group by hydrogenolysis, the resulting alcohol **53** underwent the acetal rearrangement noted previously with acetone, CSA and anhydrous copper sulphate to give the more stable 6-ring acetal **54**. Finally, **54** was converted to the volatile iodide **35** *via* its mesylate, followed by displacement with iodide in the normal way (Scheme 11).

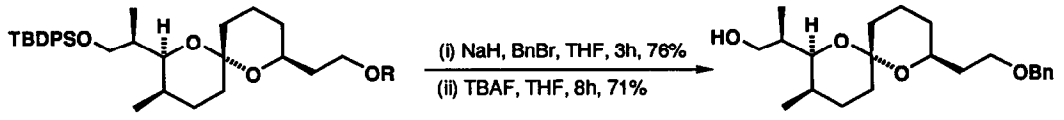


Scheme 11

(i) 9-BBN, THF, OH^-/H_2O_2, 65°C, 3h, 95%; (ii) 2,2- Dimethoxypropane, CSA, CH_2Cl_2, RT,1h, 97%; (iii) H_2, Pd/C, EtOH, RT,12h, 80%; (iv) Acetone, CSA, $CuSO_4$, RT, 10h, 88%; Et_3N/MsCl, CH_2Cl_2; NaI, Acetone, 40°C, 3h, 80%.

With good supplies of the coupling partners **34** and **35** in hand, we next studied their conversion to spiroketals. We found the sulphone **34** to be less reliable as a coupling partner compared to previous model studies. Nevertheless, we were able to react the anion derived from **34** by treatment with *n*-butyl lithium at -78°C with the iodide **35** and after treatment with CSA in wet CH_2Cl_2 for 12 hours obtained the spiroketal **36** in 64% yield. In order to correlate this material with the previously synthesised spiroketal **33**, compound **36** was benzylated with benzyl bromide using sodium hydride to effect the deprotonation, followed by removal of the TBDPS protection with tetra-*n*-butylammonium fluoride (TBAF) to give **33** identical in all respects to the

previously prepared compound (Scheme 12). This alternative coupling approach further exemplifies the power of this sulphone based methodology for the preparation of spiroketals.

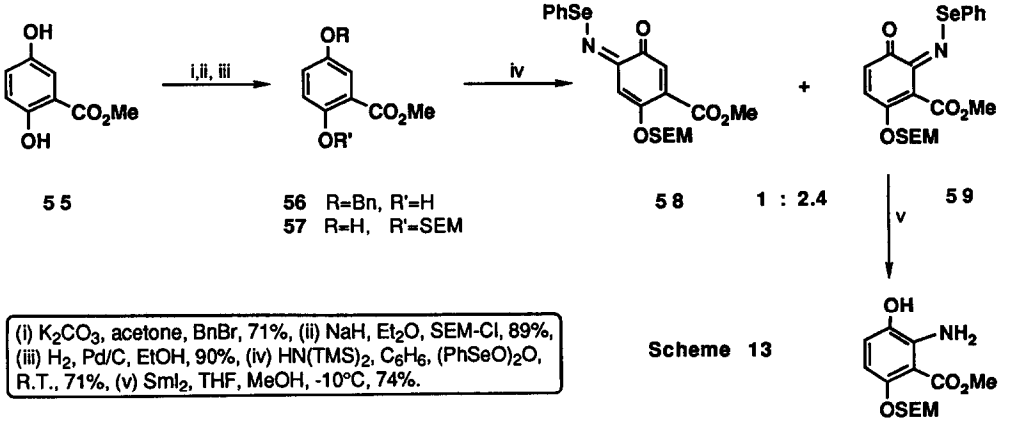


36 R=H
36a R=Bn

33

Scheme 12

The next phase of our work required the synthesis of fragments **4** and **5** proposed in Scheme 1 for the convergent construction of the natural product routiennocin **1**. The SEM-pyrrole **4** was obtained using our previously established methods.[39] However, the aminophenol fragment **5** required the development of some new chemistry. Although it was reported in the literature[40] that gentistic acid derivatives could be nitrated to give materials which would serve as precursors for the preparation of the fragment **5**, we found these reactions to be unreliable and inconvenient. Moreover, it was not possible to carry acid sensitive groups such as the SEM group during these phenol nitration steps. We therefore chose a novel alternative approach to establish the required aromatic 1,2,3,4-tetra-substitution pattern. Selective alkylation of commercially available gentistic acid methyl ester **55** with potassium carbonate and benzyl bromide gave the mono benzyl ether **56**, together with a small amount of the corresponding bis-benzyl ether which was easily removed by chromatography. Alkylation with SEM-Cl in the presence of sodium hydride, followed by hydrogenolysis with palladium on carbon in ethanol gave phenol **57** in an excellent 81% overall yield. Reaction of **57** with benzeneselenenic anhydride[41] and hexamethyldisilazane in benzene at room temperature gave two intensely coloured phenylselenoimines **58** and **59**, in 21% and 50% yield respectively. The phenylselenoimine **59** was then subjected to reduction at -10°C with samarium diiodide[42] in THF to give **5** (Scheme 13). As the *ortho*-phenolic aniline **5** was unstable, due to ready oxidation, we found that flash column chromatography of the crude reaction mixture was the most convenient work-up, affording a 74% yield of **5**. This new procedure is mild, selective and particularly advantageous when compared to those sequences involving strongly acidic conditions for the preparation of aminophenols.



55

56 R=Bn, R'=H
57 R=H, R'=SEM

58 1 : 2.4 **59**

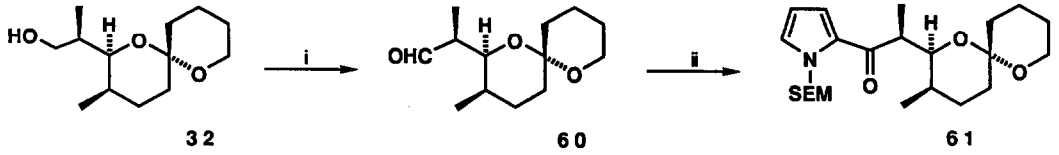
(i) K_2CO_3, acetone, BnBr, 71%, (ii) NaH, Et_2O, SEM-Cl, 89%, (iii) H_2, Pd/C, EtOH, 90%, (iv) $HN(TMS)_2$, C_6H_6, $(PhSeO)_2O$, R.T., 71%, (v) SmI_2, THF, MeOH, -10°C, 74%.

Scheme 13

5

During this work on the synthesis of routiennocin we also investigated the preparation of many other aminophenol fragments with alternative functional group protection but all proved unsatisfactory for various reasons and could not be processed to the final natural product. None of these alternatives are therefore discussed here.[43]

Although all the elements of the routiennocin synthesis were now established, we wished to test the viability of certain key transformations on model systems prior to commiting more precious material. Firstly, we investigated the incorporation of the pyrrolylcarbonyl unit into spiroketal precursors. Therefore, the model spiroketal alcohol **32** prepared earlier was oxidised to the aldehyde **60** using oxalyl chloride-activated dimethyl sulphoxide. To this aldehyde was added 2-lithio-1-[β-(trimethylsilyl)ethoxymethyl] pyrrole **4** at -10°C in dimethoxyethane to give an intermediate coupled product which was immediately oxidised using DDQ in dioxane[44] to give a 34% yield of ketopyrrole **61**, (Scheme 14). We were encouraged by this result, but hoped to improve yields on the real system.

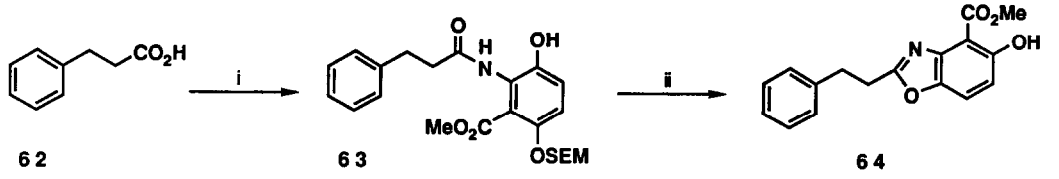


32 60 61

(i) Me_2SO, $(COCl)_2$, CH_2Cl_2, Et_3N, -60°C, 1h, 71%;
(ii) **4**, DME, -10°C; DDQ, dioxane, RT,1h, 34% overall

Scheme 14

Secondly we examined benzoxazole formation on a model carboxylic acid **62**. Several aminophenol derivatives were studied but eventually we chose to effect the coupling of the SEM protected derivative **5** prepared above. This was achieved by reaction of phenylpropionic acid **62** with ethylchloroformate at -10°C to form the activated anhydride, which reacted with **5** to form initially a mixture of both an ester and the amide **63**. However, exposure of this crude mixture of coupling products to pyridinium-*p*-toluenesulphonic acid (PPTS) in methanol and 1,2-dichloroethane at reflux, gave the benzoxazole **64** in 58% overall yield, (Scheme 15).

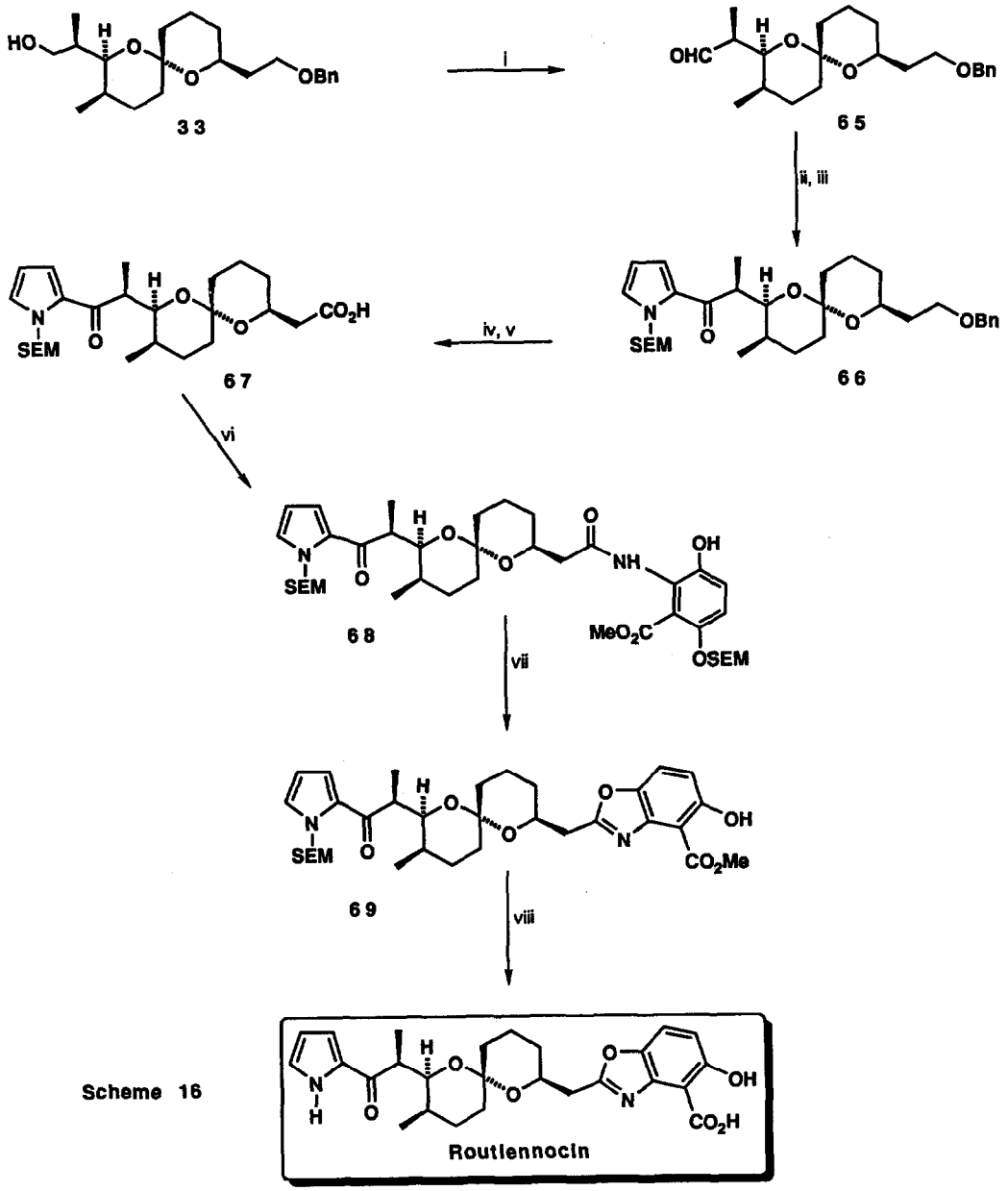


62 63 64

(i) $ClCO_2Et$, Et_3N, CH_2Cl_2, then **5**, -10°C, 17h, 63%; (ii) PPTS, MeOH, 1,2-dichloroethane, 80°C, 3h, 92%;

Scheme 15

While this process worked well for the model compound, it required further modification for the real system (*vide infra*). Nevertheless, we were now confident to proceed with the natural product synthesis.



Scheme 16

(i) TPAP, NMO, CH_2Cl_2, 4Å mol sieves,1h, 98%; (ii) **4**, 4:1 DME/THF, -10°C; (iii) TPAP, NMO, CH_3CN, 4 Å mol sieves, 3h, 61% overall; (iv) H_2, Pd/C, EtOH, 5h; (v) CrO_3, H_2SO_4, acetone, 1h, 72%; (vi) $ClCO_2Et$, Et_3N, CH_2Cl_2, **5**, -10°C, 12h, 77%; (vii) PPE, $CHCl_3$, 60°C, 1h, 71%; (viii) TBAF, THF, 4h; aq. LiOH, THF, RT, 12h, 82% overall.

Oxidation of the spiroketal alcohol **33** with our catalytic room temperature oxidant TPAP[45] proceeded smoothly to give the spiroketal aldehyde **65** in an excellent 98% yield with no detectable racemization of the α stereogenic centre. This aldehyde could then be coupled with **4** in a 4:1 mixture of THF and DME at -10°C, and the intermediate diastereomeric mixture of alcohols oxidised with TPAP to afford the ketopyrrole **66** in a pleasing 61% overall yield. Next, we turned our attention to the final important coupling reaction, that of installing the benzoxazole unit. Accordingly, the benzyl group was removed from **66** by hydrogenolysis, and the resulting alcohol oxidised with Jones' reagent to produce acid **67** in 72% overall yield. An alternative two step oxidation was also investigated, using TPAP followed by sodium chlorite,[46] however the yield was inferior (66%) to the direct oxidation method.

As in the model study, the spiroketal acid **67** reacted well with ethylchloroformate and the aminophenol **5** to give a mixture of both the desired ester and amide coupled materials. Exposure of this crude mixture to silica gel in dichloromethane gave the amide **68** in 77% yield. Attempted benzoxazole formation using the PPTS conditions established earlier failed. The problem was overcome by using ethyl polyphosphate[47] (PPE) in chloroform at reflux for 1h, to give benzoxazole **69** in which the SEM protecting group on the phenolic oxygen had been selectively removed (71%). The final steps of the synthesis were achieved by deprotection of **69** with anhydrous TBAF[48] in THF to remove the remaining SEM group from the pyrrole nitrogen atom, and then saponification with aqueous lithium hydroxide to give the ionophore routiennocin **1** in 82% overall yield (Scheme 16). The synthetic sample was identical in all respects ($[\alpha]_D^{20}$, i.r., t.l.c., nmr, m.s.) to an authentic sample kindly provided by Pfizer Inc, U.S.A.

The above reactions constitute the first total synthesis of routiennocin and moreover they harness a number of methods developed by our group in the synthesis of a challenging synthetic target molecule.

Acknowledgements:

We thank the SERC and Pfizer Central Research for financial support and a CASE award (HMO), The Ministerio de Education y Ciencia and the British Council for a Fleming Fellowship (DDM, JCM), and Farmitalia Carlo Erba for study leave for (SM). The SERC Mass Spectroscopy Centre, University College, Swansea, is gratefully acknowledged for mass spectral data.

Experimental

^1H and ^{13}C nmr spectra were recorded in $CDCl_3$ unless otherwise stated, using a Jeol JSX, Bruker WM 270 or AM-500 nmr spectrometer, using residual protic solvent $\underline{C}HCl_3$ (δ_H =7.26 ppm) or $\underline{C}DCl_3$ (δ_C=77.0 ppm, t) as internal reference. Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer. Mass spectra were recorded using VG-7070B, VG 12-253 and VG ZAB-E instruments in the Imperial College Chemistry Department and the SERC Mass Spectrometry Service in Swansea. Microanalyses were performed in the Department microanalytical laboratory and by MEDAC Ltd at Brunel University . Melting points were determined on a Reichert hot stage apparatus. Optical rotations were measured using an Optical Activity AA-1000 polarimeter. Molecular modelling was performed using the MACROMODEL package,[37] on an Evans and Sutherland PS-390 graphics terminal. All experiments were carried out in oven dried glassware under an

argon atmosphere unless otherwise stated. Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) unless otherwise stated. Florisil refers to 200-300 U.S. mesh Florisil as supplied by BDH Ltd. Diethyl ether, tetrahydrofuran and dimethoxyethane solvents were distilled from sodium benzophenone ketyl; dichloromethane from phosphorous pentoxide; toluene from sodium; acetonitrile and dimethyl sulphoxide from calcium hydride; methanol from magnesium; triethylamine and diisopropylamine from potassium hydroxide. Petrol refers to petroleum ether b.pt. 40-60°C which was distilled prior to use as was ethyl acetate. Other solvents and reagents were purified by standard procedures as necessary. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised by acidic ammonium molybdate (IV). Numbering for ^1H nmr assignments follows the calcimycin nomenclature. Coupling constants are measured in Hertz.

(*E*)-Methyl 5-(benzyloxy)-2-pentenoate (7).

carbomethoxymethylenetriphenylphosphorane (19.42g, 58.1mmol) was added to a solution of aldehyde **6** (8.65g, 52.7mmol) in dry dichloromethane (200ml) at room temperature, and the resulting solution stirred for 5h. The reaction mixture was filtered through a pad of silica and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 15% ether-petrol yielding the *α,β-unsaturated ester* **7** (9.4g, 81%) as a colourless oil; υ_{max}(film) 2949, 2858, 1721, 1657, 1484, 1434, 1316, 1272, 1102 and 699cm^{-1}; δ_H(270MHz) 7.30 (5H, m, Ar-H), 6.85 (1H, dt, *J* 15.3 and 7.1Hz, H-3), 5.85 (1H, dt, *J* 15.3 and 1.8Hz, H-2), 4.43 (2H, s, OCH_2Ph), 3.7 (3H, s, CO_2CH_3), 3.55 (2H, t, *J* 6.2Hz, H_2-5) and 2.42 (2H, qd, *J* 6.2 and 1.5Hz, H_2-4); *m/z* 220 (M^+) 189 (M^+-CH_3O), 121 (M^+-$C_5H_7O_2$), 117 ($C_7H_7O^+$), 91 ($C_7H_7^+$); Found: C, 70.95; H, 7.30. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%.

