Total Synthesis of (+)-Macbecin I

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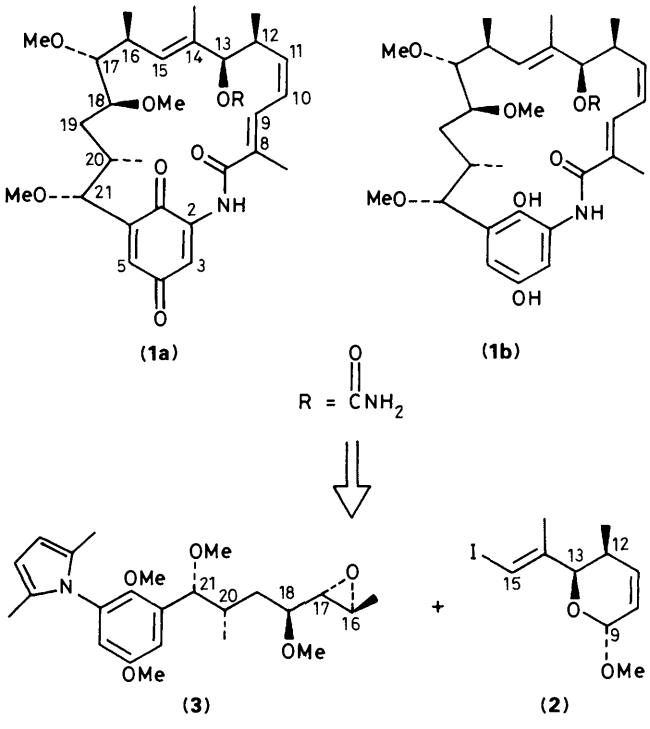
The first total enantiospecific synthesis of (+)-macbecin I has been performed in a convergent manner by coupling the epoxide (**3**) with a higher order cyanocuprate derived from the vinyl iodide (**46**). The required absolute stereochemistries at C(20)–C(21) and C(12)–C(13) were accessible by enantioselective aldol condensations while that at C(16)–C(17) was achieved by Sharpless epoxidation of a secondary (*E*)-allylic alcohol (**39**), efficiently prepared by reaction of the aldehyde (**37**) with $CrCl_2$–CH_3CHI_2. The remaining stereocentre at C-18 was introduced by an asymmetric hydroxylation of an enolate. Macrocyclization of the amino acid (**59**) to give the lactam (**60**) was successfully achieved by its reaction with either 2-mesitylenesulphonyl chloride or bis(2-oxo-3-oxazolidinyl)phosphinic chloride. Incorporation of the carbamate functionality was achieved by reaction of the parent hydroxy derivative with sodium cyanate and trifluoroacetic acid. The final oxidation to the quinone was accomplished with cerium(IV) ammonium nitrate.

Macbecin I (**1a**) and II (**1b**) are new antitumour antibiotics isolated from the fermentation broth of *Nocardia* sp (No C-14919).[1] Their structure and absolute configuration have been determined by Muroi *et al.*[2] in 1980 from partial degradation studies and *X*-ray crystallographic analysis and they were assigned to the ansamicin group of antibiotics which also includes geldanamycin,[3] herbimycin,[4] and ansamitocin.[5] They were shown to be macrocyclic (19 member) lactams, joining C-2 and C-6 of a benzoquinone and hydrobenzoquinone ring respectively, and contain seven chiral centres, an isolated trisubstituted double bond, a conjugated (*Z*,*E*)-diene system, and a carbamate function. Macbecin I can also be converted into macbecin II by reduction with sodium dithionite. Both compounds are moderately active against several gram-positive bacteria and fungi and they showed marked antitumour activity against leukemia P388, melanoma B16, and Ehrlich carcinoma *in vivo*.[6] Although some efforts have been directed towards the synthesis of the macbecins,[7] our work represents the first total asymmetric synthesis of (+)-macbecin.



Scheme 1.

Results and Discussion

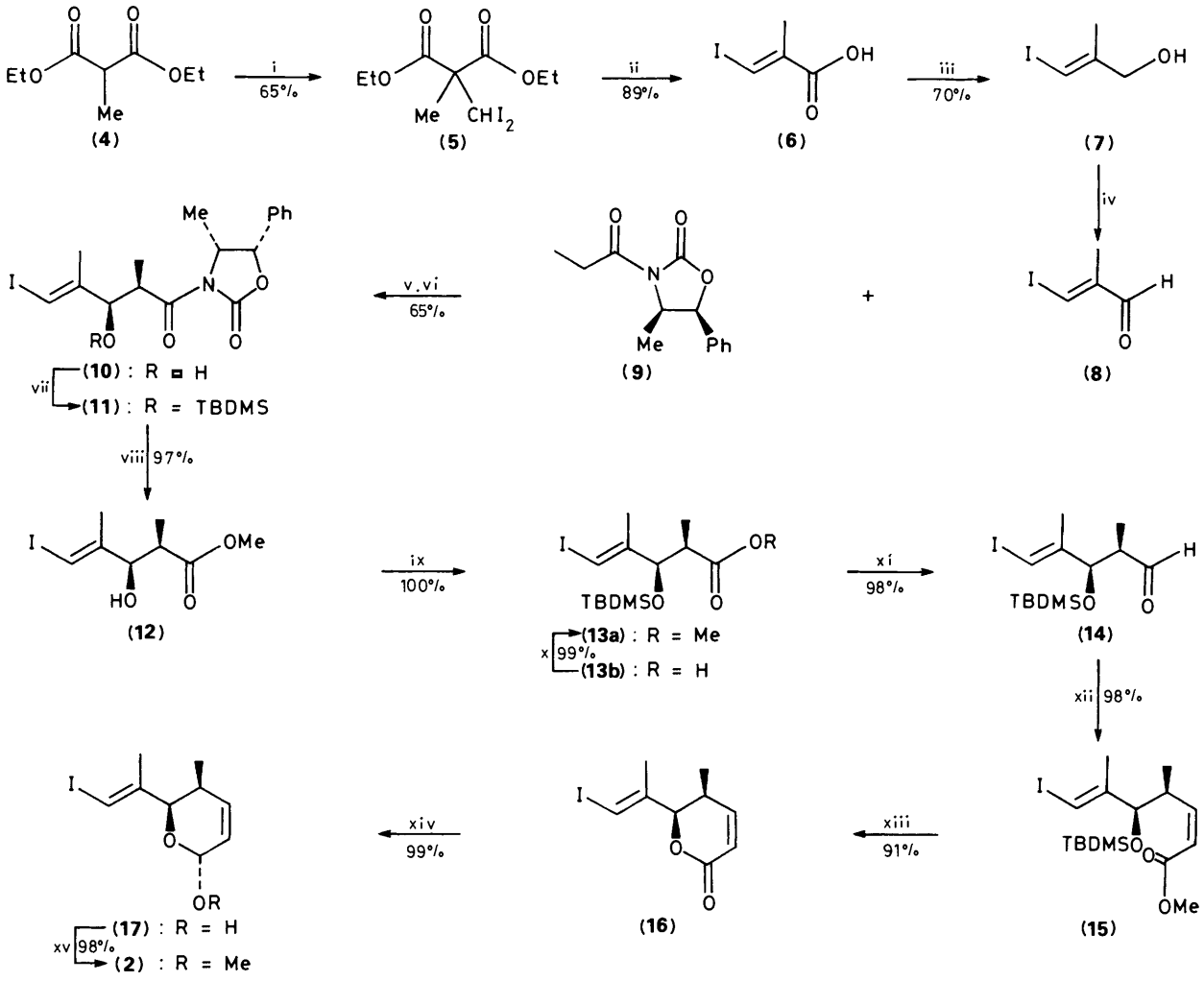
Retrosynthetic analysis of macbecin followed disconnection of the C(15)–C(16) bond which we considered could be formed in a stereoselective manner by reaction of the appropriate epoxide (**3**) with a higher order cyanocuprate derived from the vinyl iodide (**2**).[10] Preliminary reports of the synthesis of (+)-macbecin have appeared.[9,8]

Synthesis of the Vinyl Iodide (**2**).—It was apparent that the absolute stereochemistry required at C-13 and C-12 in (**2**) would be accessible by an enantioselective aldol condensation[11] while the (*Z*) C(10)–C(11) double bond could be prepared either by dehydration of a β-hydroxy-δ-lactone or *via* a (*Z*)-selective Horner–Emmons olefination.[12] The first of these two alternatives has been previously described[8] but the route suffered from a number of drawbacks on a large scale and a new route to the allylic alcohol (**7**) was first sought. Thus treatment of diethyl methylmalonate (**4**) with di-iodocarbene (CHI_3, NaH) in refluxing ether gave diethyl di-iodomethylmethylmalonate (**5**) in 65% yield; this was easily converted into (*E*)-3-iodo-2-methyl-2-propenoic acid (**6**) in 89% yield by reaction with KOH (3 equiv.) in refluxing ethanol–water.† Reduction of the acid with $LiAlH_4$ afforded the required allylic alcohol (**7**) in 70% yield.

Preparation of the *erythro* aldol compound (**10**) was performed as previously described.[8] Thus the allylic alcohol (**7**) was oxidized to the aldehyde (**8**) (MnO_2,CH_2Cl_2) which, after removal of the manganese salts and drying over 4A sieves, was used in the next step without further purification. Reaction of this aldehyde (**8**) with the (*Z*)-boron enolate (9-BBN-OTf,‡ $^iPr_2NEt$, CH_2Cl_2, 0 °C) of the chiral propionyl oxazolidinone

† This approach had been previously used to prepare (*E*)-3-chloro- and (*E*)-3-bromo-2-methylprop-2-enoic acids.[13]

‡ 9-BBN-OTf = 9-borabicyclo[3.3.1]nonyl trifluoromethanesulphonate, TBDMS-OTf = t-butyldimethylsilyl trifluoromethanesulphonate.



Scheme 2. *Reagents:* i, CHI_3 (1.1 equiv.), NaH (1.1 equiv.), refluxing Et_2O, 18 h; ii, KOH (3 equiv.), EtOH–water (3:1), reflux, 24 h; iii, $LiAlH_4$ (1 mol equiv.), THF, 5 to 25 °C, 6 h; iv, MnO_2, CH_2Cl_2; v, 9-BBN-OTf, $^iPr_2NEt$, CH_2Cl_2, 0 °C; vi, (**8**), −78 to 25 °C; vii, TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C; viii, NaOMe (1.1 equiv.), CH_2Cl_2–MeOH, −25 °C, 20 min; ix, TBDMS-OTf (1.5 equiv.), 2,6-lutidine (2.5 equiv.), CH_2Cl_2, 0 °C, 1.5 h; x, NaH (1.2 equiv.), MeI (5 equiv.), THF–DMF (3:1), 25 °C, 2.5 h; xi, DIBAL-H (1.6 equiv.), toluene, −80 °C, 1 h; xii, $(CF_3CH_2O)_2P(O)CH_2COOMe$ (1.15 equiv.), 18-crown-6 (2.5 equiv.), $KN(SiMe_3)_2$ (1.1 equiv.), THF, −80 °C, 1 h; xiii, AcOH–TFA–water (4:1:1), 85 °C, 2 h; xiv, DIBAL-H (1.6 equiv.), toluene, −80 °C, 1 h; xv, MeOH, PPTS (cat.), 25 °C, 16 h

(**9**), according to the methodology of Evans *et al.*,[14] gave a 65% isolated yield of the *erythro*-alcohol (**10**). Only traces of other isomers were detected in this reaction. Removal of the chiral auxiliary was efficiently performed at this stage by treatment of (**10**) with NaOMe in MeOH–CH_2Cl_2 at −23 °C to give (**12**) in 97% isolated yield. Protection of the hydroxy group as the TBDMS derivative using standard conditions (TBDMS-OTf,* 2,6-lutidine) afforded (**13a**) in quantitative yield. Reduction of the ester (**13a**) to the aldehyde (**14**) was cleanly performed (98% isolated yield) by reaction with DIBAL-H at −80 °C for 1 h. Although treatment of the silylated aldol compound (**11**) with NaOMe in MeOH–CH_2Cl_2 at −20 °C or DIBAL-H at −80 °C gave only products derived from attack on the oxazolidinone carbonyl, reaction of (**11**) with LiOOH (LiOH, H_2O_2, THF–H_2O)[15] at 5 °C for 2 h produced the required acid (**13b**) in 84% isolated yield. This could be converted into the methyl ester (**13a**) by reaction of its sodium salt (NaH) with MeI in THF–DMF (99% isolated yield).

In this approach to the synthesis of (**2**), formation of the (*Z*) C(10)–C(11) double bond was anticipated to be accessible by a (*Z*)-selective Horner–Emmons olefination. Thus, treatment of the aldehyde (**14**) with 1.1 equiv. of the potassium enolate of trimethyl phosphonoacetate [$KN(SiMe_3)_2$, THF, −80 °C, 15 min] in the presence of 18-crown-6 (5 equiv.) at −80 °C for 1 h afforded a 58% isolated yield of the (*Z*)-α,β-unsaturated ester (**15**) together with a 34% yield of the corresponding (*E*)-isomer. Fortunately, when the Still and Gennari[12] modification using bis(2,2,2-trifluoroethyl)methoxycarbonylmethylphosphonate [$(CF_3CH_2O)_2P(O)CH_2COOMe$] instead of trimethyl phosphonoacetate was followed, the required (*Z*)-olefin (**15**) was obtained in 98% isolated yield with no (*E*)-isomer being detected. Conversion of (**15**) into (**16**) required some investigation. Thus treatment of (**15**) with TBAF (2 equiv.) at 0 °C for 8 h in THF gave a complex mixture of compounds from which the lactone (**16**) was isolated in 7% yield. On the other hand, the silylated compound (**15**) was found to be stable in 80% AcOH–water after 2 h at room temperature and 2 h at 85 °C which represent the normal conditions for removing TBDMS groups. The transformation could successfully be achieved, however, by reaction of (**15**) with 4:1:1 AcOH–TFA–water at 85 °C for 2 h to give (**16**) in 91% isolated yield.

Reduction of the lactone (**16**) (DIBAL-H, −80 °C) followed by reaction of the corresponding lactol (**17**) with MeOH–PPTS (cat.) gave the methyl acetal (**2**) in 97% overall yield as a 20:1

* See footnote ‡ on p.1

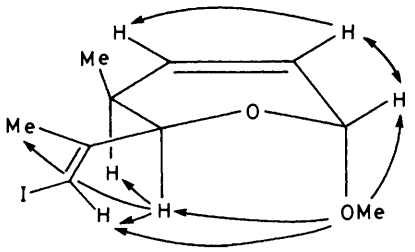
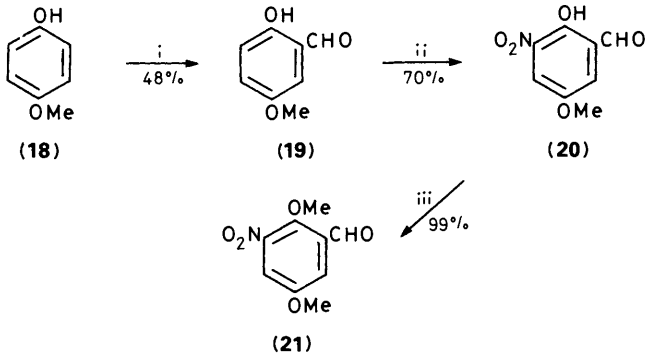
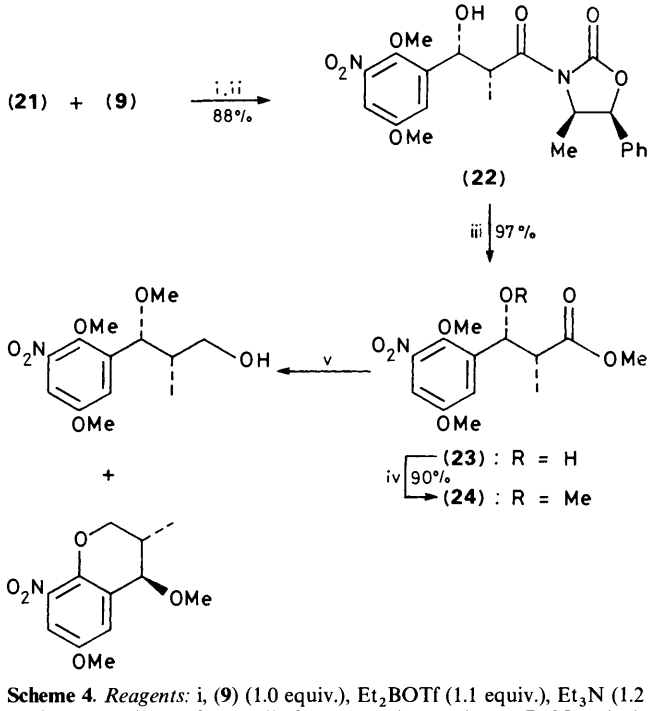


Figure. N.O.e. experiments on (**2**)



Scheme 3. *Reagents:* i, $CHCl_3$ (1.0 equiv.), 40% NaOH (16 equiv.), 70 °C, 7 h; ii, 70% HNO_3 (1.5 equiv.), AcOH, 10 °C, 3 h; iii, K_2CO_3 (2.0 equiv.), Me_2SO_4 (8.0 equiv.), DMF, 25 °C, 24 h



Scheme 4. *Reagents:* i, (**9**) (1.0 equiv.), Et_2BOTf (1.1 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, −2 °C, 1 h; ii, (**21**) (1.0 equiv.), 0.5 h at −78 °C and 1 h at 0 °C; iii, NaOMe (1.2 equiv.), MeOH–CH_2Cl_2, −17 °C, 15 min; iv, NaH (1.1 equiv.), Me_2SO_4 (2.0 equiv.), THF–DMF (3:1), −5 °C, 16 h; v, $LiBH_4$ (3.0 equiv.), THF, 25 °C

mixture of α and β anomers. The stereochemistry at the anomeric centre was proved by n.O.e. experiments (see Figure), where the n.O.e. observed between 9-OMe and 13-H and that of 13-H and 12-H are indicative of an α-disposition for the OMe group, as expected from the relative stabilities for α and β anomers based on the anomeric effect.[16] This route (Scheme 2) yielded (**2**) in 9 steps with an overall yield of 53% from (**7**).

Synthesis of Epoxide (**3**).—As in the case of vinyl iodide (**2**) formation of the required absolute stereochemistry at C-20 and C-21 in (**3**) was accessible by application of an enantioselective aldol condensation while the C(16)–C(17) epoxy unit could be formed by Sharpless epoxidation.[17] The remaining stereocentre at C-18 was planned to be formed *via* the recently developed asymmetric hydroxylations of enolates.[18]

The necessary 2,5-dimethoxy-3-nitrobenzaldehyde (**21**)[19] was prepared from *p*-methoxyphenol by Reimer–Teimann reaction followed by nitration and methylation (Scheme 3). Reaction of (**21**) with the preformed (*Z*)-boron enolate of the propionyl oxazolidinone (**9**) (Et_2B–OTf, Et_3N, CH_2Cl_2, −78 °C to 0 °C) gave the required *erythro* alcohol (**22**) in 88% isolated yield. The use of $^iPr_2NEt$ instead of Et_3N for generating the (*Z*)-boron enolate of (**9**) resulted, for this aldehyde, in a total loss of stereocontrol in the aldol condensation with all four possible isomers being formed.[20] The chiral auxiliary was then removed under the usual conditions (NaOMe, MeOH–CH_2Cl_2, −17 °C) and the β-hydroxy group methylated (NaH, Me_2SO_4, THF) to give the ester (**24**) in 88% overall yield (Scheme 4).

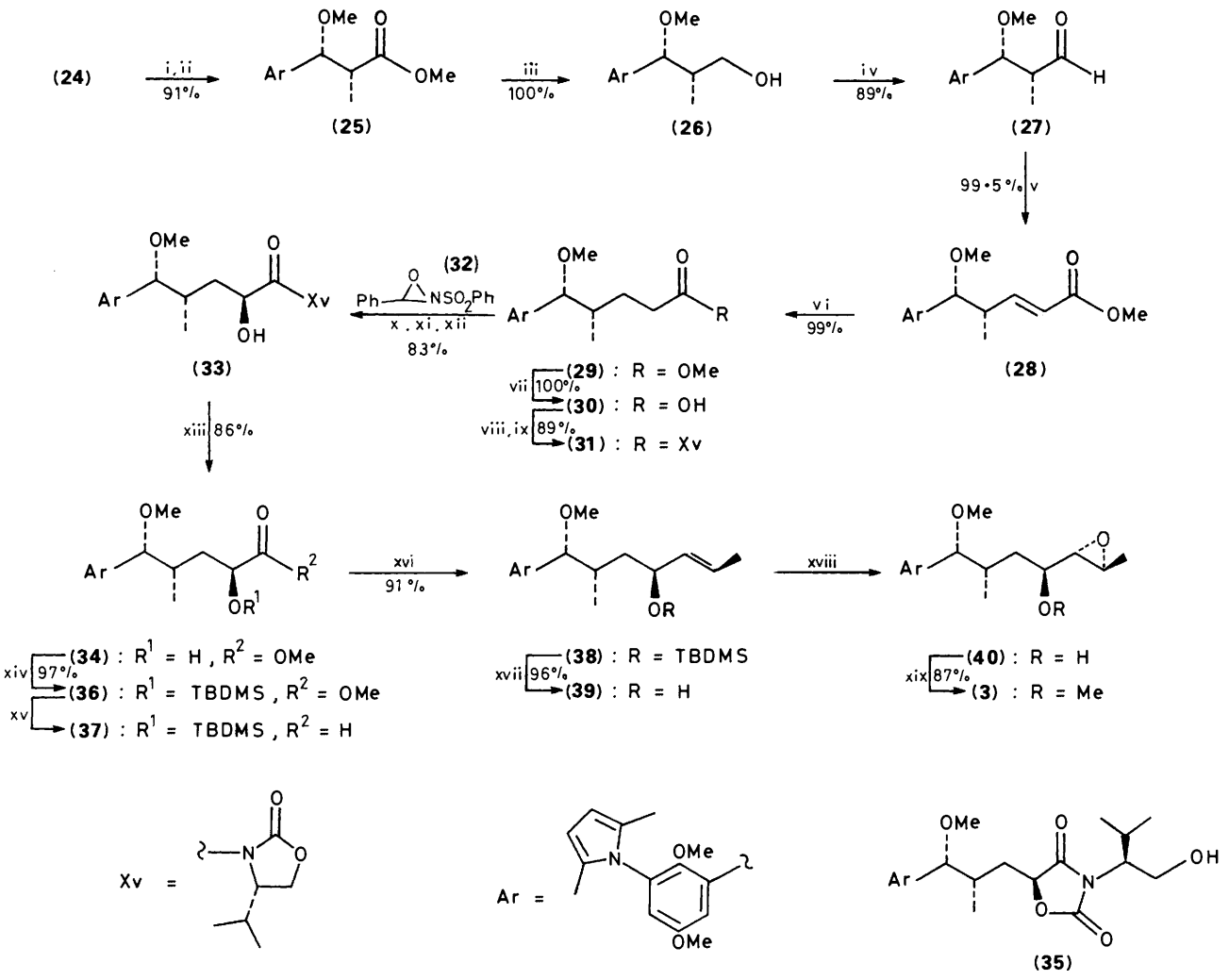
Attempted reduction of the ester (**24**) with $LiBH_4$ in THF at room temperature was complicated by the fact that, under these basic conditions, intramolecular displacement of the methoxy group *ortho* to the nitro group by the newly created alkoxide occurred. In this way, a mixture of the required alcohol and a cyclic ether was obtained, in 28 and 38% yields respectively. To overcome this problem and to avoid possible future complications in the cuprate opening of the epoxide, the nitro group was converted into the 2,3-dimethylpyrrole[21] by successive catalytic hydrogenation and condensation with acetonylacetone (91% for two steps) (Scheme 5). The protected compound (**25**) could now be quantitatively reduced to the alcohol (**26**) using $LiAlH_4$. Nevertheless, Swern oxidation[22] [$(COCl)_2$, DMSO, Et_3N, −60 °C] of (**26**) gave less than 2% of the required aldehyde (**27**) with no recovery of the starting alcohol, probably due to reaction of the pyrrole moiety with the activated DMSO. Fortunately the aldehyde (**27**) could be isolated in 89% yield when a solution of the alcohol (**26**) in DMSO–Et_3N–THF was treated at 25 °C with solid SO_3–pyridine complex (3 equiv.) for 40 min.* Homologation of the chain was achieved by Wittig reaction of the above aldehyde with Ph_3P=CHCOOMe in refluxing dichloromethane. Thus, the α,β-unsaturated ester (**28**) was obtained in excellent (99.5%) yield and with more than 98% (*E*)-selectivity (limit of ^1H n.m.r. detection). Reduction of the double bond using 10% Pd–C in ethanol cleanly afforded the ester (**29**), the basic material for introduction of the hydroxy group at C-18.†

The hydroxylation of acyl oxazolidinones[18d] was chosen to introduce the C(18)-hydroxy group in view of its high degree of enantioselection. Thus, the ester (**29**) was quantitatively hydrolysed to the acid (**30**) (LiOH, MeOH) and this was coupled with the lithium salt (BuLi, THF, −78 °C) of (*S*)-4-isopropyloxazolidin-2-one (Xv–H; see Scheme 5), either by activating the acid with carbonyl di-imidazole,[24] 2,2′-dipyridyldisulphide,[25] or with pivaloyl chloride,[26] to give (**31**) in 50, 78, and 89% yields respectively.

