

STUDIES TOWARD AN ASYMMETRIC SYNTHESIS OF CP-263,114 AND CP-225,917

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday in recognition of his outstanding contributions to the area of organic stereochemistry.

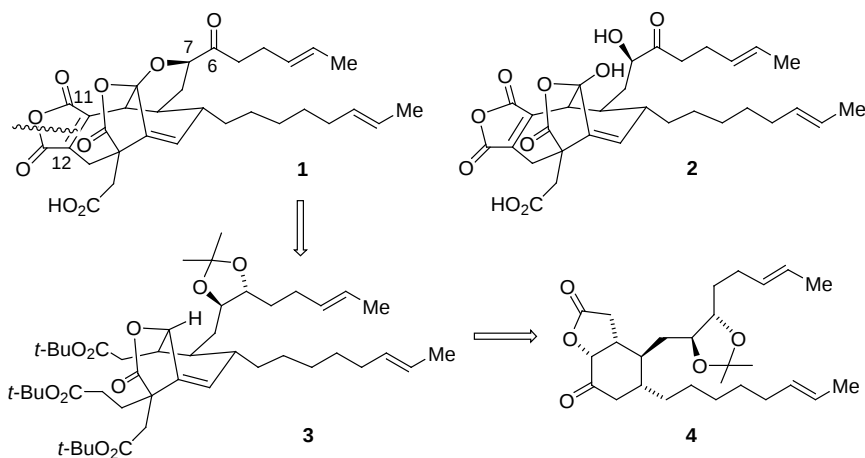
An enantioselective approach to construction of the complex framework of the CP compounds is presented. The synthesis relies on initial elaboration of the two sidechains. The "upper" appendage was asymmetrically dihydroxylated with both AD-mix reagents in order to lend flexibility to the scheme and provide the necessary handle for evolving the additional stereogenic centers. These fragments were linked to benzoic acid *via* Birch reduction-alkylation and subsequent cuprate addition. A series of functionalization reactions including dissolving metal reduction, Claisen rearrangement, iodolactonization, regioselective epoxide cleavage-oxidation, and intramolecular Wadsworth-Emmons cyclization took advantage of highly efficient stereocontrol. However, this flexibility was thwarted when deprotonation of a penultimate intermediate failed to be regioselective in the proper direction.

Key words: Dihydroxylation; Birch reduction; Allylic oxidation; Iodolactonization; Claisen rearrangement; CP compounds; Total synthesis.

Two fungal metabolites, known by the unglamorous names CP-263,114 (**1**) and CP-225,917 (**2**), have captured the attention of the synthetic organic community as a result of their impressive biological properties and unprecedented structural features¹. These complex nonadrides have been identified as inhibitors of Ras farnesyltransferase² and squalene synthase³, whose biological effects are of considerable current interest. While a number of strategies have recently been reported for accessing the central framework of **1** and **2** (ref.⁴), only in mid-1999 has one group succeeded in accomplishing a racemic total synthesis⁵. While the relative configuration of C7 was not established at the time of original disclosure⁶, its relative configura-

tion is now recognized to be as shown. The absolute stereochemistry of **1** and **2** remains elusive, although their chemical interconversion has been realized.

The synthetic plan for elaborating the nine-membered ring and pendant side chains of the title compounds was envisioned to be possible by oxidative coupling⁷ of ester enolate anions positioned at C11 and C12. Further disconnection of **3** led us back to the keto lactone **4** where the four contiguous stereogenic centers about the cyclohexanone ring were expected to be set in an absolute sense by reference back to the configuration of C6 and C7 within the dioxolane substructure (Scheme 1). The workability of the numerous bond connections demanded by this blueprint are detailed herein.



