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ENANTIOSELECTIVE TOTAL SYNTHESIS OF INGRAMYCIN

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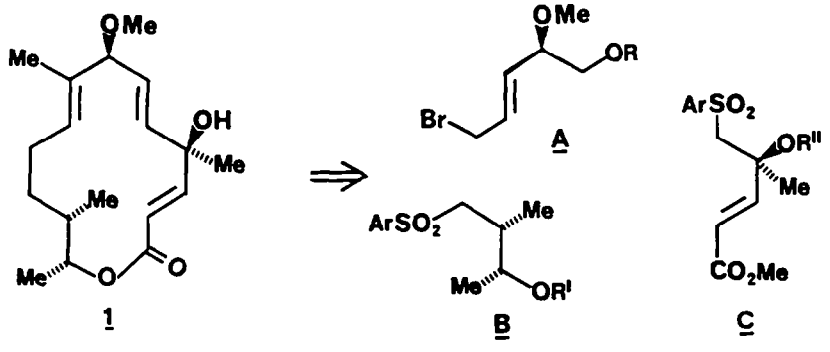
Abstract - An enantioselective total synthesis of the 14-membered macrolide antibiotic ingramycin, 1, is described. In a convergent approach three chiral fragments A, B and C are assembled, the allylic bromide A deriving its chirality from L-serine while the asymmetric centres in sulfones B and C are introduced via the Sharpless enantioselective epoxidation technique. After coupling of these fragments and a highly efficient macrolactonisation (82% yield) a final deprotection step furnishes the target compound.

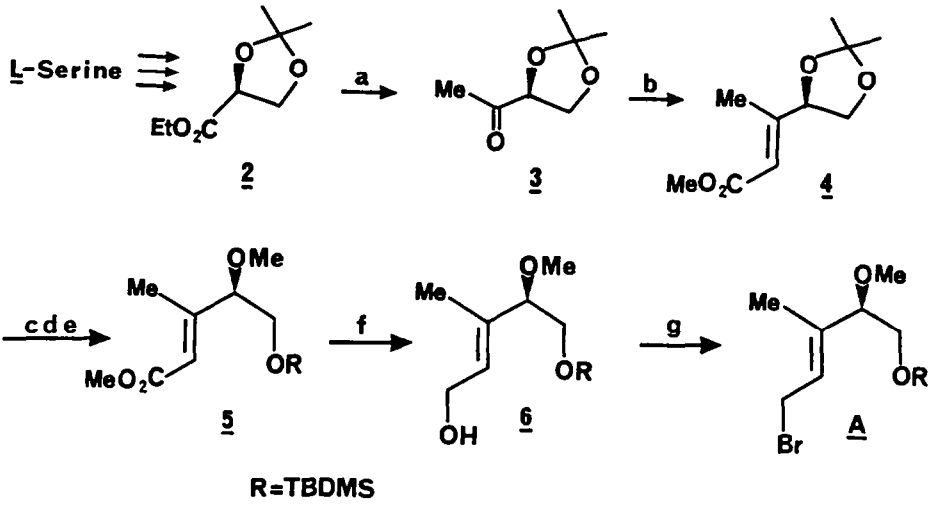
Ingramycin, 1 (also known as albocycline) is a macrolide antibiotic isolated from various strains of Streptomyces by workers in Japan[1] and the United States[2]. This 14-membered lactone displays biological activity primarily against staphylococci, the in vitro action being inhibition of nicotinate biosynthesis[3]. Following deduction of the gross chemical structure[4a-d] the relative and absolute stereochemistry of 1 were determined, using X-ray crystallography, in two independent investigations by Thomas and Chidester[5] and Furusaki et al[6]. A protected form of the seco acid of ingramycin has recently been the subject of Steliou's investigations of novel macrolactonisation reagents[7]. In the present paper we wish to report a convergent enantioselective total synthesis of the title antibiotic.



Scheme 1

Retrosynthetic analysis of Ingramycin, 1

The general synthetic approach is depicted in Scheme 1, the four asymmetric centres of the target being embedded in the three chiral fragments A, B and C. The first of this trio is a derivative of L-serine[8] while the preparation of the sulfones B and C relies on the Sharpless asymmetric epoxidation protocol[9] for initial introduction of chirality. Coupling of A and B via the anion of the latter followed by suitable adjustment of functionality would subsequently allow the installation of the final fragment according to the Julia-Lythgoe[10] procedure. The major problem remaining would then be the macrolactonisation step for which, fortunately, a variety of reagents is now available[11a,b]. The successful implementation of the proposed strategy and attainment of the synthetic goal are described in detail below.

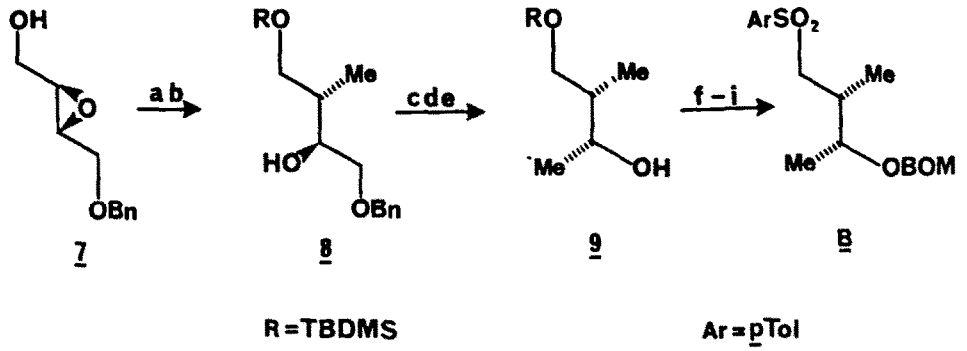


Scheme 2

For compound 2, see ref.8. (a) See ref.12 (b) $(EtO)_2P(O)CH_2COOMe$,NaH, THF,0°C, 77% yield (c)H_2SO_4,MeOH,93% (d) TBDMSCl,DMAP,NEt_3,CH_2Cl_2,91% (e) MeI,Ag_2O,DMF,68% (f) DIBAL, CH_2Cl_2,88% (g) CBr_4/PPh_3,CH_2Cl_2,83%.

Scheme 2 depicts the synthesis of fragment A. Thus, the known ketone 3 which is readily procured in 96% e.e. by our published procedure[12] was subjected to an E-selective Wittig-Horner reaction, followed by hydrolysis of the acetonide moiety. The primary hydroxyl of the resultant 1,2-diol was selectively protected as the ^{t}butyldimethylsilyl (TBDMS) ether and the secondary hydroxyl then methylated, albeit with unexpected difficulty, using MeI/Ag_2O in DMF. The ester 5 was then transformed to the desired allylic bromide via DIBAL reduction followed by bromination (CBr_4/PPh_3). Fragment A was thus available in six steps and 32% total yield from ketone 3

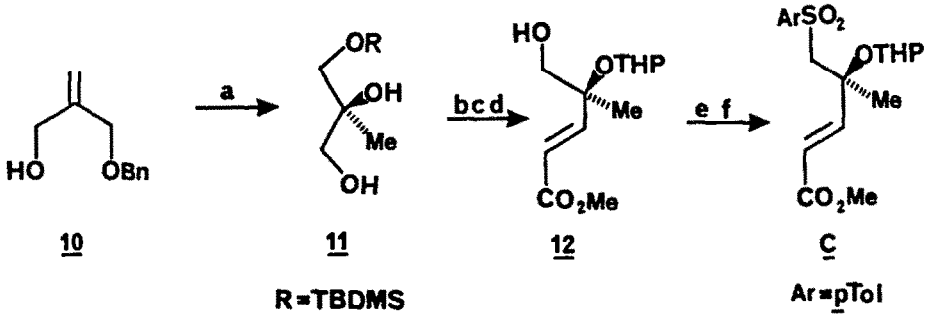
The starting point for fragment B was the known[13] epoxy alcohol 7, itself available in>98% e.e. via Sharpless asymmetric epoxidation. Epoxide ring-opening by $LiMe_2Cu$ gave an inseparable 10:1 mixture of regioisomeric diols in 95% yield. These could be separated chromatographically via the corresponding primary TBDMS ethers, the major component being the desired (and expected[14]) 8. Efficient debenzylation, selective tosylation of the resultant primary hydroxyl, and subsequent hydride reduction ($LiB(Et)_3H$) furnished 9, the secondary hydroxyl of which was protected as the benzyloxymethyl (BOM) ether. Standard operations then led uneventfully to the required sulfone B, the overall yield from 7 being 34% for the nine steps. (See Scheme 3).



