Enantioselective Synthesis of the Unsymmetrical Bis(lactone) (–)-(3*E*,6*R*,9*E*,12*S*,14*R*)-Colletol Induced by Chiral Sulfoxides and an Approach to (+)-Colletodiol by Asymmetric Hydroxylation of an α,β-Hydroxy Lactone

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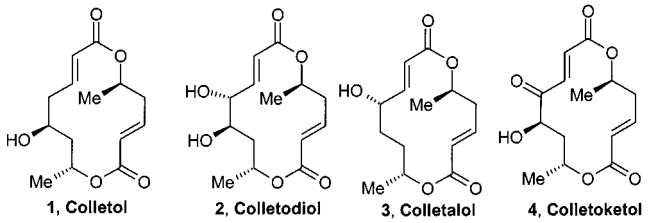
A general synthetic strategy towards the two bis(lactones) (–)-colletol (**1**) and (+)-colletodiol (**2**) is described. A common intermediate in this synthesis is the 6-membered hydroxy lactone (+)-(3*R*,5*R*)-3-hydroxy-5-hexanolide (**6**), readily prepared by stereoselective reduction of (+)-(*SR*)-methyl 3,5-dioxo-6-(*p*-toluenesulfinyl)hexanoate (**7**). Stereoselective hydroxylation of this hydroxy lactone has allowed efficient access to (+)-colletodiol (**2**).

Colletol **1** was first isolated from the fermentation broth of *colletotrichum capsici* in 1973, along with three other related metabolites, colletodiol **2**, colletalol **3**, and colletoketol **4** (Scheme 1).[1]

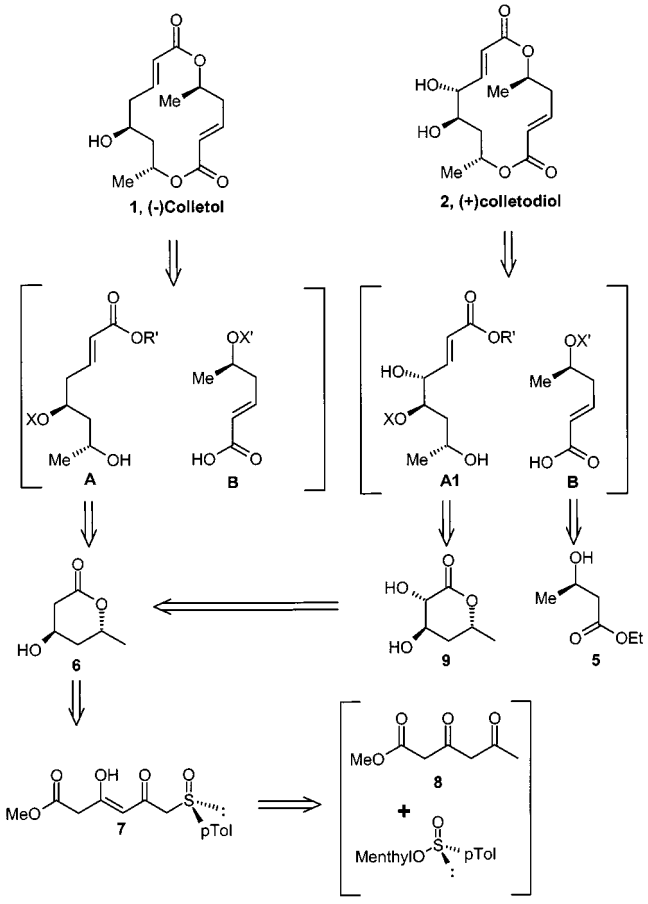


Scheme 1

Interest in this group of unsymmetrical bis(macrolides) came to the fore only in 1980, when Ronald[2] reported the isolation and structural determination of grahamimycin A_1 and described significant antibacterial activity against a variety of pathogenic microorganisms.

The promising biological activity and unique structure of this family of fungal metabolites make them attractive synthetic targets. However, synthetic work in this area has been limited. Colletodiol has been synthesized by Seebach[3] and by Mitsunobu,[4] but both groups encountered considerable difficulties, particularly in the final macrolactonization. Keck′s group reported the first total synthesis of colletol[5] in 1991, following a synthesis of colletodiol[6] in 1989 based on the same methodology. These two syntheses involved a Lewis acid mediated addition of triphenylallylstannane to an aldehyde. In 1993, Shimizu[7] described a total synthesis of colletol involving palladium-catalyzed hydrogenolysis of optically active alkenyloxiranes. More recently, Sharma[8] described a synthesis of (–)-colletol based on a coupling of two protected hydroxy acids derived from D-xylose.

In this paper, we report a general synthetic strategy towards the two macrolactones (–)-colletol and (+)-colletodiol involving stereoselective construction of two optically active hydroxy ester fragments, **A** or $\mathbf{A_1}$ and **B** (Scheme 2).



Scheme 2

As shown in the retrosynthetic scheme, the key intermediate for the synthesis of fragment **A** was lactone **6**, in which the two stereogenic centers could be obtained by stereose-

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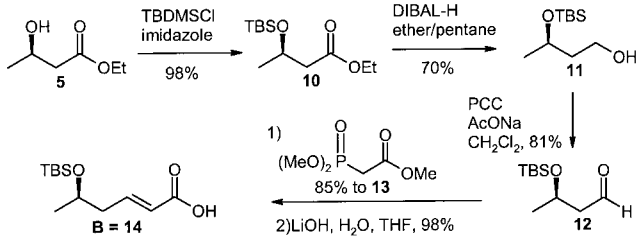
lective reduction of (+)-(*R*)-methyl 3,5-dioxo-6-(*p*-toluenesulfinyl)hexanoate **7**, which, in turn, was readily prepared in one step by condensation of the trianion of dioxo ester **8** with (−)-menthyl (*S*)-*p*-toluenesulfinate. Furthermore, lactone **6** also allowed the preparation of colletodiol precursor fragment $\mathbf{A}_1$ by stereospecific hydroxylation. Fragment **B** could be prepared from commercially available (*R*)-ethyl 3-hydroxybutanoate **5**.

Results

Synthesis of Fragment B (14)

Hydroxy ester **5** was protected as its TBDMS ether, reduced with diisobutylaluminum hydride (DIBAL), and oxidized with pyridinium chlorochromate to give aldehyde **12** in 56% overall yield (Scheme 3). This aldehyde was then allowed to react with stabilized trimethyl phosphonoacetate to give ester **13** in 85% yield, which was hydrolyzed to the corresponding acid **14** (fragment **B**) in high yield.



Scheme 3

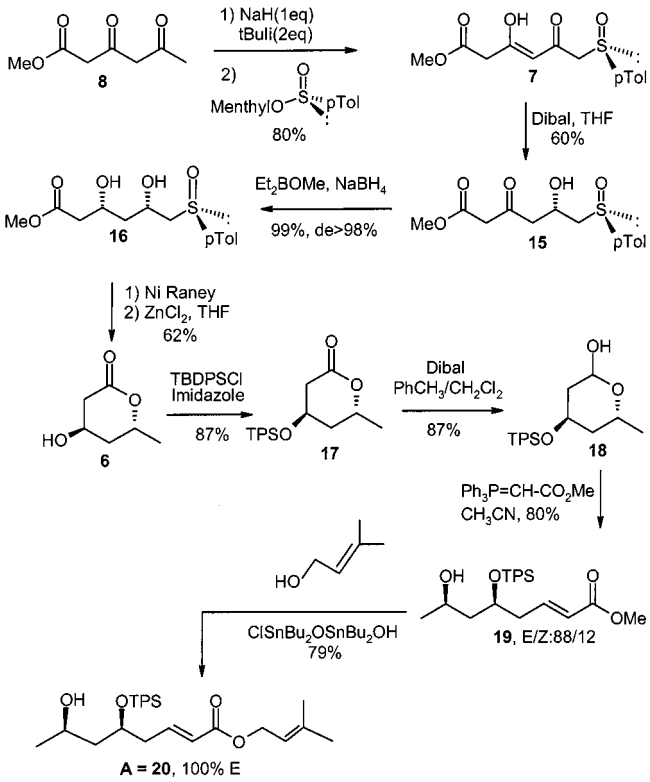
Synthesis of Fragment A (20)

Dioxo ester **8** was obtained in one step by a known procedure[9] from commercially available dehydroacetic acid (Scheme 4). Condensation of the trianion of **8** with (−)-menthyl (*S*)-*p*-toluenesulfinate afforded (*R*)-β,δ-dioxo sulfoxide **7** in high yield. As expected in the light of previous results,[10] the δ carbonyl was entirely enolized and reduction with DIBAL gave only the diastereomer **15** in 60% yield.

The absolute (5*S*,S*R*) configuration of the β-hydroxy sulfoxide **15** was deduced from our previous results[10] and confirmed by correlation with the known final product.

