Total Synthesis of Dolatrienoic Acid: A Subunit of Dolastatin 14

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The (7*R*,15*R*)- and (7*S*,15*R*)-diastereomers of dolatrienoic acid were synthesized using a convergent strategy. Fragment C5−C9 was obtained through enantiodifferentiation of racemic pentane-1,3,5-triol as the key step, fixing the chirality at C7 of fragments **4** and *ent*-**4**. The chirality at C15 of the fragment C10−C16 was introduced from L-glutamic acid. Coupling of these two fragments led to the aldehydes (7*R*,15*R*)- and (7*S*,15*R*)-**2** which were homologated by Horner−Wadsworth−Emmons condensation to give (7*R*,15*R*)- and (7*S*,15*R*)-dolatrienoic acids.

Introduction

The Indian Ocean sea hare *Dolabella auricularia* is a rich source of pseudopeptide metabolites with potent antiproliferative activity.[1] By 1980, Pettit and co-workers had isolated, identified, and evaluated seven major compounds named dolastatins, among which only the cyclic dolastatin 3 and the two linear dolastatins 10 and 15 have been fully characterized and synthesized. Due to their *in vitro* and *in vivo* antineoplastic properties, both dolastatin 10 and dolastatin 15 have received much attention. In the series of cyclic dolastatins, dolastatin 14 presents the highest antiproliferative activity against a human tumor cell line minipanel from the NCI primary screen. This macrocyclic depsipeptide is a remarkable association composed of a heptapeptide and an unsaturated hexadecanoic acid called dolatrienoic acid (**1**) (DTA) (Scheme 1).[2] Several other macrolactones of marine origin with promising pharmacological activity are composed of a peptide and a lipid moiety such as jasplakinolide,[3] cryptophycin A,[4] doliculide,[5] dolastatin G,[6] and aurilide.[7] G. Pettit assumed that the heptapeptide residues were (*S*) configured by comparison with other metabolites extracted from this marine organism.[2] Because of the very small amounts of dolastatin 14 available, neither the absolute nor the relative configuration of the two asymmetric carbons C7 and C15 (DTA numbering) could be determined in the natural compound. This would only be possible after total synthesis of dolastatin 14, which necessitates the synthesis of the four possible diastereoisomers of DTA and subsequent coupling with the heptapeptide. We present herein our results on the stereocontrolled synthesis of (7*S*,15R) and (7*R*,15*R*) diastereoisomers of DTA and a suitable methodology for the preparation of the other diastereoisomeric pair.

Retrosynthetic Analysis of Dolatrienoic Acid (1)

Retrosynthetic analysis of **1** (Scheme 2) led us to an initial disconnection between positions C4 and C5 which imposed the construction of the conjugated diene in the final steps of the synthesis starting from the aldehyde **2**. The stereochemistry of the isolated (*E*) double bond between C10 and C1 in **2** should be secured after hydride reduction of the corresponding alkyne **3**, allowing a second disconnection between the carbon atoms C9 and C10. The resulting new subtargets **4** and **5** allowed independent control of the stereocenters at positions C7 and C15, respectively. Stereodifferentiation of the triol **6**, using Harada's methodology,[8] served to obtain the iodide intermediates (*R*)- or (*S*)-**4**. The natural L-Glu was chosen from the chiral pool as the starting material for the synthesis of the alkyne **5** since the preparation of the chiral intermediate **16** is well documented. Such a versatile approach was found to be suitable for the preparation of the four possible diastereoisomers of DTA since L-Glu could be replaced by its D-form to obtain the (15*S*)-isomer.

Synthesis of the Fragments C5−C9 and C10−C16

Enantiodifferentiation of prochiral diols was efficiently promoted by Harada's group and was successfully applied to obtain the spiroketals **7** and **8**[8a] using (−)-menthone as a chiral template (Scheme 3). We have simplified the original procedure by using a more conventional ketalization step (catalytic TsOH at ambient temperature) and starting from unprotected pentane-1,3,5-triol **6**[9] instead of the persilylated derivatives described by Harada.[8a] The use of an excess of trimethyl orthoformate was crucial to complete the reaction. Under these conditions we observed the formation of **7** and **8** as the major products together with their corresponding formate esters as assessed by ^{1}H NMR spectroscopy analysis. These latter esters were saponified *in situ* to give alcohols **7** and **8** as an inseparable mixture (62% combined yield). Tosylation

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(3) (a) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797−2800. (b) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 3123−3124.

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(9) The triol **6** was readily prepared by reduction of diethyl 3-hydroxyglutarate according to: Thiam, M.; Slassi, A.; Chastrette, F.; Amouroux, R. *Synth. Commun.* **1992**, *22*, 83−95.

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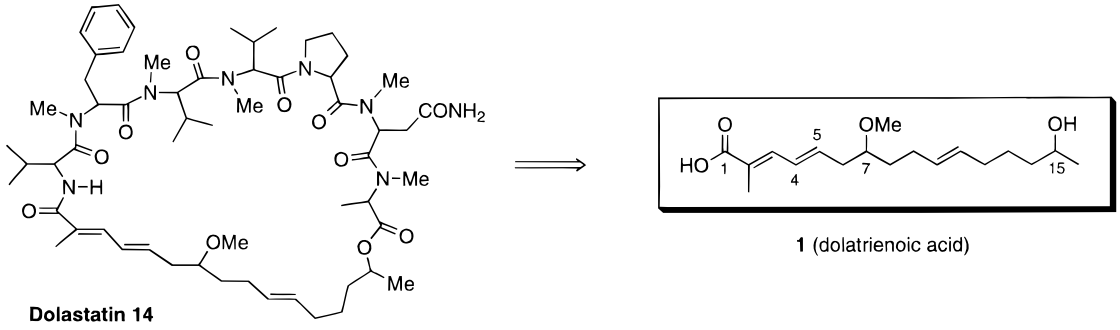
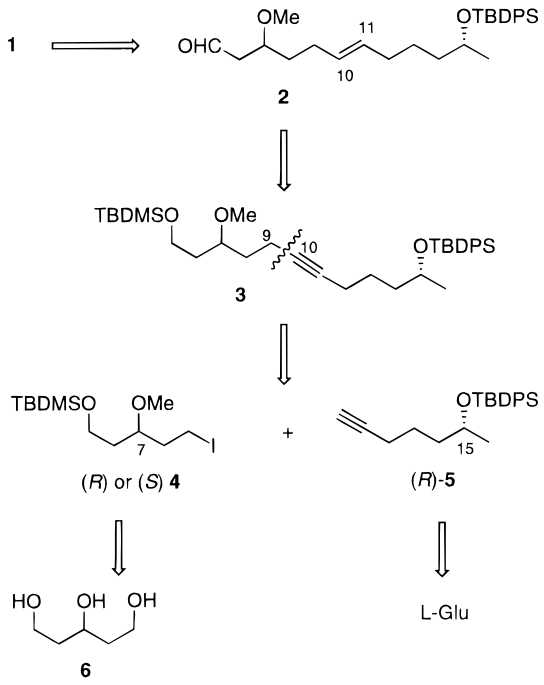
Scheme 1



Scheme 2



of the crude mixture afforded spiroketals **9** and **10** in a ratio of 69:31 and a 57% yield from racemic **6**. After chromatographic separation, the complete assignment of the stereoisomers **9** and **10** was made by comparison with Harada's spiroketals **7** and **8**.[10] The synthesis was pursued on enantiomerically pure compound **9**, using Conia's procedure[11] for the deprotection of the spiroketal. The diol **11** was submitted without purification to a regioselective silylation[12] (TBDMSCl, DIEA, cat. DMAP). Under these conditions we observed the formation of the TBDMS ether **12** together with the chloro derivative **13** (70%, 60:40). Compounds **12** and **13** could either be separated and then methylated (NaH, MeI, DMF) or more conveniently used as a mixture for methylation, since the resulting methyl ethers **14** and **15** led to the same iodide derivative (*S*)-**4** after treatment with sodium iodide in refluxing acetone. The same sequence of reactions was applied to the spiroketal **10** to give the isomer (*R*)-**4**.