(*E*)-5-(Benzyloxy)-2-penten-1-ol (8).

Diisobutylaluminium hydride (63ml of 1.5M solution in toluene, 94.41mmol) was added dropwise to a solution of the α,β-unsaturated ester **7** (10.38g, 47.2mmol) in toluene (100ml) at -78°C under argon, and the resulting solution stirred for 4h. Water (6ml) was added carefully, and the reaction mixture warmed slowly to room temperature, continuing stirring until the reaction mixture became gelatinous. This was diluted with ethyl acetate (80ml) and poured into a stirred slurry of sodium sulphate (50g) in ethyl acetate (200ml). After 15min., the liquid was decanted, and the solid re-extracted with ethyl acetate as described before. The combined ethyl acetate extracts were evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with 50% ether-petrol to give the *allylic alcohol* **8** (7.8g, 86%) as a clear oil; υ_{max}(film) 3250, 2930, 2858, 1670, 1603, 1361, 1098 and 737cm^{-1}; δ_H(270MHz), 7.28 (5H, m, Ar-H), 5.64 (2H, m, H-2, H-3), 4.46 (2H, s, OCH_2Ph), 4.0 (2H, br s, H_2-1), 3.47 (2H, t, *J* 6.6Hz, H_2-5), 2.31 (2H, m, H_2-4), and 2.12 (1H, br s, OH); *m/z* 192 (M^+), 174 (M^+-H_2O), 120 (M^+-C_4H_8O), 107 ($C_7H_7O^+$) and 91 ($C_7H_7^+$); Found: M^+, 192.1145. $C_{12}H_{16}O_2$ requires *M*, 192.1150; Found: C, 74.91; H, 8.44. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%.

(*2S,3R*)-3-[2-(Benzyloxy)ethyl]-2-oxiranemethanol (9).

D-(-)Diethyltartrate (7.38ml, 43.27mmol) was added dropwise to a solution of titanium tetra-isopropoxide (12.85ml, 43.17mmol) in dry dichloromethane (300ml) at -25°C under argon. The mixture was stirred for 15min before adding a solution of allylic alcohol **8** (8.28g, 43.17mmol) in dry dichloromethane (100ml) and *tert*-butyl hydroperoxide (24.66ml, 86.34mmol). The resulting yellow mixture was stirred at -25°C for 12h.

After this time, 10% aqueous tartaric acid (100ml) was added dropwise and the stirring continued for a further 1h at -25°C. The reaction mixture was allowed to warm to room temperature over 1h and the organic layer separated, washed with brine (300ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel eluting with 60% ether-petrol affording the *epoxy alcohol* **9** (7.2g, 80%) as a colourless oil, $[\alpha]_D^{23}$ +29.76 (c 1.47 in $CHCl_3$); υ_{max}(film) 3422, 2863, 1746, 1451, 1365, 1103, 884 and 740cm^{-1}; δ_H(500MHz) 7.35 (5H, m, Ar-H), 4.51 (2H, s, OCH_2Ph), 3.90 (1H, ddd, *J* 12.5, 5.5 and 2.5Hz, H-1), 3.62 (3H, m, H-1 and H_2-5), 3.18 (1H, td, *J* 5.7 and 2.3Hz, H-3), 2.97 (1H, td, *J* 4.5 and 2.4Hz, H-2), 2.95 (2H, m, H_2-4) and 1.78 (1H, dd, *J* 7.2 and 5.5Hz, OH); *m/z* 208 (M^+), 207 (M^+-H), 190 (M^+-H_2O), 177 (M^+-OCH_3), 107 ($C_7H_7O^+$), and 91 ($C_7H_7^+$); Found: C, 69.20; H, 7.72. $C_{12}H_{16}O_3$ requires C, 69.19; H, 7.75%.

(*2R,3R*)-3-[2-(Benzyloxy)ethyl]-2-oxiranecarboxaldehyde (10).

Pyridinium dichromate (15.2g, 44mmol) was added portionwise to a solution of the epoxy alcohol **9** (6.24g, 30mmol) in dry dichloromethane (150ml) containing 4Å molecular sieves (5g), and the mixture stirred at room temperature overnight. The dark brown mixture was diluted with ether (200ml) and filtered through a pad of celite after which the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 30% ether-petrol to afford the *epoxy aldehyde* **10** (5.31g, 86%) as a colourless oil, $[\alpha]_D^{25}$ -15.86 (c 1.5 in $CHCl_3$); υ_{max}(film) 2950, 2870, 1725, 1420, 1100, 740 and 699cm^{-1}; δ_H(270MHz) 9.1 (1H, d, *J* 6.1Hz, H-1), 7.38 (5H, m, Ar-H), 4.45 (2H, s, OCH_2Ph), 4.35 (2H, t, *J* 6Hz, H_2-5), 3.42 (1H, td, *J* 6.1 and 2Hz, H-3), 3.21 (1H, dd, *J* 6.1 and 1.9Hz, H-2), 1.95 (2H, m, H_2-4); *m/z* 206 (M^+), 205 (M^+-H), 160 (M^+-CH_2O_2), 107 ($C_7H_7O^+$) and 91 ($C_7H_7^+$); Found: M^+-H, 205.0868. $C_{12}H_{13}O_3$ requires *M-H*, 205.0868: Found: C, 69.92; H, 6.85. $C_{12}H_{14}O_3$ requires C, 69.87; H, 6.85%.

(*2S,3R*)-3-[2-(Benzyloxy)ethyl]-2-ethenyloxirane (11).

Hexamethyl disilazane (5.7ml, 28.6mmol) was added dropwise to a stirred suspension of potassium hydride (1.09g, 26mmol, from 3.15g of 35% by weight suspension in paraffin oil, washed with petrol (4x10ml)) in dry tetrahydrofuran (50ml), at room temperature until effervescence had ceased. The resulting cloudy solution was cooled to -20°C and transferred *via* cannula to a stirred suspension of methyltriphenylphosphonium bromide (9.6g, 28.6mmol) in toluene (50ml) at -20°C under argon. The bright yellow suspension was stirred at room temperature for 20min., re-cooled to -20°C and the epoxy aldehyde **10** (1.84g, 8.94mmol) in tetrahydrofuran (30ml) was added *via* cannula. T.L.C. (10% ether-petrol) indicated complete disappearance of the aldehyde **10**. The reaction mixture was poured into brine (50ml) and extracted with ether (3x50ml). The combined organic extract was dried ($MgSO_4$), concentrated and filtered through a pad of florisil. The solvent was evaporated *in vacuo* giving the *vinyl epoxide* **11** (1.33g, 73%) as a colourless oil, $[\alpha]_D^{25}$ -2.80 (c 1.67 in $CHCl_3$); υ_{max}(film) 2900, 2857, 1639, 1451, 1361, 1104, 926, 879 and 739cm^{-1}; δ_H(270MHz), 7.30 (5H, m, Ar-H), 5.55 (1H, ddd, *J* 16, 10 and 6.5Hz, H-2), 5.50 (1H, dd, *J* 15 and 2Hz, H-1), 5.22 (1H, dd, *J* 10 and 2Hz, H-1), 4.42 (2H, s, OCH_2Ph), 3.58 (2H, t, *J* 7Hz, H_2-6), 3.16 (1H, dd, *J* 6.5 and 2Hz, H-3), 2.95 (1H, dt, *J* 6 and 2Hz, H-4), and 1.82 (2H, m, H_2-5); *m/z* 204 (M^+), 186 (M^+-H_2O), 158 (M^+-C_2H_6O), 107 ($C_7H_7O^+$), and 91 ($C_7H_7^+$); Found: M^+, 204.1152. $C_{13}H_{16}O_2$ requires *M*, 204.1150; Found: C, 76.36; H, 7.27. $C_{13}H_{16}O_2$ requires C, 76.43; H, 7.30%.

(*exo*,4*R*) and (*endo*,4*R*)-π-Allyl-1,2,3-η-3-[4-carbonyloxyhex-2-en-3-ylate-6-(*tert*-butyldiphenylsilyloxy)] tricarbonyliron (12) and (13).

A solution of the vinyl epoxide **11** (2.21g, 10.8mmol) in dry tetrahydrofuran (50ml) was added to a stirred solution of diironnonacarbonyl (5.13g, 14.1mmol) at room temperature under argon and stirring continued for 6h. The green reaction mixture was concentrated *in vacuo* without warming the flask or evaporation to dryness. The resulting dark liquid was purified by chromatography on silica gel, loading in toluene, and eluting with 70% ether-petrol (to separate the iron carbonyl residues), to give a mixture of *ferrilactones* **12** and **13** (2.7g, 72%) as a yellow oil ; υ_{max}(film) 3375, 2969, 2083, 2030, 1637, 1583, 1479, 1210 and 848cm^{-1}; δ_H(270MHz) 7.3 (5H, m, Ar-H), 4.3 (2H, m, OCH_2Ph), 4.15 (1H, m, H-4), 3.9-3.7 (1H, m, H-2), 3.25 (3H, m, H_2-3 and H-6), 2.9 (1H, m, H-1), 1.45 (2H, m, H_2-5).

(*S*)-6-[2-(Benzyloxy)ethyl]-3,6-dihydro-2-pyranone and (*S*)-6-[2-(Benzyloxy)ethyl] -5,6-dihydro-2-pyranone (14).

A solution of diastereomeric ferrilactones **12** and **13** (2.7g, 7.5mmol) in dry benzene (50ml), was heated at 90°C under a carbon monoxide pressure of 250 atm overnight, in a high pressure steel reaction vessel. The resulting brown reaction mixture was filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 50% ether-petrol to give the mixture of *unsaturated lactones* **14** (1.15g, 66%,α,β:β,γ; 9:1) as a colourless oil; υ_{max}(film) 3442, 2866, 1717, 1637, 1601, 1450, 1400, 1251, 1096 and 738cm^{-1}; δ_H(270MHz) 7.30 (5H, m, Ar-H), 6.82 (1H, dt, *J* 9.2 and 4.5Hz, H-4), 5.95 (1H, dt, *J* 9.5 and 1.6Hz, H-3), 4.61 (1H, dq, 7.2 and 4Hz, H-6), 4.22 (2H, d, *J* 14.3Hz, OCH_2Ph), 3.62 (2H, m, H_2-2'), 2.32 (2H, m, H_2-5) and 1.98 (2H, ddt, 12.7 and 4.5Hz, H_2-1'); *m/z* 232 (M^+), 204 (M^+-CO), 91 ($C_7H_7^+$); Found: M^+, 232.1101. $C_{14}H_{16}O_3$ requires *M*, 232.1099.

(*S*)-6-[2-(Benzyloxy)ethyl]tetrahydro-2-pyranone (15).

Platinum (IV) oxide on carbon (100mg, 0.44mmol) was added to a solution of α,β-unsaturated ester **18** (10g, 37.8mmol) in dichloromethane (100ml) under argon at room temperature. Argon was exchanged for hydrogen and the mixture stirred vigorously for 4h, then filtered through celite, washing with dichloromethane. The solvent was reduced *in vacuo* to leave a solution of the crude ester (50ml solution in dichloromethane). Camphorsulphonic acid (5mg) was added and the mixture stirred at room temperature for 24h. Evaporation of the solvent *in vacuo* and purification by column chromatography on silica gel eluting with petrol-ether (40%), afforded the *lactone* **15** (7.36g, 83%) as a colourless oil; $[\alpha]_D^{20}$ +97.5 (c 0.37 in $CHCl_3$); υ_{max} (film) 2960, 2870, 1755, 1450, 1360, 1280, 1100 and 745cm^{-1}; δ_H(270MHz) 7.31 (5H, m, Ar-H), 4.49 (2H, d, *J* 12Hz, OCH_2Ph), 4.47 (1H, m, H-6), 3.62 (2H, m, H_2-2'), 2.42 (2H, m, H_2-3) and 1.87-1.53 (6H, m, H_2-4, H_2-5, H_2-1'); *m/z* 234 (M^+), 206 (M^+-CO), 143 (M^+-C_7H_7), 128 (M^+-C_7H_7O), 107 ($C_7H_7O^+$), 100 ($C_5H_8O_2^+$) and 91 ($C_7H_7^+$); Found: M^+, 234.1261. $C_{14}H_{18}O_3$ requires *M*, 234.1256; Found: C, 71.57; H, 7.84. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%.

Platinum (IV) oxide (0.1g) was added to a solution of the unsaturated lactone **14** (1.39g, 6mmol) in dry ethyl acetate (50ml) and the suspension stirred at room temperature under an atmosphere of hydrogen until t.l.c. (80% ether-petrol) showed disappearance of the starting material. The resulting suspension was filtered and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 60% ether-petrol to afford the *lactone* **15** (1.05g, 75%) as a colourless oil.

(*2RS,6S*)-6-[2-(Benzyloxy)ethyl]tetrahydro-*2H*-pyran-2-ol (16).

Diisobutylaluminium hydride (7.98ml of a 1.5M solution in toluene, 11.97mmol) was added to a stirred suspension of lactone **15** (2g, 8.55mmol) in toluene (60ml) at -78°C under Argon. The mixture was stirred at this temperature for 2h, after which acetic acid (7.5ml) was added dropwise, followed by water (7.5ml) and the mixture slowly warmed to room temperature. Sodium bicarbonate and magnesium sulphate were added until a thick paste had formed, which was extracted with ethyl acetate (3x50ml). The extracts were filtered through celite, washing with ethyl acetate, dried ($MgSO_4$), and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with petrol-ether (70%) to give *lactol* **16** (1.75g, 87%, 7:3 anomeric mixture); υ_{max}(film) 3406, 3062, 3029, 2941, 2865, 1717, 1602, 1451, 1360, 1273, 1194, 1100, 1028, 967, 855 and 698cm^{-1}; δ_H(270MHz) 7.30 (5H, m, Ar-H), 5.21 (0.3H, br s, H-2 (minor anomer)), 4.62 (0.7H, dd, *J* 9 and 2.2Hz, H-2 (major anomer)), 4.42 (2H, d, *J* 12.2Hz, OCH_2Ph), 4.12 (0.3H, m, H-6 (minor anomer)), 4.07 (0.7H, m, H-6 (major anomer)), 3.58 (2H, m, H_2-2'), 2.91 (0.7H, d, *J* 6.2Hz, OH), 2.40 (0.3H, br s, OH) and 1.92-1.07 (8H, m, H_2-3, H_2-4, H_2-5, H_2-1'); *m/z* 236 (M^+), 235 (M^+-H), 218 (M^+-H_2O), 159 (M^+-C_6H_5), 127 (M^+-C_7H_7O) and 91 ($C_7H_7^+$); Found: M^+-H_2O, 218.1306. $C_{14}H_{20}O_3$ requires *M-H$_2$O*, 218.1307; Found: C, 70.91; H, 8.61. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%.

(*2RS,6S*)-6-[2-(Benzyloxy)ethyl]tetrahydro-2-(phenylsulphonyl)-*2H*-pyran (2).

Sodium benzenesulphinate (4.2g, 26mmol) was added to aqueous sulphuric acid (7%, 72ml, 51.5mmol), and the solution stirred for 30min. The mixture was extracted with dichloromethane (3x30ml); and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give solid benzenesulphinic acid. This material, together with a catalytic amount of camphorsulphonic acid (30mg) and calcium chloride (2.22g, 24mmol) were added to a solution of lactol **16** (3.78g, 16mmol) in dichloromethane (75ml) at 0°C. The mixture was stirred at room temperature for 5h. Saturated sodium bicarbonate solution (50ml) was added and the mixture stirred vigorously for 2min. The organic layer was separated and the aqueous phase extracted with ether (3x30ml). The combined organic extracts were washed with brine (30ml), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica gel eluting with petrol-ether (40%) gave the *sulphone* **2** (4.15g, 72%, 8:2 mixture of anomers) as a colourless oil; υ_{max}(film) 2942, 2862, 1811, 1720, 1585, 1494, 1450, 1363, 1306, 1203, 1100, 980, 882 and 720cm^{-1}; δ_H(270MHz) 7.95-7.18 (10H, m, Ar-H), 4.65 (0.8H, dd, *J* 7.0 and 2.2Hz, H-2 (major anomer)), 4.56 (1H, m, H-6), 4.42 (2H, d, *J* 14Hz, OCH_2Ph), 4.12 (0.2H, dd, *J* 13 and 2.1Hz, H-2 (minor anomer)), 3.25 (2H, m, H_2-2'), 2.58 (1H, m, H-3), 2.15 (1H, m, H-3) and 1.75-1.25 (6H, m, H_2-4, H_2-5, H_2-1'); *m/z* 360 (M^+), 218 (M^+-$PhSO_2H$), 142 ($PhSO_2H^+$), 107 ($C_7H_7O^+$), 91 ($C_7H_7^+$); Found: C, 66.78; H, 6.85. $C_{20}H_{24}SO_4$ requires C, 66.64; H, 6.71%.

(*S*)-6-(Benzyloxy)-1-hexen-4-ol (17).

Allylmagnesium bromide (110ml of a 1M solution in ether, 110mmol) was added dropwise to the (-)B-methoxy diisopinocampheyl borane (34.8g, 110mmol, Aldrich) in ether (50ml) at -78°C under argon. The reaction mixture, after 15min. of stirring at -78°C was removed from the dry ice/acetone bath and allowed to warm to 25°C (1h). The formation of $IPc_2BCH_2CH{=}CH_2$ was indicated by the precipitation of the magnesium salts. The mixture was recooled to -78°C and aldehyde **6** (18g, 110mmol) was added dropwise with stirring. The mixture was stirred at this temperature for 2h, and allowed to warm to room temperature over 1h. The mixture was then sequentially treated with 3M aqueous sodium hydroxide solution (72ml), 30% aqueous hydrogen

peroxide (30ml) and the mixture was refluxed for 2h. After cooling, the organic layer was separated and washed with water (50ml), brine (50ml) and dried ($MgSO_4$). The residue after evaporation of solvent *in vacuo* was chromatographed on silica gel eluting with petrol-ether (60%) to afford the *alkenol* **17** (18.78g, 83%) as a colourless oil; $[\alpha]_D^{17}$ 3.1 (c 0.4 in $CHCl_3$); υ_{max}(film) 3386, 3066, 3027, 2918, 1636, 1449, 1382, 1365, 1207, 1090, 1040, 914, 830 and 736cm^{-1}; δ_H(500MHz) 7.31 (5H, m, Ar-H), 5.84 (1H, ddd, *J* 17.2, 10.1 and 7.1Hz, H-2), 5.13 (1H, dd, *J* 17.1 and 1.44Hz, H-1), 5.11 (1H, dd, *J* 10.0 and 1.4Hz, H-1), 4.52 (2H, s, OCH_2Ph), 3.87 (1H, m, H-4), 3.72 (1H, dd, *J* 9.4 and 5.4Hz, H-6), 3.65 (1H, dd, *J* 9.4 and 7.0Hz, H-6), 2.85 (1H, d, *J* 2.9Hz, OH), 2.54-2.34 (2H, m, H_2-3) and 2.25 (2H, dt, *J* 7.1 and 1.7Hz, H_2-5); *m/z* 206 (M^+), 165 (M^+-C_3H_5), 135 ($C_9H_{11}O^+$), 129 (M^+-C_6H_5), 120 (M^+-$C_5H_{10}O$), 115 (M^+-C_7H_7), 107 ($C_7H_7O^+$) and 91 ($C_7H_7^+$); Found: C, 75.64; H, 8.69. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.8%.

