Oxazoline *N*-Oxide-Mediated [2 + 3] Cycloadditions: Application to a Total Synthesis of the Hypocholesterolemic Agent 1233A

Olivier Dirat, Cyrille Kouklovsky, and Yves Langlois*,†

Laboratoire de Synthèse des Substances Naturelles, Associé au CNRS, ICMO, Bâtiment 410, Université de Paris-Sud, 91405 Orsay, France

Received April 30, 1998

Oxetanone 1233A **1** has been synthesized in 22 steps and 3.43% overall yield from 3-methylglutaric anhydride. Asymmetric carbon at C_7 was introduced by a diastereoselective esterification of 3-methylglutaric anhydride, whereas the two asymmetric carbons at $C_{2'}$ and $C_{3'}$ were controlled by an asymmetric [2 + 3] cycloaddition using camphor-derived oxazoline *N*-oxide as dipole.

Introduction and Retrosynthetic Planning

2-Oxetanone derivatives constitue a new class of natural products of increasing importance with respect of their various biological properties such as esterase inhibitors, antibiotics, or hypocholesterolemic agents.[1] Antibiotic 1233A **1** isolated from various species of fungi[2] exhibits significant hypocholesterolemic activity and is a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A synthase (HMG-CoA synthase).[3] In the past this compound has been the subject of several total syntheses mainly from pharmaceutical companies.[4] From a strategic point of view, the asymmetric carbon at C_7, which is disconnected by four carbons from the other asymmetric centers on the oxetane ring, has to be introduced separatly. In the previous syntheses, this asymmetric center came from the terpenic chiral pool. The two other asymmetric centers resulted from an asymmetric aldol condensation,[4a] from an enzymatic resolution,[4b] or from [2,3] Wittig rearrangement starting with an enantiomerically pure allylic ether.[4c]

We described some years ago a new efficient asymmetric [2 + 3] cycloaddition using camphor-derived oxazoline *N*-oxides as dipoles.[5] This method can be considered as an "asymmetric hydroxyacylation" of alkenes. The usefulness of this process has been demonstrated by several syntheses,[5,6] and we applied particuliary this method to the synthesis of a model β-lactone.[7] To test this method with an α,β-unsaturated ester substituted by a long chain, a model study was first developed with ethyl decenoate **4** as dipolarophile. Accordingly, oxazoline *N*-oxide **3** prepared from the readily available hydroxylaminoisoborneol hydrochloride **2**[5] was condensed with ester **4**. A single adduct **5** was isolated after 18 h at 80 °C. Compound **5**, after functional group transformation, was cleaved by an oxidative acidic hydrolytic process. The aldehyde intermediate was not isolated but directly submitted to sodium chlorite oxidation[8] without protection of the primary and secondary alcohols. The hydroxyacid **9** was thus conveniently isolated in high yield with ketol **8**, a precursor of the chiral auxiliary **2**.[5] After tritylation, final lactonization furnished in high yield the anticipated oxetanone **10** (Scheme 1).

This synthesis demonstrated the feasibility of β-lactone synthesis through the [2 + 3] cycloaddition of oxazoline *N*-oxides and prompt us to embark on a synthesis of 1233A **1**. The anticipated retrosynthetic analysis is presented in Scheme 2. To obtain the absolute configurations requisite for carbons $C_{2'}$ and $C_{3'}$ in the natural product, (−)-camphor has to be used as chiral inducer. We also anticipated that the asymmetric center at C_7 in **1** could be introduced by diastereoselective esterification of the prochiral 3-methylglutaric anhydride. From a tactic point of view, two options were still opened at this stage: the Heck coupling, disconnection of C_3-C_4, can be performed before or after removal of the chiral auxiliary, this latter option being indicated in the retrosynthetic scheme.

Synthesis of Dipolarophile

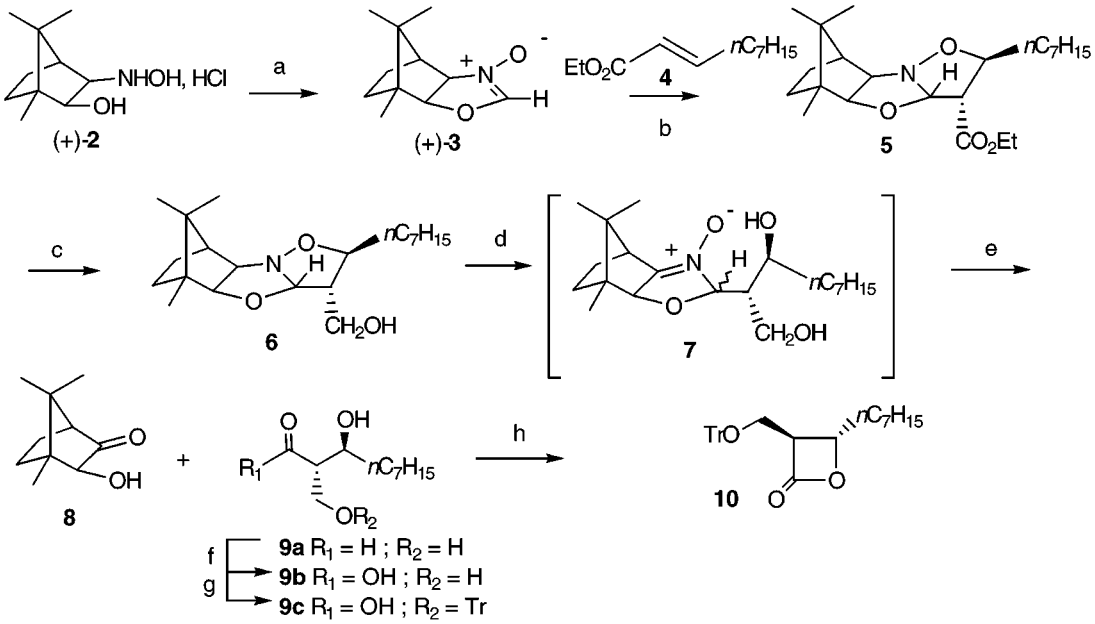
The synthesis started with the desymmetrization of 3-methylglutaric anhydride **14**. This reaction was performed under the Heathcock protocol[9] with (*R*)-(+)-1-(1′-naphthyl)ethanol **15** (Scheme 3). This alcohol was itself obtained after reduction of the corresponding ketone with the Corey's oxaborolidine reagent[10] and isolated in 99% ee after recrystallization according to Fleming.[11] Acid ester **13** was thus obtained in 91% yield and 87% de.[12]

† Fax: 33 1 69 15 46 79. E-mail: langlois@icmo.u-psud.fr.

(1) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729.
(2) (a) Turner, W. B.; Alridge, D. C. *Chem. Commun* **1970**, 639. (b) Turner, W. B.; Alridge, D. C. *J. Chem. Soc. C* **1971**, 3888.
(3) Omura, S.; Greenspan, M. D. *J. Antibiot.* **1987**, 1356.
(4) Total syntheses: (a) Chiang, Y.-C.; Yang, S. S.; Heck, J.; Chabala, J. C.; Chang, M. N. *J. Org. Chem.* **1989**, *54*, 570.(b) Mori, K.; Takahashi, Y. *Liebigs Ann. Chem.* **1991**, 1057.(c) Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832. (d) We thank Professor Kocienski for sending us a draft of his paper concerning a new synthesis of 1233A (Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. Submitted for publication). Formal syntheses: (e) Wattanasin, S.; Do, H. D.; Bhongle, N.; Kathawala, F. G. *J. Org. Chem.* **1993**, *58*, 1610. (f) Guanti, G.; Banfi, L.; Schmid, G. *Tetrahedron Lett.* **1994**, *35*, 4239.
(5) Berranger, T.; Langlois, Y. *J. Org. Chem.* **1995**, *60*, 1720.
(6) (a) Berranger, T.; Langlois, Y. *Tetrahedron Lett.* **1995**, *36*, 5523. (b) Kouklovsky, C.; Dirat, O.; Berranger, T.; Langlois, Y.; Tran-Huu-Dau, M. E.; Riche, C. *J. Org. Chem.* **1998**, *63*, 5123.
(7) Dirat, O.; Berranger, T.; Langlois, Y. *Synlett* **1995**, 935.
(8) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
(9) Thiesen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142.
(10) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 1725. (b) Mathre, D. J.; Jones, T. K.; Blacklock, T. J. *J. Org. Chem.* **1991**, *56*, 751.
(11) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1994**, 99.
(12) Diastereomeric excess was measured at this stage after esterification with methanol, see ref 9.