The preparation of the alkyne **5** has already been described either through baker's yeast reduction of the corresponding 1-heptyne-6-one[13] or starting from (*S*)-propylene oxide.[14] We decided to follow another route consisting of the condensation of a lithio acetylide with an activated (*R*)-pentane-1,4-diol, obtained from L-Glu. This procedure can alternatively give the (*S*)-enantiomer of **5**, starting from D-Glu. The (*R*)-pentane-1,4-diol **16** was prepared (Scheme 4) according to Barbier's procedure.[15] Regioselective tritylation of the primary alcohol and then silylation of the secondary one afforded **18** (80% over the two steps). Compound **18** was selectively deprotected (PPTS in hot ethanol), and the resulting primary hydroxyl group of **19** was tosylated to give **20** (68% over the two steps). Finally, the tosylate group was displaced by means of the lithium acetylide−ethylenediamine complex[16] in good yield (86%) to give the C10−C16 intermediate **5**.

Synthesis of the Aldehydes (7*R*,15*R*)-2 and (7*S*,15*R*)-2

The C5−C16 fragment was obtained by condensation of the C5−C9 and the C10−C16 fragments prepared above. Nucleophilic displacement of the iodide (*S*)-**4** was done by the lithio derivative of the alkyne **5** (Scheme 5). Reduction of the alkyne **3** by $LiAlH_4$ in refluxing diglyme[17] furnished the diol **22** directly but in low yield. To overcome this difficulty, the protecting groups were first removed (TBAF in THF) to yield **21** which in turn was reduced to the alkene **22** (64% over the two steps). ^1H NMR spectroscopy revealed the presence of a pure (*E*) double bond by homodecoupling irradiation at the allylic position ($J_{10,11}$ = 15.7 Hz). The following steps to obtain the key aldehyde (7*R*,15*R*)-**2** were straightforward and involved a sequence of protection−deprotections before the final oxidation of the alcohol **25** using Swern's protocol.[18] The same sequence of reactions was performed starting from the alkyne **5** and the iodo derivative (*R*)-**4** as the key intermediates and allowed the preparation of the aldehyde (7*S*,15*R*)-**2**.

Preparation of Dolatrienoic Acid (1)

For homologation of the aldehyde **2** into dolatrienoic acid (**1**), we explored two distinct pathways: first vinylogous Mukaiyama aldol condensation of a silyl dienol ether

(10) ^1H NMR spectroscopic data for compounds **9** and **10** are in full agreement with Harada's results.[8a]

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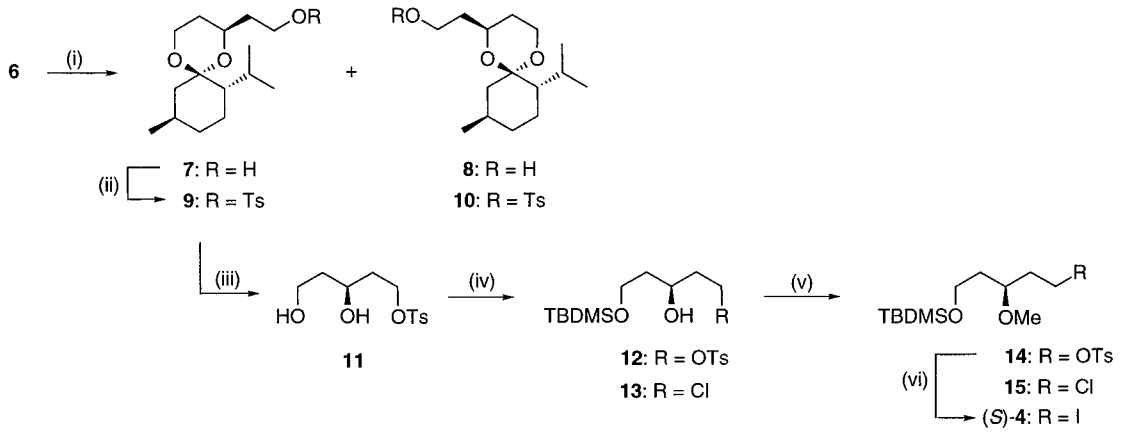
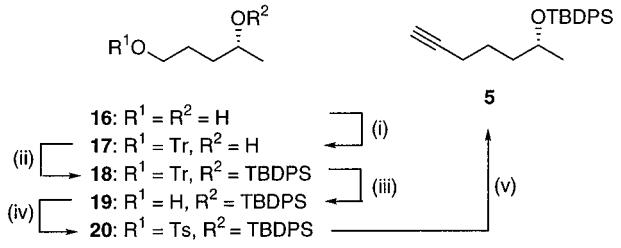
Scheme 3



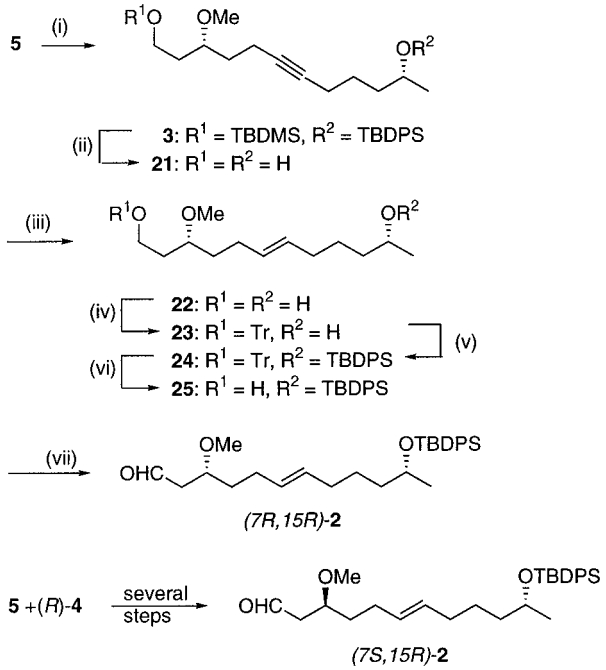
(i) a) (-)-menthone, $HC(OMe)_3$, cat TsOH; b) NaOH 1 N, MeOH; (ii) TsCl, CH_2Cl_2, DMAP (57% overall); (iii) 6 N HCl, SiO_2, CH_2Cl_2 (98%); (iv) TBDMSCl, DIEA, cat DMAP, CH_2Cl_2 (70% combined yield); (v) MeI, NaH, DMF (93%); (vi) NaI, acetone (98%).

Scheme 4



(i) TrCl, CH_2Cl_2, DMAP (83%); (ii) TBDPSCl, imidazole, DMF (96%); (iii) PPTS, EtOH (88%); (iv) TsCl, CH_2Cl_2, DMAP (77%); (v) Li-C≡C-H, EDA complex, DMSO (86%).

Scheme 5



(i) nBuLi (1.1 eq) then (S)-**4**, HMPT; (ii) TBAF, THF (64% overall); (iii) $LiAlH_4$ in refluxing diglyme; (iv) TrCl, CH_2Cl_2, DMAP (60% over the 2 steps); (v) TBDPSCl, imidazole, DMF; (vi) PPTS, EtOH (64% over the 2 steps); (vii) $(COCl)_2$, DMSO, NEt_3 (98%).

followed by dehydration of the resulting allylic alcohol (Scheme 6), and secondly the Horner−Wadsworth−Emmons (HWE) condensation using ethyl (*E*)-4-(dimethoxyphosphonyl)-2-methyl-2-butenoate (Scheme 7).[19]

Vinylogous Mukaiyama Aldol Condensation. We first synthesized the silylketene acetal[20a] **27** (Scheme 6) derived from ethyl tiglate starting from ethyl (*E*)-crotonate through successive methylation and trimethylsilylation in a one-pot procedure. In our hands, this protocol gave better results than direct trimethylsilylation of ethyl tiglate. After distillation, the acetal **27**, obtained as a mixture of (*E*)- and (*Z*)- isomers (45:55), was allowed to react with the aldehyde (7*R*,15*R*)-**2** under Mukaiyama's conditions,[21] giving the expected aldol **28** in only 18% isolated yield together with related but unidentified compounds. ^{1}H NMR analysis of the aldol **28** showed the presence of two epimers (65:35) at the newly created stereocenter which were directly submitted to mesylation and subsequent elimination (DBU, toluene). Isomerization of the resulting mixture of conjugated (*E*,*E*) and (*E*,*Z*) dienes, obtained in a ratio of 71:29, was done using catalytic amounts of iodine and led to isomerically pure protected dolatrienoic acid ethyl ester (7*R*,15*R*)-**30** in an 8% yield from the aldehyde (7*R*,15*R*)-**2**. This low overall yield led us to follow a different strategy.