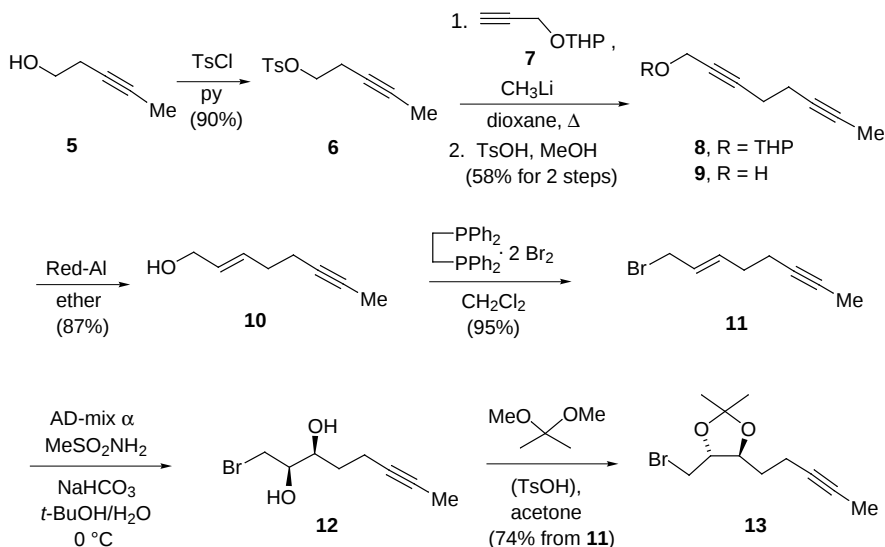
SCHEME 1

RESULTS AND DISCUSSION

Synthesis of the C1–C7 Lateral Chain

The synthesis of octa-2,6-diyne-1-ol (**9**) has previously been reported⁸. In line with the earlier observations, pent-3-yn-1-ol (**5**) underwent smooth tosylation and subsequent displacement with the lithium acetylide **7** in refluxing dioxane (Scheme 2). The success of this step appears to be linked to the use of ethereal methyllithium with evaporation of low-boiling solvent prior to the high temperature reaction. Subsequent removal of the THP group proceeded to deliver **9** in 58% overall yield.

Regiocontrolled reduction of one of the triple bonds in **9**, accomplished with Red-Al (ref.⁹), afforded **10** and set the stage for high-efficiency conversion to bromide **11** in the presence of DIPHOS dibromide¹⁰. The introduc-

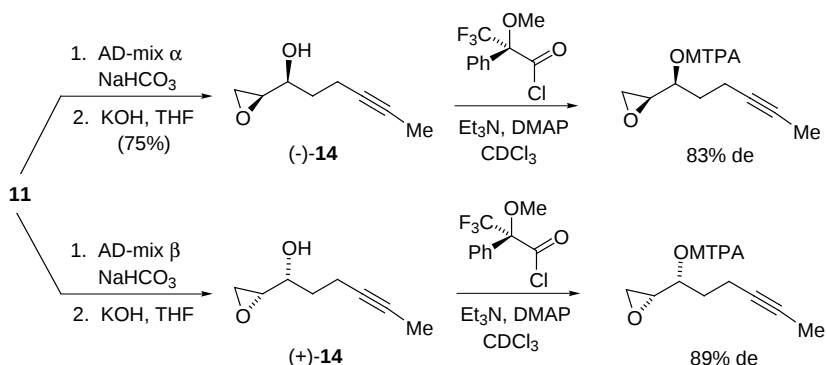


SCHEME 2

tion of chirality was realized by Sharpless asymmetric dihydroxylation following the classical procedure¹¹, but with proper attention to the sensitivity of product bromo diol to base. The acquisition of acetal **13** finalized the synthesis of this building block¹².

The enantiomeric excess resident in **13** was determined by the Mosher ester method¹³. Treatment of the unpurified AD-mix α reaction mixture with KOH afforded levorotatory **14**, $[\alpha]_{\text{D}}^{20} -6.0$ (c 1.91, CHCl_3). The de of its (*R*)-MTPA ester was found to be 83%. The absolute configurations were assigned in accordance with established face selection criteria and proved by comparison of the ^1H NMR chemical shifts of the (*S*)-MTPA and (*R*)-MTPA esters of (*-*)-**14** (Scheme 3).