Treatment of the sodium enolate [$NaN(SiMe_3)_2$, THF, −78 °C] of (**31**) with 2-benzenesulphonyl-3-phenyloxaziridine (**32**) (1.8 equiv., THF, −78 °C, 20 min) afforded the required

* If SO_3·py is first dissolved in DMSO and this solution cannulated into a solution of the alcohol in DMSO–Et_3N, as originally reported,[23] no oxidation takes place.

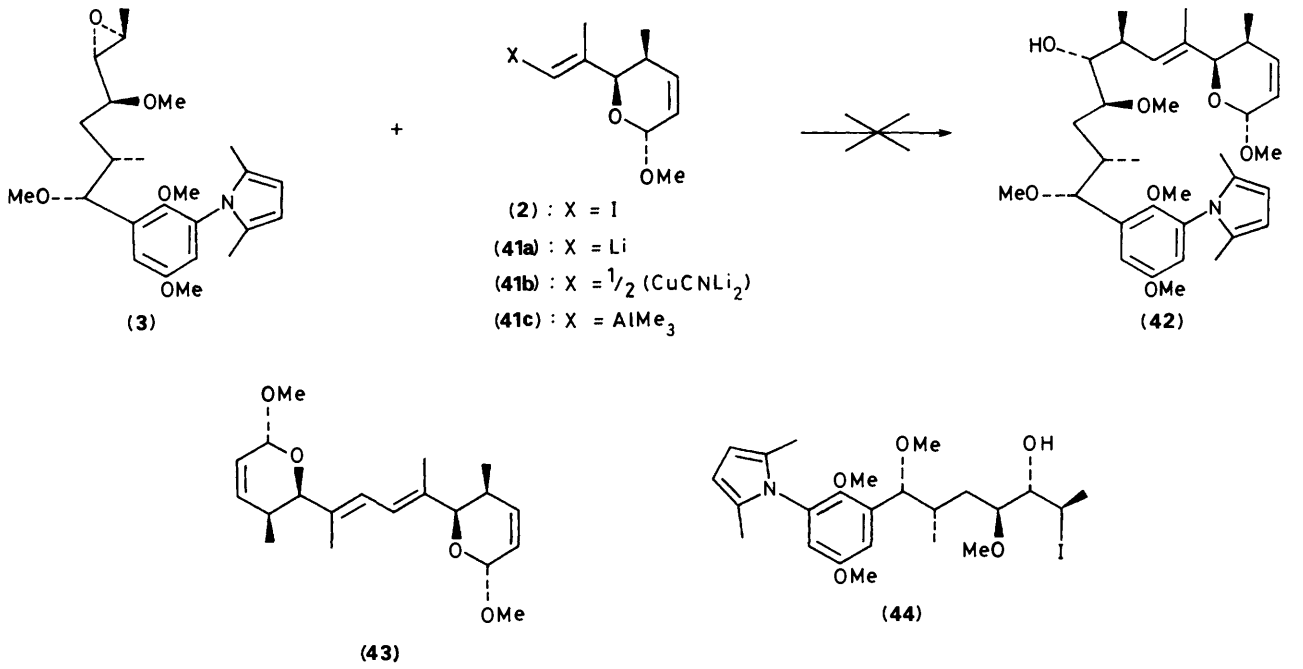
† It is important to stop this hydrogenation after 1 equiv. of H_2 has been used (*ca.* 0.5 h) because slow reduction of the pyrrole ring then begins.



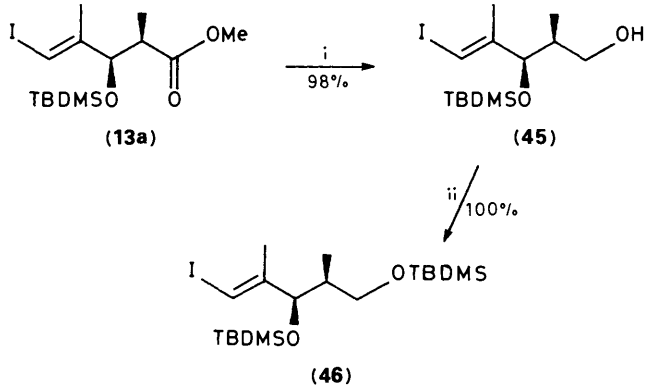
Scheme 5. *Reagents:* i, H_2, 10% Pd–C, EtOH, 1 atm, 2.5 h; ii, acetonylacetone (3.0 equiv.), isobutyric acid (cat.), refluxing toluene, Dean–Stark trap, 65 h; iii, $LiAlH_4$ (1 mol equiv.), THF, 0 °C, 3 h; iv, SO_3•Py (3.0 equiv.), Et_3N (7.0 equiv.), DMSO–THF (6.5:1), 25 °C, 45 min; v, Ph_3P=CHCOOMe (2.0 equiv.), CH_2Cl_2, 40 °C, 24 h; vi, H_2, 10% Pd–C, EtOH, 1 atm, 40 min; vii, LiOH (5.0 equiv.), MeOH–THF–water (3:1:1), 25 °C, 18 h; viii, pivaloyl chloride (1.01 equiv.), Et_3N (1.01 equiv.), toluene, 0 °C; 1 h; ix, Li–Xv (2.3 equiv.), THF, −78 °C, 1 h; x, $NaN(SiMe_3)_2$ (1.3 equiv.), THF, −78 °C, 25 min; xi, 2-benzenesulphonyl-3-phenyloxaziridine (1.8 equiv.), −78 °C, 20 min; xii, AcOH (10 equiv.), −78 °C to 25 °C; xiii, MeOMgCl (2.2 equiv.), CH_2Cl_2–MeOH (3.5:1), −10 °C, 1 h; xiv, TBDMS–OTf (1.5 equiv.), 2,6-lutidine (2.5 equiv.), CH_2Cl_2, 0 °C, 1 h; xv, DIBAL-H (1.6 equiv.), toluene, −80 °C, 2 h; xvi, $CrCl_2$ (8.0 equiv.), CH_3CHI_2 (2.0 equiv.), THF, 25 °C, 5 h, 91% from (**36**); xvii, Bu_4NF (2.0 equiv.), THF, 25 °C, 16 h; xviii, (+)-DIPT (1.2 equiv.), $Ti(O^iPr)_4$ (1.0 equiv.), TBHP (2.0 equiv.), CH_2Cl_2, −20 °C, 22 h; xix, NaH (1.3 equiv.), MeI (5.0 equiv.), THF, −15 to 0 °C, 2 h 88% from (**39**)

hydroxy compound (**33**) in 83% yield after flash chromatography. This reaction was found to be very sensitive to the quenching conditions employed. Thus, the recommended camphorsulphonic acid could not be used because of decomposition of the pyrrole moiety in this very acidic medium. Moreover, decomposition (Et_3N, −78 °C, 20 min) of the excess of oxidizing agent has to be performed before warming up the reaction mixture since the pyrrole is quickly oxidized at room temperature. Finally, an aqueous work up (AcOH–water) is necessary owing to silylation of the hydroxy group under these conditions with $HN(SiMe_3)_2$. Successful removal of the chiral auxiliary from (**33**) was achieved by reaction with MeOMgCl in MeOH–CH_2Cl_2 at 0 °C to give (**34**) in 82–86% yields; a *ca.* 15% yield of (**35**) was observed. The secondary hydroxy group of (**34**) was then protected as the TBDMS derivative (TBDMS–OTf, 2,6-lutidine, CH_2Cl_2; 97% yield) and the resulting ester (**36**) was cleanly reduced to the aldehyde (**37**) using DIBAL-H at −80 °C. Preparation of the (*E*)-olefin (**38**) was achieved in 91% isolated yield from (**36**), and with more than 99% (*E*)-selectivity, by reaction of aldehyde (**37**) with $CrCl_2$–CH_3CHI_2 in THF at room temperature following the procedure of Takai *et al.*[27] Under these extremely mild conditions no epimerization of the aldehyde occurred and we believe that this method offers one of the best alternatives to the Schlosser modification of the Wittig reaction for preparing (*E*)-olefins.[28]

Deprotection of the hydroxy group of (**38**) under standard conditions (TBAF, THF) afforded the secondary (*E*)-allylic alcohol (**39**) required for epoxidation. Although (**39**) presents the C-18 hydroxy group in the right absolute stereochemistry to reinforce the preferential asymmetric induction of the Sharpless epoxidation when (+)-DIPT is used as the chiral auxiliary, attempted epoxidation under catalytic conditions [(+)-DIPT (0.12 equiv.), $Ti(O^iPr)_4$ (0.10 equiv.)] gave a 5.3:1 mixture of the expected epoxide (**40**) and its corresponding isomer in 97% combined yield. This ratio could, however, be increased to 95:5 under stoicheiometric conditions [(+)-DIPT (1.2 equiv.), $Ti(O^iPr)_4$ (1.0 equiv.)] to give a 96% combined yield from (**38**). Methylation (NaH, MeI, THF, 0 °C) of this mixture followed by



Scheme 6.



Scheme 7. *Reagents:* i, DIBAL-H (2.6 equiv.), toluene, −20 °C, 1.5 h; ii, TBDMS-Cl (1.5 equiv.), imidazole (3.0 equiv.), DMF, 25 °C, 17 h

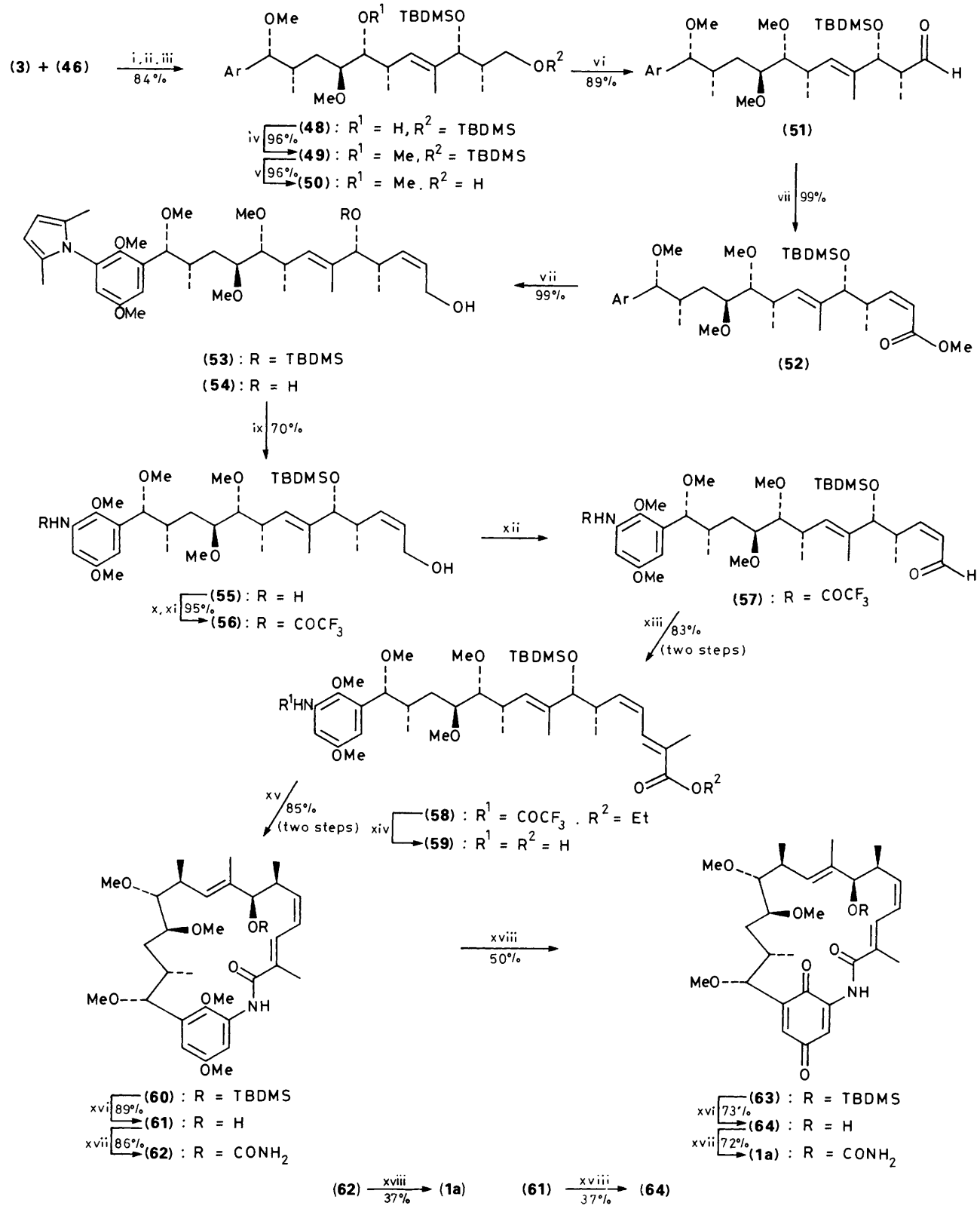
flash chromatography gave pure (**3**) in 88% yield and with the correct absolute stereochemistry in all its centres. Thus, epoxide (**3**) has been prepared in 19 steps and 28.5% overall yield from (**21**).

Attempted Coupling of Epoxide (**3**) *and Vinyl Iodide* (**2**).—The plan for reaction of the epoxide (**3**) and the vinyl iodide (**2**) was to utilize ring opening of the epoxide with a higher order cyanocuprate[10] derived from (**2**). Nevertheless, in spite of extensive efforts we were unable to obtain any of the desired coupled product (**42**) (Scheme 6). Thus, treatment of (**2**) with either ^{t}BuLi (2 equiv.) or BuLi (1 equiv.) at −80 °C to achieve halogen-metal exchange (**41a**) followed by transmetalation with CuCN (0.5 equiv.) to generate (**41b**) and subsequent reaction with epoxide (**3**) led only to quantitative recovery of the epoxide together with variable amounts (*ca.* 20%) of dimer (**43**), arising from thermal decomposition of the cuprate. The epoxide was also recovered unchanged from its reaction with an aluminate (**41c**), prepared by reaction of (**41a**) with Me_3Al.[29] The most obvious modification to overcome the low reactivity of the 2,3-disubstituted epoxide would be to utilize Lewis acid catalysis in the reaction.[30] This would be, however, incompatible with the reactivity of the α,β-unsaturated methoxy lactol moiety in (**2**)[31] and indeed reaction of (**3**) with the vinyl lithium derivative (**41a**) and BF_3·OEt_2[30c] at −78 °C afforded only small amounts of a product (**44**) due to iodide opening of the epoxide together with extensive decomposition of (**41a**).

We had, therefore, to consider an alternative strategy; on the basis of previous reports[32] the use of a vinyl iodide such as (**46**) appeared to represent a viable approach. Thus, DIBAL-H reduction of ester (**13a**) at −20 °C followed by silylation of the primary alcohol (TBDMS-Cl, imidazole) gave the bis-silylated compound (**46**) in 98% overall yield (Scheme 7). Although reaction of the epoxide (**3**) with the higher order cyanocuprate derived from (**46**) (2 equiv. ^{t}BuLi, −80 °C, 2 h; 0.5 equiv. CuCN, −78 to −15 °C, 15 min) gave less than 5% of the coupled product (**48**) after 48 h at −30 °C, addition of BF_3·OEt_2[30a] (2 equiv.) to a solution of the epoxide (**3**) and the cuprate in ether at −78 °C afforded, after 1 h at that temperature, an 83% isolated yield of (**48**); a 12% yield of compound (**44**) was also isolated under these conditions (Scheme 8). The secondary hydroxy group was methylated under the usual conditions (NaH, MeI, THF, 25 °C) to give (**49**) in excellent (96%) yield. N.O.e. experiments on (**49**) corroborated that the C(14)–C(15) olefin geometry had been preserved during the cuprate coupling because of the lack of an n.O.e. between 15-H and 14-Me and positive n.O.e.s between 15-H and both 13-H and 17-H.

Selective removal of the primary TBDMS group in the presence of the secondary one was obtained with good selectivity (>95:5) by using 1:3:3 HF·Py–Py–THF in MeOH for 6 h at room temperature and conversion of (**49**) into (**50**) was achieved in 95% isolated yield. The remaining 4% of bis-deprotected diol was recoverted into (**49**) [TBDMS–OTf (3 equiv.), 2,6-lutidine (5 equiv.)] and deprotected as before to give a total yield of (**50**) in excess of 98%.

A Horner–Emmons reaction was employed to introduce the (*Z*) C(10)–C(11) double bond. Alcohol (**50**) was oxidized to the aldehyde (**51**) with SO_3·Py complex in DMSO–Et_3N–THF at room temperature (89% yield) and this was reacted with the potassium anion of $(CF_3CH_2O)_2P(O)CH_2COOMe$, using the same conditions described for (**15**), to give (**52**) in 99% isolated yield. Reduction of the ester function with DIBAL-H at −33 °C afforded a 98% isolated yield of allylic alcohol (**53**).



Scheme 8. *Reagents:* i, (**46**) (2.4 equiv.), ^{t}BuLi (4.8 equiv.), −80 °C, 2 h; ii, CuCN (1.2 equiv.), −78 to −10 °C, 15 min; iii, (**3**) (1.0 equiv.), BF_3•OEt_2 (2.0 equiv.), −78 °C, 1 h; iv, NaH (1.3 equiv.), MeI (5.0 equiv.), THF, 25 °C, 6 h; v, HF•Py–Py–THF (1:3:3; 20 equiv. HF), MeOH, 25 °C, 6.5 h; vi, SO_3•Py (7.0 equiv.), Et_3N (15 equiv.), DMSO–THF (6.5:1), 25 °C, 1.5 h; vii, $(CF_3CH_2O)_2P(O)CH_2COOMe$ (1.15 equiv.), 18-crown-6 (2.5 equiv.), $KN(SiMe_3)_2$ (1.1 equiv.), THF, −78 °C, 1 h; viii, DIBAL-H (2.6 equiv.), toluene, −20 °C, 1.5 h; ix, H_2NOH•HCl (30 equiv.), KOH (20 equiv.), EtOH–water (2:1), reflux, 68 h; x, TFAA (3.0 equiv.), Et_3N (6.0 equiv.), CH_2Cl_2, 0 to 25 °C, 1 h; xi, pH 7 phosphate buffer, MeOH, 25 °C, 15 min; xii, PDC (2.0 equiv.), CH_2Cl_2, 25 °C, 6 h; xiii, $Ph_3P{=}C(Me)COOEt$ (2.0 equiv.), CH_2Cl_2, 40 °C, 40 h; xiv, LiOH (10 equiv.), THF–MeOH–water (2:2:1), 25 °C, 24 h; xv, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (4.0 equiv.), ^{i}Pr$_2$NEt (10 equiv.), toluene, 85 °C, 15 h; xvi, Bu_4NF (5.0 equiv.), THF, 25 °C, 40 h; xvii, NaOCN (12 equiv.), TFA (12 equiv.), CH_2Cl_2, 0 to 25 °C, 3 h; xviii, CAN (3.0 equiv.), MeCN–water, 0 °C, 10 min

We had then arrived at what we believed to be the best stage for removing the pyrrole protecting group, in view of the nucleophilic conditions usually required for this purpose.[21,33] However, treatment of (**53**) with H_2NOH·HCl (5 equiv.) in refluxing EtOH–water produced only desilylation of the secondary alcohol to give (**54**) in 78% isolated yield after 16 h. Extended reaction times usually led to decomposition compounds. Although almost no reaction was observed when H_2NOH·HCl–KOH (3 and 2 equiv. respectively) were used, under more forcing conditions (30 equiv. H_2NOH·HCl–20 equiv. KOH, refluxing EtOH–water, 68 h) a 70% isolated yield of (**55**) was obtained together with 25% recovered (**53**). This was recycled under the same conditions to give (**55**) in a total combined yield of 87%.

The nitrogen group was reprotected as the trifluoroacetamide under normal conditions (trifluoroacetic acid anhydride, $^iPr_2NEt$, CH_2Cl_2) to give (**56**) in 95% yield. Oxidation of the allylic alcohol to the corresponding aldehyde was found to be, however, more difficult than expected. Thus, SO_3·Py–DMSO failed to give reasonable yields of (**57**) and activated MnO_2 afforded a moderate (65%) yield of the aldehyde together with extensive amounts of decomposition products. Satisfactory oxidation was achieved with pyridinium dichromate (PDC)[34] in CH_2Cl_2 at 25 °C although a 9% (*Z*) to (*E*) isomerization of the C(10)–C(11) double bond occurred during the reaction. Both isomers could not be separated at this point but this was achieved in the next step. Thus, the aldehyde mixture was reacted with (ethoxycarbonylethylidene)triphenylphosphorane (Ph_3P=CMeCOOEt) in CH_2Cl_2 to give, after flash chromatography, a 83% isolated yield (two steps) of pure (*Z*,*E*)-diene (**58**).

We had, therefore, arrived at the crucial stage of the synthesis since removal of the trifluoroacetamide protecting group and hydrolysis of the ester would yield the amino acid (**59**) required for macrolactamization. Treatment of (**58**) with LiOH (10 equiv.) in MeOH–water–THF for 24 h gave (**59**), easily extracted from water (pH 5), and which was used in the next step without further purification after being azeotropically dried with toluene. Excitingly, macrocyclization was achieved much more quickly than anticipated after only four attempts. Thus, although the use of DCC, diethyl cyanophosphonate,[35] or diphenylphosphoryl azide[36] did not induce the required ring closure reaction, this was successfully achieved by reaction in the presence of 2-mesitylenesulphonyl chloride[37] or bis(2-oxo-3-oxazolidinyl)phosphinic chloride.[38] Syringe pump addition of a solution of (**59**) (1 mg/ml) and $^iPr_2NEt$ (2 equiv.) in toluene to a 10M solution of 2-mesitylenesulphonyl chloride and $^iPr_2NEt$ (20 equiv. each) in toluene at 65 °C gave, after 14 h, a 71% isolated yield of (**60**). On the other hand, reaction of (**59**) with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (4 equiv.) and $^iPr_2NEt$ (10 equiv.) in toluene (1.5×10^{-3}M) afforded an 85% isolated yield of (**60**) after 15 h at 85 °C. We are impressed by the simplicity and efficiency of this second set of conditions. We had, therefore, achieved one of our major goals and had now to find a procedure for incorporation of the carbamate function at C-13 and oxidation to the quinone level.