Scheme 3

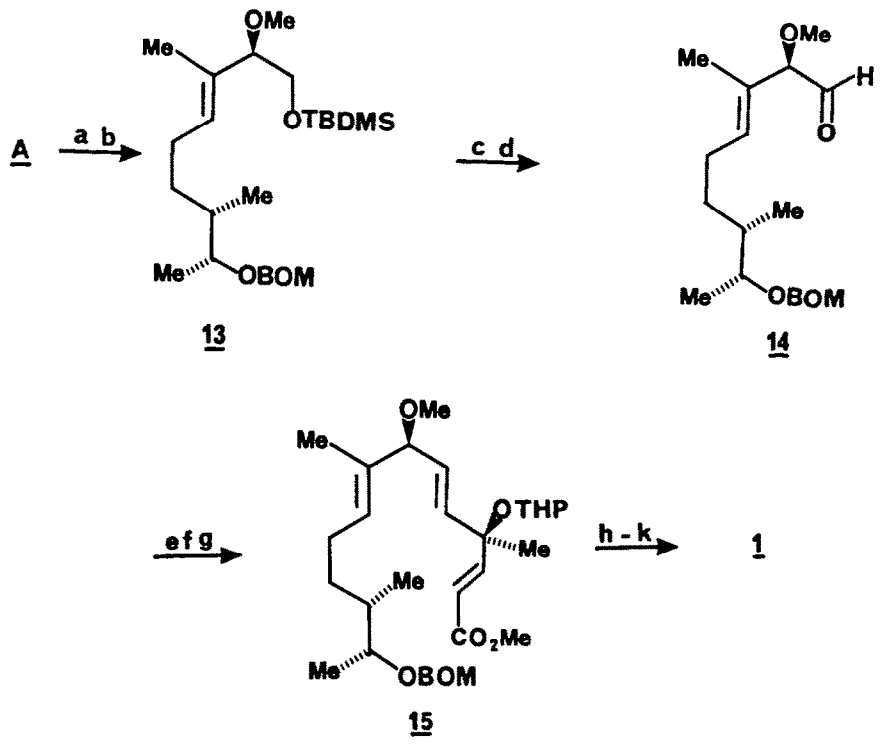
(a) $LiMe_2Cu$,Et_2O,-78 to -30°C,95% total yield (b) TBDMSCl,DMAP,NEt_3, CH_2Cl_2,100% (c) H_2,$Pd(OH)_2/C$,EtOH,100% (d) pTsCl,pyridine,-20°C,92% (e) $LiB(Et)_3H$,THF,84% (f) BOMCl,NEt_3,CH_2Cl_2,72% (g) Bu_4NF,THF,96% (h) CBr_4/PPh_3,CH_2Cl_2,92% (i) Na toluenesulfinate, DMF,80%.

Continuing the asymmetric epoxidation theme, we then addressed the preparation of the final synthon, sulfone C. Using our previously described procedure[15] the enantiomerically pure diol 11 (Scheme 4) is easily acquired, and this material proved amenable to elaboration to the α,β-unsaturated ester 12, the key step being the very convenient one-pot "Swern-Wittig" procedure described recently by Ireland and Norbeck[16]. Of the protecting groups tested for the blocking of the tertiary alcohol function in 12, tetrahydropyranyl (THP) was found to be by far the most suitable in terms of ease of introduction (DHP, PPTS, CH_2Cl_2, RT) and chemical yield (98%). The obvious disadvantage, implicit in the stereochemically uncontrolled generation of an extraneous chiral centre, was that 12 (and then C) was obtained as a mixture of diastereomers. Final introduction of the required sulfone moiety proved troublesome, presumably for steric reasons, but could eventually be achieved in high yield by conversion of the primary hydroxyl of 12 to the labile triflate (100%) followed by nucleophilic displacement by sodium para-toluenesulfinate (DMF, 15-crown-5, 83%; overall yield of C 55%, five steps from 11). With all three fragments in hand, the stage was set for the key coupling reactions (Scheme 5).



Scheme 4

(a) See ref. 15. (b) $(COCl)_2$,DMSO,CH_2Cl_2,-78°C,then NEt_3. Add Ph_3PCHCO_2Me 70% overall (c) DHP,PPTS,CH_2Cl_2,98% (d) Bu_4NF,THF,97% (e) $(CF_3SO_2)_2O$, NEt_3,CH_2Cl_2,-20°C (f) Na p-toluenesulfinate,15-crown-5,DMF,83% from 12.



Scheme 5

(a) Anion of B, THF,-65°C,76% (b) Na(Hg),Na_2HPO_4,MeOH,87% (c) Bu_4NF,THF, 98% (d) $(COCl)_2$,DMSO,CH_2Cl_2,-60°C,then NEt_3,90% (e) anion of C,THF-HMPA, -90°C (f) Ac_2O, py, DMAP, -90°C to RT (g)Na(Hg) Na_2HPO_4,MeOH,-20°C, 30% from 14 (h) LiOH,THF/H_2O,98% (i)H_2,$Pd(OH)_2$/C,EtOAc-hexane,68% (j) DCC, DMAP,DMAP—trifluoroacetate,$CHCl_3$,reflux,82% (k) PPTS,MeOH,RT,87%.

Coupling of A and B *via* the sulfone anion proceeded smoothly to yield a separable mixture of two diastereomeric tertiary sulfones, both of which furnished 13 upon treatment with Na-amalgam. Desilylation and Swern oxidation then led to aldehyde 14 which was diastereomerically pure within the limits of high-field ^{1}H NMR spectroscopic detection, indicating that the untoward minor epimerisation recently observed by Williams[17] upon Swern oxidation of certain α-alkoxy alcohols had not occurred in the present case. Although the claim for the diastereomeric purity of 14 may seem inconsistent with the fact that the enantiomeric purity of synthon A was "only" 96%, we attribute this enhancement to the adventitious removal of any minor diastereomer(s) during chromatographic purification of intermediates earlier in the synthetic sequence leading to 14. The Julia-Lythgoe coupling of 14 with sulfone C was complicated by the not unexpected propensity of the anion of the latter to indulge in E1cB elimination[18]. This undesired course of events could be (not totally) suppressed by formation of the anion at low temperature (LDA, -90°C) in a 9:1 mixture of THF and HMPA. Rapid addition of a cold THF solution of 14 followed by a 15-minute reaction time led to consumption of most of the aldehyde (TLC analysis). The resultant β-hydroxy sulfone was then acetylated *in situ*[19], the acetylated product being obtained as an extremely complex mixture of diastereomers (^{1}H NMR analysis) which, without extensive purification, was converted (Na-amalgam[20]) to the desired 15. Isomerically pure 15 could be isolated by flash chromatography. The ester moiety of 15 was hydrolysed (LiOH) and the BOM group then removed by catalytic hydrogenation over the Pearlman catalyst ($Pd(OH)_2$/C, 1:5 EtOAc-hexane, RT, 45 min, 68% yield,