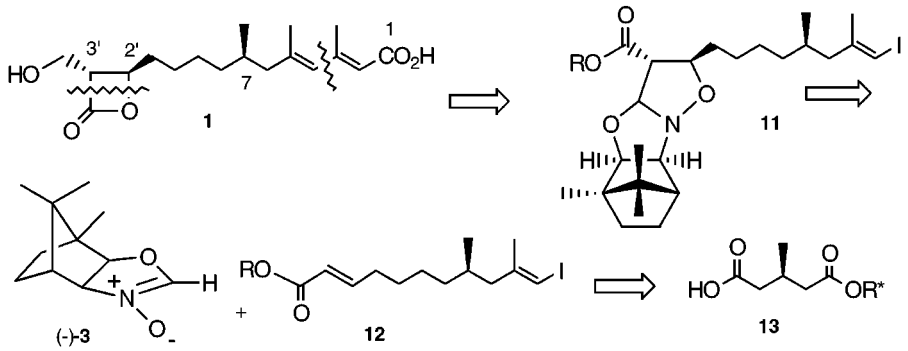
S0022-3263(98)00813-5 CCC: $15.00
Published on Web 08/29/1998

Scheme 1[a]



[a] Key: (a) $HC(OMe)_3$, $CaCO_3$, MS 4 Å, PhMe, 40 °C, 4 h; (b) **4**, PhMe, 80 °C, 18 h; 67%; (c) DIBALH, PhMe; 85%; (d) *m*-CPBA, CH_2Cl_2; (e) HCl (2 N), THF; (f) $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN, H_2O; 88%; (g) TrCl, pyridine, 70 °C; 100%; (h) $PhSO_2Cl$, pyridine; 87%.

Scheme 2



Reduction of the acid functional group with borane–dimethyl sulfide complex afforded in high yield the ester alcohol **16** which was in turn protected as its THP derivative **17**. The ester group in compound **17** was reduced with diisobutylaluminum hydride in toluene and furnished aldehyde derivative **18a**. This reduction was contaminated with a small amount, ca. 15%, of the corresponding primary alcohol **18b** which was removed by purification by column chromatography.[13] At this stage, it was difficult to separate the chiral auxiliary **15** and aldehyde **18a**. For this reason, this mixture of compounds was submitted to the following step. Accordingly, this mixture was submitted to a mild reaction in the presence of the Bestmann reagent[14] and the alkyne derivative **19** was isolated after purification in 83% overall yield from ester **17**. Chiral alcohol **15** was also recovered in 98% yield and 99% ee. At this stage, an enantiomeric excess of aldehyde **8a** was also checked. An enantiomeric excess of 87% was measured by the Courtieu method[15] after sequential transformation of aldehyde **18a** or alcohol **18b**.[16]

With the acetylenic derivative **19** in hand the trisubstituted double bond introduction via a Negishi process[17] was then examined. It turned out that a tetrahydropyranyl protecting group was troublesome and the expected carbometalation iodination occurred with a simultaneous reductive ring opening of the tetrahydropyranyl ring. Fortunately, this reaction can be performed in high yield with the unprotected alcohol derivative **20** and afforded the vinylic iodide **21** together with a small amount of the regioisomer. It is worthy of note that neat trimethylaluminum had to be used for this carbometalation; a toluene solution of this reagent gave very poor yields.

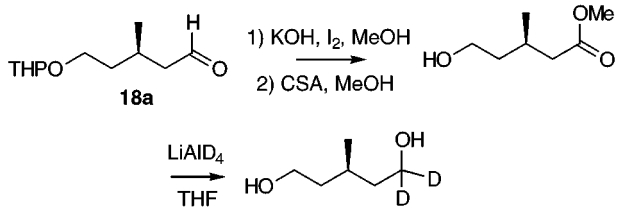
Oxidation of primary alcohol in **21** was perfomed in high yield under Swern conditions. After other prospec-

(13) Alcohol **18b** was recycled after Swern oxidation.

(14) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

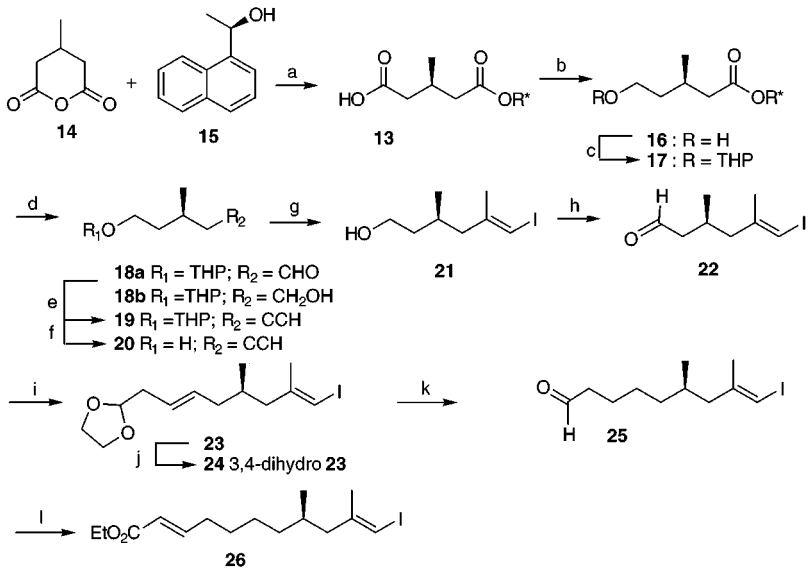
(15) Canet, I.; Meddour, A.; Loewenstein, A.; Péchiné, J. M.; Courtieu, J. *J. Am. Chem. Soc.* **1995**, *117*, 6520.

(16) For measurement with this method, aldehyde **18a** was oxidized to the corresponding methyl ester which was in turn reduced with $LiAlD_4$:



(17) Negishi, E.-I.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.

Scheme 3[a]



[a] Key: (a) DMAP, CH_2Cl_2, −40 °C, 5 d; 91%; ed = 87%; (b) BH_3−DMS, THF; 97%; (c) DHP, PPTS, CH_2Cl_2; 95%; (d) DIBALH, PhMe; (e) $MeCOC(N_2)PO(OMe)_2$; K_2CO_3, MeOH; 83%; (f) CSA, MeOH; (g) Cp_2ZrCl_2, Me_3Al, I_2, $Cl(CH_2)_2Cl$; 77%; (h) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2; 98%; (i) $BrPh_3P(CH_2)_2CH(OCH_2)_2$, BuLi, THF; 99%; (j) $NH_2OH{\cdot}HCl$, KOH, DMF, EtOAc; (k) HCl (2 N), THF; 54%; (l) Ph_3PCHCO_2Et, PhMe; 99%.

tive studies,[18] a three-carbon homologation through a Wittig olefination of the resulting aldehyde **22** furnished the dioxolane derivative **23**. After several unsuccessful attempts to hydrogenate the C_3−C_4 double bond with various catalysts or hydrides, diimide-mediated reduction appeared as the best reagent for this step according to a recent publication.[19] Unexpectingely, compound **23** proved to be unreactive under classical diimide reduction conditions. Finally, it turned out that when diimide was prepared from hydroxylamine hydrochloride,[20] the dihydro compound **24** was isolated without reduction of the iodovinylic moiety. Classical acidic hydrolysis furnished the aldehyde **25** which was submitted in turn to a second Wittig olefination giving rise to the desired dipolarophile **26**. At this stage, compound **26** was obtained in 12 steps and in 28% overall yield from 3-methylglutaric anhydride **14**.

Cycloaddition and Completion of the Synthesis

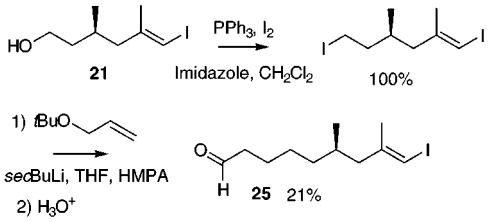
As in our previous work,[5,7] oxazoline *N*-oxide (−)-**3** was prepared and submitted to in situ cycloaddition with dipolarophile **26** (Scheme 4). A single adduct **27** was isolated in 58% yield after heating at 80 °C for 18 h. As previously observed with β-substituted α,β-unsaturated esters, the cycloaddition was regio- and stereoselective.[21] Classical reduction of the ester group and protection of the resulting alcohol **28** as its trityl ether furnished in high yield compound **29**.[22]

The following step of the synthesis was the assembly of the dienic moiety on the side chain via Heck coupling with *tert*-butyl crotonate. To avoid partial isomerization of the C_4−C_5 double bond after the coupling, reaction conditions using palladium diacetate, silver carbonate, and triethylamine as described by the Hoffmann-La Roche group[4c] were used. Consequently, the expected coupling product **30** was obtained in 84% yield as a single (*E*,*E*) isomer.

Compound **30** was then submitted to the oxidative hydrolytic process developed in our laboratory.[5] Thus, oxidation of oxazolidine ring with *m*-chloroperbenzoic acid in ether[23] was followed by acidic hydrolysis affording an aldehyde intermediate.[24] To preclude any isomerization at this stage, this compound was directly oxidized, following a process described in our model study. Acid alcohol **31** was isolated after purification in 65% overall yield for these three steps.

Formation of β-lactone was performed under Adam's conditions[25] and furnished compound **32**. Direct double deprotection of the *tert*-butyl ester and trityl ether gave

(18) Iodo alcohol **21** was transformed into the corresponding diiodo derivative. Alkylation of this compound with homoenolate equivalent obtained after deprotonation of *tert*-butylvinyl ether gave only poor yield of aldehyde **25** (ca. = 20%):



For alkylation of such homoenolates, see: (a) Still, W. C.; Macdonald, T. L. *J. Org. Chem.* **1976**, *41*, 3620. (b) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560.

