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Total Syntheses of Close Analogues of the Immunosuppressant FK506

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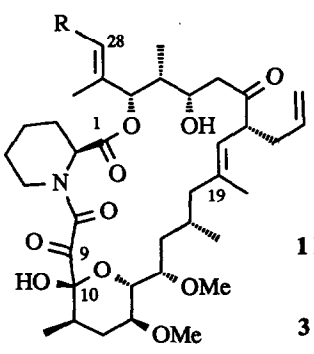
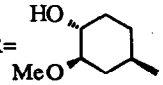
Abstract: The total synthesis of an analogue of FK506, in which the substituted cyclohexyl residue at C_{28} has been replaced by a phenyl group, is described. This synthesis demonstrates (i) the successful application of new methodology for the introduction of the masked tricarbonyl grouping (C_8-C_{10}), and (ii) new synthetic routes to the (C_{10}-C_{19}) and (C_{22}-C_{26}) regions.

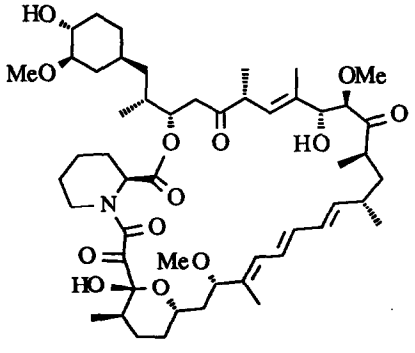
The modes of action of the immunosuppressant molecules FK506 **1**[1] and rapamycin **2**[2] have been the subject of intense research effort in recent years. Schreiber and others have provided great insight, not only into their cellular targets, but also into T-cell signalling mechanisms[3]. Armed with this wealth of knowledge, which includes two landmark total syntheses[4,5] of FK506 and more recently a total synthesis of rapamycin[6], chemists are now examining the possibilities of removing the drugs' undesirable biological effects by means of structural modification. As a consequence, studies directed towards the total synthesis of structural analogues of FK506 and rapamycin, and the construction of functionalities common to both molecules, continue to be important.



1 FK506 R=



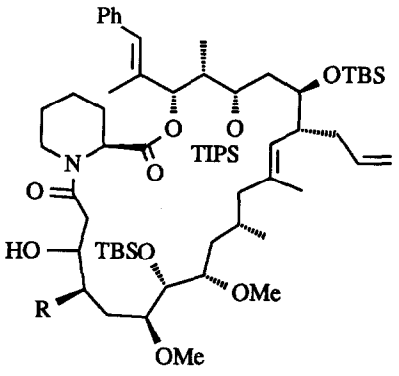
3 R= Ph



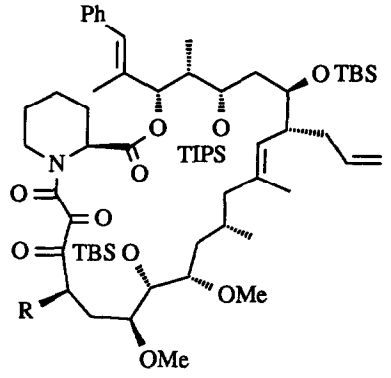
2 Rapamycin

Recognition of the masked tricarbonyl region (C_8-C_{10} in FK506)(common to both FK506 and rapamycin) as being important for the binding of these molecules to their primary receptors has ensured continuing research into improved methods for the creation of this functionality. In a recent communication[7] we described a method for the conversion of β-hydroxy- and β-ketoamides, esters and ketones to the corresponding tricarbonyl compounds, and its application to the synthesis of a precursor **5** of a structural analogue of FK506 **3**. We now wish to describe the synthesis of the macrocyclic substrates chosen to demonstrate the practicality of this reaction, the completion of the synthesis of the C_{28}-phenyl version of FK506, and to disclose the practical details for the key oxidation.

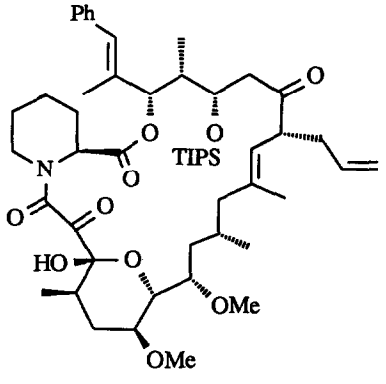
Scheme 1



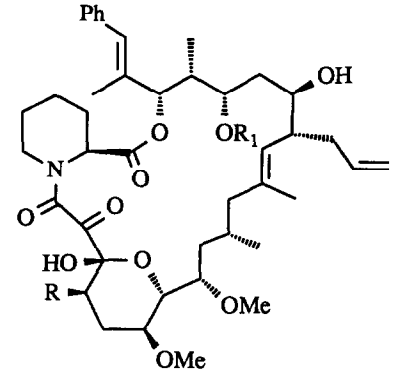
4 R= H **4a** R= Me



5 R= H **5a** R= Me



8



6 R= R_1= H **6a** R= Me, R_1= H

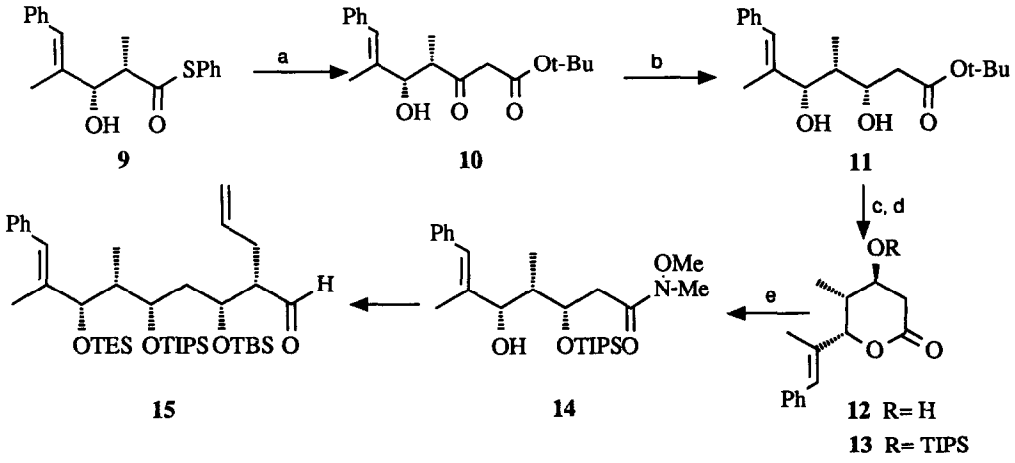
7 R= Me R_1= TIPS

Schank and Lick[8] reported that ozonolysis of the ylide formed by the reaction of iodobenzene diacetate {I(III)-reagent} with β-dicarbonyl compounds gave the corresponding tricarbonyl systems. It occurred to us that the Dess-Martin periodinane reagent {I(V)-reagent} might convert β-dicarbonyl and β-hydroxycarbonyl compounds to tricarbonyl compounds in one step. Having shown that this was indeed the

case, and in particular that treatment of a β-hydroxy amide with 3-4 equivalents of the Dess-Martin reagent together with 6-8 equivalents of pyridine afforded the corresponding tricarbonyl compound in good yield[7], we were ready to apply this methodology to the total synthesis of FK506 analogues. We therefore prepared the macrocyclic β-hydroxyamides **4** and **4a** (Scheme 1). These compounds differ from substrates suitable for the total synthesis of FK506 only in that the C_{28}-cyclohexyl substituent is replaced by a phenyl group in compound **4a** and in addition, in compound **4** the C_{11}-methyl substituent is replaced by hydrogen. The compounds **4** and **4a** were treated (1.25 h) with the Dess-Martin periodinane-pyridine reagent at room temperature and yielded the tricarbonyl compounds **5** (59%) and **5a** (78%).

The final steps towards the synthesis of the FK506 analogue **3** followed the example provided by the Merck total synthesis[4] of FK506 itself. All the silyl groups were removed by HF/acetonitrile treatment to provide the hemiacetals **6** and **6a**. The yields for this reaction and subsequent hydrofluoric acid treatments were disappointing (50%). We suspected that the cinnamyl ester portion was acid sensitive. At low temperatures the t-butyldimethylsilyl groups could be removed in preference to the triisopropylsilyl group. Unfortunately this reaction was also troublesome. However, this result allowed us to identify the products of selective reprotection. Similar to the reaction of 22-dihydro-FK506[4], treatment of **6a** with triisopropylsilyl triflate and 2,6-lutidine gave a mixture of products including compound **7** in which only the C_{24}-OH was protected. This compound **7** was the same as the product obtained when selective removal of the t-butyldimethylsilyl groups had been successful. This fact, combined with the change in the ^1H NMR chemical shift of H_{21} from δ 2.74 to 3.52 on treatment of the monosilyl derivative **7** with the Dess-Martin periodinane, gave good evidence that the C_{24}-OH and not the C_{22}-OH had been protected. Selective reprotection to give compound **7** was achieved in 41% yield and oxidation of the C_{22}-OH gave ketone **8** (84%). Removal of the silyl protection (HF/acetonitrile) then afforded compound **3**, the 28-phenyl analogue of FK506.

Scheme 2



a) TMSCl/ TEA, lithio t-butyl acetate, H^+; b) BEt_3/ MeOH/ $NaBH_4$; c) NaOH; d) TIPSCl/ imidazole
e) $AlMe_3$/ Me(MeO)NH.HCl

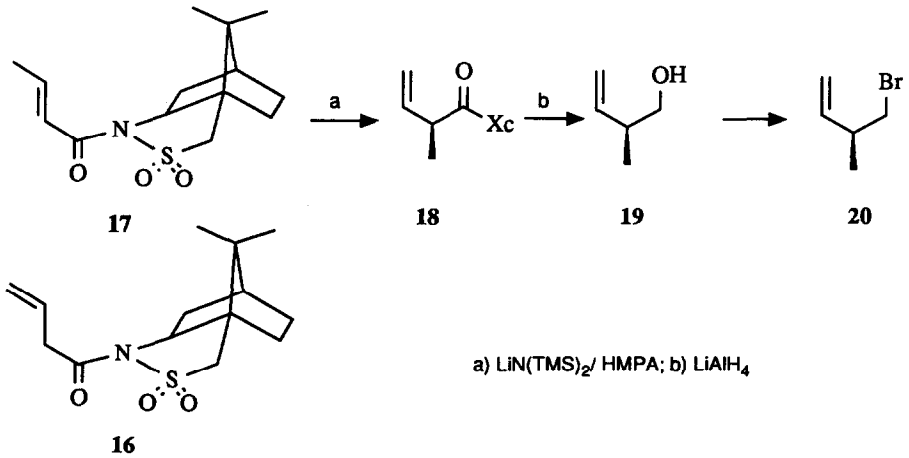
The C_{28}-phenyl analogue of FK506 **3** was chosen as a synthetic target for two reasons. First, to provide a suitable substrate on which to demonstrate the scope of the oxidation reaction described above, and second, to provide information on the minimum structural requirements for FK506-like biological activity. We decided to use the eminently practical route[4] described by the Merck group as a model for our synthesis of the β-hydroxyamide macrocyles **4** and **4a** (Scheme 1). This route entailed the synthesis of

aldehyde **15** (Scheme 2) which represents C_{20}-C_{28}, and the known Wittig reagent **31** (Scheme 4) which represents C_{10}-C_{19}. We now describe the synthesis of these molecules, concentrating on the areas in which we have departed from the Merck precedents[4].

The C_{20}-C_{28} fragment was prepared as shown in Scheme 2. Condensation of α-methylcinnamaldehyde and S-phenyl propanethioate[9], under conditions described by Corey[10], afforded the chiral thioester **9** (54%). This hydroxythioester **9** was treated with a mixture of trimethylsilyl chloride, triethylamine and THF before the whole mixture was added to an excess of lithio t-butyl acetate at -70°C. Acidic workup afforded the desired β-ketoester **10** in high yield (93%). Owing to a competing retro aldol reaction, omission of the trimethylsilyl protection step resulted in low yields. Syn reduction[11] of the C_{24} carbonyl afforded diol **11** (84%), which on alkaline hydrolysis and thermolysis of the resulting crude acid yielded the crystalline hydroxy lactone **12** (76%), thereby differentiating the two hydroxyl substituents at C_{24} and C_{26}. The protected lactone **13** was prepared (90%) by treatment of the lactone **12** with triisopropylsilyl chloride and imidazole in DMF at 60°C. Weinreb amination[12] of lactone **13** afforded the linear compound **14** (92%). The synthesis of key aldehyde **15** was then completed by direct analogy with the literature[4].

The C_{10}-C_{12} fragment was provided by the Grignard reagent derived from [2*S*]-1-bromo-2-methylbut-3-ene **20**. Although the synthesis of this Grignard reagent had been described[13] before, we found the route shown in Scheme 3 to be the more convenient. Oppolzer[14] described the benzylation of the chiral N-(3-butenoyl)sultam **16**, this led to α-substitution and good chiral induction. We decided to methylate the more conveniently prepared crotonyl sultam **17**[15]. On the basis that the deprotonated intermediate would be the same in both cases a similar result was expected. This type of chiral deconjugative methylation has already been described for iron acyl chiral induction[16,17]. Deprotonation of sultam **17** with a mixture of lithium hexamethyldisilazide and HMPA followed by treatment with methyl iodide afforded, after recrystallisation, the homogeneous sultam **18** (81%). The water soluble alcohol **19** was conveniently prepared (77%) by reduction of the sultam **18** with lithium aluminium hydride. Saturated sodium sulphate workup precipitated the chiral auxiliary leaving an ethereal solution of the alcohol which was then purified by fractional distillation and converted to bromide **20** by known methodology[13].