Three alternative pathways were considered and worked out. We had the option to introduce the carbamate group followed by oxidation or the reverse. In the first approach the TBDMS group on (**60**) was removed under the usual conditions (TBAF, THF, 25 °C) to give (**61**) in 89% yield. Although carbamoylation of (**16**) could not be achieved by its reaction with phosgene (to generate the corresponding chloroformate derivative) followed by quenching with ammonia,[39] treatment of (**61**) with sodium cyanate[40] (12 equiv.) and trifluoroacetic acid (12 equiv.) in CH_2Cl_2 at 25 °C for 3 h gave the required carbamate (**62**) in 86% isolated yield. Oxidation of (**62**) with cerium(IV) ammonium nitrate (CAN; 3 equiv.) in MeCN–water[41] at 0 °C for 10 min afforded (+)-macbecin I (**1a**) in 37% isolated yield. Comparable yields of (**1a**) (32%) were obtained when silver(II) dipicolinate[42] was used as the oxidizing agent. Alternatively, oxidation of (**60**) with CAN as previously described gave the quinone (**63**) in 50% isolated yield, which was converted into macbecin I (**1a**) by desilylation (TBAF, THF, 25 °C; 73%) and carbamoylation (72% yield). In addition, decarbamoyl macbecin I (**64**) was also prepared in 37% yield by CAN oxidation of (**61**) as above.*

* Quinones (**63**), (**64**), and (**1a**) are not very stable and they decompose to some extent during crystallization.

Experimental

Unless otherwise stated, n.m.r. spectra were recorded on a Bruker AM-360 spectrometer (360 MHz for ^1H and 90.6 MHz for ^{13}C) using $CDCl_3$ as the solvent and TMS as the internal reference. Macbecin numbering is used in the assignation of these spectra which is based on decoupling techniques, 2D n.m.r., and n.O.e. experiments. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet). I.r. spectra were determined on a Perkin-Elmer 782 spectrometer. Mass spectra and high-resolution mass spectra (h.r.m.s.) were obtained in a VC 70—250 spectrometer. Optical rotations were measured on a Perkin-Elmer Lambda 5 apparatus using dichloromethane (distilled from CaH_2) as the solvent. Melting and boiling points are uncorrected.

Anhydrous diethyl ether (Et_2O), tetrahydrofuran (THF), dimethylformamide (DMF), and toluene were obtained from the Aldrich Co. Triethylamine, di-isopropylethylamine, 2,6-lutidine, and dichloromethane were distilled from CaH_2. Dimethylsulphoxide (DMSO) and pyridine were distilled from CaH_2 and stored over 4-A molecular sieves. Dimethyl sulphate was dried over anhydrous K_2CO_3 for 24 h. Methyl iodide and 1,1-di-iodoethane were passed through a column of neutral alumina prior to use. Anhydrous $CrCl_2$ and t-butyl hydroperoxide (3M in iso-octane) were obtained from the Aldrich Co.

Diethyl Di-iodomethylmethylmalonate (**5**).—Diethyl methylmalonate (100 g, 0.57 mol) was slowly added to sodium hydride (55% in mineral oil; 27.6 g, 0.58 mol) in anhydrous diethyl ether (700 ml) during 1 h with vigorous stirring and the resulting thick mixture was refluxed for a further 2.5 h. Iodoform (226 g, 0.57 mol) was added in one portion and the mixture refluxed for 20 h under nitrogen. After being cooled to 0 °C (ice–water bath), 10% aqueous HCl (200 ml) was added and the mixture stirred for 10 min. The organic phase was decanted, dried ($MgSO_4$), and concentrated. The remaining residue was diluted with light petroleum (100 ml) and the precipitated iodoform was removed by filtration. The solvent was removed at reduced pressure and the remaining liquid distilled (b.p. 129—131 °C at 4 mmHg) to give the title compound (**5**) (165 g, 65%) as a pale pink oil; δ_H(60 MHz, $CDCl_3$) 5.9 (1 H, s, CHI_2), 4.3 (4 H, q, *J* 6 Hz, OCH_2), 1.9 (3 H, s, Me), and 1.4 (6 H, t, *J* 6 Hz, OCH_2Me).

(E)-3-*Iodo*-2-*methylpropen*-2-*oic Acid* (**6**).—A solution of diethyl di-iodomethylmethylmalonate (**5**) (164 g, 0.37 mol) and KOH (63.2 g, 1.13 mol) in EtOH–water (3:1, 500 ml) was refluxed for 24 h. After being cooled to room temperature the solvent was removed under reduced pressure and the residue redissolved in 10% aqueous K_2CO_3 (300 ml) and washed with CH_2Cl_2 (2 × 100 ml). The basic solution was acidified with 12M HCl, extracted with CH_2Cl_2 (7 × 70 ml), dried ($MgSO_4$), and concentrated to a solid. Crystallization from light petroleum gave the acid (**6**) (69.9 g, 89%) as white needles, m.p. 51—53 °C; δ_H(60 MHz, $CDCl_3$) 10.8 (1 H, s, COOH), 7.9 (1 H, d, *J* 1 Hz, 3-H), and 2.0 (3 H, d, *J* 1 Hz, 2-Me) (Found: C, 22.79; H, 2.46%. $C_4H_5IO_2$ requires C, 22.66; H, 2.38%).

(E)-3-*Iodo*-2-*methylprop*-2-*enol* (**7**).—To a cooled (0 °C) and stirred solution of (*E*)-3-iodo-2-methylprop-2-enoic acid (**6**) (45.5 g, 214.6 mmol) in dry THF (350 ml), solid $LiAlH_4$ (8.15 g, 214.6 mmol) was slowly added over 2.5 h. After being stirred at room temperature for a further 3 h, the reaction mixture was recooled to 0 °C and the excess of hydride was destroyed by careful dropwise addition of saturated aqueous Na_2SO_4. Ether (200 ml) was added and the mixture was poured into cold 2M H_2SO_4 (300 ml), then the organic phase was decanted off and the aqueous solution extracted with CH_2Cl_2 (2 × 100 ml). The combined organic solutions were concentrated and the remaining oil dissolved in CH_2Cl_2 (200 ml) and washed with 10% aqueous K_2CO_3 (100 ml). The basic aqueous phase was re-extracted with CH_2Cl_2 (2 × 100 ml), then the combined organic extracts were dried ($MgSO_4$) and the solvent removed under vacuum. Distillation at reduced pressure (b.p. 94—96 °C at 9 mmHg) afforded the title compound (29.7 g, 70%) as a colourless liquid; $\nu_{max.}$(film) 3 350, 2 940, 1 620, 1 450, 1 380, 1 280, 1 080, and 1 020 cm^{-1}; δ_H 6.26 (1 H, t, *J* 1.4 Hz, 3-H), 4.09 (2 H, s, 1-H), 2.71 (1 H, br s, OH), and 1.83 (3 H, d, *J* 1.4 Hz, 2-Me); δ_C 147.2 (s, C-2), 77.2 (d, C-3), 67.0 (t, C-1), and 21.3 (q, 2-Me); *m*/*z* (e.i.) 198 (M^+, 11%), 91 (15), 71 (34), 57 (80), and 43 (100) (Found: C, 24.32; H, 3.67. C_4H_7IO requires C, 24.26; H, 3.56%).

(E)-3-*Iodo*-2-*methylprop*-2-*enal* (**8**).—Activated MnO_2 (28 g, 320 mmol) was added, in one portion, to a solution of the alcohol (**7**) (10 g, 50.5 mmol) in dry CH_2Cl_2 (200 ml) and the resulting mixture was stirred under argon for 42 h at room temperature. The manganese salts were removed by filtration through a plug of silica gel and washed with anhydrous CH_2Cl_2 (100 ml). The resulting yellow solution of the crude aldehyde (**8**) was dried over freshly activated 4-A sieves (6 g) and used in the next step without further purification.

erythro-*Aldol Compound* (**10**).—To a cooled (−5 °C) and stirred solution of the propionyl oxazolidinone (**9**)[14,43] (11.8 g, 50.5 mmol) in dry CH_2Cl_2 (200 ml) was added dropwise, under argon, a solution of 9-BBN-OTf[44] (15 g, 11.7 ml, 55.5 mmol) in dry CH_2Cl_2 (200 ml) followed by dry $^iPr_2NEt$ (10.6 ml, 60.6 mmol) at such a rate as to keep the temperature below −2 °C. Stirring was continued at this temperature for 1 h before the solution was cooled to −76 °C and the aldehyde (**8**) was added dropwise over 2 h. After being stirred for 1 h at −76 °C and 1 h at 25 °C, the solution was poured into 10% aqueous NaH_2PO_4 (170 ml) and the organic phase was decanted off. The aqueous solution was extracted once with ether (120 ml) and the combined organic extracts were concentrated under vacuum. The remaining yellow oil was dissolved in MeOH (180 ml) and oxidized at 0 °C with 30% H_2O_2–pH 7 phosphate buffer (1:1, 110 ml) for 1 h. Water (100 ml) was added and the MeOH removed at reduced pressure (temp. below 30 °C). The aqueous solution was extracted with ether (2 × 250 ml) and the organic phases were washed with 5% aqueous $NaHCO_3$ (50 ml), brine (90 ml), dried (Na_2SO_4), and concentrated. Crystallization from hexane–20% EtOAc (two crops, white needles) and column chromatography on silica gel (CH_2Cl_2–5% Et_2O) of the mother liquids gave compound (**10**) (14.1 g, 65%) as a white solid, m.p. 106.5—108 °C; $[\alpha]_D$ +14.50° (*c* 0.92 in CH_2Cl_2); $\nu_{max.}$($CHCl_3$) 3 600—3 250, 2 990, 2 940, 2 920, 2 880, 1 780, 1 685, 1 455, 1 385, 1 365, 1 340, 1 150, 1 120, 1 090, 1 070, 1 030, 885, and 860 cm^{-1}; δ_H 7.45—7.29 (5 H, m, Ph), 6.43 (1 H, s, 15-H), 5.71 (1 H, d, *J* 7.2 Hz, 5′-H), 4.78 (1 H, qn, *J* 6.8 Hz, 4′-H), 4.52 (1 H, br s, 13-H), 4.01 (1 H, dq, *J* 7.0, *J*′ 3.2 Hz, 12-H), 3.15 (1 H, d, *J* 2.8 Hz, OH), 1.85 (3 H, s, 14-Me), 1.17 (3 H, d, *J* 7.0 OHz, 12-Me), and 0.90 (3 H, d, *J* 6.6 Hz, 4′-Me); δ_C 176.3, 152.4, 146.2, 133.2, 128.9, 125.5, 78.9, 75.0, 54.8, 30.5, 21.6, 14.2, and 10.1; *m*/*z* (e.i.) 302 (M^+ − 127, 0.3%), 233 (1), 196 (3), and 57 (100) (Found: C, 47.58; H, 4.68; N, 3.33. $C_{17}H_{20}INO_4$ requires C, 47.57; H, 4.70; N, 3.26%).

Silylated Aldol Compound (**11**).—TBDMS-OTf (5.43 ml, 23.6 mmol) was added dropwise *via* cannula over 10 min to a cooled (−5 °C) and stirred solution of the aldol compound (**10**) (6.75 g, 15.75 mmol) and dry 2,6-lutidine (4.6 ml, 39.37 mmol) in dry CH_2Cl_2 (80 ml). After being stirred at 0 °C for a further 2 h, the mixture was quenched with water (60 ml), diluted with ether (150 ml), washed with 1M HCl (60 ml), 5% aqueous $NaHCO_3$ (60 ml), and brine (60 ml), then dried ($MgSO_4$) and concentrated. Column chromatography of the remaining residue (silica gel, hexane–5% Et_2O) gave the silylated compound (**11**) (8.73 g, 98%) as a colourless viscous oil; $[\alpha]_D$ −11.2° (*c* 0.96 in CH_2Cl_2); $\nu_{max.}$(film) 3 060, 2 960, 2 930, 2 880, 2 860, 1 780, 1 700, 1 610, 1 455, 1 350, 1 260, 1 230, 1 190, 1 150, 1 120, 1 090, 1 025, 960, 870, 840, and 775 cm^{-1}; δ_H 7.45—7.30 (5 H, m, Ph), 6.22 (1 H, s, 15-H), 5.67 (1 H, d, *J* 7.0 Hz, 5′-H), 4.61 (1 H, qn, *J* 6.8 Hz, 4′-H), 4.40 (1 H, d, *J* 7.5 Hz, 13-H), 4.08 (1 H, qn, *J* 7.3 Hz, 12-H), 1.85 (3 H, s, 14-Me), 1.22 (1 H, d, *J* 6.8 Hz, 12-Me), 0.91 (9 H, s, ^{t}BuSi), 0.90 (3 H, d, *J* 7.0 Hz, 4′-Me), 0.07 (3 H, s, MeSi), and 0.00 (3 H, s, MeSi); δ_C 174.21 (s), 152.75 (s), 148.82 (s), 133.04 (s), 128.76 (d), 128.70 (d), 79.18 (d), 79.04 (d), 78.72 (d), 55.47 (d), 42.96 (d), 25.72 (q), 19.83 (q), 18.18 (s), 14.31 (q), 12.86 (q), −4.86 (q), and −5.26 (q); *m*/*z* (e.i.) 486 (M^+ − 57, 66%), 442 (32), 314 (60), 290 (100), 246 (92), and 190 (47) [Found: *m*/*z* 486.0604. $C_{19}H_{25}INO_4Si$ (M^+ − C_4H_9) requires *m*/*z* 486.0598].

Preparation of Hydroxyester (**12**).—Sodium methoxide in MeOH (0.40M, 134 ml) was added, under nitrogen, over 12 min to a cooled (−25 °C) and stirred solution of the aldol compound (**10**) (20.8 g, 48.48 mmol) in dry CH_2Cl_2 (400 ml). After being stirred for a further 8 min, the reaction mixture was neutralized by addition of amberlite IR-118. The amberlite was filtered off and washed with CH_2Cl_2 (3 × 100 ml), then the combined organic solutions were washed once with brine (100 ml) and dried (Na_2SO_4). Evaporation of the solvent followed by flash chromatography (silica gel, CH_2Cl_2–5% Et_2O) gave the required ester (**12**) (13.36 g, 97%) as a colourless liquid; $[\alpha]_D$ + 19.8° (*c* 0.64 in CH_2Cl_2); $\nu_{max.}$(film) 3 650—3 200, 2 980, 2 945, 1 725, 1 615, 1 455, 1 435, 1 380, 1 350, 1 260, 1 200, 1 170, 1 120, 1 095, 1 070, and 1 035 cm^{-1}; δ_H 6.38 (1 H, s, 15-H), 4.48 (1 H, s, 13-H), 3.71 (3 H, s, OMe), 2.84—2.68 (2 H, m, 12-H and OH), 1.79 (3 H, s, 14-Me), and 1.12 (3 H, d, *J* 7.1 Hz, 12-Me); δ_C 175.74 (C-11), 145.93 (C-14), 79.32 (C-15), 75.77 (C-13), 52.10 (OMe), 42.19 (C-12), 21.17 (14-Me), and 10.51 (12-Me); *m*/*z* (e.i.) 267 (M^+ − 17, 41%), 197 (47), 157 (100), 139 (70), 125 (28), 88 (75), and 69 (45) [Found: *m*/*z* 266.9799. $C_8H_{12}IO_2$ (M^+ − OH) requires *m*/*z* 266.9882].

Silylated Hydroxyester (**13a**).—To a cooled (−5 °C) and stirred solution of the hydroxyester (**12**) (12.83 g, 45.17 mmol) and dry 2,6-lutidine (12.7 ml, 112.9 mmol) in dry CH_2Cl_2 (200 ml) was added TBDMS-OTf (15.6 ml, 67.8 mmol) dropwise over 12 min under nitrogen. After being stirred for 1.5 h at this temperature, the reaction mixture was quenched with water (150 ml), diluted with ether (400 ml), washed with 1M HCl (150 ml), 5% aqueous $NaHCO_3$ (150 ml), and brine (150 ml), then dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, hexane–7% Et_2O) of the remaining residue afforded (**13a**) (18.0 g, 100%) as a colourless liquid; $[\alpha]_D$ +18.6° (*c* 0.66 in CH_2Cl_2); $\nu_{max.}$(film) 2 950, 2 930, 2 860, 1 740, 1 470, 1 460, 1 435, 1 360, 1 260, 1 195, 1 165, 1 080, 1 025, 880, 840, and 780 cm^{-1}; δ_H 6.19 (1 H, t, *J* 1.0 Hz, 15-H), 4.34 (1 H, d, *J* 6.8 Hz, 13-H), 3.63 (3 H, s, OMe), 2.63 (1 H, qn, *J* 6.9 Hz, 12-H), 1.79 (3 H, d, *J* 1.0 Hz, 14-Me), 1.14 (3 H, d, *J* 6.9 Hz, 12-Me), 0.88 (9 H, s, ^{t}BuSi), 0.03 (3 H, s, MeSi), and −0.03 (3 H, s, MeSi); δ_C 174.30

(C-11), 148.29 (C-14), 78.96 (C-15*), 78.62 (C-13*), 51.68 (OMe), 44.90 (C-12), 25.68 (^{t}BuSi), 19.91 (14-Me), 18.14 (^{t}BuSi), 12.11 (12-Me), −4.82 (MeSi), and −5.36 (MeSi); *m/z* (e.i.) 341 (M^+ − 57, 85%), 311 (15), 214 (23), 145 (28), and 89 (100) [Found: *m/z* 341.0102. $C_{10}H_{18}IO_3Si$ (M^+ − C_4H_9) requires *m/z* 341.0070].

Preparation of Aldehyde (**14**).—DIBAL-H in toluene (1M, 1.9 ml) was added dropwise to a cooled (−80 °C) and stirred solution of the ester (**13a**) (480 mg, 1.2 mmol) in anhydrous toluene (12 ml) at such a rate as to keep the temperature below −77 °C (*ca.* 10 min). After being stirred at −82 °C for 1 h the reaction was quenched by dropwise addition of MeOH (1 ml) keeping the temperature below −78 °C. Citric acid (10% aqueous solution, 10 ml) was then added, the mixture was allowed to warm to room temperature and products were extracted with CH_2Cl_2 (2 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, hexane–13% Et_2O) of the residue gave the aldehyde (**14**) (435 mg, 98%) as a colourless liquid; $[\alpha]_D$ +40.0° (*c* 0.60 in CH_2Cl_2); $\nu_{max.}$(film) 2 960, 2 930, 2 860, 1 730, 1 470, 1 460, 1 390, 1 380, 1 360, 1 255, 1 140, 1 110, 1 080, 1 035, 840, and 780 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 9.67 (1 H, d, *J* 1.5 Hz, 11-H), 6.28 (1 H, t, *J* 1.0 Hz, 15-H), 4.56 (1 H, d, *J* 4.6 Hz, 13-H), 2.57—2.46 (1 H, m, 12-H), 1.79 (3 H, d, *J* 1.0 Hz, 14-Me), 1.06 (3 H, d, *J* 7.0 Hz, 12-Me), 0.88 (9 H, s, ^{t}BuSi), 0.04 (3 H, s, MeSi), and 0.00 (3 H, s, MeSi); δ_C 203.43 (C-11), 147.35 (C-14), 79.16 (C-15*), 76.27 (C-13*), 50.39 (C-12), 25.69 (^{t}BuSi), 21.00 (14-Me), 18.13 (^{t}BuSi), 8.21 (12-Me), −4.69 (MeSi), and −5.03 (MeSi): *m/z* (e.i.) 353 (M^+ − 15, 15%), 311 (100), 184 (34), and 115 (15) [Found: *m/z* 310.9991. $C_9H_{16}IO_2Si$ (M^+ − C_4H_9) requires *m/z* 310.9964].

(*Z*)-α,β-*Unsaturated Ester* (**15**).—$KN(SiMe_3)_2$ in toluene (0.5M, 28 ml) was added dropwise to a cooled (−80 °C) and stirred solution of bis(2,2,2-trifluoroethyl)methoxycarbonylmethylphosphonate (4.66 g, 14.65 mmol) and 18-crown-6 (8.42 g, 31.85 mmol) in anhydrous THF (200 ml), under nitrogen over 15 min. The mixture was stirred at −80 °C for another 10 min before the aldehyde (**14**) (4.69 g, 12.74 mmol) in anhydrous THF (25 ml) was added dropwise over 15 min (< −78 °C). Stirring was continued at this temperature for 1 h and the reaction was quenched by addition of saturated aqueous NH_4Cl (200 ml) and allowed to warm to room temperature. The organic phase was decanted off and the aqueous layer extracted with Et_2O (2 × 200 ml). The combined organic solutions were washed once with brine (150 ml), dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, hexane–4% Et_2O) of the residue gave the required (*Z*)-olefin (**15**) (5.3 g, 98%) as a colourless liquid; $[\alpha]_D$ +118.7° (*c* 0.54 in CH_2Cl_2); $\nu_{max.}$(film) 2 960, 2 930, 2 860, 1 725, 1 640, 1 470, 1 460, 1 440, 1 405, 1 375, 1 360, 1 260, 1 200, 1 180, 1 080, 1 030, 1 005, 940, 880, 865, 840, and 775 cm^{-1}; δ_H 6.14 (1 H, t, *J* 1.0 Hz, 15-H), 5.98 (1 H, dd, *J* 11.5, *J'* 10.2 Hz, 11-H), 5.73 (1 H, dd, *J* 11.5, *J'* 0.8 Hz, 10-H), 4.03 (1 H, d, *J* 5.7 Hz, 13-H), 3.71 (3 H, s, OMe), 3.76—3.64 (1 H, m, 12-H), 1.77 (3 H, d, *J* 1.0 Hz, 14-Me), 0.98 (3 H, d, *J* 6.7 Hz, 12-Me), 0.89 (9 H, s, ^{t}BuSi), 0.01 (3 H, s, MeSi), and −0.05 (3 H, s, MeSi); δ_C 166.50 (C-9), 152.45 (C-11), 149.18 (C-14), 118.55 (C-10), 80.56 (C-15*), 78.04 (C-13*), 51.13 (OMe), 36.85 (C-12), 25.77 (^{t}BuSi), 20.38 (14-Me), 18.20 (^{t}BuSi), 14.89 (12-Me), −4.79 (MeSi), and −5.20 (MeSi); *m/z* (e.i.) 367 (M^+ − 57, 21%), 311 (100), 171 (11), 127 (11) [Found: *m/z* 367.0275. $C_{12}H_{20}IO_3Si$ (M^+ − C_4H_9) requires *m/z*, 367.0226].

α,β-*Unsaturated Lactone* (**16**).—A solution of the silylated hydroxyester (**15**) (5.74 g, 13.53 mmol) in 80% AcOH–TFA (5:1, 240 ml) was heated at 85—90 °C for 2 h 20 min under nitrogen. After being cooled to room temperature, solvents were removed under reduced pressure. Flash chromatography of the residue (silica gel, hexane–75% Et_2O) gave the title compound (3.43 g, 91%) as a colourless liquid; $[\alpha]_D$ +320.4° (*c* 0.44 in CH_2Cl_2); $\nu_{max.}$(film) 3 090, 2 980, 2 930, 2 880, 1 730, 1 630, 1 450, 1 380, 1 370, 1 280, 1 245, 1 110, 1 065, 1 000, 820, and 760 cm^{-1}; δ_H 7.00 (1 H, dd, *J* 9.6, *J'* 6.3 Hz, 11-H), 6.61 (1 H, q, *J* 1.3 Hz, 15-H), 6.01 (1 H, d, *J* 9.6 Hz, 10-H), 4.90 (1 H, br d, *J* 2.9 Hz, 13-H), 2.62 (1 H, dqn, *J* 7.0, *J'* 3.4 Hz, 12-H), 1.84 (3 H, s, 14-Me), and 0.94 (3 H, d, *J* 7.0 Hz, 12-Me); δ_C 163.35 (C-9), 150.96 (C-11), 140.85 (C-14), 119.92 (C-10), 82.10 (C-15*), 80.24 (C-13*), 31.28 (C-12), 21.80 (14-Me), and 11.90 (12-Me); *m/z* (e.i.) 278 (M^+, 11%), 151 (26), 95 (11), 82 (100), and 69 (30) (Found: *m/z* 277.9758. $C_9H_{11}IO_2$ requires *m/z*, 277.9804).