(19) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1997**, *119*, 103.

(20) Wade, P. A.; Amin, N. V. *Synth. Commun.* **1982**, *12*, 287. The temperature of the diimide reduction used in this reaction condition is probably determining.

(21) As in previous [2 + 3] cycloadditions in this series, the stereoselectivity of this reaction was deduced after NOE and COSY experiments. At this stage, we were not able to detect any minor diastereomer at C_7.

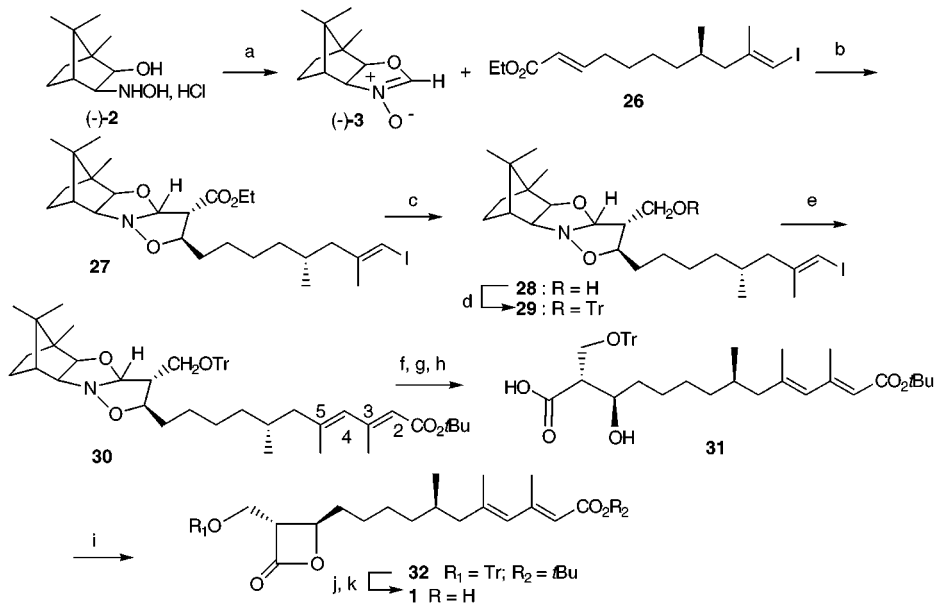
(22) It appeared that protection of primary alcohol was necessary at this stage, since chlorite oxidation as in the model study failed to give the expected acid.

(23) Diethyl ether as the solvent gave better yield than dichloromethane because of better solubility.

(24) Trisubstituted C_4−C_5 double bond is probably not conjugated with trisubstituted C_2−C_3 double bond for steric reasons. Nevertheless, no side reaction occurred at this stage and oxazolidine nitrogen was oxidized whithout epoxidation of the C_4−C_5 double bond.

(25) Adam, W.; Baeza, J.; Ju-Chao, L. *J. Am. Chem. Soc.* **1972**, *94*, 2000.

Scheme 4[a]



[a] Key: (a) $HC(OMe)_3$, $CaCO_3$, MS4Å, PhMe, 40 °C, 4 h; (b) **26**, PhMe, 80 °C, 18 h; 58%; (c) DIBALH, PhMe, −78 °C; 89%; (d) TrCl, pyridine; 100%; (e) $MeCHCHCO_2tBu$, $Pd(OAc)_2$, Ag_2CO_3, Et_3N, CH_2Cl_2; 84%; (f) *m*-CPBA, Et_2O; (g) HCl (2 N), THF; (h) $NaClO_2$, NaH_2PO_4, $MeCHC(Me)_2$, tBuOH, H_2O; 65%; (i) $PhSO_2Cl$, pyridine; 73%; (j) TsOH, PhH; (k) TFA, CH_2Cl_2; 60%.

poor yield. Better results were obtained in a two-step process.[26] Thus, trityl ether acidolysis in the presence of *p*-toluenesulfonic acid was followed by trifluroacetic acid cleavage of the *tert*-butyl ester group affording 1233A **1** in 60% yield. Synthetic 1233A was identical in all respects (TLC, IR, ^1H and ^{13}C NMR) to an authentic sample of natural product.[27]

The overall yield of this synthesis from 3-methylglutaric anhydride **14**, 3.43% for 22 steps (86% for each step), is quite competitive with the previously published syntheses. This synthesis also demonstrates the usefulness of the asymmetric [2 + 3] cycloaddition of oxazoline *N*-oxides and the possible use of complex dipolarophiles in these reactions.

Experimental Section

Generalities. ^1H and ^{13}C NMR spectra were recorded at 200, 250, 400, or 600 MHz and 50 or 62.5 MHz, respectively. Optical rotations were recorded at 20 °C. Elemental analyses were performed at the CNRS, Gif sur Yvette, France. Unless otherwise stated, chromatographic purifications were performed on 230−400 mesh silica gel (Merck 9385) using the indicated solvent system. Dichloromethane, acetonitrile, DMF, pyridine, and trimethyl orthoacetate were distilled from calcium hydride. Toluene, diethyl ether, and THF were distilled from sodium metal/benzophenone ketyl. Methanol and ethanol were distilled from magnesium. Chloroform used for optical measurements was filtered through basic alumina before use. All nonaqueous reactions were performed under an argon atmosphere using oven-dried glassware.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-5,10,10-Trimethyl-2-heptyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid Ethyl Ester (5). To a suspension of 3-hydoxylamino-2-isoborneol hydrochloride **2** (0.5 g, 2.26 mmol), calcium carbonate (226 mg, 2.26 mmol), and powdered 4 Å molecular sieves (0.3 g) in toluene (10 mL) was added trimethyl orthoformate (1.2 mL, 9 mmol, 4 equiv), and the mixture was stirred at 45 °C for 4 h. A solution of ethyl 2-decenoate **4** (720 mg, 3.4 mmol, 1.5 equiv) in 2 mL of toluene was then added, the oil bath temperature raised to 80 °C, and the mixture stirred overnight. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (10% diethyl ether/pentane, $R_f = 0.27$) to give the cycloadduct as a colorless oil (595 mg; 67% yield).

^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.38 (1H, d, J = 7.6 Hz), 4.35 (1H, dt, J = 10.4 and 5.9 Hz), 4.18 (2H, m), 3.88 (1H, d, J = 7.5 Hz), 3.27 (1H, d, J = 7.5 Hz), 2.89 (1H, dd, J = 7.6 and 10.4 Hz), 2.04 (1H, d, J = 4.3 Hz), 1.68 (2H, m), 1.50 (2H, m), 1.35 (2H, m), 1.30−1.18 (13H, m), 0.95−0.70 (12H, m). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 169.0, 98.6, 89.8, 78.4, 75.8, 60.9, 58.3, 49.2, 48.4, 45.8, 32.0, 31.6, 31.4, 29.5, 29.0, 25.7, 25.4, 22.6, 22.1, 18.9, 14.2, 14.0, 10.7. $[\alpha]^{20}_D = -113$ (c = 0.52, $CHCl_3$). Mass (DCI NH_3): m/z 394 (M + 1), 232, 199, 180 (100%). High-resolution mass spetctrum: calcd for $C_{23}H_{39}NO_4$ 393.2879, found 393.2875.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-5,10,10-Trimethyl-2-heptyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-methanol (6). A solution of **5** (0.541 g, 1.37 mmol) in toluene (15 mL) was cooled to −78 °C, and a diisobutylaluminum hydride solution (1.5 M in toluene, 2.29 mL, 3.44 mmol, 2.5 equiv) was added dropwise. After stirring for 1 h at −78 °C, the excess hydride reagent was neutralized by careful addition of a saturated ammonium chloride solution with subsequent warming to room temperature. The solution was then extracted with diethyl ether (50 mL) and washed twice with a 1 N sodium potassium tartrate solution (30 mL). The aqueous phases were back-extracted with 30 mL of diethyl ether, and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by chromatography (25% diethyl ether/heptane, $R_f = 0.32$) gave the alcohol **6** (0.408 g, 85% yield) as a colorless oil.

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.33 (1H, d, J = 6.6 Hz), 3.84 (1H, d, J = 7.5 Hz), 3.74 (3H, m), 3.32 (1H, d, J = 7.5 Hz), 2.41 (1H, t, J = 6.4 Hz), 2.17 (1H, m), 2.07 (1H, d, J = 4.3 Hz), 1.65 (2H, m), 1.45 (2H, m), 1.35 (2H, m), 1.30−1.20 (10H, m), 0.95−0.70 (12H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 100.2, 90.4, 77.6, 77.2, 59.7, 53.8, 49.4, 48.8, 45.6, 32.0, 31.7, 31.6, 29.6, 29.1, 25.8, 25.5, 22.6, 22.2, 18.8, 14.1, 10.9. $[\alpha]^{20}_D = -106.5$ (c = 1.09, $CHCl_3$). Mass (DCI NH_3): m/z 352

(26) Partial retritylation in the presence of trifluoroacetic acid was observed when triphenylmethanol was present in the reaction medium.