In the next step, the δ carbonyl group was reduced with $Et_2BOMe/NaBH_4$[11] to give the *syn*-diol **16** in quantitative yield and with *de* > 98% (only one stereoisomer was detected by ^{1}H-NMR). Desulfurization with Raney nickel and lactonization of the corresponding hydroxy ester afforded the β-hydroxy lactone **6** in 62% overall yield.

After protection of the hydroxy group with *tert*-butyldiphenylsilyl chloride, reduction of this lactone with DIBAL gave lactol **18** in 87% yield. The presence of a masked aldehyde group facilitated the addition of a triphenylphosphorane to give an 88:12 (*E*/*Z*) mixture of vinylic ester **19** in 80% yield. The (*E*) isomer was separated and transesterified[12] with 3-methyl-2-buten-1-ol (prenol) in the presence of a catalytic amount of 1-chloro-3-hydroxytetrabutyldistannoxane to furnish prenyl ester **20** (fragment **A**) in 79% yield without any detectable isomerization.



Scheme 4

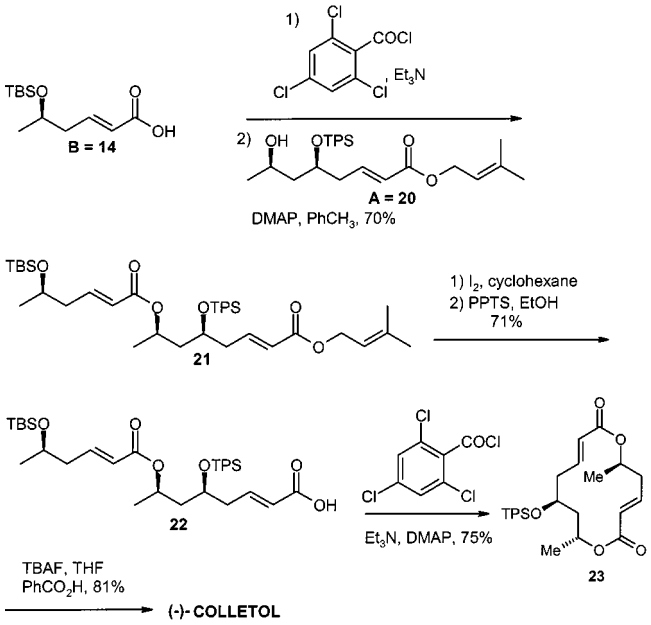
Synthesis of (−)-Colletol (1)

Esterification of **B** (= 1**4**) with **A** (= 2**0**) using 2,4,6-trichlorobenzoyl chloride gave **21** in 70% yield (Scheme 5). Removal of the allylic moiety using iodine in cyclohexane followed by deprotection of the TBDMS ether gave hydroxycarboxylic acid **22** in 71% overall yield. Finally, lactonization with 2,4,6-trichlorobenzoyl chloride and deprotection of the TBDPS group with tetrabutylammonium fluoride in benzoic acid gave (−)-colletol **1** in 81% yield; $[\alpha]_D = -36$ (c = 1, $CHCl_3$), showing all the known characteristic spectroscopic and analytical data.[5][7]

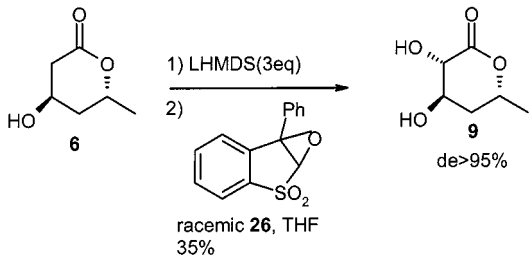
Synthesis of α,β-Dihydroxy Lactone (9)

For the synthesis of colletodiol, a possible route from α,β-dihydroxy lactone **9** was envisaged (Scheme 2). This precursor could be obtained by stereoselective hydroxylation of β-hydroxy lactone **6**.

We first investigated the hydroxylation of enolates generated from ethyl β-hydroxybutyrate **24** by *N*-sulfonyloxaziridines, which are known to oxidize chiral enolates to α-hydroxy carbonyl compounds.[13] The best results were ob-



Scheme 5



Scheme 7

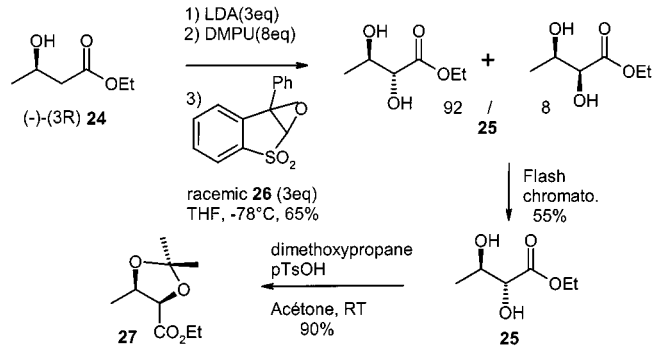
stability of the α,β-dihydroxy lactone in the basic medium.

The relative *trans*-diequatorial configuration of **9** was confirmed by comparison of its ^{1}H-NMR spectrum with that of the known *cis* isomer.[17]

Lactone **9** could be transformed into fragment $\mathbf{A}_1$ using the methodology described for the transformation of **6** into **A**. Finally, access to (+)-colletodiol **2** required the formation of the bis(lactone) ring from the two components $\mathbf{A}_1$ and **B** in a manner similar to the formation of bis(lactone) **1**.

tained using racemic bicyclic *N*-sulfonyloxaziridine (±)-**26**.[14]

Enolization of (−)-(3*R*)-ethyl 3-hydroxybutanoate with LDA in DMPU/THF followed by hydroxylation at −78°C with oxaziridine (±)-**26** afforded the desired product **25** with



Scheme 6

excellent diastereoselectivity (92:8) in 65% yield (Scheme 6).

The two isomers were separated by flash chromatography and the relative *anti* configuration of the major product was confirmed by ^{13}C-NMR[15] and ^{1}H-NMR[16] analysis of acetonide **27**.

In the light of these results, we then carried out the hydroxylation of β-hydroxy lactone **6**, in order to gain access to the α,β-dihydroxy lactone **9**.

Enolization of (+)-(3*R*,5*R*)-3-hydroxy-5-hexanolide **6** with lithium hexamethyldisilazane (LHMDS) in THF, followed by hydroxylation at −78 °C with oxaziridine (±)-**26** afforded the hydroxylated product **9** with excellent diastereoselectivity (98:2) albeit in only moderate 35% yield (Scheme 7). This low yield may be attributed to the low

Experimental Section

General Remarks: ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC-200 spectrometer at 200 and 50 MHz respectively. Chemical shifts δ in ppm relative to solvent signal (residual proton signal for proton spectra or carbon signal for carbon spectra). − IR spectra: Perkin−Elmer 257 spectrophotometer in cm^{-1}. − Elemental analyses: Microanalytical Service of CNRS of Strasbourg. − Analytical TLC: precoated Merck silica gel 60F-254 glass plates; detection by UV (λ = 254 nm or 365 nm) and/or visualization by spray reagents (ethanolic vanillin/H_2SO_4, *p*-anisaldehyde/H_2SO_4 or phosphomolybdic acid). − Preparative (column) chromatography: Silica gel Geduran Si 60 (40−63 μm; 70−230 mesh) from E. Merck.

Methyl (+)-(*SR*)-3,5-Dioxo-6-(*p*-toluenesulfinyl)hexanoate (7): To a cold (0°C) suspension of NaH (1.82 g, 75.8 mmol) in THF (250 mL) was added dropwise a solution of dioxo ester **8** (11.86 g, 75 mmol) in THF (50 mL). After stirring for 15 min at 0°C, a 1.5 M solution of *tert*-butyllithium in pentane (100 mL, 0.15 mol) was added dropwise. A solution of (−)-(*S*)-menthyl *p*-toluenesulfinate (11.04 g, 37.5 mmol) in THF (45 mL) was then added to the red-black solution. After stirring for 2 h at 0°C, the mixture was hydrolyzed with satd. NH_4Cl solution (120 mL) and diluted with AcOEt (100 mL). After adjusting to pH 3 with 10% aqueous H_2SO_4, the aqueous layer was extracted with AcOEt (4 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvents were evaporated to leave a brown oil. The crude product was purified by column chromatography on metal-free silica gel (hexane/CH_2Cl_2 gradient to elute menthol and the excess dioxo ester; CH_2Cl_2/AcOEt gradient to elute the dioxo sulfoxide) and subsequent recrystallization from diethyl ether to provide the dioxo sulfoxide **7** as a pale-yellow solid (7.8 g, 70%); m.p. 51−52°C. − R_f = 0.42 (AcOEt/CH_2Cl_2, 1:1). − $[\alpha]_D$ = +262 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.39 (s, 3 H, Me *p*-Tol), 3.34 (s, 2 H, 2-H), 3.62 (AB, 2 H, J_{AB} = 13 Hz, Δν = 17 Hz, 6-H), 3.71 (s, 3 H, OMe), 5.64 (s, 1 H, 4-H), 7.40 [$(AB)_2$, 4 H, J_{AB} = 8 Hz, Δν = 39 Hz, arom. H], 14.4 (br. s, 1 H, enol H). − ^{13}C NMR ($CDCl_3$): δ = 21.4 (Me *p*-Tol), 45.1 (C-2), 52.5 (OMe), 64.7 (C-6),

102.7 (C-4), 123.9 and 130.0 (CH arom.), 139.5 and 142.3 (Cq arom.), 167.3 (C-1), 179.5 (C-3), 188.8 (C-5). − IR ($CHCl_3$): $\tilde{\nu}$ = 3080−2900, 1730, 1600 cm^{-1}. − $C_{14}H_{16}O_5S$ (296.3): calcd. C 56.74, H 5.44; found C 56.67, H 5.53.