mass balance mostly unreacted starting material). The most remarkable, and pleasing, aspect of this reaction was that very little concomitant reduction of the disubstituted olefinic double bonds occurred in the presence of this particular catalyst, which displayed very different behaviour from "normal" Pd/C and we have noted similar results with both ingramycin itself and its THP derivative. It may be recalled that in the course of their structural studies Nagahama *et al*[4c] subjected ingramycin to hydrogenation over 10% Pd/C (EtOH, RT, 30 min) and observed the rapid disappearance of starting material and formation of no fewer than eight products (TLC) four of which were isolated and identified; in the present work, hydrogenation of the antibiotic over the Pearlman catalyst (EtOAc-hexane, RT, 30 min) yielded a trace of starting material and only two new products which, according to ^{1}H NMR spectroscopic analysis, were the result of reduction of one and both of the disubstituted double bonds, respectively. More significantly, when the THP ether derivative of ingramycin was exposed to the latter hydrogenation conditions no appreciable reaction occurred and we attribute this to a steric "shielding" of the said olefinic moieties by the bulk of the centrally disposed THP entity. From inspection of molecular models it was concluded that the same effect is operative in the acid corresponding to 15 and that the benzylic site of the BOM ether should be more easily available to the catalyst surface; the THP ether thus serves as a protecting group in more than one sense.

At this point, then, the THP-ether derivative of the ingramycin seco acid was in hand and the synthetic material proved to be chromatographically and spectroscopically identical with an authentic sample prepared from ingramycin *via* a modification of the Steliou procedure[7]. This in turn meant that a formal total synthesis of the antibiotic had been achieved, since Steliou[7] had already demonstrated that the material in question can be reconverted to ingramycin *via* macrolactonisation followed by deprotection. However, the Steliou protocol suffers from two main disadvantages in that the yield of the reported tin-mediated macrolactonisation was rather modest (30%) and that the recovered ingramycin showed extensive loss of optical purity attributed to facile epimerisation at the tertiary (and doubly allylic) alcohol site in the presence of the acid catalyst (CSA) used in the THP protection-deprotection steps. We found that the latter obstacle could be overcome simply by switching to the milder acid catalyst PPTS[21] for the blocking-deblocking sequence (protection: DHP, CH_2Cl_2, RT, 98% yield; deprotection: MeOH, RT, 87%). The recovered ingramycin then showed an optical purity of 94-96% according to polarimetry.

Turning finally to the macrolactonisation problem, we had noted with interest the impressive yields of large-ring lactones obtained by Boden and Keck[11b] using a rationally designed reagent system consisting of DCC, DMAP and the hydrochloride salt of the latter. A minor modification of this particular reagent combination (use of the trifluoroacetate salt) had also been employed, with excellent results, by Stork and Rychnovsky[22] in their recent landmark synthesis of (+)-(9*S*)-dihydroerythronolide A. It was therefore to our delight that exposure of the synthetic THP-ether derivative of the ingramycin seco acid to the Keck cyclisation conditions allowed subsequent isolation of the desired macrolide in no less than 82% yield. Deprotection as outlined above then furnished synthetic ingramycin as a crystalline solid (95% *e.e.*) which by the usual criteria was identical with the natural product.

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EXPERIMENTAL

For general remarks, see ref. 15.

Ester 4. NaH (55% oil suspension, 386mg, 8.8mmol) was washed thrice with pentane under argon and then suspended in dry THF (25 ml) and cooled to 0°C. Methyl diethylphosphonoacetate (1.63ml, 8.91mmol) was added via syringe and the resultant mixture stirred under argon for 15min at 0°C. A solution of ketone 3 (924 mg, 6.4 mmol) in THF (5 ml) was then added dropwise and the mixture stirred for a further 30 min at 0°C. The reaction mixture was poured into water and the aqueous phase extracted thrice with ether. The combined organics were dried over Na_2SO_4 and the solvent removed. Chromatography on silica gel (10% ether-pentane) yielded the ester. Yield: 986 mg, 77%. ^{1}H NMR (270 MHz, $CDCl_3$/TMS): δ 6.05 (1H,m,vinylic) 4.47 (1H,dd,J=8,7Hz; methine) 4.16 (1H, dd,J=8,7.5,methylene) 3.66 (3H,s,CO_2Me) 3.61 (1H,dd,J=7.5,7,methylene) 2.07 (3H,bs,vinylic Me) 1.45 and 1.39 (both 3H,s,Me). IR: 1720(ester) 1150, 1070(ketal) cm^{-1}. MS: 185 (M-Me). $[\alpha]_D$ -44.4° (c 1.73, CH_2Cl_2).

Ester 5. The ester 4 (1.42 g, 7.1 mmol) was dissolved in methanol (10 ml) and 30% H_2SO_4 (5 ml) added dropwise. The resultant mixture was refluxed for 3 h, cooled, then extracted thoroughly with ether. The combined extracts were dried (Na_2SO_4) and stripped down to yield an oily residue which was purified by flash chromatography (silica gel, ether) to yield the 1,2-diol as an oil.(1.06g, 93%). NMR: 6.06 (1H,m,vinylic) 4.22 (1H,dd,J=7.5,3,methine) 3.78 (1H,dd,J=11,3,methylene) 3.72 (3H,s,CO_2Me) 3.56 (1H,dd,J=11,7.5,methylene)2.40 (1H,b,OH) 2.14 (3H,bs,vinylic Me) 1.89 (1H,b,OH). IR: 3400 (b,vs,OH) 1720 (ester). MS: 160 (M$^+$). $[\alpha]_D$ -9.98° (c 1.53, CH_2Cl_2).

The diol (1.368 g, 8.6 mmol) was dissolved under argon in dry CH_2Cl_2 (30 ml) together with 4-dimethylaminopyridine (42 mg) and triethylamine (1.31 ml, 9.4 mmol) and t-butyldimethylsilyl chloride (1.546 g, 10.3 mmol) was added. The mixture was stirred overnight, then poured into water-methylene chloride and the phases were separated. The aq. phase was back-extracted thrice with methylene chloride and the combined organics dried (Na_2SO_4) and stripped down. Chromatography (silica gel, 20% ether-pentane) yielded the primary TBDMS ether as an oil. (2.138 g, 91%). NMR: 6.10 (1H,m,vinylic) 4.15 (1H,dd,J=7.1,3.9,methine) 3.78 (1H,dd,J=9.5,3.9, methylene) 3.71 (3H,s,CO_2Me) 3.48 (1H,dd,J=9.5,7.1,methylene) 2.76 (1H,b,OH) 2.12 (3H,bs,vinylic Me) 0.91 (9H,s,t-Bu) 0.07 (6H,s,$SiMe_2$). IR: 3450 (b,OH) 1720 (ester) 1100 (s,OSi). MS: 217 (M-t-Bu). $[\alpha]_D$ -3.6° (c 1.4, CH_2Cl_2).