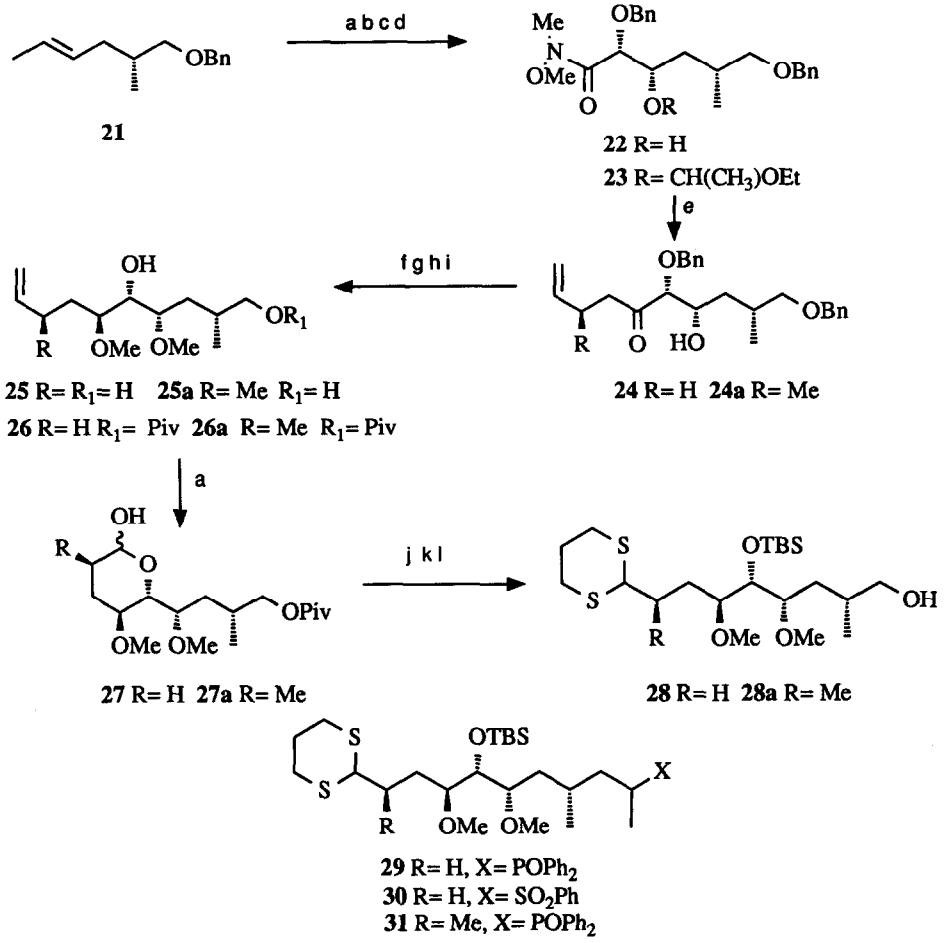
Scheme 3



The syntheses of the C_{10}-C_{19} fragments are illustrated by Scheme 4. We began with the benzyl ether **21**[18] which we converted to the amide **22** by a route similar to the one described by the Merck group[4,19]. The C_{10}-C_{12} fragment was provided by the Grignard reagent derived from the bromomethylbutene **20** in the synthesis of ketone **26a** while the Grignard reagent derived from bromobut-3-ene was used for the

C_{11}-desmethyl series. We had found that protection of the C_{15}-OH in compound **22** before reaction with the Grignard reagent accelerated the reaction rate and decreased the amount of Grignard reagent required. Good results were achieved in the desmethyl series with C_{15}-OH protected as a trimethylsilyl ether. This tactic proved less successful in the preparation of the C_{11}-methyl compound **24a**. Optimum results were obtained with the ethoxyethylether derivative **23**. Thus treatment of the amide **23** with 2.5 equivalents of the Grignard reagent derived from bromide **20**, followed by acidic workup, afforded the hydroxyketone **24a** in 88% yield. The hydroxyketone **24** was prepared (90%) in an analogous manner.

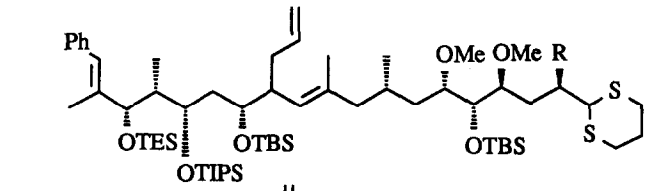
Scheme 4



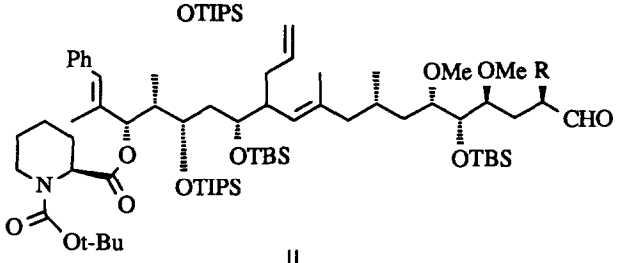
a) O_3/ PPh_3; b) (4R,5S)-3-benzyloxyacetyl-4-methyl-5-phenyl-2-oxazolidinone[23], TEA, Bu_2BOTf;
c) $AlMe_3$/ HN(OMe)Me. HCl; d) i-Pr_2NEt/ ClCH(Me)OEt; e) 20 or bromobut-3-ene/ Mg; f) $NMe_4BH(OAc)_3$
g) NaH/ MeI; h) Na/ NH_3; i) PivCl/ Py; j) $CH_2(CH_2SH)_2$/ BF_3.OEt; k) TBSOTf/ 2,6-lutidine; l) $LiAlH_4$

The key alcohols **28** and **28a** were prepared in eight steps from the hydroxyketones **24** and **24a** with similar yields in each series. Anti reduction[20] of the hydroxy ketones **24** and **24a** led to minor quantities of the syn-diols. These could not be separated until the C_{13}- and C_{15}-hydroxyls had been methylated and the C_{14}- and C_{18}-benzyl protecting groups had been removed. The benzyl groups were removed by sodium/

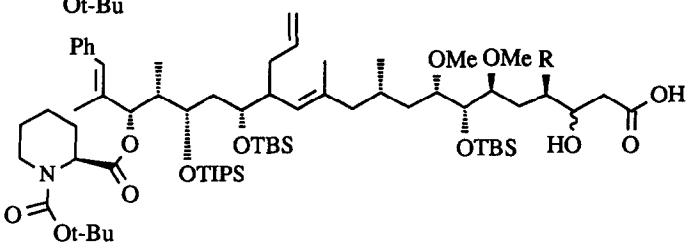
ammonia reduction affording, after chromatography, the homogeneous diols **25** and **25a**. Following protection of the primary hydroxyls as the pivaloates **26** and **26a**, ozonolysis afforded the lactols **27** and **27a** which were converted to their respective dithianes by boron trifluoride/ propanedithiol treatment. The sequence was completed by silyl protection and reductive removal of the pivaloate to yield the primary alcohols **28** and **28a**. The known compound **28a** gave spectral data in accordance with the literature[4].



32 R=H **32a** R=Me



33 R=H **33a** R= Me



34 R=H **34a** R=Me

The alcohols **28** and **28a** were converted to phosphine oxides **29** and **31**. These steps followed known protocols[4]. The Wittig coupling of aldehyde **15** and phosphine oxide **31** proceeded as expected. Much to our surprise, we were unable to prepare the C_{11}-desmethyl olefin **32** from aldehyde **15** and the phosphine oxide **29**. Treatment of phosphine oxide **29** with *n*-butyl lithium and TMEDA followed by the aldehyde **15** resulted in the formation of products resulting from metallation of the phosphine oxide phenyl groups, a product resulting from elimination of C_{22}-OTBS from the C_{20}-C_{28} fragment **15**, and only small quantities of the required phosphine oxide-aldehyde adducts[4]. The olefin **32** was eventually prepared by a Julia type coupling between the sulphone **30** and aldehyde **15**. This method and the preparation of the sulphone **31** were directly analogous to those described by Danishefsky in his studies[21] on the synthesis of FK506. Fortunately the geometric isomers could be separated from each other by chromatography and the desired *E*-isomer **32** was obtained in 33% yield. The aldehydes **33** and **33a** were prepared from dithianes **32** and **32a** in three steps by the published procedures[4]. The boron mediated aldol condensations between these aldehydes and (4*R*,5*S*)-3-acetyl-4-methyl-5-phenyl-2-oxazolidinone provided aldol products which were hydrolysed to the hydroxy acids **34** and **34a** directly. Yields over the two steps were above 80%. Although other methods were used to introduce the acetic acid moiety C_8-C_9, the boron mediated addition of the acetyloxazolidinone gave the most consistent results. These acids **34** and **34a** were converted to the macrolactams **4** (45%) and **4a** (58%) using the Merck three step protocol[4].

Experimental

Melting points were determined on a a Kofler hot stage apparatus and are uncorrected. Optical rotations were measured on an Optical Activity Ltd. AA-100 digital polarimeter. Infrared spectra were taken on a Pye-Unicam SP3-200s spectrophotometer and peaks are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform on a Bruker WP 200SY spectrometer. Selected signals are reported. Assignments were made by analysis of COSY and ^1H-^{13}C correlation experiments, and these are reported with reference to the relevant carbon atoms in the FK506 molecule with the accepted numbering. Elemental analyses were performed by CHN Analysis Ltd. Mass spectra were obtained on VG Micromass ZAB 1F or VG Autospec spectrometers.

Flash chromatography was performed on Sorbsil C60-H (Rhône-Poulenc). Moisture sensitive reactions were carried out in oven-dried apparatus under an atmosphere of dry nitrogen. Solvents were dried before use: tetrahydrofuran was distilled from potassium; toluene and diethyl ether were stored with sodium; methanol, methylene chloride, dimethylformamide, and acetonitrile were stored over molecular sieves. Reagents were used as supplied or purified where necessary[24].

28-Phenyl-FK506 3. The silyl ether **8** (38 mg, 41.8 μM) was divided into five batches, dissolved in acetonitrile (3 ml) and treated with 48% hydrofluoric acid (1 drop per batch) for an average time of 3 h. The mixtures were worked up and purified in the usual way to give a total of 7 mg (23%) of a glass: $[\alpha]^{23}_D$ -67.6° (c, 0.068, CH_2Cl_2); IR ($CHCl_3$) 3520 (OH), 2940, 1740 (ester C=O), 1725 (C=O), 1710 (C=O), 1643 (amide C=O), 1455, 1385, 1290, 1190, 1170, 1140, 1100, 1035, 995, 915; ^1H NMR δ 7.28 (m, Ar), 6.37 (s, H_{28}), 5.72 (m, H_{21b}), 5.53 (d, H_{26}), 5.03 ($C_{21c}H_2$, H_{20}), 4.71 (H_2), 4.45 (d, H_6), 4.28 (OH). 3.99 (H_{24}), 3.70 (H_{14}), 3.59 (H_{15}), 3.39 (OCH_3), 3.38 (H_{13}, H_{21}), 3.30 (OCH_3), 3.15 (OH), 3.06 (H_6), 2.83 (H_{23}), 2.48 (H_{21a}), 2.18 (H_3, H_{18}, H_{21a}), 2.15 (H_{12}), 2.10 (H_{23}), 2.03 (H_{25}), 1.95 (H_3, H_{18}), 1.87 ($C_{27a}H_3$), 1.76 (H_5), 1.62 ($C_{19a}H_3$), 1.58 (H_{16}), 1.46 (H_5, H_{12}), 1.08 (H_{16}), 0.97 ($C_{25a}H_3$); ^{13}C NMR δ 212.7 (C_{22}), 196.1 (C_9), 169.1 (C_1), 164.6 (C_8), 135.5 (C_{21b}), 116.7 (C_{21c}), 97.0 (C_{10}), 9.5 (C_{25a}). FAB HRMS (DTT/DTE + NaOAc) Calcd for $C_{43}H_{61}NO_{10}$.Na 774.4193, found 774.4292.

The Macrocycle 4. The hydroxy acid **34** was converted to the macrocycle **4** (45%) by the three step procedure described in the literature[4]. The compound **4** was a mixture of diastereomers at C_{10} and rotamers, the major signals in the spectra have been assigned. ^1H NMR δ 7.26 (m, Ar), 6.26 (H_{28}), 5.69 (m, H_{21b}), 5.47 (m, H_{26}), 5.35 (br, H_2), 4.93 (m, $C_{21c}H_2$, H_{20}), 4.56 (m, H_6), 4.22 (H_{10}), 4.02 (H_{24}), 3.86 (H_{14}), 3.46 (OCH_3), 3.31 (OCH_3), 3.18 (br, H_{13}, H_{15}, H_{22}), 3.10 (H_6), 2.46 (C_9H_2, $C_{21a}H_2$), 2.27 (H_{21}), 2.23 ($C_{18}H_2$), 2.06 (H_{23}), 1.98 (H_{17}), 1.92 ($C_{27a}H_3$); ^{13}C NMR δ 172.0 (C_1), 170.4 (C_8), 138.0 (C_{21b}), 131.8 (C_{28}), 129.8 (C_{20}), 115.1 (C_{21c}), 83.7 (C_{26}), 82.2 and 80.0 (C_{13} and C_{15}), 75.4 (C_{14}), 73.1 (C_{22}), 69.9 (C_{24}), 66.5 (C_{10}), 59.3 and 57.3 (OCH_3), 51.9 (C_2), 46.3 (C_{21}), 38.3 (C_{25}), 19.6 (C_{17a}), 16.3 (C_{19a}), 8.6 (C_{25a}).