Preparation of Lactol (**17**).—Reduction of the lactone (**16**) (3.43 g, 12.33 mmol) with DIBAL-H in toluene (1M, 19.7 ml) in toluene at −80 °C, using the same conditions described for the aldehyde (**14**), gave the lactol (**17**) (3.4 g, 99%) as a 11.5:1 mixture of α and β anomers after flash chromatography on silica gel (hexane–45% Et_2O); $[\alpha]_D$ +252.8° (*c* 0.64 in CH_2Cl_2); $\nu_{max.}$(film) 3 600—3 100, 3 090, 3 040, 2 970, 2 930, 2 880, 1 660, 1 620, 1 450, 1 380, 1 370, 1 250, 1 190, 1 150, 1 095, 1 060, 1 020, 925, 900, 820, 765, and 745 cm^{-1}; δ_H 6.32—6.30 (1 H, m, 15-H), 6.07 (1 H, dd, *J* 9.9, *J'* 5.8 Hz, 11-H), 5.74 (1 H, ddd, *J* 9.9, *J'* 2.8, *J''* 1.2 Hz, 10-H), 5.44 (1 H, br s, 9-H), 4.55 (1 H, br s, 13-H), 2.66 (1 H, d, *J* 4.6 Hz, OH), 2.64—2.22 (1 H, m, 12-H), 1.81 (3 H, s, 14-Me), and 0.78 (3 H, d, *J* 7.0 Hz, 12-Me); δ_C 144.74 (C-14), 135.00 (C-11), 124.58 (C-10), 89.51 (C-9), 77.50 (C-15), 72.86 (C-13), 30.99 (C-12), 22.28 (14-Me), and 12.59 (12-Me); *m/z* (e.i.) 263 (M^+ − 17, 7%), 197 (9), 136 (13), 91 (32), and 84 (100) [Found: *m/z*, 262.9935. $C_9H_{12}IO$ (M^+ − OH) requires *m/z*, 262.9933].

Methyl Acetal (**2**).—Pyridinium toluene-*p*-sulphonate (294 mg, 1.17 mmol) was added to a solution of the hemiacetal (**17**) (3.28 g, 11.71 mmol) in anhydrous MeOH (120 ml) and the resulting colourless mixture was stirred at room temperature for 16 h under nitrogen. The solvent was removed under reduced pressure and the resulting residue was flash chromatographed on silica gel (hexane–10% Et_2O) to give a 20:1 mixture of α and β anomers of the methyl acetal (**2**) (3.27 g, 98%) as a colourless liquid; $[\alpha]_D$ +215.8° (*c* 0.62 in CH_2Cl_2); $\nu_{max.}$(film) 3 090, 3 040, 2 970, 2 930, 2 890, 2 820, 1 660, 1 620, 1 450, 1 400, 1 375, 1 360, 1 340, 1 250, 1 190, 1 110, 1 090, 1 045, 1 000, 970, 900, 820, 765, and 730 cm^{-1}; δ_H 6.35—6.34 (1 H, m, 15-H), 6.04 (1 H, dd, *J* 10.0, *J'* 5.8 Hz, 11-H), 5.69 (1 H, ddd, *J* 10.0, *J'* 2.9, *J''* 1.1 Hz, 10-H), 4.89 (1 H, d, *J* 2.9 Hz, 9-H), 4.43 (1 H, br s, 13-H), 3.39 (3 H, s, 9-OMe), 2.67—2.20 (1 H, m, 12-H), 1.79 (3 H, d, *J* 0.9 Hz, 14-Me), and 0.78 (3 H, d, *J* 7.0 Hz, 12-Me); δ_C 144.97 (C-14), 134.99 (C-11), 123.99 (C-10), 96.10 (C-9), 77.13 (C-15), 72.71 (C-13), 55.32 (9-OMe), 31.08 (C-12), 22.14 (14-Me), and 12.54 (12-Me); *m/z* (c.i.) 294 (M^+, 11%), 263 (23), 152 (55), 137 (56), 135 (100), 133 (94), 106 (70), and 91 (75) (Found: *m/z* 294.0123. $C_{10}H_{15}IO_2$ requires *m/z*, 294.0117).

Silylated β-*Hydroxy Acid* (**13b**).—Hydrogen peroxide (30%, 4 ml, *ca.* 40 mmol) was added dropwise over 5 min to a cooled (0 °C) and stirred solution of the acyl oxazolidinone (**11**) (5.33 g, 9.79 mmol) in THF–water (4:1; 50 ml) under nitrogen, followed by a solution of $LiOH·H_2O$ (0.82 g, 19.6 mmol) in water (25 ml) over 7 min. After being stirred at 5 °C for 2 h, a solution of Na_2SO_3 (5.5 g) in water (40 ml) was added dropwise and stirring was continued at 7 °C for 30 min. The resulting reaction mixture (pH 13) was buffered to pH 9 with 5% aqueous $NaHCO_3$ and the THF removed. The basic aqueous solution was extracted with CH_2Cl_2 (4 × 100 ml) to give a mixture of the oxazolidinone chiral auxiliary and the required acid. After drying over $MgSO_4$, the solvent was removed under vacuum and the residue purified by flash chromatography (silica gel,

CH_2Cl_2–40% Et_2O) to give the acid (**13b**) (3.16 g, 84%) as a colourless viscous oil.

Preparation of the Ester (**13a**) *by Methylation of the Acid* (**13b**).—Sodium hydride (80% dispersion in oil, 290 mg, 9.7 mmol) was added to a cooled (−15 °C) and stirred solution of the acid (**13b**) (3.1 g, 8.06 mmol) in dry THF (40 ml), dry DMF (15 ml), and dry MeI (2.5 ml, 40.3 mmol) under nitrogen. After being stirred at −10 °C for 0.5 h and at room temperature for 2.5 h, the mixture was diluted with Et_2O (150 ml), washed with water (50 ml) and brine (35 ml), then dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, hexane–7% Et_2O) of the remaining yellow liquid afforded the methyl ester (**13a**) (3.18 g, 99%) as a colourless liquid.

2-*Hydroxy*-5-*methoxybenzaldehyde* (**19**).—A hot solution of NaOH (640 g, 16 mol) in water (800 ml) was added to *p*-methoxyphenol (250 g, 2 mol) followed by dropwise addition of chloroform (320 ml, *ca.* 2 mol) at such a rate as to keep the internal temperature at 70—80 °C (6.5 h). Stirring was continued for a further 30 min, and after being cooled to room temperature, the reaction mixture was acidified with 5M H_2SO_4 with formation of a large amount of precipitate. The solid was filtered off, the aqueous solution extracted with CH_2Cl_2 (6 × 200 ml) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining dark brown oil was distilled under vacuum (b.p. *ca.* 90 °C at 2 mmHg) to give a mixture of the required aldehyde and starting phenol. This mixture was vigorously shaken with a saturated aqueous solution of sodium metabisulphite (450 ml) for 30 min. The mixture was allowed to stand for 1 h and the solid bisulphite addition compound was filtered off and washed with cold absolute EtOH (100 ml) and Et_2O (2 × 250 ml). 2M H_2SO_4 (500 ml) was added to the solid and the mixture refluxed for 30 min. The acid phase was extracted with CH_2Cl_2 (6 × 200 ml) and the organic solutions were dried ($MgSO_4$) and concentrated. The remaining liquid was distilled at reduced pressure (b.p. 101—102 °C at 2 mmHg) to give the title compound (147 g, 48%) as a yellow liquid (lit.,[45] b.p. 133 °C at 15 mmHg).

2-*Hydroxy*-5-*methoxy*-3-*nitrobenzaldehyde* (**20**).—A solution of nitric acid (70%, 80 ml, 1.28 mol) in acetic acid (300 ml) was added dropwise to a cooled and stirred solution of the aldehyde (**19**) (130 g, 0.85 mol) in AcOH (650 ml) at such a rate as to maintain the temperature between 10—15 °C (2.5 h). After being stirred for another 45 min, water (1.5 l) was added and the solid was filtered off and crystallized from AcOH to give the title compound (118 g, 70%) as yellow needles, m.p. 132—133 °C [lit.,[19] m.p. 132 °C (AcOH)]; δ_H(60 MHz, $CDCl_3$) 10.8 (1 H, s, exch. D_2O, OH), 10.4 (1 H, s, CHO), 7.8 and 7.7 (2 H, AB system, *J* 3.5 Hz, ArH), and 3.9 (3 H, s, OMe).

2,5-*Dimethoxy*-3-*nitrobenzaldehyde* (**21**).—Anhydrous K_2CO_3 (100.5 g, 727 mmol) followed by Me_2SO_4 (76 ml, 800 mmol) was added to a solution of 2-hydroxy-5-methoxy-3-nitrobenzaldehyde (**20**) (71.6 g, 363.5 mmol) in dry DMF (800 ml) and the mixture was stirred at room temperature for 16 h. As starting phenol still remained, more Me_2SO_4 (50 ml) was added, followed after 3 h by a further portion of Me_2SO_4 (30 ml). After further 2.5 h, the solvents were removed under vacuum, the remaining residue was poured into water (2 l) and products extracted with CH_2Cl_2 (8 × 200 ml). The combined organic solutions were dried ($MgSO_4$), concentrated and the residue crystallized from $CHCl_3$ to give the title compound (75.5 g, 99%) as yellow needles, m.p. 115—116.5 °C [lit.,[19] m.p. 113 °C ($CHCl_3$)]; δ_H(60 MHz, $CDCl_3$) 10.4 (1 H, s, CHO), 7.6 and 7.5 (2 H, AB system, *J* 3 Hz, ArH), 4.0 (3 H, s, OMe), and 3.9 (3 H, s, OMe).

erythro-*Aldol Compound* (**22**).—To a cooled (−75 °C) and stirred solution of the propionyl oxazolidinone (**9**) (18.8 g, 80.6 mmol) in dry CH_2Cl_2 (160 ml) was added dropwise Et_2BOTf[46] (19.3 g, 88.7 mmol) followed by dry Et_3N (14.2 ml, 101.6 mmol) over 15 min and the resulting pale yellow solution was stirred at −75 °C for 0.5 h and at −3 °C for 1 h under argon. After being recooled down to −73 °C, the aldehyde (**21**) (17.0 g, 80.6 mmol) in dry CH_2Cl_2 (80 ml) was added over 15 min and the mixture was vigorously stirred at −72 °C for 0.5 h and at 0 °C for 1 h. The reaction was quenched with pH 7 phosphate buffer (160 ml), diluted with MeOH (650 ml), and oxidized at 0 °C with MeOH–30% H_2O_2 (2:1; 240 ml) for 1 h. Volatiles were removed *in vacuo* and the products extracted into CH_2Cl_2 (3 × 300 ml), washed with 5% aqueous $NaHCO_3$ (1 × 85 ml), dried ($MgSO_4$), and concentrated to give a yellow solid. Crystallization from CH_2Cl_2–EtOAc (three crops) gave the title compound (31.5 g, 88%) as yellow crystals, m.p. 201—203 °C; $[\alpha]_D$ +82° (*c* 2.0 in CH_2Cl_2); $\nu_{max.}$($CHCl_3$) 3 500, 2 960, 1 790, 1 700, 1 540, and 1 350 cm^{-1}; δ_H 7.45—7.28 (7 H, m, ArH and Ph), 5.69 (1 H, d, *J* 7.3 Hz, 5′-H), 5.41 (1 H, t, *J* 3.0 Hz, 21-H), 4.82 (1 H, qn, *J* 6.8 Hz, 4′-H), 4.05 (1 H, dq, *J* 7.1, *J′* 3.0 Hz, 20-H), 3.88 (1 H, d, *J* 2.4 Hz, OH), 3.86 (3 H, s, OMe), 3.85 (3 H, s, OMe), 1.19 (3 H, d, *J* 7.1 Hz, 20-Me), and 0.91 (3 H, d, *J* 6.6 Hz, 4′-Me); δ_C(25.2 MHz, $CDCl_3$) 179.4 (s), 155.2 (s), 152.2 (s), 144.4 (s), 143.5 (s), 138.2 (s), 133.1 (s), 129.0 (d), 128.8 (d), 125.7 (d), 119.4 (d), 109.2 (d), 79.1 (d), 68.4 (d), 62.7 (q), 56.1 (q), 54.8 (d), 42.5 (d), 14.3 (q), and 10.9 (q); *m/z* (e.i.) 444 (M^+, 1%), 133 (27), 107 (100), and 57 (89) (Found: *m/z* 444.1531; C, 59.60; H, 5.30; N, 6.20. $C_{22}H_{24}N_2O_8$ requires *m/z*, 444.1533; C, 59.45; H, 5.45; N, 6.30%).

Methyl β-*Hydroxy Ester* (**23**).—Removal of the chiral auxiliary from (**22**) (21.5 g, 48.4 mmol) with NaOMe (0.4M in MeOH; 133.3 ml, 53.3 mmol) at −20 °C, using the same conditions described for compound (**10**), gave the methyl ester (**23**) (14.1 g, 97%) as a yellow viscous oil after flash chromatography on silica gel (CH_2Cl_2–5% Et_2O); $[\alpha]_D$ +3.8° (*c* 11.3 in CH_2Cl_2); $\nu_{max.}$(film) 3 520, 1 740, 1 540, and 1 360 cm^{-1}; δ_H 7.38 (1 H, d, *J* 1.3 Hz, ArH), 7.30 (1 H, d, *J* 1.3 Hz, ArH), 5.42 (1 H, t, *J* 2.8 Hz, 21-H), 3.85 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.39 (1 H, d, *J* 3.0 Hz, OH), 2.98 (1 H, dq, *J* 7.2, *J′* 2.8 Hz, 20-H), and 1.04 (3 H, d, *J* 7.2 Hz, 20-Me); *m/z* (e.i.) 299 (M^+, 11%), 212 (74), and 88 (100) (Found: *m/z* 299.1016. $C_{13}H_{17}NO_7$ requires *m/z*, 299.1005).

Preparation of Methyl Ether (**24**).—To a cooled (−12 °C) and stirred solution of the hydroxy ester (**23**) (13.96 g, 46.6 mmol) in anhydrous THF (295 ml) and anhydrous DMF (98 ml) was added Me_2SO_4 (8.9 ml, 94 mmol) followed by NaH (80% dispersion in oil; 1.54 g, 51.3 mmol). The resulting mixture was stirred at −3 °C for 15 h under nitrogen before dry Et_3N (26 ml, 186.7 mmol) was added and stirring was continued for 0.5 h. Water (170 ml) was then added and the products were extracted into Et_2O (3 × 200 ml), washed with brine (1 × 100 ml), dried ($MgSO_4$), and concentrated. Flash chromatography of the remaining residue (silica gel, hexane–40% Et_2O) afforded the methyl ether (**24**) (13.2 g, 90%) as a yellow oil; $[\alpha]_D$ +36.4° (*c* 1.4 in CH_2Cl_2); $\nu_{max.}$(film) 1 740, 1 540, 1 360, and 1 090 cm^{-1}; δ_H 7.30 (1 H, d, *J* 3.3 Hz, ArH), 7.18 (1 H, d, *J* 3.3 Hz, ArH), 4.98 (1 H, d, *J* 4.6 Hz, 21-H), 3.89 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.69 (3 H, s, OMe), 3.29 (3 H, s, 21-OMe), 2.87 (1 H, dq, *J* 7.1, *J′* 4.6 Hz, 20-H), and 1.08 (3 H, d, *J* 7.1 Hz, 20-Me); δ_C(25.2 MHz, $CDCl_3$) 174.0 (s), 155.4 (s), 150.0 (s), 145.3 (s), 137.4 (s), 119.1 (d), 109.2 (d), 78.3 (d), 62.8 (q), 57.1 (q), 56.1 (q), 51.9 (q), 44.7 (d), and 10.7 (q); *m/z* (e.i.) 313 (M^+, 11%), 253 (16), 226 (100), 196 (11), and 149 (22) (Found: *m/z* 313.1175. $C_{14}H_{19}NO_5$ requires *m/z* 313.1161).

2′,5′-*Dimethylpyrrole Compound* (**25**).—To a solution of the

nitro compound (**24**) (16.28 g, 54.42 mmol) in absolute EtOH (300 ml) was added 10% Pd on C (2.35 g) and the mixture was hydrogenated at 1 atm for 2.5 h at room temperature. The catalyst was removed by filtration through Hyflo filter aid, washed with EtOH (150 ml), and the combined solvents were removed under vacuum to give the crude amine which was azeotropically dried with toluene (1 × 200 ml).

A solution of the above amine, acetonylacetone (19.2 ml, 163.3 mmol), and isobutyric acid (3 ml) in toluene (350 ml) was refluxed for 65 h under nitrogen using a Dean–Stark apparatus. After being cooled to room temperature, the yellow solution was diluted with Et_2O (350 ml) and washed with 5% aqueous $NaHCO_3$ (2 × 100 ml). The aqueous phase was extracted once with Et_2O (200 ml) and the combined organic solutions were washed once with brine (150 ml), dried ($MgSO_4$), and concentrated. Column chromatography on silica gel (hexane–30% Et_2O) of the remaining residue gave the pyrrole compound (**25**) (17.8 g, 91%) as a pale yellow viscous oil; $[\alpha]_D$ +46° (*c* 0.2 in CH_2Cl_2); $\nu_{max.}$(film) 2 960, 1 740, 1 630, 1 490, 1 350, 1 240, 1 090, and 1 050 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 6.9 (1 H, d, *J* 3 Hz, 5-H), 6.6 (1 H, d, *J* 3 Hz, 3-H), 5.9 (2 H, s, ArH), 4.9 (1 H, d, *J* 5 Hz, 21-H), 3.8 (3 H, s, 4-OMe), 3.65 (3 H, s, COOMe), 3.30 (3 H, s, 21-OMe), 3.20 (3 H, s, 1-OMe), 3.10—2.70 (1 H, m, 20-H), 2.10 (3 H, s, ArMe), 2.00 (3 H, s, ArMe), and 1.15 (3 H, d, *J* 7 Hz, 20-Me); *m/z* (e.i.) 361 (M^+, 100%), 274 (71), and 59 (13) (Found: *m/z* 361.1889. $C_{20}H_{27}NO_5$ requires *m/z* 361.1918).

Preparation of Alcohol (**26**).—To a cooled (0 °C) and stirred solution of the ester (**25**) (18.35 g, 50.80 mmol) in anhydrous THF (500 ml) was added solid $LiAlH_4$ (1.92 g, 50.70 mmol) over 10 min under nitrogen. The resulting mixture was stirred at 0 °C for 3 h then excess of hydride was destroyed by dropwise addition of a saturated aqueous solution of Na_2SO_4 (55 ml). The aluminium salts were filtered off and washed with THF (1 × 150 ml), Et_2O (1 × 150 ml), and CH_2Cl_2 (2 × 250 ml). The combined organic solutions were washed once with brine (100 ml), dried (Na_2SO_4), and concentrated. Column chromatography (silica gel, hexane–60% Et_2O) of the residue afforded the title compound (16.9 g, 100%) as a colourless viscous oil which solidified on standing; $[\alpha]_D$ +84.3° (*c* 0.28 in CH_2Cl_2); $\nu_{max.}$(film) 3 500, 2 940, 1 610, 1 480, 1 230, and 1 050 cm^{-1}; δ_H 6.97 (1 H, d, *J* 3.2 Hz, 5-H), 6.67 (1 H, d, *J* 3.2 Hz, 3-H), 5.92 (2 H, s, ArH), 4.57 (1 H, d, *J* 6.6 Hz, 21-H), 3.80 (3 H, s, 4-OMe), 3.50 (2 H, br s, 19-H), 3.30 (3 H, s, 21-OMe), 3.21 (3 H, s, 1-OMe), 2.44 (1 H, br s, OH), 2.09 (3 H, s, ArMe), 2.01 (3 H, s, ArMe), 1.94—1.85 (1 H, m, 20-H), and 1.05 (3 H, d, *J* 7.0 Hz, 20-Me); δ_C 155.68, 147.93, 135.26, 131.50, 129.63, 128.00, 114.50, 111.98, 106.30, 105.95, 80.32, 65.76, 60.04, 57.47, 55.70, 41.99, 12.98, 12.54, and 12.40; *m/z* (e.i.) 333 (M^+, 21%), 274 (33) and 69 (100) (Found: *m/z* 333.1930. $C_{19}H_{27}NO_4$ requires *m/z* 333.1940).

Aldehyde (**27**).—To a stirred solution of the alcohol (**26**) (16.9 g, 50.70 mmol) in dry DMSO (325 ml), dry THF (50 ml), and dry Et_3N (50 ml, 360 mmol) was added portionwise solid SO_3–Py complex (25 g, 157 mmol) over 30 min at room temperature under nitrogen. After a further 15 min, the mixture was acidified to pH 4 with 10% aqueous HCl (ice–water bath) and diluted with water (250 ml). The aqueous solution was extracted with hexane–EtOAc (1:1; 2 × 250 ml) and the combined organic phases were washed with 10% HCl (80 ml) and brine (100 ml), then dried ($MgSO_4$) and concentrated. The resulting oil was purified by flash chromatography (silica gel, hexane–20% Et_2O) to give the aldehyde (**27**) (14.9 g, 89%) as a colourless viscous oil; $[\alpha]_D$ +69.3° (*c* 0.54 in CH_2Cl_2); $\nu_{max.}$(film) 2 980, 2 940, 2 825, 1 730, 1 610, 1 480, 1 450, 1 430, 1 400, 1 350, 1 230, 1 200, 1 080, 1 050, and 1 005 cm^{-1}; δ_H 9.75 (1 H, d, *J* 0.9 Hz, 19-H), 6.95 (1 H, d, *J* 3.1 Hz, 5-H), 6.66 (1 H, d, *J* 3.1 Hz, 3-H), 5.91 (2 H, s, ArH), 5.01 (1 H, d, *J* 4.5 Hz, 21-H), 3.80 (3 H, s, 4-OMe), 3.33 (3 H, s, 21-OMe), 3.18 (3 H, s, 1-OMe), 2.69 (1 H, m, 20-H), 2.09 (3 H, s, ArMe), 1.99 (3 H, s, ArMe), and 1.08 (3 H, d, *J* 7.1 Hz, 20-Me); δ_C 203.15 (d), 155.23 (s), 147.43 (s), 133.62 (s), 131.37 (s), 129.37 (s), 128.27 (s), 114.37 (d), 112.51 (d), 106.27 (d), 106.02 (d), 77.16 (d), 59.61 (q), 57.57 (q), 55.71 (q), 51.68 (d), 12.89 (q), 12.48 (q), and 8.3 (q); *m/z* (e.i.) 331 (M^+, 36%), 274 (31), 244 (16), 176 (38), 131 (100), 103 (54), and 77 (46) (Found: *m/z* 331.1788. $C_{19}H_{25}NO_4$ requires *m/z* 331.1783).

(E)-α,β-*Unsaturated Ester* (**28**).—A solution of the aldehyde (**27**) (14.96 g, 45.17 mmol) and Ph_3P=CHCOOMe (30.2 g, 90.34 mmol) in dry CH_2Cl_2 (350 ml) was refluxed under nitrogen for 48 h. The solvent was removed under vacuum and the residue was passed through a plug of silica gel (eluting with Et_2O) to remove most of the unreacted phosphorane and triphenylphosphine oxide. Further flash chromatography purification (silica gel, hexane–20% Et_2O) gave the (*E*)-olefin (**28**) (17.40 g, 99.5%) as a colourless viscous oil; $[\alpha]_D$ +70.0° (*c* 0.36 in CH_2Cl_2); $\nu_{max.}$(film) 2 930, 2 825, 1 725, 1 655, 1 610, 1 590, 1 480, 1 450, 1 400, 1 340, 1 270, 1 225, 1 200, 1 175, 1 100, 1 050, and 1 005 cm^{-1}; δ_H 6.90 (1 H, d, *J* 3.3 Hz, 5-H), 6.69 (1 H, dd, *J* 15.8, *J'* 7.9 Hz, 19-H), 6.64 (1 H, d, *J* 3.3 Hz, 3-H), 5.90 (1 H, d, *J* 4.1 Hz, ArH), 5.89 (1 H, d, *J* 4.1 Hz, ArH), 5.70 (1 H, dd, *J* 15.8, *J'* 1.2 Hz, 18-H), 4.49 (1 H, d, *J* 6.7 Hz, 21-H), 3.79 (3 H, s, 4-OMe), 3.67 (3 H, s, COOMe), 3.37 (3 H, s, 21-OMe), 3.14 (3 H, s, 1-OMe), 2.67 (1 H, m, 20-H), 2.06 (3 H, s, ArMe), 1.97 (3 H, s, ArMe), and 1.13 (3 H, d, *J* 6.7 Hz, 20-Me); δ_C 166.83, 155.15, 150.70, 148.25, 134.60, 131.21, 129.40, 128.29, 120.94, 114.71, 111.91, 106.07, 105.80, 80.21, 59.57, 57.26, 55.63, 51.34, 43.23, 15.06, 12.79, and 12.39 *m/z* (e.i.) 387 (M^+, 45%), 274 (100), and 244 (17) (Found: *m/z*, 387.2051. $C_{22}H_{29}NO_5$ requires *m/z*, 387.2046).