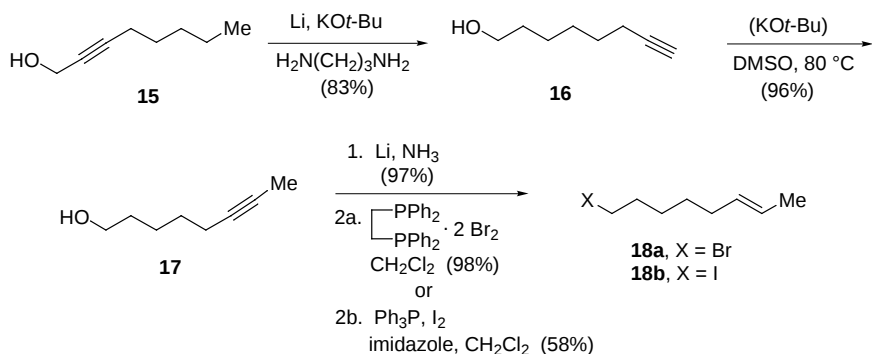
Our initial efforts in this area were completed prior to the time when the relative configuration at C7 was recognized. The arbitrary choice was made by us to pursue the use of AD-mix α . Although this choice turned out to be incorrect, the route was too advanced to make a late-stage adjustment when the findings in ref.¹ became known to us^{6b}.



SCHEME 3

Elaboration of the Second Lateral Chain

The triple bond in commercially available oct-2-yn-1-ol (**15**) was isomerized to the free terminus of the chain with potassium hydride in 1,3-diaminopropane¹⁴, and the resulting carbinol **16** was “mono-unzipped” by exposure to a catalytic quantity of potassium *tert*-butoxide in DMSO (Scheme 4). The further conversion of alkynol **17** to bromide **18a** and iodide **18b** followed precedent¹⁵.

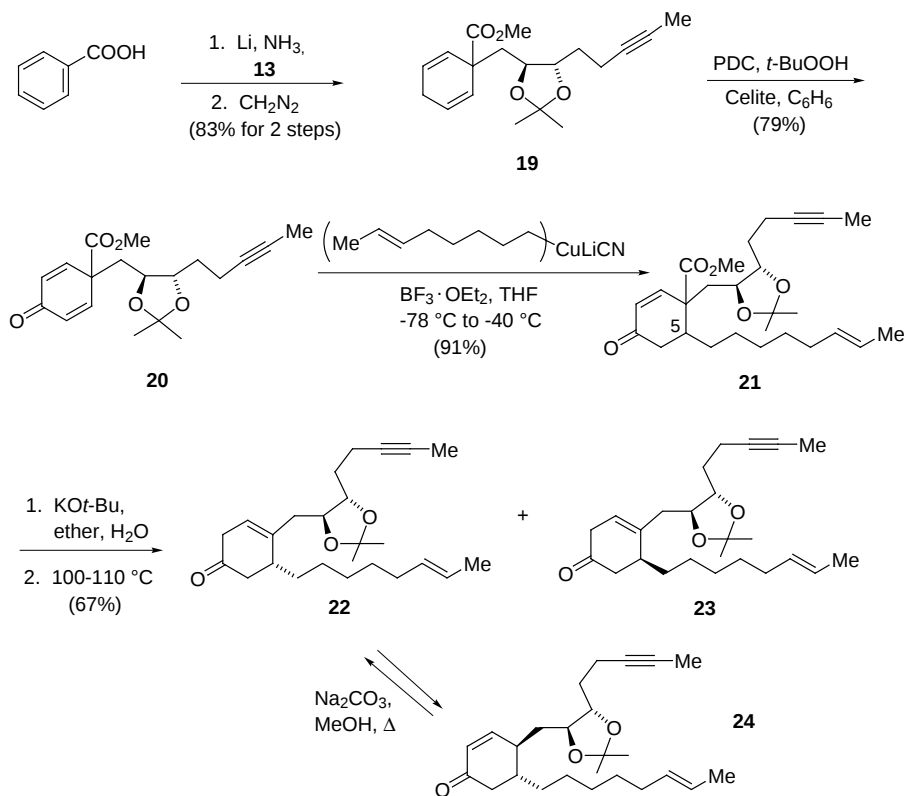


SCHEME 4

Assembly of the 4,5-Disubstituted Cyclohex-2-en-1-one

As foreshadowed by our retrosynthetic strategy, proper attachment of **13** and **18** to a functionalized six-membered ring had now to be addressed. To this end, benzoic acid was subjected to Birch reduction and the resulting

dianion¹⁶ was alkylated with bromide **13** (Scheme 5). Esterification of the resulting carboxylic acid with diazomethane furnished **19** in 83% overall yield. The bis-allylic position could then be oxidized¹⁷, thereby leading to the crystalline cyclohexadienone **20**. Conjugate addition of various cuprates derived from **18a** to **20** initially proved to be problematical. However, the discovery was ultimately made that the desired conversion to **21** could be effected with the cyano cuprate in the presence of boron trifluoride-