(*E*,*S*)-Methyl-7-(benzyloxy)-5-hydroxy-2-heptenoate (18)

A mixture of ozone and oxygen (ozoniser voltage, 140v; 40 l/h) was bubbled through a solution of *alkenol* **17** (13g, 63mmol) in dichloromethane (150ml), at -78°C for 7h. Triphenylphosphine (13.12g, 50mmol) was added and the mixture warmed to 0°C for 3h. Carbomethoxymethylenetriphenylphosphorane (31.52g, 95mmol) was added and the stirred solution allowed to warm to room temperature over 48h. The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel eluting with petrol-ether (50%) to obtain the *unsaturated ester* **18** (12.98g, 78%, E/Z 20:1) as a colourless oil; υ_{max}(film) 3455, 3405, 3028, 2945, 1719, 1654, 1435, 1274, 1205, 1167, 1039, 984, 824 and 699cm^{-1}; δ_H(500MHz) 7.37 (5H, m, Ar-H), 6.98 (1H, dt, *J* 15.6 and 7.4Hz, H-3), 5.88 (1H, dt, *J* 15.6 and 1.47Hz, H-2), 4.52 (2H, s, OCH_2Ph), 3.98 (1H, m, H-5), 3.79 (1H, m, H-7), 3.72 (3H, s, OMe), 3.65 (1H, ddd, *J* 12.5, 8.1 and 4.5Hz, H-7), 3.12 (1H, d, *J* 2.9Hz, OH), 2.38 (2H, m, H_2-4) and 1.77 (2H, m, H_2-6); *m/z* 264 (M^+), 246 (M^+-H_2O), 204 (M^+-$C_2H_4O_2$), 173 (M^+-C_7H_7), 165 (M^+-$C_5H_7O_2$), 157 (M^+-C_7H_7O), 100 ($C_5H_8O_2^+$) and 91 ($C_7H_7^+$); Found: M^+, 264.1363. $C_{15}H_{20}O_4$ requires *M*, 264.1361; found: C, 68.24; H, 7.42. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.63%.

(*4R*)-S-*tert*-Butyl 3-hydroxy-2,4-dimethyl-6-(benzyloxy)hexanethioate (21).

Boron trifluoride etherate (0.92ml, 7.92mmol) was added dropwise to a mixture of aldehyde **19** (1.29g, 6.71mmol) and (*Z*)-ketene mono thioacetal **20** (2.64g, 1.02mmol) in dichloromethane (100ml) at -78°C with stirring. The reaction mixture was stirred for 45min. then quenched with pH 7 buffer solution (40ml) and allowed to warm to room temperature. The mixture was poured into brine (50ml), the organic phase separated and the aqueous phase extracted with dichloromethane (3x50ml). The combined organic extracts were dried ($MgSO_4$), and the solvent evaporated *in vacuo* to afford a yellow oil, which was chromatographed on silica gel eluting with 5% ether-petrol to give four diasteromers. The two major diasteromers; **21**, were obtained as a colourless oil (1.64g, 72%) and as an inseparable 70:30 mixture; υ_{max}(film) 3480, 2960, 2910, 2885, 1675, 1450, 1360, 1095, 955, 735 and 695cm^{-1}; δ_H(270MHz), 7.38 (5H, m, Ar-H), 4.58 (0.58H, s, OCH_2Ph, minor diastereomer), 4.57 (1.42H, s, OCH_2Ph, major diastereomer), 3.75 (0.70H, dd, *J* 8 and 2.4Hz, H-3, major diastereomer), 3.55 (2.30H, m, H-3, minor diastereomer and H_2-6), 2.78 (2H, m, H-2 and OH), 1.9-1.6 (3H, m, H-4 and H_2-5), 1.50 (6.4H, s, t-Bu, major diastereomer), 1.48 (2.6H, s, t-Bu, minor diastereomer), 1.24 (0.9H, d, *J* 7Hz, Me-2, minor diastereomer), 1.15 (2.1H, d, *J* 7 Hz, Me-2, major diastereomer), 1.0 (0.9H, d, *J* 7Hz, Me-4

minor diastereomer), and 0.90 (2.1, d, *J* 7Hz, Me-4, major diastereomer); *m/z* 338 (M^+), 249 (M^+-^tBuS), 191 (M^+-$C_7H_{15}SO$), and 91 ($C_7H_7^+$); Found: C, 67.41; H, 9.03. $C_{19}H_{30}SO_3$ requires C, 67.42; H, 8.93%.

(*4R*)-2,4-Dimethyl-6-(benzyloxy)-1,3-hexanediol (22).

Sodium borohydride (0.107g, 2.81mmol) was added portionwise to a solution of the mixture of inseparable thioesters **21** (0.210g, 0.62mmol) in dry ethanol (15ml) at room temperature. The mixture was stirred for 48h, after which it was quenched by carefull addition of saturated ammonium chloride solution (10ml). The resulting mixture was poured into brine (50ml) and extracted with dichloromethane (3x20ml). The combined organic extracts were dried, ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 50% ether-petrol to give the *diols* **22** (0.121g, 77%) as an inseparable mixture; υ_{max}(film) 3423, 2962, 2933, 1421, 1341, 1271, 1100, 736 and 697cm^{-1}; δ_H(500MHz), 7.36 (5H, m, Ar-H), 4.55 (2H, s, OCH_2Ph), 4.0-3.4 (5H, m, H_2-1, H-3, H_2-6), 3.0 (2H, br s, OH), 2.0-1.6 (4H, m, H_2-2, H-4, H_2-5), 0.99 (0.9H, d, *J* 6.5Hz, Me-2, minor diastereomer), 0.94 (0.9H, d, *J* 6.5Hz, Me-4, minor diastereomer), 0.89 (2.1H, d, *J* 6.5Hz, Me-2, major diastereomer) and 0.78 (2.1H, d, *J* 6.5Hz, Me-4, major diastereomer); *m/z* 253 (MH^+), 162 (MH^+-C_7H_7), 193 (MH^+-C_3H_8O), 146 (MH^+-C_7H_7O) and 91 ($C_7H_7^+$); Found: MH^+, 253.1830. $C_{15}H_{25}O_3$ requires MH^+, 253.1803.

[*4R,5S,*(*R*)]-4-[4-(Benzyloxy)butyl]-2,2,5-trimethyl-1,3-dioxane (23) and [*4S,5R,*(*R*)]-4-[4-(Benzyloxy)butyl]-2,2,5-trimethyl-1,3-dioxane (24).

The mixture of inseparable diols **22** (0.08g, 0.35mmol) were added to a solution of dichloromethane (10ml) and 2,2-dimethoxypropane (20ml) containing a catalytic amount of camphorsulphonic acid, at room temperature. The resulting solution was stirred for 24 h before being diluted with dichloromethane (30ml) and washed with saturated sodium bicarbonate solution (30ml). The organic layer was separated and the aqueous phase extracted with ether (3x15ml). The combined extracts were dried ($MgSO_4$), and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel; gradient elution 1-5% ether-petrol affording the *major protected diol* **24** (0.071g, 70%) as a clear oil, $[\alpha]_D^{25}$ -22.3 (c 1.82 in $CHCl_3$); υ_{max}(film) 2933, 1382, 1235, 1198, 1172, 1061 and 698cm^{-1}; δ_H(500MHz, $CDCl_3$), 7.35 (5H, m, Ar-H), 4.55 (1H, d, *J* 12.5Hz, OCHPh), 4.47 (1H, d, *J* 12.5Hz, OCHPh), 3.68 (1H, dd, *J* 11.5 and 5Hz, H-6), 3.50 (2H, m, H_2-4'), 3.46 (1H, t, *J* 11.3Hz, H-6), 3.39 (1H, dd, *J* 10.3 and 2.3Hz, H-4), 1.19 (1H, qt, *J* 6.9 and 2.3Hz, H-2'), 1.84 (1H, m, H-5), 1.67 (2H, m, H_2-3'), 1.34 (3H, s, Me), 1.33 (3H, s, Me), 0.87 (3H, d, *J* 7Hz, Me-2') and 0.71 (3H, d, *J* 7Hz, Me-5); *m/z* 292 (M^+), 277 (M^+-Me), 234 (M^+-C_3H_6O), and 91 ($C_7H_7^+$); Found: C, 74.0; H, 9.76. $C_{18}H_{28}O_3$ requires C, 73.93; H, 9.65%; and *the minor protected diol* **23** (0.019g, 19%) as a clear oil, $[\alpha]_D^{25}$ +19.8 (c 1.91 in $CHCl_3$); υ_{max}(film) 2929, 1382, 1199, 1102, 1062 and 764cm^{-1}; δ_H(500MHz), 7.30 (5H, m, Ar-H), 4.55 (1H, d, *J* 15Hz, OCHPh), 4.48 (1H, d, *J* 15Hz, OCHPh), 3.66 (1H, dd, *J* 11.5 and 5Hz, H-6), 3.55 (1H, ddd, *J* 9.5, 7.5 and 5Hz, H-4'), 3.46 (1H, ddd, *J* 10, 8 and 7Hz, H-4'), 3.45 (1H, t, *J* 11.2Hz, H-6), 3.34 (1H, dd, *J* 10.2 and 2Hz, H-4), 1.85 (3H, m, H-5, H-2', H-3'), 1.45 (1H, m, H-3'), 1.40 (3H, s, Me), 1.35 (3H, s, Me), 0.96 (3H, d, *J* 7Hz, Me-5), and 0.74 (3H, d, *J* 7Hz, Me-2'); *m/z* 292 (M^+), 277 (M^+-Me), 234 (M^+-C_3H_6O), 185 (M^+-C_7H_7O) and 91 ($C_7H_7^+$); Found: C, 73.88; H, 9.80. $C_{18}H_{28}O_3$ requires C, 73.93; H, 9.65%.

[*4S,5R,(R)*]-4-[4-(Hydroxy)butyl]-2,2,5-trimethyl-1,3-dioxane (25)

A solution of the protected diol **24** (0.145g, 0.5mmol) in ethanol (10ml) containing 10% palladium on activated carbon (0.02g) was stirred under hydrogen for 3h. The reaction mixture was diluted with dichloromethane (50ml), filtered on a pad of celite and the solvent evaporated *in vacuo*. The crude product was chromatographed on silica gel eluting with 40% ether-petrol to give the *alcohol* **25** (0.084g, 87%) as a colourless oil, $[\alpha]_D^{25}$ -23.9 (c 1.15 in $CHCl_3$); υ_{max}(film) 3406, 2902, 2964, 2876, 1409, 1383, 1302, 1268, 1236, 1199, 1169, 1061, 956 and 862cm^{-1}; δ_H(500MHz) 3.72 (1H, m, H-4'), 3.68 (1H, dd, *J* 12 and 5.1Hz, H-6), 3.62 (1H, m, H-4'), 3.48 (1H, t, *J* 11.8Hz, H-6), 3.46 (1H, dd, *J* 10 and 2Hz, H-4), 2.16 (1H, br s, OH), 1.96 (1H, qd, *J* 6.8 and 2Hz, H-2'), 1.87 (1H, m, H-5), 1.72-1.54 (2H, m, H_2-3'), 1.42 (3H, s, Me), 1.37 (3H, s, Me), 0.91 (3H, d, J 7Hz, Me-5) and 0.73 (3H, d, *J* 6.8Hz, Me-2'); *m/z* 202 (M^+), 187 (M^+-Me), 144 (M^+-C_4H_{10}) and 129 (M^+-C_5H_{13}); Found: M^+-Me, 187.1338. $C_{10}H_{19}O_3$ requires *M-Me*, 187.1334; Found: C, 65.35; H, 11.10. $C_{11}H_{22}O_3$ requires C, 65.31; H, 10.96%.

10% palladium on carbon (200mg) was added to a solution of the acetonide **29** (8.5g, 29.1mmol) in redistilled ethanol (100ml) under argon at room temperature. Argon was exchanged for hydrogen and the mixture stirred vigorously for 12h, then filtered through celite, washing with dichloromethane. The solvent was evaporated *in vacuo* to leave the alcohol **30** as an oil. This was immediately taken up into acetone (100ml), and anhydrous copper sulphate (2g) added with a trace of camphorsulphonic acid (20mg). The mixture was stirred at room temperature for 1h, then washed with water (50ml), sodium bicarbonate solution (50ml) and the organic layer separated, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with petrol-ether (60%) to give the *alcohol* **25** (4.06g, 69%) as a colourless oil, identical to the compound prepared above. The stereochemistry of this compound was proved by X-ray crystallography.

[*4S,5R,(R)*]-4-[4-(Iodo)butyl]-2,2,5-trimethyl-1,3-dioxane (3).

Triethylamine (2.32g, 3.19ml, 22.9mmol) was added to a solution of alcohol **25** (3g, 14.85mmol) in dichloromethane (100ml) at -10°C under argon. Methanesulphonyl chloride (1.84g, 1.25ml, 16.31mmol) was added dropwise and the solution stirred for 1h, after which it was poured into saturated sodium bicarbonate solution (50ml) and extracted with dichloromethane (3x50ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The crude mesylate was immediately dissolved in dry acetone (100ml) containing anhydrous sodium iodide (13.34g, 89mmol) and heated at 40°C for 4h under argon. After cooling, the mixture was diluted with ether (150ml) and washed with 10% sodium thiosulphate (50ml) followed by brine (50ml). The organic layer was separated and the aqueous phase extracted with ether (3x50ml); the combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with petrol-ether (95%) to give *iodide* **3** (4.26g, 92%) as a colourless oil, $[\alpha]_D^{20}$ -37.1 (c 1.5 in $CHCl_3$); υ_{max}(film) 2963, 2930, 2263, 1383, 1235, 1198 and 1061cm^{-1}; δ_H(500MHz) 3.69 (1H, dd, *J* 11.5 and 5Hz, H-6), 3.50 (1H, t, *J* 11.5Hz, H-6), 3.41 (1H, dd, *J* 10.2 and 1.7Hz, H-4), 3.22 (2H, t, *J* 6.8Hz, H_2-4'), 1.9-1.75 (4H, m, H-5, H-2', H_2-3'), 1.4 (3H, s, Me), 1.34 (3H, s, Me), 0.88 (3H, d, *J* 6.5Hz, Me-5) and 0.73 (3H, d, *J* 6.7Hz, Me-2'); *m/z* 311 (M^+-H), 297 (M^+-Me), 237 (M^+-$C_4H_{11}O$) and 91 ($C_7H_7^+$); Found: M^+-Me, 297.0348. $C_{10}H_{18}O_2I$ requires *M-Me*, 297.0351; Found: C, 42.15; H, 6.91; I, 40.74. $C_{11}H_{21}IO_2$ requires C, 42.15; H, 6.78; I, 40.64%.

(*3R,4S,5R*)-6-(Benzyloxy)-3,5-dimethyl-1-hexen-4-ol (27).

Cis-butene (24g, 40ml, 0.43mol) was condensed into a measuring cylinder at -78°C, then transferred *via* cannula into a stirred solution of potassium-*tert*-butoxide (15.6g, 0.14mol) in tetrahydrofuran (250ml) at -78°C. *n*-Butyllithium (2.5M in hexane, 56ml, 0.14mol) was added dropwise, and the bright yellow mixture was warmed to -45°C for 10min. The reaction was recooled to -78°C, before adding (-)-B-methoxy diisopinocampheyl borane (53g, 0.16mol, Aldrich) in ether (100ml) *via* cannula. Stirring was continued for 45min., then the mixture was cooled to -90°C. Boron trifluoride etherate (28.4g, 25ml, 0.20mol) was added, followed immediately by a pre-cooled (-78°C) solution of the aldehyde **26** (23.14g, 0.13mol) in ether (100ml). Stirring was continued at -90°C for 16h. The reaction mixture was allowed to warm to room temperature, 3N aqueous sodium hydroxide solution (150ml) added, then heated to a gentle reflux, before adding 30% hydrogen peroxide solution (60ml) dropwise. The mixture was refluxed for 5h, cooled to room temperature, the organic phase separated and washed with saturated sodium sulphite solution and the combined aqueous layer extracted with ethyl acetate (4x150ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography of the residue on silica gel eluting with petrol-ether (80%, 3 columns required) afforded the *alkenol* **27** (21.9g, 72%, single diastereomer by 500MHz NMR) as a colourless oil $[\alpha]_D^{20}$ -2.9 (c 0.8 in $CHCl_3$); υ_{max}(film) 3488, 3066, 3029, 2965, 2908, 1811, 1722, 1636, 1493, 1451, 1362, 1310, 1252, 1206, 1091, 1028, 809 and 698 cm^{-1}; δ_H(500MHz) 7.37-7.26 (5H, m, Ar-H), 5.86 (1H, ddd, *J* 17.7, 10.3, and 7Hz, H-2), 5.04 (1H, dd, *J* 17.4 and 1.2Hz, H-1), 5.03 (1H, dd, *J* 10.5 and 1.0Hz, H-1), 4.52 (2H, s, OCH_2Ph), 3.66 (1H, dd, *J* 9.1 and 4.3Hz, H-6), 3.50 (1H, dd, *J* 9.1 and 6.3Hz, H-6), 3.41 (1H, dt, *J* 7 and 4.7Hz, H-4), 3.19 (1H, d, *J* 4.4Hz, OH), 2.33 (1H, Sex, *J* 4.7Hz, H-3), 1.95 (1H, qd, *J* 6.8 and 4.3Hz, H-5), 1.05 (3H, d, *J* 6.8Hz, Me-5) and 0.97 (3H, d, *J* 7.04Hz, Me-3); *m/z* 235 (MH^+), 234 (M^+), 179 (M^+-C_4H_7), 149 (M^+-C_5H_9O), 107 ($C_7H_7O^+$) and 91($C_7H_7^+$); Found: MH^+, 235.1698. $C_{15}H_{22}O_2$ requires *MH*, 235.1698; Found: C, 76.73; H, 9.41. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%.