(27) We thank Dr. C. Jonhstone, Zeneca Pharmaceutical, Macclesfield, U.K., for the generous gift of an authentic sample of 1233A.

(M + 1) (100%), 180. High-resolution mass spetctrum: calcd for $C_{21}H_{37}NO_3$ 351.2773, found 351.2773.

(2*S*,3*S*)-3-Hydroxy-2-(hydroxymethyl)decanoic Acid (9b). To a solution of the alcohol **6** (0.249 g, 0.71 mmol) in dichloromethane (10 mL) was added *m*-chloroperoxybenzoic acid (0.246 g, 1.42 mmol, 2 equiv) in one portion. The solution was stirred at room temperature for 30 min and then washed four times with an aqueous 5% $NaHCO_3$ solution (4 × 10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude nitrone **7** was used immediately in the next reaction.

The crude nitrone was redissolved in tetrahydrofuran (3 mL), and a 2 N hydrochloric acid solution (3 mL) was added. The solution was stirred for 5 min at room temperature and then extracted three times with 10 mL of dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a mixture of ketol **8** and aldehyde **9a**. This crude mixture was used in the next reaction without further purification.

The above mixture was redissolved in acetonitrile (5 mL), and 5 mL of a stock solution (prepared by dissolving 1.6 g of sodium dihydrogen phosphate and 5 mL of 30% hydrogen peroxide in 20 mL of water) was added. The mixture was cooled to 10 °C, and a solution of sodium chlorite (0.12 g) in water (1 mL) was added. The solution was stirred for 40 min at 10 °C and then quenched by addition of 0.1 g of solid sodium sulfite. The pH was raised to 14 by addition of solid sodium carbonate and the solution extracted with ethyl acetate to remove the unreacted ketol. The solution was then reacidified to pH 1 by addition of 2 N hydrochloric acid solution and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the pure acid **9b** (0.135 g, 88% overall yield) as a colorless oil.

R_f = 0.16 (5% methanol/ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 6.66 (3H, broad s, exchangeable with D_2O), 3.88 (3H, m), 2.66 (1H, m), 1.50 (2H, m), 1.24 (10H, broad s), 0.85 (3H, t, J = 6.3, Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 177.2, 71.2, 61.9, 52.7, 35.2, 32.0, 29.6, 29.4, 25.9, 22.6, 14.2. Mass (DCI NH_3): m/z 236 (M + 18) (100%), 219 (M + 1), 218 (M^+), 201, 190, 172.

(2*S*,3*S*)-3-Hydroxy-2-(triphenylmethoxymethyl)decanoic Acid (9c). The acid **9b** (0.044 g, 0.2 mmol) was dissolved in pyridine (2 mL) and triphenylmethyl chloride (trityl chloride) (0.225 g, 0.8 mmol, 4 equiv) was added. The reaction mixture was stirred overnight at 70 °C and then cooled to room temperature, diluted with water (3 mL), and stirred 3 h. The acid was extracted with diethyl ether (4 × 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude acid (200 mg) was used in the next reaction without purification. An analytical sample was prepared by chromatography (ethyl acetate, R_f = 0.51).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 8.57 (1H, m), 7.38−7.11 (15H, m), 3.86 (1H, dt, J = 5.Hz), 3.42 (2H, ABX system), 2.64 (1H, dt, J = 5.7 and 5.3 Hz), 1.28 (2H, m), 1.15 (10H, broad s), 0.79 (3H, t, J = 7 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 177.7, 143.5, 128.6, 127.2, 127.1, 87.0, 70.3, 62.5, 51.0, 34.8, 31.8, 29.4, 29.2, 25.6, 22.6, 14.1. $[\alpha]^{20}_D = -1.7$ (c = 1.66, $CHCl_3$). High-resolution mass spectrum: calcd for $C_{30}H_{36}O_4$ 460.2613, found 460.2619.

(2*S*,3*S*)-2-(Triphenylmethoxymethyl)-β-decanolactone (10). The crude acid **9c** was redissolved in pyridine (1 mL) and the solution cooled to 0 °C. Benzenesulfonyl chloride (77 μL, 0.6 mmol, 3 equiv) was added by syringe, and the mixture left for 18 h at 3 °C. The solution was then diluted with water (3 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by chromatography (25% diethyl ether/heptane, R_f 0.20) gave the title compound as a colorless oil (77 mg, 87% overall yield from acid **9b**).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40−7.10 (15H, m), 4.43 (1H, dt, J = 6.7 and 4 Hz), 3.50 (1H, dd J_{gem} = 9.5 Hz, J = 5.4 Hz), 3.30 (1H, ddd with J_{2-3} = 4 Hz), 3.20 (1H, dd, J_{gem} = 9.5 Hz, J = 3.4 Hz), 1.80 (1H, m), 1.65 (1H, m), 1.35−1.10 (10H, broad s), 0.81 (3H, t, J = 6.3 Hz). $[\alpha]^{20}_D = -22.0$ (c = 1.02, $CHCl_3$). Mass (DCI NH_3): m/z 442 (M^+), 243 (100%). High-resolution mass spectrum: calcd for $C_{30}H_{43}O_3$ 442.2508, found 442.2506.

(3*R*,1′*R*)-5-Hydroxy-3-methylpentanoic Acid (1′-α-Naphthyl)ethyl Ester (16). A solution of the known[9] acid ester **13** (1.75 g, 5.83 mmol) in tetrahydrofuran (12 mL) was cooled to 0 °C, and a 2 M solution of borane−dimethyl sulfide in tetrahydrofuran (3.5 mL, 7 mmol, 1.2 equiv) was added dropwise. The solution was stirred for 1 h at 0 °C and then 24 h at room temperature. The excess borane reagent was quenched by careful addition of water (1 mL). The mixture was diluted with diethyl ether (100 mL) and washed with a 1 N sodium hydroxide solution (25 mL). The aqueous layer was back-extracted with 25 mL of diethyl ether, and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the ester alcohol **16** as a colorless oil (1.61 g, 97% yield), sufficiently pure for the next reaction.

R_f = 0.19 (50% diethyl ether/heptane). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.08 (1H, d, J = 8.4 Hz), 7.87 (1H, d, J = 7.8 Hz), 7.80 (1H, d, J = 8.2 Hz), 7.60 (1H, d, J = 7.1 Hz), 7.51 (3H, m), 6.67 (1H, q, J = 6.6 Hz), 3.62 (2H, t, J = 6.5 Hz), 2.43 (1H, dd, J = 14.8 and 6.4 Hz), 2.38 (1H, dd, J = 14.8 and 5.8 Hz), 2.20 (1H, m), 1.78 (3H, d, J = 6.6 Hz), 1.50 (2H, m), 0.95 (3H, d, J = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 172.6, 137.4, 133.8, 130.2, 128.9, 128.4, 126.3, 125.6, 125.3, 123.2, 123.1, 69.3, 60.4, 41.8, 39.3, 26.9, 21.6, 19.9. IR (film): ν (cm^{-1}) 3340, 3022, 2975, 2932, 1712, 1365, 1060. $[\alpha]^{20}_D$ = +35.9 (c = 0.87, $CHCl_3$). Mass (DCI NH_3): m/z 304 (M + 18), 286, 172 (100%), 155 (100%), 132 (100%), 115 (100%).

(3*R*,1′*R*,2″*RS*)-3-Methyl-5-(2-tetrahydropyranyloxy)-pentanoic Acid (1′-α-naphthyl)ethyl Ester (17). To a solution of the alcohol **16** (1.079 g, 3.77 mmol) in 20 mL of dichloromethane were added pyridinium paratoluenesulfonate (0.189 g, 0.74 mmol, 0.2 equiv) and dihydropyrane (1.03 mL, 10.33 mmol, 3 equiv). After stirring for 12 h at room temperature, diethyl ether (50 mL) was added and the solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by filtration through a pad of silica gel (20% diethyl ether/heptane, R_f = 0.45) gave the protected alcohol **17** (1.327 g, 95% yield) as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.08 (1H, d, J = 8.4 Hz), 7.87 (1H, d, J = 7.8 Hz), 7.80 (1H, d, J = 8.2 Hz), 7.60 (1H, d, J = 7.1 Hz), 7.51 (3H, m), 6.67 (1H, q, J = 6.6 Hz), 4.53 (1H, m), 3.75 (2H, m), 3.40 (2H, m), 2.47 (1H, m), 2.20 (2H, m), 1.78 (3H, d, J = 6.6 Hz), 1.50 (8H, m), 0.95 (3H, d, J = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 172.1, 137.4, 133.7, 130.1, 128.8, 128.3, 126.1, 125.5, 125.2, 123.1, 123.0, 98.5, 69.0, 65.1, 62.0, 42.0, 36.1, 30.6, 27.7, 25.4, 21.6, 19.6, 19.4. IR (film): ν (cm^{-1}) 3021, 2985, 1707, 1369, 1057. Mass (DCI NH_3): m/z 388 (M + 18), 304, 287, 172, 155 (100%), 132, 115, 102. Anal. Calcd for $C_{23}H_{30}O_4$ (370.4931): C, 74.56; H, 8.16. Found: C, 74.38; H, 8.10.