SCHEME 5

ide etherate. The use of ether as the reaction medium for conversion of iodide **18b** into the organolithium reagent is particularly critical¹⁸. ¹H NMR analysis indicated that **21** consisted of a mixture of four isomers in the ratio 60 : 12 : 16 : 12. Recourse to medium pressure liquid chromatography on silica gel resulted in the separation of **21a** and **21b** from the other pair

(**21c/21d**). Although the absolute configuration at C5 in these molecules was not established, it was subsequently made clear that **21a** and **21d** share the identical stereochemistry at that position.

A study of the saponification-decarboxylation of **21** was next undertaken. Whereas exposure to KOH or LiOH induced gradual decomposition and the conditions developed by Krapcho¹⁹ (NaCl, DMSO) and by Liotta²⁰ (PhSeH, NaH, HMPA) led to intractable tars, hydrolysis could be realized with potassium *tert*-butoxide in moist THF (ref.²¹). Decarboxylation occurred simultaneously, although heating of the neat product at 100 °C for several minutes was usually carried out to complete the process.

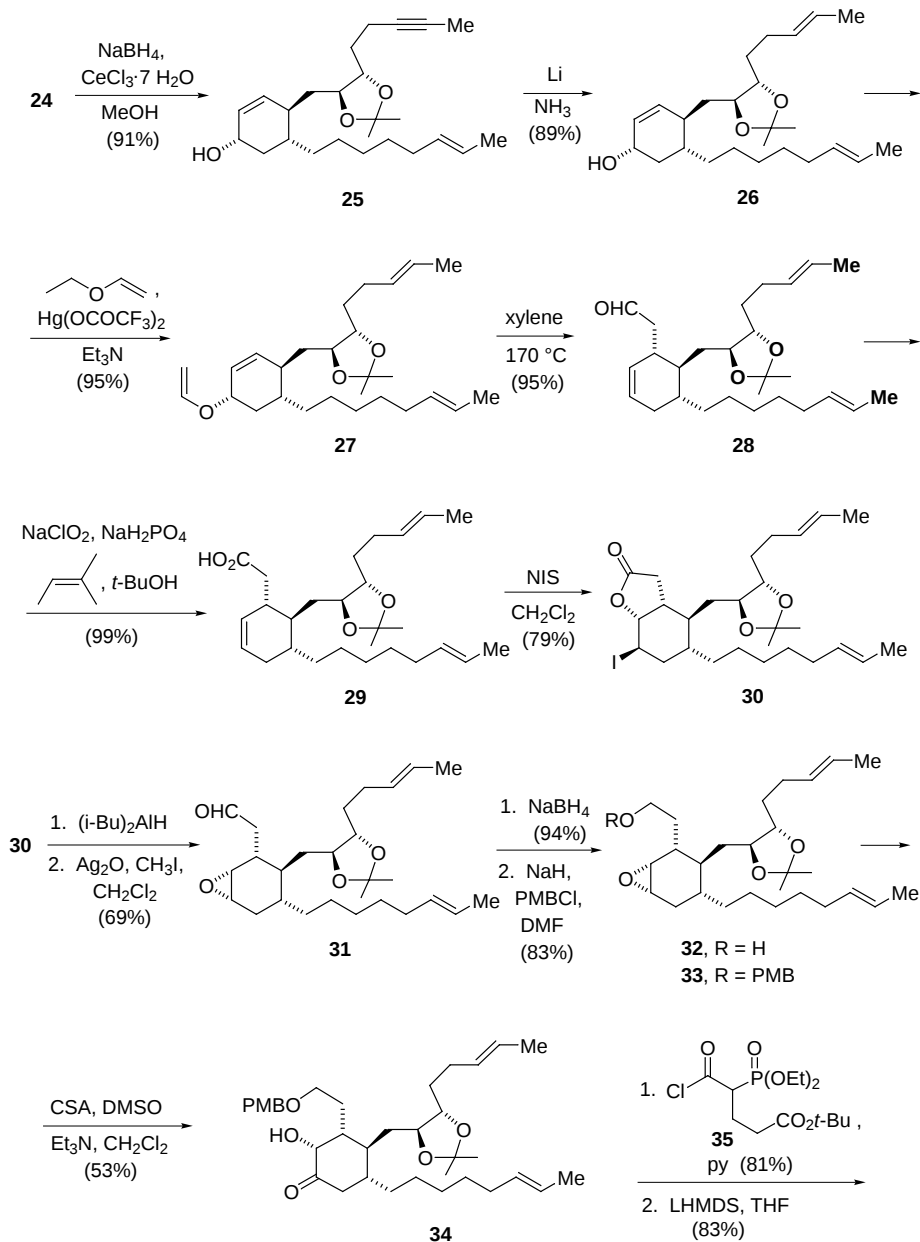
The discovery that β,γ -unsaturated ketones **22** and **23** (formed in a ratio of 3.2 : 1) could be conveniently separated by medium pressure liquid chromatographic methods precluded the need to effect the partial separation of esters **21**, although these experiments were performed to validate configurational interrelationships. An unqualified distinction between **22** and **23** was not uncovered, and the major constituent **22** was therefore utilized in the studies defined below. As a consequence, the absolute stereochemistry about the cyclohexane ring is not known with certainty and has been arbitrarily assigned.