(*3R,4S,5R*)-6-(Benzyloxy)-3,5-dimethyl-1,4-hexanediol (28).

9-Borabicyclo [3.3.1] nonane (290ml of a 0.5M solution in tetrahydrofuran, 145mmol) was added dropwise *via* cannula to a stirred solution of the alkenol **27** (11.3g, 48.3mmol) in anhydrous tetrahydrofuran (100ml) at room temperature under argon. The reaction was heated at 65°C for 2h. The reaction mixture was then cooled to 0°C and quenched by the cautious, dropwise addition of water (10ml) with vigorous stirring. After 5min., 3N aqueous sodium hydroxide solution (130ml) and 30% aqueous hydrogen peroxide solution (50ml) were added sequentially; the mixture was warmed to room temperature and stirred for 3h. The organic layer was separated and the aqueous phase extracted with ether (3x150ml). The combined organic extracts were washed with brine (50ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was columned on silica gel eluting with petrol-ether (20%) to give *diol* **28** (11.20g, 92%) as a colourless oil, $[\alpha]_D^{18}$ -33.09 (c 1.16 in $CHCl_3$); υ_{max} (film) 3391, 3352, 3062, 3028, 2931, 2336, 2314, 1602, 1493, 1451, 1376, 1310, 1206, 1076, 1028, 984 and 698cm^{-1}; δ_H(500MHz) 7.37-7.26 (5H, m, Ar-H), 4.53 (1H, d, *J* 11.8Hz, OCHPh), 4.52 (1H, d, *J* 11.8Hz, OCHPh), 4.15 (1H, br s, OH), 3.74 (1H, m, H-4), 3.64 (1H, m, H-1), 3.60 (1H, dd, *J* 9.1 and 4.3Hz, H-6), 3.50 (1H, dd, *J* 9.1 and 2.4Hz, H-6), 3.47 (1H, m, H-1), 2.85 (1H, br s, OH), 1.98 (1H, m, H-3), 1.85 (1H, qd, *J* 6.6 and 2.4Hz, H-5), 1.76-1.61 (2H, m, H_2-2), 0.91 (3H, d, *J* 6.93Hz, Me-5) and 0.80 (3H, d, *J* 6.94Hz, Me-3); *m/z* 252 (M^+), 234 (M^+-H_2O), 216 (M^+-$(H_2O)_2$) 202 ($C_{13}H_{14}O_2^+$), 149

($C_{10}H_{13}O^+$), 145 (M^+-$C_7H_7O^+$), 103 (M^+-$C_{10}H_{13}O$) and 91 ($C_7H_7^+$); Found: C, 71.14; H, 9.81. $C_{15}H_{24}O_3$ requires C, 71.39; H, 9.81%.

[*4S,5R,(R)*]-4-[3-(Benzyloxy)propyl]-2,2,5-trimethyl-1,3-dioxepane (29).

2,2-Dimethoxypropane (9.3g, 11ml, 89mmol) was added to a solution of the diol **28** (9g, 35.7mmol) in dichloromethane (50ml) containing camphorsulphonic acid (50mg) under argon at room temperature, with stirring. The mixture was stirred at room temperature for 5h. Evaporation of the excess reagent and solvent *in vacuo* followed by chromatography on silica gel eluting with petrol-ether (80%) afforded *acetonide* **29** (10.01g, 96%), as a colourless oil $[\alpha]_D^{19}$ +8.2 (c 1.9 in $CHCl_3$); υ_{max}(film) 3027, 2963, 1602, 1493, 1325, 1306, 1263, 1218, 1171, 1026, 924, 901 and 834cm^{-1}; δ_H(500MHz) 7.38-7.27 (5H, m, Ar-H), 4.49 (1H, d, *J* 11.8Hz, OCHPh), 4.44 (1H, d, *J* 11.8Hz, OCHPh), 3.82 (1H, t, *J* 12.3Hz, H-7), 3.66 (1H, dd, *J* 10.4 and 0.9Hz, H-4), 3.51 (1H, dd, *J* 8.7 and 3.2Hz, H-3'), 3.48 (1H, dt, *J* 12.3 and 3.1Hz, H-7), 3.41 (1H, dd, *J* 8.7 and 5.9Hz, H-3'), 1.97 (1H, m, H-2'), 1.84 (1H, m, H-5), 1.75 (1H, m, H-6), 1.36 (1H, m, H-6), 1.31 (3H, s, Me), 1.27 (3H, s, Me), 0.98 (3H, d, *J* 6.9Hz, Me-2'), 0.90 (3H, d, *J* 6.9Hz, Me-5); *m/z* 292 (M^+), 277 (M^+-Me), 274 (M^+-H_2O), 234 (M^+-C_3H_6O), 217 (M^+-$C_3H_7O_2$), 201 (M^+-C_7H_7), 143 (M^+-$C_{10}H_{13}O$) and 91 ($C_7H_7^+$); Found: C, 73.78; H, 9.65. $C_{18}H_{28}O_3$ requires C, 73.93; H, 9.65%.

(*βR,2S,3R,6S*)-β,3-Dimethyl-1,7-dioxaspiro[5.5]undecane-2-ethanol (32).

n-Butyl lithium (0.167ml of a 2.45M solution in hexane, 0.41mmol) was added dropwise to a solution of the sulphone **31** (0.093g, 0.41mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidone (DMPU) (0.1ml) in tetrahydrofuran (3ml) at -78°C under argon. The resulting bright yellow solution was stirred for 20min., then the iodide **3** (64mg, 0.21mmol) in tetrahydrofuran (1ml) was added dropwise *via* cannula. During the addition the yellow colour faded but remained yellow for 90min. while stirring at -78°C. The mixture was allowed to warm to room temperature, poured into saturated ammonium chloride solution (10ml) and extracted with ether (4x10ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was immediately dissolved in wet dichloromethane (5ml) containing a catalytic amount of camphorsulphonic acid and the mixture was stirred at room temperature for 24h. The reaction mixture was diluted with dichloromethane (15ml) and washed with saturated sodium bicarbonate solution (10ml). The organic layer was separated and the aqueous phase extracted with ether (3x15ml), the combined extracts dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with ether-petrol (30%) to afford the *spiroketal* **32** (0.024g, 52%) as a colourless oil, $[\alpha]_D^{25}$ +39.4 (c 2.1 in $CHCl_3$); υ_{max}(film) 3471, 2937, 1068, 999, 971, 924, 901 and 834cm^{-1}; δ_H(500MHz), (natural product numbering) 3.9-3.4 (6H, m, H_2-10, H-18, H_2-20, OH), 2.02 (1H, tt, *J* 14 and 4.5Hz, H-16), 1.9-1.35 (11H, m, H_2-11, H_2-12, H_2-13, H_2-15, H-16, H-17, H-19), 0.95 (3H, d, *J* 7Hz, Me-17) and 0.75 (3H, d, *J* 7.5Hz, Me-19); *m/z* 228 (M^+), 198 (M^+-CH_2O), 183 (M^+-C_2H_5O), 169 (M^+-C_3H_7O) and 101 ($C_5H_9O_2^+$); Found: M^+, 228.1727. $C_{13}H_{24}O_3$ requires *M*, 228.1725.

(*βR,2S,3R,6S,8S*)-8-[2-(Benzyloxy)ethyl]-β,3-dimethyl-1,7-dioxaspiro[5.5]undecane-2-ethanol (33).

n-Butyllithium (11.5ml of a 1.6M solution in hexane, 18.1mmol) was added dropwise to a solution of the sulphone **2** (6.5g, 18.1mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidone (DMPU) (0.5ml) in tetrahydrofuran (15ml) at -78°C under argon. The resulting bright orange solution was stirred at -78°C for

30min., then the iodide **3** (2.21g, 7.1mmol) in tetrahydrofuran (5ml) was added dropwise *via* cannula. During the addition, the colour faded but remained yellow suggesting the sulphone anion was still present. The reaction mixture was stirred for 30min. and allowed to warm to room temperature over 1h. The cloudy reaction mixture was poured into saturated aqueous ammonium chloride solution (50ml) and extracted with ether (3x50ml). The combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The mixture of enol ethers was dissolved in wet dichloromethane (50ml) and camphorsulphonic acid (25mg) added. The resulting solution was stirred rapidly for 12h at room temperature. The mixture was washed with saturated sodium bicarbonate solution (50ml), the organic layer separated, the aqueous phase extracted with ether (3x30ml) and the combined organic extracts dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel eluting with petrol-ether (60%) to give the *spiroketal alcohol* **33** (1.74g, 68%) as a colourless oil, $[\alpha]_D^{20}$ -71.89 (c 0.21 in $CHCl_3$); υ_{max}(film) 3500, 2934, 2234, 1450, 1385, 1217, 986, 900, 735 and 698 cm^{-1}; δ_H(500MHz), (natural product numbering) 7.35 (5H, m, Ar-H), 4.55 (1H, d, *J* 12Hz, OCHPh), 4.47 (1H, d, *J* 12Hz, OCHPh), 3.76 (1H, m, H-10), 3.69 (1H, ddd, *J* 9.11, 4.93 and 4.2Hz, H-8), 3.58 (3H, m, H-18, H-20, OH), 3.51 (2H, m, H-8, H-20), 2.05 (1H, tt, *J* 13 and 4.3Hz, H-16), 1.77 (4H, m, H-9, H-11, H-17, H-19), 1.70 (1H, m, H-9), 1.61 (5H, m, H_2-12, H_2-13, H-16), 1.38 (2H, m, H_2-15), 1.2 (1H, m, H-11), 0.95 (3H, d, *J* 7Hz, Me-17) and 0.72 (3H, d, *J* 7.1Hz, Me-19); *m/z* 362 (M^+), 344 (M^+-H_2O), 302 (M^+-C_3H_7O), 232 (M^+-$C_8H_{18}O$) and 91 ($C_7H_7^+$); Found: M^+, 362.2456. $C_{22}H_{34}O_4$ requires *M*, 362.2457; Found: C, 72.91; H, 9.38. $C_{22}H_{34}O_4$ requires C, 72.89; H, 9.45%.

Tetra-*n*-butylammonium fluoride (0.83ml of a 1M solution in THF, 0.83mmol) was added dropwise to a stirred solution of the silyl ether **36a** (0.25g, 0.42mmol) in tetrahydrofuran (3ml) under argon, and the solution stirred at room temperature for 8h. Evaporation of the solvent *in vacuo* followed by column chromatography of the residue on silica gel, eluting with petrol-ether (50%) afforded the *spiroketal alcohol* **33** (0.107g, 71%) identical to the material prepared above.

(*βR,2S,3R,6S,8S*)-2-[α-tert-butyldiphenylsilyloxy)ethyl]-β,3-dimethyl-1,7-dioxaspiro[5.5]undecane-8-ethanol (36).

n-Butyllithium (0.29ml of a 1.6M solution in hexane, 0.47mmol) was added dropwise to a solution of the sulphone **34** (0.25g, 0.47mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidone (DMPU) (0.05ml) in tetrahydrofuran (3ml) at -78°C under argon. The resulting bright orange solution was stirred at -78°C for 10min., then the iodide **35** (0.053g, 0.187mmol) in tetrahydrofuran (5ml) was added dropwise *via* cannula. During the addition, the colour faded but remained yellow suggesting the sulphone anion was still present. The reaction mixture was stirred for 20min. and allowed to warm to room temperature over 1h. The cloudy reaction mixture was poured into saturated aqueous ammonium chloride solution (5ml) and extracted with ether (3x5ml). The combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The mixture of enol ethers was dissolved in wet dichloromethane (3ml) and a catalytic amount of camphorsulphonic acid added. The resulting solution was stirred rapidly for 16h at room temperature. The mixture was washed with saturated sodium bicarbonate solution (5ml), the organic layer separated, the aqueous phase extracted with ether (3x5ml) and the combined extracts dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel eluting with petrol-ether (50%) to give the *spiroketal alcohol* **36** (0.061g, 64%) as a colourless oil, $[\alpha]_D^{20}$ +37.8 (c 0.34 in $CHCl_3$); υ_{max}(film) 3708, 3442, 3069, 2934, 2858, 1589, 1462, 1427, 1306, 1272, 1178, 1112, 860, 732, 702 and 698cm^{-1}; δ_H(500MHz), (natural product numbering) 7.66 (4H, m, Ar-H),

7.38 (6H, m, Ar-H), 3.94 (1H, dd, *J* 9.47 and 3.5Hz, H-20), 3.62 (2H, m, H_2-8), 3.51 (1H, dd, *J* 9.45 and 7.5Hz, H-20), 3.48 (1H, m, H-10), 3.33 (1H, dd, *J* 10.38 and 2.28Hz, H-18), 2.95 (1H, t, *J* 5.32Hz, OH), 1.88 (1H, tt, *J* 13.3 and 4.5Hz, H-16), 1.79-1.11 (13H, m, H_2-9, H_2-11, H_2-12, H_2-13, H_2-15, H-16, H-17, H-19), 1.07 (9H, s, $(Me)_3Si$), 0.95 (3H, d, *J* 6.75Hz, Me-17) and 0.87 (3H, d, *J* 6.95Hz, Me-19); *m/z* 511 (MH^+), 492 (M^+-H_2O), 453 (M^+-C_4H_9), 433 (M^+-C_6H_5), 297 ($C_{19}H_{25}SiO^+$) and 255 (M^+-TBDPSO); Found: MH^+, 511.3244. $C_{31}H_{46}SiO_4$ requires *MH*, 511.3243.

(*βR,2S,3R,6S,8S*)-2-[α-*tert*-Butyldiphenylsilyloxy)ethyl]-8-[2-(benzyloxy)ethyl]-β,3-dimethyl-1,7-dioxaspiro[5.5]undecane (36a)

Alcohol **36** (0.3g, 0.59mmol) was added to a suspension of sodium hydride (16mg, 0.65mmol from 27mg of a 60% dispersion of mineral oil, pre-washed with light petroleum (3x2ml)) in dry tetrahydrofuran (2ml) at 0°C under argon, *via* cannula and the mixture stirred at room temperature until effervescence had ceased. Benzyl bromide (0.1g, 0.07ml, 0.59mmol) was added, and the mixture stirred at room temperature for 3h. Excess sodium hydride was quenched by the careful addition of water (0.5ml) with cooling. The reaction mixture was poured into brine (2ml) and the organic phase separated. The aqueous layer was extracted with dichloromethane (2x5ml) and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo*. The residue was columned on silica gel, eluting with petrol-ether (90%) to give the *spiroketal* **36a** (0.268g, 76%) as a colourless oil, $[\alpha]_D^{20}$ +15.38 (c 0.13 in $CHCl_3$); (natural product numbering) υ_{max}(film) 2930, 2857, 1647, 1457, 1427, 1388, 1218, 1112, 988, 822, 738 and 700cm^{-1}; δ_H(500MHz) 7.62 (5H, m, Ar-H), 7.29 (10H, m, Ar-H), 4.2 (2H, d, *J* 12Hz, OCH_2Ph), 4.06 (1H, dd, *J* 9.45 and 3.55Hz, H-20), 3.4 (3H, m, H_2-8, H-20), 3.3 (1H, m, H-10), 3.23 (1H, dd, *J* 10.44 and 2.92Hz, H-18), 1.98 (1H, tt, *J* 13.3 and 4.5Hz, H-16), 1.83-1.08 (13H, m, H_2-9, H_2-11, H_2-12, H_2-13, H_2-15, H-16, H-17, H-19), 1.02 (9H, s, ^{t}Bu), 0.93 (3H, d, *J* 6.7Hz, Me-17) and 0.85 (3H, d, *J* 6.7Hz, Me-19); *m/z* 600 (M^+), 543 (M^+-C_4H_9), 467 (M^+-$C_{10}H_{13}$), 300 (M^+-$C_{19}H_{25}SiO$), 297 ($C_{19}H_{25}SiO^+$), 239 ($TBDPS^+$) and 91 ($C_7H_7^+$); Found: M-^{t}Bu, 543.2927. $C_{38}H_{52}SiO_4$ requires *M-^{t}Bu*, 543.2931.

(*E,4S*)-Ethyl-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethyl-2-pentenoate (38)

Ethoxycarbonylethylidenetriphenylphosphorane (127.5g, 352.1mmol) in dichloromethane (200ml) was added to a stirred solution of aldehyde **37** (34.8g, 106.7mmol) in dichloromethane (200ml) at room temperature. The mixture was stirred for 5h, the solvent evaporated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with 5% ether-petrol, to give the *α,β-unsaturated ester* **38** (41.6g, 95%) as a colourless oil; $[\alpha]_D^{20}$ -2.3 (*c* 1.56 in $CHCl_3$); υ_{max}(film), 2959, 2932, 2858, 1709, 1649, 1509, 1428, and 1112cm^{-1}; δ_H(270MHz), 7.70-7.40 (10H, m, Ar-H), 6.60 (1H, d, *J* 10Hz, H-3), 4.18 (2H, q, *J* 7.0Hz, $C\underline{H}_2CH_3$), 3.55 (2H, d, *J* 7.0Hz, H_2-5), 2.75 (1H, m, H-4), 1.82 (3H, d, *J* 1.5Hz, Me-2), 1.30 (3H, t, *J* 7.0Hz, $CH_2C\underline{H}_3$), and 1.06 (12H, s, ^{t}Bu, Me-4); *m/z* 353 (M^+-^{t}Bu); Found: C, 73.10; H, 8.55. $C_{25}H_{34}O_3Si$ requires C, 73.17; H, 8.39%.

[2*S*,3*R*(*S*)]-3-[3-(*tert*-Butyldiphenylsilyloxy)propyl]-2-methyl-2-oxiranemethanol (39)

Diisobutylaluminium hydride (151.3ml of a 1.5 M solution in toluene, 227 mmol) was added dropwise to a stirred solution of ester **38** (42.3g, 103mmol) in dry toluene (500ml) under argon at -78°C. The solution was stirred for 30min., quenched with water (9ml) and allowed to warm to room temperature; upon gelling the

slurry was stirred with solid $NaHCO_3$ and an excess of ethyl acetate. The ethyl acetate solution upon clearing was decanted through a pad of celite and the process repeated twice. The combined filtrates were evaporated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with 20% ether-petrol, to give the *alcohol* (36.5g, 96%) as an oil; $[\alpha]_D^{20}$ +18.9 (*c* 1.33 in $CHCl_3$); υ_{max}(film), 3347, 2959, 2932, 2858, 1589, 1428, 1387, and 1112 cm^{-1}; δ_H(270MHz), 7.60-7.40 (10H, m, Ar-H), 5.13 (1H, dq, *J* 9.5 and 1.5Hz, H-3), 3.93 (2H, m, H_2-5), 3.51 (2H, m, H_2-1) 2.61 (1H, m, H-4), 1.58 (3H, d, *J* 1.5Hz, Me-2), 1.02 (9H, s, ^tBu), 0.98 (3H, d, *J* 7Hz, Me-4); *m/z* 311 (M^+-^tBu), and 293 (M^+-$C_4H_{11}O$); Found: C, 74.9; H, 8.86. $C_{23}H_{32}O_2Si$ requires C, 75.0; H, 8.75%.