Methyl (+)-(5*S*,S*R*)-5-Hydroxy-3-oxo-6-(*p*-toluenesulfinyl)hexanoate (15): To a cooled (30 min at −78 °C) solution of dioxo sulfoxide **7** (6.8 g, 0.23 mmol) in THF (340 mL) was added dropwise a cooled (30 min at −60 °C) 1 M solution of DIBAL in toluene (0.46 mmol). After 30 min at −78 °C, the reaction mixture was quenched with methanol (200 mL), allowed to warm to room temperature, and the solvents were evaporated. The residue was diluted with AcOEt (200 mL) and hydrolyzed with satd. sodium tartrate solution (200 mL). On stirring overnight, the mixture separated into 2 phases. Then, after adjusting to pH 4 with 10% aq. H_2SO_4, the aqueous layer was extracted with AcOEt (3 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by column chromatography on metal-free silica gel (hexane/CH_2Cl_2 gradient and CH_2Cl_2/AcOEt gradient) and subsequent recrystallization from a diethyl ether/CH_2Cl_2 mixture to give the β-hydroxy δ-oxo sulfoxide **15** as a white solid (3.0 g, 44%); m.p. 118 °C. − R_f = 0.44 (AcOEt). − $[\alpha]_D$ = +211 (*c* = 1, $CHCl_3$). − *de* > 95% (only one diastereomer observed by ^1H NMR). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.42 (s, 3 H, Me *p*-Tol), 2.80 (A_2 of A_2X, 2 H, J_{AX} = 17 Hz, 4-H), 2.90 (AB of ABX, 2 H, J_{AB} = 13.5 Hz, J_{AX} = 9.5 Hz, J_{BX} = 2.5 Hz, Δν = 66 Hz, 6-H), 3.48 (s, 2 H, 2-H), 3.71 (s, 3 H, OMe), 4.27 (d, 1 H, *J* = 3.5 Hz, OH), 4.63 (m, 1 H, 5-H), 7.43 [$(AB)_2$, 4 H, J_{AB} = 8 Hz, Δν = 34 Hz, arom. H]. − ^{13}C NMR ($CDCl_3$): δ = 21.4 (Me *p*-Tol), 49.0 (C-4), 49.6 (C-2), 52.5 (OMe), 60.6 (C-6), 63.4 (C-5), 124.0 and 130.1 (CH arom.), 139.2 and 141.8 (Cq arom.), 167.2 (C-1), 201.5 (C-3). − IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 3100−2900, 1730−1710 cm^{-1}. − $C_{14}H_{18}O_5S$ (298.4): calcd. C 56.36, H 6.08; found C 56.3, H 5.98.

Methyl (+)-(3*R*,5*S*,S*R*)-3,5-Dihydroxy-6-(*p*-toluenesulfinyl)hexanoate (16): To a cold (−78 °C) solution of β-hydroxy δ-oxo sulfoxide **15** (2.11 g, 7.07 mmol) in THF (67 mL) and methanol (16 mL) was added a 1 M solution of diethylmethoxyborane in THF (7.78 mmol). After 45 min at −78 °C, sodium borohydride (295 mg, 7.78 mmol) was added in two portions. The mixture was stirred for 5 h at −78 °C and then hydrolyzed with 1 M AcOH (50 mL). After 15 min, the organic layer was diluted with AcOEt (50 mL) and satd. sodium bicarbonate solution (85 mL) was added. After stirring for 30 min, the aqueous layer was adjusted to pH 4 with 10% aq. H_2SO_4 and extracted with AcOEt (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvents were evaporated. Methanol was added and the crude oily product was heated under atmospheric pressure to distil the azeotrope MeOH/Et_2BOMe. This operation was repeated 4 times and then the crude diol was purified by column chromatography on metal-free silica gel (AcOEt) to provide the β,δ-dihydroxy sulfoxide **16** as a white solid (1.9 g, 90%); m.p. 91 °C. − R_f = 0.29 (AcOEt). − $[\alpha]_D$ = +227 (*c* = 1.1, $CHCl_3$). − *de* > 95% (only one diastereomer observed by ^1H NMR). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.49−1.75 (m, 2 H, 4-H), 2.29 (s, 3 H, Me *p*-Tol), 2.42 (A_2 of A_2X, 2 H, J_{AX} = 16 Hz, 2-H), 2.80 (AB of ABX, 2 H, J_{AB} = 13 Hz, J_{AX} = 9.5 Hz, J_{BX} = 3 Hz, Δν = 26 Hz, 6-H), 3.56 (s, 3 H, OMe), 4.22 (m, 1 H, 3-H), 4.39 (m, 1 H, 5-H), 4.39 (br. s, 1 H, OH), 5.12 (br. s, 1 H, OH), 7.32 [$(AB)_2$, 4 H, J_{AB} = 8 Hz, Δν = 42 Hz, arom. H]. − ^{13}C NMR ($CDCl_3$): δ = 21.1 (Me *p*-Tol), 41.5 (C-4), 42.1 (C-2), 51.4 (OMe), 64.1 (C-6), 65.1 (C-3), 67.0 (C-5), 123.7 and 129.8 (CH arom.), 139.7 and 141.3 (Cq arom.), 172.0 (C-1). − IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 3060−2930, 1700 cm^{-1}. − $C_{14}H_{20}O_5S$ (300.4): calcd. C 55.98, H 6.71; found C 56.23, H 6.72.

(+)-(3*R*,5*R*)-3-Hydroxy-5-hexanolide (6). − 1. A solution of the β,δ-dihydroxysulfoxide **16** (3.0 g, 10 mmol) in methanol (45 mL) was treated with Raney nickel until no more sulfurated products could be detected by TLC. After 6 h, the catalyst was filtered off by passage through Celite, washed with methanol, and the combined filtrate and washings were concentrated to dryness. The crude product was purified by chromatography on silica gel [CH_2Cl_2/AcOEt, 7:3, to elute a by-product (8%); AcOEt] to provide the diol (1.2 g, 75%) as a yellow oil. − **2.** To an activated mixture of zinc chloride (1.0 g, 7.4 mmol) and 4 Å molecular sieves under argon was added a solution of the aforementioned diol (1.2 g, 7.4 mmol) in THF (170 mL). The resulting mixture was heated under reflux for 4 h. The molecular sieves were then filtered off, the filtrate was concentrated to dryness, and AcOEt (50 mL) and satd. brine (40 mL) were added to the oily residue. The aqueous layer was extracted with AcOEt (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/AcOEt, 1:1) to give an oil, which crystallized on refrigeration. After recrystallization from diethyl ether, lactone **6** was obtained as a white solid (800 mg, 83%); m.p. 69−71 °C (ref.[18] 69 °C). − R_f = 0.27 (CH_2Cl_2/AcOEt, 1:1). − $[\alpha]_D$ = +36 (*c* = 1, $CHCl_3$) [ref.[19] +23.1 (*c* = 1, $CHCl_3$)]; $[\alpha]_D$ = +25 (*c* = 0.9, acetone) [ref.[18] −22 (*c* = 0.92, acetone) for the (*S*,*S*) isomer]. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.36 (d, 3 H, J_{6-5} = 6 Hz, 6-H), 1.68 (ddd, 1 H, $J_{4ax-4eq}$ = 14 Hz, J_{4ax-5} = 11 Hz, J_{4ax-3} = 3 Hz, 4ax-H), 1.97 (dt, 1 H, $J_{4eq-4ax}$ = 14 Hz, J_{4eq-3} = J_{4eq-5} = 3 Hz, 4eq-H), 2.62 (m, 2 H, 2-H), 3.03 (br. s, 1 H, OH), 4.32 (m, 1 H, 3-H), 4.82 (qdd, 1 H, 5-H, J_{5-6} = 6 Hz, J_{5-4ax} = 11 Hz, J_{5-4eq} = 3 Hz). − ^{13}C NMR ($CDCl_3$): δ = 21.3 (C-6), 37.5 (C-4), 38.3 (C-2), 62.5 (C-3), 72.6 (C-5), 171.2 (C-1). − IR ($CHCl_3$): $\tilde{\nu}$ = 3600−3300, 3100−2900, 1725 cm^{-1}. − $C_6H_{10}O_3$ (130.4): calcd. C 55.37, H 7.75; found C 55.44, H 7.50.