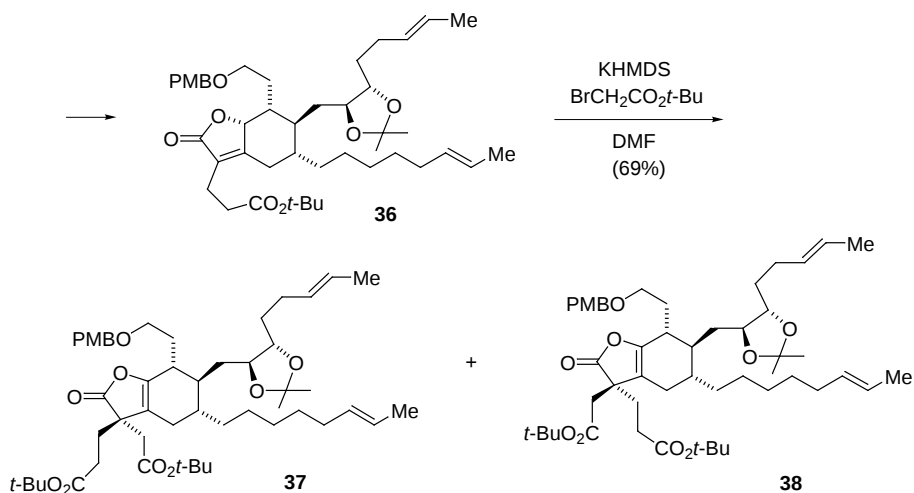
Isomerization of **22** to its α,β -unsaturated isomer **24** was accomplished with catalytic quantities of sodium carbonate in refluxing degassed methanol for several hours²². As a result of competing degradation, considerable effort was expended in the optimization of this process. The most favorable conditions involved arresting the heating process at the point where it was possible to isolate 46% of **24** alongside 22% of recovered **22**.

Incorporation of all the Carbon Centers

Reduction of **24** under Luche conditions²³ gave alcohol **25** with a selectivity in excess of 95% (Scheme 6). At this point, advantage was taken of the limited level of functionalization to reduce the alkyne linkage under dissolving metal conditions. The resulting alcohol **26** was subsequently transformed into vinyl ether **27** (ref.²⁴) in advance of Claisen rearrangement to provide aldehyde **28**. Following oxidation to carboxylic acid **29**, iodolactonization made possible the stereoselective introduction of two additional stereogenic centers around the cyclohexane ring periphery.