D-(-)-Diethyltartrate (26.8g, 81.5mmol) was added to titanium tetraisopropoxide (20.1ml, 67.9mmol) in dry dichloromethane (500ml) under argon at -20°C. The mixture was stirred for 5min. before adding the alcohol (25g, 67.9mmol) in dry dichloromethane (200ml) and *tert*-butylhydroperoxide (45.3ml of a 3M solution in toluene, 135.8mmol). The mixture was stirred overnight at - 20°C, then 10% aqueous tartaric acid (150ml) was added, the mixture stirred for 30 min. at -20°C and for 1h at room temperature until the aqueous phase cleared. The organic phase was washed with water (25ml), dried (Na_2SO_4), and the solvent evaporated *in vacuo* to afford the crude product contaminated with *tert*-butylhydroperoxide. The oil was diluted with ether (500ml), cooled to 5°C and stirred with NaOH (200ml of a 1M aqueous solution) for 30min. The organic phase was washed with brine (25ml), dried (Na_2SO_4), the solvent evaporated *in vacuo* and purified by column chromatography on silica gel, eluting with 30% ether-petrol, to give the *epoxy alcohol* **39** (25.3g, 97%) as a colourless oil; $[\alpha]_D^{20}$ +17.3 (c 0.78 in $CHCl_3$); υ_{max}(film), 3450, 2932, 2858, 1589, 1428, 1387, 1112, 1031, 823, and 703 cm^{-1}; δ_H(270MHz), 7.60-7.40 (10H, m, Ar-H), 3.77 (1H, dd, *J* 10. and 4.2Hz, H-5), 3.75 (1H, dd, *J* 10 and 5.8Hz, H-5), 3.66 (1H, dd, *J* 12.2 and 4.5Hz, H-1), 3.58 (1H, dd, *J* 12.2 and 8.7Hz, H-1), 3.19 (1H, m, H-3), 1.60 (1H, m, H-4), 1.25 (3H, s, Me-2), 1.03 (9H, s, ^tBu), 1.00 (3H, d, *J* 6.5Hz, Me-4); *m/z* 309 (M^+- $C_4H_{11}O$); Found: C, 71.79; H, 8.43. $C_{23}H_{32}O_3Si$ requires C, 71.88; H, 8.39%.

[2*S*,3*R*(*S*)]-2-[3-(*tert*-Butyldiphenylsilyloxy)propyl]-2-ethenyl-2-methyloxirane (40)

Dimethylsulphoxide (8.53ml, 120.3mmol) was added dropwise to a solution of oxalyl chloride (5.25ml, 45mmol) in dry dichloromethane (300ml) at -78°C. The mixture was stirred for 5min., then the epoxy alcohol **39** (21.0g, 54.7mmol) in dichloromethane (10ml) was added. The solution was stirred for a further 20min. at -78°C, then quenched with triethylamine (44.5 ml, 320mmol) and allowed to warm to room temperature. The mixture was poured into water and extracted with ether (3x30ml). The combined organic extract was washed with water (30ml), brine (30ml), dried (MgSO4) and the solvent evaporated *in vacuo* to give a residue which was purified by column chromatography on silica gel, eluting with 10% ether-petrol, to furnish the *epoxy aldehyde* (18.4g, 88%) as an oil; $[\alpha]_D^{20}$ -59.3 (c 1.21 in $CHCl_3$); υ_{max}(film), 2961, 2932, 2858, 1727, 1471, 1428, 1112, 1031, 823, 740 and 703cm^{-1}; δH(270MHz), 8.86 (1H, s, H-1), 7.70-7.40 (10H, m, Ar-H), 3.83 (1H, dd, *J* 10.0 and 5.1Hz, H-5), 3.78 (1H, dd, *J* 10.0 and 4.2Hz, H-5), 3.11 (1H, d, *J* 9.3Hz, H-3), 1.65 (1H, m, H-4), 1.40 (3H, s, Me-2), 1.09 (9H, s, ^tBu), 1.06 (3H, d, *J* 7.3Hz, Me-4); *m/z* 325 (M^+-^tBu); Found: C, 72.09; H, 8.11. $C_{23}H_{30}O_3Si$ requires C, 72.25; H, 7.90%.

Hexamethyldisilazane (56.0ml, 265mmol) was added to a suspension of potassium hydride (30.3g of 35% by weight paraffin oil dispersion, 265mmol, washed with THF (3x20 ml)) in THF (300ml) and stirred for 30min. under argon. The resulting cloudy solution was allowed to settle, then added dropwise to methyl-triphenylphosphonium bromide (94.4g, 265mmol) in toluene (20ml) at -20°C under argon *via* cannula. The

mixture was warmed to room temperature to allow complete formation of the yellow ylide and then cooled back to -20°C. The epoxy aldehyde (16g, 41.9mmol) in THF (150ml) was added dropwise and the mixture warmed to room temperature, poured into brine (30ml) and extracted with ether (3x30ml). The combined organic extract was dried ($MgSO_4$), the solvent evaporated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with ether-petrol (1%) to give the *vinyl epoxide* **40** (15.44g, 97%) as a colourless oil; $[\alpha]_D^{20}$ -3.0 (c 1.84 in $CHCl_3$); υ_{max}(film) 2961, 2932, 2858, 1589, 1471, 1428, 1112, and 703cm^{-1}; δ_H(270MHz), 7.70-7.20 (10H, m, Ar-H), 5.60 (1H, dd, *J* 17.6 and 10.5Hz, H-2), 5.25 (1H, dd, *J* 17.6 and 1.2Hz, H-1), 5.10 (1H, dd, *J* 10.5 and 1.0Hz, H-1), 3.72 (1H, dd, *J* 9.8 and 3.9Hz, H-6), 3.67 (1H, dd, *J* 9.8 and 5.9Hz, H-6), 2.65 (1H, d, *J* 9.5Hz, H-4), 1.64 (1H, m, H-5), 1.32 (3H, s, Me-3), 1.01 (9H, s, ^{t}Bu), 1.00 (3H, d, *J* 8.8Hz, Me-5); *m/z* 323 (M^+-^{t}Bu); Found: M^+-^{t}Bu 323.1473; $C_{24}H_{32}O_2Si$ requires *M-^{t}Bu*, 323.1467.

(*exo*,4*R*,5*S*) and (*endo*,4*R*,5*S*)-π-Allyl-1,2,3-η-3-[4-carbonyloxyhex-2-en-3-ylate-3,5-dimethyl-6-(*tert*-butyldiphenylsilyloxy)] tricarbonyliron (41) and (42).

Diironnonacarbonyl (19.8g, 56.8mmol) was added to a solution of the vinyl epoxide **40** (15.0g, 39.5mmol) in dry tetrahydrofuran (400ml) and the mixture stirred for 8h; the solvent was evaporated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with 20% ether-petrol to give the *ferrilactone complex* **42** (10.6g, 49%) as an oil; υ_{max}(film), 3070, 2930, 2078, 2002, 1671, 1462, 1112, 1014 and 703cm^{-1}; δ_H(270MHz, C_6D_6), 7.80-7.30 (10H, m, Ar-H), 4.10 (1H, d, 5.9Hz, H-4), 3.83 (1H, dd, *J* 12.9 and 8.5Hz, H-2), 3.80 (1H, dd, *J* 10.0 and 4.2Hz, H-6), 3.60 (1H, dd, *J* 10.0 and 7.3Hz, H-6), 2.6 (1H, dd, *J* 8.5 and 2.2Hz, H-1), 2.41 (1H, dd, *J* 12.9 and 2.2Hz, H-1), 1.70 (1H, m, H-5), 1.40 (3H, s, Me-3), 1.22 (9H, s, ^{t}Bu), 1.14 (3H, d, *J* 6.8Hz, Me-5); *m/z* 436 (M^+-4CO), 199 (Ph_2SiOH); Found: M^+-4CO, 436.1521; $C_{28}H_{32}O_6SiFe$ requires *M-4CO*, 436.1531; and *ferrilactone* **41** as an oil (3.5g, 16%); υ_{max}(film), 3070, 3043, 2959, 2931, 2078, 2018, 1663, 1427, 1112, and 703cm^{-1}; δ_H(270MHz, C_6D_6), 7.9-7.2 (10H, m, Ar-H), 4.02 (1H, dd, *J* 10.0 and 3.9Hz, H-6), 3.98 (1H, dd, *J* 12.9 and 8.1Hz, H-2), 3.92 (1H, dd, *J* 10 and 8.1Hz, H-6), 3.47 (1H, d, *J* 4.2Hz, H-4), 2.54 (1H, dd, *J* 8.1 and 2Hz, H-1), 2.37 (1H, dd, *J* 12.9 and 2.0Hz, H-1), 1.85 (1H, m, H-5), 1.28 (3H, s, Me-3), 1.22 (9H, s, ^{t}Bu), 1.17 (3H, d, *J* 6.6Hz, Me-5); *m/z* 436 (M^+-4CO); 199 (Ph_2SiOH^+); Found: M^+-4CO, 436.1521; $C_{28}H_{32}O_6SiFe$ requires *M-4CO*, 436.1529).

[5*R*,6*S*(*S*)]-6-[3-(*tert*-Butyldiphenylsilyloxy)propyl]-5,6-dihydro-5-methyl-2-pyranone (44).

Ferrilactone **42** (2.8g, 5.1mmol) in dry benzene (15ml) was heated at 90°C for three days under a pressure of 240atm of carbon monoxide in a high pressure steel vessel. The mixture was then filtered through a cotton wool plug; the solvent evaporated *in vacuo* and the residue purified by column chromatography on silica gel eluting with 10% ether-petrol to afford the *α,β-unsaturated lactone* **44** (2.04g, 98%) as an oil, $[\alpha]_D^{20}$ -89.9 (c 0.94 in $CHCl_3$); υ_{max}(film), 3069, 2930, 1724, 1426, 1251, 1112, 823 and 703cm^{-1}; δ_H(270MHz), 7.8-7.3 (10H, m, Ar-H), 7.0 (1H, dd, *J* 9.5 and 6.4Hz, H-4), 6.0 (1H, dd, *J* 9.5 and 0.5Hz, H-3), 4.40 (1H, dd, *J* 10.7 and 2.9Hz, H-6), 4.0 (1H, dd, *J* 9.8 and 4.4Hz, H-3'), 3.73 (1H, dd, *J* 9.8 and 2.9Hz, H-3'), 2.4 (1H, ddq, *J* 6.6, 6.4 and 2.9Hz, H-5), 1.99 (1H, m, H-2'), 1.05 (9H, s, ^{t}Bu), 1.05 (3H, d, *J* 6.8Hz, Me-2') and 1.02 (3H, d, *J* 6.6Hz, Me-5); *m/z*, 393 (M^+-Me), 351 (M^+-^{t}Bu), 199 (Ph_2SiOH^+); Found: M^+-^{t}Bu, 351.1417; $C_{25}H_{32}O_3Si$ requires *M-^{t}Bu*, 351.1419; Found: C, 73.56; H, 8.05. $C_{25}H_{32}O_3Si$ requires C, 73.51; H, 7.84%.

Ferrilactone **41** (1.7g, 3.1mmol) in dry benzene (20ml) was heated at 90°C for three days under a pressure of 240atm of carbon monoxide in a high pressure steel vessel. The mixture was then filtered through a cotton wool plug; the solvent evaporated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with 10% ether-petrol to give a mixture of *unsaturated lactones* **43, 44** and **45** (2:2:1), (1.27g, 100%). Lactone **43**; δ_H(270MHz), 7.7-7.4 (10H, m, Ar-H), 6.62 (1H, dd, *J* 10.1 and 3.4Hz, H-4), 5.93 (1H, dd, *J* 10.1 and 2.7Hz, H-3), 4.08 (1H, dd, *J* 10 and 3.4Hz, H-6), 3.87 (1H, dd, *J* 10.8 and 6.8Hz, H-3'), 3.6 (1H, dd, *J* 10.8 and 5.1Hz, H-3'), 2.95 (1H, m, H-5), 2.18 (1H, m, H-2'), 1.05 (9H, s, ^{t}Bu), 1.05 (6H, d, J 6.5Hz, Me-5 and Me-2'); lactone **44** as described and lactone **45** as an oil, $[\alpha]_D^{20}$ -13.4 (c 3.02 in $CHCl_3$); υ_{max}(film), 3069, 2929, 1742, 1589, 1461, 1427, 1388, 1211, 1112, 823 and 703cm^{-1}; δ_H(400MHz), 7.7-7.4 (10H, m, Ar-H), 5.46 (1H, br s, H-4), 4.82 (1H, br s, H-6), 3.59 (2H, m, H_2-3), 2.92 (2H, m, H_2-3'), 2.18 (1H, m, H-2'), 1.10 (3H, d, *J* 6.5Hz, Me-2') and 1.05 (9H, s, ^{t}Bu); *m/z* 351 (M^+-^{t}Bu); Found: M^+-^{t}Bu, 351.1412; $C_{25}H_{32}O_3Si$ requires *M*-^{t}*Bu*, 351.1419.

[5*R*,6*S*,(*S*)]-6-[3-(*tert*-Butyldiphenylsilyloxy)propyl]-5-methyltetrahydro-2-pyranone (46)

The α,β-unsaturated lactone **44** (1.57g, 3.85mmol) was stirred vigorously (12h) in ethyl acetate (15ml) with catalytic platinum (IV) oxide under an atmosphere of hydrogen. The mixture was filtered through a pad of florisil, the solvent evaporated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with 10% ether-petrol to give the *lactone* **46** (1.53g, 97%) as a colourless oil; $[\alpha]_D^{20}$ +44.2 (c 2.94 in $CHCl_3$); υ_{max}(film) 3069, 2961, 1741, 1427, 1238, 1112, 823 and 703cm^{-1}; δ_H(500MHz), 7.70-7.30 (10H, m, Ar-H), 4.26 (1H, dd, *J* 10.5 and 2.2Hz, H-6), 3.97 (1H, dd, *J* 9.7 and 4.4Hz, H-3'), 3.73 (1H, dd, *J* 9.7 and 2.7Hz, H-3'), 2.50 (2H, m, H_2-3), 2.12 (2H, m, H_2-4), 1.88 (1H, m, H-2'), 1.65 (1H, m, H-5), 1.07 (9H, s, ^{t}Bu), 1.04 (3H, d, *J* 6.8Hz, Me-2') and 0.94 (3H, d, *J* 7.1Hz, Me-5); *m/z* 353 (M^+-^{t}Bu); Found: M^+-^{t}Bu, 353.1573; $C_{25}H_{34}O_3Si$ requires *M*-^{t}*Bu*, 353.1569. The unsaturated lactone **45**, (0.14g, 0.34mmol) under the same conditions affords identical lactone **46** (0.134g, 95%).

tert-Butyldimethylsilylchloride (0.538g, 3.57mmol) was added to a stirred solution of the lactone **50** (0.41g, 2.38mmol) and imidazole (0.243g, 3.57mmol) in dry dimethylformamide (2ml) at room temperature under argon. After 3h, the mixture was poured into water and the aqueous phase extracted with ether (3x5ml). The combined organic extract was washed with water (5ml) and then with brine (5ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Column chromatography of the residue on silica gel, eluting with ether-petrol (20%) afforded *lactone* **46** (0.89g, 91%) identical to the material prepared above.

[2*RS*,5*R*,6*S*,(*S*)]-6-[3-(*tert*-Butyldiphenylsilyloxy)propyl]-5-methyltetyrahydro-2-(2*H*)-pyranol (47)

Diisobutylaluminium hydride (2.95ml of a 1.5 M solution in toluene, 4.43mmol) was added to a stirred solution of the lactone **46** (1.6g, 3.9mmol) in dry toluene (50ml) under argon at -78°C. The solution was stirred for 1h, quenched with water (1.5ml) and allowed to warm to room temperature. The mixture was then poured into water and extracted with ethyl acetate (3x15ml). The combined organic extract was washed with water (10ml), brine (10ml), dried over ($MgSO_4$), the solvent evaporated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with 15% ether-petrol, to give a 2:1 mixture of *anomeric lactols* **47** (1.54g, 96%) as a colourless oil; υ_{max}(film) 3418, 3048, 2958, 2929, 1460, 1427, 1388, 1112, 1036, 1016, 823, 703 and 614cm^{-1}; δ_H(270MHz), 7.7-7.4 (10H, m, Ar-H), 5.11 (0.33H, m, H-2, minor anomer),

4.40 (0.66H, m, H-2, major anomer), 3.93 (1H, dd, *J* 9.3 and 4.2Hz, H-3'), 3.8 (0.33H, dd, *J* 7.2 and 4.1Hz, H-6, minor anomer), 3.70 (1H, dd, *J* 9.3 and 2.4Hz, H-3'), 3.42 (0.66H, dd, *J* 10.8 and 2.4Hz, H-6, major anomer), 2.30 (1H, d, *J* 2.5Hz, OH), 1.85-1.2 (6H, m, H_2-3, H_2-4, H-5, H-2'), 1.08 (9H, s, ^{t}Bu), 1.05-0.8 (6H, m, Me-5, Me-2'); *m/z* 394 (M^+-H_2O), 355 (M^+-^{t}Bu); Found: M^+-^{t}Bu, 355.1729; $C_{25}H_{36}O_3Si$ requires *M*-^{t}*Bu*, 355.1720; Found: C, 72.84; H, 8.97. $C_{25}H_{36}O_3Si$ requires C, 72.80; H, 8.74%.

[*2RS,5R,6S,(S)*]-6-[3-(*tert*-Butyldiphenylsilyloxy)propyl]-5-methyltetrahydro-2-(phenylsulphonyl)-*2H*-pyran (34).