(3*R*,2″*RS*)-3-Methyl-5-(2-tetrahydropyranyloxy)pentanal (18a). A solution of compound **17** (1.39 g, 3.76 mmol) in toluene (40 mL) was cooled to −78 °C, and a diisobutylaluminum hydride solution (1.5 M in toluene, 2.75 mL, 4.12 mmol, 1.3 equiv) was slowly added (one drop every 20 s). After stirring for 30 min at −78 °C, the excess hydride reagent was quenched by careful addition of a saturated ammonium chloride solution (15 mL) and the mixture was warmed to room temperature. The solution was then poured into 300 mL of diethyl ether and washed twice with 150 mL of a 1 M sodium potassium tartrate solution. The aqueous layers were extracted with 100 mL of ether, and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. TLC analysis of the crude product (50% diethyl ether/heptane) showed the presence of four compounds: some remaining starting material (R_f = 0.62), the aldehyde (R_f = 0.46), (1-naphthyl)ethyl alcohol (R_f = 0.40), and some overreduction alcohol (R_f = 0.05). Increasing the DIBAL-H addition rate or reaction time resulted in an increase in the yield of unwanted primary alcohol. Purification by chromatography (25% diethyl ether/heptane) gave in order of

elution the starting ester (42 mg, 3% recovery), followed by a mixture of the aldehyde **18a** and the chiral alcohol **15** (1.046 g), followed by the alcohol **18b** (0.114 g,15% yield). The aldehyde was carried into the next reaction as a mixture with the naphthyl alcohol. An analytical sample was prepared by preparative thin-layer chromatography (50% diethyl ether/heptane).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.73 (1H, s), 4.55 (1H, m), 3.80 (2H, m), 3.40 (2H, m), 2.45 (1H, m), 2.20 (2H, m), 1.50 (8H, m), 0.95 (3H, d, J = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 202.7, 98.8, 65.1, 62.3, 50.9, 36.4, 30.7, 25.4, 20.1, 20.0, 19.6. IR (film): ν (cm^{-1}) 3021, 2940, 2905, 2600, 1715, 1059. Anal. Calcd for $C_{11}H_{20}O_3$ (200.2803): C, 65.97; H, 10.07. Found: C, 66.12; H, 9.95.

(4*R*,2″*RS*)-4-Methyl-6-(2-tetrahydropyranyloxy)-1-hexyne (19). The crude aldehyde **18a** (1.046 g) was dissolved in methanol (30 mL), and solid potassium carbonate (1.12 g, 8.15 mmol) was added, followed by 1-diazo-2-oxopropyl diethyl phosphonate (1.08 g, 5.62 mmol). The mixture was stirred 24 h at room temperature and then poured into a mixture of aqueous 5% sodium bicarbonate solution (100 mL) and diethyl ether (100 mL). The layers were separated, and the organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by chromatography (25% diethyl ether/heptane) gave in order of elution the alkyne **19** (0.609 g, 83% overall yield) followed by the unreacted chiral alcohol **15** (98% recovery), recovered >99% enantiomerically pure as determined by chiral CPG (25 m β-cyclodextrin column, 145 °C; retention times *R* isomer, 19.26 min; *S* isomer, 18.8 min).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.55 (1H, m), 3.80 (2H, m), 3.45 (2H, m), 2.15 (2H, m), 1.95 (1H, t, J = 2.6 Hz), 1.9−1.7 (3H, m), 1.7−1.4 (6H, m), 0.95 (3H, d, J = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 98.8, 83.0, 69.4, 65.5, 62.3, 35.6, 30.8, 29.5, 25.9 (C_3), 25.5, 19.6, 19.3. IR (film): ν (cm^{-1}) 3295, 3022, 2945, 2151, 1253, 726. $[\alpha]^{20}_D$ = −3.1 (c = 0.9, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}O_2$ (196.2920): C, 73.43; H, 10.27. Found: C, 73.05; H, 10.05.

(*S*)-3-Methyl-5-hexyn-1-ol (20). A solution of the alkyne **19** (4.522 g, 23 mmol) in methanol (50 mL) was treated at room temperature with a catalytic amount of camphorsulfonic acid. After 1 h, 20 mL of a saturated sodium carbonate solution and 200 mL of water were added and the solution was extracted with 9/1 pentane/dichloromethane (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and carefully concentrated in vacuo. The highly volatile crude alcohol **20** (2.58 g) was used immediately in the next reaction without further purification.

R_f = 0.24 (50% diethyl ether/heptane). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.64 (2H, dt, J = 5.6 and 1.4 Hz), 2.12 (2H, m), 1.93 (1H, t, J = 2.6 Hz), 1.75 (1H, m), 1.45 (2H, m), 0.95 (3H, d, J = 6.6 Hz).

(3*S*,5*E*)-6-Iodo-3,5-dimethyl-5-hexen-1-ol (21). A flame-dried 250 mL flask was charged with zirconocene dichloride (6.72 g, 23 mmol). Meanwhile, in a separate flask, a trimethylaluminum solution in 1,2-dichloroethane was prepared by adding neat trimethylaluminum (6.75 mL, 70 mmol, 3 equiv) (CAUTION: highly pyrophoric material) to dry 1,2-dichloroethane (20 mL). This solution was transferred via cannula to the flask containing zirconocene dichloride, and the resulting lemon yellow solution was stirred for 15 min at room temperature before being cooled to −5 °C. A solution of the crude alkyne **20** (2.576 g, 23 mmol) in 1,2-dichloroethane was added dropwise. The mixture was stirred for 24 h at room temperature and then cooled to −20 °C. A solution of iodine (30 g, 115 mmol, 5 equiv) in tetrahydrofuran (100 mL) was slowly added via cannula. The dark solution was stirred 2 h at −20 °C and then cooled to −50 °C. The excess trimethylaluminum reagent was quenched by careful addition of a 1/1 tetrahydrofuran/water solution (100 mL). After warming to room temperature, the mixture was diluted with diethyl ether (500 mL) and washed with water (100 mL). The aqueous layer was extracted with diethyl ether (100 mL), and the combined organic layer was washed with a 10% sodium thiosulfate solution (200 mL) and then with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. TLC analysis of the crude product showed the presence of two regiomeric products, the less polar being predominant. Purification by chromatography (25% diethyl ether/heptane) gave in order of elution the title compound **21** (R_f = 0.30, 4.611 g, 77% yield from **19**) as a colorless oil, followed by its 5-iodo isomer (R_f = 0.10, 0.555 g).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.84 (1H, s), 3.68 (2H, m), 2.19 (1H, dd, J = 13.7 and 7 Hz), 2.02 (1H, dd, J = 13.7 and 7.9 Hz), 1.78 (3H, s), 1.55 (1H, m), 1.37 (2H, m), 0.83 (3H, d, J = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 146.8, 75.6, 60.8, 47.6, 39.3, 27.6, 23.6, 19.3. IR (film): ν (cm^{-1}) 3452, 3021, 2939, 2901, 1600, 1540, 1372, 1252, 738. $[\alpha]^{20}_D$ = −3.5 (c = 1.03, $CHCl_3$). High-resolution mass spectrum: calcd for $C_8H_{15}IO$ 254.0169, found 254.0198. Anal. Calcd: C, 37.81; H, 5.95. Found: C, 37.48; H, 6.07.

(3*S*,5*E*)-6-Iodo-3,5-dimethyl-5-hexenal (22). A solution of oxalyl chloride (825 μL, 9.45 mmol, 1.2 equiv) in dichloromethane (40 mL) was cooled to −78 °C with stirring, and dimethyl sulfoxide (1.34 mL, 18.9 mmol, 2.4 equiv) was slowly added (gas evolution). After 30 min, a solution of the alcohol **21** (2 g, 7.874 mmol) in dichloromethane (10 mL) was added at such a rate that the reaction temperature remained below −60 °C. After 30 min, triethylamine (5.5 mL, 40 mmol, 5 equiv) was slowly added and the solution was allowed to warm to room temperature. The mixture was partitioned between 20 mL of water and 200 mL of diethyl ether. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by filtration through a short pad of silica gel (25% diethyl ether/heptane) gave the aldehyde **22** as a volatile, colorless liquid (1.94 g, 98% yield).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 9.72 (1H, s), 5.88 (1H, s), 2.5−2.1 (4H, m), 1.80 (3H, s), 1.75 (1H, m), 0.95 (3H, d, J = 6.2 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 201.8, 146.0, 76.5, 50.2, 46.9, 26.1, 23.6, 19.7. Mass (DCI NH_3): m/z 270 (M + 18), 252 (M^+), 167, 125 (M − 127), 106 (100%). IR (film): ν (cm^{-1}) 3021, 2940, 2902, 2606, 1716, 1605, 1447, 1370, 1253, 735. $[\alpha]^{20}_D$ = −5.3 (c = 1.12, $CHCl_3$). Anal. Calcd for $C_8H_{13}IO$ (252.0013): C, 38.12; H, 5.20. Found: C, 37.95; H, 4.92.