Horner−Wadsworth−Emmons (HWE) Condensation. We prepared the phosphonate **34** starting from 2-hydroxy-2-methyl-3-butenoic acid **32** (Scheme 7).[22] Esterification with benzyl bromide under basic conditions afforded the corresponding benzyl ester **33**, which is more easily purified than its volatile methyl counterpart. The ester **33** was chlorinated ($SOCl_2$) and the resulting chloro compound was converted to the desired phosphonate **34** by Arbuzov displacement in refluxing trimethyl phosphite. Under NaH treatment, the anion of **34** reacted cleanly with the aldehyde (7*S*,15*R*)-**2** to furnish the

(19) Alternatively, we also tried the double homologation starting with a Wittig reaction using (formylmethylene)triphenylphosphorane followed by the HWE reaction on the α,β-unsaturated aldehyde with ethyl (diethoxyphosphonyl) propionate, but with no clean reaction.

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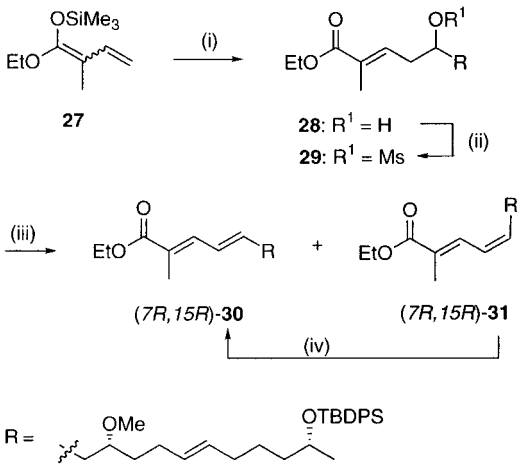
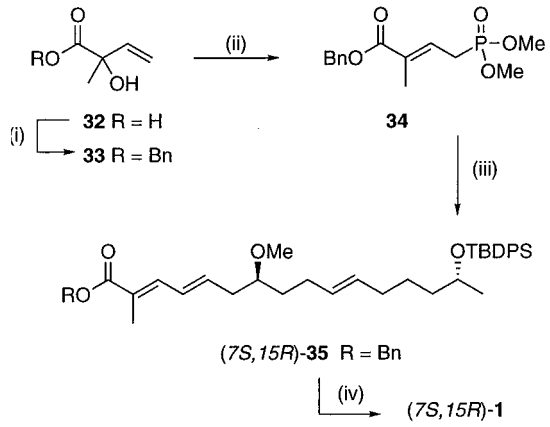
(22) Kitahara, I.; Horiguchi, A.; Mori, K. *Tetrahedron* **1988**, *44*, 4713−4720.

Scheme 6



(i) (7R,15R)-**2** (0.5 eq), CH_2Cl_2/Et_2O (90:10), -78°C (20%); (ii) MsCl, NEt_3, CH_2Cl_2; (iii) DBU, Toluene; (iv) I_2, $CHCl_3$ (46% over 3 steps).

Scheme 7



(i) $NaHCO_3$, BnBr, DMF (53%); (ii) $SOCl_2$, CH_2Cl_2 then $P(OMe)_3$, reflux (82%); (iii) a) NaH, THF then (7S,15R)-**2**; b) I_2, $CHCl_3$ (70%); (iv) 10 M HF/hexane/CH_3CN, 0°C then 0.4 M KOH/MeOH (33%).

dolatrienoic benzyl ester as a mixture of (*E*,*E*)- and (*E*,*Z*)-dienes in a ca. 50/50 ratio. This mixture was isomerized as above with iodine crystals yielding the pure (*E*,*E*)-diene (7*S*,15*R*)-**35** in a 70% yield. The last deprotection steps were conducted on the ester **35** using sequentially an aqueous solution of HF in hexane/acetonitrile then methanolic KOH to furnish the desired (7*S*,15*R*)-**1** in 33% yield. The ester (7*R*,15*R*)-**30** gave (7*R*,15*R*)-**1** in 37% yield under the same conditions of deprotection.

The structure of the final compound (7*S*,15*R*)-**1** was ascertained by NMR correlation experiments. Absence of migration of the C10−C11 (*E*) double bond during the synthesis was confirmed from both COSY-DQF and HMQC-TOCSY experiments which showed unambiguous connections from H10 to H7 protons. The correct geometry of the conjugated (*E*,*E*) diene was deduced from the $J_{4,5}$ coupling constant (15.0 Hz). Moreover, on the basis of a NOESY experiment, the spatial proximities of the H3 and H5 protons on the one hand and the C2-methyl and H4 protons on the other hand confirm this geometry.

Conclusion

We have synthesized (7*S*,15*R*)- and (7*R*,15*R*)-dolatrienoic acids, which are key intermediates in the total synthesis of dolastatin 14 and are essential for the assignment of the absolute configuration of the C7 and C15 stereocenters present in the natural compound. The proposed synthesis involves a convergent assembling of three fragments. Fragment C5−C9 was obtained by stereodifferentiation of a functionalized pentane-1,3,5-triol. L-Glu was chosen to fix the chirality of fragment C10−C16. These two fragments were coupled to give (7*S*,15*R*)- and (7*R*,15*R*)-**2**. These aldehydes were then homologated by Horner−Wadsworth−Emmons condensation to give (7*S*,15*R*)- and (7*R*,15*R*)-**1**. Coupling of these two acids with the heptapeptide included in dolastatin 14 and the macrocyclization of the resulting amides are in progress.

Experimental Section

General Procedures. ^{1}H-NMR spectra were recorded either at 200 or 360 MHz and chemical shifts are reported in ppm and referenced to $CHCl_3$ (7.24 ppm) unless otherwise noted. NMR correlation experiments were recorded at 400 MHz in C_6D_6. ^{31}P-NMR spectra were recorded at 81 MHz, and chemical shifts are reported in ppm and referenced to H_3PO_4. Mass spectra were performed in the FAB^+ mode unless otherwise noted, by the Department of Physical Measurements of the University of Montpellier II. Elemental analyses were performed by the CNRS, at the Ecole Nationale Supérieure de Chimie de Montpellier. Optical rotations were run at 20 °C. Column chromatography was conducted by using silica gel (70−230 or 240−400 mesh) as the stationary layer. Analytical TLC was performed on silica gel 60F254 aluminum sheets. Analytical HPLC was carried out with a Kromasil C8 column (5 μm, 4.6 × 150 mm) using a gradient of acetonitrile + 0.1% TFA (solvent B) in water + 0.1% TFA (solvent A) at a 1.5 mL/min rate (conditions A) or with an Ultrasphere Si column (5 μm, 4.6 × 250 mm) using a gradient of ethyl acetate (solvent B) in hexane (solvent A) at the same rate (conditions B). Semipreparative HPLC was carried out with an Ultrasphere ODS column (10 μm, 10 × 250 mm) using a gradient of acetonitrile + 0.1% TFA in water + 0.1% TFA at 4 mL/min (conditions C).

(2*RS*,6*S*,7*S*,10*R*)-7-Isopropyl-10-methyl-2-[(4-methylbenzenesulfonyl)oxy]-1,5-dioxaspiro[5.5]undecane (9 and 10). To a stirred solution of **6**[10] (6.04 g, 50 mmol), (−)-menthone (8.4 mL, 55 mmol), and TsOH (475 mg, 2.5 mmol) in dry CH_2Cl_2 (250 mL) was added trimethyl orthoformate (16.4 mL, 0.15 mol) at rt. The solution was stirred overnight, and then additional trimethyl orthoformate (5.3 mL, 0.05 mol) was added. Stirring was continued for another 4 h. At 0 °C a solution of 1 N NaOH (55 mL) in MeOH (200 mL) was added to the mixture and was stirred for 12 h at rt. The aqueous layer was extracted with diethyl ether (3 × 100 mL), and then the combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. Filtration and concentration of the solvent under vacuum yielded a mixture of diastereoisomeric alcohols **7** and **8** (7.94 g, 62% combined yield). This mixture was used as such for the next step.