(+)-(3*R*,5*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5-hexanolide (17): To a magnetically stirred solution of hydroxy lactone **6** (409 mg, 3.14 mmol) in dry DMF (15 mL) were added imidazole (641 mg, 9.4 mmol) and *tert*-butyldiphenylsilyl chloride (2.4 mL, 9.4 mmol). After 2 d at room temperature, the mixture was diluted with diethyl ether (50 mL) and water (20 mL). The resulting mixture was stirred until a clear separation of the phases had occurred and then extracted with diethyl ether (4 × 40 mL). The combined organic layers were washed with satd. NH_4Cl solution (3 × 150 mL) and brine (2 × 150 mL), dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (hexane/diethyl ether, 7:3) to provide compound **17** (960 mg, 87%) as a colourless viscous oil; R_f = 0.25 (hexane/diethyl ether, 7:3). − $[\alpha]_D$ = +13 (*c* = 1, $CHCl_3$). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.08 (s, 9 H, *t*BuSi), 1.36 (d, 3 H, J_{6-5} = 6.5 Hz, 6-H), 1.50 (ddd, 1 H, $J_{4ax-4eq}$ = 14 Hz, J_{4ax-5} = 11 Hz, J_{4ax-3} = 3 Hz, 4ax-H), 1.84 (dddd, 1 H, $J_{4eq-4ax}$ = 14 Hz, J_{4eq-5} = 3 Hz, J_{4eq-3} = 4 Hz, J_{4eq-2} = 2 Hz, 4eq-H), 2.51 (AB of ABX, A coupled with 4eq-H, 2 H, J_{AB} = 17.5 Hz, J_{AX} = 3 Hz, J_{BX} = 4 Hz, J_{A-4eq} = 2 Hz, Δν = 32 Hz, 2-H), 4.29 (m, 1 H, 3-H), 4.96 (qdd, 1 H, J_{5-6} = 6.5 Hz, J_{5-4ax} = 11 Hz, J_{5-4eq} = 3 Hz, 5-H), 7.35−7.66 (m, 10 H, arom. H). − ^{13}C NMR ($CDCl_3$): δ = 18.9 (Me_3CSi), 21.4 (C-6), 26.7 (Me_3CSi), 37.5, 38.5 (C-2, C-4), 64.4 (C-3), 72.3 (C-5), 127.7, 129.9, 135.4 (CH arom.), 132.9, 133.0 (Cq arom.), 170.1 (C-1). − IR ($CHCl_3$): $\tilde{\nu}$ = 3100−2850, 1730 cm^{-1}. − $C_{22}H_{28}O_3Si$ (368.5): calcd. C 71.69, H 7.66; found C 71.92, H 7.69.

Methyl (+)-(5*S*,7*R*,2*E*)-5-(*tert*-Butyldiphenylsilyloxy)-7-hydroxyoctenoate (19). − 1. To a cooled (−78 °C) cloudy solution of lactone **17** (888 mg, 2.4 mmol) in a dry toluene/CH_2Cl_2 (41 mL/15 mL) mixture was added dropwise a 1 M solution of DIBAL in toluene

(3.1 mmol). The homogeneous solution thus obtained was stirred at −78°C until the starting material could no longer be detected by TLC. After 30 min, the reaction mixture was quenched with methanol (30 mL) and allowed to warm to room temperature. Then, diethyl ether (80 mL) and satd. sodium tartrate solution (50 mL) were added. The mixture was stirred until a clear separation of the phases had occurred (30 min). After adjusting to pH 5 with 10% aq. HCl, the aqueous layer was extracted with diethyl ether (3 × 50 mL), the combined organic layers were dried ($MgSO_4$), and the volatile solvents were evaporated without heating. The crude product was purified by column chromatography on silica gel (CH_2Cl_2 to elute toluene; CH_2Cl_2/diethyl ether, 1:1 → neat diethyl ether) to provide the corresponding diastereomeric lactol **18** (780 mg, 87%) as a colourless oily liquid; R_f = 0.09 (CH_2Cl_2). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.09 and 1.11 (s, 9 H, *t*BuSi), 1.21 (d, 3 H, J_{6-5} = 5 Hz, 6-H), 1.25−1.40 (m, 2 H, 4-H), 1.46−2.08 (m, 2 H, 2-H), 3.41 and 5.60 (d, 1 H, OH), 4.14−4.59 (m, 2 H, 3-H, 5-H), 5.19−5.35 (m, 1 H, 1-H), 7.33−7.69 (m, 10 H, arom. H). − ^{13}C NMR ($CDCl_3$): δ = 18.9 and 19.1 (Me_3CSi), 21.2 and 21.4 (C-6), 26.9 (Me_3CSi), 35.6 and 39.1, 39.7 (C-2, C-4), 58.8 and 67.8 (C-5), 66.8 and 67.0 (C-3), 92.7 (C-1), 127.6 and 127.8, 129.6 and 130.1, 135.5 (CH arom.), 132.4 and 132.6, 133.6 and 133.6 (Cq arom.). − IR ($CHCl_3$): $\tilde{\nu}$ = 3500−3400, 3100−2850 cm^{-1}. − **2.** A yellow solution of the aforementioned lactol **18** (780 mg, 2.1 mmol) in anhydrous CH_3CN (20 mL) was treated with methyl triphenylphosphoralynidene acetate (3.0 g, 8.8 mmol). The resulting heterogeneous mixture (becoming homogeneous at 70°C) was then heated under reflux for 12.5 h. After cooling to 0°C, the cloudy orange solution obtained was hydrolyzed with water (10 mL), diluted with diethyl ether (10 mL), and the excess Wittig reagent and the triphenylphosphane oxide formed were filtered off. The aqueous layer was extracted with diethyl ether (2 × 50 mL), the combined organic layers were dried ($MgSO_4$), and the solvents were evaporated. The (*E*) isomer was purified from the mixture of isomers (*E*/*Z* = 88:12 by ^{1}H NMR) by twofold column chromatography on silica gel (pentane/diethyl ether, 1:1) to give the more polar (*E*)-alkene **19** as a pale-yellow viscous oil (716 mg, 80%); R_f = 0.32 (pentane/diethyl ether, 1:1). − $[\alpha]_D$ = +42.5 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.07 (s, 9 H, *t*BuSi), 1.08 (d, 3 H, J_{8-7} = 6 Hz, 8-H), 1.61 (AB of ABXY, 2 H, J_{AB} = 14 Hz, J_{AX} = 14 Hz, J_{BX} = 5.5 Hz, J_{AY} = 7.5 Hz, J_{BY} = 4 Hz, Δν = 26 Hz, 6-H), 2.17−2.45 (m + br. s, 3 H, 4-H + OH), 3.69 (s, 3 H, OMe), 3.87−4.12 (m, 2 H, 5-H + 7-H), 5.63 (dt, 1 H, J_{2-3} = 15.5 Hz, J_{2-4} = 1.5 Hz, 2-H), 6.77 (dt, 1 H, J_{3-2} = 15.5 Hz, J_{3-4} = 7.5 Hz, 3-H), 7.34−7.74 (m, 10 H, arom. H). − ^{13}C NMR ($CDCl_3$): δ = 19.2 (Me_3CSi), 23.7 (C-8), 26.9 (Me_3CSi), 39.9 (C-6), 45.2 (C-4), 51.4 (OMe), 66.1 (C-7), 71.9 (C-5), 123.4 (C-2), 127.7, 127.8, 129.86, 129.96, 135.8 (CH arom.), 133.2, 133.7 (Cq arom.), 144.8 (C-3), 166.6 (C-1). − IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3100−2860, 1720, 1660, 1610 cm^{-1}. − $C_{25}H_{34}O_4Si$ (426.6): calcd. C 70.38, H 8.03; found C 70.11, H 7.98.