A solution of lactols **47** (0.5g, 1.21mmol) in dry dichloromethane (30ml) was treated with anhydrous powdered calcium chloride (0.15g, 1.4mmol) and a solution of freshly prepared benzenesulphinic acid (0.34g, 2.4mmol) in dichloromethane (10ml), under argon. The reaction mixture was stirred at room temperature for 20h and then treated with 1ml of a saturated aqueous solution of potassium carbonate diluted with water (10ml). The resulting emulsion was stirred at room temperature for 5min., diluted with dichloromethane (20ml), the organic layer separated, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The crude sulphone was chromatographed on silica gel, eluting with 15% ether-petrol to afford the *anomeric sulphones* **34** (0.6g, 92%) as an oil; υ_{max}(film) 2930, 2856, 1446, 1427, 1321, 1147, 1112, 1081, 823, 744, 723, 704 and 687cm^{-1}; δ_H(270MHz) 7.75-6.90 (15H, m, Ar-H), 4.67 (0.66H, d, *J* 6.3Hz, H-2, major anomer), 4.23 (0.33H, m, H-2, minor anomer), 3.96 (0.66H, dd, *J* 10.2 and 2.3Hz, H-6, major anomer), 3.51 (0.33H, dd, *J* 9.7 and 3.4Hz, H-3', minor anomer), 3.44 (0.66H, dd, *J* 9.6 and 3.7Hz, H-3', major anomer), 3.25 (0.33H, m, H-6, minor anomer), 3.16 (0.33H, dd, *J* 9.7 and 1.8Hz, H-3', minor anomer), 3.06 (0.66H, t, *J* 9.6Hz, H-3', major anomer), 2.47-2.25 (2H, m, H_2-3), 2.10 (1H, m, H-5), 1.95-1.40 (3H, m, H_2-4, H-2'), 1.06-0.85 (15H, m, ^{t}Bu, Me-5, Me-2'); *m/z* 479 (M^+-^{t}Bu); Found: M^+-^{t}Bu, 479.1704; $C_{31}H_{40}O_4SSi$ requires *M*-^{t}*Bu*, 355.1712.

(*E,4R,5S,6S*)-Methyl-7-(benzyloxy)-4,6-dimethyl-5-hydroxy-2-heptenoate (48).

A mixture of ozone and oxygen (ozoniser voltage, 140v; 40 l/h) was bubbled through a solution of alkenol **27** (10g, 42.74mmol) in dichloromethane (200ml), at -78°C for 2.5h. Triphenylphosphine (10g, 38.12mmol) was added and the mixture warmed to 0°C for 30min. Carbomethoxymethylenetriphenylphosphorane (21.4g, 64mmol) was added and the stirred solution allowed to warm to room temperature over 14h. The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel eluting with petrol-ether (70%) to obtain the *α,β-unsaturated ester* **48** (9.86g, 79%, E/Z, 8:1) as a colourless oil; υ_{max}(film) 3438, 2926, 1683, 1646, 1442, 1379, 1343, 1261, 1196, 1167, 1082, 1042, 750 and 697cm^{-1}; δ_H(500MHz) 7.36-7.28 (5H, M, Ar-H), 6.99 (1H, dd, *J* 15.8 and 7.7Hz, H-3), 5.82 (1H, dd, *J* 15.8 and 1.3Hz, H-2), 4.50 (2H, d, *J* 1.7Hz, OCH_2Ph), 3.72 (3H, s, OMe), 3.65 (1H, dd, *J* 9.2 and 3.8Hz, H-5), 3.51-3.45 (3H, m, H_2-7, OH), 2.45 (1H, m, H-4), 1.91 (1H, qd, *J* 6.8 and 3.8Hz, H-6), 1.02 (3H, d, *J* 6.8Hz, Me-6) and 0.95 (3H, d, *J* 7.02Hz, Me-4); *m/z* 274 (M^+-H_2O), 261 (M^+-OMe), 201 (M^+-C_7H_7), 179 (M^+-$C_6H_9O_2$) and 91 ($C_7H_7^+$); Found: C, 69.85; H, 8.40. $C_{17}H_{24}O_4$ requires C, 69.84; H, 8.27%.

[*5R,6S,(S)*]-6-[3-(Benzyloxy)propyl]-5-methyltetrahydro-2-pyranone (49).

Platinum (IV) oxide on carbon (100mg, 0.44mmol) was added to a solution of unsaturated ester **48** (8.5g, 29.1mmol) in dichloromethane (100ml) under argon at room temperature. Argon was exchanged for hydrogen and the mixture stirred vigorously for 6h, then filtered through celite washing with dichloromethane. The

solvent was evaporated *in vacuo* to leave a solution of the crude ester (50ml in dichloromethane). Camphorsulphonic acid (0.1g) was added and the mixture stirred at room temperature for 12h, after which the solvent was evaporated *in vacuo*. Purification by column chromatography on silica gel eluting with petrol-ether (20%), afforded *lactone* **49** (6.33g, 83%) as a colourless oil, $[\alpha]_D^{20}$ +66.7 (c 0.46 in $CHCl_3$); υ_{max}(film) 2973, 2918, 2858, 1675, 1493, 1426, 1396, 1262, 1201, 1162, 1077, 1045, 1028, 972, 823, 733 and 703 cm^{-1}; δ_H(500MHz) 7.37-7.22 (5H, m, Ar-H), 4.50 (2H, s, OCH_2Ph), 4.17 (1H, dd, *J* 10.3 and 2.3Hz, H-6), 3.64-3.59 (2H, m, H_2-3'), 2.50 (2H, dd, *J* 8.6 and 6.3Hz, H_2-3), 2.14 (1H, m, H-5), 2.10 (1H, m, H-4), 1.97 (1H, m, H-2'), 1.65 (1H, m, H-4), 1.01 (3H, d, *J* 6.9Hz, Me-5) and 0.95 (3H, d, *J* 7.04Hz, Me-2'); *m/z* 262 (M^+), 171 (M^+-C_7H_7), 141 (M^+-C_8H_9O), 114 (M^+-$C_{10}H_{12}O$) and 91 ($C_7H_7^+$); Found: C, 73.24; H, 8.55. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%.

[*5R,6S,(S)*]-6-[3-(Hydroxy)propyl]-5-methyltetrahydro-2-pyranone (50).

10% palladium on activated carbon (0.05g, 10% w/w) was added to a solution of the lactone **49** (0.874g, 3.23mmol) in ethanol (10ml) at room temperature under argon. The flask was flushed with hydrogen and the mixture stirred vigorously under a hydrogen atmosphere. After 6h, the flask was reflushed with argon; the mixture filtered through a pad of celite and the solvent evaporated *in vacuo*. Column chromatography of the residue on silica gel, eluting with ether-petrol (40%) afforded *lactone* **50** (0.423g, 76%) as an oil, $[\alpha]_D^{18}$ +31.3 (c 0.33 in $CHCl_3$); υ_{max}(film) 3310, 3175, 2947, 2841, 1678, 1409, 1426, 1387, 1305, 1206, 1120, 1081, 966, 926 and 854 cm^{-1}; δ_H(500MHz) 4.0 (1H, dd, *J* 10.2 and 2.3Hz, H-6), 3.63 (2H, m, H_2-3'), 2.47 (2H, dd, *J* 8.1 and 6.1Hz, H_2-3), 2.10 (1H, m, H-5), 2.06 (1H, m, H-4), 1.97 (1H, m, H-2'), 1.61 (1H, m, H-4), 0.97 (3H, d, *J* 6.9Hz, Me-5) and 0.94 (3H, d, *J* 7.04Hz, Me-2'); *m/z* 172 (M^+), 154 (M^+-H_2O) and 113 (M^+-C_3H_7); Found: (M^+-H_2O),154.099; $C_9H_{16}O_3$ requires *M-H_2O*, 154.099.

(*S*)-6-(Benzyloxy)-1,4-hexanediol (51).

9-Borabicyclo [3.3.1] nonane (132ml of a 0.5M solution in tetrahydrofuran, 66mmol) was added dropwise, *via* cannula to a stirred solution of the alkenol **17** (4.52g, 21.9mmol) in anhydrous tetrahydrofuran (50ml) at room temperature under argon. The reaction was heated at 65°C for 3h. The reaction mixture was then cooled to 0°C and quenched by the cautious, dropwise addition of water (5ml) with vigorous stirring. After 5min., 3N aqueous sodium hydroxide solution (70ml) and 30% aqueous hydrogen peroxide solution (30ml) were added sequentially and the mixture was warmed to room temperature and stirred for 1h. The organic layer was separated and the aqueous phase extracted with ether (3x30ml). The combined organic extract was washed with brine (25ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was columned on silica gel eluting with petrol-ether (30%) to give *diol* **51** (4.67g, 95%) as a colourless oil, $[\alpha]_D^{19}$ -8.98 (c 3.42 in $CHCl_3$); υ_{max} (film) 3368, 2922, 1448, 1363, 1093, 735 and 697cm^{-1}; δ_H(270MHz) 7.36-7.27 (5H, m, Ar-H), 4.51 (2H, s, OCH_2Ph), 3.84 (1H, m, H-4), 3.71 (1H, m, H-1), 3.64 (3H, m, H-1, H_2-6), 1.84-1.51 (6H, m, H_2-2, H_2-3, H_2-5); *m/z* 206 (M^+-H_2O), 178 (M^+-C_2H_6O), 165 (M^+-C_3H_7O), 133 (M^+-C_7H_7) and 91 ($C_7H_7^+$); Found: C, 69.36; H, 8.97. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%.

(*4S*)-4-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxepane (52).

2,2-Dimethoxypropane (3.6g, 4.25ml, 34.6mmol) was added to a solution of the diol **51** (3.1g, 13.8mmol) in dichloromethane (15ml) containing camphorsulphonic acid (10mg) under argon at room temperature with

stirring. The mixture was stirred at room temperature for 1h. Evaporation of the excess reagent and solvent *in vacuo* followed by chromatography on silica gel eluting with petrol-ether (80%) afforded *acetonide* **52** (3.54g, 97%), as a colourless oil $[\alpha]_D^{20}$ +9.89 (c 1.76 in $CHCl_3$); υ_{max}(film) 3508, 3084, 3061, 3027, 2792, 2716, 1945, 1809, 1493, 1290, 1158, 1047, 822 and 698cm^{-1}; δ_H(270MHz) 7.37-7.27 (5H, m, Ar-H), 4.49 (1H, d, *J* 11.6Hz, OCHPh), 4.45 (1H, d, *J* 11.6Hz, OCHPh), 3.98 (1H, td, *J* 9.94 and 3.4Hz, H-7), 3.75 (1H, m, H-4), 3.62 (1H, m, H-2'), 3.51 (2H, m, H-2', H-7), 1.8-1.34 (6H, m, H_2-5, H_2-6, H_2-1'), 1.33 (3H, s, Me) and 1.31 (3H, s, Me); *m/z* 249 (M^+-Me), 206 (M^+-C_3H_6O), 188 (M^+-$C_3H_8O_2$), 129 (M^+-$C_9H_{11}O$), 107 ($C_7H_7O^+$) and 91 ($C_7H_7^+$); Found: C, 72.45; H, 9.31. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%.

(*S*)-4-[3-(Hydroxy)propyl]-2,2-dimethyl-1,3-dioxane (54)

10% palladium on carbon (20mg) was added to a solution of the acetonide **52** (1.92g, 7.27mmol) in redistilled ethanol (10ml) under argon at room temperature. Argon was exchanged for hydrogen and the mixture stirred vigorously for 12h, then filtered through celite, washing with dichloromethane. The solvent was evaporated *in vacuo* to leave the *alcohol* **53** as an oil. This was immediately taken up into acetone (15ml), and anhydrous copper sulphate (0.5g) added with a trace of camphorsulphonic acid (5mg). The mixture was stirred at room temperature for 10h, then washed with water (10ml), sodium bicarbonate solution (10ml) and the organic layer separated, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with petrol-ether (30%) to give the *alcohol* **54** (0.89g, 70%) as a colourless oil, $[\alpha]_D^{17}$ -19.5 (c 1.0 in $CHCl_3$); υ_{max}(film) 3418, 2989, 2942, 2867, 1379, 1270, 1246, 1199, 1162, 1098, 1052, 969 and 870cm^{-1}; δ_H(270MHz) 3.96 (1H, td, *J* 12.1 and 3.17Hz, H-6), 3.85 (2H, m, H-4, H-3'), 3.64 (2H, m, H-6, H-3'), 2.28 (1H, t, *J* 5.5Hz, OH), 1.71-1.52 (6H, m, H_2-5, H_2-1', H_2-2'), 1.46 (3H, s, Me), 1.39 (3H, s, Me); *m/z* 159 (M^+-Me), 129 (M^+-C_2H_5O), 115 (M^+-C_3H_7O) and 99 (M^+-$C_3H_7O_2$); Found: M^+-Me, 159.1028. $C_9H_{18}O_3$ requires *M-Me*, 159.1021.

(*S*)-4-[3-(Iodo)propyl]-2,2-dimethyl-1,3-dioxane (35).

Triethylamine(0.873g, 1.2ml, 8.63mmol) was added to a solution of alcohol **54** (1g, 5.75mmol) in dichloromethane (30ml) at -10°C under argon. Methanesulphonyl chloride (0.73g, 0.49ml, 6.33mmol) was added dropwise and the solution stirred for 1h, after which it was poured into saturated sodium bicarbonate solution (10ml) and extracted with dichloromethane (3x20ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was immediately dissolved in dry acetone (25ml) containing anhydrous sodium iodide (5.2g, 34.5mmol) and heated at 40°C for 3h under argon. After cooling, the mixture was diluted with ether (30ml) and washed first with a 10% solution of sodium thiosulphate (10ml) and then with brine (10ml). The organic layer was separated and the aqueous phase extracted with ether (3x20ml), the combined organic extracts dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with petrol-ether (90%) to give *iodide* **35** (1.31g, 80%) as a colourless oil, $[\alpha]_D^{18}$ -44.2 (c 1.9 in $CHCl_3$); υ_{max}(film) 2988, 2940, 2862, 2718, 1429, 1378, 1268, 1239, 1197, 1179, 1160, 1057, 967, 870, 795 and 663cm^{-1}; δ_H(270MHz) 3.95 (1H, td, *J* 12.1 and 2.9Hz, H-6), 3.87 (2H, m, H-6, H-4), 3.21 (1H, dd, *J* 7 and 2.6Hz, H-3'), 3.18 (1H, dd, *J* 7 and 2.5Hz, H-3'), 1.96 (1H, sept, *J* 7.1Hz, H-2'), 1.85 (1H, sept, *J* 7.1Hz, H-2'), 1.62 (2H, m, H_2-1'), 1.55 (2H, m, H_2-5), 1.44 (3H, s, Me) and 1.37 (3H, s, Me); *m/z* 285 (M+H), 269 (M^+-Me) and 209 (M^+-$C_3H_7O_2$); Found: M^+-Me, 269.003. $C_9H_{17}IO_2$ requires *M-Me*, 269.004.

Methyl 5-benzyloxy-2-hydroxy benzoate (56).

Gentistic acid methyl ester **55** (4.95g, 29.5mmol) in acetone (20ml) was added dropwise to a solution of potassium carbonate (4.07g, 29.5mmol) in dry acetone (50ml) at room temperature under argon, *via* cannula and the yellow suspension stirred at room temperature for 1h. Benzyl bromide (5.05g, 3.51ml, 29.5mmol) was added, and the mixture stirred at room temperature for 12h. The reaction was quenched by the addition of water (10ml); diluted with ether (50ml), poured into brine (20ml) and the organic phase separated. The aqueous layer was extracted with ether (3x30ml), the combined organic extract dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with petrol-ether (90%) to give *phenol* **56** (5.39g, 71%) as a yellow oil, υ_{max}(film) 3490, 3350, 2253, 1675, 1484, 1379, 1217, 908, 736 and 650cm^{-1}; δ_H(270MHz) 10.5 (1H, s, OH), 7.45-7.35 (5H, m, Ar-H), 7.33 (1H, d, *J* 3.17Hz, Ar-H), 7.15 (1H, dd, *J* 9.04 and 3.17Hz, Ar-H), 6.91 (1H, d, *J* 9.04Hz, Ar-H), 5.02 (2H, s, OCH_2Ph) and 3.95 (3H, s, OMe); *m/z* 258 (M^+), 227 (M^+-OMe), 181 (M^+-C_6H_5), 167 (M^+-C_7H_7) and 91 ($C_7H_7^+$); Found: C, 69.87; H, 5.53. $C_{15}H_{14}O_4$ requires C, 69.76; H, 5.46%.

Methyl 2-[[2-(trimethylsilyl)ethoxy]methoxy]-5-hydroxy benzoate (57).

Phenol **56** (3.1g, 12mmol) in ether (20ml) was added dropwise *via* cannula to a suspension of sodium hydride (0.374g, 15.6mmol from 0.62g of a 60% dispersion of mineral oil, pre-washed with light petroleum (3x2ml)) in dry ether/dimethylformamide (50ml, 45:5) at 0°C under argon, and the mixture stirred at room temperature until effervescence had ceased. 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) (2.2g, 2.34ml, 13.2mmol) was added, and the green solution stirred at room temperature for 3h. Excess sodium hydride was quenched by the careful addition of water (10ml) with cooling. The reaction mixture was poured into brine (20ml) and the organic phase separated. The aqueous layer was extracted with dichloromethane (3x30ml) and the combined organic extract dried ($MgSO_4$), then concentrated *in vacuo*. The residue was columned on silica gel, eluting with petrol-ether (90%) to give the *aromatic ester* (4.15g, 89%) as an oil, υ_{max}(film) 3061, 3029, 2949, 2894, 1947, 1871, 1732, 1607, 1581, 1492, 1450, 1404, 1379, 1247, 1188, 1025, 918 and 785cm^{-1}; δ_H(270MHz) 7.45-7.31 (5H, m, Ar-H), 7.28 (1H, d, *J* 3.17Hz, Ar-H), 7.15 (1H, d, *J* 9.04Hz, Ar-H), 7.05 (1H, dd, *J* 9.04 and 3.17Hz, Ar-H), 5.21 (2H, s, OCH_2O) 5.04 (2H, s, OCH_2Ph), 3.89 (3H, s, OMe), 3.80 (2H, m, $OC\underline{H}_2CH_2$), 0.95 (2H, t, *J* 7.3Hz, $CH_2C\underline{H}_2Si$) and 0.01 (9H, s, $(Me)_3Si$); *m/z* 388 (M^+), 344 (M^+-C_3H_8), 330 (M^+-$C_2H_2O_2$), 315 (M^+-TMS), 301 (M^+-CH_2TMS) and 91 ($C_7H_7^+$); Found: C, 65.02; H, 7.36. $C_{21}H_{28}O_5Si$ requires C, 64.92; H, 7.26%.