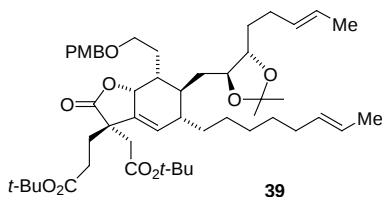
To advance lactone **30**, it was necessary to effect its reduction to the lactol stage in advance of conversion to epoxy aldehyde **31** by addition of silver(I) oxide. Hydride reduction and *p*-methoxybenzyl protection of the acetaldehyde side chain set the stage for regiocontrolled oxidative cleavage





SCHEME 6

of the oxirane ring²⁵. Esterification of **34** with the acid chloride **35** (ref.²⁶) in tandem with subsequent intramolecular Wadsworth–Emmons cyclization provided lactone **36** in excellent yield. This advanced intermediate was deprotonated with lithium hexamethyldisilazide (and other bases) in the expectation that enolization would take place distal from the oxygen center because of the usual inductive contributions²⁷. Despite numerous attempts to override highly regioselective deprotonation from within the butenolide ring, no evidence was found for the generation of the targeted product **39**. Examples of such kinetic control are known but few in number^{28–32}. Since the ring system apparently plays an important role in this outcome, we were clearly at an impasse. It is important to recognize that enolization of **36** toward the oxygen center destroys a key stereogenic center that causes **37** and **38** to be formed in near equal amounts (ratio 2 : 1). This complication would not arise when progressing to **39** where electrophilic capture from the less sterically congested enolate π -surface is anticipated. Based on these experiments, alternative methods for properly setting the projected bridgehead double bond have been explored and will be described elsewhere.



EXPERIMENTAL

Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230–400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high-field ^1H NMR. IR spectra (wavenumbers in cm^{-1}) were recorded on a Perkin–Elmer Model 1320 spectrometer. ^1H , ^{13}C and ^{19}F NMR spectra were taken on a Bruker AC 300 instrument. Chemical shifts are given in ppm (δ scale), coupling constants (J) in Hz. The high-resolution and fast atom-bombardment spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA, U.S.A. Specific rotations are given in $\text{deg cm}^3 \text{g}^{-1} \text{dm}^{-1}$.

Pent-3-yn-1-yl Tosylate (**6**)

A solution of pent-3-yn-1-ol (39.00 g, 0.46 mol) in anhydrous pyridine (310 ml) was treated at 5 °C during 30 min with TsCl (101.65 g, 1.22 equivalents – previously dissolved in ether and washed with 10% NaOH solution until the organic phase was colorless, dried, and recrystallized at –40 °C). The reaction mixture was stirred at 20 °C for 3 h, poured into water, and extracted with ether (3×200 ml). The combined organic phases were washed with 6 M HCl (4×100 ml), water, saturated NaHCO_3 solution (15 ml), and brine (50 ml). The acidic aqueous layers were reextracted with ether and these extracts were processed in the predescribed manner prior to being combined. The ethereal solutions were dried and concentrated to leave a dark brown solid. Trituration of this material with petroleum ether–ether (4 : 1) furnished 99.10 g (90%) of **6** as a tan solid, which was used without further purification. ^1H NMR (200 MHz, CDCl_3): 7.74 (dt, $J = 8.6, 1.8, 2$ H); 7.30 (d, $J = 8.6, 2$ H); 4.00 ($J_{\text{AB}} = 7.2, 2$ H); 2.42 (m, 2 H); 2.40 (s, 3 H); 1.65 (t, $J = 2.5, 3$ H). ^{13}C NMR (50 MHz, CDCl_3): 144.8, 132.8, 129.8 (2 C); 127.8 (2 C); 78.1, 73.0, 68.2, 21.5, 19.5, 3.3.

Octa-2,6-diyn-1-ol⁸ (**9**)

A solution of freshly distilled **7** (16.82 g, 1.30 equivalents) in dioxane (200 ml, distilled from sodium benzophenone ketyl) was treated at 0 °C under N_2 with 1.4 M methyllithium in ether (84.2 ml, 1.18 mol) during 30 min. The ether was removed at 20 °C and 70 Torr. At 0 °C, 23.83 g (0.12 mol) of **6** dissolved in dioxane (100 ml) was introduced over 5 min, and the reaction mixture was refluxed while mechanically stirred for 15 h, poured into ice water (200 ml) and ether (300 ml), and extracted with ether (3×100 ml). The combined organic phases were washed with brine, dried, and concentrated to leave **8** as a dark brown oil.