3-Chloro-1-hydroxytetrabutyldistannoxane: A heterogeneous mixture of di-*n*-butyltin oxide (1.65 g, 6.6 mmol) and di-*n*-butyltin dichloride (2.0 g, 6.6 mmol) in benzene (33 mL) was refluxed for 20 h, in the course of which the dibutyltin oxide dissolved. After cooling to room temperature, the solution was concentrated to give 1,3-dichlorotetrabutyldistannoxane as a white solid (3.4 g, 93%); m.p. 109−111°C (ref.[20]: 110−112°C). This compound was recrystallized from ethanol to provide 1-ethyloxy-3-chlorotetrabutyldistannoxane as a white solid (3.0 g, 87%); melting range 85−120°C (ref.[21]: 85−140°C). The aforementioned ethyloxy compound was dissolved in the minimum volume of hot acetone and treated with an equimolar amount of water. The acetone/ethanol azeotrope was evaporated under atmospheric pressure. Recrystallization from acetone provided the 1-hydroxy-3-chlorotetrabutyldistannoxane as a bright white solid (2.5 g, 87%); melting range 107−113°C (ref.[12b]: 107−115°C). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.94 and 0.95 (2 t, 12 H, *J* = 7 Hz, Me), 1.40 (m, 8 H), 1.76 (m, 16 H). − ^{13}C NMR ($CDCl_3$): δ = 13.6 (C-CH_2), 26.5, 26.6, 27.1, 27.3, 32.3, and 32.9 (C-CH_3). − IR (CCl_4): $\tilde{\nu}$ = 2980−2860 cm^{-1}.

3′-Methyl-2′-butenyl (+)-(5*S*,7*R*,2*E*)-5-(*tert*-Butyldiphenylsilyloxy)-7-hydroxyoctenoate (20): A solution of methyl ester **19** (686 mg, 1.6 mmol) in dry toluene (20 mL) was refluxed for 15 h in the presence of a large excess of 3-methyl-2-buten-1-ol (prenol) (1.6 mL, 16 mmol) and a catalytic amount of 1-hydroxy-3-chlorotetrabutyldistannoxane (86 mg, 0.16 mmol). After cooling, the crude reaction mixture was passed through a silica gel column (CH_2Cl_2) to eliminate toluene. The mixture of prenyl ester and excess prenol was then purified by twofold column chromatography on silica gel (gradient pentane/diethyl ether, 8:2 → pentane/diethyl ether, 3:7) to provide compound **20** as a colourless, viscous oil (607 mg, 79%); R_f = 0.45 (pentane/diethyl ether, 1:1). − $[\alpha]_D$ = +47 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.07 (s, 9 H, *t*BuSi), 1.08 (d, 3 H, J_{8-7} = 6 Hz, 8-H), 1.60 (m, 2 H, 6-H), 1.72 and 1.77 (2 s, 2 × 3 H, 4′-H), 2.27 (m, 2 H, 4-H), 3.94 (m, 1 H, 7-H), 4.06 (m, 1 H, 5-H), 4.60 (d, 2 H, $J_{1'-2'}$ = 7 Hz, 1′-H), 5.35 (ts, 1 H, $J_{2'-1'}$ = 7 Hz, $J_{2'-4'}$ = 1.5 Hz, 2′-H), 5.64 (dt, 1 H, J_{2-3} = 15.5 Hz, J_{2-4} = 1 Hz, 2-H), 6.77 (dt, 1 H, J_{3-2} = 15.5 Hz, J_{3-4} = 7.5 Hz, 3-H), 7.34−7.74 (m, 10 H, arom. H). − ^{13}C NMR ($CDCl_3$): δ = 18.0 and 25.7 (C-4′), 19.2 (Me_3CSi), 23.7 (C-8), 26.9 (Me_3CSi), 40.1 (C-6), 45.2 (C-4), 61.2 (C-1′), 66.2 (C-7), 71.9 (C-5), 118.6 (C-2′), 123.7 (C-2), 127.7, 127.8, 129.86, 129.96, and 135.8 (CH arom.), 133.2 and 133.7 (Cq arom.), 138.9 (C-3′), 144.6 (C-3), 166.2 (C-1). − IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3100−2860, 1710, 1660, 1610 cm^{-1}. − $C_{29}H_{40}O_4Si$ (480.7): calcd. C 72.46, H 8.39; found C 72.63, H 8.44.

Ethyl (−)-(3*R*)-3-(*tert*-Butyldimethylsilyloxy)butanoate (10): To a stirred solution of (−)-(3*R*)-ethyl 3-hydroxybutanoate (2.0 g, 15 mmol) in dry DMF (37 mL) at 0°C were added imidazole (3.1 g, 45 mmol) and *tert*-butyldimethylsilyl chloride (3.4 g, 22.5 mmol). The mixture was stirred for 45 h at room temperature and then diluted with diethyl ether (30 mL) and water (15 mL). The resulting mixture was stirred until a clear separation of the phases had occurred (15 min) and then extracted with diethyl ether (4 × 100 mL). The combined organic layers were washed with satd. NH_4Cl solution (3 × 150 mL) and brine (2 × 100 mL), dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (pentane/diethyl ether, 95:5) to provide compound **10** (3.67 g, 98%) as a slightly yellow liquid; R_f = 0.28 (pentane/diethyl ether, 95:5). − $[\alpha]_D$ = −28 (*c* = 1.1 $CHCl_3$) [ref.[22]: −26.9 (*c* = 1.02, $CHCl_3$)]. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.02 and 0.04 (2 s, 2 × 3 H, Me_2Si), 0.84 (s, 9 H, *t*BuSi), 1.17 (d, 3 H, J_{4-3} = 6 Hz, 4-H), 1.23 (t, 3 H, $J_{2'-1'}$ = 7 Hz, 2′-H), 2.39 (AB of ABX, 2 H, J_{AB} = 14.5 Hz, J_{AX} = 7.5 Hz, J_{BX} = 5.5 Hz, Δν = 28 Hz, 2-H), 4.09 (q, 2 H, $J_{1'-2'}$ = 7 Hz, 1′-H), 4.26 (qdd, 1 H, J_{3-4} = 6 Hz, J_{3-A} = 7.5 Hz, J_{3-B} = 5.5 Hz, 3-H). − ^{13}C NMR ($CDCl_3$): δ = −5.1 and −4.5 (MeSi), 14.2 (C-2′), 17.9 (Me_3CSi), 23.9 (C-4), 25.7 (Me_3CSi), 44.9 (C-2), 60.2 (C-1′), 65.8 (C-3), 171.6 (C-1).

(−)-(3*R*)-3-(*tert*-Butyldimethylsilyloxy)butan-1-ol (11): To a cooled (0°C) solution of ester **10** (3.6 g, 15 mmol) in a dry pentane/diethyl ether mixture (1.5 L:165 mL) was added dropwise a 1 M solution of DIBAL in toluene (45 mmol). After 3 h at 0°C, the starting material had been completely consumed. The reaction mixture was then quenched with methanol (50 mL) and allowed to warm to room temperature. The solvents were evaporated and the oily residue was

diluted with AcOEt (150 mL) and hydrolyzed with satd. sodium tartrate solution (200 mL). After stirring until a clear phase separation had occurred (1 h), the pH was adjusted to 5 with 10% aq. HCl and the aqueous layer was extracted with AcOEt (4 × 150 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (hexane/diethyl ether, 8:2) to give alcohol **11** (2.1 g, 70%) as a colourless liquid; R_f = 0.43 (hexane/diethyl ether, 6:4). − $[\alpha]_D$ = −29 (*c* = 1, $CHCl_3$) [ref.[22] −30.1 (*c* = 1.09, $CHCl_3$)]. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.04 (s, 6 H, MeSi), 0.85 (s, 9 H, *t*BuSi), 1.5−1.8 (m, 2 H, 2-H), 2.86 (br. s, 1 H, OH), 3.59−3.82 (m, 2 H, 1-H), 3.97−4.12 (m, 1 H, 3-H). − ^{13}C NMR ($CDCl_3$): δ = −5.0 and −4.4 (MeSi), 17.9 (Me_3CSi), 23.4 (C-4), 25.8 (Me_3CSi), 40.5 (C-2), 60.4 (C-1), 68.3 (C-3).