10% Palladium on activated carbon (0.05g,) was added to a solution of the aromatic ester (2.2g, 5.67mmol) in ethanol (20ml) at room temperature under argon. The flask was flushed with hydrogen and the mixture stirred vigorously under a hydrogen atmosphere. After 2.5h, the flask was reflushed with argon; the mixture filtered through a pad of celite and the solvent evaporated *in vacuo*. Column chromatography of the residue on silica gel, eluting with ether-petrol (50%) afforded *phenol* **57** (1.52g, 90%) as an oil, υ_{max}(film) 3307, 3203, 2951, 1676, 1611, 1485, 1439, 1341, 1284, 1215, 1094, 1075 and 1008cm^{-1}; δ_H(270MHz) 7.27 (1H, d, *J* 3.17Hz, Ar-H), 7.1 (1H, d, *J* 8.79Hz, Ar-H), 6.93 (1H, dd, *J* 8.79 and 3.17Hz, Ar-H), 5.20 (2H, s, OCH_2O) 3.88 (3H, s, OMe), 3.78 (2H, m, $OC\underline{H}_2CH_2$), 0.95 (2H, t, *J* 8.4Hz, $CH_2C\underline{H}_2Si$) and 0.01 (9H, s, $(Me)_3Si$); *m/z* 297 (M^+-H), 283 (M^+-Me), 225 (M^+-TMS), 210 (M^+-$C_4H_{12}Si$) and 73 (TMS^+); Found: C, 56.02; H, 7.66. $C_{14}H_{22}O_5Si$ requires C, 56.35; H, 7.43%.

Methyl 5-oxo-4-[(phenylselenyl)imino]-2-[[2-(trimethylsilyl)ethoxy]methoxy] -1,3-cyclohexadienecarboxylate (58) and Methyl 5-oxo-6-[(phenylselenyl) imino]-2-[[2-(trimethylsilyl)ethoxy]methoxy]-1,3-cyclohexadienecarboxylate (59).

The phenol **57** (1.92g, 6.44mmol) was dissolved in dry benzene (10ml), and hexamethyldisilazane (1.63g, 7.74mmol) and benzeneselenenic anhydride (2.55g, 7.08mmol) added; a intense red colour developed immediately. The reaction was stirred at room temperature for 15min., diluted with chloroform (10ml) and filtered through a pad of celite. Evaporation of the solvent *in vacuo* and column chromatography of the residue, eluting with petrol-ether (80%) afforded the *phenylselenoimine* **59** (1.46g, 50%) as a deep purple oil, υ_{max}(film) 2948, 1732, 1595, 1424, 1215, 1143, 1096, 1049, 998, 833 and 738cm^{-1}; δ_H(500MHz) 7.75 (2H, dd, *J* 8.1 and 1.3Hz, SePh), 7.5 (1H, d, *J* 10.3Hz, Ar-H), 7.43 (2H, t, *J* 7.9Hz, SePh), 7.32 (1H, m, SePh), 6.82 (1H, d, *J* 10.3Hz, Ar-H), 5.26 (2H, s, OCH_2O) 3.94 (3H, s, OMe), 3.82 (2H, t, *J* 7.1Hz, $OC\underline{H}_2CH_2$), 0.97 (2H, t, *J* 7.1Hz, $CH_2C\underline{H}_2Si$) and 0.02 (9H, s, $(Me)_3Si$); *m/z* 467 (M^+), 452 (M^+-Me), 409 (M^+-$C_2H_2O_2$), 311 (M^+-SePh), 297 (M^+-NSePh) and 73 (TMS^+); Found: M^+-Me, 452.0439. $C_{20}H_{25}NO_5SeSi$ requires *M-Me*, 452.0432; and *phenylselenoimine* **58** (0.612g, 21%) as a deep red oil, δ_H(500MHz, $CDCl_3$) 7.83 (2H, dd, *J* 8.04 and 1.23Hz, SePh), 7.47 (2H, m, SePh), 7.36 (1H, m, SePh), 6.92 (1H, s, Ar-H), 6.82 (1H, s, Ar-H), 5.27 (2H, s, OCH_2O) 3.93 (3H, s, OMe), 3.77 (2H, t, *J* 8.4Hz, $OC\underline{H}_2CH_2$), 0.98 (2H, t, *J* 8.4Hz, $CH_2C\underline{H}_2Si$) and 0.02 (9H, s, $(Me)_3Si$); Found: C, 49.91; H, 5.26; N, 2.72. $C_{20}H_{25}NO_5SeSi$ requires C, 51.06; H, 5.36; N, 2.97%.

Methyl 2-amino-3-hydroxy-6-[[2-(trimethylsilyl)ethoxy]methoxy] benzoate (5).

Samarium (II) iodide (4.28ml of a 0.1M solution in tetrahydrofuran, 0.428mmol) was added to a solution of the phenylselenoimine **59** (0.1g, 0.214mmol) in dry tetrahydrofuran/methanol (2.5ml, 4:1) at room temperature under argon. After 15min., the deep purple mixture was filtered through a pad of florisil and the solvent evaporated *in vacuo*. The residue was immediately chromatographed on silica gel, eluting with petrol-ether (50%) to afford the *aminophenol* **5** (0.045g, 74%) as a yellow oil, υ_{max}(film) 3510, 3497, 3302, 2951, 1652, 1611, 1557, 1489, 1249, 1119, 1075 and 836cm^{-1}; δ_H(500MHz) 6.65 (1H, d, *J* 8.58Hz, Ar-H), 6.28 (1H, d, *J* 8.58Hz, Ar-H), 5.20 (2H, br s NH_2), 5.13 (2H, s, OCH_2O) 4.45 (1H, br s OH), 3.87 (3H, s, OMe), 3.76 (2H, t, *J* 8.52Hz, $OC\underline{H}_2CH_2$), 0.96 (2H, t, *J* 8.52Hz, $CH_2C\underline{H}_2Si$) and 0.01 (9H, s, $(Me)_3Si$); *m/z* 313 (M^+), 295 (M^+-H_2O), 254 (M^+-CO_2Me), 182 (M^+-SEM), 166 (M^+-OSEM) and 73 (TMS^+); Found: (M^+), 313.1348. $C_{14}H_{23}NO_5Si$ requires *M*, 313.1345.

(*αR,2S,3R,6S*)-α,3-Dimethyl-1,7-dioxaspiro[5.5]undecane-2-ethanal (60).

Dimethylsulphoxide (0.041ml, 0.58mmol) was added dropwise to a solution of oxalyl chloride (0.025ml, 0.29mmol) in dry dichloromethane (1ml) at -65°C. The mixture was stirred for 5min., then the spiroketal alcohol **32** (0.02g, 0.09mmol) in dichloromethane (1ml) was added. The solution was stirred for a further 20min. at -60°C, then quenched with triethylamine (0.2ml, 1.45mmol) and allowed to warm to room temperature. The mixture was poured into water and extracted with ether (3x5ml). The combined organic extract was washed with water (5ml), brine (5ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give a residue which was purified by column chromatography on silica gel, eluting with 40% ether-petrol, to furnish

the *spiroketal aldehyde* **60** (0.014g, 71%) as a colourless oil; $[\alpha]_D^{25}$ +76.9 (c 1.3 in $CHCl_3$); υ_{max}(film), 2938, 2720, 1725, 1067, 997, 978 and 875cm^{-1}; δH(500MHz), (natural product numbering) 9.9 (1H, d, *J* 3Hz, H-20), 3.92 (1H, dd, *J* 10.5 and 2.5Hz, H-18), 3.60 (1H, m, H-10), 3.50 (1H, dt, *J* 11 and 3.5Hz, H-10), 2.54 (1H, ddq, *J* 10.5, 7.1 and 3Hz, H-19), 2.09 (1H, tt, *J* 13 and 4Hz, H-16), 1.80-1.35 (11H, m, H_2-11, H_2-12, H_2-13, H_2-15, H-16, H-17, H-19), 0.93 (3H, d, *J* 7.1Hz, Me-17) and 0.92 (3H, d, *J* 7Hz, Me-19); *m/z* 227 (MH^+), 198 (M^+-CO), 169 ($C_{10}H_{17}O_2^+$) and 101 ($C_5H_9O_2^+$); Found: MH^+, 227.1654. $C_{13}H_{23}O_3$ requires *MH*, 227.1647.

[2*S*(2*S*,3*R*,6*S*)]-2-[3-Methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-1-[1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-pyrrolidyl]-1-propanone (61).

n-Butyllithium (0.23ml of a 2.46M solution in hexane, 0.58mmol) was added to a solution of 1-[(trimethylsilyl)-ethoxymethyl] pyrrole (SEM-pyrrole) (0.113g, 0.58mmol) in dimethoxyethane (0.9ml) at -10°C under argon, and the mixture allowed to stir for 10min. The resulting pale yellow solution was added to the spiroketal aldehyde **60** (0.013g, 0.058mmol) in dimethoxyethane (0.5ml) at -15°C *via* cannula. The reaction mixture was stirred at room temperature for 30min. before pouring into saturated aqueous ammonium chloride solution (5ml). The organic layer was separated and the aqueous phase extracted with ether (3x5ml); the combined organic extract was dried ($MgSO_4$) and the residue chromatographed on silica gel to separate excess SEM-pyrrole. The diastereomeric mixture of alcohols was dissolved in 1,4-dioxane (2ml), 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) (0.006g, 0.026mmol) was added, and the resulting dark coloured solution stirred at room temperature for 1h. The mixture was poured into water (5ml) and extracted with ether (4x10ml), the ether extracts were combined, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with petrol-ether (70%) to afford the *ketopyrrole* **61** (0.008g, 34%) as a colourless oil, $[\alpha]_D^{25}$ +70.7 (c 0.45 in $CHCl_3$); υ_{max}(film) 2937, 1647, 1412, 1063, 997 and 836cm^{-1}; δ_H(500MHz), (natural product numbering) 7.10 (1H, dd, *J* 3 and 2Hz, H-22), 7.08 (1H, dd, *J* 4 and 2Hz, H-24), 6.21 (1H, dd, *J* 4 and 3Hz, H-23), 5.83 (1H, d, *J* 10Hz, NCHO), 5.64 (1H, d, *J* 10Hz, NCHO), 3.98 (1H, dd, *J* 10 and 2.3Hz, H-18), 3.55 (2H, t, *J* 8.5Hz, $OC\underline{H}_2CH_2$), 3.48 (2H, m, H_2-10), 3.33 (1H, dq, *J* 10 and 7Hz, H-19), 2.09 (1H, tt, *J* 13.5 and 4.5Hz, H-16), 1.82 (1H, m, H-17), 1.57 (1H, dt, *J* 14 and 4.5Hz, H-13), 1.45-1.08 (7H, m, H_2-11, H_2-12, H-13, H-15, H-16), 1.04 (3H, d, *J* 7Hz, Me-19), 1.01 (3H, d, *J* 7Hz, Me-17), 0.95-0.8 (3H, m, $CH_2C\underline{H}_2Si$, H-15) and 0.01 (9H, s, $(Me)_3Si$); *m/z* 421 (M^+), 320 (M^+-$C_5H_{13}Si$), 303 (M^+-$C_5H_{14}SiO$), 225 ($C_{13}H_{21}O_3^+$), 196 ($C_{10}H_{18}NOSi^+$), 169 ($C_{10}H_{17}O_2^+$) and 73 (TMS^+); Found: M^+, 421.2648. $C_{23}H_{39}NO_4Si$ requires *M*, 421.2636.

N-[6-Hydroxy-2-(methoxycarbonyl)-3-[[2-(trimethylsilyl)ethoxy]methoxy]phenyl] benzenepropanamide (63).

Ethyl chloroformate (0.027g, 0.024ml, 0.25mmol) was added to a stirred solution of 3-phenylpropionic acid **62** (29mg, 0.19mmol) and triethylamine (0.077g, 0.106ml, 0.76mmol) in dichloromethane (2ml) at -10°C under argon. After stirring for 15min., a solution of the amine **5** (0.119g, 0.38mmol) in dichloromethane (2ml) was added and the resulting solution left to warm up to room temperature overnight. The solvent was evaporated *in vacuo* and the residue extracted with ether (3x5ml). The combined ether extract was washed with brine (5ml) and dried ($MgSO_4$). After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel eluting with 20% ether-petrol to give the *model amide* **63** (0.054g, 63%) as an oil, υ_{max}(film) 3492,

3310, 2951, 1723, 1660, 1628, 1471, 1193, 1129 and 781cm^{-1}; δ_H(270MHz) 9.81 (1H, s, OH), 8.30 (1H, br s, NH), 7.25 (5H, m, Ar-H), 7.06 (1H, d, *J* 9.02Hz, Ar-H), 6.88 (1H, d, *J* 9.01Hz, Ar-H), 5.27 (2H, s, OCH_2O), 3.98 (3H, s, OMe), 3.63 (2H, t, *J* 7.51Hz, $OC\underline{H_2}CH_2$), 3.13 (2H, t, *J* 7.1Hz, $PhCH_2$), 2.85 (2H, m, CH_2CO), 1.07 (2H, t, *J* 7Hz, $CH_2C\underline{H_2}Si$) and 0.01 (9H, s, $(Me)_3Si$); *m/z* 445 (M^+), 427 (M^+-H_2O), 414 (M^+-MeOH), 312 (M^+-C_9H_9O) and 73 (TMS^+); Found: C, 59.91; H, 7.08; N, 3.27. $C_{23}H_{31}NO_6Si$ requires C, 61.0; H, 7.01; N, 3.14%.

Methyl 5-hydroxy-2-(2-phenethyl)-4-benzoxazolecarboxylate (64).

A solution of the amide **63** (0.025g, 0.056mmol) and pyridinium *p*-toluenesulfonic acid (0.01g) in methanol (2ml) was refluxed for 1h. The methanol was removed, 1,2-dichloroethane (2ml) added and the mixture refluxed for 3h. The resulting solution was poured into a saturated solution of sodium bicarbonate and stirred for 10min. at room temperature then extracted with ether (3x5ml). The combined ether extract was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 40% ether-petrol to give the *model benzoxazole* **64** (0.016g, 92%) as plates, mp. 124-125°C; υ_{max}(film) 3398, 1668, 1622, 1499, 1437, 1349, 1221, 1045, 808 and 699cm^{-1}; δ_H(270MHz) 10.62 (1H, s, OH), 7.58 (1H, d, *J* 8.8Hz, Ar-H), 7.3 (5H, m, Ar-H), 6.97 (1H, d, *J* 8.8Hz, Ar-H), 4.12 (3H, s, OMe), 3.3-3.18 (4H, m, CH_2CH_2); *m/z* 297 (M^+), 265 (M^+-MeOH), 105 ($C_8H_9^+$), 91 ($C_7H_7^+$) and 28 (CO^+); Found: C, 68.66; H, 5.23; N, 4.48. $C_{17}H_{15}NO_4$ requires C, 68.68; H, 5.09; N, 4.71%.

(*αR,2S,3R,6S,8S*)-8-[2-(Benzyloxy)ethyl]-α,3-dimethyl-1,7-dioxaspiro[5.5]undecane-2-ethanal (65).

The spiroketal alcohol **33** (1.0g, 2.76mmol) was added dropwise to a solution of 4-methylmorpholine-*N*-oxide (NMO) (0.35g, 3.03mmol) in dichloromethane (10ml) containing powdered 4Å sieves (2g). The resulting mixture was stirred at room temperature for 10min. before the addition of tetra-*n*-propylammonium perruthenate (TPAP) (0.02g, 0.06mmol). The initial green solution darkened as the reaction proceeded. After stirring for 1h, the resulting mixture was washed with saturated sodium sulphite solution (10ml) and with saturated copper (II) sulphate solution (10ml). The organic phase was separated, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with petrol-ether (50%) to give the *spiroketal aldehyde* **65** (0.975g, 98%) as a clear oil, $[\alpha]_D^{22}$ +52.5 (c 0.25 in $CHCl_3$); υ_{max}(film) 3422, 3030, 2936, 2725, 1716, 1425, 1409, 1385, 1363, 1309, 1272, 1235, 1217, 1179, 1102, 1082, 900, 873, 793 and 697cm^{-1}; δ_H(500MHz), (natural product numbering) 9.7 (1H, d, *J* 3.7Hz, H-20), 7.32 (5H, m, Ar-H), 4.52 (1H, d, *J* 11.9Hz, OCHPh), 4.48 (1H, d, *J* 11.89Hz, OCHPh), 3.87 (1H, dd, *J* 10.51 and 2.46Hz, H-18), 3.68 (1H, dd, *J* 9.05 and 5.47Hz, H-8), 3.62 (1H, m, H-10), 3.54 (1H, m, H-8), 2.37 (1H, ddq, *J* 10.55, 7.01 and 3.68Hz, H-19), 2.11 (1H, tt, *J* 13.3 and 4.3Hz, H-16), 1.82-1.0 (12H, m, H_2-9, H_2-11, H_2-12, H_2-13, H_2-15, H-16, H-17), 0.92 (3H, d, *J* 7Hz, Me-17) and 0.83 (3H, d, *J* 7Hz, Me-19); *m/z* 360 (M^+), 342 (M^+-H_2O), 332 (M^+-CO), 303 (M^+-C_3H_5O), 276 (M^+-C_5H_8O), 269 (M^+-C_7H_7), 232 (M^+-$C_8H_{16}O$), 107 ($C_7H_7O^+$), 91 ($C_7H_7^+$) and 28 (CO^+); Found: M^+, 360.2298. $C_{22}H_{32}O_4$ requires *M*, 360.3000.