Preparation of Ester (**29**).—To a solution of the α,β-unsaturated ester (**28**) (6.94 g, 17.92 mmol) in absolute EtOH (175 ml) was added 10% Pd on C (700 mg) and the mixture was hydrogenated at 1 atm for 30 min at room temperature. The catalyst was removed by filtration through hyflo filter aid and washed with EtOH–Et_2O (1:1; 250 ml), and solvents were then removed under vacuum. The remaining residue was purified by flash chromatography (silica gel, hexane–20% Et_2O) to give the title compound (6.88 g, 99%) as a colourless viscous oil; $[\alpha]_D$ + 64.2° (*c* 0.58 in CH_2Cl_2); $\nu_{max.}$(film) 2 935, 2 825, 1 740, 1 610, 1 590, 1 480, 1 450, 1 400, 1 340, 1 230, 1 200, 1 170, 1 100, 1 080, 1 050, and 1 010 cm^{-1}; δ_H 6.92 (1 H, d, *J* 3.2 Hz, 5-H), 6.64 (1 H, d, *J* 3.2 Hz, 3-H), 5.91 (1 H, d, *J* 4.0 Hz, ArH), 5.90 (1 H, d, *J* 4.0 Hz, ArH), 4.38 (1 H, d, *J* 5.6 Hz, 21-H), 3.79 (3 H, s, 4-OMe), 3.63 (3 H, s, COOMe), 3.26 (3 H, s, 21-OMe), 3.16 (3 H, s, 1-OMe), 2.44—2.23 (2 H, s, 18-H), 2.08 (3 H, s, ArMe), 2.01 (3 H, s, ArMe), 1.80—1.66 (2 H, s, 19-H and 20-H), 1.56—1.46 (1 H, m, 19-H), and 0.94 (3 H, d, *J* 6.7 Hz, 20-Me); δ_C 174.13, 155.18, 148.32, 135.70, 131.27, 129.40, 128.33, 114.14, 112.19, 106.05, 105.82, 80.99, 59.58, 57.38, 55.66, 51.46, 38.74, 31.98, 28.39, 14.59, 12.86, and 12.52; *m/z* (e.i.) 389 (M^+, 66%), 358 (15), 274 (100), 244 (15), and 83 (66) (Found: *m/z* 389.2193. $C_{22}H_{31}NO_5$ requires *m/z*, 389.2202).

Preparation of Acid (**30**).—To a solution of the ester (**29**) (2.74 g, 7.04 mmol) in MeOH–water–THF (3:1:1; 100 ml) was added $LiOH{\cdot}H_2O$ (1.77 g, 42.24 mmol) and the resulting yellow solution was stirred at room temperature for 24 h under nitrogen. The reaction mixture was acidified to pH 2 with aqueous 10% HCl, volatiles were removed *in vacuo* and the aqueous solution was extracted with CH_2Cl_2 (3 × 60 ml). The combined organic phases were dried ($MgSO_4$) and concentrated to give the crude acid (**30**) (2.70 g, 100%) which was used in the

next step without further purification after being azeotropically dried with toluene (2 × 50 ml).

Acyl Oxazolidinone (**31**).—(*a*) *Preparation of the mixed anhydride.* To a cooled (−15 °C) and stirred solution of the crude acid (**30**) (2.25 g, 6.0 mmol) in anhydrous toluene (18 ml) was added dry Et_3N (0.84 ml, 6.06 mmol) followed by pivaloyl chloride (0.75 ml, 6.06 mmol), and the resulting mixture was stirred at −10 °C for 10 min and at 0 °C for 40 min, under nitrogen.

(*b*) *Preparation of the lithiated oxazolidinone.* To a cooled (−75 °C) and stirred solution of (*S*)-4-isopropyl-2-oxazolidinone[14] (1.78 g, 13.8 mmol) in anhydrous THF (42 ml) was added dropwise, under nitrogen, BuLi (1.6M in hexane; 8.6 ml, 13.8 mmol) over 10 min and stirring was continued for a further 15 min at the same temperature.

(*c*) *Preparation of* (**31**). To the above cooled suspension of the lithium salt of the oxazolidinone, the above mixed anhydride mixture was added dropwise and stirring was continued for 1 h at −75 °C. Saturated aqueous NH_4Cl (65 ml) was added, the mixture was allowed to warm to room temperature and the products were extracted into Et_2O (3 × 80 ml). The combined organic extracts were washed with 5% aqueous $NaHCO_3$ (50 ml) and brine (50 ml), then dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, hexane–50% Et_2O) of the residue gave the title compound (2.62 g, 89%) as a colourless viscous oil [together with recovered starting acid (**30**) (130 mg, 4.5%)]; $[\alpha]_D$ +87.5° (*c* 0.40 in CH_2Cl_2); $\nu_{max.}$(film) 2 985, 2 960, 1 780, 1 700, 1 610, 1 480, 1 390, 1 180, 1 100, 1 050, and 1 010 cm^{-1}; δ_H 6.94 (1 H, d, *J* 3.1 Hz, 5-H), 6.63 (1 H, d, *J* 3.1 Hz, 3-H), 5.90 (2 H, s, ArH), 4.43 (1 H, d, *J* 5.2 Hz, 21-H), 4.39 (1 H, m, 4′-H), 4.26—4.17 (2 H, m, 5′-H), 3.79 (3 H, s, 4-OMe), 3.27 (3 H, s, 21-OMe), 3.16 (3 H, s, 1-OMe), 2.97 (2 H, br t, *J* 8.6 Hz, 18-H), 2.40—2.30 (1 H, m, 4′-H), 2.07 (3 H, s, ArMe), 2.00 (3 H, s, ArMe), 1.86—1.73 (2 H, m, 19-H and 20-H), 1.57—1.48 (1 H, m, 19-H), 0.95 (3 H, d, *J* 6.7 Hz, 20-Me), 0.90 (3 H, d, *J* 7.0 Hz, Me), and 0.85 (3 H, d, *J* 6.9 Hz, Me); δ_C 173.21, 155.15, 153.97, 148.32, 135.85, 131.27, 129.34, 128.38, 114.23, 112.25, 106.02, 105.79, 80.93, 63.32, 59.59, 58.43, 57.40, 55.66, 38.63, 33.40, 28.45, 27.96, 17.98, 14.71, 14.50, 12.81, and 12.54; *m/z* (e.i.) 486 (M^+, 23%), 274 (44), 149 (12), and 83 (100) [Found (c.i.-h.r.m.s.): *m/z* 485.2629. $C_{27}H_{37}N_2O_6$ (M^+ − H) requires *m/z*, 485.2652].

α-Hydroxyacyl Oxazolidinone (**33**).—To a cooled (−78 °C) and stirred solution of $NaN(SiMe_3)$ (1M in THF; 36.4 ml) in anhydrous THF(200 ml) was added dropwise a solution of the acyl oxazolidinone (**31**) (13.59 g, 27.96 mmol) in anhydrous THF (80 ml) over 20 min under nitrogen. After being stirred at this temperature for 25 min, a precooled (−78 °C) solution of 2-benzenesulphonyl-3-phenyl-oxaziridine[18d] (13.14 g, 50.33 mmol) in anhydrous THF (50 ml) was added *via* cannula over 7 min and stirring was continued for a further 20 min. The excess of oxidizing agent was destroyed by reaction with dry Et_3N (11.7 ml, 83.9 mmol) for 20 min at −78 °C and the reaction was quenched with AcOH (16 ml, 280 mmol) and allowed to warm to room temperature. Water (100 ml) was added and the two phase system was vigorously stirred for 15 min before it was diluted with Et_2O (250 ml). The organic phase was decanted off, washed with water (1 × 100 ml), 5% aqueous $NaHCO_3$ (2 × 60 ml), and brine (1 × 70 ml), then dried ($MgSO_4$) and concentrated. Flash chromatography of the remaining residue (silica gel, 1 × CH_2Cl_2–5% Et_2O and 1 × hexane–55% Et_2O) gave the title compound (11.6 g, 83%) as a white solid which crystallized from Et_2O–hexane, m.p. 131.5—132 °C; $[\alpha]_D$ +81° (*c* 0.40 in CH_2Cl_2); $\nu_{max.}$(CH_2Cl_2) 3 600—3 400, 1 970, 1 940, 1 785, 1 695, 1 610, 1 480, 1 450, 1 430, 1 390, 1 210, 1 100, 1 050, 1 020, and 1 010 cm^{-1}; δ_H 6.93 (1 H, d, *J* 3.1 Hz, 5-H), 6.63 (1 H, d, *J* 3.1 Hz, 3-H), 5.90 (2 H, s, ArH), 5.07 (1 H, br t, 18-H), 4.73 (1 H, d, *J* 5.8 Hz, 21-H), 4.40—4.26 (3 H, m, 4′-H and 5′-H), 3.79 (3 H, s, 4-OMe), 3.30 (1 H, d, *J* 7.5 Hz, OH), 3.26 (3 H, s, 21-OMe), 3.17 (3 H, s, 1-OMe), 2.43 (1 H, m, 4′-CH), 2.24—2.10 (1 H, m, 20-H), 2.07 (3 H, s, ArMe), 1.99 (3 H, s, ArMe), 1.69—1.48 (2 H, m, 19-H), 1.03 (3 H, d, *J* 6.8 Hz, 20-Me), 0.93 (3 H, d, *J* 7.1 Hz, Me), and 0.88 (3 H, d, *J* 6.9 Hz, Me); δ_C 175.10, 155.19, 153.69, 148.43, 135.70, 131.31, 129.26, 128.42, 114.13, 112.34, 106.02, 105.83, 81.71, 69.04, 64.07, 59.65, 58.94, 57.31, 55.66, 37.59, 35.74, 28.23, 17.94, 14.53, 13.96, 12.80, and 12.57; *m/z* (e.i.) 502 (M^+, 92%), 375 (19), 274 (100), and 244 (22) (Found: *m/z* 502.2700; C, 64.45; H, 7.61; N, 5.55%. $C_{27}H_{38}N_2O_7$ requires *m/z*, 502.2679; C, 64.52; H, 7.62; N, 5.57%).

Methyl α-Hydroxy Ester (**34**).—To a cooled (−10 °C) and stirred solution of the hydroxyacyl oxazolidinone (**33**) (12.13 g, 24.15 mmol) in dry CH_2Cl_2 (250 ml) was added dropwise, under nitrogen, a solution of MeOMgCl (prepared from 17.7 ml of 3M MeMgCl in THF and 73 ml of anhydrous MeOH) over 10 min. After being stirred for 1 h at −10 °C, the reaction was quenched with 10% aqueous NaH_2PO_4 (160 ml) and the products were extracted into CH_2Cl_2 (3 × 150 ml). The combined organic extracts were washed once with brine (100 ml), then dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, CH_2Cl_2–12% EtOAc) of the residue afforded the methyl ester (**34**) (8.38 g, 86%) as a colourless viscous oil; $[\alpha]_D$ +58.9° (*c* 0.54 in CH_2Cl_2); $\nu_{max.}$(film) 3 600—3 300, 2 940, 2 830, 1 740, 1 610, 1 590, 1 480, 1 450, 1 430, 1 400, 1 345, 1 255, 1 230, 1 200, 1 180, 1 100, 1 050, and 1 010 cm^{-1}; δ_H 6.93 (1 H, d, *J* 3.2 Hz, 5-H), 6.64 (1 H, d, *J* 3.2 Hz, 3-H), 5.90 (2 H, s, ArH), 4.42 (1 H, d, *J* 5.8 Hz, 21-H), 4.22 (1 H, m, 18-H), 3.79 (3 H, s, 4-OMe), 3.75 (3 H, s, COOMe), 3.27 (3 H, s, 21-OMe), 3.16 (3 H, s, 1-OMe), 2.67 (1 H, d, *J* 5.8 Hz, OH), 2.16—2.05 (1 H, m, 20-H), 2.07 (3 H, s, ArMe), 1.99 (3 H, s, ArMe), 1.72—1.54 (2 H, m, 19-H), and 1.00 (3 H, d, *J* 6.8 Hz, 20-Me); δ_C 176.07 (s), 155.25 (s), 148.40 (s), 135.40 (s), 131.34 (s), 129.36 (s), 128.33 (s), 114.20 (d), 112.26 (d), 106.09 (d), 105.87 (d), 81.57 (d), 68.77 (d), 59.63 (q), 57.34 (q), 55.65 (q), 52.42 (q), 37.91 (t), 35.61 (d), 14.15 (q), 12.83 (q), and 12.44 (q); *m/z* (e.i.) 405 (M^+, 59%), 274 (100), and 244 (12) (Found: *m/z* 405.2159. $C_{22}H_{31}NO_6$ requires *m/z*, 405.2151).

Silylated α-Hydroxy Ester (**36**).—Reaction of the hydroxy ester (**34**) (17.40 g, 42.94 mmol) with TBDMS-OTf (17.0 g, 64.4 mmol) and 2,6-lutidine (12 ml, 107.4 mmol) in CH_2Cl_2 (200 ml) at 0 °C, using the same conditions described for the hydroxy ester (**13a**), gave the title compound (21.65 g, 97%) as a colourless viscous oil after flash chromatography on silica gel (CH_2Cl_2–2% EtOAc); $[\alpha]_D$ +34.0° (*c* 0.60 in CH_2Cl_2); $\nu_{max.}$(film) 2 950, 2 930, 2 860, 1 760, 1 740, 1 610, 1 590, 1 520, 1 480, 1 450, 1 430, 1 400, 1 345, 1 250, 1 230, 1 200, 1 175, 1 145, 1 110, 1 050, 1 010, 840, 780, and 760 cm^{-1}; δ_H 6.87 (1 H, d, *J* 3.2 Hz, 5-H), 6.59 (1 H, d, *J* 3.2 Hz, 3-H), 5.86 (2 H, s, ArH), 4.31 (1 H, d, *J* 5.6 Hz, 21-H), 4.19 (1 H, dd, *J* 9.8, *J′* 3.4 Hz, 18-H), 3.74 (3 H, s, 4-OMe), 3.64 (3 H, s, COOMe), 3.23 (3 H, s, 21-OMe), 3.10 (3 H, s, 1-OMe), 2.10—2.00 (1 H, m, 20-H), 2.04 (3 H, s, ArMe), 1.94 (3 H, s, ArMe), 1.71—1.54 (2 H, m, 19-H), 0.88 (3 H, d, *J* 6.8 Hz, 20-Me), 0.84 (9 H, s, ^{t}BuSi), 0.03 (3 H, s, MeSi), and 0.01 (3 H, s, MeSi); *m/z* (e.i.) 519 (M^+, 28%), 430 (26), 398 (11), 356 (13), 274 (43), 244 (17), 202 (26), 147 (35), and 89 (100) (Found: *m/z*, 519.3013. $C_{28}H_{45}NO_6Si$ requires *m/z*, 519.3016).

Aldehyde (**37**).—Reduction of the ester (**36**) (10.7 g, 20.56 mmol) with DIBAL-H (1M in toluene; 32.9 ml) in toluene at −80 °C, using the conditions described for the aldehyde (**14**), gave the crude aldehyde (**37**) (10.1 g) as a pale yellow viscous oil which was used in the next step without further purification after being azeotropically dried with toluene (2 × 200 ml). A sample purified by flash chromatography (silica gel, CH_2Cl_2–2.5% Et_2O) showed: $[\alpha]_D$ +34.3° (*c* 0.70 in CH_2Cl_2); $\nu_{max.}$(film)

2 950, 2 930, 2 860, 1 740, 1 610, 1 590, 1 480, 1 450, 1 430, 1 400, 1 345, 1 255, 1 230, 1 200, 1 180, 1 100, 1 050, 1 010, 840, 780, and 760 cm^{-1}; δ_H 9.48 (1 H, d, *J* 1.7 Hz, 17-H), 6.85 (1 H, d, *J* 3.2 Hz, 5-H), 5.58 (1 H, d, *J* 3.2 Hz, 3-H), 5.85 (2 H, s, ArH), 4.31 (1 H, d, *J* 5.5 Hz, 21-H), 3.98 (1 H, ddd, *J* 9.7, *J'* 3.7, *J''* 1.7 Hz, 18-H), 3.72 (3 H, s, 4-OMe), 3.22 (3 H, s, 21-OMe), 3.09 (3 H, s, 1-OMe), 2.05—1.98 (1 H, m, 20-H), 2.02 (3 H, s, ArMe), 1.93 (3 H, s, ArMe), 1.60—1.42 (2 H, m, 19-H), 0.86 (3 H, d, *J* 6.8 Hz, 20-Me), 0.83 (9 H, s, ^{t}BuSi), 0.03 (3 H, s, MeSi), and 0.01 (3 H, s, MeSi); *m/z* (e.i.) 489 (M^+, 42%), 428 (15), 400 (60), 274 (59), 244 (15), 191 (19), 149 (70), and 91 (100) (Found: *m/z*, 489.2891. $C_{27}H_{43}NO_5Si$ requires *m/z* 489.2910).

Preparation of (E)-*Olefin* (**38**).—To a stirred suspension of anhydrous $CrCl_2$ (20.2 g, 164.5 mmol) in anhydrous THF (400 ml) was added dropwise, under nitrogen, a solution of the crude aldehyde (**37**) (10.1 g, 20.6 mmol) and 1,1-di-iodoethane (11.6 g, 41.12 mmol) in anhydrous THF (75 ml) over 15 min. After being vigorously stirred at room temperature for 5 h, water (400 ml) was added and the organic phase was decanted off. The aqueous layer was extracted with Et_2O (3 × 250 ml) and the combined organic phases were washed once with brine (100 ml), dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, hexane–7% Et_2O) of the remaining residue gave the (*E*)-olefin (**38**) (9.37 g, 91%) as a colourless viscous oil; $[\alpha]_D$ +43.5° (*c* 0.46 in CH_2Cl_2); $\nu_{max.}$(film) 2 930, 2 860, 1 610, 1 590, 1 520, 1 480, 1 450, 1 430, 1 400, 1 345, 1 255, 1 230, 1 200, 1 180, 1 090, 1 055, 1 010, 970, 840, 775, and 760 cm^{-1}; δ_H 6.92 (1 H, d, *J* 3.2 Hz, 5-H), 6.62 (1 H, d, *J* 3.2 Hz, 3-H), 5.90 (2 H, s, ArH), 5.51 (1 H, dq, *J* 15.2, *J'* 6.4 Hz, 16-H), 5.34 (1 H, dd, *J* 15.2, *J'* 7.0 Hz, 17-H), 4.34 (1 H, d, *J* 5.6 Hz, 21-H), 4.13—4.05 (1 H, m, 18-H), 3.78 (3 H, s, 4-OMe), 3.26 (3 H, s, 21-OMe), 3.14 (3 H, s, 1-OMe), 2.07 (3 H, s, ArMe), 2.00 (3 H, s, ArMe), 2.06—1.94 (1 H, m, 20-H), 1.62 (3 H, d, *J* 6.4 Hz, 16-Me), 1.58—1.49 (1 H, m, 19-H), 1.29—1.21 (1 H, m, 19-H), 0.89 (3 H, d, *J* 6.8 Hz, 20-Me), 0.84 (9 H, s, ^{t}BuSi), and 0.03 (6 H, s, MeSi); *m/z* (e.i.) 501 (M^+, 38%), 357 (25), 338 (29), 274 (100), 244 (21), 185 (19), and 159 (23) (Found: *m/z* 501.3268. $C_{29}H_{47}NO_4Si$ requires *m/z*, 501.3274).

Allylic Alcohol (**39**).—To a solution of the TBDMS-protected alcohol (**38**) (9.25 g, 18.45 mmol) in anhydrous THF (170 ml) was added TBAF (1M in THF; 36.9 ml) and the resulting pale green solution was stirred at room temperature for 16 h under nitrogen. Ether (500 ml) was added and the organic solution was washed with saturated aqueous NH_4Cl (2 × 140 ml) and brine (1 × 140 ml), then dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, hexane–55% Et_2O) of the residue gave the title compound (6.94 g, 97%) as a colourless viscous oil; $[\alpha]_D$ +56.8° (*c* 0.44 in CH_2Cl_2); $\nu_{max.}$(film) 3 650—3 200, 2 930, 2 830, 1 610, 1 590, 1 520, 1 480, 1 450, 1 430, 1 400, 1 380, 1 345, 1 230, 1 200, 1 180, 1 100, 1 050, 1 010, 970, 865, and 760 cm^{-1}; δ_H 6.95 (1 H, d, *J* 3.2 Hz, 5-H), 6.64 (1 H, d, *J* 3.2 Hz, 3-H), 5.91 (2 H, s, ArH), 5.64 (1 H, dq, *J* 15.3, *J'* 6.3 Hz, 16-H), 5.45 (1 H, ddq, *J* 15.3 *J'* 6.7, *J''* 1.4 Hz, 17-H), 4.43 (1 H, d, *J* 5.5 Hz, 21-H), 4.11 (1 H, m, 18-H), 3.79 (3 H, s, 4-OMe), 3.28 (3 H, s, 21-OMe), 3.16 (3 H, s, 1-OMe), 2.08 (3 H, s, ArMe), 2.01 (3 H, s, ArMe), 2.05—1.94 (1 H, m, 20-H), 1.70 (1 H, d, *J* 4.1 Hz, OH), 1.67 (3 H, dd, *J* 6.3, *J'* 1.4 Hz, 16-Me), 1.59 (1 H, ddd, *J* 14.1, *J'* 9.1, *J''* 5.2 Hz, 19-H), 1.34 (1 H, ddd, *J* 14.1, *J'* 8.5, *J''* 4.4 Hz, 19-H), and 0.95 (3 H, d, *J* 6.8 Hz, 20-Me); δ_C 155.13 (s), 148.34 (s), 135.59 (s), 134.71 (s), 131.27 (s), 129.41 (s), 128.31 (s), 126.11 (d), 114.07 (d), 112.43 (d), 106.04 (d), 105.79 (d), 81.47 (d), 70.81 (d), 59.60 (q), 57.37 (q), 55.65 (q), 40.86 (t), 35.82 (d), 17.68 (q), 15.09 (q), 12.89 (q), and 12.56 (q); *m/z* (e.i.) 387 (M^+, 47%), 274 (100), 244 (18), and 142 (89) (Found: *m/z* 387.2404. $C_{23}H_{33}NO_4$ requires *m/z* 387.2409).

Epoxy Alcohol (**40**).—To a cooled (−20 °C) and stirred solution of (L)-(+)-DIPT (4.97 g, 21.23 mmol) in dry CH_2Cl_2 (100 ml) was added $Ti(O^iPr)_4$ (5.26 ml, 17.69 mmol) followed by the allylic alcohol (**39**) (6.58 g, 17.69 mmol) in dry CH_2Cl_2 (25 ml) at such a rate as to keep the temperature below −19 °C. After being stirred for 30 min at this temperature under argon, TBHP (3M in iso-octane; 11.8 ml, 35.38 mmol) was added dropwise over 5 min and stirring was continued at −20 °C for 23 h. The mixture was allowed to warm to 0 °C, then water (100 ml) and CH_2Cl_2 (100 ml) were added and the two-phase system was vigorously stirred at 0 to 25 °C for 55 min. 30% Aqueous NaOH (20 ml) and brine (2 ml) were added and stirring was resumed for a further 55 min. Water (120 ml) was added and the products were extracted into CH_2Cl_2 (3 × 250 ml), dried (Na_2SO_4), and concentrated. Flash chromatography (silica gel, hexane–60% Et_2O) of the residue gave a 95:5 mixture (7.10 g, 99.6%) of the required epoxide (**40**) and its corresponding isomer, respectively. This mixture could be purified by column chromatography on alumina (CH_2Cl_2–10% EtOAc) to give pure (**40**) as a colourless viscous oil; $[\alpha]_D$ +66.4° (*c* 0.60 in CH_2Cl_2); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 2 830, 1 610, 1 590, 1 520, 1 480, 1 450, 1 430, 1 400, 1 380, 1 345, 1 230, 1 200, 1 180, 1 100, 1 050, and 1 010 cm^{-1}; δ_H 6.97 (1 H, d, *J* 3.2 Hz, 5-H), 6.65 (1 H, d, *J* 3.2 Hz, 3-H), 5.91 (2 H, s, ArH), 4.46 (1 H, d, *J* 5.6 Hz, 21-H), 3.85—3.79 (1 H, m, 18-H), 3.79 (3 H, s, 4-OMe), 3.28 (3 H, s, 21-OMe), 3.17 (3 H, s, 1-OMe), 3.03 (1 H, dq, *J* 5.3, *J'* 2.3 Hz, 16-H), 2.69 (1 H, dd, *J* 3.4, *J'* 2.3 Hz, 17-H), 2.14—2.02 (1 H, m, 20-H), 2.08 (3 H, s, ArMe), 2.01 (3 H, s, ArMe), 1.55—1.40 (2 H, m, 19-H), 1.30 (3 H, d, *J* 5.3 Hz, 16-Me), and 0.97 (3 H, d, *J* 6.8 Hz, 20-Me); δ_C 155.16 (s), 148.36 (s), 135.30 (s), 131.26 (s), 129.31 (s), 128.22 (s), 114.12 (d), 112.40 (d), 106.07 (d), 105.81 (d), 81.60 (d), 66.90 (d), 62.19 (d), 59.60 (q), 57.32 (q), 55.63 (q), 51.10 (d), 36.50 (t), 35.83 (d), 17.25 (q), 14.82 (q), 12.87 (q), and 12.54 (q); *m/z* (e.i.) 403 (M^+, 34%), 274 (100), 244 (11), and 149 (13) (Found: *m/z* 403.2363. $C_{23}H_{33}NO_5$ requires *m/z*, 403.2359).