Methyl (−)-(5*R*,2*E*)-5-(*tert*-Butyldimethylsilyloxy)hexenoate (13). − 1. To a mixture of dried sodium acetate (321 mg, 3.9 mmol) and PCC (3.4 g, 15.7 mmol) in anhydrous CH_2Cl_2 (20 mL), a solution of the aforementioned alcohol (1.6 g, 7.8 mmol) in anhydrous CH_2Cl_2 (20 mL) was added by means of a cannula. The resulting brown-black heterogeneous mixture was stirred for 21 h at room temperature (starting material no longer detected by TLC). Diethyl ether (20 mL) was then added and the black sticky paste thus obtained was triturated, which resulted in its transformation to a brittle solid. After decantation, the liquid was filtered through Florisil and diethyl ether was added. This operation was repeated 5 times. The solvents were then evaporated without heating and the crude product was purified by column chromatography on silica gel (hexane/diethyl ether, 9:1) to furnish aldehyde **12** (1.28 g, 81%) as a yellow oily liquid; R_f = 0.37 (hexane/diethyl ether, 9:1). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.06 and 0.04 (2 s, 2 × 3 H, MeSi), 0.85 (s, 9 H, *t*BuSi), 1.22 (d, 3 H, J_{4-3} = 6 Hz, 4-H), 2.48 (AB of ABMX, 2 H, J_{AB} = 16 Hz, J_{AX} = 7 Hz, J_{BX} = 5 Hz, $J_{AM} = J_{BM}$ = 2.5 Hz, Δν = 36 Hz, 2-H), 4.33 (qdd, 1 H, J_{3-4} = 6 Hz, $J_{3\text{-}A}$ = 7 Hz, $J_{3\text{-}B}$ = 5 Hz, 3-H), 9.77 (t, 1 H, $J_{1\text{-}A} = J_{1\text{-}B}$ = 2.5 Hz, 1-H). − **2.** Trimethyl phosphonoacetate (1.1 mL, 7.6 mmol) was added to a suspension of dried lithium chloride (322 mg, 7.6 mmol) in dry CH_3CN (23 mL). After 10 min, DBU (0.94 mL, 6.3 mmol) was added, which rendered the mixture homogeneous, followed, after 10 min, by a solution of aldehyde **12** (1.28 g, 6.3 mmol) in CH_3CN (39 mL). A precipitate immediately appeared and the mixture was stirred at room temperature until the starting aldehyde could no longer be detected by TLC. After 2 h, the mixture was hydrolyzed at 0 °C with satd. NH_4Cl solution (50 mL) and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether (3 × 100 mL), the combined organic layers were dried ($MgSO_4$), and the solvents were evaporated without heating. The crude (*E*) isomer (*E*/*Z* = 100:0 by ^{1}H NMR) was purified by column chromatography on silica gel (pentane/diethyl ether, 95:5) to give the (*E*)-alkene **13** (1.4 g, 86%) as a colourless syrup; R_f = 0.3 (pentane/diethyl ether, 95:5). − $[\alpha]_D$ = −9 (*c* = 1, $CHCl_3$) [ref.[22]: +8.94 (*c* = 1.01, $CHCl_3$) for the (*S*) isomer]. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.020 and 0.019 (2 s, 2 × 3 H, MeSi), 0.85 (s, 9 H, *t*BuSi), 1.13 (d, 3 H, J_{6-5} = 6 Hz, 6-H), 2.29 (ddd, 2 H, J_{4-2} = 1.5 Hz, J_{4-3} = 7.5 Hz, J_{4-5} = 6 Hz, 4-H), 3.70 (s, 3 H, OMe), 3.90 (sext., 1 H, $J_{5-6} = J_{5-4}$ = 6 Hz, 5-H), 5.82 (dt, 1 H, J_{2-3} = 15.5 Hz, J_{2-4} = 1.5 Hz, 2-H), 6.94 (dt, 1 H, J_{3-2} = 15.5 Hz, J_{3-4} = 7.5 Hz, 3-H). − ^{13}C NMR ($CDCl_3$): δ = −4.9 and −4.6 (MeSi), 18.0 (Me_3CSi), 23.7 (C-6), 25.8 (Me_3CSi), 42.4 (C-4), 51.3 (OMe), 67.6 (C-5), 122.7 (C-2), 146.3 (C-3), 166.8 (C-1). − IR (neat): $\tilde{\nu}$ = 2936−2858, 1727, 1657, 1464, 1437, 1370 cm^{-1}. − $C_{13}H_{26}O_3Si$ (258.4): calcd. C 60.42, H 10.14; found C 60.37, H 10.08.

(−)-(3*R*,2*E*)-3-(*tert*-Butyldimethylsilyloxy)hexenoic Acid (14): A solution of the aforementioned ester (526 mg, 2 mmol) in THF/H_2O (30 mL:30 mL) was treated with $LiOH·H_2O$ (252 mg, 6 mmol) and the resulting mixture was stirred for 17 h at room temperature. Upon addition of CH_2Cl_2 (20 mL), a white precipitate appeared. After washing with CH_2Cl_2 (2 × 20 mL), the aqueous layer was acidified to pH 4 with 10% aq. HCl, saturated with NaCl, and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated to give acid **14** (478 mg, 98%) as a colourless oily liquid; R_f = 0.44 (hexane/diethyl ether, 1:1). − $[\alpha]_D$ = −10.5 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.05 (s, 6 H, MeSi), 0.88 (s, 9 H, *t*BuSi), 1.16 (d, 3 H, J_{6-5} = 6 Hz, 6-H), 2.35 (ddd, 2 H, J_{4-5} = 6 Hz, J_{4-3} = 7.5 Hz, J_{4-2} = 1 Hz, 4-H), 3.94 (sext., 1 H, $J_{5-6} = J_{5-4}$ = 6 Hz, 5-H), 5.84 (dt, 1 H, J_{2-3} = 15.5 Hz, J_{2-4} = 1 Hz, 2-H), 7.08 (dt, 1 H, J_{3-2} = 15.5 Hz, J_{3-4} = 7.5 Hz, 3-H), 10.4 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = −4.8 and −4.5 (MeSi), 18.1 (Me_3CSi), 23.8 (C-6), 25.8 (Me_3CSi), 42.5 (C-4), 67.5 (C-5), 122.6 (C-2), 149 (C-3), 171.6 (C-1). − IR ($CHCl_3$): $\tilde{\nu}$ = 3500−3000, 2960−2860, 1700, 1660, 1460, 1420 cm^{-1}. − $C_{12}H_{24}O_3Si$ (244.4): calcd. C 58.97, H 9.89; found C 59.26, H 9.81.

3′-Methyl-2′-butenyl (+)-(5*S*,7*R*,13*R*,2*E*,10*E*)-13-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-7-methyl-9-oxo-8-oxatetradeca-2,10-dienoate (21): To a solution of acid **14** (305 mg, 1.25 mmol) in dry THF (2 mL) under argon was added anhydrous NEt_3 (0.19 mL, 1.38 mmol). After 15 min, this mixture was tranferred by means of a cannula into a solution of trichlorobenzoyl chloride (0.2 mL, 1.31 mmol) in THF (2 mL) over a period of 30 min. The resulting heterogeneous mixture was stirred for 3 h at room temperature, until the starting acid could no longer be detected by TLC (hexane/diethyl ether, 9:1). The mixture was then filtered under argon and the filtrate was concentrated to dryness. The resulting oily residue was taken up in dry toluene (7 mL) and this solution was treated with DMAP (169 mg, 1.38 mmol) under argon, which resulted in the immediate formation of a heterogeneous yellow mixture. A solution of alcohol **20** (372 mg, 0.77 mmol) in toluene (3 mL) was then added and the mixture was heated at 85 °C for 1.5 h. After cooling, the crude mixture was purified by column chromatography on silica gel (pentane/diethyl ether, 9:1) to furnish compound **21** (381 mg, 70%) as a slightly yellow oil; R_f = 0.27 (pentane/diethyl ether, 9:1). − $[\alpha]_D$ = +19 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.03 and 0.04 (2 s, 2 × 3 H, MeSi), 0.86 (s, 9 H, *t*BuSi), 1.04 (d, 3 H, $J_{7\text{-Me}}$ = 4.5 Hz, 7-Me), 1.06 (s, 9 H, *t*BuSi), 1.15 (d, 3 H, J_{14-13} = 6 Hz, 14-H), 1.55−1.90 (m, 2 H, 6-H), 1.72 and 1.77 (2 s, 2 × 3 H, 4′-H), 2.21−2.46 (m, 4 H, 12-H + 4-H), 3.89 (m, 2 H, 13-H + 5-H), 4.61 (d, 2 H, $J_{1'\text{-}2'}$ = 7 Hz, 1′-H), 5.03 (m, 1 H, 7-H), 5.36 (ts, 1 H, $J_{2'\text{-}1'}$ = 7 Hz, $J_{2'\text{-}4'}$ = 1.5 Hz, 2′-H), 5.66 and 5.75 (2 d, 2 H, $J_{2-3} = J_{10-11}$ = 15.5 Hz, 2-H + 10-H), 6.81 and 6.91 (2 dt, 2 H, $J_{3-2} = J_{11-10}$ = 15.5 Hz, $J_{3-4} = J_{11-12}$ = 7.5 Hz, 3-H + 11-H), 7.31−7.69 (m, 10 H, arom. H). − ^{13}C NMR ($CDCl_3$): δ = −4.8 and −4.5 (MeSi), 18.0 and 25.8 (C-4′), 18.0 and 19.2 (Me_3CSi), 20.3 (7-Me), 23.8 (C-14), 25.8 and 26.9 (Me_3CSi), 39.0 (C-6), 42.5 (C-4 + C-12), 61.1 (C-1′), 67.6 (C-5 + C-13), 69.2 (C-7), 118.7 (C-2′), 123.4 and 123.8 (C-2 + C-10), 127.6, 129.7 and 135.9 (CH arom.), 133.8 (Cq arom.), 138.8 (C-3′), 145.0 and 145.9 (C-3 + C-11), 165.6 and 166.3 (C-1 + C-9). − IR ($CHCl_3$): $\tilde{\nu}$ = 3000−2860, 1710, 1660, 1460, 1430, 1380 cm^{-1}. − $C_{41}H_{62}O_6Si_2$ (707.1): calcd. C 69.64, H 8.84; found C 69.76, H 8.77.