(5*S*,2*E*,*Z*,7*E*) 2′-(5,7-Dimethyl-8-iodo-2,7-octadien-1-yl)-1′,3′-dioxolane (23). 2-(1′,3′-Dioxolan-2′-yl)ethyltriphenylphosphonium bromide was prepared by refluxing a solution of 2-bromoethyl-1,3-dioxolane (6 g, 33.1 mmol) and triphenylphosphine (8.69 g, 33.1 mmol) in acetonitrile (30 mL) for 24 h. After cooling to room temperature, the solvent was removed in vacuo and the residue triturated with ethyl acetate (50 mL). The yellow-brown phosphonium salt was collected by filtration (14 g, 95% yield).

^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 8.00−7.65 (15H, broad s), 5.01 (1H, t, J = 6.7 Hz), 3.92 and 3.79 (4H, 2m), 3.65 (2H, m), 1.83 (2H, m).

A solution of the above phosphonium salt (3.16 g, 7.1 mmol, 2 equiv) in tetrahydrofuran (50 mL) was cooled to −78 °C with stirring, and a 2.5 M *n*-butyllithium solution in hexanes (2.86 mL, 7.1 mmol, 2 equiv) was added dropwise. The orange solution was stirred for 40 min at −78 °C; then a solution of the aldehyde **22** (900 mg, 3.6 mmol) in tetrahydrofuran (20 mL) was added dropwise. The reaction mixture was allowed to warm to −40 °C within 30 min, the cooling bath was then removed, and the mixture was stirred 2 h at room temperature. The reaction was quenched by addition of a saturated ammonium chloride solution (10 mL); the solution was diluted with diethyl ether (300 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by filtration through a short pad of silica gel, eluting with 25% diethyl ether/heptane. Concentration in vacuo gave the title compound as a colorless oil (1.19 g, 99% yield, stereochemistry unknown).

R_f = 0.68 (50% diethyl ether/pentane). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.82 (1H, s), 5.50 (2H, m), 4.85 (1H, t, J = 4.8 Hz), 3.95 and 3.83 (4H, 2m), 2.39 (2H, ddd, J = 5, 5 and 1 Hz), 2.23 (1H, d, J = 5.3 Hz), 2.18 (1H, d, J = 6.1 Hz), 2.00 (2H, m), 1.77 (3H, s), 1.70 (1H, m), 0.80 (3H, d, J = 6.6 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 146.9, 130.9, 123.9, 103.9, 75.4, 64.9, 46.9, 34.2, 32.3, 31.4, 23.7, 19.2. IR (film):

ν (cm^{-1}) 3020, 2975, 2947, 1608, 1417, 1372, 1262, 1128, 738. $[\alpha]^{20}_D = +5.2$ ($c = 0.54$, $CHCl_3$). Mass (DCI NH_3): m/z 355 (M + 19), 338 (M + 2), 174, 130 (100%). Anal. Calcd for $C_{13}H_{21}IO_2$ (336.0586): C, 46.44; H, 6.30. Found: C, 46.67; H, 5.95.

(6*R*,8*E*)-6,8-Dimethyl-9-iodo-8-nonenal (25). Finely powdered potassium hydroxide (59 g, 1 mol) was added to a solution of hydroxylamine hydrochloride (62.2 g, 0.9 mol) in dimethylformamide (185 mL). After stirring for 10 min at room temperature, the solution was filtered under argon atmosphere, the filtrate was cooled to 0 °C, and ethyl acetate (38.5 mL) was added. Then 30 mL aliquots of this solution were added every 30 min to compound **24** (1.161 g, 3.45 mmol) at 100 °C. After heating for a total time of 3 h, the solution was cooled to room temperature, a 1/1 heptane/diethyl ether mixture was added (500 mL), and the resulting solution was washed three times with 100 mL of a 5% sodium bicarbonate solution and then with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was immediately taken into the next reaction.

The crude product was dissolved in tetrahydrofuran (30 mL) and 2 N hydrochloric acid solution (30 mL) and stirred at reflux for 3 h. The solution was basified by addition of solid potassium carbonate and the product extracted with dichloromethane (4 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by chromatography (25% diethyl ether/heptane) gave the aldehyde **25** as a light yellow oil (0.547 g, 54% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.73 (1H, t, $J = 1.5$ Hz), 5.80 (1H, s), 2.41 (2H, td, $J = 7.3$ and 1.5 Hz), 2.12 (1H, dd, $J = 13.2$ and 6.3 Hz), 1.96 (1H, dd, $J = 13.3$ and 8.2 Hz), 1.77 (3H, s), 1.64 (3H, m), 1.32 (4H, m), 0.78 (3H, d, $J = 6.5$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 202.7, 147.0, 75.3, 47.5, 43.9, 36.3, 30.7, 26.5, 23.7, 22.2, 19.2. IR (film): ν (cm^{-1}) 3020, 2900, 1703, 1455, 1254, 733. Mass (DCI NH_3): m/z 312 (M + 18), 294 (M^+), 243, 167 (M − 127), 106 (100%). $[\alpha]^{20}_D = +0.8$ ($c = 1.01$, $CHCl_3$). High-resolution mass spectrum: calcd for $C_{11}H_{19}IO$ 294.0482, found 294.0471.

(8*R*,2*E*,10*E*)-8,10-Dimethyl-11-iodo-2,10-undecadienoic Acid Ethyl Ester (26). A solution of the above aldehyde (0.043 g, 0.15 mmol) (ethoxycarbonylidene)triphenylphosphorane (0.1 g, 0.29 mmol, 2 equiv) in toluene (5 mL) was stirred at 80 °C for 4 h. The mixture was then cooled to room temperature and the solvent evaporated in vacuo. The residue was triturated with pentane (10 mL), filtered, and concentrated in vacuo. Purification by chromatography (25% diethyl ether/pentane) gave the pure α,β-unsaturated ester as a colorless oil (54 mg, 99% yield).

$R_f = 0.78$ (50% diethyl ether/heptane). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 6.89 (1H, dt, $J = 15.5$ and 7 Hz), 5.76 (1H, s), 5.75 (1H, dt, $J = 17$ and 1 Hz), 4.12 (2H, q, $J = 7.1$ Hz), 2.11 (3H, m), 1.91 (1H, dd, $J = 13.3$ and 8.2 Hz), 1.72 (3H, s), 1.55 (1H, m), 1.45−0.90 (6H, m), 1.22 (3H, t, $J = 7.1$ Hz), 0.73 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 166.7, 149.2, 147.1, 121.3, 75.2, 60.1, 47.5, 36.3, 32.2, 30.8, 28.2, 26.5, 23.7, 19.2, 14.3. IR (film): ν (cm^{-1}) 3018, 2958, 1705, 1646, 1453, 1297, 1042, 740. Mass (DCI NH_3): m/z 382 (M + 18), 365 (M + 1) (100%), 256, 239, 163. $[\alpha]^{20}_D = -4.0$ ($c = 0.62$, $CHCl_3$). Anal. Calcd for $C_{15}H_{25}IO_2$ (364.0901): C, 49.46; H, 6.92; I, 34.84. Found: C, 49.83; H, 6.95; I, 34.46.

(2*R*,3*R*,3a*R*,4*R*,4a*R*,5*S*,8*R*,8a*S*,5′*S*,7′*E*)-2-(5′,7′-Dimethyl-8′-iodo-7′-octen-1′-yl)-5,10,10-trimethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid Ethyl Ester (27). Trimethyl orthoformate (1.2 mL, 3.21 mmol, 1.42 equiv) was added to a suspension of (1*S*)-3-hydroxylaminoisoborneol hydrochloride **(−)-3** (0.5 g, 2.26 mmol), flame-dried calcium carbonate (0.5 g, 5 mmol, 2.2 equiv), and powdered 4Å molecular sieves (0.6 g) in toluene (10 mL). The white suspension was stirred at 40 °C for 4 h, and the dipolarophile **26** (1.17 g, 3.21 mmol, 1.42 equiv) was added. The temperature was raised to 80 °C and the reaction mixture stirred for 18 h. After cooling to room temperature, the suspension was filtered through a pad of Celite and concentrated in vacuo. Purification by chromatography (10% diethyl ether/heptane) gave, in order of elution, the excess dipolarophile (345 mg, 0.95 mmol, 100% recovery), followed by the cycloadduct which was isolated as a colorless oil (0.732 g, 58% yield).