The unpurified **8** was taken up in methanol (300 ml), treated with 1.14 g (6 mole %) of TsOH , refluxed for 12 h, cooled, admixed with 1 g of NaHCO_3 , and freed of methanol under reduced pressure. Water (100 ml) was added and the product was extracted into ether (4×110 ml). The combined organic layers were washed with brine, dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 30% ether in petroleum ether) afforded 8.44 g (58%) of **9** as a light tan solid. ^1H NMR (200 MHz, CDCl_3): 4.12 (m, 2 H); 3.25 (br s, 1 H); 2.35–2.20 (m, 4 H); 1.60 (t, $J = 2.4, 3$ H). ^{13}C NMR (50 MHz, CDCl_3): 83.8, 78.9, 76.1, 76.0, 50.2, 18.7, 18.3, 2.8.

(E)-Oct-2-en-6-yn-1-ol⁸ (**10**)

A 3.3 M solution of Red-Al in toluene (49.6 ml, 2.5 equivalents) was diluted with anhydrous ether (65 ml) and treated dropwise with a solution of **9** (8.00 g, 65.6 mmol) in dry ether (60 ml) such that the temperature was maintained at 0–5 °C. The reaction mixture was stirred at 20 °C for 2 h, returned to 0 °C, carefully quenched with 3.6 M sulfuric acid (350 ml). The combined organic phases were washed with water (100 ml) and brine (60 ml), dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 30% ether in petroleum ether) gave 7.09 g (87%) of **10** as a colorless oil. ¹H NMR (200 MHz, CDCl₃): 5.65–5.59 (m, 2 H); 4.00 (d, *J* = 4.4, 2 H); 2.14–2.10 (m, 4 H); 1.68 (t, *J* = 2.5, 3 H). ¹³C NMR (50 MHz, CDCl₃): 130.8, 130.1, 78.4, 75.9, 63.2, 31.7, 18.7, 3.3.

(E)-1-Bromooct-2-en-6-yne (**11**)

A magnetically stirred solution of 1,2-bis(diphenylphosphino)ethane (13.01 g, 0.6 equivalents) in CH₂Cl₂ (340 ml) was treated dropwise at 0–5 °C with a solution of bromine (10.44 g, 1.2 equivalents) in CH₂Cl₂ (50 ml). A solution of **10** (6.76 g, 54.4 mmol) in CH₂Cl₂ (68 ml) was next introduced at the same temperature. The reaction mixture was stirred at 20 °C for 3 h, diluted with ether (200 ml) and pentane (1 l), and filtered through a short pad of silica gel. After the solids had been rinsed with 2 : 1 pentane–ether, the combined filtrates were evaporated and the residue was purified by flash chromatography on silica gel (elution with 1.5% ether in petroleum ether) to provide 9.68 g (95%) of **11** as a colorless oil. IR (CHCl₃): 1 662, 1 436. ¹H NMR (300 MHz, CDCl₃): 5.83–5.69 (m, 2 H); 3.95 (d, *J* = 6.7, 2 H); 2.24–2.19 (m, 4 H); 1.77 (t, *J* = 2.4, 3 H). ¹³C NMR (75 MHz, CDCl₃): 134.4, 127.3, 77.9, 76.2, 32.9, 31.5, 18.4, 3.3. HR MS (EI), *m/z*: (*M*⁺) calculated: 186.0044; found: 186.0042. For C₈H₁₁Br (187.1) calculated: 51.36% C, 5.93% H; found: 51.12% C, 5.84% H.

(4*R*,5*S*)-4-(Bromomethyl)-2,2-dimethyl-5-(pent-3-ynyl)-1,3-dioxolane (**13**)

A solution of AD-mix α (35.0 g), sodium bicarbonate (6.30 g, 3 equivalents), and methanesulfonamide (2.38 g, 1 equivalents) in water (125 ml) and *tert*-butyl alcohol (125 ml) was cooled to 0 °C, treated with **11** (4.68 g, 25.0 mmol), and vigorously stirred at 0 °C for 26 h. Sodium metabisulfite (25 g) was next cautiously introduced during 20 min. After an additional 40 min of stirring, ethyl acetate (100 ml) and water (70 ml) were added, and the separated organic layer was washed with water (80 ml) and brine (80 ml). The aqueous phase was extracted with ethyl acetate (5 × 100 ml), and the combined organic extracts were washed with water and brine prior to drying and solvent removal. Flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) furnished 5.14 g of a mixture of **12** and (–)-**14** as a crystalline solid.