The Macrocycle 4a. The hydroxy acid **34a** (298 mg) was converted to the macrocycle **4a** (158 mg, 58%) by the sequence described in the literature[4]. The epimers at C_{10} were separated and spectra are reported for a single compound. The compound existed as a mixture of rotamers and the signals for the major componant are reported. ^1H NMR δ 7.26 (5H, m, Ar), 6.66 (1H, s, H_{28}), 5.7 (1H, m, H_{21b}), 5.53 (1H, d, H_2), 5.25 (1H, d, H_{26}), 4.91 (2H, m, $C_{21c}H_2$), 4.74 (1H, d, H_{20}), 4.22 (1H, m, H_{10}), 4.05 (1H, m, H_{24}), 3.83 (1H, d, H_6), 3.74 (1H, d, $C_{14}H$), 3.54 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.18 (1H, m, H_{15}), 3.03 (2H, m, H_{13}, H_{22}), 2.89 (1H, m, H_6), 2.60 ($C_{21a}H_2$), 1.90 ($C_{27a}H_3$), 1.59 ($C_{19a}H_3$), 0.85 (C_{25a}), 0.77 (C_{17a}). ^{13}C NMR δ 170.6 (C_1), 169.4 (C_8), 137.7 (C_{21b}), 131.5 (C_{28}), 129.3 (C_{20}), 129.2, 127.9, 126.6 (Ar), 115.3 (C_{21c}), 84.6 (C_{13}), 83.5 (C_{26}), 80.3 (C_{15}), 75.9 (C_{14}), 72.8 (C_{10}), 72.6 (C_{22}), 69.1 (C_{24}), 60.3 (CH_3), 57.7 (OCH_3), 51.4 (C_2), 47.2 (C_{21}), 41.0 (C_{23}), 38.9, 38.8 (C_{11}, C_{25}), 36.5 (C_{21a}), 34.7 (C_9), 25.7 (C_{17}), 20.3 (C_{17a}), 19.2 (C_{11a}), 16.0 (C_{19a}), 14.1 (C_{27a}), 7.9 (C_{25a}).

The Dione 5. Dry pyridine (58 μl, 0.72 mmol) followed by Dess-Martin periodinane[22] (152 mg, 0.36 mmol) was added to a stirred solution of the hydroxyamide **4** (79 mg, 0.071 mmol) in methylene chloride (1 ml). The mixture was stirred at room temperature for 1.25 h, then cooled to 0°C and treated with saturated

aqueous sodium sulphite (5 ml). The mixture was stirred at 0°C for 5 min, diluted with water, and extracted three times with methylene chloride. The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10-20% ethyl acetate/ hexane) to give 47 mg (59%) of a yellow oil. The product existed as a mixture of rotamers and hydrates, data are given for the major compound. ^1H NMR δ 7.28 (Ar), 6.66 (H_{28}), 5.64 (H_{21b}), 5.44 (H_{26}), 5.24 (H_2), 4.95 ($C_{21c}H_2$), 4.85 (H_{20}), 4.41 (H_6), 4.03 (H_{24}), 3.75 (H_{14}), 3.46 (H_6, OCH_3), 3.28 (OCH_3), 3.18 (H_{15}, H_{22}), 3.15 (H_{13}), 2.94 (H_{11}), 2.52 (H_{21a}), 2.31 (H_{21}), 2.10 (H_{23}), 1.97 (H_{25}), 1.91 (H_{12}, $C_{27}H_3$), 1.87 (H_{17}), 1.72 (H_{21a}), 1.69 (H_{23}), 1.67 (H_3), 1.58 (H_{12}, $C_{19a}H_3$), 1.43 (H_5), 1.35 (H_{16}), 0.95 ($C_{25a}H_3$), 0.80 ($C_{17a}H_3$); ^{13}C NMR δ 197.7 (C_{10}), 186.0 (C_9), 168.9 (C_1), 165.0 (C_8).

The Dione 5a was prepared (78%) from hydroxyamide **4a** using the method described above. The compound existed as a mixture of rotamers and hydrates therefore only major peaks are assigned. ^1H NMR δ 7.27 (5H, m, Ar), 6.64 (1H, s, H_{28}), 5.71 (1H, m, H_{21b}), 5.45 (1H, d, H_{26}), 5.28 (1H, br, H_2), 4.93 (3H, m, $C_{21c}H_2$, H_{20}), 4.04 (1H, m, H_{24}), 3.74 (1H, m, H_{14}), 3.33 (OCH_3), 1.88 (s, $C_{27a}H_3$), 1.61 ($C_{19a}H_3$), 1.19 (d, $C_{11a}H_3$); ^{13}C NMR δ 199.2 (C_{10}), 185.8 (C_9), 168.8 and 165.6 (C_1 and C_8).

The Hemiacetal 6. The compound was prepared (55%) by direct analogy to the literature[4]. Data are provided for the major rotamer. ^1H NMR δ 7.26 (m, Ar), 6.31 (s, H_{28}), 5.76 (H_{21b}), 5.67 (H_{26}), 5.21 (OH), 4.96 ($C_{21c}H_2$), 4.93 (H_{20}), 4.56 (H_2), 4.44 (H_6), 3.94 (H_{24}), 3.90 (H_{14}), 3.87 (H_{22}), 3.60 (H_{13}), 3.46 (H_{15}), 3.38 (OCH_3), 3.31 (OCH_3), 3.03 (H_6), 2.61 (H_{21}), 2.26 (H_3), 2.15 (H_{25}), 2.11 (H_{18}, H_{21a}), 2.03 (H_3), 1.88 ($C_{27a}H_3$), 1.77 (H_{16}, H_{23}), 1.71 (H_5, H_{18}), 1.60 (H_{12}, $C_{19a}H_3$), 1.52 (H_{17}), 1.43 (H_5), 1.40 (H_4), 1.36 (H_{23}), 1.30 (H_{12}), 0.99 ($C_{17a}H_3$), 0.94 (H_{16}, $C_{25a}H_3$); ^{13}C NMR δ 197.3 (C_9), 169.1 (C_1), 165.4 (C_8), 116.0 (C_{21c}), 95.7 (C_{10}). FAB HRMS (mNBA + NaOAc) calcd for $C_{42}H_{61}NO_{10}$.Na 762.4193, found 762.4227.

The Hemiacetal 6a. The compound was prepared by direct analogy to the literature[3]. Data are given for the major rotamer. ^1H NMR δ 7.27 (5H, m, Ar), 6.31 (1H, s, H_{28}), 5.79 (1H, d, H_{26}), 5.74 (1H, m, H_{21b}), 5.5 (1H, s, OH), 4.97 (3H, m, $C_{21c}H_2$, H_{20}), 4.43 (2H, m, H_2, H_6), 3.97 (H_{24}), 3.89 (H_{22}), 3.73 (H_{14}), 3.37 (OCH_3), 3.31 (OCH_3), 2.97 (H_6), 2.70 (H_{21}), 2.46 (H_{11}), 2.30 (H_{25}), 2.24 (H_3), 2.14 (H_{18}), 2.07 ($C_{12}H_2$), 2.01 ($C_{21a}H_2$), 1.88 ($C_{27a}H_3$), 1.84 (H_{16}), 1.79 (H_{23}), 1.74 ($C_{18}H_2$), 1.68 (H_5), 1.61 ($C_{19a}H_3$), 1.47 (H_5 and H_{12}), 1.41 (H_{23}), 1.35 (H_{17}), 1.03 ($C_{17a}H_3$), 0.96 ($C_{16}H$), 0.90 ($C_{11a}H_3$ and $C_{25a}H_3$); ^{13}C NMR δ 199.6 (C_9), 169.3 (C_1), 165.9 (C_8), 137.3, 136.8, 136.3, 136.1 (C_{21b}, C_{27}, C_{29}, C_{19}), 128.9 (Ar), 128.1 (Ar), 126.4, 125.4, 124.0 (Ar, C_{28}, C_{20}), 115.9 (C_{21c}), 98.8 (C_{10}), 77.2, 75.2, 74.7, 74.1, 73.8, 73.6 (C_{26}, C_{15}, C_{13}, C_{14}, C_{22}, C_{24}), 57.1 (OCH_3), 56.0 (OCH_3), 49.0 (C_{21}), 43.13 (C_{18}), 38.9, 37.8 (C_6, C_{23}), 34.9, 37.85 (C_{12}, C_{25}), 32.9, 32.45 (C_{21a}, C_{11}), 27.7, 26.8, 26.1, 24.2 (C_{17}, C_{16}, C_3, C_4, C_5), 21.7 (C_{17a}), 16.1, (C_{19a}, C_{11a}), 15.6 (C_{27a}), 10.5 (C_{25}); FAB HRMS (DTT/DTE + NaOAc) Calcd for $C_{43}H_{63}NO_{10}$.Na 776.4350, found 776.4284.

The Silylether 7. 2,6-Lutidine (44 mg, 0.41 mmol) followed by triisopropylsilyl triflate (63 mg, 0.21 mmol) was added to a stirred solution of the alcohol **6a** (31 mg, 0.041 mmol) in methylene chloride (1.5 ml) at -70°C. The mixture was kept at -70°C for 1.25 h and at 0°C for 2 h. The mixture was quenched with water then extracted three times with ethyl acetate. The combined organic extracts were washed twice with copper sulphate solution, once with water, then dried ($MgSO_4$) and concentrated. The major product was purified by HPLC [Hichrom column (S5W-2871)-methylene chloride/ 4% ethyl acetate] to afford 38 mg (41%) of the desired product. ^1H NMR δ 7.26 (5H, m, Ar), 6.3 (1H, s, H_{28}), 5.74 (2H, m, H_{26},H_{21b}), 5.29 (1H, s, OH), 4.97 (3H, m, $C_{21c}H_2$, H_{20}), 4.42 (1H, brd, H_6), 4.32 (1H, br, H_2), 4.11 (H_{24}), 3.98 (1H, br, H_{22}), 3.37 (OCH_3, H_{13}), 3.35 (H_{15}), 3.29 (OCH_3), 3.0 (H_6), 2.74 (H_{21}), 2.53 (H_{11}), 2.23 (H_{25}, H_3), 2.1 ($C_{18}H_2$), 2.05 (H_{12}, $C_{21a}H_3$), 1.97 (H_{23}), 1.87 ($C_{27a}H_3$), 1.85 (H_{16}), 1.76 (H_{18}), 1.72 (H_5), 1.61 ($C_{19a}H_3$), 1.57 (H_{23}), 1.49 (H_5), 1.44 (H_{12}), 1.38 (H_{17}), 1.18, 1.05 ($C_{17a}H_3$), 0.93 ($C_{25a}H_3$), 0.89 (H_{16}), 0.88 ($C_{11a}H_3$); ^{13}C NMR δ 198.2 (C_9), 168.8 (C_1), 166.2 (C_8), 137.2, 136.8, 136.1 (C_{21b}, C_{27}, C_{29}, C_{19}), 128.9, 128.1, 126.5 (Ar), 124.9, 124.6 (C_{28}, C_{20}), 115.8 (C_{21c}), 98.9 (C_{10}), 77.2, 74.5, 74.2, 73.7, 72.7 (C_{26}, C_{15}, C_{13}, C_{14}, C_{22}, C_{24}), 57.0 (OCH_3), 56.4 (C_2), 56.3 (OCH_3), 49.5 (C_{21}), 43.15, 39.7, 38.7, 38.3, 36.0, 34.7, 33.0, 32.3, 29.7, 27.8, 26.8, 24.22, 21.9, 21.6, 18.4 , 18.3, 16.13, 15.5, 14.1, 13.4, 13.1, 11.1.

The Ketone 8. Dry pyridine (13 mg, 167 μmol) and Dess-Martin periodinane[22] (36 mg, 81 μmol)

were added to a stirred solution of the alcohol **7** (19 mg, 21 μmol) in methylene chloride (1 ml). The mixture was kept at room temperature for 2 h then cooled to 0°C. The mixture was treated with saturated aqueous sodium sulphite then sodium bicarbonate and stirred at 0°C for 5 min before being diluted with water. The mixture was extracted twice with ethyl acetate and the combined extracts were washed with aqueous sodium bicarbonate, copper sulphate, and sodium chloride in turn. The extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (methylene chloride/ 1-5% acetone) to afford 16 mg (84%) of a glass. Data are provided for the major rotamer. ^1H NMR δ 7.29 (m, Ar), 6.55 (H_{28}), 5.67 (H_{21b}), 5.45 (H_{26}), 4.98 ($C_{21c}H_2$), 4.80 (H_{20}), 4.44 (H_2), 4.36 (H_6), 4.32 (H_{24}), 4.21 (OH), 3.84 (H_{14}), 3.58 (H_{15}), 3.52 (H_{21}), 3.44 (H_{13}), 3.39 (OCH_3), 3.31 (OCH_3), 3.28 (H_6), 2.99 (H_{23}), 2.42 (H_{21a}), 2.31 (H_{11}, H_{23}), 2.21 (H_{18}, H_{21a}), 2.15 (H_{12}), 1.90 (H_3), 1.78 (H_{18}, H_{25}), 1.73 (H_{17}), 1.69 ($C_{19a}H_3$, $C_{27a}H_3$), 1.48 (H_{12}), 1.44 (H_5), 1.38 (H_{16}), 1.03, 0.96 ($C_{11a}H_3$, $C_{25a}H_3$), 0.84 ($C_{17a}H_3$); ^{13}C NMR δ 208.9 (C_{22}), 196.7 (C_9), 169.2 (C_1), 164.6 (C_8), 97.7 (C_{10}).