^{1}H NMR (400 MHz with COSY, $CDCl_3$): δ (ppm) 5.79 (1H, s), 5.40 (1H, d, $J = 7.6$ Hz), 4.37 (1H, dt, $J = 10.4$ and 6.1 Hz), 4.19 (2H, m), 3.89 (1H, d, $J = 7.6$ Hz), 3.28 (1H, d, $J = 7.5$ Hz), 2.90 (1H, dd, $J = 10.5$ and 7.6 Hz), 2.15 (1H, dd, $J = 13.5$ and 6.1 Hz), 2.05 (1H, d, $J = 4.3$ Hz), 1.94 (1H, dd, $J = 13.4$ and 8.4 Hz), 1.76 (3H, s), 1.68 (2H, m), 1.58 (1H, m), 1.53 (2H, m), 1.35 (2H, m), 1.30−1.15 (6H, m), 1.26 (3H, t, $J = 7.1$ Hz), 0.92−0.75 (12H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 169.0, 147.1, 98.6, 89.8, 78.3, 75.9, 75.2, 61.0, 58.3, 49.2, 48.4, 47.5, 45.9, 36.4, 32.1, 31.4, 30.8, 26.9, 25.5, 26.0, 23.7, 22.1, 19.2, 18.9, 14.2, 10.7. IR (film): ν (cm^{-1}) 3017, 2965, 1728, 1607, 1452, 1372, 1268, 1032. Mass (DCI NH_3): m/z 560 (M + 1), 180 (100%). $[\alpha]^{20}_D = +62.0$ ($c = 1.08$, $CHCl_3$). Anal. Calcd for $C_{26}H_{42}NIO_4$ (559.2160): C, 55.81; H, 7.57; N, 2.50; I, 22.68. Found: C, 55.42; H, 7.34; N, 2.17; I, 22.68. High-resolution mass spectrum: found 559.2151.

(2*R*,3*R*,3a*R*,4*R*,4a*R*,5*S*,8*R*,8a*S*,5′*S*,7′*E*)-2-(5′,7′-Dimethyl-8′-iodo-7′-octen-1′-yl)-5,10,10-trimethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-methanol (28). The above cycloadduct **27** (0.917 g, 1.64 mmol) was dried by azeotropic evaporation with toluene and then dissolved in toluene (30 mL), and the solution was cooled to −78 °C. A 1.5 M toluene solution of diisobutylaluminum hydride (3 mL, 4.5 mmol, 2.75 equiv) was added dropwise. The solution was stirred for 2 h at −78 °C and then allowed to warm to −40 °C in 1 h, and the excess hydride reagent was quenched by careful addition of a saturated ammonium chloride solution (10 mL). The cooling bath was removed and the solution allowed to warm to room temperature. A 1 N sodium potassium tartrate solution (100 mL) was added and the biphasic mixture vigorously stirred overnight and then separated. The aqueous phase was extracted with diethyl ether (100 mL), and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by chromatography (50% diethyl ether/heptane, $R_f = 0.36$) afforded the alcohol **28** (0.758 g, 89% yield) as a colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.77 (1H, s), 5.32 (1H, d, $J = 6.5$ Hz), 3.83 (1H, d, $J = 7.5$ Hz), 3.72 (3H, m), 3.32 (1H, d, $J = 7.5$ Hz), 2.40 (1H, broad s, exchangeable with D_2O), 2.17 (2H, m), 2.07 (1H, d, $J = 4.4$ Hz), 1.94 (1H, dd, $J = 13.3$ and 8.1 Hz), 1.75 (3H, s), 1.68 (2H, m), 1.58 (1H, m), 1.53 (2H, m), 1.35 (2H, m), 1.30−1.15 (6H, m), 0.92−0.75 (12H, m). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 147.1, 100.1, 90.4, 77.6, 77.3, 75.2, 59.7, 53.7, 49.4, 48.8, 47.5, 45.6, 36.3, 32.0, 31.6, 30.7, 27.0, 26.0, 25.5, 23.7, 22.2, 19.2, 18.7, 10.9. IR (film): ν (cm^{-1}) 3440, 3018, 2965, 1608, 1451, 1375, 1270, 1031, 743. Mass (DCI NH_3): m/z 518 (M + 1) (100%). $[\alpha]^{20}_D = +59.3$ ($c = 0.95$, $CHCl_3$). Anal. Calcd for $C_{24}H_{40}NIO_3$ (517.2053): C, 55.70; H, 7.79; N, 2.71; I, 24.52. Found: C, 55.43; H, 7.85; N, 2.50; I, 24.31.

(2*R*,3*R*,3a*R*,4*R*,4a*R*,5*S*,8*R*,8a*S*,5′*S*,7′*E*)-2-(5′,7′-Dimethyl-8′-iodo-7′-octen-1′-yl)-5,10,10-trimethyl-3-[(1,1,1-triphenyl)-methoxymethyl]-5,8-methanooctahydro-2*H*-isoxazolo-[3,2-*b*]benzoxazole (29). A solution of the alcohol **28** (0.594 g, 1.15 mmol) in pyridine (20 mL) was treated with trityl chloride (1.3 g, 4.66 mmol, 4 equiv) and the solution stirred overnight at 70 °C. After cooling to room temperatrure, the mixture was diluted with water and with brine (10 mL each) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The remaining pyridine was coevaporated with toluene. The residue was taken up with pentane (20 mL) and filtered to remove the trityl impurities. This operation was repeated twice. The crude product was purified by chromatography (25% diethyl ether/heptane) to give the protected alcohol **29** as a colorless oil (0.872 g, 100% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40−7.10 (15H, m), 5.81 (1H, s), 5.26 (1H, d, $J = 6.9$ Hz), 3.61 (1H, ddd, $J = 10.3$, 7.3 and 2.8 Hz), 3.51 (1H, d, $J = 7.6$ Hz), 3.44 (1H, dd, $J = 9.4$ and 6.0 Hz), 3.15 (1H, d, $J = 7.5$ Hz), 2.95 (1H, dd, $J = 9.4$ and 7.1 Hz), 2.25 (1H, m), 2.16 (1H, dd, $J = 14$ and 6.4 Hz),

2.04 (1H, d, J = 4.1 Hz), 1.95 (1H, dd, J = 14 and 8.5 Hz), 1.78 (3H, s, Me-$C_{7'}$), 1.68 (2H, m), 1.58 (1H, m), 1.53 (2H, m), 1.35 (2H, m), 1.30−1.15 (6H, m), 0.92−0.75 (12H, m). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 147.2, 143.9, 128.7, 127.9, 127.2, 99.0, 89.8, 86.9, 79.7, 76.5, 75.2, 60.4, 51.5, 49.2, 48.5, 47.5, 45.6, 36.4, 32.4, 31.5, 30.8, 27.0, 25.9, 25.5, 23.7, 22.2, 19.2, 18.9, 10.9. IR (film): ν (cm^{-1}) 3080, 3050, 3018, 2965, 1608, 1450, 1372, 1275, 1121, 742. Mass (DCI NH_3): m/z 760 (M + 1) (100%), 634, 180. $[\alpha]^{20}_D$ = +18.3 (c = 1.34, $CHCl_3$). Anal. Calcd for $C_{43}H_{54}NIO_3$ (759.3150): C, 67.97; H, 7.16; N, 1.84; I, 16.70. Found: C, 68.12; H, 7.03; N, 1.55; I, 17.02.

(2*R*,3*R*,3a*R*,4*R*,4a*R*,5*S*,8*R*,8a*S*,5′*S*,7′*E*)-2-[10′-(1,1-Dimethylethyloxycarbonyl-5′,7′,9′-trimethyl-7′,9′-decadien-1′-yl]-3-[(1,1,1-triphenyl)methoxymethyl]-5,10,10-trimethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole (30). To a stirred solution of the protected alcohol **29** (0.872 g, 1.15 mmol) in dichloromethane/absolute ethanol (6 mL/1.4 mL) were successively added *tert*-butyl crotonate (6.5 mL), silver carbonate (0.35 g, 1.26 mmol, 1.1 equiv), triethylamine (350 μL, 2.53 mmol, 2.2 equiv), and finally a solution of palladium(II) acetate (0.035 g, 0.11 mmol, 0.1 equiv) in dichloromethane (6 mL). The mixture was stirred for 3 h at room temperature in the dark and then filtered through a short pad of silica gel, eluting with diethyl ether. The filtrate was concentrated in vacuo and the residue purified by chromatography (25% diethyl ether/heptane, R_f = 0.48) to give the dienic ester **30** as a single (*E*,*E*) isomer (colorless oil, 0.708 g, 84% yield).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.40−7.10 (15H, m), 5.64 (1H, s), 5.56 (1H, s), 5.24 (1H, d, J = 6.9 Hz), 3.61 (1H, ddd, J = 10.3, 7.3 and 2.8 Hz), 3.52 (1H, d, J = 7.5 Hz), 3.45 (1H, dd, J = 9.5 and 6.0 Hz), 3.16 (1H, d, J = 7.5 Hz), 2.97 (1H, dd, J = 9.5 and 7.2 Hz), 2.23 (1H, m), 2.20 (3H, s), 2.16 (1H, m), 2.04 (1H, d, J = 3.8 Hz), 1.98 (1H, m), 1.77 (3H, s), 1.68 (2H, m), 1.58 (1H, m), 1.53 (2H, m), 1.48 (9H, s), 1.35 (2H, m), 1.30−1.15 (6H, m), 0.92−0.75 (12H, m). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 166.7, 152.7, 143.9, 140.5, 129.5, 128.7, 127.7, 126.9, 119.2, 99.0, 89.8, 86.9, 79.7, 79.4, 76.5, 60.4, 51.5, 49.3, 48.9, 48.5, 45.6, 36.7, 32.4, 31.5, 30.8, 28.3, 27.1, 25.9, 25.5, 22.2, 19.4, 19.2, 18.9, 18.3, 10.9. IR (film): ν (cm^{-1}) 3080, 3050, 3019, 2964, 1721, 1622, 1453, 1153, 740. Mass (DCI NH_3): m/z 774 (M + 1), 243, 180 (100%). $[\alpha]^{20}_D$ = +38.1 (c = 0.99, $CHCl_3$). High-resolution mass spectrum: calcd for $C_{51}H_{67}NO_5$ 773.5019, found 773.5014. Anal. Calcd: C, 79.13; H, 8.72; N, 1.81. Found: C, 78.92; H, 8.35; N, 1.70.