To the preceding mixture of alcohols **7** and **8** dissolved in dry CH_2Cl_2 (200 mL) was added DMAP (5.23 g, 42.9 mmol) at rt. To the resulting solution cooled to −5 °C was slowly added TsCl (7.1 g, 37.2 mmol) dissolved in dry CH_2Cl_2 (40 mL). The solution was stirred at rt overnight and then washed successively with 1 N HCl (2 × 60 mL), saturated aqueous $NaHCO_3$ (60 mL), and brine (60 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford a mixture of diastereoisomeric tosylates **9** and **10** in the ratio 69:31 (11.68 g, 57% overall yield) as colorless oils after purification by flash column chromatography (pentane/EtOAc, 95:5).

Major 9: R_f 0.22 (pentane/EtOAc, 95:5); ^{1}H-NMR δ 7.77 (d, *J* 8.3 Hz, 2H), 7.33 (d, *J* 8.3 Hz, 2H), 4.20−4.07 (m, 2H), 4.03 (td, *J* 11.5, 2.7 Hz, 1H), 3.88 (ddt, *J* 11.7, 9.1, 2.6 Hz, 1H), 3.75 (ddd, *J* 11.5, 5.3, 1.4 Hz, 1H), 2.61 (ddd, *J* 13.6, 3.4, 1.9 Hz, 1H), 2.44 (s, 3H), 2.32 (hept.d, *J* 7.0, 1.8 Hz, 1H), 1.84−1.10 (m, 9H), 0.85 (d, *J* 6.6 Hz, 3H), 0.84 (d, *J* 7.0 Hz, 3H),

0.76 (d, *J* 7.0 Hz, 3H), 0.64 (dd, *J* 13.5, 12.6 Hz, 1H); MS *m/e* (rel intens) 411 ($M + H^+$, 50), 353(33), 325(58), 257(20), 239(13), 211(13), 173(38), 155(64), 137(33), 67(100), 55(92); $[\alpha]_D = +3$ (*c* 0.67, MeOH).

Minor 10: R_f 0.31 (pentane/EtOAc, 95:5); ^{1}H-NMR δ 7.78 (d, *J* 8.2 Hz, 2H), 7.32 (d, *J* 8.2 Hz, 2H), 4.17−4.08 (m, 2H), 4.03 (tdd, *J* 11.5, 8.1, 3.4 Hz, 1H), 3.79 (td, *J* 12.2, 2.6 Hz, 1H), 3.71 (ddd, *J* 11.6, 5.5, 1.3 Hz, 1H), 2.55 (ddd, *J* 13.5, 3.3, 1.9 Hz, 1H), 2.44 (s, 3H), 2.21 (hept.d, *J* 7.0, 2.5 Hz, 1H), 1.84−1.24 (m, 8H), 0.99 (ddd, *J* 12.6, 3.9, 2.6 Hz, 1H), 0.86 (d, *J* 6.6 Hz, 3H), 0.81 (d, *J* 7.0 Hz, 6H), 0.47 (dd, *J* 13.5, 12.6 Hz, 1H); MS *m/e* (rel intens) 411($M + H^+$, 45), 353(13), 325(22), 257(6), 239(5), 211(5), 173(14), 155(22), 137(15), 67(100), 55(49); $[\alpha]_D = -35$ (*c* 1.23, MeOH).

(*S*)-5-[(4-Methylbenzenesulfonyl)oxy]pentane-1,3-diol (11). Silica gel (70−230 mesh) was suspended in CH_2Cl_2 (14 mL) containing 6 N HCl (0.4 mL) and stirred for 5 min. To this suspension was slowly added a solution of **9** (1.6 g, 4 mmol) in CH_2Cl_2 (14 mL). The reaction mixture was stirred overnight at rt. Solid $NaHCO_3$ (0.8 g) was then added and the suspension stirred for 15 min. After filtration over a plug of silica gel, the reaction mixture was washed with pentane (100 mL), and the pentane washings were discarded. The silica gel was then washed with a mixture of CH_2Cl_2/MeOH (150 mL, 90:10). Concentration under vacuum of the filtrate afforded **11** as a pale-yellow oil (0.85 g, 98%): R_f 0.43 (CH_2Cl_2/MeOH, 95:5), ^{1}H-NMR δ 7.76 (d, *J* 8.1 Hz, 2H), 7.33 (d, *J* 8.1 Hz, 2H), 4.24 (ddd, *J* 10.0, 8.6, 5.2 Hz, 1H), 4.12 (ddd, *J* 10.0, 5.4, 5.4 Hz, 1H), 4.00 (m, 1H), 3.87−3.77 (m, 2H), 2.43 (s, 3H), 1.90−1.69 (m, 2H), 1.66 (q, *J* 5.8 Hz, 2H); MS *m/e* (rel intens) 275($M + H^+$, 73), 257(21), 173(35), 155(32), 85(49); $[\alpha]_D = +9.8$ (*c* 2.5, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O_5S$: C, 52.32; H, 6.53. Found: C, 52.54; H, 6.61.

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-[(4-methylbenzenesulfonyl)oxy]pentan-3-ol (12). To a solution of diol **11** (2.65 g, 9.67 mmol) in dry CH_2Cl_2 (40 mL) were added DIEA (2 mL, 10 mmol) and DMAP (58 mg, 0.4 mmol) at rt. The solution was cooled to 0 °C, and then TBDMSCl (1.65 g, 10 mmol) was added to the reaction mixture which was stirred for 24 h at rt. CH_2Cl_2 (20 mL) was added to the crude mixture, and the organic layer was treated successively with a 5% $KHSO_4$ solution (75 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford a mixture of the oily compounds **12** (1.6 g, 42%) and **13** (0.7 g, 28%) after purification by flash column chromatography (cyclohexane/EtOAc, 90:10).

12. R_f 0.33 (cyclohexane/EtOAc, 80:20), ^{1}H-NMR δ 7.76 (d, *J* 8.3 Hz, 2H), 7.33 (d, *J* 8.3 Hz, 2H), 4.20 (ddd, *J* 9.8, 8.1, 6.0 Hz, 1H), 4.15 (ddd, *J* 9.8, 6.0, 5.4 Hz, 1H), 3.91 (m, 1H), 3.86 (ddd, *J* 10.1, 4.6, 4.6 Hz, 1H), 3.76 (ddd, *J* 10.1, 8.4, 4.2 Hz, 1H), 3.45 (bs, 1H), 2.42 (s, 3H), 1.81 (dddd, *J* 14.4, 6.5, 4.1, 4.1 Hz, 1H), 1.74 (dddd, *J* 14.4, 8.4, 5.6, 5.6 Hz, 1H), 1.64 (dddd, *J* 14.4, 8.4, 8.4, 4.2 Hz, 1H), 1.57 (dddd, *J* 14.4, 4.6, 3.6, 3.6 Hz, 1H); MS *m/e* (rel intens) 389($M + H^+$, 82), 331(18), 275(94), 257(21), 229(73), 154(51), 120(42), 91(76), 73(100), 57(39); $[\alpha]_D = +8$ (*c* 1, MeOH). Anal. Calcd for $C_{18}H_{32}O_5SiS$: C, 55.64; H, 8.30. Found: C, 55.48; H, 8.31.

13. R_f 0.67 (cyclohexane/EtOAc, 80:20), ^{1}H-NMR δ 4.05 (m, 1H), 3.88 (ddd, *J* 10.2, 4.6, 4.6 Hz, 1H), 3.83 (ddd, *J* 10.2, 6.4, 4.2 Hz, 1H), 3.71 (ddd, *J* 10.7, 8.7, 6.3 Hz, 1H), 3.65 (ddd, *J* 10.7, 6.9, 5.3 Hz, 1H), 3.52 (bs, 1H), 1.99−1.79 (m, 2H), 1.75−1.60 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H); MS *m/e* 253($M + H^+$, 100), 235(29), 189(22), 139(33), 131(49), 123(51), 115(78), 97(100), 65(24); $[\alpha]_D = +36$ (*c* 0.41, MeOH). Anal. Calcd for $C_{11}H_{25}O_2ClSi$: C, 52.25; H, 9.97. Found: C, 51.88; H, 9.54.