(+)-(5*S*,7*R*,13*R*,2*E*,10*E*)-5-(*tert*-Butyldiphenylsilyloxy)-13-hydroxy-7-methyl-9-oxo-8-oxatetradeca-2,10-dienoic Acid (22). − 1. To a 0.1 M solution of allylic ester **21** (265 mg, 0.38 mmol) in cyclohexane (3.8 mL) was added freshly sublimed iodine (143 mg, 0.56 mmol). The resulting black-purple mixture was stirred for 6 h at room temperature and was then diluted with CH_2Cl_2 (10 mL)

and hydrolyzed with 0.9 M sodium carbonate solution (20 mL). The heterogeneous mixture thus obtained was stirred until a yellow colour developed. The aqueous layer was acidified to pH 4 with 6 M HCl, saturated with NaCl, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with satd. $Na_2S_2O_5$ solution, dried ($MgSO_4$), and the solvents were evaporated. The crude yellow oil obtained was found to consist of the acid and the product of partial hydrolysis (60%) of the TBS group. − **2.** PPTS (93 mg, 0.37 mmol) was added to a solution of the aforementioned yellow oil (212 mg, 0.37 mmol) in ethanol (8 mL) and the resulting mixture was stirred for 2 d at room temperature. The reaction mixture was then hydrolyzed with satd. brine (15 mL), the solvent was evaporated, and the aqueous layer was extracted with AcOEt (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (AcOEt/CH_2Cl_2, 1:1; neat AcOEt, and AcOEt/AcOH, 99:1). The isolated hydroxy acid was finally purified by azeotropic distillation of the AcOH with toluene. This purification procedure was repeated 5 times to obtain pure *seco*-acid **22** (140 mg, 71%, 2 steps) as a yellow oil; R_f = 0.27 (AcOEt/CH_2Cl_2, 1:1). − $[\alpha]_D$ = +24 (*c* = 1.5, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.07 (s, 9 H, *t*BuSi), 1.08 (d, 3 H, $J_{7\text{-Me}}$ = 5.5 Hz, 7-Me), 1.23 (d, 3 H, J_{14-13} = 6 Hz, 14-H), 1.27 (d, 1 H, *J* = 2.5 Hz, OH), 1.58−1.93 (m, 2 H, 6-H), 2.25−2.50 (m, 4 H, 4-H + 12-H), 3.84−4.03 (m, 2 H, 5-H + 13-H), 5.06 (m, 1 H, 7-H), 5.74 (d, 2 H, J_{2-3} = J_{10-11} = 15.5 Hz, 2-H + 10-H), 6.85 and 7.00 (2 dt, 2 H, J_{3-2} = J_{11-10} = 15.5 Hz, J_{3-4} = J_{11-12} = 7.5 Hz, 3-H + 11-H), 7.32−7.69 (m, 10 H, arom. H). − ^{13}C NMR ($CDCl_3$): δ = 19.2 (Me_3CSi), 20.3 (7-Me), 23.1 (C-14), 26.9 (Me_3CSi), 39.1 (C-6), 41.8 and 42.4 (C-4 + C-12), 66.7 and 67.7 (C-5 + C-13), 69.1 (C-7), 123.9 (C-2 + C-10), 127.6, 129.8 and 135.9 (CH arom.), 133.7 (Cq arom.), 145.1 and 147.6 (C-3 + C-11), 165.7 (C-9), 170.9 (C-1). − IR (neat): $\tilde{\nu}$ = 3600−3160, 2930, 2856, 1707, 1655 cm^{-1}.

(+)-(6*R*,14*R*,12*S*,3*E*,9*E*)-6,14-Dimethyl-12-(*tert*-butyldiphenylsilyloxy)-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione (23): To a solution of *seco*-acid **22** (113 mg, 0.21 mmol) in anhydrous THF (4.5 mL) under argon was added Et_3N (33.7 mL, 0.24 mmol), followed, after 30 min, by trichlorobenzoyl chloride (32.8 mL, 0.21 mmol). The resulting heterogeneous mixture was stirred at room temperature until the starting acid could no longer be detected by TLC (AcOEt/CH_2Cl_2, 1:1). After 3 h, the reaction mixture was diluted with dry toluene (40 mL) and the supernatant solution was transferred to a flask containing further toluene (68 mL). The resulting solution was slowly added (3 mL/h) over 43 h to a refluxing solution of DMAP (657 mg, 5.4 mmol) in toluene (108 mL). The mixture was refluxed for a further 11 h, then diluted with diethyl ether (50 mL), and hydrolyzed with satd. $KHSO_4$ solution (50 mL). The organic layer was washed with satd. brine, dried ($MgSO_4$), and the solvents were evaporated. The crude product was purified by twofold column chromatography on silica gel (hexane/diethyl ether, 8:2; hexane/AcOEt, 8:2) to provide macrolactone **23** (82 mg, 75%) as a yellow oil; R_f = 0.19 (hexane/diethyl ether, 8:2). − $[\alpha]_D$ = +8 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.05 (s, 9 H, *t*BuSi), 1.16 (d, 3 H, $J_{14\text{-Me}}$ = 6.5 Hz, 14-Me), 1.33 (d, 3 H, $J_{6\text{-Me}}$ = 6.5 Hz, 6-Me), 1.79 (AB of ABX coupled with 14-H, 2 H, J_{AB} = 15.5 Hz, J_{AX} = 6 Hz, J_{BX} = 5 Hz, $J_{A\text{-}14}$ = 3 Hz, $J_{B\text{-}14}$ = 5 Hz, Δν = 34.5 Hz, 13-H), 2.17 (ddd, 1 H, J_{5-5} = 12.5 Hz, J_{5-6} = 6 Hz, J_{5-4} = 10 Hz, 5-H), 2.31 and 2.32 (2 ddd, 2 H, J_{11-10} = 7.5 Hz, J_{11-12} = 6 Hz, J_{11-12} = 5 Hz, 11-H), 2.45 (dddd, 1 H, J_{5-5} = 12.5 Hz, J_{5-6} = 3 Hz, J_{5-4} = 5 Hz, J_{5-3} = 1 Hz, 5-H), 4.05 (tt, 1 H, J_{12-11} = J_{12-13} = 6 Hz, J_{12-11} = J_{12-13} = 5 Hz, 12-H), 5.04 (qdd, 1 H, $J_{14\text{-Me}}$ = 6.5 Hz, J_{14-13} = 5 Hz, J_{14-13} = 3 Hz, 14-H), 5.18 (qdd, 1 H, $J_{6\text{-Me}}$ = 6.5 Hz, J_{6-5} = 6 Hz, J_{6-5} = 3 Hz, 6-H), 5.47 (dt, 1 H, J_{3-4} = 15.5 Hz, J_{3-5} = 1 Hz, 3-H), 5.61 (d, 1 H, J_{9-10} = 15.5 Hz, 9-H), 6.64 (ddd, 1 H, J_{4-3} = 15.5 Hz, J_{4-5} = 10 Hz, J_{4-5} = 5 Hz, 4-H), 6.66 (dt, 1 H, J_{10-9} = 15.5 Hz, J_{10-11} = 7.5 Hz, 10-H), 7.34−7.78 (m, 10 H, arom. H). − ^{13}C NMR ($CDCl_3$): δ = 19.1 (Me_3CSi), 19.3 (14-Me), 20.5 (6-Me), 26.9 (Me_3CSi), 39.7 (C-13), 40.8 and 41.3 (C-11 + C-5), 67.6 (C-12), 68.4 and 69.4 (C-14 + C-6), 124.5 and 126.5 (C-3 + C-9), 127.6, 127.7, 129.8, 129.9, and 135.8 (CH arom.), 133.7 and 134.1 (Cq arom.), 143.2 and 144.5 (C-4 + C-10), 165.4 and 166.4 (C-2 + C-8). − IR ($CHCl_3$): $\tilde{\nu}$ = 2931, 2857, 1716, 1653 cm^{-1}. − $C_{30}H_{38}O_5Si$ (506.7): calcd. C 71.11, H 7.56; found C 69.93, H 7.70.