Epoxide (**3**).—To a cooled (−15 °C) solution of the epoxy alcohol (**40**) (containing 5% of other isomer; 14.46 g, 35.86 mmol) and MeI (11.2 ml, 180 mmol) in anhydrous THF (180 ml) was added portionwise, under nitrogen, NaH (80% dispersion in oil; 1.40 g, 46.6 mmol) and the mixture was stirred at −15 °C for 15 min and at 0 °C for 3 h. Water (100 ml) and Et_2O (250 ml) were added, the organic phase was decanted off and the aqueous layer extracted with Et_2O (2 × 200 ml). The combined organic phases were washed once with brine (100 ml), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel (CH_2Cl_2–5% EtOAc) afforded the diastereoisomerically pure epoxy ether (**3**) (13.18 g, 88%) as a colourless oil which solidified on standing; $[\alpha]_D$ +48.2° (*c* 0.56 in CH_2Cl_2); $\nu_{max.}$(film) 2 970, 2 930, 2 820, 1 610, 1 590, 1 520, 1 480, 1 450, 1 430, 1 400, 1 380, 1 345, 1 230, 1 200, 1 175, 1 100, 1 050, 1 010, 955, 870, and 760 cm^{-1}; δ_H 6.94 (1 H, d, *J* 3.1 Hz, 5-H), 6.63 (1 H, d, *J* 3.1 Hz, 3-H), 5.90 (2 H, s, ArH), 4.39 (1 H, d, *J* 5.9 Hz, 21-H), 3.79 (3 H, s, 4-OMe), 3.34 (3 H, s, 18-OMe), 3.26 (3 H, s, 21-OMe), 3.16 (3 H, s, 1-OMe), 3.06 (1 H, ddd, *J* 9.9, *J'* 5.8, *J''* 3.1 Hz, 18-H), 2.97 (1 H, dq, *J* 5.2, *J'* 2.1 Hz, 16-H), 2.51 (1 H, dd, *J* 5.8, *J'* 2.1 Hz, 17-H), 2.07 (3 H, s, ArMe), 2.02 (3 H, s, ArMe), 2.10—1.98 (1 H, m, 20-H), 1.56 (1 H, ddd, *J* 14.0, *J'* 9.9, *J''* 4.2 Hz, 19-H), 1.43 (1 H, ddd, *J* 14.0, *J'* 9.9, *J''* 3.1 Hz, 19-H), 1.30 (3 H, d, *J* 5.2 Hz, 16-Me), and 0.93 (3 H, d, *J* 6.7 Hz, 20-Me); δ_C 155.15 (s), 148.42 (s), 135.73 (s), 131.21 (s), 129.33 (s), 128.38 (s), 114.06 (d), 112.34 (d), 106.00 (d), 105.80 (d), 81.77 (d), 78.54 (d), 60.71 (d), 59.59 (q), 57.89 (q), 57.34 (q), 55.64 (q), 53.47 (d), 35.78 (t), 35.31 (d), 17.33 (q), 14.61 (q), 12.85 (q), and 12.61 (q); *m/z* (e.i.) 417 (M^+, 58%), 274 (100), and 244 (15) (Found: *m/z* 417.2514; C, 69.02; H, 8.49; N, 3.40. $C_{24}H_{35}NO_5$ requires *m/z*, 417.2515; C, 69.04; H, 8.45; N, 3.35%).

Preparation of Alcohol (**45**) *by Reduction of Ester* (**13a**).—To

a cooled (−60 °C) and stirred solution of the ester (**13a**) (22.1 g, 55.5 mmol) in anhydrous toluene (400 ml) was added dropwise, under nitrogen, DIBAL-H (1M in toluene; 128 ml) over 40 min. The resulting colourless solution was allowed to warm to −20 °C and was stirred for 1 h before it was quenched with MeOH (40 ml). Citric acid (10% aqueous solution; 500 ml) was added, the organic phase was decanted off and the aqueous layer was extracted with CH_2Cl_2 (3 × 400 ml). The combined organic phases were dried ($MgSO_4$), the solvent was removed under vacuum and the residue purified by flash chromatography (silica gel, hexane–25% Et_2O) to give the alcohol (**45**) (20.1 g, 98%) as a colourless liquid; $[\alpha]_D$ +44.5° (*c* 0.60 in CH_2Cl_2); $\nu_{max.}$(film) 3 650—3 150, 2 960, 2 930, 2 890, 2 860, 1 615, 1 470, 1 460, 1 260, 1 140, 1 110, 1 080, 1 030, 840, and 780 cm^{-1}; δ_H 6.18 (1 H, s, 15-H), 4.21 (1 H, d, *J* 5.1 Hz, 13-H), 3.58—3.42 (2 H, m, 11-H), 1.90—1.76 (1 H, m, 12-H), 1.78 (3 H, s, 14-Me), 1.61 (1 H, br s, OH), 0.90 (9 H, s, ^{t}BuSi), 0.86 (3 H, d, *J* 6.7 Hz, 12-Me), 0.06 (3 H, s, MeSi), and −0.02 (3 H, s, MeSi); δ_C 148.95 (s), 78.20 (d), 77.98 (d), 65.24 (t), 39.63 (d), 25.79 (q), 21.08 (q), 18.18 (s), 11.58 (q), −4.79 (q), and −5.32 (q); *m/z* (e.i.) 313 (M^+ − 57, 58%), 271 (79), 186 (58), and 75 (100); *m/z* (c.i.) 371 (M^+ + 1, 18%), 313 (51), 271 (39), 239 (24), 186 (55), 111 (100), and 92 (64) [Found: *m/z* (c.i.-h.r.m.s.), 313.0108. $C_9H_{18}IO_2Si$ (M^+ − C_4H_9) requires *m/z* 313.0121].

Bis-silylated Diol (**46**).—To a solution of the alcohol (**45**) (27.38 g, 73.98 mmol) and imidazole (15.11 g, 221.94 mmol) in anhydrous DMF (250 ml) was added TBDMSCl (16.73 g, 110.97 mmol) and the mixture was stirred at room temperature for 20 h under argon. Ether (650 ml) was added and the solution was washed with water (200 ml), 1M HCl (180 ml), 5% aqueous $NaHCO_3$ (180 ml), and brine (180 ml), then dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, hexane) of the residue gave the title compound (35.8 g, 100%) as a colourless liquid; $[\alpha]_D$ +26.1° (*c* 0.44 in CH_2Cl_2); $\nu_{max.}$(film) 2 960, 2 930, 2 900, 2 860, 1 615, 1 470, 1 460, 1 390, 1 360, 1 255, 1 140, 1 100, 1 070, 1 030, 1 005, 940, 880, 835, 810, and 775 cm^{-1}; δ_H 6.11 (1 H, t, *J* 1.2 Hz, 15-H), 4.20 (1 H, d, *J* 5.2 Hz, 13-H), 3.43 (1 H, dd, *J* 10.0, *J'* 5.4 Hz, 11-H), 3.34 (1 H, dd, *J* 10.0, *J'* 5.4 Hz, 11-H), 1.73 (3 H, d, *J* 1.2 Hz, 14-Me), 1.75—1.66 (1 H, m, 12-H), 0.88 (18 H, s, 2 × ^{t}BuSi), 0.82 (3 H, d, *J* 6.7 Hz, 12-Me), 0.02 (9 H, s, MeSi), and 0.04 (3 H, s, MeSi); δ_C 149.23 (s), 77.38 (d), 77.07 (d), 64.69 (t), 39.78 (d), 25.86 (q), 25.79 (q), 20.75 (q), 18.19 (s), 11.29 (q), −4.81 (q), −5.32 (q), −5.41 (q), and −5.46 (q); *m/z* (c.i.) 484 (M^+, 5%), 469 (3), 427 (22), 385 (13), 353 (100), 311 (26), 238 (72), 206 (32), 164 (31), 132 (22), and 90 (28) [Found: *m/z* (e.i.-h.r.m.s.) 427.1000. $C_{15}H_{32}IO_2Si_2$ (M^+ − C_4H_9) requires *m/z*, 247.0986].

Coupling of the Epoxide (**3**) *and the Vinyl Iodide* (**46**): *Preparation of the Alcohol* (**48**).—To a cooled (−77 °C) and stirred solution of the vinyl iodide (**46**) (780 mg, 1.61 mmol) in anhydrous Et_2O (5 ml) was added dropwise, under argon, ^{t}BuLi (1.43M in pentane; 2.25 ml, 3.22 mmol) over 5 min. After being stirred at −80 °C for 2 h, the newly formed vinyl lithium reagent was quickly cannulated into a cooled (−70 °C) suspension of CuCN (72 mg, 0.81 mmol) in anhydrous Et_2O (1.5 ml). The mixture was allowed to warm to 0 °C and was stirred at this temperature for 2 min to give a pale yellow solution of the cuprate which was immediately recooled to −75 °C. The epoxide (**3**) (280 mg, 0.67 mmol) in anhydrous Et_2O (2 ml) was added dropwise to the cuprate solution, followed by dry BF_3·OEt_2 (165 μl, 1.34 mmol) over 2 min, and stirring was continued for 1 h at −80 °C before the reaction was quenched with saturated NH_4Cl–NH_3(c) (9:1, 8 ml). After being stirred at room temperature for 25 min, the products were extracted into Et_2O (2 × 50 ml) and the combined organic solutions were washed once with brine (20 ml), dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, hexane–20% EtOAc) of the residue gave the coupled product (**48**) (435 mg, 84%) as a colourless thick gum together with the iodocompound (**44**) (45 mg, 12%). Compound (**48**): $[\alpha]_D$ +32.2° (*c* 0.45 in CH_2Cl_2); $\nu_{max.}$(film) 3 600—3 300, 2 960, 2 930, 2 860, 1 610, 1 590, 1 520, 1 480, 1 430, 1 400, 1 345, 1 250, 1 230, 1 200, 1 180, 1 100, 1 050, 1 010, 840, 810, 775, and 755 cm^{-1}; δ_H 6.94 (1 H, d, *J* 3.2 Hz, 5-H), 6.62 (1 H, d, *J* 3.2 Hz, 3-H), 5.90 (2 H, s, ArH), 5.11 (1 H, d, *J* 10.3 Hz, 15-H), 4.36 (1 H, d, *J* 5.8 Hz, 21-H), 4.03 (1 H, d, *J* 4.4 Hz, 13-H), 3.78 (3 H, s, 4-OMe), 3.62 (1 H, dd, *J* 9.4, *J'* 2.8 Hz, 17-H), 3.47 (1 H, dd, *J* 9.8, *J'* 6.5 Hz, 11-H), 3.33 (1 H, dd, *J* 9.8, *J'* 7.1 Hz, 11-H), 3.30 (3 H, s, 18-OMe*), 3.25 (3 H, s, 21-OMe*), 3.16 (3 H, s, 1-OMe), 3.15—3.13 (1 H, m, 18-H), 2.47—2.36 (1 H, m, 16-H), 2.07 (3 H, s, ArMe), 2.06 (1 H, s, OH), 2.02 (3 H, s, ArMe), 2.06—1.96 (1 H, m, 20-H), 1.70—1.54 (2 H, m, 19-H and 12-H), 1.54 (3 H, br s, 14-Me), 1.26—1.08 (1 H, m, 19-H), 1.04 (3 H, d, *J* 6.5 Hz, 16-Me), 0.90 (9 H, s, ^{t}BuSi), 0.89 (9 H, s, ^{t}BuSi), 0.86 (3 H, d, *J* 6.7 Hz, 20-Me), 0.79 (3 H, d, *J* 6.8 Hz, 12-Me), 0.03 (6 H, s, 2 × MeSi), 0.00 (3 H, s, MeSi), and −0.04 (3 H, s, MeSi); δ_C 155.14 (s), 148.44 (s), 136.57 (s), 135.81 (s), 131.23 (s), 129.53 (s), 128.27 (s), 126.99 (d), 113.99 (d), 112.35 (d), 106.00 (d), 105.70 (d), 82.40 (d), 79.89 (d), 76.55 (d), 73.62 (d), 65.39 (t), 59.54 (q), 57.34 (q), 56.71 (q), 55.64 (q), 40.31 (d), 35.23 (d), 34.41 (d), 30.46 (t), 25.96 (q), 25.92 (q), 18.25 (s), 27.88 (q), 14.63 (q), 13.14 (q), 12.88 (q), 12.62 (q), 11.15 (q), −4.26 (q), −5.03 (q), −5.16 (q), and −5.23 (q); *m/z* (e.i.) 776 (M^+, 74%), 470 (17), 358 (51), 330 (43), 274 (100), and 147 (51) (Found: *m/z* 775.5242. $C_{43}H_{77}NO_7Si_2$ requires *m/z*, 775.5239).

Methyl Ether (**49**).—To a cooled (0 °C) and stirred solution of the hydroxy compound (**48**) (15.24 g, 19.65 mmol) and dry MeI (12.2 ml, 197 mmol) in anhydrous THF (98 ml) was added NaH (80% dispersion in oil; 830 mg, 27.6 mmol) in one portion under argon. After 10 min, the mixture was allowed to warm to room temperature and stirred for 6 h. Ether (300 ml) and water (80 ml) were added and the organic phase was decanted off. The aqueous layer was extracted with Et_2O (2 × 200 ml) and the combined organic phases were washed once with brine (80 ml), dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, hexane–20% Et_2O) of the remaining residue gave the methyl ether (**49**) (14.85 g, 96%) as a colourless viscous oil; $[\alpha]_D$ +42.7° (*c* 0.60 in CH_2Cl_2); $\nu_{max.}$(film) 2 960, 2 930, 2 860, 2 830, 1 610, 1 590, 1 480, 1 430, 1 400, 1 345, 1 250, 1 230, 1 200, 1 180, 1 100, 1 080, 1 055, 1 010, 840, 775, and 760 cm^{-1}; δ_H 6.95 (1 H, d, *J* 3.2 Hz, 5-H), 6.62 (1 H, d, *J* 3.2 Hz, 3-H), 5.90 (2 H, br s, ArH), 5.15 (1 H, d, *J* 10.1 Hz, 15-H), 4.37 (1 H, d, *J* 5.7 Hz, 21-H), 3.98 (1 H, d, *J* 4.8 Hz, 13-H), 3.78 (3 H, s, 4-OMe), 3.47 (1 H, dd, *J* 9.9, *J'* 6.3 Hz, 11-H), 3.41 (3 H, s, 17-OMe), 3.30 (3 H, s, 18-OMe*), 3.26 (3 H, s, 21-OMe*), 3.31—3.18 (2 H, m, 11-H and 18-H), 3.16 (3 H, s, 1-OMe), 3.09 (1 H, dd, *J* 8.4, *J'* 2.4 Hz, 17-H), 2.52—2.40 (1 H, m, 16-H), 2.07 (3 H, s, ArMe), 2.02 (3 H, s, ArMe), 2.07—1.96 (1 H, m, 20-H), 1.74—1.54 (2 H, m, 19-H and 12-H), 1.53 (3 H, d, *J* 1.0 Hz, 14-Me), 1.33—1.24 (1 H, m, 19-H), 0.99 (3 H, d, *J* 6.6 Hz, 16-Me), 0.89 (9 H, s, ^{t}BuSi), 0.88 (9 H, s, ^{t}BuSi), 0.86 (3 H, d, *J* 6.8 Hz, 20-Me), 0.85 (3 H, d, *J* 6.8 Hz, 12-Me), 0.03 (3 H, s, MeSi), 0.02 (3 H, s, MeSi), 0.01 (3 H, s, MeSi), and −0.03 (3 H, s, MeSi); δ_C 155.07 (s), 148.45 (s), 136.25 (s), 136.06 (s), 131.16 (s), 129.40 (s), 128.69 (d), 128.44 (s), 114.02 (d), 112.36 (d), 105.91 (d), 105.69 (d), 84.75 (d), 82.56 (d), 80.90 (d), 77.24 (d), 65.38 (t), 60.73 (q), 59.55 (q), 57.39 (q), 56.92 (q), 55.63 (q), 40.57 (d), 35.46 (d), 34.85 (d), 32.68 (t), 25.94 (q), 25.91 (q), 18.23 (s), 17.20 (q), 14.51 (q), 12.91 (q), 12.18 (q), 12.62 (q), 11.58 (q), −4.25 (q), −5.05 (q), −5.20 (q), and −5.24 (q); *m/z* (e.i.) 790 (M^+, 42%), 676 (17), 489 (27), 404 (44), 328 (81), and 274 (100) [Found: *m/z* (c.i.-h.r.m.s.), 788.5292. $C_{44}H_{78}NO_7Si_2$ (M^+ − H) requires *m/z* 788.5317].

Mono-silylated Diol (**50**).—To a solution of the bis-silylated

diol (**49**) (1.11 g, 1.40 mmol) in anhydrous MeOH (16 ml) was added, under argon, HF·Py–Py–THF (1:3:3, 5.6 ml) and the resulting colourless solution was stirred at room temperature for 6.5 h. Solvents were removed under vacuum and the residue was dissolved in Et_2O (250 ml), washed with 1M HCl (50 ml), 5% aqueous $NaHCO_3$ (50 ml), and brine (50 ml), then dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, hexane–55% Et_2O) of the residue afforded the title compound (906 mg, 96%) as a colourless viscous oil; $[\alpha]_D$ +43.7° (*c* 0.60 in CH_2Cl_2); $\nu_{max.}$(film) 3 600—3 300, 2 960, 2 930, 2 860, 2 830, 1 610, 1 590, 1 520, 1 480, 1 430, 1 400, 1 345, 1 250, 1 230, 1 200, 1 180, 1 100, 1 055, 1 010, 870, 840, 775, and 760 cm^{-1}; δ_H 6.95 (1 H, d, *J* 3.2 Hz, 5-H), 6.62 (1 H, d, *J* 3.2 Hz, 3-H), 5.90 (2 H, s, ArH), 5.16 (1 H, d, *J* 10.0 Hz, 15-H), 4.40 (1 H, d, *J* 5.4 Hz, 21-H), 3.89 (1 H, d, *J* 6.6 Hz, 13-H), 3.78 (3 H, s, 4-OMe), 3.51 (1 H, dd, *J* 10.8, *J'* 6.6 Hz, 11-H), 3.41 (3 H, s, 17-OMe), 3.39 (1 H, dd, *J* 10.8, *J'* 5.2 Hz, 11-H), 3.30 (3 H, s, 18-OMe*), 3.26 (3 H, s, 21-OMe*), 3.29—3.23 (1 H, m, 18-H), 3.16 (3 H, s, 1-OMe), 3.09 (1 H, dd, *J* 8.0, *J'* 2.5 Hz, 17-H), 2.60—2.49 (1 H, m, 16-H), 2.07 (3 H, s, ArMe), 2.02 (3 H, s, ArMe), 2.06—1.96 (1 H, m, 20-H), 1.91—1.79 (1 H, m, 12-H), 1.71—1.63 (1 H, m, 19-H), 1.60 (3 H, d, *J* 1.1 Hz, 14-Me), 1.40—1.25 (1 H, m, 19-H), 1.01 (3 H, d, *J* 6.7 Hz, 16-Me), 0.95 (3 H, d, *J* 6.8 Hz, 12-Me), 0.89 (9 H, s, ^{t}BuSi), 0.88 (3 H, d, *J* 6.6 Hz, 20-Me), 0.05 (3 H, s, MeSi), and −0.01 (3 H, s, MeSi); δ_C 154.94 (s), 148.25 (s), 136.20 (s), 135.97 (s), 131.16 (s), 129.79 (d), 129.32 (s), 128.33 (s), 113.98 (d), 112.33 (d), 105.94 (d), 105.70 (d), 85.13 (d), 82.36 (d), 80.86 (d), 80.64 (d), 65.64 (t), 60.33 (q), 59.56 (q), 57.37 (q), 56.90 (q), 55.62 (q), 40.19 (d), 35.56 (d), 34.68 (d), 33.05 (t), 25.85 (q), 18.14 (s), 17.04 (q), 14.30 (q), 13.18 (q), 12.81 (q), 12.58 (q), 12.43 (q), −4.36 (q), and −5.10 (q); *m/z* (e.i.) 676 (M^+, 71%), 404 (31), 340 (58), and 274 (46) [Found: *m/z* (c.i.-h.r.m.s.) 674.4448. $C_{38}H_{64}NO_7Si$ (M^+ − H) requires *m/z* 674.4452].

Aldehyde (**51**).—Oxidation of the alcohol (**50**) (2.53 g, 3.74 mmol) with SO_3·Py (7.16 g, 45 mmol) in DMSO–THF (6:1; 30 ml) and Et_3N (10 ml, 72 mmol), using the conditions described for the aldehyde (**27**), produced the aldehyde (**51**) (2.24 g, 89%) as a colourless viscous oil after flash chromatography on silica gel (hexane–15% EtOAc); $[\alpha]_D$ +43.4° (*c* 0.50 in CH_2Cl_2); $\nu_{max.}$(film) 2 960, 2 930, 2 860, 2 820, 1 725, 1 075, 1 610, 1 590, 1 520, 1 480, 1 450, 1 425, 1 395, 1 340, 1 250, 1 225, 1 200, 1 185, 1 100, 1 050, 1 005, 840, 775, and 755 cm^{-1}; δ_H 9.67 (1 H, d, *J* 1.8 Hz, 11-H), 6.95 (1 H, d, *J* 3.2 Hz, 5-H), 6.62 (1 H, d, *J* 3.2 Hz, 3-H), 5.90 (2 H, s, ArH), 5.23 (1 H, d, *J* 10.1 Hz, 15-H), 4.37 (1 H, d, *J* 5.6 Hz, 21-H), 4.26 (1 H, d, *J* 6.3 Hz, 13-H), 3.78 (3 H, s, 4-OMe), 3.40 (3 H, s, 17-OMe), 3.29 (3 H, s, 18-OMe*), 3.26 (3 H, s, 21-OMe*), 3.16 (3 H, s, 1-OMe), 3.16—3.11 (1 H, m, 18-H), 3.06 (1 H, dd, *J* 8.3, *J'* 2.5 Hz, 17-H), 2.54 (1 H, dqn, *J* 6.7, *J'* 1.8 Hz, 12-H), 2.50—2.40 (1 H, m, 16-H), 2.07 (3 H, s, ArMe), 2.02 (3 H, s, ArMe), 2.04—1.94 (1 H, m, 20-H), 1.67—1.57 (1 H, m, 19-H), 1.57 (3 H, d, *J* 1.1 Hz, 14-Me), 1.30—1.24 (1 H, m, 19-H), 1.04 (3 H, d, *J* 6.7 Hz, 12-Me), 1.01 (3 H, d, *J* 6.6 Hz, 16-Me), 0.88 (9 H, s, ^{t}BuSi), 0.85 (3 H, d, *J* 6.7 Hz, 20-Me), 0.04 (3 H, s, MeSi), and 0.00 (3 H, s, MeSi); δ_C 203.97 (d), 155.08 (s), 148.42 (s), 136.04 (s), 134.60 (s), 131.18 (s), 130.86 (d), 129.41 (s), 128.43 (s), 114.02 (d), 112.33 (d), 105.92 (d), 105.69 (d), 84.65 (d), 82.51 (d), 80.69 (d), 77.92 (d), 60.73 (q), 59.57 (q), 57.39 (q), 56.94 (q), 55.64 (q), 51.17 (d), 35.46 (d), 34.82 (d), 32.73 (t), 25.79 (q), 18.14 (s), 16.94 (q), 14.39 (q), 12.82 (q), 12.63 (q), 12.47 (q), 9.47 (q), −4.28 (q), and −5.05 (q); *m/z* (e.i.) 674 (M^+, 2%), 541 (13), 328 (13), 274 (25), 181 (29), and 125 (100) (Found: *m/z* (c.i.-h.r.m.s.) 672.4269. $C_{38}H_{62}NO_7Si$ (M^+ − H) requires *m/z* 672.4295].