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-1-[(4-methylbenzenesulfonyl)oxy]pentane (14). To a solution of **12** (1.94 g, 5 mmol) in anhydrous DMF (20 mL) was added NaH (0.45 g, 11 mmol) at −5 °C. After being stirred for 15 min, MeI (5 mL, 80 mmol) was added to the resulting suspension and stirred for 1 h at −5 °C, and then allowed to reach rt for 3 h. CH_2Cl_2 (50 mL) was added to the reaction mixture which was washed with brine (3 × 500 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford **14** (1.93 g, 93%) as a pale-yellow oil after purification by flash column chromatography (cyclohexane/EtOAc, 90:10): R_f 0.42 (cyclohexane/EtOAc, 80:20), ^{1}H-NMR δ 7.77 (d, *J* 8.3 Hz, 2H), 7.32 (d, *J* 8.3 Hz, 2H), 4.12 (m, 2H), 3.62 (m, 2H), 3.38 (m, 1H), 3.21 (s, 3H), 2.43 (s, 3H), 1.92−1.82 (m, 1H), 1.79−1.64 (m, 2H), 1.61−1.53 (m, 1H), 0.86 (s, 9H), 0.017 (s, 6H); MS *m/e* (rel intens) 403 ($M + H^+$, 40), 345(15), 287(13), 229(59) 145(22), 89(100), 73(99), 55(68); $[\alpha]_D = +5$ (*c* 1.1, MeOH). Anal. Calcd for $C_{19}H_{34}O_5SiS$: C, 56.68; H, 8.51. Found: C, 56.96; H, 8.52.

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-chloro-3-methoxypentane (15). By the same procedure, the alcohol **13** (1.71 g, 6.8 mmol) yielded **15** (1.50 g, 83%) as a pale-yellow oil: R_f 0.7 (cyclohexane/EtOAc, 80:20), ^{1}H-NMR δ 3.71−3.60 (m, 4H), 3.55 (m, 1H), 3.35 (s, 3H), 1.95−1.88 (m, 2H), 1.78−1.60 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); MS (EI) no molecular ion, 231(12), 185(21), 95(72), 55(100); $[\alpha]_D = +5$ (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{27}O_2ClSi$: C, 54.01; H, 10.20. Found: C, 54.17; H, 10.32.

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-iodo-3-methoxypentane (4). A solution of **14** (1.64 g, 4 mmol) and sodium iodide (1.84 g, 12 mmol) in acetone (40 mL) was refluxed for 16 h. Acetone was removed by vacuum evaporation, and the resulting white precipitate was suspended in diethyl ether (200 mL). Filtration and concentration under vacuum yielded **4** (1.36 g, 98%) as a pale-yellow oil: R_f 0.54 (cyclohexane/EtOAc, 80:20), ^{1}H-NMR δ 3.72−3.62 (m, 2H), 3.41 (m, 1H), 3.36 (s, 3H), 3.24 (m, 2H), 2.04−1.97 (m, 2H), 1.77−1.58 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); MS *m/e* (rel intens) 359($M + H^+$, 13), 327(8), 301(19), 231(13), 185(12), 95(85), 55(100); HRMS *m/e* calcd for $C_{12}H_{27}O_2SiI$: ($[M + H]^+$), 359.0903; found: ($[M + H]^+$) 359.0901.

(*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-iodo-3-methoxypentane (4). HRMS *m/e* calcd for $C_{12}H_{27}O_2SiI$: ($[M - I]^+$), 231.1801; found: ($[M - I]^+$) 231.1780.

(*R*)-1-[(Triphenylmethyl)oxy]pentan-4-ol (17). A solution of diol **16**[15] (3.00 g, 28.8 mmol), DMAP (161 mg, 1.32 mmol), and Et_3N (6.1 mL, 43.8 mmol) in CH_2Cl_2 (25mL) was treated with TrCl (8.84 g, 31.7 mmol). The mixture was stirred for 24 h, then it was poured into cold H_2O (25 mL) and it was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), then dried over Na_2SO_4 and the solvent was evaporated to give **17** (8.3 g, 83%) as a colorless oil after purification by flash column chromatography (pentane/EtOAc, 70:30): R_f 0.50 (pentane/EtOAc, 50:50); ^{1}H-NMR (DMSO-d_6) δ 7.40−7.23 (m, 15H), 4.30 (d, *J* 4.7 Hz, 1H), 3.49−3.54 (m, 1H), 2.95 (t, *J* 6.5 Hz, 2H), 1.50−1.66 (m, 2H), 1.32−1.38 (m, 2H), 1.01 (d, *J* 6.2 Hz, 3H); MS no molecular ion, 243(95), 199(12), 165(21), 154(100), 136(80), 105(20), 89(29), 77(36); $[\alpha]_D = -3.1$ (*c* 1.3 EtOH). Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.2; H, 7.56. Found: C, 83.54; H, 7.79.

(*R*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(triphenylmethyl)oxy]pentane (18). A solution of **5** (7.41 g, 21.4 mmol) and imidazole (3.24 g, 47.6 mmol) in anhydrous DMF (30 mL) was treated with TBDPSCl (6.2 mL, 23.8 mmol). The mixture was stirred for 17 h, and then it was diluted with EtOAc (75 mL) and washed with H_2O and brine (3 × 75 mL each). The organic layer was dried over Na_2SO_4 and concentrated to give **18** (12.0 g, 96%) which was purified by flash column chromatography (pentane/EtOAc, 98:2) as a colorless oil: R_f 0.74 (pentane/EtOAc, 95:5); ^{1}H-NMR (DMSO-d_6) δ 7.62−7.22 (m, 25H), 3.83−3.78 (m, 1H), 2.91−2.82 (m, 2H), 1.57−1.40 (m, 4H), 1.07−0.93 (m, 12H); $[\alpha]_D = +9.8$ (*c* 1.1 EtOH). Anal. Calcd for $C_{40}H_{44}O_2Si$: C, 82.14; H, 7.58. Found: C, 81.93; H, 7.37.

(*R*)-4-[(*tert*-Butyldiphenylsilyl)oxy]pentan-1-ol (19). A solution of **18** (9.05 g, 15.5 mmol) and PPTS (1.25 g, 5 mmol) in absolute EtOH (350 mL) was stirred at 55 °C for 6 h. The solvent was evaporated under vacuum, and the residue was dissolved in EtOAc (150 mL). The organic layer was successively washed with H_2O (60 mL) and brine (60 mL), and then dried over Na_2SO_4. Filtration and concentration under vacuum yielded **19** (4.66 g, 88%) as a pale-yellow oil which was purified by flash column chromatography (cyclohexane/EtOAc, 80:20): R_f 0.22 (cyclohexane/EtOAc, 80:20); ^{1}H-NMR (DMSO-d_6) δ 7.61 (m, 4H), 7.48−7.38 (m, 6H), 4.32 (t, *J* 5.1 Hz, 1H), 3.85 (m, 1H), 3.28 (m, 2H), 1.47−1.36 (m, 2H), 1.00 (d, *J* 6.0 Hz, 3H),

0.99 (s, 9H); MS *m/e* (rel intens) 343 (M + H^+, 71), 285(13), 265(11), 239(28), 199(100), 135(57), 87(37), 69(38); $[\alpha]_D = +10.3$ (*c* 1 EtOH). Anal. Calcd for $C_{21}H_{30}O_2Si$: C, 73.64; H, 8.83. Found: C, 73.63; H, 8.90.

(*R*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(4-methylbenzenesulfonyl)oxy]pentane (20). To the alcohol **19** (5.56 g, 17.5 mmol) dissolved in dry CH_2Cl_2 (120 mL) was added DMAP (3.42 g, 28 mmol) at rt. To the solution cooled to −5 °C was slowly added TsCl (4.01 g, 21 mmol) dissolved in dry CH_2Cl_2 (30 mL). The solution was stirred at rt overnight and then washed successively with 1 N HCl (2 × 40 mL), saturated $NaHCO_3$ (40 mL), and brine (40 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford **20** (5.62 g, 77%) as a colorless oil after purification by flash column chromatography (cyclohexane/EtOAc, 90:10): R_f 0.72 (cyclohexane/EtOAc, 80:20); ^{1}H-NMR (DMSO-d_6) δ 7.72 (d, *J* 8.1 Hz, 2H), 7.58−7.38 (m, 12H), 3.93 (m, 2H), 3.76 (m, 1H), 2.40 (s, 3H), 1.62-1.53 (m, 2H), 1.41−1.28 (m, 2H), 0.96 (s, 9H), 0.93 (d, *J* 6.2 Hz, 3H); MS *m/e* (rel intens) 497 (M + H^+, 11), 297(20), 239(55), 199(100), 135(77), 73(29), 57(18); $[\alpha]_D = +7.2$ (*c* 1.2 EtOH). Anal. Calcd for $C_{28}H_{36}O_4SiS$: C, 67.70; H, 7.31. Found: C, 67.95; H, 7.45.