(−)-(6*R*,14*R*,12*S*,3*E*,9*E*)-6,14-Dimethyl-12-hydroxy-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione; (−)-Colletol (1): To a solution of silylated lactone **23** (58 mg, 0.11 mmol) in THF (7 mL) were added benzoic acid (77 mg, 0.63 mmol) and a 1.1 M TBAF solution in THF (0.6 mL, 0.58 mmol) and the resulting mixture was stirred at room temperature for 3 d. The mixture was then hydrolyzed with water (5 mL) and diluted with AcOEt (10 mL). The aqueous layer was saturated with sodium chloride and extracted with AcOEt (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (diethyl ether) to give colletol (25 mg, 81%) as a white solid; m.p. 102−103°C (ref.[5]: 102°C). − R_f = 0.49 (diethyl ether). − $[\alpha]_D$ = −36 (*c* = 1, $CHCl_3$) [ref.[5]: −38.4 (*c* = 0.95, $CHCl_3$)]. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.34 (2 d, 6 H, $J_{14\text{-Me}}$ = $J_{6\text{-Me}}$ = 6.5 Hz, 6-Me and 14-Me), 1.74 (AB of ABX coupled with 14-H, 2 H, J_{AB} = 15.5 Hz, J_{AX} = 3.5 Hz, J_{BX} = 6 Hz, $J_{A\text{-}14}$ = $J_{B\text{-}14}$ = 3 Hz, Δν = 98 Hz, 13-H), 2.16−2.57 (m, 4 H, 5-H + 11-H), 4.02 (m, 1 H, 12-H), 5.10−5.32 (2 qdd, 2 H, 14-H + 6-H), 5.76 and 5.79 (2 d, 2 H, J_{9-10} = J_{3-4} = 15.5 Hz, 3-H + 9-H), 6.66 and 6.69 (2 ddd, 2 H, J_{4-3} = J_{10-9} = 15.5 Hz, 4-H + 10-H). − ^{13}C NMR ($CDCl_3$): δ = 18.2 and 20.6 (C-14 + C-6), 40.0, 40.3 and 40.9 (C-5 + C-11 + C-13), 68.2 and 68.4 (C-12 + C-6 + C-14), 125.1 and 126.2 (C-9 + C-3), 143.8 and 144.1 (C-10 + C-4), 165.3 and 166.0 (C-2 + C-8). − IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3000−2860, 1720, 1660 cm^{-1}. − $C_{14}H_{20}O_5$ (268.3): calcd. C 62.67, H 7.51; found C 62.85, H 7.74.

(−)-(2*R*,3*R*)-Ethyl 2,3-Dihydroxybutanoate (25): To a cold (−15°C) solution of diisopropylamine (1.7 mL, 12 mmol) in dry THF (25 mL) was added dropwise a solution of *n*BuLi (7.6 mL, 1.5 M in hexane, 11.3 mmol). After 30 min at −15°C, the mixture was cooled to −78°C and a solution of (−)-(3*R*)-ethyl 3-hydroxybutanoate (0.46 mL, 3.78 mmol) in THF (5 mL) was added by means of a cannula. After stirring for 1.5 h, a solution of DMPU (3.7 mL, 30 mmol) in THF (10 mL) was added. After a further 30 min, this mixture was cannulated into a solution of oxaziridine **26** (2.94 g, 11.3 mmol) in THF (15 mL) at −78°C. The resulting yellow-orange solution was stirred for 1.5 h at −78°C and then hydrolyzed with satd. NH_4Cl solution (20 mL). AcOEt (10 mL) was then added and the pH was adjusted to 4 with 10% aq. HCl. The aqueous layer was saturated with NaCl and extracted with AcOEt (4 × 40 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated. The oxaziridine derivatives were separated by column chromatography on metal-free silica gel (gradient 100% CH_2Cl_2 to elute oxaziridine → 100% Et_2O to elute the diol/DMPU mixture). The diastereomeric diols were subsequently purified by column chromatography (AcOEt) and were isolated in 65% yield with a *dr* of 92:8. Separation of the two diastereomers was achieved by further column chromatography (gradient CH_2Cl_2/Et_2O, 80:20, → 100% Et_2O). − ***anti*-25:** 308 mg, 55%; colourless liquid; R_f = 0.35 (Et_2O). − $[\alpha]_D$ = −9 (*c* = 1.7, CH_2Cl_2); $[\alpha]_D$ = −10 (*c* = 1,

EtOH). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.17 (d, 3 H, $J_{4,3}$ = 6.5 Hz), 1.29 (t, 3 H, $J_{2',1'}$ = 7 Hz), 2.84 (br. s, 1 H), 3.45 (br. s, 1 H), 4.06 (qd, 1 H), 4.19 (d, 1 H, $J_{2,3}$ = 3 Hz), 4.25 (ABX_3, $J_{1',2'}$ = 7 Hz). – ^{13}C NMR ($CDCl_3$): δ = 14.1 (OCH_2CH_3), 17.3 (C-4), 61.9 (OCH_2CH_3), 69.1 (C-3), 74.4 (C-2), 172.7 (C-1). – IR ($CHCl_3$): $\tilde{\nu}$ = 3200–3600, 2800–3000, 1725 cm^{-1}. – $C_6H_{12}O_4$: calcd. C 48.64, H 8.16; found C 48.73, H 8.10. – ***syn*-25:** R_f = 0.42 (Et_2O). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.3 (t, 3 H, $J_{2'-1'}$ = 7 Hz), 1.29 (d, 3 H, J_{4-3} = 6 Hz), 2.74 (br. s, 1 H), 3.35 (br. s, 1 H), 3.99 (d, 1 H, $J_{2,3}$ = 3 Hz), 4.07 (qd, 1 H), 4.26 (ABX_3, 2 H, $J_{1',2'}$ = 7 Hz). – ^{13}C NMR ($CDCl_3$): δ = 14.1 (OCH_2CH_3), 19.5 (C-4), 61.8 (OCH_2CH_3), 68.7 (C-2), 69.1 (C-3), 172.7 (C-1).

(–)-(2*R*,3*R*)-Ethyl 2,3-(Isopropylidenedioxy)butanoate (27): To a solution of diol ***anti*-25** (149.4 mg, 1 mmol) in a mixture of acetone (12 mL) and dimethoxypropane (1.2 mL) was added *p*TsOH (19 mg, 0.1 mmol). After stirring for 12 h, the mixture was hydrolyzed at 0°C with satd. $NaHCO_3$ solution (6 mL) and then diluted with AcOEt (10 mL). The aqueous layer was extracted with AcOEt (3 × 20 mL), the combined organic layers were dried ($MgSO_4$), and the solvents were evaporated. Purification by column chromatography (CH_2Cl_2/hexane, 90:10) afforded **27** as a colourless liquid (169 mg, 90%); R_f = 0.59 (CH_2Cl_2). – $[\alpha]_D$ = –24 (*c* = 2.4, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.25 (d, 3 H, $J_{4,3}$ = 6 Hz), 1.29 (t, 3 H, $J_{2',1'}$ = 7 Hz), 1.37 and 1.60 (2 s, 2 × 3 H), 4.22 (q, 2 H, $J_{1',2'}$ = 7 Hz), 4.43–4.56 (m, 2 H). – ^{13}C NMR ($CDCl_3$): δ = 14.2 (OCH_2CH_3), 15.6 (C-4), 25.5 and 26.9 (C-6), 60.9 (OCH_2CH_3), 73.5 (C-3), 77.7 (C-2), 110.3 (C-5), 170.2 (C-1).

(+)-(2*S*,3*R*, 5*R*)-2,3-Dihydroxy-5-hexanolide (9): To a cold (–78°C) solution of LHMDS (1 M in THF, 1.15 mL, 1.15 mmol) in THF (15 mL) was added a cold (–40°C) solution of hexanolide **6** (50 mg, 0.38 mmol) in THF (2 mL). This mixture was stirred for 2 h and then cannulated into a cold (–75 °C) solution of oxaziridine **26** (299 mg, 1.15 mmol) in THF (5 mL). After stirring for 15 min at –75 °C, the mixture was allowed to warm to –10°C over a period of 2 h. It was then hydrolyzed with satd. NH_4Cl solution (5 mL) and AcOEt (20 mL) was added. After adjusting to pH 4 with 10% HCl, the aqueous layer was saturated with NaCl and extracted with AcOEt (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated. Purification by column chromatography on metal-free silica gel (CH_2Cl_2/acetone, 80:20, to elute the oxaziridine derivatives; neat AcOEt to elute the diol) afforded dihydroxyhexanolide **9** as a beige solid (19.5 mg, 35%); R_f = 0.15 (CH_2Cl_2/acetone, 80:20). – $[\alpha]_D$ = +41 (*c* = 1, acetone). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.40 (d, 3 H, $J_{6,5}$ = 6 Hz), 1.91–2.2 (m, 2 H), 3.15 (br. s), 3.65 (br. s), 4 (td, 1 H, $J_{3,2}$ = $J_{3,4ax}$ = 8 Hz, $J_{3,4eq}$ = 3.5 Hz), 4.32 (d, 1 H, $J_{2,3}$ = 8 Hz), 4.74 (m, 1 H). – ^{13}C NMR ($CDCl_3$): δ = 20.8 (C-6), 38.2 (C-4), 69.6 (C-3), 72.3 (C-2), 73.2 (C-5), 173.9 (C-1). – IR ($CHCl_3$): $\tilde{\nu}$ = 3200–3600, 2850–3050, 1750 cm^{-1}.

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