(Z)-α,β-*Unsaturated Ester* (**52**).—The title compound (a colourless viscous oil) was prepared in 99% isolated yield (after flash chromatography on silica gel, hexane–15% EtOAc) from aldehyde (**51**) following the methodology described for the unsaturated ester (**15**); $[\alpha]_D$ +95.5° (*c* 0.40 in CH_2Cl_2); $\nu_{max.}$(film) 2 960, 2 930, 2 860, 2 830, 1 725, 1 645, 1 610, 1 590, 1 520, 1 480, 1 400, 1 340, 1 255, 1 230, 1 200, 1 180, 1 100, 1 010, 960, 875, 840, 775, and 755 cm^{-1}; δ_H 6.94 (1 H, d, *J* 3.2 Hz, 5-H), 6.62 (1 H, d, *J* 3.2 Hz, 3-H), 5.98 (1 H, dd, *J* 11.6, *J'* 10.2 Hz, 11-H), 5.90 (2 H, s, ArH), 5.65 (1 H, dd, *J* 11.6, *J'* 0.7 Hz, 10-H), 5.16 (1 H, d, *J* 10.0 Hz, 15-H), 4.36 (1 H, d, *J* 5.9 Hz, 21-H), 3.79 (1 H, d, *J* 6.5 Hz, 13-H), 3.78 (3 H, s, 4-OMe), 3.72—3.65 (1 H, m, 12-H), 3.66 (3 H, s, COOMe), 3.38 (3 H, s, 17-OMe), 3.29 (3 H, s, 18-OMe*), 3.25 (3 H, s, 21-OMe*), 3.19—3.15 (1 H, m, 18-H), 3.16 (3 H, s, 1-OMe), 3.05 (1 H, dd, *J* 8.3, *J'* 2.5 Hz, 17-H), 2.48—2.36 (1 H, m, 16-H), 2.07 (3 H, s, ArMe), 2.02 (3 H, s, ArMe), 2.04—1.92 (1 H, m, 20-H), 1.64—1.56 (1 H, m, 19-H), 1.55 (3 H, d, *J* 1.1 Hz, 14-Me), 1.30—1.22 (1 H, m, 19-H), 1.00 (3 H, d, *J* 6.6 Hz, 12-Me), 0.98 (3 H, d, *J* 6.6 Hz, 16-Me), 0.90 (9 H, s, ^{t}BuSi), 0.83 (3 H, d, *J* 6.7 Hz, 20-Me), 0.02 (3 H, s, MeSi), and −0.03 (3 H, s, MeSi); δ_C 166.40 (s), 155.09 (s), 153.14 (d), 148.49 (s), 136.47 (s), 136.14 (s), 131.17 (s), 129.93 (d), 129.40 (s), 128.43 (s), 118.17 (d), 114.09 (d), 112.28 (d), 105.92 (d), 105.59 (d), 84.84 (d), 82.57 (d), 82.01 (d), 80.78 (d), 60.62 (q), 59.54 (q), 57.36 (q), 56.81 (q), 55.64 (q), 50.95 (q), 37.32 (d), 35.56 (d), 34.65 (d), 32.78 (t), 25.86 (q), 18.19 (s), 16.86 (q), 16.02 (q), 14.57 (q), 12.80 (q), 12.59 (q), 12.13 (q), −4.25 (q), and −4.93 (q); *m/z* (e.i.) 729 (M^+, 33%), 340 (15), 274 (10), and 149 (100) [Found: *m/z* (c.i.-h.r.m.s.), 728.4535. $C_{41}H_{66}NO_8Si$ (M^+ − H) requires *m/z* 728.4558].

Allylic Alcohol (**53**).—Reduction of the ester (**52**) (11.14 g, 15.27 mmol) with DIBAL-H (1M in toluene; 39.7 ml) in toluene (130 ml) at −33 °C, according to the method described for the alcohol (**45**), afforded the allylic alcohol (**53**) (10.55 g, 99%) as a colourless viscous oil after flash chromatography on silica gel (hexane–60% Et_2O); $[\alpha]_D$ +68.9° (*c* 0.52 in CH_2Cl_2); $\nu_{max.}$(film) 3 650—3 250, 2 960, 2 930, 2 860, 1 610, 1 590, 1 520, 1 480, 1 430, 1 400, 1 345, 1 250, 1 230, 1 200, 1 180, 1 100, 1 050, 1 010, 875, 840, 775, and 755 cm^{-1}; δ_H 6.95 (1 H, d, *J* 3.2 Hz, 5-H), 6.62 (1 H, d, *J* 3.2 Hz, 3-H), 5.90 (2 H, s, ArH), 5.52 (1 H, dt, *J* 10.9, *J'* 6.9 Hz, 10-H), 5.23 (1 H, t, *J* 10.9 Hz, 11-H), 5.09 (1 H, d, *J* 10.1 Hz, 15-H), 4.38 (1 H, d, *J* 5.6 Hz, 21-H), 4.19—4.07 (2 H, m, 9-H), 3.79 (3 H, s, 4-OMe), 3.69 (1 H, d, *J* 7.6 Hz, 13-H), 3.38 (3 H, s, 17-OMe), 3.29 (3 H, s, 18-OMe*), 3.26 (3 H, s, 21-OMe*), 3.26—3.20 (1 H, m, 18-H), 3.16 (3 H, s, 1-OMe), 3.04 (1 H, dd, *J* 7.5, *J'* 3.0 Hz, 17-H), 2.72—2.59 (1 H, m, 12-H), 2.54—2.42 (1 H, m, 16-H), 2.07 (3 H, s, ArMe), 2.02 (3 H, s, ArMe), 2.04—1.94 (1 H, m, 20-H), 1.68—1.57 (2 H, m, 19-H and OH), 1.52 (3 H, d, *J* 1.2 Hz, 14-Me), 1.36—1.25 (1 H, m, 19-H), 0.98 (6 H, d, *J* 6.6 Hz, 12-Me and 16-Me), 0.89 (9 H, s, ^{t}BuSi), 0.89 (3 H, d, *J* 6.7 Hz, 20-Me), 0.04 (3 H, s, MeSi), and −0.02 (3 H, s, MeSi); δ_C 155.09(s), 148.43 (s), 136.13 (s), 136.05 (s), 135.52 (d), 131.19 (s), 130.58 (d), 129.35 (s), 128.43 (s), 128.17 (d), 114.03 (d), 112.36 (d), 105.95 (d), 105.72 (d), 85.35 (d), 83.29 (d), 82.48 (d), 80.45 (d), 60.26 (q), 59.57 (q), 58.61 (t), 57.39 (q), 56.76 (q), 55.63 (q), 37.13 (d), 35.53 (d), 34.50 (d), 33.12 (t), 25.90 (q), 18.27 (s), 18.13 (q), 16.83 (q), 14.59 (q), 12.81 (q), 12.61 (q), 11.77 (q), −4.33 (q), and −4.93; *m/z* (e.i.) 701 (M^+, 5%), 404 (25), 340 (40), 274 (50), and 149 (50) [Found: *m/z* (c.i.-h.r.m.s.), 700.4614. $C_{40}H_{66}NO_7Si$ (M^+ − H) requires *m/z* 700.4609].

Preparation of the Aniline (**55**).—To a solution of the pyrrole compound (**53**) (5.18 g, 7.38 mmol) in absolute EtOH (60 ml) was added a solution of H_2NOH·HCl (15.38 g, 221.4 mmol) and KOH (8.28 g, 148 mmol) in water (25 ml) and the resulting white suspension was refluxed (bath temperature 125 °C) for 48 h under argon. After being cooled to room temperature, water (100 ml) was added and the ethanol was removed under reduced pressure. The remaining aqueous solution was basified with 10% NaOH, extracted with Et_2O (2 × 200 ml), and the combined organic phases were washed once with brine (75 ml), dried (Na_2SO_4), and concentrated. Flash chromatography of

the residue (silica gel, CH_2Cl_2–50% EtOAc) gave recovered (**53**) (1.3 g, 25%) and amine (**55**) [3.23 g, 70%; 93% based on recovered (**53**)] as a colourless viscous oil; $[\alpha]_D$ +51.1° (*c* 1.0 in CH_2Cl_2); $\nu_{max.}(CHCl_3)$ 3 550—3 300, 3 000, 2 960, 2 930, 2 860, 1 610, 1 490, 1 460, 1 350, 1 250, 1 240, 1 200, 1 170, 1 155, 1 100, 1 070, 1 050, 1 005, and 840 cm^{-1}; δ_H 6.30 (1 H, d, *J* 3.0 Hz, ArH), 6.23 (1 H, d, *J* 3.0 Hz, ArH), 5.50 (1 H, dt, *J* 10.9, *J'* 6.9 Hz, 10-H), 5.20 (1 H, t, *J* 10.9 Hz, 11-H), 5.08 (1 H, d, *J* 9.9 Hz, 15-H), 4.36 (1 H, d, *J* 4.6 Hz, 21-H), 4.17—4.05 (2 H, m, 9-H), 3.73 (3 H, s, ArOMe), 3.71 (3 H, s, ArOMe), 3.67 (1 H, d, *J* 7.8 Hz, 13-H), 3.44 (3 H, s, 17-OMe), 3.30 (3 H, s, 18-OMe*), 3.25 (3 H, s, 21-OMe*), 3.25—3.20 (1 H, m, 18-H), 3.06 (1 H, dd, *J* 7.4, *J'* 3.0 Hz, 17-H), 2.69—2.58 (1 H, m, 12-H), 2.55—2.44 (1 H, m, 16-H), 2.04—1.95 (1 H, m, 20-H), 1.75—1.66 (1 H, m, 19-H), 1.50 (3 H, d, *J* 1.3 Hz, 14-Me), 1.40—1.32 (1 H, m, 19-H), 1.00 (3 H, d, *J* 6.7 Hz, 16-Me), 0.98 (3 H, d, *J* 6.6 Hz, 12-Me), 0.89 (9 H, s, ^{t}BuSi), 0.86 (3 H, d, *J* 6.8 Hz, 20-Me), 0.04 (3 H, s, MeSi), and −0.02 (3 H, s, MeSi); δ_C 156.32 (s), 140.15 (s), 139.93 (s), 136.10 (s), 135.27 (d), 135.03 (s), 130.64 (d), 128.31 (d), 101.80 (d), 101.05 (d), 85.46 (d), 83.40 (d), 82.25 (d), 80.85 (d), 60.28 (q), 59.85 (q), 58.64 (t), 57.31 (q), 56.78 (q), 55.40 (q), 37.11 (d), 35.71 (d), 34.38 (d), 33.52 (t), 25.89 (q), 18.22 (q and s), 16.77 (q), 14.27 (q), 11.56 (q), −4.34 (q), and −4.94 (q); *m/z* (e.i.) 623 (M^+, 10%), 326 (40), 262 (100), 196 (53) [Found: *m/z* (c.i.-h.r.m.s.), 622.4154. $C_{34}H_{60}NO_7Si$ (M^+ − H) requires *m/z* 622.4139].

Trifluoroacetamide (**56**).—To a cooled (−8 °C) and stirred solution of the aniline (**55**) (7.63 g, 12.24 mmol) in dry CH_2Cl_2 (65 ml) and dry Et_3N (10.2 ml, 73.4 mmol) was added dropwise, under nitrogen, trifluoroacetic anhydride (TFAA; 5.2 ml, 36.7 mmol) over 10 min. The reaction mixture was then allowed to warm to room temperature and stirred for a further 40 min before it was quenched with pH 7 phosphate buffer (130 ml). Methanol (400 ml) was added and stirring was continued for 15 min. Volatiles were removed under vacuum and products were extracted into Et_2O (3 × 250 ml), washed with 5% aqueous $NaHCO_3$ (100 ml), 1M HCl (100 ml), and brine (100 ml), then dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, hexane–60% Et_2O) of the residue gave the trifluoroacetamide (8.33 g, 95%) as a colourless thick gum; $[\alpha]_D$ +38.9° (*c* 0.60 in CH_2Cl_2); $\nu_{max.}(CHCl_3)$ 3 550—3 360, 3 000, 2 960, 2 940, 2 860, 1 730, 1 600, 1 540, 1 470, 1 430, 1 360, 1 330, 1 170, 1 100, 1 050, 1 000, 880, and 840 cm^{-1}; δ_H 8.63 (1 H, br s, NH), 7.73 (1 H, d, *J* 3.1 Hz, 3-H), 6.77 (1 H, d, *J* 3.1 Hz, 5-H), 5.51 (1 H, dt, *J* 10.9, *J'* 6.8 Hz, 10-H), 5.51 (1 H, t, *J* 10.9 Hz, 11-H), 5.07 (1 H, d, *J* 10.6 Hz, 15-H), 4.37 (1 H, d, *J* 4.5 Hz, 21-H), 4.11 (2 H, d, *J* 6.8 Hz, 9-H), 3.80 (3 H, s, ArOMe), 3.75 (3 H, s, ArOMe), 3.67 (1 H, d, *J* 7.9 Hz, 13-H), 3.44 (3 H, s, 17-OMe), 3.31 (3 H, s, 18-OMe*), 3.25 (3 H, s, 21-OMe*), 3.24—3.18 (1 H, m, 18-H), 3.08 (1 H, dd, *J* 7.7, *J'* 2.8 Hz, 17-H), 2.68—2.56 (1 H, m, 12-H), 2.52—2.42 (1 H, m, 16-H), 2.02—1.90 (1 H, m, 20-H), 1.73—1.64 (2 H, m, 19-H and OH), 1.49 (3 H, d, *J* 1.2 Hz, 14-Me), 1.40—1.32 (1 H, m, 19-H), 1.01 (3 H, d, *J* 6.7 Hz, 16-Me), 0.98 (3 H, d, *J* 6.7 Hz, 12-Me), 0.89 (9 H, s, ^{t}BuSi), 0.82 (3 H, d, *J* 6.8 Hz, 20-Me), 0.04 (3 H, s, MeSi), and −0.02 (3 H, s, MeSi); δ_C 156.19 (s), 154.65 (q, *J* 37.3 Hz, CF_3CO), 141.78 (s), 136.33 (s), 135.44 (d), 135.41 (s), 130.52 (d), 129.30 (s), 128.15 (d), 118.01 (q, *J* 288 Hz, CF_3), 110.40 (d), 105.77 (d), 85.04 (d), 83.35 (d), 82.12 (d), 81.03 (d), 61.65 (q), 60.38 (q), 58.66 (t), 57.44 (q), 56.62 (q), 55.70 (q), 37.05 (d), 35.75 (d), 34.47 (d), 33.26 (t), 25.85 (q), 18.22 (q and s), 16.89 (q), 13.98 (q), 11.54 (q), −4.37 (q), and −4.98 (q); *m/z* (c.i.) 718 (M^+ − 1, 23%), 699 (100), and 519 (10) [Found: *m/z*, 718.3962. $C_{36}H_{59}F_4NO_8Si$ (M^+ − H) requires 718.3962].

Aldehyde (**57**).—To a solution of the allylic alcohol (**56**) (5.92 g, 8.23 mmol) in dry CH_2Cl_2 (100 ml) was added PDC (6.19 g, 16.46 mmol) and the resulting mixture was stirred at room temperature for 6.5 h under nitrogen. The chromium salts were removed by filtration through a plug of flash silica gel and washed with Et_2O (*ca.* 1 l). Solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel, hexane–50% Et_2O) to give a 11:1 mixture (5.58 g, 95%) of the required aldehyde (**57**) and the corresponding (*E*)-isomer at C(10)–C(11), which crystallized together from hexane, m.p. 118—119 °C; $[\alpha]_D$ +60.8° (*c* 0.50 in CH_2Cl_2); $\nu_{max.}(CHCl_3)$ 3 400, 2 960, 2 930, 2 860, 1 730, 1 680, 1 600, 1 540, 1 480, 1 430, 1 175, 1 100, 1 075, 1 000, and 840 cm^{-1}; δ_H(major isomer) 10.01 (1 H, d, *J* 8.0 Hz, 9-H), 8.56 (1 H, br s, NH), 7.76 (1 H, d, *J* 3.1 Hz, 3-H), 6.76 (1 H, d, *J* 3.1 Hz, 5-H), 6.35 (1 H, t, *J* 11.1 Hz, 11-H), 5.86 (1 H, dd, *J* 11.1, *J'* 8.0 Hz, 10-H), 5.21 (1 H, d, *J* 9.8 Hz, 15-H), 4.35 (1 H, d, *J* 4.5 Hz, 21-H), 3.81 (3 H, s, ArOMe), 3.79 (1 H, d, *J* 7.6 Hz, 13-H), 3.75 (3 H, s, ArOMe), 3.44 (3 H, s, 17-OMe), 3.42—3.30 (1 H, m, 12-H), 3.31 (3 H, s, 18-OMe*), 3.26 (3 H, s, 21-OMe*), 3.18—3.11 (1 H, m, 18-H), 3.06 (1 H, dd, *J* 7.8 , *J'* 2.6 Hz, 17-H), 2.51—2.42 (1 H, m, 16-H), 1.99—1.90 (1 H, m, 20-H), 1.73—1.65 (1 H, m, 19-H), 1.52 (3 H, s, 14-Me), 1.02 (3 H, d, *J* 6.6 Hz, 16-Me), 0.90 (9 H, s, ^{t}BuSi), 0.77 (3 H, d, *J* 6.8 Hz, 20-Me), 0.06 (3 H, s, MeSi), and 0.00 (3 H, s, MeSi); δ_C(major isomer) 190.67 (d), 156.15 (s), 154.78 (d), 141.72 (s), 135.59 (s), 135.23 (s), 131.54 (d), 129.26 (s), 129.16 (d), 110.32 (d), 105.63 (d), 84.77 (d), 82.44 (d), 82.06 (d), 80.94 (d), 61.65 (q), 60.62 (q), 57.40 (q), 56.90 (q), 55.70 (q), 37.58 (d), 35.54 (d), 34.48 (d), 33.32 (t), 25.81 (q), 18.18 (s), 17.86 (q), 16.52 (q), 13.94 (q), 11.79 (q), −4.32 (q), and −4.96 (q); *m/z* (c.i.) 717 (M^+, 100%), 633 (19), 519 (10) (Found: *m/z* 717.3867; C, 60.10; H, 8.10; N, 1.93. $C_{36}H_{58}F_3NO_8Si$ requires *m/z*, 717.3884; C, 60.23; H, 8.14; N, 1.95%).

(Z,E,)-*Diene* (**58**).—To a solution of the aldehyde (**57**) (11:1 *Z*:*E*, 5.40 g, 7.52 mmol) in dry CH_2Cl_2 (75 ml) was added Ph_3P=CMeCOOEt (5.45 g, 15.05 mmol) and the resulting yellow solution was refluxed under nitrogen for 40 h. The reaction was worked up as in the case of olefin (**28**) and the residue was purified by flash chromatography on silica gel (toluene–15% Et_2O) to give pure (*Z*,*E*)-diene (**58**) [5.26 g, 83% from (**56**)] as a white solid which crystallized from 90% EtOH–H_2O, m.p. 110—111 °C; $[\alpha]_D$ +101.3° (*c* 0.40 in CH_2Cl_2); $\nu_{max.}(CHCl_3)$ 3 400, 2 960, 2 940, 2 860, 1 730, 1 700, 1 600, 1 540, 1 470, 1 430, 1 370, 1 330, 1 250, 1 170, 1 100, 1 050, 1 000, 875, and 840 cm^{-1}; δ_H 8.46 (1 H, br s, NH), 7.78 (1 H, d, *J* 3.1 Hz, 3-H), 7.42 (1 H, br d, *J* 11.9 Hz, 9-H), 6.74 (1 H, d, *J* 3.1 Hz, 5-H), 6.13 (1 H, t, *J* 11.7 Hz, 15-H), 5.53 (1 H, t, *J* 10.7 Hz, 11-H), 5.12 (1 H, d, *J* 7 Hz, 15-H), 4.32 (1 H, d, *J* 4.6 Hz, 21-H), 4.20 (2 H, q, *J* 7.1 Hz, OCH_2), 3.80 (3 H, s, ArOMe), 3.74 (3 H, s, ArOMe), 3.73 (1 H, d, *J* 7.1 Hz, 13-H), 3.44 (3 H, s, 17-OMe), 3.30 (3 H, s, 18-OMe*), 3.22 (3 H, s, 21-OMe*), 3.18—3.12 (1 H, m, 18-H), 3.07 (1 H, dd, *J* 8.3, *J'* 2.4 Hz, 17-H), 2.96—2.84 (1 H, m, 12-H), 2.46—2.36 (1 H, m, 16-H), 2.01—1.90 (1 H, m, 20-H), 1.83 (3 H, d, *J* 1.1 Hz, 8-Me), 1.71—1.61 (1 H, m, 19-H), 1.51 (3 H, d, *J* 1.1 Hz, 14-Me), 1.35—1.26 (1 H, m, 19-H), 1.30 (3 H, t, *J* 7.1 Hz, OCH_2*Me*), 1.01 (3 H, d, *J* 7.0 Hz, 12-Me), 1.00 (3 H, d, *J* 7.0 Hz, 16-Me), 0.90 (9 H, s, ^{t}BuSi), 0.74 (3 H, d, *J* 6.8 Hz, 20-Me), 0.01 (3 H, s, MeSi), and 0.00 (3 H, s, MeSi); δ_C 168.44 (s), 156.19 (s), 141.85 (d), 141.61 (s), 136.40 (s), 135.32 (s), 132.52 (d), 130.55 (d), 129.28 (s), 127.67 (s), 123.07 (d), 110.20 (d), 105.55 (d), 84.73 (d), 82.29 (d), 82.28 (d), 80.97 (d), 61.71 (q), 60.72 (q), 60.56 (t), 57.38 (q), 56.81 (q), 55.68 (q), 37.50 (d), 35.44 (d), 34.57 (d), 33.28 (t), 25.88 (q), 18.22 (s), 17.72 (q), 16.76 (q), 14.33 (q), 13.90 (q), 12.32 (q), 11.87 (q), −4.27 (q), and −4.88 (q); *m/z* (c.i.) 802 (M^+ + 1, 100%) (Found: C, 61.35; H, 8.50; N, 1.75. $C_{41}H_{66}F_3NO_9Si$ requires C, 61.40; H, 8.29; N, 1.75%).