The secondary alcohol from above (2.138 g, 7.8 mmol) was dissolved under argon in dry DMF (25 ml). Methyl iodide (1.21 ml, 19.5 mmol) was added followed by Ag_2O 2.71 g, 11.7 mmol) and the mixture stirred overnight at RT. The reaction mixture was then partitioned between water and ether, the aq. phase was extracted several times with ether, and the combined ethereal phases dried over Na_2SO_4. After removal of solvent, the residue was flash chromatographed on silica gel (10% ether -pentane) to yield the desired methyl ether as an oil (1.53 g, 68%). NMR: 5.90 (1H, m,vinylic) 3.72 (3H,s,CO_2Me) 3.65 (3H,complex m, methine and methylene) 3.29 (3H,s,OMe) 2.11 (3H,bs,vinylic Me) 0.89 (9H,s,t-Bu) 0.05 (6H,2s,$SiMe_2$) IR: 1725 (ester) 1125 (OMe) 1110 (OSi). MS: 231 (M-tBu). $[\alpha]_D$ -15.7° (c 3.2, CH_2Cl_2).

The methyl ether from above (2.208 g, 7.7 mmol) was dissolved in dry methylene chloride (70 ml) and cooled with stirring under argon to -78°C. DIBAL (23 ml of 1M in hexanes, 23 mmol) was added dropwise and the resultaht mixture stirred for 3 h at -78°C. After the usual work-up (Rochelle salt/methylene chloride) and flash chromatography (50% ether-pentane) the desired allylic alcohol was obtained as an oil. (1.76 g, 88%). NMR: 5.65 (1H, t with fine splitting,J_{gem}=7,vinylic) 4.26 (1H,dd,J=10,7,CHOH) 4.19 (1H,dd,J=10,7,CHOH) 3.69-3.52 (3H,complex m,CHOMe and CH_2OSi) 3.18 (3H,s,OMe) 1.39 (1H,b,OH) 1.63 (3H,bs,vinylic Me) 0.90 (9H,s,tBu) 0.06 (6H,2s,$SiMe_2$). IR: 3350 (b,s,OH) 1130 (OMe) 1100 (OSi). MS: 260(M$^+$), 203 (M-tBu). $[\alpha]_D$ -19.1° (c 1,CH_2Cl_2).

Bromide A. Alcohol 6 (1.388 g, 5.3 mmol) was dissolved under argon in dry CH_2Cl_2 (40 ml) and cooled with stirring to -40°C. Carbon tetrabromide (2.39 g, 7.2 mmol) was added in portions followed by triphenylphosphine (1.82 g, 6.9 mmol). The mixture was stirred at -40°C for 1 h, and then the solvent was removed. The residue was triturated with ether to precipitate triphenylphosphine oxide, which was removed by filtration. The filtrate was then concentrated to give a heavy oil which was flash chromatographed on silica gel (5% ether-pentane) to yield the desired bromide as an oil. (1.42 g, 83%). NMR: 5.80 (1H,tq,J=8.5,1,vinylic) 4.05 (2H,AB-m,J=10.5,CH_2Br) 3.60-3.45 (3H,complex m,CHOMe and CH_2OSi) 3.25 (3H,s,OMe) 1.70 (3H,d,J=1,vinylic Me) 0.90 (9H,s,t-Bu) 0.06 (6H,s,$SiMe_2$). IR: 1125 (OMe) 1100 (OSi). $[\alpha]_D$ -5.13° (c 1.60, CH_2Cl_2). This material was used as soon as possible after isolation.

Silyl ether 8. Copper iodide (17.62 g, 92.6 mmol) was slurried in dry ether (100 ml) under argon and cooled with stirring to -78°C. Methyl lithium (115 ml of 1.6 M in ether, 185 mmol) was added via syringe and the resultant pale brown solution stirred for 20 min. A solution of epoxy alcohol 7 (7.182 g, 37 mmol) in dry ether (30 ml) was added dropwise and the resultant mixture placed in the freezer (-25°C) overnight. After the usual work-up, the crude product was flash chromatographed on silica gel (ether) to yield a 10:1 mixture of regioisomeric diols, the major component being the desired product from ring-opening at C-2. NMR: (major diastereomer) 7.30 (5H,m,aromatic) 4.56 (2H,AB-m,J=12,benzylic) 3.75 (1H,bm,CHOH, coupled to OH) 3.67 (2H,bm,CH_2OH,coupled to OH) 3.60 (1H,dd,J=9,3.2,CHOBn) 3.44 (1H,dd,J=9,7.5,CHOBn) 2.85 (2H,b,2xOH) 1.82 (1H,apparent septet,J=7,CHMe) 0.86 (3H,d,J=7,Me). Decoupling of the methine "septet" at 1.82 affected only the methyl doublet and the broadened multiplets at 3.75 and 3.67, thus confirming the proposed structure. IR: 3400 (b,vs,OH). Total yield: 7.38 g, 95%.
The mixture of diols from above (6.83 g, 32.5 mmol) was silylated as described for compound 5 above. The diastereomeric silyl ethers were separated by flash chromatography (silica, 10% ether-pentane, two runs) to yield the desired 8 as an oil (9.09g, 100% based on the 10:1 ratio obtained for the first step). NMR: 7.35 (5H,m,aromatic) 4.41 (2H,AB-m,J=13,benzylic) 3.75 (1H, dd,J=10,4.4,CHOSi) 3.73 (1H,unresolved m,CHOH,coupled to OH) 3.63 (1H,dd,J=10,6,CHOSi) 3.52 (1H,dd, J=10,3.8,CHOBn) 3.49 (1H,dd,J=10,7.6,CHOBn) 3.37 (1H,b,OH) 1.88 (1H,m,CHMe) 0.92 (3H,d,J=7,Me) 0.88 (9H,s,t-Bu) -0.04 (3H,s,SiMe) -0.09 (3H,s,SiMe). IR: 3450 (b, OH) 1100 (OSi). MS: 324 (M^+), 267 (M - tBu). $[\alpha]_D$ +6.5° (c 1.6,CH_2Cl_2).
Primary silyl ether 8 (7.728 g, 23.9 mmol) was hydrogenated over the Pearlman catalyst($Pd(OH)_2/C$) at RT in absolute ethanol (30 ml) for 4 h. The catalyst was then filtered off onto Celite, the filter-cake washed thoroughly with fresh EtOH and the combined filtrate and washings stripped down to yield the desired 1,2-diol as an oil in quantitative yield (5.59g). NMR: 4.01 (1H,b,OH) 3.79 (1H,dd,J= 10,4,CHOSi) 3.70-3.55 (3H,complex m,b,CHOH,CH_2OH) 3.62 (1H,dd,J=10,7,CHOSi) 2.45 (1H,b,OH) 1.88 (1H,complex m, CHMe) 0.91 (9H,s,t-Bu) 0.85 (3H,d,J=7,Me) 0.09 (6H, s,$SiMe_2$). IR: 3350 (b,s,OH) 1100 (OSi). MS: 177 (M - tBu). $[\alpha]_D$ +15.7° (c 2 , CH_2Cl_2).
The 1,2-diol from above (2.71 g, 11.58 mmol) was dissolved under argon in dry pyridine (15 ml) and the solution stirred at -20°C during addition of para-toluenesulfonyl chloride (2.429 g, 12.7 mmol). The resultant solution was then stored overnight at -20°C, poured into ether, and the pyridine removed by repeated washing with $CuSO_4$.aq. The ethereal layers were combined, dried over Na_2SO_4 and the solvent was then removed. Flash chromatography of the residue (silica, 50% ether-pentane) yielded the desired primary tosylate as an oil (4.15g 92%). NMR: 7.83 and 7.36 (each 2H,"d",J=9,aromatic) 4.08 (2H,d,J=4.5,CH_2OTs) 3.75 (1H,dt,J=6,4.5,CHOH) 3.72 (1H,dd,J=11,4,CHOSi) 3.56 (1H,dd,J=11,6.5,CHOSi) 2.55 (3H,s,tosyl Me) 1.87 (1H,qddd,J=7,6.5,6,4,CHMe) 0.89 (3H,d,J=7,Me) 0.86 (9H,s,tBu) 0.04 (6H,s,$SiMe_2$). IR: 3450 (b,OH) 1360 and 1180 (tosyl) 1100 (OSi). $[\alpha]_D$ +9.58 (c 1.9 CH_2Cl_2).