The Thioester 9. Boron tribromide (1M in CH_2Cl_2) (79 ml, 79 mmol) was added to a stirred suspension of (1*R*,2*R*)-(+)-*N*,*N'*-bis-4-nitrobenzenesulphonyl-1,2-diphenylethylenediamine (23.0 g, 39.48 mmol) in 1,2-dichloroethane (300 ml). The mixture was stirred at 55°C under nitrogen for 3.5 h then evaporated to dryness. The residue was treated with 1,2-dichloroethane (120 ml) then evaporated to dryness. This procedure was repeated twice, before the residue was kept under high vacuum for 20 min. The resulting solid could then be kept overnight under nitrogen.

The brown solid was dissolved in methylene chloride (400 ml) and cooled to -78°C. A solution of the thiophenyl propionate[9] (6.56 g, 39.48 mmol) in methylene chloride (15 ml) was added dropwise, followed by a solution of ethyldiisopropylamine (17.2 ml, 12.75 g, 98.69 mmol). The mixture was stirred at -78°C for 5 min then at -25°C for 3h. The mixture was cooled to -78°C and a solution of α-methylcinnamaldehyde (6.06 g, 41.45 mmol) in methylene chloride (70 ml) was added dropwise during 40 min, while maintaining the temperature. After stirring at -78°C for 110 min, the cold mixture was quenched by the dropwise addition of methanol (37 ml). While still cold, the mixture was poured into pH7 phosphate buffer (370 ml), 30% hydrogen peroxide (37 ml) was added and the mixture stirred for 20 min. The mixture was diluted with methylene chloride (400 ml), and water (1 l). The bisnitrobenzenesulphonyl-1,2-diphenylethylenediamine precipitate was filtered off and the phases separated. The aqueous phase was extracted with methylene chloride and the combined organic phases were washed twice with water then dried ($MgSO_4$). The solution was filtered and concentrated to a small volume whereupon more of the chiral auxiliary crystallised. This was removed before the filtrate was concentrated and the residue chromatographed (5% ethyl acetate/ hexane) to give an oil which crystallised from ethyl acetate/ light petroleum (40-60°) as 6.65 g (54%) of colourless needles: m.p. 77-78°C; $[\alpha]^{21}_D$ +71.9° (c 0.112, $CHCl_3$); IR (KBr disc) 3340 (OH), 1685 (C=O), 1435, 1320, 1050, 1030, 900, 855, 840, 695, 685; ^1H NMR δ 7.43-7.19 (10H, m, Ar), 6.63 (1H, s, H_{28}), 4.54 (1H, t, *J*= 4.5, H_{26}), 3.08 (1H, m, H_{25}), 2.52 (1H, d, *J*=3.0, OH), 1.91 (3H, d, *J*= 0.62, $C_{27a}H_3$), 1.33 (3H, d, *J*=6.9, $C_{25a}H_3$); ^{13}C NMR δ 201.6 (C_{24}), 137.4 (C_{27}), 136.2, 134.5, 129.6, 129.2, 129.0, 128.1, 127.2 (Ar), 127.1 (C_{28}), 126.6 (Ar), 77.0 (C_{26}), 51.1 (C_{25}), 14.7 (C_{27a}), 11.9 (C_{25a}). Anal. Calcd for $C_{19}H_{20}O_2S$: C, 73.04; H, 6.45; S, 10.26. Found: C, 73.08, H, 6.47, S, 10.21.

The ketoester 10. A 1.4M solution of n-butyl lithium (63 ml, 88 mmol) was added to a stirred mixture of diisopropylamine (8.9 g, 88 mmol) and tetrahydrofuran (200 ml) at -70°C under nitrogen. The mixture was kept at -50°C for 45 min then allowed to reach -10°C. The mixture was cooled to -70°C whereupon t-butyl acetate (10.22 g, 88 mmol) was added. The resulting mixture was stirred at -40°C for 50 min.

Trimethylsilyl chloride (3.13 ml, 24.65 mmol) was added to a stirred mixture of the thiophenyl ester **9** (5.5 g, 17.6 mmol), triethylamine (7.13 g, 70.4 mmol), N,N-dimethylaminopyridine (55 mg), and tetrahydrofuran (85 ml). This mixture was stirred under nitrogen for 90 min then added to the pre-prepared lithio t-butyl acetate solution at -70°C. The mixture was stirred at -40°C for 30 min then allowed to warm to 0°C before being quenched by the dropwise adddition of saturated aqueous ammonium chloride. The mixture was diluted with water and extracted twice with ether (150 ml). The combined extracts were washed twice with water (200 ml), dried ($MgSO_4$) and concentrated. The oily residue was dissolved in acetone (120

ml) and treated with 1M hydrochloric acid (13 ml). The mixture was stirred at room temperature for 30 min, then the most part of the acetone was removed under reduced pressure. The residue was partitioned between ether (300 ml) and water, (200 ml). The organic layer was washed twice with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed (5-20% ethyl acetate/ hexane) to give 5.22 g (93%) of a colourless oil which was used in the next stage. The chromatography was repeated to give an analytically pure sample: $[\alpha]^{21}_D$ -33.2° (c 0.49, CH_2Cl_2); IR (film) 3475 (OH), 2980, 1725 (ester C=O), 1700 (ketone C=O), 1375, 1315, 1280, 1215, 1145, 750, 700; ^{1}H NMR δ 7.30 (5H, m, Ar), 6.63 (1H, s, H_{28}), 4.56 (1H, brs, d on D_2O shake, *J*= 3.5, H_{26}), 3.50 (2H, s, C_{21} H_2), 2.97 (1H, m, H_{25}), 2.82 (1H, brs, OH), 1.83 (3H, s, C_{27a} H_3), 1.47 (9H, s, t-Bu), 1.16 (3H, d, *J*= 9.9, C_{25a} H_3); ^{13}C NMR δ 207.3 (C_{24}), 166.4 (C_{22}), 137.5 (C_{27}), 136.4, 128.9, 128.1, 126.4 (Ar), 126.1 (C_{28}), 82.2 (t-Bu), 75.2 (C_{26}), 49.5 (C_{23}), 48.9 (C_{25}), 27.9 (t-Bu), 15.2 (C_{27a}), 9.5 (C_{25a}). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.60; H, 8.23.

The Diol 11. A 1M solution of triethylborane (18.9 ml, 18.9 mmol) was added dropwise to a stirred mixture of dry methanol (25.16 g, 785 mmol) and tetrahydrofuran (50 ml) under nitrogen at room temperature. The mixture was stirred for 1h at room temperature then cooled to -78°C before a solution of the hydroxyketone **10** (5 g, 15.7 mmol) in tetrahydrofuran (10 ml) was added. The mixture was kept at -78°C for 1h, then sodium borohydride (0.71 g, 18.8 mmol) was added in one batch. The mixture was kept at -78°C for 2h then quenched by the dropwise addition of saturated aqueous ammonium chloride. When the effervescence had stopped a 30% aqueous solution of hydrogen peroxide (10 ml) was added, followed by water (50 ml). The mixture was extracted twice with ethyl acetate (250 ml). The combined extracts were washed with water (200 ml), then brine (200 ml), dried ($MgSO_4$) and concentrated. The residue was dissolved in methanol then concentrated under vacuum. This process was repeated six times. The residue was chromatographed (10-30% ethyl acetate/ hexane) to give 4.25 g (84%) of a colourless oil: $[\alpha]^{21}_D$ -49.7° (c 0.574, CH_2Cl_2); IR (film) 3385 (OH), 2935, 1685 (ester C=O), 1355, 1225, 1125, 1085, 725, 670; ^{1}H NMR δ 7.18-7.37 (Ar), 6.65 (1H, s, H_{28}), 4.41 (1H, brs, H_{26}), 4.33 (1H, m, dt on D_2O shake, *J*= 15.0, 2.2, H_{24}), 3.65 (1H, d, *J*= 2.1, OH), 3.33 (1H, d, *J*= 1.5, OH), 2.58 (1H, dd, *J*= 16.4, 9.5, H_{23}), 2.35 (1H, dd, *J*= 16.4, 3.4, H_{23}), 1.75 (4H, m, C_{27a} H_3, H_{25}), 1.47 (9H, s, t-Bu), 0.92 (3H, d, *J*= 7.1, C_{25a} H_3); ^{13}C NMR δ 172.5 (C_{22}), 137.9 (C_{27}), 137.8, 129.0, 128.0, 126.2 (Ar), 124.8 (C_{28}), 81.5 (t-Bu), 78.8 (C_{26}), 72.3 (C_{24}), 40.6 (C_{23}), 39.2 (C_{25}), 28.1 (t-Bu), 15.6 (C_{27a}), 5.2 (C_{25a}). Anal. Calcd for $C_{19}H_{28}O_4.14H_20$: C, 70.65; H, 8.83. Found: C, 70.65; H, 8.72.

The Hydroxylactone 12. 2M sodium hydroxide (43.6 ml, 87.3 mmol) was added to a stirred solution of the ester **11** (9.32 g, 29.1 mmol) in methanol (160 ml). The mixture was stirred at room temperature for 4.5 h before the most part of the methanol was removed under vacuum. The residue was diluted with water (50 ml), cooled to 10°C, and acidified with 2M sulphuric acid. The mixture was extracted three times with ether (100 ml). The combined extracts were washed with water (100 ml), dried ($MgSO_4$), and concentrated. The residue was heated with benzene (150 ml) under Dean and Stark conditions for 6.5h, then the mixture was concentrated. The resulting oil was chromatographed (1-5% methanol/ methylene chloride) in order to remove polar material and then crystallised from ethyl acetate/ hexane to give 5.50 g (77%) of colourless needles: mp. 98-99°C; $[\alpha]^{21}_D$ -114.8° (c 0.26, $CHCl_3$); IR (KBr disc) 3460 (OH), 1710 (C=O), 1440, 1400, 1330, 1270, 1240, 1205, 1120, 1165, 1130, 1060, 990, 980; ^{1}H NMR δ 7.19-7.38 (5H, m, Ar), 6.71 (1H, s, H_{28}), 5.28 (1H, s, H_{26}), 4.20 (1H, m, H_{24}), 2.89 (1H, dd, *J*= 18.0, *J*= 5.1, H_{23}), 2.64 (1H, dd, *J*= 18.0, *J*= 2.8, H_{23}), 2.53 (1H, brs, OH), 2.26 (1H, m, H_{25}), 1.84 (3H, s, C_{27a} H_3), 0.89 (3H, d *J*= 7.3, C_{25a} H_3); ^{13}C NMR δ 170.1 (C_{22}), 137.2 (Ar), 132.5 (C_{27}), 129.0, 128.1, 126.6 (Ar), 125.9 (C_{28}), 80.0 (C_{26}) 68.4 (C_{24}), 36.5 (C_{25}), 33.6 (C_{23}), 15.4 (C_{27a}), 10.3 (C_{25a}). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.15, H, 7.50.

The lactone 13. A stirred mixture of the hydroxylactone **12** (3.8 g, 15.43 mmol), imidazole (4.2 g, 61.71 mmol), triisopropylsilyl chloride (5.95 g, 30.86 mmol), and dry DMF (8.5 ml) was kept at 60°C for 6.5 h. The mixture was cooled, poured into water, then extracted twice with ethyl acetate. The combined extracts were washed twice with water, dried ($MgSO_4$) and concentrated. The oily residue was purified by flash chromatography using pure hexane as eluant to remove non polar impurities. The eluant polarity was then increased by the addition of up to 10% ethyl acetate. This treatment gave 5.61 g (90%) of a colourless

oil: $[\alpha]^{22}_D$ -73.53° (c 0.102, $CHCl_3$); IR ($CHCl_3$) 2950, 2870, 1725(C=O), 1460, 1240, 1088, 1070, 880; ^1H NMR δ 7.29 (5H, m, Ar), 6.71 (1H, s, H_{28}), 5.32 (1H, s, H_{26}), 4.20 (1H, m, H_{24}), 2.82 (1H, dd, H_{23}), 2.62 (1H, dd, H_{23}), 2.22 (1H, m, H_{25}), 1.83 (3H, s, C_{27a} H_3), 1.09 (21H, s), 0.87 (3H, d, *J*= 7.3, C_{25a} H_3); ^{13}C NMR δ 170.0 (C_{22}), 137.3, 129.0, 128.1, 126.5 (Ar), 132.7 (C_{27}), 125.7 (C_{28}), 79.9 (C_{26}), 69.2 (C_{24}), 37.0 (C_{25}), 36.2 (C_{23}), 18.0, 15.4(C_{27a}), 12.1, 10.2 (C_{25a}). Anal. Calcd for $C_{24}H_{38}O_3Si$: C, 71.59; H, 9.51. Found: C 71.57, H 9.70.