(*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]hept-1-yne (5). To a suspension of lithium acetylide−ethylenediamine complex (1.84 g, 20 mmol) in dry DMSO (30 mL) was slowly added a solution of **20** (4.72 g, 10 mmol) in dry DMSO (10 mL) at rt. Stirring was maintained at rt for 1 h, and then H_2O (150 mL) was cautiously added to the brownish reaction mixture. The aqueous layer was extracted with pentane (3 × 50 mL), and the pentane extracts were washed with brine (2 × 50 mL) and dried over Na_2SO_4. Filtration and concentration under vacuum yielded **5** (3.01 g, 86%) as a pale-yellow oil which was purified by filtration over a plug of silica gel: R_f 0.80 (cyclohexane/EtOAc, 98:2); ^{1}H-NMR (DMSO-d_6) δ 7.61 (d, *J* 7.0 Hz, 4H), 7.47−7.40 (m, 6H), 3.85 (m, 1H), 2.70 (t, *J* 2.4 Hz, 1H), 2.05 (td, *J* 6.6, 2.4 Hz, 2H), 1.57−1.39 (m, 4H), 1.00 (d, *J* 6.0 Hz, 3H), 0.99 (s, 9H); MS *m/e* (rel intens) 351 (M + H^+, 3), 321(4), 295(10), 240(7), 200(100), 138(56), 75(32); $[\alpha]_D = +13.1$ (*c* 1.1 EtOH). Anal. Calcd for $C_{23}H_{30}OSi$: C, 78.80; H, 8.63. Found: C, 78.94; H, 8.58.

(3*R*,11*R*)-3-Methoxydodec-6-yne-1,11-diol (21). To an ice-cooled solution of the alkyne **5** (2.13 g, 6.1 mmol) in anhydrous THF (20 mL) was added dropwise n-BuLi (1.5 M in hexane, 4.26 mL, 6.4 mmol), and the mixture was stirred for 1 h at rt. At 0 °C a solution of the iodide **4** (2.25 g, 6.3 mmol) in HMPT (10 mL) was slowly added, and the reaction mixture was stirred for 16 h at rt. This mixture was hydrolyzed with a 5% $KHSO_4$ solution (100 mL), and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (3 × 70 mL) and dried over Na_2SO_4. Filtration and concentration under vacuum yielded **3** (2.20 g, 71%) as a pale-yellow oil which was used as such in the next step.

To the crude **3** was added TBAF (1 M in THF, 20 mL, 20 mmol), and the mixture was stirred 16 h at rt. To this were successively added diethyl ether (150 mL) and brine (50 mL). The aqueous layer was extracted with diethyl ether (3 × 30 mL), and the ethereal extracts were washed with brine (3 × 30 mL) and were dried over Na_2SO_4. Filtration and concentration under vacuum yielded **5** (890 mg, 64%) after purification by flash column chromatography (CH_2Cl_2/MeOH, 95:5): R_f 0.2 (CH_2Cl_2/MeOH, 95:5); ^{1}H-NMR δ 3.83−3.69 (m, 3H), 3.53 (quint, *J* 5.9 Hz, 1H), 3.36 (s, 3H), 2.24−2.14 (m, 4H), 1.81−1.49 (m, 8H), 1.18 (d, *J* 5.9 Hz, 3H); MS *m/e* (rel intens) 229(M + H^+, 100), 197(20), 179(11), 161(12); HRMS *m/e* calcd for $C_{13}H_{24}O_3$: (M + H^+), 229.1804; found: (M + H^+), 229.1849; $[\alpha]_D = -9.0$ (*c* 1.1 $CHCl_3$).

(3*R*,11*R*)-1-[(Triphenylmethyl)oxy]-3-methoxydodec-6(*E*)-en-11-ol (23). To the alkyne **21** (380 mg, 1.65 mmol) was slowly added $LiAlH_4$ (0.5 M in diglyme, 13 mL, 6.5 mmol) at 0 °C. The mixture was refluxed 24 h. At rt the reaction was quenched with a piece of crushed ice, 1 N HCl (0.7 mL), and H_2O (0.7 mL). The aqueous phase was treated with 1 N HCl (pH 1) and was extracted with diethyl ether (3 × 10 mL). The organic phases were washed with brine (2 × 10 mL), and then dried over Na_2SO_4. The solvents were evaporated under high vacuum to afford **22** containing traces of diglyme.

Crude **22** was protected as for compound **17** to give **23** (449 mg, 60% over the two steps) after purification by flash column chromatography (cyclohexane/EtOAc/NEt_3, 70:30:0.5): R_f 0.71 (CH_2Cl_2/MeOH, 90:10); ^{1}H-NMR δ 7.43−7.20 (m, 15H), 5.39−5.36 (m, 2H), 3.76 (dd, *J* 5.9, 5.9 Hz, 1H), 3.35 (quint, *J* 5.9 Hz, 1H), 3.22 (s, 3H), 3.15 (m, 2H), 2.00−1.90 (m, 4H), 1.74 (m, 2H), 1.53 (m, 6H), 1.15 (d, *J* 5.9 Hz, 3H); MS *m/e* (rel intens) 495(M + Na^+, 3), 243(100); $[\alpha]_D = -6.0$ (*c* 0.8 $CHCl_3$)

(3*R*,11*R*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-3-methoxydodec-6(*E*)-en-1-ol (25). Compound **23** (396 mg, 0.84 mmol) was silylated as for **18** giving the fully protected triol **24**. This latter derivative was then treated with PPTS (64 mg, 0.24 mmol) in absolute EtOH (15 mL) as for compound **19** to give **25** as an oil (252 mg, 64%): R_f 0.10 (cyclohexane/EtOAc, 90:10); ^{1}H-NMR δ 7.64 (m, 4H), 7.42−7.32 (m, 6H), 5.36 (dd, *J* 15.7, 5.8 Hz, 1H), 5.29 (dd, *J* 15.7, 5.8 Hz, 1H), 3.82 (m, 1H), 3.80−3.70 (m, 2H), 3.39 (m, 1H), 3.33 (s, 3H), 2.46 (bs, 1H), 2.00−1.96 (m, 2H), 1.85−1.75 (m, 2H), 1.76−1.63 (m, 4H), 1.52−1.29 (m, 2H), 1.04 (d, *J* 5.7 Hz, 3H), 1.03 (s, 9H); MS *m/e* (rel intens) 469 (M + H^+, 3), 229(8), 197(40); $[\alpha]_D = +6.0$ (*c* 0.6 $CHCl_3$). Anal. Calcd for $C_{29}H_{44}O_3Si$: C, 74.31; H, 9.46. Found: C, 74.45; H, 9.63.

(3*S*,11*R*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-3-methoxydodec-6(*E*)-en-1-ol (25). This compound was obtained through the same sequence of reactions starting from the alkyne **5** and the iodide derivative (*R*)-**4**: R_f 0.10 (cyclohexane/EtOAc, 90:10); ^{1}H-NMR δ 7.65 (m, 4H), 7.40−7.25 (m, 6H), 5.30 (dd, *J* 15.7, 5.8 Hz, 2H), 3.87−3.65 (m, 3H), 3.36 (m, 1H), 3.33 (s, 3H), 2.00−1.80 (m, 4H), 1.78−1.13 (m, 8H), 1.04 (d, *J* 5.7 Hz, 3H), 1.03 (s, 9H); $[\alpha]_D = +29$ (*c* 1.0 $CHCl_3$). Anal. Calcd for $C_{29}H_{44}O_3Si$: C, 74.31; H, 9.46. Found: C, 74.60; H, 9.56.