Silyl ether 9. The primary tosylate from above (4.15 g, 10.7 mmol) was dissolved with stirring under argon in dry THF (100 ml) at 0°C. Lithium triethylborohydride (23.6 ml of 1M THF solution, 23.6 mmol) was added dropwise and the resultant solution stirred for 30 min at 0°C. The reaction was quenched by slow addition of water, and the mixture poured into ether-water. The aq. phase was extracted with ether and the combined organics were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica, 20% ether-pentane) yielded 9 as an oil (1.966 g, 84%). NMR: 3.89 (1H,b,OH) 3.69 (1H,dd,J=10,4,CHOSi) 3.61 (1H,dq,J=7,6,CHOH) 3.48 (1H,dd,J=10,8,CHOSi) 1.59 (1H,dqdd,J=8,7,7,4,CHMe) 1.09 (3H,d,J=6,Me) 0.83 (9H,s,tBu) 0.73 (3H,d,J=7,Me) 0.02 (6H,s,$SiMe_2$). IR: 3450 (b,OH) 1090 (OSi) MS: 218 (M^+) 161 (M - tBu). $[\alpha]_D$ +1.44° (c 1.73, CH_2Cl_2).

Sulfone B. Silyl ether 9 (3.164 g, 14.5 mmol) was dissolved with stirring under argon in dry CH_2Cl_2 (40 ml) and cooled to 0°C. Diisopropylethyl amine (3.79 ml, 21.8 mmol) was added, followed by benzyl chloromethyl ether (2.32 ml, 16.7 mmol). The mixture was allowed to reach RT overnight and was then evaporated to dryness. The residue was partitioned between ether and water, the layers were separated, and the organic phase was washed once with water. The organics were dried over Na_2SO_4 and the solvent was then removed to yield the crude BOM ether which was purified by flash chromatography (silica, 5% ether-pentane). There was obtained 3.53 g (72%) of the desired product as an oil. NMR: 7.39 (5H,m,aromatic) 4.80 (2H AB-m,J=6.5,OCH_2OBn) 4.63 (2H,AB-m,J=11.5,benzylic) 3.79 (1H,apparent quintet,J=6, CHOBOM) 3.58 (1H,dd,J=9,5.5,CHOSi) 3.52 (1H,dd,J=9,5.9,CHOSi) 1.86 (1H,qddd,J=7, 6,5.9,5.5,CHMe) 1.13 (3H,d,J=6,Me) 0.89 (3H,d,J=7,Me) 0.87 (9H,s,tBu) 0.03 (6H,s, $SiMe_2$). IR: 1100 (OSi). MS: 281 (M - tBu). $[\alpha]_D$ -8.04° (c 0.93, CH_2Cl_2).
The above BOM ether (3.177 g, 9.4 mmol) was dissolved under argon in dry THF (50 ml) and stirred at 0°C during the dropwise addition of tetrabutylammonium fluoride (14.1 ml of 1M THF solution, 14.1 mmol). The resultant mixture was stirred at 0°C for 1h, and then at RT for 2h. The reaction mixture was then poured into ether and the organics were washed with water, dried (Na_2SO_4) and then stripped down to yield an oily residue which was flash chromatographed (silica, 30% ether-pentane). There was obtained 2.02 g (96%) of the desired primary alcohol as an oil. NMR: 7.37 (5H,m,aromatic) 4.73 (2H,AB-m,J=6.9,OCH_2OBn) 4,57

(2H,AB-m,J=11.5,benzylic) 3.72 (1H,apparent quintet,J=6,CHOBOM) 3.70 (1H,dd,J=11.5,3.9,CHOH) 3.57 (1H,dd,J=11.5,6,CHOH) 1.73(1H,qddd,J=7,6,6,3.9,CHMe) 1.21 (3H,d,J=6,Me) 0.95 (3H,d,J=7,Me). IR: 3450 (b,s,OH). MS: 224 (M^+). $[\alpha]_D$ -54.8° (c 2, CH_2Cl_2).
This primary alcohol (2.67 g, 11.9 mmol) was converted to the corresponding bromide in the same fashion as described above for bromide A. There was obtained 3.152 g (92%) of the desired primary bromide as an oil after flash chromatography (2% to 5% ether-pentane). NMR: 7.35 (5H,m,aromatic) 4.82 (2H,AB-m,J=7,OCH_2OBn) 4.64 (2H,AB-m,J=12,benzylic) 3.75 (1H,quintet, J=6.5,CHOBOM) 3.54 (1H,dd,J=10,5.5 CHBr) 3,48 (1H,dd,J=10,4.5,CHBr) 1.96 (1H,qddd,J=7,6.5,5.5,4.5,CHMe) 1.18 (3H,d, J=6.5,Me) 1.03 (3H,d,J=7,Me). $[\alpha]_D$ -27.6° (c 1.47, CH_2Cl_2). This material was used immediately in the next step.
The primary bromide (3.127g, 10.9mmol) was dissolved with stirring under argon in dry DMF (50 ml). Anhydrous sodium para-tolunesulfinate (3.882 g, 21.8 mmol) was added,followed by tetrabutylammonium bromide (0.176 g, 0.545 mmol) and the resultant mixture stirred at 40°C for 8h. The reaction mixture was cooled and then partitioned between ether and water, and the aq. phase back-extracted with three 25-ml portions of ether. The combined ethereal fractions were dried over Na_2SO_4 and the solvent was removed. Flash chromatography of the residue yielded sulfone B as a viscous oil which resisted crystallisation. (3.156 g, 80%). NMR: 7.80 and 7.35 (each 2H,"d",J=8,p-Tol) 7.30 (5H,m,BOM aromatics) 4.70 (2H,AB-m,J=7,OCH_2OBn) 4.56 (2H,AB-m,J=12.5,benzylic) 3.66 (1H,qd,J=6.5,5,CHOBOM) 3.31 (1H,dd J=14,3,$CHSO_2$) 2.89 (1H,dd,J=14,9,$CHSO_2$) 2.44 (3H,s,p-Tol Me) 2.10 (1H,dqdd,J=9,7, 5,3,CHMe) 1.14 (3H,d,J=7,Me) 1.10 (3H,d,J=6.5,Me). IR: 1310(s) and 1140(s, sulfone). MS: 362 (M^+). $[\alpha]_D$ -11.74° (c 1.13, CH_2Cl_2).