The Amide 14. A solution of trimethylaluminium (2M in toluene) (10.1 ml, 20.2 mmol) was added to a stirred mixture of N,O-dimethyl hydroxylamine hydrochloride (1.97 g, 20.18 mmol) and dry toluene (50 ml) at 0°C. The mixture was kept at room temperature for 1 h then cooled to -5°C before a solution of the lactone **13** (3.87 g, 9.61 mmol) in dry toluene (10 ml) was added dropwise. The mixture was kept for 4 h at -5°C then cold 1M tartaric acid (80 ml) was added in portions. After 50 min stirring, the mixture was extracted three times with ethyl acetate. The combined extracts were washed twice with water, dried ($MgSO_4$) and concentrated. The oily residue was purified by flash chromatography (5-25% ethyl acetate/ hexane) to give 4.11 g (92%) of colourless oil: $[\alpha]^{21}_D$ -12.5° (c 0.100, $CHCl_3$); IR ($CHCl_3$) 2970, 2945, 2870, 1647 (C=O), 1460, 1388, 1245, 1205, 1095, 1035, 995, 882; ^1H NMR δ 7.29 (5H, m, Ar), 6.66 (1H, s, H_{28}), 4.62 (1H, m, H_{26}), 4.37(1H, m, H_{24}), 3.71 (3H, s, OCH_3), 3.19 (3H, s, NCH_3), 2.96 (1H , dd, H_{23}), 2.69 (1H, dd, H_{23}), 1.96 (1H, m, H_{25}), 1.82 (3H, s, C_{27a} H_3), 1.11 (21H, s), 0.97 (3H, d, *J*= 7.0, C_{25a} H_3); ^{13}C NMR δ 171.9 (C_{22}), 138.1 and 138.4 (Ar, C_{27}), 129.0, 127.9, 126.0 (Ar), 125.1 (C_{28}), 78.2 (C_{26}), 73.1 (C_{24}), 61.2 (OCH_3), 40.4 (C_{25}), 37.8 (C_{23}), 32.0 (NCH_3), 18.2, 18.09 , 15.3 (C_{27a}), 13.0, 6.5 (C_{25a}). Anal Calcd for $C_{26}H_{45}NO_4Si$: C 67.34, H 9.78, N 3.02. Found: H 67.09, H 9.68, N 2.92; HRMS calcd for $C_{26}H_{45}NO_4Si$: 463.3118, found 463.3098.

The Aldehyde 15. The amide **14** was converted to the key aldehyde **15** using the seven step process reported by the Merck group in their synthesis of the analogous region of FK506[4]. These steps included (i) protection of the C_{26}-OH as the triethylsilyl ether (83%) {mp 37-38°C; $[\alpha]^{21}_D$ +54.3° (c 1.104, $CHCl_3$); Anal. Calcd for $C_{32}H_{59}NO_4Si_2$: C, 66.50; H, 10.29; N, 2.42. Found: C, 66.72, H, 10.21, N, 2.33.}; (ii) reduction of the amide to an aldehyde (92%) {$[\alpha]^{21}_D$ +21.7° (c 1, CH_2Cl_2); IR (film) 1730 (C=O); ^1H NMR δ 9.79 (1H, t, *J*= 2.0, H_{22}); ^{13}C NMR δ 201.1 (C_{22})}; (iii) aldol condensation (86%) {$[\alpha]^{21}_D$ +62.8° (c 0.109, $CHCl_3$). Anal. Calcd for $C_{45}H_{71}NO_6Si_2$: C, 69.45; H, 9.20; N, 1.80. Found: C, 69.14; H, 9.15; N, 1.84.}; (iv) removal of the chiral auxiliary by hydrolysis to give a hydroxyacid (94%) {$[\alpha]^{22}_D$ +52.9° (c 0.69, $CHCl_3$)}; (v) conversion to an hydroxy amide (92%) {$[\alpha]^{21}_D$ +56.48° (c 0.525, $CHCl_3$)}; (vi) protection of the C_{22}-OH as a t-butyldimethylsilyl ether(93%) {$[\alpha]^{21}_D$ +14.24° (c 0.516, $CHCl_3$). Anal Calcd for $C_{43}H_{81}NO_5Si_3$: C, 66.52; H, 10.52; N, 1.80. Found: C. 66.61; H, 10.45; N, 1.76.}; (vii) reduction of the amide to aldehyde **15** (98%) . The aldehyde **15** was purified by flash chromatography (2-4% ethyl acetate/ hexane) to give a colourless oil which was used directly in the next step. ($[\alpha]^{21}_D$ +48.6° (c 0.56, $CHCl_3$); IR ($CHCl_3$) 2950, 2865, 1720 (C=O), 1460, 1350, 1250, 1075, 1035, 920, 880, 830; ^1H NMR δ 9.86 (1H, s, H_{20}), 7.29 (5H, m, Ar), 6.47 (1H, s, H_{28}), 5.73 (1H, m, H_{21b}), 5.10 (2H, m, $C_{21c}H_2$), 4.30 (1H, d, J=8.6, H_{26}), 3.96 (1H, m, H_{24}), 3.94 (1H, m, H_{22}), 2.54 (1H, m, H_{21}, and 1H, m, H_{21a}), 2.04 (1H, m, H_{21a}), 1.95 (1H, m, H_{23}), 1.85 (3H, d, J=1.2, $C_{27a}H_3$), 1.76 (1H, m, H_{25}), 1.67 (1H, m, H_{23}), 1.07 (21H), 1.00 (3H, d, $C_{25a}H_3$), 0.95 (9H), 0.82 (9H), 0.62 (6H), 0.05 (3H), -0.06 (3H); ^{13}C NMR δ 204.0 (C_{20}), 137.6, 139.3 (Ar, C_{27}), 135.5 (C_{21b}), 129.0 (Ar), 128.0, 128.0 (Ar, C_{28}), 126.3 (Ar), 117.1 (C_{21c}), 80.3 (C_{26}), 69.8 (C_{24}), 69.6 (C_{22}), 57.4 (C_{21}), 40.8 (C_{25}), 40.0 (C_{23}), 28.9 (C_{21a}), 25.7, 18.5, 18.5, 18.0, 13.4 (C_{27a}), 9.1 (C_{25a}), 7.0, 5.0, -4.2.

The Sultam 18. A solution of the sultam **17**[15] (12.2 g, 45.3 mmol) in THF (100 ml) was added dropwise during 15 min to a stirred mixture of a 1M solution of lithium hexamethyldisilazide (46.2 ml, 46.2 mmol) in THF and HMPA (24.1 ml), while keeping the temperature below -60°C. The mixture was stirred for 40 min at -70°C then a solution of methyl iodide (19.7 g, 138.6 mmol) in THF (50 ml) was added dropwise while maintaining the temperature. The resulting clear yellow solution was kept at -60°C for 50 min, then quenched by the addition of saturated aqueous ammonium chloride (400 ml). The mixture was extracted with a 1:1 mixture of ethylacetate/ hexane (2x400 ml). The combined organic extracts were

washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated to leave an oily residue. The residue was crystallised from methanol and the mother liquors were purified by flash chromatography (methyl chloride), to give a total of 10.36 g (81%) of colourless crystals; mp 168-170°C; $[\alpha]^{21}_D$ +104.8° (c 0.53, CH_2Cl_2); IR (pellet) 2960, 2880, 1680, 1450, 1410, 1380, 1350, 1320, 1310, 1280, 1270, 1235, 1220, 1160, 1130, 1110, 1060, 1040, 915, 780, 765; ^{1}H NMR δ 5.93 (1H, m, H_{10}), 5.18 (2H, m, $C_{10a}H_2$), 3.88 (1H, t), 3.8 (1H, m, H_{11}), 3.48 (2H, 2d), 2.1(2H, m), 1.89 (3H, m), 1.37 (2H, m), 1.33 (3H, d *J*= 7, $C_{11a}H_3$), 1.16 (3H, s), 0.98 (3H, s); Anal. Calcd. for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71; S, 10.78; Found: C, 60.71: H, 7.78; N, 4.66; S, 10.84.

Alcohol 19[13]. A solution of the sultam **18** (20.69 g, 73.1 mmol) in dry ether (550 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (5.55 g, 146 mmol) in dry ether (100 ml) at 0°C . The mixture was kept at room temperature for 1 h then cooled to 0°C. Saturated aqueous sodium sulphate solution was added dropwise until a granular suspension formed. The mixture was stirred for 1h at room temperature then filtered. The solids were washed with ether and the combined filtrate and washings were concentrated by fractional distillation. Purification was completed by Kügelröhr distillation to give 4.48 g (77%) of the alcohol; $[\alpha]^{22}_D$ -30.2 (c 0.8 CH_2Cl_2).

The Benzyl Ether 21. A solution of (2*R*,4*E*)-2-methyl-4-hexen-1-ol[18] (25.5 g, 22.4 mmol) in ether (50 ml) was added dropwise to a stirred mixture of 80% sodium hydride (10.1 g, 33.7 mmol) which had been washed with hexane, DMF (255 ml), and benzyl bromide (40.26 g, 23.5 mmol), under nitrogen at 5°C. The mixture was kept at room temperature for 2 h then quenched by the dropwise addition of water (10 ml) under ice cooling. The mixture was diluted with a mixture of light petroleum (40-60°) and ether (1:1) (500 ml), then washed with water (3x500 ml). Each aqueous wash was reextracted with the petrol/ ether mixture (500ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10-50% CH_2Cl_2 in hexane) to give 45.5 g (99%) of an oil: $[\alpha]_D^{21}$ -0.43° (c 7.9, $CHCl_3$); IR (film) 2960, 2920, 2850, 1455, 1298, 965, 734, 697; ^{1}H NMR δ 7.3 (5H, m, Ar), 5.4 (2H, m), 4.50 (2H, s, Bn), 3.27 (2H, m, H_{18}), 2.14 (1H, m, H_{17}), 1.86 (2H, m, H_{16}), 1.63 (3H, d, $C_{17}H_3$), 0.92 (3H, d); Anal. Calc. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.24; H, 9.80.

The Hydroxyamide 22. The olefin **21** was converted to the amide **22** using a similar procedure to the one described by the Merck group[4] in their synthesis of the analogous region of FK506. The steps included (i) ozonolysis of the olefin **22** to give an aldehyde (73%); (ii) aldol addition of the aldehyde and the appropriate oxazolidinone[23] (75%) {$[\alpha]^{21}_D$ +34.4° (c 0.750, CH_2Cl_2). Anal. Calcd for $C_{31}H_{35}NO_6$: C, 71.93; H, 6.82; N, 2.71. Found C, 72.29; H, 6.82; N, 2.53.}; (iii) removal of the oxazolidinone under Weinreb conditions. This hydroxy amide **22** was used in the next step without purification .

The Ethoxyethylether 23. A solution of chloroethylethylether (0.17 g, 0.94 mmol) in dry methylene chloride (1 ml) was added dropwise *via* a syringe to a stirred mixture of crude amide **22** (0.44 g), dry methylene chloride (3 ml), and diisopropylethylamine (0.41 g, 3.2 mmol) under nitrogen at -10°C. The mixture was kept for 1 h then diluted with light petroleum (60-80°) (20 ml). The mixture was washed with 1M hydrochloric acid (3x10 ml), water (2x10 ml), and saturated sodium bicarbonate (10 ml). The organic layer was finally washed with water (2x10 ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (20% ethyl acetate/ methylene chloride) to give 0.25 g of an inseparable mixture of diastereomers: IR (film) 2950, 2910, 2850, 1655 (C=0), 1440, 1365, 1090, 1040, 1015, 980, 725, 690; Anal. Calcd for $C_{27}H_{39}NO_6$: C, 68.47; H, 8.30; N, 2.96. Found: C, 68.18; H, 8.18; N, 2.98.