(2*E*,4*E*,7*R*,12*R*,13*S*)-12-Hydroxy-3,5,7-trimethyl-13-[(1,1,1-triphenyl)methoxymethyl]-2,4-tetradecadiene-1,-14-dioic Acid 1-(1,1-Dimethylethyl) Ester (31). A solution of compound **30** (0.186 g, 0.24 mmol, 1 equiv) in diethyl ether (5 mL) was treated with *m*-chloroperoxybenzoic acid (0.166 g, 1 mmol, 4 equiv) and the clear and colorless solution was stirred for 1 h at room temperature. An aqueous 10% sodium bicarbonate/10% sodium thiosulfate solution (10 mL) was added and the biphasic solution vigorously stirred for 1 h. Diethyl ether (20 mL) was added, and the layers were separated. The organic layer was washed with a 5% $NaHCO_3$ solution (3 × 10 mL) and then washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to a white foam. This crude product was used immediately in the next reaction.

This crude nitrone was dissolved in tetrahydrofuran (3 mL), and a 2 N hydrochloric acid solution (3 mL) was added. The turbid solution was stirred for 30 min at room temperature and then diluted with water (5 mL) and extracted three times with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude aldehyde was used immediately in the oxidation reaction.

The crude aldehyde (in mixture with camphor-derived ketol) was dissolved in *tert*-butyl alcohol (2 mL) and 2-methyl-2-butene (0.5 mL). Then 1 mL of a freshly prepared aqueous 10% sodium chlorite/sodium dihydrogen phosphate solution was added and the solution stirred for 1 h at room temperature. Water was added (5 mL) and the solution extracted three times with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by preparative TLC on silica gel (10% methanol/dichloromethane, R_f = 0.45) gave the pure acid as a colorless oil (97 mg, 65% yield for three steps).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40−7.10 (15H, m), 5.65 (1H, s), 5.56 (1H, s), 3.88 (1H, m), 3.57−3.48 (2H, m), 2.68 (1H, m), 2.18 (3H, s), 2.00 (1H, m), 1.87 (1H, m), 1.76 (3H, s), 1.58 (1H, m), 1.53 (2H, m), 1.48 (9H, s), 1.30−1.15 (6H, m), 0.75 (3H, d, J = 6.6 Hz). Mass (electrospray): m/z 663.7 (M + Na) (100%). High-resolution mass spectrum: calcd for $C_{41}H_{52}O_6Na$ (M + Na) 663.3662, found 663.3664.

(2*E*,4*E*,2′*R*,3′*R*,7*R*)-[3′-(Triphenyl)methoxymethyl-4′-oxo-2′oxetanyl]-3,5,7-trimethyl-2,4-undecadienoic Acid 1,1-Dimethylethyl Ester (32). A solution of the acid **31** (0.034 g, 53 μmol) in pyridine (0.5 mL) was treated at 0 °C with benzenesulfonyl chloride (25 μL, 160 μmol, 3 equiv) and then left overnight in a refrigerator (3 °C). After warming to room temperature, water (5 mL) was added and the product extracted three times with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by chromatography (50% diethyl ether/heptane, R_f = 0.59) gave the β-lactone **32** as a colorless oil (0.024 g, 73% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40−7.10 (15H, m), 5.65 (1H, s), 5.56 (1H, s), 4.48 (1H, dt, J = 6.6 and 4.0 Hz), 3.56 (1H, dd, J = 9.6 and 5.4 Hz), 3.37 (1H, ddd, J = 5.4, 4.0 and 3.4 Hz), 3.26 (1H, dd, J = 9.6 and 3.4 Hz), 2.18 (3H, s), 2.04 (1H, dd, J = 12.6 and 5.7 Hz), 1.87 (1H, m), 1.76 (3H, s), 1.58 (1H, m), 1.53 (2H, m), 1.47 (9H, s), 1.40−1.15 (6H, m), 0.79 (3H, d, J = 6.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 169.5, 166.8, 152.7, 143.3, 140.3, 129.7, 128.5, 128.0, 127.2, 119.3, 86.9, 79.6, 75.5, 58.7, 56.8, 48.9, 36.7, 34.1, 30.8, 28.3, 26.7, 25.2, 19.5, 19.3, 18.3. IR (film): ν (cm^{-1}) 3080, 3050, 3015, 2965, 1820, 1719, 1623, 1152, 720. Mass (electrospray): m/z 645.5 (M + Na) (100%). $[\alpha]^{20}_D$ = +3.3 (c = 1.07, $CHCl_3$). Anal. Calcd for $C_{41}H_{50}O_5$ (622.8527): C, 79.06; H, 8.09. Found: C, 79.42; H, 8.08.

1233-A (1). A few crystals of *p*-toluenesulfonic acid hydrate were added to a solution of the β-lactone **32** (0.011 g, 0.17 mmol) in benzene/dichloromethane (1 mL/0.2 mL). The solution was stirred for 2 h at room temperature and then diluted with water (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (50% diethyl ether/heptane). The polar fractions (R_f < 0.2) were collected and taken into the next reaction.

The crude detritylated material was dissolved in dichloromethane (1 mL), the solution was cooled to 0 °C, and trifluoroacetic acid (1 mL) was added. The bright yellow solution was stirred at 0 °C for 40 min, toluene (3 mL) was added, and the mixture was concentrated in vacuo. Synthetic 1233-A **1** was obtained by preparative TLC on silica gel (10% methanol/dichloromethane, R_f = 0.40; authentic sample R_f = 0.40) as a nearly colorless solid (3.4 mg, 60% overall yield for deprotection steps).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 5.71 (1H, s, C_4-H), 5.67 (1H, s, C_2-H), 4.57 (1H, ddd, J = 7.2, 6.2, and 4.2 Hz, $C_{2'}$-H), 4.04 (1H, dd, J = 11.6 and 4.9 Hz, one of CH_2-OH), 3.87 (1H, dd, J = 11.6 and 4.0 Hz, one of CH_2-OH) 3.39 (1H, q, J = 4.2 Hz, $C_{3'}$-H), 2.23 (3H, s, Me-C_3), 2.06 (1H, dd, J = 13.1 and 6.2 Hz, one of C_6-H), 2.00−1.80 (2H, m, C_{11}-H × 2), 1.84 (1H, dd, J = 13.2 and 7.9 Hz, one of C_6-H), 1.79 (3H, s, Me-C_5), 1.70−1.55 (1H, m, C_7-H), 1.50−1.05 (6H, m, C_8-H × 2, C_9-H × 2, C_{10}-H × 2), 0.82 (3H, d, J = 6.5 Hz, Me-C_7). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 171.5 (C_1), 169.7 ($C_{4'}$), 157.1 (C_3), 142.1 (C_5), 129.5 (C_4), 116.6 (C_2), 74.9 ($C_{2'}$), 58.6 ($C_{3'}$), 58.0 (CH_2-OH), 49.0 (C_6), 36.5 (C_8), 34.0 (C_{11}), 30.9 (C_7), 26.6 (C_9), 25.2 (C_{10}), 20.0 (Me-C_3), 19.4 (Me-C_7), 18.5 (Me-C_5). IR (film): ν (cm^{-1}) 3019, 2933, 2850, 1816 (β-lactone), 1684, 1616, 1419, 1210, 770. $[\alpha]^{20}_D$ = +27.0 (c = 0.90, $CHCl_3$); $[\alpha]^{20}_D$ lit.[4a] = +28.6 (c = 0.62, $CHCl_3$). Mass (electrospray): m/z 347.3 (M + Na) (100%).

Acknowledgment. Glaxo-Wellcome is gratefully acknowledged for a grant to O.D. and Dr. A. Meddour for NMR measurements in chiral medium.

Supporting Information Available: NMR spectra of synthetic intermediates **16**−**32** and of synthetic **1** and ^{2}D spectra in chiral medium for the determination of the enantiomeric excess of **18** (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980813U