Ester 12. Oxalyl chloride (0.88 ml, 10.1 mmol) was added dropwise to dry CH_2Cl_2 (150 ml) at -78°C,under argon. Dry DMSO (1.43 ml, 20.1 mmol) was then added dropwise,and the solution stirred for 15 min before addition of a solution of the diol 11 (2.01 g, 9.1 mmol) in dry CH_2Cl_2 (6 ml). After 20 min at -78°C, triethylamine (3.82 ml, 27.4 mmol) was added and the resultant mixture stirred for a further 20 min. A solution of methyl (triphenylphosphoranylidene)acetate (9.165 g 27.4 mmol) in dry CH_2Cl_2 (15 ml) was added in a single portion and the reaction temperature allowed to reach RT, followed by stirring for a further 4 h. The reaction mixture was partitioned between water and CH_2Cl_2, the layers were separated and the aq. phase was back-extracted with three portions of CH_2Cl_2. The combined organics were dried over Na_2SO_4 and the solvent was removed to yield a sticky residue which was flash chromatographed on silica (20 to 30% ether-pentane) There was obtained 1.745 g (70% based on 11) of the relevant α,β-unsaturated ester as an oil. NMR: 6.91 (1H,d,J=15.5,β-vinyl) 6.11 (1H,d,J=15.5,α-vinyl) 3.72 (3H,s,CO_2Me) 3.50 (2H,AB-m,J=9,CH_2OSi) 2.69 (1H,b,OH) 1.27 (3H,s,Me) 0.90 (9H,s, tBu) 0.02 (6H 2xs,$SiMe_2$). IR: 3450 (b,OH) 1725 (s,ester) 1095 (s,OSi). MS: 217 (M - tBu). $[\alpha]_D$ -3.97°(c 1.1, CH_2Cl_2).
The tertiary alcohol function was then protected as follows. The"ester-alcohol" from above was dissolved with stirring in dry CH_2Cl_2 (15 ml) under argon at RT. Pyridinium p-tolunesulfonate (PPTS, 0.167 g, 0.66 mmol) was added,followed by freshly distilled 3,4-dihydro-2H-pyran (DHP, 0.803 g, 9.55 mmol) and the resultant mixture was stirred at RT for 12 h. The mixture was then poured into ether (75 ml) and the resultant solution washed once with brine. The organic phase was dried over Na_2SO_4 and the solvent removed. Flash chromatography of the residue (silica, 20% ether-pentane) yielded the tertiary THP-ether as an oil. (2.234 g, 98%). This material was a chromatographically inseparable 1:1 mixture of diastereomers. NMR: 7.00 (2xd,J=16,β-vinyl) 6.03 (2xd,J=16,α-vinyl) 4.89 and 4.75 (2x"t",OCHO in THP) 3.95 (m, THP) 3.73 (2xs,CO_2Me) 3.63 and 3.59 (2xAB-m,J= 9.5,CH_2OSi) 3.46 (m,THP) 1.9-1.45 (complex m,THP) 1.36 (2xs,Me) 0.89 (s,tBu) 0.03 (2xs,$SiMe_2$). IR: 1725 (s,ester) 1100 (s,OSi). MS: 301 (M - tBu).
The primary silyl ether in this material was removed using tetrabutyl ammonium fluoride as described above. There was obtained 1.477 g (97%) of ester 12 as an oil (mixture of diastereomers after flash chromatography, silica, 75% ether-pentane). NMR: 6.89 (2xd,J=16,β-vinyl) 6.06 (2xd,J=16,α-vinyl) 4.79 and 4.62 (2x"t",OCHO in THP) 4.00 (m,THP) 3.74 (2xs,CO_2Me) 3.70 (b,OH) 3.52 (complex m, CH_2OH coupled to OH, THP) 1.9-1.5 (complex m,THP) 1.35 (2xs,Me). IR: 3450 (b,OH) 1720 (ester). MS: 244 (M^+).

Sulfone C. Ester 12 (1.477 g, 6.05 mmol) was dissolved with stirring under argon in dry CH_2Cl_2 (25 ml) and cooled to -20°C. Dry pyridine (0.61 ml,7.56 mmol) was added followed by trifluoromethanesulfonic anhydride (1.18 ml, 7.02 mmol). The resultant mixture was stirred at -20°C for 30 min, diluted with ether, and washed quickly with $CuSO_4$.aq. The organics were dried and the solvent was removed under reduced pressure at 0°C. The residue,a pale yellow oil,was used immediately in the next step. (2.27 g, 100%) IR: 1720 (ester) 1410,1210 and 1145 (triflate).
The crude triflate was added to a solution of anhydrous sodium para-toluenesulfinate (3.24 g, 18.2 mmol) and 15-crown-5 (0.11 g, 0.5 mmol) in dry DMF (20ml). The resultant solution was stirred overnight at RT and then poured into ether-water. The organics were separated, washed with water,and stripped down to yield the crude sulfone which was purified by flash chromatography (silica, 40% ether-pentane). Yield: 1.92 g, 83%. (Mixture of diastereomers). NMR: 7.75 and 7.32(2x"d" J=8,p-Tol) 6.64 (2xd,J=16,β-vinyl) 6.00 (2xd,J=16,α-vinyl) 4.70 (2x"t",OCHO,THP)

3.85 (m,THP) 3.73 (2xs,CO_2Me) 3.42 (m,THP) 3.30 (2xAB-m,J=9.5,CH_2SO_2) 2.44 (s,p-Tol Me) 2.00-1.45 (complex m,THP) 1.35 (2xs,Me). IR: 1720 (s,ester) 1350 and 1145 (s,sulfone). MS: 382 (M^+).

Coupling of A and B: Silyl ether 13. Sulfone B (1.748 g, 4.8 mmol) was dissolved with stirring under argon in dry THF (40 ml) and cooled to -40°C. Butyllithium (3.31 ml of 1.6M hexane solution, 5.3 mmol) was added dropwise and the mixture stirred at -40°C for 90 min. HMPA (2.3 ml, anhydrous) was added and the solution cooled to -65°C and stirred for a further 10 min. A solution of allylic bromide A (1.300 g, 4.0 mmol) in dry THF (5 ml) was added dropwise and the reaction temperature allowed to reach -10°C over 2.5 h. The reaction was quenched by addition of NH_4Cl.aq. and the mixture poured into ether-water. The separated aq. phase was extracted with ether and the combined organics were washed with brine, dried,and stripped down. The residue was flash chromatographed (silica, 30-40% ether-pentane, two runs) to yield two diastereomeric tertiary sulfones. Total yield 1.849 g, 76%. Data for the major diastereomer: NMR: 7.77 and 7.33 (each 2H "d",J=8,p-Tol) 7.31 (5H,m,BOM aromatics) 5.30 (1H,bt,J=6.5,vinylic) 4.70 (2H,AB-m,J=7,OCH_2OBn) 4.57 (2H,s,benzylic) 3.65 (1H,td,J=8,1.9,$CHSO_2$) 3.57-3.35 (4H, complex m,CHOBOM,CHOMe,CH_2OSi) 3.13 (3H,s,OMe) 2.67 (1H,ddd,J=16,8,6.5,allylic) 2.54 (1H,ddd,J=16,8,6.5,allylic) 2.44 (3H,s,p-Tol Me) 2.37 (1H,dqd,J=8,7,1.9, CHMe) 1.50 (3H,bs,vinylic Me) 1.13 (3H,d,J=6,Me) 1.03 (3H,d,J=7,Me) 0.90 (9H,s, tBu) 0.03 (6H,s,$SiMe_2$). IR: 1310 and 1140 (s,sulfone) 1130 (OMe). MS: 547 (M-tBu) $[\alpha]_D$ -10.7° (c 1.8, CH_2Cl_2).
The mixture of sulfones could be carried on directly to the next step. Thus, the mixture of sulfones (1.555 g, 2.6 mmol) was dissolved with stirring in dry MeOH (20 ml) and Na_2HPO_4 (1.461 g, 10.3 mmol) was added. The mixture was stirred at RT and finely powdered 6% Na-amalgam (4g) was added in portions. After 2h, TLC analysis showed complete disappearance of the starting material,and the methanol was decanted into ether-water. The separated organic phase was washed with water and then dried over Na_2SO_4. Solvent removal was followed by flash chromatography (silica, 10% ether-pentane) to yield compound 13 as an oil. (1.018 g, 87%). NMR: 7.30 (5H,m,aromatic) 5.39 (1H,bt,J=7,vinylic) 4.79 (2H,AB-m,J=7,OCH_2OBn) 4.63 (2H,s,benzylic) 3.66 (1H,qd,J=6.5,5,CHOBOM) 3.64 (1H,dd,J=9,4,CHOSi) 3.56 (1H,dd,J=9,4,CHOSi) 3.52 (1H,t,J=4,CHOMe) 3.22 (3H,s,OMe) 2.07 (2H,m,allylic) 1.69 (1H,qddd,J=7,5,4.5,4,CHMe) 1.55 (3H,bs,vinylic Me) 1.49 (1H,m,J_{gem}=12, homoallylic) 1.21 (1H,m,J_{gem}=12,homoallylic) 1.13 (3H,d,J=6.5,Me) 0.94 (3H d,J=7,Me) 0.89 (9H,s,tBu) 0.04 (6H,s,$SiMe_2$). IR: 1130 (OMe) 1100 (OSi). MS: 393 (M - tBu). $[\alpha]_D$ -14.6° (c 3.0, CH_2Cl_2).
The silyl ether was removed using tetrabutylammonium fluoride as described above. From 0.900 g (2.0 mmol) of the silyl ether there was obtained 0.659 g (98%) of the corresponding primary alcohol. NMR: 7,33 (5H,m,aromatic) 5.44 (1H, bt,J=7,vinylic) 4.79 (2H.AB-m,J=6.9,OCH_2OBn) 4.63 (2H,s,benzylic) 3.65 (1H,qd, J=6,5,CHOBOM) 3.58 (1H,apparent t,J=7.5,CHOMe) 3.51 (2H,bm,CH_2OH,coupled to OH) 3.25 (3H,s,OMe) 2.08 (2H,m,allylic) 1.96 (1H,b,OH) 1.67 (1H,narrow m,methine) 1.54 (3H,bs,vinylic Me) 1.50 (1H,m,homoallylic) 1.20 (1H,m,homoallylic) 1.09 (3H d,J=6,Me) 0.91 (3H,d,J=7,Me). IR: 3450 (b,s,OH) 1120 (OMe). MS: 336 (M^+). $[\alpha]_D$ -29.5° (c 2.4, CH_2Cl_2).