The Hydroxyketone 24. Dibromoethane (1.09 g, 5.8 mmol) was added to a mixture of magnesium (6.7 g, 0.276 mol), one crystal of iodine, and THF (250 ml) under nitrogen at room temperature. Once the reaction had started 4-bromo-1-butene (25.1 g, 0.186 mol) was added dropwise taking care to keep the temperature below 50°C. The mixture was kept at 50°C for 1 h, then the solution was transferred to a dry 1 litre flask with more THF (50 ml). The mixture was cooled to 10°C then a solution of the ethoxyethylether **22** (22.0 g, 46.5 mmol) in THF (150 ml) was added dropwise during 10 min. The mixture was stirred at room temerature for 2 h then 4M hydrochloric acid (100 ml, 0.4 mol) was added slowly. The mixture was stirred vigorously for a further 2 h then the phases were separated. The aqueous phase was extracted with

ether (2x100 ml). The combined organic phases were washed with water (200 ml), saturated sodium bicarbonate (200 ml), and saturated sodium chloride (200 ml), then dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (ethyl acetate/ hexane 1:9) to give 16.6 g (90%) of a colourless oil: $[\alpha]^{21}_D$ +27.5° (c 2.0, CH_2Cl_2); IR (film) 3480, 2965, 2935, 2875, 1712 (C=O), 1455, 1365, 1095, 1030, 917, 740; ^{1}H NMR δ 7.3 (10H, *m*, Ar), 5.7 (1H, *m*, H_{10}), 5.0 (2H, *m*, $C_{10a}H_2$), 4.66, 4.44 (2H, dd *J*= 11.6, Bn), 4.48 (2H, s, Bn), 3.99 (1H, m, H_{15}), 3.70 (1H, d *J*= 3.6, H_{14}), 3.32 (2H, m, $C_{18}H_2$), 2.68 (2H, t *J*= 7.6, $C_{12}H_2$), 2.55 (1H, br, OH), 2.31 (2H, m, $C_{11}H_2$), 1.96 (1H, m, H_{17}), 1.52 (2H, m, $C_{16}H_2$), 0.95 (3H, d *J*= 6.9, C_{17a}); ^{13}C NMR δ 211.9 (C_{13}), 138.2 (Ar), 137.2 (C_{10}), 137.0 (Ar), 128.5, 128.3, 128.2, 128.1, 127.5, (Ar), 115.2 (C_{10a}), 87.1 (C_{14}), 75.2 (C_{18}), 73.5 (Bn), 73.1 (Bn), 70.4 (C_{15}), 38.6 (C_{12}), 38.0 (C_{16}), 30.2 (C_{17}), 26.9 (C_{11}), 17.8 (C_{17a}). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.72; H, 8.13. Found: C, 75.33; H, 8.21.

The Hydroxyketone 24a. The bromide **20** (6.05 g, 40.6 mmol), followed by 1,2-dibromoethane (6.2 g, 32.98 mmol) was added to a stirred mixture of crushed magnesium (3.21 g, 132 mmol) and THF (94 ml) under nitrogen, taking care to keep the temperature below 40°C. The mixture was kept at 40°C for 1h then the solution was transferred to a dry flask with more THF (50 ml). The mixture was cooled to 5°C then a solution of the amide **23** (7.81 g, 16.49 mmol) in THF (70 ml) was added while maintaining the temperature. The mixture was allowed to reach room temperature, kept for 0.5 h, then 2M hydrochloric acid (60 ml) was added and the mixture stirred vigorously for 1.5 h. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3x150 ml). The combined organic extracts were washed with saturated sodium bicarbonate (150 ml), then saturated sodium chloride solution (2x150 ml). The extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10-20% ethyl acetate/ hexane) to give 5.98 g (88%) of a colourless oil: $[\alpha]^{25}_D$ +27.2° (c 2.0, CH_2Cl_2); IR (film) 3470, 2960, 2930,2870, 1710 (C=O), 1455, 1365, 1095, 915, 740, 700; ^{1}H NMR δ 7.30 (10H, m, Ar), 5.70 (1H, m, H_{10}), 4.90 (2H, m, $C_{10a}H_2$), 4.67 and 4.47 (2H, dd *J*= 11.5, Bn), 4.47 (2H, s, Bn), 4.0 (1H, m, H_{15}), 3.69 (1H, d *J*= 3.6, H_{14}), 3.3 (2H, m, $C_{18}H_2$), 2.7 (1H, m, H_{11}), 2.66 (1H, d, *J*= 6.3, OH), 2.5 (2H, m, $C_{12}H_2$), 2.0 (1H, m, H_{17}), 1.5 (2H, m, $C_{16}H_2$), 0.98 (6H, 2t, $C_{11a}H_3$ and $C_{17a}H_3$); ^{13}C NMR δ 210.8 (C_{13}), 142.9 (C_{10}), 138.3, 137.1, 128.5, 128.3, 128.2, 128.1, 127.5 (Ar), 113.0 (C_{10a}), 87.2 (C_{14}), 75.3 (C_{18}), 73.3 (CH_2Ar), 73.1 (Bn), 70.2 (C_{15}), 45.9 (C_{12}), 38.0 (C_{16}), 32.2 (C_{11}), 30.3 (C_{17}), 19.8, 17.8 (C_{11a}, C_{17a}). Anal. Calcd. for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35. Found: C, 75.95; H, 8.33.

The Diol 25. A stirred mixture of tetramethylammonium triacetoxyborohydride (4.5 g, 17.1 mmol), dry acetonitrile (15 ml), and acetic acid (7.3 ml) was kept at room temperature under nitrogen for 10 min. The mixture was cooled to -40°C then a mixture of the hydroxyketone **24** (2 g, 5.04 mmol), acetonitrile (6 ml), and water (0.93 ml) was added *via* a syringe. The resulting mixture was stirred at -40°C for 20 h, then acetone (2.9 ml) was added . After stirring at 0°C for 15 min a 1M solution of sodium potassium tartrate (29 ml) was added and the resulting mixture was stirred at room temperature for 1 h. The mixture was neutralised by the cautious addition of saturated sodium bicarbonate (70 ml). The resulting clear solution was extracted with ethyl acetate (4x100 ml). The combined organic extracts were washed with saturated sodium bicarbonate (200 ml), dried ($MgSO_4$), concentrated and chromatographed (10-30% ethyl acetate/ hexane) to afford 1.81 g (90%) of a mixture of diols (isomer at C_{13}) (91:9) as an oil which solidified on standing. NMR data are given for the major isomer: IR (film) 3310, 2940, 2920, 2880, 1448, 1098, 1082, 1044, 1023, 743, 692; ^{1}H NMR δ 7.30 (10H, m, Ar), 5.81 (1H, m, H_{10}), 5.07 (2H, m, $C_{10a}H_2$), 4.68, 4.57 (2H, dd *J*= 11.5, Bn), 4.50 (2H, s, Bn), 4.03 (1H, m, H_{15}), 3.90 (1H, m, H_{13}), 3.36 (2H, m, $C_{18}H_2$), 3.18 (1H, m, H_{14}), 2.88 (2H, bs, 2OH), 2.32-1.95 (3H, m, $C_{11}H_2$, H_{17}), 1.60 (4H, m, $C_{12}H_2$, $C_{16}H_2$), 0.98 (3H, d *J*= 6.7, $C_{17a}H_3$); ^{13}C NMR δ 138.4 (C_{10}), 138.0, 128.4, 128.0, 127.8, 127.7 (Ar), 114.9 (C_{10a}), 81.9 (C_{14}), 75.5 (C_{18}), 73.2, 73.0 (Bn), 71.1 (C_{13}), 69.1 (C_{15}), 38.0 (C_{16}), 32.9 (C_{12}), 30.3, 30.2 (C_{11}, C_{17}), 17.7 (C_{17a}). Anal Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.30; H, 8.61.

The resulting diol (1.75 g, 4.39 mmol) was dissolved in dry THF (5 ml) and added to a stirred mixture of 80% sodium hydride suspension in oil (0.55 g, 18.3 mmol) and dry THF (13.5 ml) under nitrogen at room temperature. The mixture was kept at 40°C for 2.5 h, then cooled to room temperature before methyl iodide (2.4 g, 16.9 mmol) was added. The mixture was stirred overnight then quenched with saturated ammonium

chloride solution. The mixture was extracted with ether (3x50 ml). The combined organic extracts were washed with water (100 ml) and saturated sodium chloride (100 ml), dried ($MgSO_4$) and concentrated. The residue was chromatographed (5-50% ethyl acetate/ CH_2Cl_2) to yield 1.7g (91%) of a mixture of isomers. NMR data is given for the major isomer: IR (film), 2920, 1448, 1360, 1090, 1020, 905, 730, 692; ^{1}H NMR δ 7.3 (10H, m, Ar), 5.84 (1H, m, H_{10}), 4.97 (2H, m, $C_{10a}H_2$), 4.71 and 4.53 (2H, dd *J*= 11.4, Bn), 4.48 (2H, s, Bn), 3.51-3.21 (5H, m, H_{15}, $C_{18}H_2$, H_{14}, H_{13}), 3.39 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 2.27-1.28 (7H, m, $C_{11}H_2$, H_{17}, $C_{12}H_2$, $C_{16}H_2$), 0.96 (3H, d *J*= 6.7, $C_{17a}H_3$); ^{13}C NMR δ 138.8 (C_{10}), 128.3, 128.2, 127.9, 127.5, 127.4 (Ar), 114.6 (C_{10a}), 80.9, 80.85, 79.6 (C_{13}, C_{14}, C_{15}), 75.6 (C_{18}), 74.3 , 73.1 (Bn), 58.3 (OCH_3), 57.5 (OCH_3), 34.8 (C_{16}), 30.5 (C_{12}), 29.8, 29.7 (C_{11}, C_{17}), 18.1 (C_{17a}). MS calcd for $C_{27}H_{38}O_4$ (M+1) 427, found (FAB) 427.

The resulting dimethyl ether (15.8 g, 37.1 mmol) was dissolved in dry ether (350 ml). Liquid ammonia (200 ml) was added to the solution at -78°C. The stirred mixture was allowed to reflux while sodium (3.2 g) was added in small pieces until the blue colour persisted. The mixture was carefully quenched with solid ammonium chloride, then the ammonia was allowed to evaporate off. The mixture was filtered and the cake was washed well with dry ether. The filtrate was concentrated and the residue purified by flash chromatography (25% ethyl acetate/ hexane) to provide 7.96 g (87%) of a colourless oil: $[\alpha]_D^{21}$ +28.3° (c 2, CH_2Cl_2); IR (film) 3490, 2920, 2810, 1440, 1365, 1180, 1090, 1030, 985, 900; ^{1}H NMR δ 5.84 (1H, m, H_{10}), 5.03 (2H, m, $C_{10a}H_2$), 3.47 (4H, m, H_{14}, H_{15}, $C_{18}H_2$), 3.43 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 3.22 (1H, m, H_{13}), 2.93, 2.73 (2H, brs, brd, 2OH), 2.20 (2H, m, $C_{11}H_2$), 1.82-1.36 (5H, m, $C_{12}H_2$, H_{17}, $C_{16}H_2$), 0.94 (3H, d *J*= 6.5, $C_{17a}H_3$); ^{13}C NMR δ 138.7 (C_{10}), 114.5 (C_{10a}), 80.2, 78.1, 72.8 (C_{13}, C_{14}, C_{15}), 68.2 (C_{18}), 57.7, 57.4 (2OCH_3), 33.9 (C_{16}), 32.3 (C_{17}), 29.0, 28.8 (C_{11}, C_{12}), 17.28 (C_{17a}). Anal. Calcd for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64. Found: C, 63.07; H, 10.50.

Diol 25a This was prepared using the same three steps described for the synthesis of diol **25**.

Thus hydroxyketone **24a** was reduced[20] to a diol (92%) which was a mixture of epimers at C_{13}. NMR data are give for the major isomer: IR ($CHCl_3$) 3510 (br)(OH), 2970, 2940, 2880, 1455, 1405, 1355, 1095,1075, 1030, 920; ^{1}H NMR δ 7.3 (10H, m, Ar), 5.6 (1H, m, H_{10}), 5.0 (2H, m, $C_{10a}H_2$), 4.62 (2H, m, Bn), 4.5 (2H, s, Bn), 4.1 (2H, m, H_{13}, H_{15}), 3.42-3.13 (4H, m, $C_{18}H_2$, H_{14}, OH), 2.91 (1H, br s, OH), 2.5 (1H, m, H_{11}), 2.0 (1H, m, H_{17}), 1.70-1.26 (4H, m, $C_{12}H_2$, $C_{16}H_2$), 1.0 (6H, overlapping t, $C_{11a}H_3$ and $C_{17a}H_3$); ^{13}C NMR δ 143.7 (C_{10}), 138.3, 138.3, 128.3, 128.3, 128.0, 127.8, 127.6, 127.4 (Ar), 113.8 (C_{10a}), 82.5 (C_{14}), 75.5 (C_{18}), 73.2 , 73.1 (Bn), 69.6, 69.3 (C_{13}, C_{15}), 40.4 (C_{16}), 38.1 (C_{12}), 34.7 (C_{11}), 30.3 (C_{17}), 21.4, 17.8 (C_{11a} and C_{17a}). MS calcd for $C_{26}H_{36}O_4$ (M+1) 413, found (FAB) 413.

The diol was converted to a dimethyl ether (96%). This was also isolated as a mixture of isomers at C_{13}. NMR data are given for the major isomer: IR (film) 3960, 3920, 3870, 1450, 1090, 730, 690; ^{1}H NMR δ 7.3 (10H, m, Ar), 5.6 (1H, m, H_{10}), 5.0 (2H, m, $C_{10a}H_2$), 4.7 (2H, 2d, Bn), 4.49 (2H, s, Bn), 3.55, (1H, m, H_{14}), 3.39 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.30 (4H, m, H_{13}, H_{15}, $C_{18}H_2$), 2.4 (1H, m, H_{11}), 1.92-1.25 (m, H_{17}, $C_{12}H_2$, $C_{16}H_2$), 1.01 and 0.98 (6H, 2d, $C_{11a}H_3$, $C_{17a}H_3$); ^{13}C NMR δ 144.4 (C_{10}), 138.9, 138.7, 128.5, 128.3, 128.2, 127.9, 127.5, 127.4 (Ar), 113.8 (C_{10a}), 81.0 (C_{14}), 80.5, 80.3, 75.6 (C_{13}, C_{15}, C_{18}), 74.2 (Bn), 73.1 (Bn), 58.5 , 57.4 (OCH_3), 38.1 (C_{16}), 35.1 (C_{11}), 30.4, 21.7, 18.3 (C_{11a}, C_{17a}). Anal. Calcd. for $C_{28}H_{40}O_4$: C, 76.33; H, 9.15. Found: C, 76.49; H, 9.21.