Amino Acid (**59**).—To a solution of the ester (**58**) (4.5 g, 5.61 mmol) in THF–MeOH–water (2:2:1; 180 ml) was added $LiOH{\cdot}H_2O$ (2.36 g, 56.1 mmol) and the resulting mixture was stirred at room temperature for 24 h under nitrogen. Methanol

and THF were removed under vacuum and the remaining aqueous solution was acidified to pH 5 with 10% aqueous NaH_2PO_4 (400 ml) and saturated with NaCl. The products were extracted into CH_2Cl_2 (3 × 200 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo* to give the crude amino acid (**59**) (3.86 g, 100%), which was used in the next step without further purification after being azeotropically dried with toluene (2 × 100 ml) and further dried at high vacuum (< 0.04 mmHg) overnight; δ_H(250 MHz, $CDCl_3$) 7.55 (1 H, d, *J* 12.0 Hz, 9-H), 6.29 (1 H, d, *J* 3.0 Hz, ArH), 6.24 (1 H, d, *J* 3.0 Hz, ArH), 6.16 (1 H, t, *J* 11.6 Hz, 10-H), 5.60 (1 H, t, *J* 10.4 Hz, 11-H), 5.14 (1 H, d, *J* 9.8 Hz, 15-H), 4.34 (1 H, d, *J* 4.7 Hz, 21-H), 3.74 (1 H, d, *J* 7.1 Hz, 13-H), 3.73 (3 H, s, ArOMe), 3.71 (3 H, s, ArOMe), 3.44 (3 H, s, 17-OMe), 3.31 (3 H, s, 18-OMe*), 3.24 (3 H, s, 21-OMe*), 3.22—3.14 (1 H, m, 18-H), 3.06 (1 H, dd, *J* 7.8, *J'* 2.5 Hz, 17-H), 3.00—2.82 (1 H, m, 12-H), 2.50—2.36 (1 H, m, 16-H), 2.00—1.88 (1 H, m, 20-H), 1.84 (3 H, s, 8-Me), 1.74—1.62 (1 H, m, 19-H), 1.50 (3 H, s, 14-Me), 1.36—1.26 (1 H, m, 19-H), 1.03 (3 H, d, *J* 7.0 Hz, 12-Me), 1.00 (3 H, d, *J* 7.1 Hz, 16-Me), 0.90 (9 H, s, ^{t}BuSi), 0.78 (3 H, d, *J* 6.8 Hz, 20-Me), 0.04 (3 H, s, MeSi), and −0.08 (3 H, s, MeSi).

Macrolactam (**60**).—*Method A:* To a warmed (60 °C) and stirred solution of 2-mesitylenesulphonyl chloride (34 mg, 0.155 mmol) and dry $^i Pr_2NEt$ (29 μl, 0.166 mmol) in anhydrous toluene (5 ml) was added dropwise (syringe pump addition; 1.2 ml/h) a solution of the amino acid (**59**) (10 mg, 0.015 mmol) and $^i Pr_2NEt$ (5.15 μl, 0.030 mmol) in anhydrous toluene (10 ml) over 8.5 h under nitrogen. Stirring was continued for a further 6 h at 60 °C before the pale yellow solution was allowed to cooled to room temperature and excess sulphonyl chloride was destroyed by reaction with wet pyridine (10% water in pyridine; 0.5 ml) for 15 min. Solvents were removed under vacuum and the residue was dissolved in Et_2O (30 ml), washed with 10% aqueous NaH_2PO_4 (6 ml) and brine (6 ml), dried (Na_2SO_4), and concentrated. Flash chromatography (silica gel, Et_2O) of the residue gave the macrolactam (**60**) (7 mg, 72%).

Method B: To a solution of the crude amino acid (**59**) (2 g, 2.95 mmol) and dry $^i Pr_2NEt$ (5.14 ml, 29.50 mmol) in anhydrous toluene (2 l) was added bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (2.25 g, 8.84 mmol) in one portion and the mixture was stirred at 85 °C for 16 h under nitrogen. After being cooled to room temperature, 10% aqueous NaH_2PO_4 (300 ml) was added, then the mixture was stirred for 5 min and the organic phase was decanted off. The aqueous layer was extracted with Et_2O (2 × 300 ml) and the combined organic phases were washed once with brine (300 ml), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (silica gel, CH_2Cl_2–40% EtOAc) gave the macrolactam (**60**) [1.65 g, 85% from (**58**)] as a white solid; all attempts to crystallize this compound have so far been unsuccessful; $[\alpha]_D$ +78.5° (*c* 0.33 in CH_2Cl_2); $\nu_{max.}$($CHCl_3$) 3 380, 3 000, 2 960, 2 930, 2 860, 1 650, 1 600, 1 480, 1 460, 1 375, 1 310, 1 250, 1 100, 1 070, 1 050, 1 005, 875, and 840 cm^{-1}; δ_H(360 MHz, [$^2H_6$]DMSO) 9.27 (1 H, br s, NH), 6.63 (1 H, d, *J* 2.9 Hz, 3-H), 6.43 (1 H, d, *J* 2.9 Hz, 5-H), 5.93 (1 H, br, d, *J* 11.2 Hz, 9-H), 5.78 (1 H, t, *J* 11.1 Hz, 10-H), 5.10 (1 H, t, *J* 10.8 Hz, 11-H), 4.87 (1 H, d, *J* 10.1 Hz, 15-H), 4.31 (1 H, d, *J* 5.3 Hz, 21-H), 3.67 (3 H, s, 4-OMe), 3.53 (1 H, d, *J* 9.6 Hz, 13-H), 3.43 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.21 (3 H, s, OMe), 3.16 (3 H, s, OMe), 3.10 (1 H, d, *J* 10.0 Hz, 17-H), 2.89—2.83 (1 H, m, 18-H), 2.49—2.40 (1 H, m, 12-H), 2.16—1.98 (2 H, m, 16-H and 20-H), 1.79 (3 H, s, 8-Me), 1.45—1.36 (1 H, m, 19-H), 0.97 (3 H, s, 14-Me), 0.90 (3 H, d, *J* 6.4 Hz, 16-Me), 0.84 (3 H, d, *J* 6.5 Hz, 12-Me), 0.83 (9 H, s, ^{t}BuSi), 0.64 (3 H, d, *J* 6.8 Hz, 20-Me), 0.60—0.50 (1 H, m, 19-H), 0.00 (3 H, s, MeSi), and −0.07 (3 H, s, MeSi); δ_C(90.6 MHz, [$^2H_6$]DMSO) 173.63 (s), 155.45 (s), 146.32 (s), 136.75 (d), 135.42 (s), 134.03 (s), 133.32 (s), 132.82 (s), 128.86 (d), 123.97 (d), 123.10 (d), 109.38 (d), 108.87 (d), 83.67 (d), 82.60 (d), 81.81 (d), 80.49 (d), 60.70 (q), 59.88 (q), 56.61 (q), 56.29 (q), 55.05 (q), 36.26 (d), 35.11 (d), 34.78 (d), 25.83 (q), 18.89 (q), 17.99 (t), 17.85 (q), 15.34 (q), 13.42 (q), 10.35 (q), −4.28 (q), and −4.88 (q); *m/z* (e.i.) 659 (M^+, 90%), 383 (47), 338 (17), 261 (25), 149 (26), and 91 (100) (Found: *m/z* 659.4211. $C_{37}H_{61}NO_7Si$ requires *m/z* 659.4217).

Macrocyclic Alcohol (**61**).—To a solution of the silylated macrolactam (**60**) (1.52 g, 2.31 mmol) in anhydrous THF (20 ml) was added TBAF (1M in THF; 12 ml) and the resulting green solution was stirred under nitrogen for 41 h. Ether (180 ml) was added and the solution was washed with saturated aqueous NH_4Cl (2 × 40 ml) and brine (40 ml), then dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, CH_2Cl_2–65% EtOAc) gave the alcohol (**61**) (1.10 g, 89%) which crystallized from 50% EtOH–water as white needles, m.p. 197—198 °C; $[\alpha]_D$ +84.5° (*c* 0.20 in CH_2Cl_2); $\nu_{max.}$(CH_2Cl_2) 3 600, 3 380, 3 050, 2 960, 2 930, 2 820, 1 655, 1 600, 1 520, 1 460, 1 360, 1 310, 1 220, 1 200, 1 170, 1 160, 1 100, 1 075, 1 050, and 1 000 cm^{-1}; δ_H(250 MHz, DMSO-d_6) 9.28 (1 H, br s, NH), 6.61 (1 H, br s, 3-H), 6.43 (1 H, d, *J* 3.1 Hz, 5-H), 5.95 (1 H, br d, *J* 11.0 Hz, 9-H), 5.77 (1 H, t, *J* 11.1 Hz, 10-H), 5.08 (1 H, br t, *J* 10.4 Hz, 11-H), 4.83 (1 H, br d, *J* 9.8 Hz, 15-H), 4.59 (1 H, d, *J* 4.4 Hz, 13-H), 4.33 (1 H, d, *J* 5.1 Hz, 21-H), 3.69 (3 H, s, 4-OMe), 3.43 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.21 (3 H, s, OMe), 3.16 (3 H, s, OMe), 3.08 (1 H, br d, *J* 8.7 Hz, 17-H), 2.94—2.84 (1 H, m, 18-H), 2.46—2.29 (1 H, m, 12-H), 2.16—1.96 (2 H, m, 16-H and 20-H), 1.80 (3 H, s, 8-Me), 1.49—1.36 (1 H, m, 19-H), 0.93 (3 H, s, 14-Me), 0.90 (3 H, d, *J* 6.5 Hz, 16-Me), 0.85 (3 H, d, *J* 6.5 Hz, 12-Me), 0.62 (3 H, d, *J* 6.8 Hz, 20-Me), and 0.63—0.50 (1 H, m, 19-H); δ_C(90.6 MHz, DMSO-d_6) 173.69 (s), 155.58 (s), 146.24 (s), 137.89 (d), 136.51 (s), 134.04 (s), 133.46 (s), 132.67 (s), 128.08 (d), 124.21 (d), 122.59 (d), 109.51 (d), 108.62 (d), 84.05 (d), 81.74 (d), 80.67 (d), 60.61 (q), 59.96 (q), 56.68 (q), 56.33 (q), 55.12 (q), 35.70 (d), 35.32 (d), 34.78 (d), 26.21 (t), 18.49 (q), 15.28 (q), 13.41 (q), and 10.86 (q); *m/z* (e.i.) 546 (M^+, 42%), 482 (19), 424 (100), 302 (24), and 196 (62) (Found: *m/z*, 545.3353; C, 67.86; H, 8.62; N, 2.54%. $C_{31}H_{47}NO_7$ *m/z*, 545.3352; C, 68.23; H, 8.68; N, 2.57%).

Macrocyclic Carbamate (**62**).—To a cooled (0 °C) and slowly stirred solution of the alcohol (**61**) (100 mg, 0.183 mmol) in dry CH_2Cl_2 (2 ml) was added solid sodium cyanate (143 mg, 2.20 mmol) in one portion followed by trifluoroacetic acid (169 μl, 2.20 mmol) over 9 min under nitrogen. The reaction mixture was allowed to warm to room temperature, then it was diluted with dry CH_2Cl_2 (2 ml) and stirring was continued for 3 h. Water (10 ml) was added and the products were extracted into CH_2Cl_2 (3 × 30 ml), washed with 5% aqueous $NaHCO_3$ (15 ml), and brine (15 ml), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (silica gel, Et_2O–15% EtOAc) gave the carbamate (**62**) (92 mg, 86%) as a white solid which did not crystallize from various solvents; $[\alpha]_D$ +91.5° (*c* 0.13 in CH_2Cl_2); $\nu_{max.}$($CHCl_3$ 3 540, 3 430, 3 380, 3 000, 2 980, 2 940, 2 880, 2 830, 1 730, 1 655, 1 585, 1 520, 1 460, 1 360, 1 310, 1 170, and 1 110 cm^{-1}; δ_H(360 MHz, [$^2H_6$]DMSO) 9.26 (1 H, br s, NH), 6.63 (1 H, br s, 3-H), 6.44 (1 H, d, *J* 3.1 Hz, 5-H), 6.32 (2 H, br s, NH_2), 6.00—5.80 (2 H, m, 9-H and 10-H), 5.14 (1 H, br t, 11-H), 4.99 (1 H, d, *J* 10.2 Hz, 15-H), 4.64—4.52 (1 H, m, 13-H), 4.35 (1 H, d, *J* 4.8 Hz, 21-H), 3.69 (3 H, s, 4-OMe), 3.44 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.22 (3 H, s, OMe), 3.17 (3 H, s, OMe), 3.12 (1 H, d, *J* 8.9 Hz, 17-H), 2.92—2.82 (1 H, m, 18-H), 2.68—2.54 (1 H, m, 12-H), 2.16—1.98 (2 H, m, 16-H and 20-H), 1.82 (3 H, s, 8-Me), 1.52—1.40 (1 H, m, 19-H), 0.99 (3 H, br s, 14-Me), 0.87 (3 H, d, *J* 6.3 Hz, 16-Me), 0.80 (3 H, d, *J* 6.5 Hz, 12-Me), 0.61 (3 H, d, *J* 6.8 Hz, 20-Me), and 0.62—0.50 (1 H, m, 19-H); δ_C(62.90 MHz, [$^2H_6$]DMSO) 173.61, 156.26, 155.52, 146.32, 135.92, 134.01, 133.41, 131.75, 123.69, 109.40, 108.91, 83.43,

81.61, 80.54, 60.62, 60.01, 56.68, 55.17, 53.28, 34.90, 33.99, 26.05, 18.44, 18.00, 15.07, 13.45, 11.40; *m/z* (e.i.) 589 (M^+, 5%), 546 (20), 514 (5), 423 (40), 391 (17), 302 (18), 196 (36), 154 (60), and 74 (100) (Found: *m/z* 588.3427. $C_{32}H_{48}N_2O_8$ requires *m/z* 588.3411).

(+)-*Macbecin* I (**1a**).—*Method A: CAN oxidation of* (**62**). To a cooled (−3 °C) and stirred solution of 1,4-dimethylmacbecin II (**62**) (47 mg, 0.08 mmol) in MeCN (5 ml) and water (0.2 ml) was added dropwise a solution of CAN (131 mg, 0.24 mmol) in MeCN–water (1 : 1, 1 ml) over 2 min. After a further 8 min at this temperature, water (10 ml) was added and products were extracted into CH_2Cl_2 (2 × 35 ml), dried ($MgSO_4$), and concentrated. Flash chromatography of the remaining residue (silica gel, Et_2O) afforded (+)-macbecin I (**1a**) (16.5 mg, 37%) as a yellow solid which crystallized from 50% EtOH–water, m.p. 205—206 °C (softening at 176 °C); $[\alpha]_D$ +377 °C (*c* 0.10, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 540, 3 430, 3 360, 3 020, 2 980, 2 940, 1 735, 1 695, 1 660, 1 650, 1 610, 1 580, 1 500, 1 385, 1 330, 1 260, and 1 095 cm^{-1}; $\lambda_{max.}$(MeOH) 240 (sh), 272 (ε 25 000), and 390 (ε 2 000) nm; δ_H 8.89 (1 H, br s, NH), 7.33 (1 H, d, *J* 2.5 Hz, 3-H), 7.13 (1 H, d, *J* 11.8 Hz, 9-H), 6.61 (1 H, dd, *J* 2.5, *J'* 1.5 Hz, 5-H), 6.33 (1 H, dt, *J* 12.1, *J'* 1.8 Hz, 10-H), 5.80 (1 H, br s, 13-H), 5.68 (1 H, dd, *J* 10.7, *J'* 6.7 Hz, 11-H), 5.28 (1 H, br d, *J* 10.1 Hz, 15-H), 4.70 (2 H, br s, NH_2), 4.58 (1 H, br s, 21-H), 3.55 (1 H, br s, 18-H), 3.53 (3 H, s, OMe), 3.34 (3 H, s, OMe), 3.30 (3 H, s, OMe), 3.29—3.20 (1 H, m, 17-H), 3.14—3.04 (1 H, m, 12-H), 2.54—2.42 (1 H, m, 16-H), 1.99 (3 H, s, 8-Me), 1.74—1.62 (2 H, m, 19-H), 1.56—1.46 (1 H, m, 20-H), 1.50 (3 H, s, 14-Me), 1.09 (3 H, d, *J* 6.5 Hz, 16-Me), 1.04 (3 H, d, *J* 7.0 Hz, 12-Me), and 0.80 (3 H, d, *J* 7.0 Hz, 20-Me); δ_C(90.6 MHz, $CDCl_3$) 187.89 (s), 183.98 (s), 169.19 (s), 155.81 (s), 144.88 (s), 141.21 (d), 138.25 (s), 133.19 (s), 132.26 (d), 131.67 (s), 129.00 (d), 127.30 (d), 124.17 (d), 112.90 (d), 83.64 (d), 83.03 (d), 79.27 (d), 77.13 (d), 60.26 (q), 58.33 (q), 55.65 (q), 34.81 (d), 33.96 (t), 33.54 (d), 17.20 (q), 15.26 (q), 15.03 (q), 13.46 (q), and 13.25 (q); *m/z* (c.i.) 560 (M^+ + 2, 9%), 517 (10), and 127 (100) [Found: *m/z* 560.3062. $C_{30}H_{44}N_2O_8$ (M^+ + 2 H) requires *m/z* 560.3097).

The spectroscopic properties of synthetic (**1a**) were in full agreement with those published in the literature.[2b] The reported melting point and optical rotation for macbecin I are 187—188 °C (decomp.) (no solvent specified) and $[\alpha]_D$ +351 °C (*c* 0.10, $CHCl_3$), respectively.

Method B: carbamoylation of (**64**). Reaction of decarbamoyl (+)-macbecin I (40 mg, 0.077 mmol) with sodium cyanate (64 mg, 0.98 mmol) and TFA (75 μl, 0.98 mmol) in CH_2Cl_2 (2 ml), using the conditions described for (**62**), gave (+)-macbecin I (**1a**) (31 mg, 72%) together with recovered (**64**) (6 mg, 15%).

Silylated Decarbamoyl Macbecin I (**63**).—CAN oxidation of lactam (**60**) (54 mg, 0.08 mmol) in MeCN–water at −3 °C, using the same conditions described for (+)-macbecin I (**1a**), afforded the title compound (26 mg, 50%) as a yellow solid after flash chromatography on silica gel (hexane–50% Et_2O). The quinone (**63**) crystallized from 90% EtOH–water as yellow needles, m.p. 192—193 °C; $[\alpha]_D$ +335° (*c* 0.12 in CH_2Cl_2); $\nu_{max.}$(CH_2Cl_2) 3 380, 2 960, 2 940, 2 880, 1 695, 1 660, 1 650, 1 610, 1 500, 1 380, 1 310, 1 250, 1 210, 1 175, 1 155, 1 120, 1 100, 1 075, 1 020, 870, and 840 cm^{-1}; δ_H 8.61 (1 H, br s, NH), 7.34 (1 H, d, *J* 2.5 Hz, 3-H), 7.11 (1 H, d, *J* 11.9 Hz, 9-H), 6.63 (1 H, dd, *J* 2.5, *J'* 1.6 Hz, 5-H), 6.31 (1 H, t, *J* 11.9 Hz, 10-H), 5.85 (1 H, dd, *J* 10.9, *J'* 7.8 Hz, 11-H), 5.48 (1 H, d, *J* 9.9 Hz, 15-H), 4.48 (2 H, br s, 21-H and 13-H), 3.56 (3 H, s, OMe), 3.48 (1 H, br s, 18-H), 3.37 (3 H, s, OMe), 3.33 (3 H, s, OMe), 3.29 (1 H, br d, *J* 9.0 Hz, 17-H), 2.98—2.88 (1 H, m, 12-H), 2.60—2.48 (1 H, m, 16-H), 2.02 (3 H, s, 8-Me), 1.78—1.66 (2 H, m, 19-H), 1.60—1.46 (1 H, m, 20-H), 1.47 (3 H, s, 14-Me), 1.07 (3 H, d, *J* 6.6 Hz, 16-Me), 0.97 (3 H, d, *J* 6.5 Hz, 12-Me), 0.97 (9 H, s, ^{t}BuSi), 0.77 (3 H, d, *J* 7.0 Hz, 20-Me), 0.10 (3 H, s, MeSi), and 0.01 (3 H, s, MeSi); δ_C 187.71 (s), 184.35 (s), 168.84 (s), 145.73 (d), 144.84 (s), 138.28 (s), 135.66 (s), 132.69 (s), 132.51 (d), 129.40 (d), 128.87 (d), 122.67 (d), 112.90 (d), 83.27 (d), 82.35 (d), 79.44 (d), 60.27 (q), 58.36 (q), 56.06 (q), 36.74 (d), 34.59 (d), 34.14 (t), 26.08 (q), 18.36 (s), 16.86 (q), 14.99 (q), 13.42 (q), 12.79 (q), 12.31 (q), −3.90 (q), and −4.34 (q); *m/z* (c.i.) 631 (M^+ + 2, 100%), 545 (21), and 127 (41) [Found: *m/z* 631.3872. $C_{38}H_{57}NO_7Si$ (M^+ + 2H) requires *m/z* 631.3904. Found: C, 66.36; H, 8.74; N, 2.11%. $C_{35}H_{55}NO_7Si$ requires C, 66.74; H, 8.80; N, 2.22%].

Decarbamoyl (+)-*Macbecin* I (**64**).—*Method A:* CAN oxidation of the macrocyclic alcohol (**61**) (30 mg, 0.05 mmol), using the conditions described for (+)-macbecin I (**1a**), gave decarbamoyl macbecin I (**64**) (10.5 mg, 37%) as a yellow solid after flash chromatography on silica gel (CH_2Cl_2–20% EtOAc).

Method B: To a solution of silylated decarbamoyl macbecin I (**63**) (120 mg, 0.19 mmol) in anhydrous THF (3 ml) was added TBAF (1M in THF; 1.9 ml) and the resulting dark blue solution was stirred at room temperature for 48 h under nitrogen. The same work-up as in the case of compound (**61**), followed by flash chromatography on silica gel (CH_2Cl_2–20% EtOAc), afforded recovered (**63**) (17 mg, 14%) and decarbamoyl (+)-macbecin I (**64**) (71 mg, 73%) which crystallized from EtOH–water as a yellow solid, m.p. 177—179 °C; $[\alpha]_D$ +359° (*c* 0.11 in $CHCl_3$) {lit.,[2b] $[\alpha]_D$ +337.7° (*c* 0.11 in $CHCl_3$)}; $\nu_{max.}$(KBr) 3 580, 3 500, 3 380, 2 930, 2 870, 2 830, 1 680, 1 660, 1 650, 1 610, 1 505, 1 375, 1 310, 1 260, 1 230, 1 200, 1 170, 1 160, 1 100, 1 070, 1 000, 930, and 870 cm^{-1}; δ_H 8.63 (1 H, br s, NH), 7.32 (1 H, d, *J* 2.5 Hz, 3-H), 7.14 (1 H, d, *J* 11.8 Hz, 9-H), 6.63 (1 H, dd, *J* 2.5, *J'* 1.7 Hz, 5-H), 6.38 (1 H, dt, *J* 12.2, *J'* 1.7 Hz, 10-H), 5.86 (1 H, dd, *J* 10.6, *J'* 6.9 Hz, 11-H), 5.53 (1 H, d, *J* 10.1 Hz, 15-H), 4.62 (1 H, br s, 13-H), 4.56 (1 H, br s, 21-H), 3.54 (3 H, s, OMe), 3.52 (1 H, br s, 18-H), 3.36 (3 H, s, OMe), 3.33 (3 H, s, OMe), 3.28 (1 H, br d, *J* 9 Hz, 17-H), 3.09—2.98 (1 H, m, 12-H), 2.55—2.42 (1 H, m, 16-H), 2.01 (3 H, s, 8-Me), 1.76—1.60 (3 H, m, 19-H and 20-H), 1.47 (3 H, s, 14-Me), 1.10 (3 H, d, *J* 6.5 Hz, 16-Me), 0.99 (3 H, d, *J* 7.0 Hz, 12-Me), and 0.79 (3 H, d, *J* 7.0 Hz, 20-Me); δ_C 187.64 (s), 184.40 (s), 168.78 (s), 144.93 (s), 143.68 (d), 138.05 (s), 134.90 (s), 133.09 (s), 132.53 (d), 129.26 (d), 127.94 (d), 123.46 (d), 112.90 (d), 83.71 (d), 83.33 (d), 77.99 (d), 76.82 (d), 60.47 (q), 58.36 (q), 55.54 (q), 38.07 (d), 34.98 (d), 33.98 (t), 17.81 (q), 15.14 (q), 13.15 (q), 12.35 (q), 11.95 (q); *m/z* (c.i.) 517 (M^+ + 2, 100%) and 485 (22) [Found: *m/z* 517.3038. $C_{29}H_{43}NO_7$ (M^+ + 2) requires *m/z*, 517.3039. Found: C, 67.49; H, 7.96; N, 2.61%. $C_{29}H_{41}NO_7$ requires C, 67.55; H, 8.01; N, 2.72%].

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