Aldehyde 14. The primary alcohol from above was subjected to the Swern oxidation as desribed previously for compound 12. From 0.659 g (1.96 mmol) of the alcohol there was obtained 0.589 g (90%) of crude aldehyde which showed a single-spot TLC and was NMR-spectroscopically pure. This material was dried azeotropically with three portions of benzene before use in the next coupling reaction. NMR: 9.44 (1H,d,J=0.9,aldehyde) 7.30 (5H,m,aromatic) 5.61 (1H,bt,J=7,vinylic) 4.80 (2H,AB-m,J=6.9,OCH_2OBn) 4.64 (2h,s,benzylic) 3.98 (1H,d,J=0.9,CHOMe) 3.65 (1H,qd J=6,5,CHOBOM) 3.32 (3H,s,OMe) 2.15 (2H,m,allylic) 1.67 (1H,m,CHMe) 1.58 (3H,bs, vinylic Me) 1.54 (1H,m,homoallylic) 1.24 (1H,m,homoallylic) 1.10 (3H,d,J=6,Me) 0.91 (3H,d,J=6.5,Me). IR: 1730 (aldehyde) 1160 (OMe).

Coupling of aldehyde 14 with sulfone C. Sulfone C (0.344 g, 0.9 mmol) was dissolved with stirring under argon in a 9:1 mixture of anhydrous THF/HMPA (5ml) and the solution cooled to -90°C. A freshly prepared 1M solution of lithium di-isopropylamide (LDA, in THF) was cooled under argon to ca. -78°C and 0.99 ml (0.99 mmol) of the cold solution added rapidly via cannula to the cold solution of the sulfone. The resultant solution was allowed to stir for 10 min at -90°C before rapid addition of a solution of freshly prepared and dried aldehyde 14 (0.250 g, 0.75 mmol) in dry THF (1 ml). The reaction mixture was stirred at -90° for 15-20 min and then acetic anhydride (0.42 ml, 4.5 mmol) dry pyridine (1.1 ml 13,5 mmol) and 4-dimethylaminopyridine (catalytic amount) were added. The reaction mixture was allowed to reach RT and then stirred for a further 8h. The reaction mixture was then poured into ether and the ethereal solution washed once with $CuSO_4$.aq., once with water, and once with brine. The organics were then dried over Na_2SO_4 and the solvent was removed. Unreacted sulfone C was removed from the residue by rough chromatography, which also yielded the acetylated derivative of the desired adduct as an extremely complex mixture of diastereomers (TLC, NMR). The mixture of β-acetoxysulfones (ca. 0.37 g) was not further purified, but dissolved in anhydrous methanol buffered with Na_2HPO_4 and then subjected to treatment with 6% Na-amalgam as described above. After the

usual work-up procedure and flash chromatography (silica, 40% ether-pentane) there was obtained 0.129 g (30 % based on 14) of compound 15 as a mixture of two diastereomers (THP). This material was isomerically pure as regards the newly-formed olefinic bond (E-configuration). NMR: 7.35 (m,aromatic) 6.91 (2xd,J=15.5, vinylic β to ester) 6.02 (2xd,J=15.5,vinylic α to ester) 5.73 (dd,J=15,1,vinylic β to CHOMe) 5.60 (dd,J=15,5,vinylic α to CHOMe) 5.40 (bt,J=6.5,vinylic) 4.79 (AB-m,J=6.9,OCH_2OBn) 4.74 and 4.69 (2x"t",OCHO in THP) 4.63 (s,benzylic) 3.94 (dd, J=5,1,CHOMe) 3.88 (m,THP) 3.72 (s,CO_2Me) 3.65 (qd,J=6,5,CHOBOM) 3.42(THP)3.19(OMe) 2.07(allylic)1.86-1.47 (complex m,THP) 1.63 (m,CHMe and homoallylic) 1.52 (bs, vinylic Me) 1.43 (2xs,tertiary Me) 1.10 (d,J=6,Me) 0.90 (d,J=6.5,Me).
IR: 1725 (ester) 1650 (olefinic) 1160 (OMe). MS: 544 (M^+).

Compound 15 (0.129 g, 0.24 mmol) was dissolved with stirring in 1:1 THF/H_2O (10 ml) and 0.72 ml of a 1M aq. solution of LiOH (0.72 mmol) was added dropwise. The reaction mixture was stirred at RT overnight and then cooled in an ice-bath before careful acidification to pH 3 (10% aq. HCl). The acidified mixture was then extracted thoroughly with ethyl acetate and the combined extracts dried (Na_2SO_4) and stripped down to yield the corresponding α,β-unsaturated acid (0.123 g, 98%). This material was pure by TLC (EtOAc,R_f=0.62) and was used directly in the next step. NMR (THP diastereomers): 7.35 (m,aromatic) 6.90 (2xd,J=16,vinylic β to COOH) 6.00 (2xd,J=16,vinylic α to COOH) 5.73 (d,J=15,vinylic β to CHOMe) 5.60 (dd,J=15,5,vinylic α to CHOMe) 5.41 (bt,J=7,vinylic) 4.79 (AB-m,J=7,OCH_2OBn) 4.75 and 4.70 (2x"t", OCHO in THP) 4.63 (s, benzylic) 3.95 (d, J=5, CHOMe) 3.90 (m,THP) 3.64 (apparent quintet, J=6, CHOBOM) 3.43 (m, THP) 3.20 (s, OMe) 2.10 (m, allylic) 1.90 - 1.45 (complex m, THP) 1.65 (m, CHMe and homoallylic) 1.53 (bs, vinylic Me) 1.49 (2xs, tertiary Me) 1.20 (m, homoallylic) 1.12 (d, J=6, Me) 0.91 (d, J=7, Me).
IR: ca. 3300 (vb, carboxylic acid) 1690 (acid) 1640 (olefinic)

The THP derivative of the Ingramycin seco acid.