The benzyl groups were removed (83%). The minor syn diastereoisomer was removed by chromatography to yield the desired diol **25a**. $[\alpha]^{25}_D$ +2.3° (c 1, CH_2Cl_2); IR (film) 3410, 2960, 2940, 2830, 1460, 1095, 1040, 995, 910; ^{1}H NMR δ 5.6 (1H, m, H_{10}), 5.0 (2H, m, $C_{10a}H_2$), 3.6 (1H, m, H_{14}), 3.46 (3H, s, OCH_3), 3.4 (3H, m, $C_{18}H_2$, H_{15}), 3.39 (3H, s, OCH_3), 3.2 (1H, m, H_{13}), 2.7 (1H, br, OH), 2.4 (2H, m, H_{11}, OH), 1.8 (2H, m, H_{17}), 1.72-1.34 (4H, m, $C_{12}H_2$, $C_{16}H_2$), 1.04 (3H, d *J*= 6.8, $C_{11a}H_3$), 0.93 (3H, d *J*= 6.7, $C_{17a}H_3$); ^{13}C NMR δ 144.2 (C_{10}), 113.8 (C_{10a}), 79.2, 78.9 (C_{13}, C_{15}), 73.2 (C_{14}), 68.2 (C_{18}), 57.8, 57.6 (2OCH_3), 37.5 (C_{12}), 34.8 (C_{11}), 34.0 (C_{16}), 32.3 (C_{17}), 21.7 (C_{11a}), 17.7 (C_{17a}). Anal. Calcd. for $C_{14}H_{28}O_4$: C, 64.58; H, 10.84. Found: C, 64.23; H, 10.77.

The Ester 26. Pivaloyl chloride (3.58 g, 29.7 mmol) was added *via* a syringe during 10 min to a stirred mixture of the diol **25** (7.7 g, 31.3 mmol) and pyridine (110 ml). The mixture was kept overnight at

room temperature then diluted with ethyl acetate (300 ml). The mixture was washed with water (3x100 ml) and the washings were extracted with ethyl acetate (100 ml). The combined organic phases were washed with saturated sodium chloride solution (200 ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-30% ethyl acetate/ methylene chloride) to give 9.85 g (95%) of a colourless oil: $[\alpha]^{21}_D$ +16.7° (c 2, CH_2Cl_2); IR (film) 3460, 2960, 2935, 1730 (C=O), 1477, 1456, 1394, 1280, 1155, 1100, 1030, 909; ^{1}H NMR δ 5.85 (1H, m, H_{10}), 5.02 (2H, m, $C_{10a}H_2$), 3.96 (2H, m, $C_{18}H_2$), 3.44 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.5-3.3 (2H, m, H_{14}, H_{15}), 3.2 (1H, m, H_{13}), 2.21-1.48 (7H, m, $C_{11}H_2$, $C_{12}H_2$, $C_{16}H_2$, H_{17}), 1.03 (9H, s, $C(CH_3)_3$), 1.0 (3H, d *J*= 6.7, $C_{17a}H_3$); ^{13}C NMR δ 178.5, 138.7 (C_{10}), 114.5 (C_{10a}), 80.3 (C_{13}), 77.4 (C_{15}), 73.2 (C_{14}), 68.9 (C_{18}), 58.1 and 57.4 ($2OCH_3$), 38.8, 34.0 (C_{16}), 29.3 (C_{17}), 29.0 (C_{12}), 28.7 (C_{11}), 27.2, 17.3 (C_{17a}). Anal. Calcd for $C_{18}H_{34}O_5$: C, 65.42; H, 10.37. Found: C, 65.43; H, 10.26.

Ester 26a was prepared by the same method as for ester **26**. $[\alpha]^{25}_D$ -4.21° (c 1, CH_2Cl_2); IR (film) 3470, 2950, 2925, 2820, 1730 (C=O), 1480, 1460, 1280, 1160, 1100; ^{1}H NMR δ 5.60 (1H, m, H_{10}), 5.0 (2H, m, $C_{10a}H_2$), 3.93 (2H, m, $C_{18}H_2$), 3.44 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.34 (2H, m, H_{13}, H_{15}), 3.18 (1H, m, H_{14}), 2.40 (1H, m, H_{11}), 2.30 (1H, brs, OH), 1.95 (1H, m, H_{17}), 1.67-1.32 (4H, m, $C_{12}H_2$, $C_{16}H_2$), 1.26 (9H, s, $C(CH_3)_3$), 1.15 (3H, d *J*= 6.8, $C_{11a}H_3$), 0.98 (3H, d *J*= 6.6, $C_{17a}H_3$); ^{13}C NMR δ 178.5, 144.3 (C_{10}), 113.7 (C_{10a}), 79.5 (C_{13}), 77.7, 73.9 (C_{14}, C_{15}), 68.8 (C_{18}), 57.8 and 57.7 (OCH_3), 38.0 (C_{16}), 34.8 (C_{11}), 33.8 (C_{12}), 29.3 (C_{17}), 27.2, 21.7 (C_{11a}), 17.4 (C_{17a}). Anal. Calcd. for $C_{19}H_{36}O_5$: C, 66.25; H, 10.53. Found: C, 66.11; H, 10.48.

The Lactol 27. Ozone was bubbled through a stirred solution of the ester **26** (1 g, 3.03 mmol) in dry methylene chloride (18 ml) at -78°C until a pale blue colour persisted. The solution was stirred for 5 min then triphenylphosphine was added (1.2 g, 4.58 mmol). The mixture was stirred at room temperature for 1 h then concentrated. The oily residue was purified by flash chromatography (25-75% ethyl acetate/ hexane) to give 0.89g (88%) of an oil which was used directly in the next stage.

The Lactol 27a. This was prepared (95%) by the same method as for lactol **27**.

The Dithiane 28. Borontrifluoride etherate (0.68 ml, 4.15 mmol) was added to a stirred mixture of the lactol **28** (0.86 g, 2.59 mmol), propanedithiol (0.41 ml, 3.51 mmol) and dry methylene chloride (18 ml) under nitrogen at 0°C. The mixture was kept at this temperature for 0.5 h then poured into a saturated solution of sodium bicarbonate (30 ml). The organic layer was separated and the aqueous layer was extracted with methylene chloride (50 ml). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography to give 1.03 g (94%) of an oil: $[\alpha]^{21}_D$ +18.1 (c 2, CH_2Cl_2); IR (film) 3460, 2920, 1720 (C=O), 1470, 1450, 1390, 1360, 1280, 1155, 1095, 1027; ^{1}H NMR δ 4.05 (1H, m, H_{10}), 4.0 (2H, m, $C_{18}H_2$), 3.5 (1H, m, H_{15}), 3.43 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.33 (1H, m, H_{14}), 3.25 (1H, m, H_{13}), 2.88 (4H, m, $2SCH_2$), 2.0-1.8 (7H, m, $C_{11}H_2$, $C_{12}H_2$, H_{17}, $SCH_2\underline{CH_2}$), 1.70 (2H, m, $C_{16}H_2$), 1.17 (9H, s, $C(CH_3)_3$), 0.97 (3H, d *J*= 6.7, $C_{17a}H_3$); ^{13}C NMR δ 178.5, 80.1, 77.3, 72.7 (C_{13},C_{14},C_{15},), 69.0 (C_{18}), 58.1 and 57.1 ($2OCH_3$), 47.6 (C_{10}), 34.0 (C_{16}), 30.2 ($S\underline{C}H_2$), 30.0, 29.2, 26.3 (C_{11},C_{12},C_{17}), 27.2 (C_{17a}). Anal Calcd for $C_{20}H_{38}O_5S_2$: C, 56.84; H, 9.06; S, 15.17. Found C, 56.64; H, 8.99; S, 14.80.

The above alcohol was protected as a t-butyldimethylsilyl ether (100%) by direct analogy to the literature[4]. $[\alpha]_D^{21}$ -26.1° (c 2.0, CH_2Cl_2); IR (film) 2930, 1724 (C=O), 1455, 1280, 1245, 1150, 1100, 830, 770; ^{1}H NMR δ 4.11-3.77 (4H, m, H_{10}, H_{14}, $C_{18}H_2$), 3.43 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.13 (2H, m, H_{13}, H_{15}), 2.84 (4H, m, $2SCH_2$), 2.08-1.40 (8H, $SCH_2\underline{CH_2}$, H_{17}, $C_{11}H_2$, $C_{12}H_2$, H_{16}), 1.32 (1H, m, H_{16}), 1.21 (9H, s, $OC(CH_3)_3$), 0.99 (3H, d *J*= 6.8, $C_{17a}H_3$), 0.9 (9H, s), 0.09 (6H, d); ^{13}C NMR δ 81.6 (C_{15}), 81.1 (C_{13}), 73.4 (C_{14}), 68.6 (C_{18}), 58.5 and 57.5 ($2OCH_3$), 47.6 (C_{10}), 38.9, 34.3 (C_{12}), 31.9 (C_{16}), 30.3 ($S\underline{C}H_2$), 30.1 (C_{17}), 27.5 (C_{11}), 27.3, 26.0, 18.3 ($SCH_2\underline{C}H_2$), 18.1 (C_{17a}), -4.4, -4.6. Anal Calcd for $C_{26}H_{52}O_5S_2Si$: C, 58.16; H, 9.76, S,11.94; Found: C, 58.17; H, 9.72; S, 11.79.

The primary alcohol protection was removed by direct analogy with the literature[4] to give the key dithiane **28** (94%) : $[\alpha]^{21}_D$ -19.3° (c 1.07, CH_2Cl_2); IR (film) 3440, 2930, 1460, 1240, 1090, 1040, 835, 775; ^{1}H NMR δ 4.00 (2H, m, H_{10}, H_{14}), 3.4 (2H,m, $C_{18}H_2$), 3.4 (3H, s, OCH_3), 3.3 (3H, 2s, OCH_3), 3.1 (3H, m, H_{13}, H_{15}, OH), 2.9 (4H, m, $S\underline{CH_2}$), 1.8 (9H, m, $C_{11}H_2$, $C_{12}H_2$, $C_{16}H_2$, H_{17}, $SCH_2\underline{CH_2}$), 0.9 (12H, m,

$SiC(CH_3)_3$, C_{17a}), 0.07 (6H, d, $SiCH_3$); ^{13}C NMR δ 81.3 (C_{13}, C_{15}), 72.7 (C_{14}), 67.9 (C_{18}), 58.1, 57.5 ($2OCH_3$), 47.6 (C_{10}), 34.4 (C_{16}), 32.6 (C_{17}), 31.9 (C_{11}), 30.4 ($S\underline{C}H_2$), 26.9 (C_{12}), 25.9, 18.2 ($SCH_2\underline{C}H_2$), 18.0 (C_{17a}), -4.6. Anal Calcd for $C_{21}H_{44}O_4S_2Si$: C, 55.71; H, 9.79; Found: C, 55.88; H, 9.82.

Dithiane 28a was prepared (63%) by the same method as for dithiane **28**. Spectral properties were in accordance with the literature[4].

The Dithianephosphine oxide 29 was prepared (81%) as a mixture of isomers from alcohol **28** by direct analogy to the literature[4]. NMR data are reported for the major isomer. IR ($CHCl_3$) 2960, 2940, 2860, 1190, 1120, 1110, 1080, 1040, 910, 840; ^1H NMR δ 7.78 (4H, m, Ar), 7.47 (6H, brs, Ar), 3.96 (1H, t, *J*= 6.7, H_{10}), 3.77 (1H, m, H_{14}), 3.34 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.08 (2H, m, H_{13}, H_{15}), 2.46 (1H, m, H_{19}), 2.03-1.61 (9H, m, H_{17}, $C_{11}H_2$, $C_{12}H_2$, $C_{18}H_2$), 1.28 (2H, m, $C_{16}H_2$), 1.13 (3H, dd *J*=7, J_{HP}=16.9, $C_{19}H_3$), 0.85 (3H, d, $C_{17a}H_3$).

The Dithianesulphone 30. Benzene sulphonylchloride (0.78 g, 4.4 mmol) was added dropwise to a stirred mixture of the alcohol **28** (1.0 g, 2.2 mmol) at 0°C during 2 min. The mixture was kept at 0°C for 1.5 h then at -20°C for 17 h. Ether (50 ml) and 1M hydrochloric acid (50 ml) were added. The organic phase was separated and the aqueous phase extracted with ether (50 ml). The combined organic extracts were washed with 1M hydrochloric acid (5x20 ml), water (30 ml), saturated sodium bicarbonate (30 ml), then dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (1:5 ethyl acetate/ hexane) to give 1.1 g (84.5%) of an oil which was used directly.