[2*S*(2*S*,3*R*,6*S*,8*S*)]-2-[3-Methyl-8-[2-(benzyloxy)ethyl]-1,7-dioxaspiro[5.5]undecan-2-yl]-1-[1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-pyrrolidyl]-1-propanone (66).

n-Butyllithium (2.55ml of a 2.5M solution in hexane, 6.25mmol) was added dropwise to a stirred solution of 1-[2'-(trimethylsilyl)ethoxymethyl] pyrrole (SEM-pyrrole) (1.23g, 6.25mmol) in freshly distilled dimethoxyethane (10ml) at -10°C under argon. After stirring for 20min., the resulting yellow solution was allowed to warm to 0°C and stirred for 0.5h at this temperature. The mixture was re-cooled to -10°C and the spiroketal aldehyde **65** (0.75g, 2.08mmol) in dimethoxyethane/tetrahydrofuran (10ml, 8:2) was added *via* cannula. Stirring was continued for a further 0.5h and the mixture allowed to warm to room temperature over 2h. The deep red mixture was poured into saturated ammonium chloride solution (20ml) and extracted with ether (3x30ml). The combined organic extract was dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give the inseparable mixture of diastereomeric alcohols. A solution of the alcohols in acetonitrile (5ml) was added dropwise to a solution of (NMO) (0.22g, 1.88mmol) in acetonitrile (10ml) containing powdered 4Å sieves (2g). The resulting mixture was stirred at room temperature for 10min. before the addition of (TPAP) (0.02g, 0.06mmol). The initial green solution darkened as the reaction proceeded. After stirring for 3h, the resulting mixture was washed with saturated sodium sulphite solution (10ml) and with saturated copper (II) sulphate solution (10ml). The organic phase was separated, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with petrol-ether (50%) to give the *protected ketopyrrole* **66** (0.705g, 61%) as a colourless oil, $[\alpha]_D^{20}$ +64.65 (c 0.4 in $CHCl_3$); υ_{max}(film) 2926, 1718, 1647, 1452, 1413, 1375, 1249, 1087, 988, 836, 737 and 697cm^{-1}; δ_H(500MHz), (natural product numbering) 7.33 (5H, m, Ar-H), 7.11 (1H, dd, *J* 2.57 and 1.65Hz, H-22), 7.04 (1H, dd, *J* 4 and 1.63Hz, H-24), 6.19 (1H, dd, *J* 4 and 2.6Hz, H-23), 5.83 (1H, d *J* 10Hz, NCHO), 5.58 (1H, d, *J* 10Hz, NCHO), 4.6 (1H, d, *J* 11.7Hz, OCHPh), 4.53 (1H, d, *J* 11.7Hz, OCHPh), 3.85 (1H, dd, *J* 10.26 and 2.38Hz, H-18), 3.70 (2H, m, H_2-8), 3.52 (2H, t, *J* 7.2Hz, $OC\underline{H_2}CH_2$), 3.36 (1H, m, H-10), 3.28 (1H, dq, *J* 10.24 and 6.89Hz, H-19), 2.05 (1H, tt, *J* 13.2 and 4.6Hz, H-16), 1.81-1.08 (12H, m, H_2-9, H_2-11, H_2-12, H_2-13, H_2-15, H-16, H-17), 1.02 (3H, d, *J* 6.9Hz, Me-19), 0.99 (3H, d, *J* 6.94Hz, Me-17), 0.92 (2H, m, $CH_2C\underline{H_2}Si$) and 0.04 (9H, s, $(CH_3)_3Si$); *m/z* 556 (MH^+), 541 (MH^+-Me), 455 (M^+-$C_5H_{12}Si$), 437 (M^+-$C_5H_{14}SiO$), 331 (M^+-$C_{11}H_{18}NO_2Si$), 303 (M^+-$C_{13}H_{22}NO_2Si$), 251 ($C_{13}H_{21}NO_2Si^+$), 196 ($C_{10}H_{18}NOSi^+$), 107 ($C_7H_7O^+$), 91 ($C_7H_7^+$) and 73 (TMS^+); Found: M^+, 555.3382. $C_{32}H_{49}NO_5Si$ requires *M*, 555.3380.

[2*S*(*S*),3*R*,6*S*,8*S*]-3-Methyl-2-[1-[[1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-pyrrolidyl]carbonyl]ethyl]-1,7-dioxaspiro[5.5]undecane-8-acetic acid (67).

10% Palladium on carbon (0.03g) was added to a stirred solution of the protected ketopyrrole **66** (0.55g, 0.99mmol) in ethanol (10ml) under argon at room temperature. Argon was exchanged for hydrogen and the mixture was stirred at room temperature for 5h, then filtered through celite, washing with dichloromethane. The solvent was evaporated *in vacuo*; purification by column chromatography on silica gel, eluting with petrol-ether (70%), afforded the *ketopyrrole alcohol* (0.396g, 86%) as a colourless oil, $[\alpha]_D^{21}$ -59.3 (c 0.76 in $CHCl_3$); υ_{max}(film) 3520, 2940, 1680, 1520, 1430, 1310, 1275, 1180 and 880cm^{-1}; δ_H(500MHz), (natural product numbering) 7.12 (1H, dd, *J* 2.64 and 1.64Hz, H-22), 7.1 (1H, dd, *J* 4 and 1.64Hz, H-24), 6.22 (1H, dd, *J* 4 and 2.64Hz, H-23), 5.75 (1H, d, *J* 10Hz, NCHO), 5.67 (1H, d, *J* 10Hz, NCHO), 4.01 (2H, m, H_2-8), 3.99 (1H, dd, *J* 10.35 and 2.33Hz, H-18), 3.70 (1H, br s, OH), 3.61 (1H, m, H-10), 3.50 (2H, m, $OC\underline{H_2}CH_2$), 3.31 (1H, dq, *J* 10.2 and 6.92Hz, H-19), 2.08 (1H, tt, *J*, 13.2 and 4.37Hz, H-16), 1.82 (1H, m,

H-17), 1.60-1.12 (11H, m, H_2-9, H_2-11, H_2-12, H_2-13, H_2-15, H-16), 1.05 (3H, d, *J* 6.9Hz, Me-19), 1.01 (3H, d, *J* 6.9Hz, Me-17), 0.85 (2H, m, $CH_2C\underline{H_2}Si$) and 0.03 (9H, s, $(CH_3)_3Si$); *m/z* 465 (M^+), 364 (M^+-$C_5H_{13}Si$), 347 (M^+-$C_5H_{14}OSi$), 225 ($C_{11}H_{19}NO_2Si^+$), 213 (M^+-$C_{13}H_{22}NO_2Si$), 196 ($C_{10}H_{18}NOSi^+$), 73 (TMS^+) and 28 (CO^+); Found: M^+, 465.2910. $C_{25}H_{43}NO_5Si$ requires *M*, 465.2910.

Jones reagent (0.68ml) (prepared from chromium trioxide (11.1g) and concentrated sulphuric acid (9.2ml) in water (45ml)) was added to a solution of the ketopyrrole alcohol (0.1g, 0.215mmol) in acetone (3ml) at -25°C. The cooling bath was allowed to warm to -5°C over 1h. Excess oxidant was destroyed by the addition of saturated sodium bisulphite solution (2ml). The organic layer was diluted with ether (10ml), washed with water (3ml), brine (3ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with ether to give the *ketopyrrole acid* **67** (0.087g, 84%) as a colourless oil, $[\alpha]_D^{24}$ +93.2 (c 0.41 in $CHCl_3$); υ_{max}(film) 3433, 2949, 2062, 1707, 1644, 1572, 1450, 1412, 1379, 1294, 1247, 1233, 1078, 1003, 988, 974, 952, 836 and 737cm^{-1}; δ_H(500MHz) (natural product numbering) 9.92 (1H, br s OH), 7.11 (1H, dd, *J* 2.6 and 1.7Hz, H-22), 7.09 (1H, dd, *J* 4 and 1.7Hz, H-24), 6.22 (1H, dd, *J* 4 and 2.6Hz, H-23), 5.76 (1H, d *J* 10Hz, NCHO), 5.67 (1H, d, *J* 10Hz, NCHO), 4.06 (1H, dd, *J* 10.3 and 2.31Hz, H-18), 3.95 (1H, m, H-10), 3.50 (2H, m, $OC\underline{H_2}CH_2$), 3.31 (1H, dq, *J* 10.3 and 7.1Hz, H-19), 2.61 (1H, dd, *J* 15.6 and 4.7Hz, H-9), 2.51 (1H, dd, *J* 15.6 and 7.6Hz, H-9), 2.06 (1H, tt, *J* 13.2 and 4.5Hz, H-16), 1.84 (1H, m, H-17), 1.6-1.15 (9H, m, H_2-11, H_2-12, H_2-13, H_2-15, H-16), 1.05 (3H, d, *J* 7.1Hz, Me-19), 0.99 (3H, d, *J* 6.92Hz, Me-17), 0.90 (2H, m, $CH_2C\underline{H_2}Si$) and 0.03 (9H, s, $(CH_3)_3Si$); *m/z* 479 (M^+), 451 (M^+-CO), 436 (M^+-C_2H_3O), 378 (M^+-$C_5H_{13}Si$), 361 (M^+-$C_5H_{14}OSi$), 284 (M^+-$C_{10}H_{17}NOSi$), 254 (M^+-$C_{11}H_{19}NO_2Si$), 227 (M^+-$C_{13}H_{22}NO_2Si$), 196 ($C_{10}H_{18}NOSi^+$), 101 ($C_5H_{13}Si^+$), 73 (TMS^+) and 28 (CO^+); Found: M^+, 479.2701. $C_{25}H_{41}NO_6Si$ requires *M*, 479.2703.

[2*S*(*S*),3*R*,6*S*,8*S*]-N-[6-Hydroxy-2-(methoxycarbonyl)-3-[[2-(trimethylsilyl)ethoxy] methoxy]phenyl]-2-[1-[[1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-pyrrolidyl]carbonyl]ethyl]-1,7-dioxaspiro[5.5]undecane-8-acetamide (68).

Ethyl chloroformate (0.012g, 0.011ml, 0.115mmol) was added to a mixture of the ketopyrrole acid **67** (0.055g, 0.115mmol) and triethylamine (0.047g, 0.064ml, 0.46mmol) in dry dichloromethane (1ml) with stirring at -10°C under argon. After stirring for 30min., a solution of the aminophenol **5** (0.04g, 0.127mmol) in dry tetrahydrofuran (1ml) was added to the mixture. Stirring was continued for 1h at -10°C and 16h at room temperature. Most of the solvent was evaporated *in vacuo* and the residue extracted with ether (3x5ml). The combined organic extract was washed with water (5ml), brine (5ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Column chromatography of the residue on silica gel, eluting with petrol-ether (60%) afforded the *ketopyrrole amide* **68** (0.068g, 77%) as a yellow oil, $[\alpha]_D^{20}$ +33.2 (c 0.19 in $CHCl_3$); υ_{max}(film) 3860, 3672, 3440, 3345, 2838, 2603, 2392, 2200, 1970, 1750, 1640, 1585, 1472, 1374, 1166 and 980cm^{-1}; δ_H(500MHz), (natural product numbering) 9.39 (1H, s, OH), 8.03 (1H, s, NH), 7.09 (1H, dd, *J* 2.6 and 1.6Hz, H-22), 7.06 (1H, d, *J* 9.05Hz, Ar-H), 7.05 (1H, dd, *J* 4 and 1.6Hz, H-24), 7.02 (1H, d, *J* 9.1Hz, Ar-H), 6.19 (1H, dd, *J* 4 and 2.6Hz, H-23), 5.71 (2H, d *J* 2.12Hz, NCH_2O), 5.13 (2H, s, OCH_2O), 3.98 (1H, dd, *J* 10.36 and 2.3Hz, H-18), 3.93 (1H, m, H-10), 3.90 (3H, s, OMe), 3.74 (2H, t, *J* 8.4Hz, $OC\underline{H_2}CH_2$), 3.55 (2H, m, $OC\underline{H_2}CH_2$), 3.27 (1H, dq, *J* 10.4 and 7Hz, H-19), 2.67 (1H, dd, *J* 14.4 and 4.8Hz, H-9), 2.49 (1H, dd, *J* 14.4 and 7.6Hz, H-9), 2.15 (1H, tt, *J* 13.04 and 4.5Hz, H-16), 1.76 (1H, m, H-17), 1.64-1.2 (9H, m, H_2-11, H_2-12, H_2-13, H_2-15, H-16), 0.96 (3H, d, *J* 7Hz, Me-19), 0.9 (3H, d, *J* 7Hz, Me-17), 0.8

(4H, m, $(CH_2CH_2Si)_2$), 0.02 (9H, s, $(CH_3)_3Si$) and 0.01 (9H, s, $(CH_3)_3Si$); *m/z* 757 (M^+-OH), and 73 (TMS^+); Found: M^+-OH, 757.3916. $C_{39}H_{62}N_2O_{10}Si_2$ requires *M-OH*, 757.3915.

[2[*2S(S),3R,6S,8S*]] Methyl 5-hydroxy-2-[3-Methyl-2-[1-[[1-[[2-(trimethylsilyl)ethoxy] methoxy]-2-pyrrolidyl]carbonyl]ethyl]-1,7-dioxaspiro[5.5]undecan-8-yl]-4-benzoxazolecarboxylate (69).

A mixture of the ketopyrrole amide **68** (0.015g, 0.019mmol) and ethyl polyphosphate (PPE) (0.2g) in dry chloroform (2ml) was refluxed under argon for 1h. After cooling, the solution was poured into saturated aqueous sodium bicarbonate and stirred at room temperature for 15min., then extracted with ether (3x10ml). The combined organic extract was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with petrol-ether (65%) to give the *protected benzoxazole* **69** (8.6mg, 71%) as a white foam, $[\alpha]_D^{21}$ +27.8 (c 0.32 in $CHCl_3$); υ_{max}(film) 3420, 2927, 1670, 1561, 1439, 1412, 1348, 1219, 1076, 988 and 835cm^{-1}; δ_H(500MHz) (natural product numbering) 11.32 (1H, s, OH), 7.7 (1H, d, *J* 8.91Hz, Ar-H), 7.07 (1H, dd, *J* 2.52 and 1.58Hz, H-22), 7.03 (1H, dd, *J* 3.85 and 1.58Hz, H-24), 6.96 (1H, d, *J* 8.9Hz, Ar-H), 6.18 (1H, dd, *J* 3.8 and 2.55Hz, H-23), 5.91 (1H, d *J* 10.2Hz, NCHO), 5.62 (1H, d, *J* 10.2Hz, NCHO), 4.11 (3H, s, OMe), 4.06 (1H, m, H-10), 3.78 (1H, dd, *J* 10.4 and 2.3Hz, H-18), 3.48 (2H, t, *J* 8.4Hz, OCH_2CH_2), 3.26 (1H, dq, *J* 10.4 and 7Hz, H-19), 3.12 (1H, dd, *J* 14.7 and 8Hz, H-9), 3.04 (1H, dd, *J* 14.7 and 5.88Hz, H-9), 1.79 (1H, m, H-16), 1.62 (1H, m, H-17), 1.59-1.27 (10H, m, H_2-11, H_2-12, H_2-13, H_2-15, H-16), 0.98 (3H, d, *J* 6.89Hz, Me-17), 0.95 (3H, d, *J* 6.93Hz, Me-19), 0.85 (2H, m, CH_2CH_2Si) and 0.06 (9H, s, $(CH_3)_3Si$); *m/z* 627 (MH^+), 525 (M^+-$C_5H_{13}Si$), 374 (M^+-$C_{13}H_{22}NO_2Si$), 124 ($C_7H_7NO^+$) and 73 (TMS^+); Found: MH^+, 627.310. $C_{33}H_{46}N_2O_8Si$ requires *MH*, 627.310.

Routiennocin (1).

Tetra-*n*-butylammonium fluoride (TBAF) (0.037ml of a 3M solution in tetrahydrofuran, 0.11mmol) was added to a solution of the protected benzoxazole **69** (7mg, 0.011mmol) in tetrahydrofuran (0.02ml) at 0°C under argon . After 10min. at this temperature, the mixture was warmed to room temperature and stirred for a further 4h. The reaction mixture was diluted with ether (10ml) and poured into water. The organic layer was separated and the organic phase extracted with ether (3x5ml). The combined organic extract was dried ($MgSO_4$), the solvent evaporated *in vacuo* and the residue purified by column chromatography on silica gel, eluting with petrol-ethyl acetate (50%) to afford *routiennocin methyl ester* (4.9mg, 88%) as a white foam, $[\alpha]_D^{21}$ +15 (c 0.42 in $CHCl_3$); υ_{max}(film) 3494, 3273, 2932, 1636, 1559, 1437, 1219 and 996cm^{-1}; δ_H(500MHz) (natural product numbering) 11.23 (1H, s, OH), 9.65 (1H, br s, NH), 7.7 (1H, d, *J* 8.98Hz, Ar-H), 6.97 (1H, d, *J* 8.93Hz, Ar-H), 6.95 (1H, dd, *J* 2.57 and 1.35Hz, H-22), 6.95 (1H, dd, *J* 3.7 and 1.33Hz, H-24), 6.92 (1H, dd, *J* 3.73 and 2.55Hz, H-23), 4.09 (3H, s, OMe), 3.93 (1H, m, H-10), 3.68 (1H, dd, *J* 10.2 and 2.1Hz, H-18), 3.20 (1H, dq, *J* 10.2 and 6.9Hz, H-19), 3.08 (1H, dd, *J* 14.67 and 8.48Hz, H-9), 2.99 (1H, dd, *J* 14.67 and 4.3Hz, H-9), 1.76 (1H, tt, *J* 13 and 4.3Hz, H-16), 1.62-0.84 (10H, m, H_2-11, H_2-12, H_2-13, H_2-15, H-16, H-17), 0.96 (3H, d, *J* 6.84Hz, Me-17) and 0.94 (3H, d, *J* 6.98Hz, Me-19); *m/z* 497 (MH^+), 290 (M^+-$C_{10}H_9NO_4$), 193 ($C_9H_7NO_4^+$), 121 ($C_7H_7NO^+$), 94 ($C_5H_4NO^+$), 66 ($C_4H_4N^+$) and 28 (CO^+); Found: MH^+, 497.2288. $C_{27}H_{32}N_2O_7$ requires *MH*, 497.2287.

Water (0.02ml) was added to a stirred solution of routiennocin methyl ester (4mg, 8.06μmol) in tetrahydrofuran (0.5ml) followed by lithium hydroxide monohydrate (tip of spatula) and the mixture stirred at room temperature

for 12h. The opaque solution was diluted with ether (2ml) and then washed with 10% aqueous H_3PO_4 (2x1ml), brine (2ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue columned on silica gel, eluting with ethyl acetate-ether (30%) to give *routiennocin* **1** (3.6mg, 93%) as a white foam identical in all respects with authentic material; $[\alpha]_D^{18}$ +228 (c 0.22 in $CHCl_3$); υ_{max}(film) 3207, 3116, 2932, 1607, 1552, 1495, 1428, 1401, 1275, 1234, 1173, 1073, 991, 911 and 825cm^{-1}; δ_H(500MHz) (natural product numbering) 14.42 (1H, s, OH), 13.47 (1H, s, OH), 7.54 (1H, br s, H-22), 7.52 (1H, d, *J* 8.91Hz, Ar-H), 7.1 (1H, m, H-24), 7.04 (1H, d, *J* 8.91Hz, Ar-H), 6.33 (1H, dd, *J* 4 and 2.1Hz, H-23), 3.70 (1H, m, H-10), 3.13 (1H, dq, *J* 10.1 and 6.65Hz, H-19), 2.77 (1H, dd, *J* 10.1 and 2.09Hz, H-18), 2.63 (2H, m, H_2-9), 1.85-0.84 (10H, m, H-11, H_2-12, H_2-13, H_2-15, H_2-16, H-17), 0.82 (3H, d, *J* 6.67Hz, Me-19), 0.78 (3H, d, *J* 6.93Hz, Me-17) and 0.61 (1H, m, H-11); *m/z* 482 (M^+), 438 (M^+-CO_2), 290 (M^+-$C_9H_6NO_4$), 193 ($C_7H_7NO_4^+$), 123 ($C_7H_9NO^+$), 94 ($C_5H_4NO^+$), 66 ($C_4H_4N^+$) and 44 (CO^+); Found: M^+, 482.2057. $C_{26}H_{30}N_2O_7$ requires *M*, 482.2053.

References and footnotes

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