The crude acid from above (0.123 g, 0.23 mmol) was dissolved with stirring in 5:1 hexane/ethyl acetate (6 ml). $Pd(OH)_2/C$ (Aldrich "moist", 6 mg) was added and the mixture stirred while the reaction vessel was alternately evacuated (water pump) and flushed with argon via a three-way stopcock. After several cycles, the procedure was repeated using hydrogen and the vessel was finally placed under balloon pressure of hydrogen and the reaction mixture stirred at RT for 45 min. At this point TLC analysis showed remaining starting material plus a new product (R_f = 0.35, EtOAc). The reaction vessel was then evacuated and flushed with argon and the catalyst filtered off onto a pad of Celite. The filter-cake was washed with fresh ethyl acetate and the combined filtrate and washings were stripped down. Careful flash chromatography (silica, EtOAc) separated the starting material (R_f= 0.6) from the product, which was shown to be the desired seco acid derivative of Ingramycin (see below). There was obtained 0.064 g (68%) of the known (ref. 7) seco acid derivative as a mixture of diastereomers. This material proved to be chromatographically and spectroscopically identical with an authentic sample prepared from ingramycin itself (see below). NMR: 6.99 (2xd, J=16, vinylic β to COOH) 6.04 (2xd J=16, vinylic α to COOH) 5.77 (d, J=15, vinylic β to CHOMe) 5.61 (dd, J=15,5.1, vinylic α to CHOMe) 5.42 (bt, J=7, vinylic) 4.76 and 4.71 (2x"t", OCHO in THP) 4.00 (bd, J=5.1, CHOMe) 3.94 (m, THP) 3.68 (apparent quintet J=6, CHOH) 3.46 (m, THP) 3.22 (s, OMe) 2.10 (m, allylic) 1.87 - 1.50 (complex m, THP) 1.70 (narrow m, CHMe) 1.61, m, homoallylic) 1.55 (bs, vinylic Me) 1.48 (2xs, tertiary Me) 1.20 (complex m, homoallylic) 1.13 (d, J=6, Me) 0.89 (d, J=6.5, Me).
IR: 3400 (b, OH) 1690 (carboxylic acid) 1640 (olefinic).
MS: 410 (M^+).
For comparison purposes, the THP ether derivative of the ingramycin seco acid was prepared from an authentic sample of the antibiotic, as follows:
Ingramycin (0.077 g, 0.25 mmol) was dissolved with stirring under argon in dry CH_2Cl_2 (2.5 ml) and PPTS (6.3 mg, 0.025 mmol) was added followed by DHP (63 mg, 0.75 mmol). The mixture was stirred at RT for 8h and then poured into ether (10 ml). The organics were washed with brine, dried, and stripped down. The residue was flash chromatographed (silica, 40% ether-pentane) to yield the desired THP ether as an oil (0.096 g, 98%) which was obtained as a mixture of diastereomers (see also ref. 7). NMR: 6.71 (2xd, J=15.5, vinylic β to C=O) 5.91 and 5.81 (each d, J=15.5, vinylic α to C=O) 5.87 and 5.67 (each d, J=16, vinylic β to CHOMe) 5.58 and 5.53 (each dd, J=16,5, vinylic α to CHOMe) 5.27 (bt, J=7, vinylic) 4,91 (2x"t", OCHO in THP) 4.58 (apparent quintet, J=6, CH-O-C=O) 4.05 (bd, J=5, CHOMe) 3.98 (m, THP) 3.52 (m, THP) 3.30 (2xs, OMe) 2.11 (m, allylic) 1.93 - 1.49 (complex m, THP) 1.84 (m, allylic and homoallylic) 1.63 (2xbs, vinylic Me) 1.55 (2xs, tertiary Me) 1.41 (m, CHMe) 1.25 (m, homoallylic) 1,21 (d, J=6, Me) 0.88 (d, J=7, Me). IR: 1710 (lactone).
The THP derivative was then transformed into the corresponding seco acid THP ether by the method of Steliou (1M LiOH, THF/H_2O, see ref. 7). The seco acid derivative was obtained in 97% yield and was shown to be chromatographically and spectroscopically identical with the synthetic material described above.
R_f= 0.36, EtOAc.

By repeating the debenzylation procedure outlined above, 0.098 g of the synthetic THP derivative of the seco acid was accumulated prior to the macrolactonisation

step, which was carried out according to Boden and Keck (ref. 11b).

Macrolactonisation.
DCC (0.099 g, 0.48 mmol), DMAP (0.088 g, 0.72 mmol) and DMAP.trifluoroacetate salt (0.114 g, 0.48 mmol) were dissolved with stirring under argon in freshly distilled ethanol-free chloroform (20 ml). The solution was brought to reflux and a solution of the synthetic seco acid THP derivative (0.098 g, 0.24 mmol) in chloroform (5 ml) was added via syringe drive over 10 h, the tip of the delivery syringe needle being positioned in the condensate formed at the lower end of the reflux condenser. When addition was complete, the reaction mixture was cooled to RT, concentrated to ca. 5 ml volume and then diluted with 15 ml of ether. After filtration, the filtrate was concentrated and the semi-solid residue dissolved in a small volume of chloroform and then applied to a short silica gel column. Elution with a gradient of 20 to 40% ether-pentane yielded the THP ether of ingramycin as an oil (mixture of diastereomers). The yield was 0.077 g (82%) and the synthetic material was shown to be chromatographically and spectroscopically identical with an authentic sample prepared from the antibiotic as described above. Careful TLC analysis in a variety of solvent systems (see ref. 7) showed the absence of dimeric/trimeric products (Ref. 7).

Synthetic ingramycin, 1.
The synthetic THP derivative (0.077 g, 0.196 mmol) was dissolved with stirring under argon in dry methanol (2 ml) at 0°C. PPTS (0.0049 g, 0.019 mmol) was added and the resultant solution stirred overnight between 0°C and RT. The solvent was then removed under reduced pressure at 0°C and the residue purified by flash chromatography (silica, 75% ether-pentane). There was obtained 0.053 g (87%) of synthetic ingramycin as a crystalline solid, m.p. 80-82°C (lit.83-84°C, see ref. 4a). The synthetic material proved to be chromatographically and spectroscopically identical with an authentic sample kindly supplied by Dr. R.C. Thomas of The Upjohn Company.
$[\alpha]_D$ -104.5° (c 1, $CHCl_3$) for the synthetic material.
$[\alpha]_D$ -110° (c 1, $CHCl_3$) for the authentic sample (see ref. 4a).

NMR: 6.89 (1H, d, J=15.5, vinylic β to C=O) 5.89 (1H, d, J=15.5, vinylic α to C=O) 5.80 (1H, d, J=16, vinylic β to CHOMe) 5.67 (1H, dd, J=16,5.9, vinylic α to CHOMe) 5.30 (1H, tq, J=6,0.5, vinylic) 4.56 (1H, dq, J=8,6.5, CH-O-C=O) 4.08 (1H, d, J=5.9, CHOMe) 3.31 (3H, s, OMe) 2.17 (2H, m, one allylic, one homoallylic) 1.85 (1H, m, allylic) 1.66 (3H, d, J=0.5, vinylic Me) 1.55 (3H, s, tertiary Me) 1.47 (1H, dqt, J=8,6.5,3, CHMe) 1.27 (1H, m, homoallylic) 1.24 (3H, d, J=6.5, Me) 0.91 (3H, d, J=6.5, Me).

IR: 1705 (lactone). MS: 308 (M^+).

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