1.1M *n*-Butyl lithium in hexanes (2.8 ml, 3.1 mmol) was added to a stirred mixture of ethylphenylsulphone (0.53 g, 3.1 mmol) and THF (6 ml) at -70°C. The mixture was kept at this temperature for 30 min before a solution of the benzene sulphonate (0.93 g, 1.57 mmol) in THF (1.5 ml) was added slowly while maintaining the temperature. The mixture was kept at -70°C for 10 min, allowed to warm to 0°C during 10 min then kept at this temperature for 45 min. The mixture was quenched with saturated sodium bicarbonate (50 ml) then extracted with ethyl acetate (3x50 ml). The combined extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (1:5 ethyl acetate/ hexane) gave 0.76g (80%) of a mixture of the two sulphone isomers. NMR data are given for the major isomer. IR (film) 2950, 2920, 2890, 2850, 1300, 1245, 1140, 1080, 1025, 905, 830, 770, 730; ^1H NMR δ 7.89 (2H, m, Ar), 7.62 (3H, m, Ar), 4.02 (1H, t *J*= 7, H_{10}), 3.86 (1H, dd *J*= 2.3, 5.2, H_{14}), 3.35 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.14 (3H, m, H_{13}, H_{15}, H_{19}), 2.86 (4H, m), 2.09-1.27 (11H, m), 1.26 (3H, d *J*=7, $C_{19a}H_3$) 0.89 (9H, s), 0.83 (3H, d *J*=7, $C_{17a}H_3$), 0.07, 0.05 (6H, 2s). Anal. Calcd for $C_{29}H_{52}O_5S_3Si$: C, 57.57; H, 8.66; Found: C, 57.39; H, 8.50.

Olefin 32. The compound was prepared (33%) in three steps by the methodology described by Danishefsky[21]. The isomers were separated by flash chromatography using 3-10% mixtures of ethyl acetate in hexane as eluent. $[\alpha]^{20}_D$ -6.8° (c 0.61, $CHCl_3$); IR (film) 2950,2860, 1460, 1250, 1090, 1035, 1005, 880, 835, 775, 740; ^1H NMR δ 7.27 (5H, m, Ar), 6.45 (1H, s, H_{28}), 5.7 (1H, m, H_{21b}), 5.02-4.89 (3H, m, $C_{21c}H_2$, H_{20}), 4.27 (1H, d *J*=9, H_{26}), 4.0 (2H, m, H_{10}, H_{24}), 3.85 (1H, dd *J*= 3, 6, H_{14}), 3.50 (1H, m, H_{22}), 3.43 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.15 (2H, m, H_{13}, H_{15}), 2.84 (4H, m), 1.87 (s, $C_{27a}H_3$), 1.47 (s, $C_{19a}H_3$); ^{13}C NMR δ 139.7 (C_{27}), 137.8 (C_{21b}), 134.8 (C_{19}), 128.9, 128.0, 127.9, 126.2 (Ar, C_{28}, C_{20}), 115.3 (C_{21c}), 81.7, 81.1 (C_{13}, C_{15}), 80.9 (C_{26}), 73.5 (C_{14}), 73.0 (C_{22}), 70.3 (C_{24}), 58.5 (OCH_3), 57.4 (OCH_3), 47.7 (C_{10}), 47.3 (C_{18}), 44.7 (C_{21}), 41.3, 41.1 (d, C_{25}, C_{21a}), 38.8 (C_{16}), 35.5, 32.1, 30.4, 27.6, 27.4 (C_{17}), 26.0, 20.0 (C_{17a}), 18.6, 18.6, 18.3, 18.1, 16.6 (C_{19a}), 13.5, 13.4 (C_{27a}), 9.2 (C_{25a}), 7.0, 5.0, -3.6, -4.3, -4.4, -4.6. Anal. Calcd for $C_{64}H_{122}O_6S_2Si_4$: C, 66.03; H, 10.56; Found: C, 66.38; H, 10.40.

The Olefin 32a was prepared (28%) from aldehyde **15** and diphenylphosphine oxide **31** by direct analogy to the literature[4]. $[\alpha]^{20}_D$ -10.4° (c 1.17, $CHCl_3$); IR (film) 2900 (br), 1460, 1380, 1250, 1090 (br), 1035, 1005, 950, 910, 880, 835, 810, 775, 760; ^1H NMR δ 7.3 (5H, m, Ar), 6.45 (1H, s, H_{28}), 5.69 (1H, m, H_{21b}), 4.95 (3H, m, H_{20}, $C_{21c}H_2$), 4.27 (1H, d *J*=9, H_{26}), 4.18 (1H, d *J*=3.2, H_{10}), 3.97 (1H, m, H_{24}), 3.89 (1H, d *J*=6, H_{14}), 3.45 (s, OCH_3), 3.33 (s, OCH_3), 3.26 (m, H_{13}), 3.15 (m, H_{15}), 1.86 (s, $C_{27a}H_3$), 1.47 (s, $C_{19a}H_3$); ^{13}C NMR δ 139.6 (C_{27}), 137.7 (C_{21b}), 134.9 (C_{19}), 129.0 (Ar), 127.9 (Ar, C_{28}, C_{20}), 126.1 (Ar), 115.3 (C_{21c}), 81.1 (C_{15}), 80.8 (C_{26}), 80.3 (C_{13}), 73.5 (C_{14}), 72.9 (C_{22}), 70.2 (C_{24}), 58.9 (OCH_3), 57.2

(OCH_3), 54.7 (C_{10}), 47.0 (C_{18}), 44.6 (C_{21}), 41.2, 41.0 (C_{25}, C_{23}), 38.9 (C_{16}), 35.4 (C_{11}), 34.6 (C_{12}), 31.3, 30.8, 27.2 (C_{17}), 26.4, 25.9, 20.2 (C_{17a}), 18.6, 18.6, 18.2, 18.1, 16.6 (C_{19a}), 13.4, 13.3 (C_{27a}), 9.1 (C_{25a}), 6.9, 4.9, -3.6, -4.3, -4.6, -4.7. Anal. Calcd for $C_{65}H_{124}O_6S_2Si_4$: C, 66.26; H, 10.61; Found: C, 66.17; H, 10.80.

The Aldehyde 33 was prepared from compound **32** by the three step route[4] described by the Merck group in their synthesis of FK506. The route included (i) removal of the protection of C_{26}-OH to give an alcohol {$[\alpha]^{22}_D$ -28.1° (c 2.26, $CHCl_3$); (ii) esterification of C_{26}-OH {IR ($CHCl_3$) 1725 (C=O), 1675 (C=O); ^{13}C NMR δ 170.9 (C_1), 155.4 (NCO.); FAB MS $C_{69}H_{125}NO_9S_2Si_3$ (M+Na+H) 1283.}; (iii) removal of the dithiane protection to give the aldehyde **33** {^1H NMR δ 9.7 (1H, s, H_{10}), 7.3 (5H, m, Ar), 6.65 (1H, s, H_{28}), 5.73 (1H, m, H_{21b}), 5.55 (1H, m, H_{26}), 4.95 (3H, m, H_{20}, $C_{21c}H_2$), 4.77 (1H, m H_2), 3.92 (m, H_{14}), 3.55 (m, H_{22}), 3.45 (s, OCH_3), 3.28 (s, OCH_3), 3.18 (H_{15}), 3.15 (H_{13}), 2.50 (t, $C_{11}H_2$), 1.95 (s, $C_{27a}H_3$), 1.0 (d, $C_{25a}H_3$), 0.8 (d, $C_{17a}H_3$); ^{13}C NMR δ 202.4 (C_{10}), 170.9 (C_1), 40.8 (C_{11}). FAB MS (nNBA + NaOAc) $C_{66}H_{119}NO_{10}Si_3$ (M+Na+H) 1193.

The Aldehyde 33a was prepared in the same way as aldehyde **33**. Selected analytical data are given for the compound: ^1H NMR δ 9.95 (1H, s, H_{10}), 7.25 (5H, m, Ar), 6.64 (1H, s, H_{28}), 5.7 (1H, m, H_{21b}), 5.53 (1H, m , H_{26}), 4.95 (3H, m, $C_{20}H$, $C_{21c}H_2$), 4.75 (1H, br, H_2), 4.03 (2H, m, H_6, H_{24}), 3.90 (1H, d, H_{14}), 3.54 (1H, m, H_{22}), 3.41 (3H, s, OCH_3), 3.19 (H_{13}), 3.18 (s, OCH_3), 3.12 (H_{15}), 2.97 (H_6), 2.52 (m, H_{11}), 2.36 (H_{21}), 2.31 ($C_{21a}H_2$), 2.18 (H_{25}, $C_{18}H_2$), 2.02 (H_{12}), 1.94 (H_{23}), 1.91 ($C_{21a}H_2$, $C_{27a}H_3$), 1.71 (H_{23}, H_{17}), 1.69 (H_{12}), 1.60 (H_3), 1.50 (H_{18}), 1.41 ($C_{19a}H_3$), 1.33 (H_4), 1.28 (H_{16}), 1.09 ($C_{11a}H_3$), 0.99 (d *J*= 6.2, $C_{25a}H_3$), 0.81 (d, *J*= 6.3, $C_{17a}H_3$). ^{13}C NMR δ 203.9 (C_{10}), 170.9 (C_1), 155.5 (NCO.O), 137.5 (C_{21b}), 130.9 (C_{28}), 129.1 (Ar), 127.9 (Ar), 127.6 (C_{20}), 126.6 (Ar), 115.5 (C_{21c}), 82.9 (C_{26}), 81.0 (C_{15}), 79.6 (NCO.OC (CH_3)$_3$), 78.7 (C_{13}), 72.9 (C_{22}, C_{14}), 69.4 (C_{24}), 58.5 (OCH_3), 56.7 (OCH_3), 54.9 (C_2), 47.2 (C_{18}), 44.2 (C_{21}), 43.2 (C_{11}), 42.0, 41.0, 40.3, 38.7 (C_{16}, C_{25}), 35.9, 31.7, 28.3, 27.2 (C_{17}), 19.9 (C_{17a}), 16.6 (C_{19a}), 14.1 (C_{27a}), 9.5 (C_{25a}).

The Hydroxyacid 34. A 1M solution of dibutylboron triflate (470 µl; 0.47 mmol) in methylene chloride then triethylamine (107 µl, 0.77mmol) were added to a stirred mixture of (4*R*,5*S*)-3-acetyl-4-methyl-5-phenyl-2-oxazolidinone (108 mg, 0.49 mmol) and methylene chloride (2.5 ml) at -60°C. The mixture was kept at -50°C for 2 h before a solution of the aldehyde **33** (235 mg, 0.21 mmol) in methylene choride (2 ml) was added dropwise while maintaining the temperature. The mixture was kept at -30°C for 4.5 h, then at -25°C for 17 h. Phosphate buffer (pH 7) (4 ml) and methanol (0.5 ml) were added to the mixture at 0°C. While maintaining the temperature, the mixture was treated dropwise with 30% hydrogen peroxide (0.6 ml) then stirred for 30 min. The mixture was diluted with water and extracted three times with ethyl acetate. The combined extracts were washed twice with dilute sodium bicarbonate and once with brine. The extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10-30% ethyl acetate/hexane) to yield 248 mg (89%) of aldol product as a mixture of epimers at C_{10}.

A solution of the aldol product (245 mg, 0.176 mmol) in a mixture of THF (3 ml) and water (0.75 ml) was treated with 30% aqueous hydrogen peroxide (160 mg, 1.41 mmol) and THF (1 ml) followed by lithium hydroxide monohydrate (15 mg, 0.35 mmol) and water (0.4 ml) at 0°C. The mixture was stirred at 0°C for 2.75 h then treated with a saturated solution of sodium thiosulphate (4 ml) and stirred at 0°C for 1 h. The mixture was acidified to pH3 (dil. $NaHSO_4$), then extracted three times with light petroleum (40-60°). The combined extracts were washed twice with water, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (20-40% ethyl acetate/ hexane) to afford 1.95 mg (90%) of the hydroxy acid as a mixture of isomers: ^1H NMR δ 7.72 (5H, m, Ar), 6.64 (1H, s, H_{28}), 5.70 (1H, m, H_{21b}), 5.53 (1H, m, H_{26}), 4.95 (3H, m, $C_{21c}H_2$, H_{20}), 4.74 (1H, br, H_2), 4.06-3.91 (4H, m, H_{10}, H_{24}, H_{14}, H_6), 3.52 (1H, br, H_{22}), 3.42 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.20 (2H, br, H_{13}, H_{15}), 2.98 (1H, m, H_6), 2.52 (C_9H_2). FAB MS (mNBA + NaOAc) $C_{68}H_{123}NO_{12}Si_3$ (M+Na+H) 1253.

The Hydroxyacid 34a was prepared (83%) as a mixture of isomers by the same method as for hydroxy acid **34**. ^1H NMR δ 7.26 (5H, m, Ar), 6.64 (1H, s, H_{28}), 5.70 (1H, m, H_{21b}), 5.54 (1H, m, H_{26}), 4.95 (3H, m, $C_{21c}H_2$, H_{20}), 4.74 (1H, br, H_2), 4.07-3.92 (H_{10}, H_{14}, H_{24}), 3.75 (1H, br, H_6), 3.53 (1H, m, H_{22}), 3.43

(3H, s, OCH_3), 3.35 and 3.32 (3H, 2xs, OCH_3), 3.15 (2H, m, H_{13}, H_{15}), 2.97 (1H, m, H_6), 1.91 (s, $C_{27a}H_3$), 0.8 (d, $C_{17a}H_3$).

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