(3*R*,11*R*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-3-methoxydodec-6(*E*)-en-1-al (2). To a solution of oxalyl chloride (35 μL, 0.41 mmol) in dry CH_2Cl_2 was added at −78 °C dry DMSO (0.58 μL, 0.8 mmol) dissolved in 2 mL of dry CH_2Cl_2. After being stirred at −78 °C for 30 min, a solution of the alcohol **25** (128 mg, 0.27 mmol) dry CH_2Cl_2 was added to the precedent mixture which was stirred for 30 min. At −78 °C triethylamine (1.14 mL, 8 mmol) was added to the reaction mixture which was allowed to reach rt. Water (15 mL) was added, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were successively washed with 1 N HCl (10 mL) and a saturated NH_4Cl aqueous solution (10 mL). The organic phase was dried over Na_2SO_4 and then concentrated under high vacuum to give the title compound **2** (125 mg, 98%) as an oil. This aldehyde was used without further purification. R_f 0.8 (cyclohexane/EtOAc, 80:20); ^{1}H-NMR δ 9.78 (t, *J* 2.0 Hz, 1H), 7.67−7.64 (m, 4H), 7.39−7.24 (m, 6H), 5.39−5.26 (m, 2H), 3.86−3.78 (m, 1H), 3.69 (m, 1H), 3.32 (s, 3H), 2.58 (ddd, *J* 15.7, 6.8, 2.6 Hz, 1H), 2.50 (ddd, *J* 15.7, 4.8, 1,8 Hz, 1H), 2.01 (q, *J* 6.5 Hz, 2H), 1.85 (q, *J* 6.6 Hz, 2H), 1.70−1.41 (m, 2H), 1.39−1.24 (m, 4H), 1.03 (d, *J* 5.9 Hz, 3H), 1.03 (s, 9H); MS *m/e* (rel intens) no molecular ion 465(1), 243(45), 239(18), 199(86), 197(42), 165(19), 135(100), 109(24), 91(36), 67(42).

(3*S*,11*R*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-3-methoxydodec-6(*E*)-en-1-al (2). ^{1}H-NMR δ 9.78 (t, *J* 2.2 Hz, 1H), 7.69−7.63 (m, 4H), 7.38−7.29 (m, 6H), 5.30 (m, 2H), 3.85−3.74 (m, 1H), 3.71−3.62 (m, 1H), 3.32 (s, 3H), 2.59 (ddd, *J* 16.2, 6.8, 2.5 Hz, 1H), 2.49 (ddd, *J* 16.2, 5.3, 2.0 Hz, 1H), 2.02 (m, 2H), 1.85 (m, 2H), 1.73−1.23 (m, 6H), 1.03 (d, *J* 5.9 Hz, 3H), 1.03 (s, 9H). Anal. Calcd for $C_{29}H_{42}O_3Si$: C, 74.63; H, 9.07. Found: C, 73.73; H, 9.12.

(5*RS*,7*R*,15*R*)-15-[(*tert*-Butyldiphenylsilyl)oxy]-5-hydroxy-7-methoxy-2-methylhexadeca-2(*E*),10(*E*)-dienoic Acid Ethyl Ester (28). To a stirred solution of **2** (100 mg, 0.2 mmol) in a mixture of dry dichloromethane/diethyl ether (2 mL, 90/10), cooled to −78 °C, was added the silyl ketene acetal **27**[20] (133 mg, 0.72 mmol) and then boron trifluoride etherate (63 mL, 0.4 mmol). Stirring was maintained over 36 h at rt, and then water (1 mL) was added at −78 °C followed by diethyl ether (5 mL) to the reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), and the

combined organic phases were dried over Na_2SO_4. After evaporation of the solvent under high vacuum, the crude product was purified by flash column chromatography (cyclohexane/EtOAc, 80:20) to give **28** as an inseparable mixture of diastereoisomers (24 mg, 20%): R_f 0.3 (cyclohexane/EtOAc, 80:20); ^{1}H-NMR δ 7.72−7.63 (m, 4H), 7.39−7.28 (m, 6H), 6.80 (tq, *J* 7.4, 1.3 Hz, 1H), 5.33 (m, 2H), 4.16 (q, *J* 7.0 Hz, 2H), 4.11−3.96 (m, 1H), 3.95−3.72 (m, 1H), 3.53−3.40 (m, 1H), 3.34 and 3.33 (2s, 3H), 2.33 (m, 2H), 1.83 (s, 3H), 2.00−1.20 (m, 12H), 1.22 (t, *J* 7.0 Hz, 3H), 1.02 (d, *J* 5.9 Hz, 3H), 1.02 (s, 9H); MS *m*/*e* (rel intens) 617(M + Na^+, 3), 595(M + H^+,4), 563(2), 537(2), 505(2), 339(6), 307(8), 289(6), 243(17), 239(18), 199(100), 197(45), 91(27), 67(37).

(7*R*,15*R*)-15-[(*tert*-Butyldiphenylsilyl)oxy]-7-methoxy-2-methylhexadeca-2(*E*),4(*E*),10(*E*)-trienoic Acid Ethyl Ester (30). The mixture of diastereoisomeric alcohols **28** and triethylamine (0.15 mL, 1 mmol) were dissolved in dry CH_2Cl_2 (1 mL). To this solution was added methanesulfonyl chloride (10 mL, 0.13 mmol) at −78 °C. The mixture was stirred at rt overnight and then diluted with CH_2Cl_2 (5 mL). The organic phase was successively washed with a 5% $KHSO_4$ aqueous solution (5 mL), a 5% $NaHCO_3$ aqueous solution (5 mL), and a saturated NH_4Cl aqueous solution (10 mL). The organic phase was dried over Na_2SO_4 and then concentrated under high vacuum. The resulting mesylate **29** was directly treated with DBU (19 mL, 0.15 mmol) in chloroform (2 mL) at rt over 24 h. The same workup as above yielded a mixture of (2*E*,4*E*) and (2*E*,4*Z*) expected esters after purification by flash column chromatography (cyclohexane/EtOAc, 95:5). The mixture of dienes was isomerized after being stirred with some freshly sublimed crystals of iodine in $CHCl_3$ for 6 h. Iodine was eliminated after washing the organic phase with a 10% $NaHSO_3$ aqueous solution. The organic phase was dried over Na_2SO_4 and then concentrated under high vacuum to give the protected dolatrienoic acid ethyl ester **30** (8 mg, 46%) as an oil: R_f 0.3 (cyclohexane/EtOAc, 95:5); ^{1}H-NMR δ 7.65 (m, 4H), 7.44−7.27 (m, 6H), 7.15 (d, *J* 10.8 Hz, 1H), 6.37 (dd, *J* 15.1, 10.8 Hz, 1H), 6.05 (td, *J* 15.1, 7.3 Hz, 1H), 5.33−5.25 (m, 2H), 4.18 (q, *J* 7.2 Hz, 2H), 3.82 (m , 1H), 3.33 (s, 3H), 3.23 (m, 1H), 2.37 (t, *J* 7.3 Hz, 2H), 2.03−1.97 (m, 2H), 1.92 (s, 3H), 1.89−1.85 (m, 2H), 1.48−1.24 (m, 11H), 1.03 (d, *J* 5.9 Hz, 3H), 1.03 (s, 9H); MS *m*/*e* (rel intens) 599(M + Na^+, 2), 577(M + H^+, 2), 575(3), 520(12), 519(28), 321(8), 239(21), 199(100); HRMS *m*/*e* calcd for $C_{36}H_{49}O_4Si$: (M-H^+), 575.3537; found: (M-H^+), 575.3625; calcd for $C_{36}H_{52}O_4Si$: (M-*t*Bu^+), 519.3061; found: (M-*t*Bu^+), 519.2996; HPLC (conditions B) t_R 2.3 min (30% B isocratic).

2-Hydroxy-2-methylbuten-3-oic Acid Phenylmethyl Ester (33). 2-Hydroxy-2-methylbuten-3-oic acid[22] (3.54 g, 30.5 mmol) was dissolved in dry DMF (120 mL). To this solution were added $NaHCO_3$ (5.12 g, 61 mmol) and then benzyl bromide (18.1 mL, 152.5 mmol) dissolved in dry DMF (120 mL). Stirring was continued overnight at rt then water (1 L) was added. The aqueous phase was extracted with ethyl acetate (3 × 200 mL). The combined organic phases were washed with brine (200 mL) and dried over Na_2SO_4. After evaporation of the solvents, the crude product was purified by flash column chromatography (cyclohexane/EtOAc, 90:10) to give the desired ester **33** (9.0 g, 53%) as an colorless oil: R_f 0.3 (cyclohexane/EtOAc, 90:10); ^{1}H-NMR δ 7.33 (m, 5H), 5.99 (dd, *J* 17.0, 10.5 Hz, 1H), 5.48 (dd, *J* 17.0, 1.0 Hz, 1H), 5.18 (s, 2H), 5.14 (dd, *J* 10.5, 1.0 Hz, 1H), 3.25 (bs, 1H), 1.48 (s, 3H); MS *m*/*e* (rel intens) 207(M + H^+, 32), 181(9), 91(100). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.75; H, 7.01.

[3-Methyl-3-[(phenylmethoxy)carbonyl]but-2(*E*)-enyl]-phosphonic Acid Dimethyl Ester (34). To a cooled (−78 °C) solution of alcohol **33** (760 mg, 3.6 mmol) in dry CH_2Cl_2 (25 mL) was added $SOCl_2$ (0.9 mL, 12.4 mmol) in dry CH_2Cl_2. Stirring was continued overnight at reflux. The reaction mixture was poured onto an ice-cooled 5% $NaHCO_3$ aqueous solution (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic phases were successively washed with a 5% $NaHCO_3$ solution (20 mL) and a saturated NH_4Cl solution (20 mL) then dried over Na_2SO_4. Evaporation of the solvent yielded 4-chloro-2-methyl-but-2(*E*)-enoic acid phenylmethyl ester (673 mg, 3 mmoL) after purification by flash column chromatography (cyclohexane/EtOAc, 90:10) as a yellow oil.

The preceding chloride compound was dissolved in trimethyl phosphite (15 mL), and the solution was heated at 120 °C for 3 h. The trimethyl phosphite was evaporated under high vacuum, and the residue was purified by flash column chromatography (cyclohexane/EtOAc, 50:50) to give the desired phosphonate **34** (885 mg, 82%): R_f 0.10 (cyclohexane/EtOAc, 50:50); ^{1}H-NMR δ 7.33−7.24 (m, 5H), 6.74 (tdq, *J* 8.2, 6.8, 1.5 Hz, 1H), 5.14 (s, 2H), 3.73 (d, *J* 11.0 Hz, 1H), 2.73 (ddd, *J* 23.4, 8.2, 0.8 Hz, 2H), 1.87 (dd, *J* 1.5, 0.8 Hz, 3H); ^{31}P-NMR δ 29.19; MS *m*/*e* (rel intens) 299(MH^+, 72), 209(2), 191(55), 109(5), 91(95). Anal. Calcd for $C_{14}H_{19}O_5P$: C, 56.38; H, 6.42. Found: C, 55.78; H, 6.61.

(7*S*,15*R*)-15-[(*tert*-Butyldiphenylsilyl)oxy]-7-methoxy-2-methylhexadeca-2(*E*),4(*E*),10(*E*)-trienoic Acid Phenylmethyl Ester (35). Sodium hydride (20.1 mg, 0.87 mmol) was suspended in dry THF (1.5 mL) and cooled in an ice-bath. To this suspension was added phosphonate **34** (260 mg, 0.87 mmol) dissolved in THF (1.5 mL), and the mixture was stirred for 2 h at 0 °C. This solution was added dropwise to a precooled (−30 °C) solution of the aldehyde **2** (140 mg, 0.3 mmol) in THF (2 mL), and the mixture was stirred for 1.5 h until the temperature reached −15 °C. Water (10 mL) was poured into the reaction mixture, and then the aqueous phase was extracted with diethyl ether (3 × 15 mL). After evaporation of the solvent, the crude product was purified by flash column chromatography (cyclohexane/EtOAc, 95:5). The resulting dienes were isomerized and worked-up as for compound **30** to give the protected dolatrienoic acid phenylmethyl ester **35** (133 mg, 70%) as an oil: R_f 0.7 (cyclohexane/EtOAc, 80:20); ^{1}H-NMR δ 7.65 (m, 4H), 7.39−7.30 (m, 6H), 7.18 (dd, *J* 11.2, 1.2 Hz, 1H), 6.38 (dd, *J* 15.0, 11.2 Hz, 1H), 6.07 (td, *J* 15.0, 7.2 Hz, 1H), 5.34−5.27 (m, 2H), 5.18 (s, 2H), 3.81 (m , 1H), 3.31 (s, 3H), 3.22 (m, 1H), 2.37 (t, *J* 6.4 Hz, 2H), 2.02−1.83 (m, 4H), 1.93 (d, *J* 1.2 Hz, 3H), 1.52−1.33 (m, 6H), 1.03 (d, *J* 5.9 Hz, 3H), 1.03 (s, 9H); MS *m*/*e* (rel intens) 661(M + Na^+, 2), 639(M + H^+, 2), 581(2), 505(11), 473(1), 423(3), 393(6), 307(5), 239(18), 199(100), 91(58); HRMS *m*/*e* calcd for $C_{41}H_{54}O_4Si$: (M + H^+), 639.3870; found: (M + H^+), 639.3917; HPLC (conditions B) t_R 2.2 min (30% B isocratic).

(7*R*,15*R*)-15-Hydroxy-7-methoxy-2-methylhexadeca-2(*E*),4(*E*),10(*E*)-trienoic Acid (1). To a solution of (7*R*,15*R*)-**30** (8 mg, 13.8 μmol) in hexane/acetonitrile (0.48 mL, 50:50), cooled to −60 °C, was added fluorhydric acid (0.35 mL of a 50% aqueous solution). Stirring was pursued over 2 days at 0 °C. Hexane (3 mL) was added, and the organic phase was washed successively with a saturated $KHCO_3$ solution (3 × 1 mL) and a saturated NH_4Cl solution until neutral. Drying over Na_2SO_4 and evaporative distillation of the solvents afforded the desired hydroxy ester which was directly saponified with a methanolic (1.3 mL) solution of KOH (0.82 mL of a 1 M aqueous solution) during 3 days at 0−10 °C. An ice-cooled 5% aqueous solution of $KHSO_4$ (2.2 mL) was added to the preceding mixture, and then methanol was evaporated under vacuum. The aqueous residue was extracted with EtOAc (3 × 3 mL), and the combined organic phases were washed with a saturated NH_4Cl solution (until pH 5) and dried over Na_2SO_4. Evaporation of the solvent led to the expected (7*R*,15*R*)-dolatrienoic acid (**1**) (1.4 mg, 33%) as a pale-yellow oil after chromatographic purification (hexane/EtOAc, 60/40): R_f 0.1 (cyclohexane/EtOAc, 60:40); ^{1}H-NMR δ 7.24 (d, *J* 11.2 Hz, 1H), 6.39 (dd, *J* 15.0, 11.2 Hz, 1H), 6.10 (dt, *J* 15.0, 7.2 Hz, 1H), 5.39 (m, 2H), 3.78 (m , 1H), 3.33 (s, 3H), 3.25 (quint, *J* 5.6 Hz, 1H), 2.39 (t, *J* 6.2 Hz, 2H), 2.05 (m, 4H), 1.92 (s, 3H), 1.65−1.31 (m, 6H), 1.16 (d, *J* 6.2 Hz, 3H); MS *m*/*e* (rel intens) 333(M + Na^+, 84%), 311(M + H^+, 30), 293(27), 262(30), 245(24), 135(84), 79(85); HRMS *m*/*e* calcd for $C_{18}H_{31}O_4$: (M + H^+), 311.2222; found: (M + H^+), 311.2198; HPLC (conditions A) t_R 7.2 min (20% to 100% B).

(7*S*,15*R*)-15-Hydroxy-7-methoxy-2-methylhexadeca-2(*E*),4(*E*),10(*E*)-trienoic Acid (1). By a similar procedure, (7*S*,15*R*)-**35** gave the desired (7*S*,15*R*)-**1** in a 37% overall yield: ^{1}H-NMR δ 7.25 (d, *J* 11.2 Hz, 1H), 6.39 (dd, *J* 14.7, 11.2 Hz, 1H), 6.10 (dt, *J* 14.7, 7.3 Hz, 1H), 5.38 (m, 2H), 3.76 (m ,

1H), 3.33 (s, 3H), 3.25 (quint, *J* 5.8 Hz, 1H), 2.38 (t, *J* 6.3 Hz, 2H), 2.02 (m, 4H), 1.91 (s, 3H), 1.54−1.38 (m, 6H), 1.16 (d, *J* 6.1 Hz, 3H); HRMS *m*/*e* calcd for $C_{18}H_{31}O_4$: $(M + H^+)$, 311.2222; found: $(M + H^+)$, 311.2141; HPLC (conditions A) t_R 7.2 min (20% to 100% B).

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Supporting Information Available: ^1H, $^1H-^1H$ COSY-DQF, HMQC, HMQC-TOCSY, and NOESY spectra for (7*S*,-15*R*)-**1** (8 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.

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