The above material was directly dissolved in acetone (70 ml) containing 2,2-dimethoxypropane (6.1 ml, >2 equivalents) and pyridinium tosylate (380 mg, >6 mole %), stirred at 20 °C for 35 h, and evaporated. Flash chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether) afforded 4.83 g (74%) of **13** in addition to 0.60 g (17%) of (–)-**14**.

Compound 13. IR (CHCl₃): 1 483, 1 382, 1 379, 1 236. ¹H NMR (300 MHz, CDCl₃): 3.96 (m, 1 H); 3.93 (m, 1 H); 3.46 (d, *J* = 5.2, 2 H); 2.33–2.24 (m, 2 H); 1.85–1.75 (m, 2 H); 1.77 (t, *J* = 2.4, 3 H); 1.41 (s, 3 H); 1.40 (s, 3 H). ¹³C NMR (75 MHz, CDCl₃): 109.4, 79.7, 78.0,

77.9, 76.3, 33.1, 32.3, 27.4, 27.2, 15.4, 3.4. HR MS (EI), m/z : (M^+) calculated: 261.0490; found: 261.0499. $[\alpha]_D^{20}$ -19.7 (c 1.54, CHCl_3).

Compound (-)-14. IR (CHCl_3): 3 599, 1 436, 1 385, 1 232. ^1H NMR (200 MHz, CDCl_3): 3.53 (br q, $J \approx 6$, 1 H); 2.95 (ddd, $J = 5.2$, 4.1, 2.8, 1 H); 2.77 (dd, $J = 4.9$, 4.2, 1 H); 2.70 (br s, 1 H); 2.69 (dd, $J = 4.9$, 2.8, 1 H); 2.30–2.20 (m, 2 H); 1.75–1.65 (m, 5 H). ^{13}C NMR (50 MHz, CDCl_3): 78.0, 76.1, 70.5, 55.1, 44.8, 33.1, 14.8, 3.2. HR MS (EI), m/z : (M^+) calculated: 140.0837; found: 140.0844. $[\alpha]_D^{20}$ -6.0 (c 1.91, CHCl_3).

(2S,3S)-1,2-Epoxyoct-6-yn-3-ol (-)-(**14**), (2R,3R)-1,2-Epoxyoct-6-yn-3-ol (+)-(**14**), and Mosher Ester Analysis

Alcohol (-)-(**14**), likewise directly obtained from the crude product of dihydroxylation of **11** (187 mg, 1.0 mmol) with AD-mix α , was treated with 200 mg of KOH in THF (5 ml) at 25 °C for 1 h. Water was added, the product was extracted into ether, and the combined organic layers were washed with saturated NaCl solution, concentrated and chromatographed (elution with 50% ethyl acetate in petroleum ether). There were isolated 105 mg of (-)-**14**.

A parallel dihydroxylation was conducted on **11** (187 mg, 1.0 mmol) with 1.4 g of AD-mix β , 252 mg of solid NaHCO_3 , 95 mg of methanesulfonamide in water (5 ml) and *tert*-butyl alcohol (5 ml) at 0 °C for 24 h. The resulting product was treated directly with 200 mg of KOH in THF (5 ml) at 0–25 °C for 1 h. Water was added, the product was extracted into ether, and the combined organic layers were washed with saturated NH_4Cl solution, dried, concentrated, and chromatographed in the predescribed manner. There were isolated 105 mg (75%) of (+)-**14**, $[\alpha]_D^{20}$ +6.2 (c 0.83, CHCl_3), spectroscopically identical to the (-)-isomer.

Preparation of the respective Mosher esters according to standard protocol afforded products which were directly analyzed³³ by ^1H and ^{19}F NMR (Table I).

TABLE I
 ^1H and ^{19}F NMR data – diastereomeric purity of MTPA esters of alcohols **14**

Parameter	(R)-MTPA ester of (-)- 14	(R)-MTPA ester of (+)- 14
-CHOH	5.10 (dt, $J = 7.8$, 6.2 Hz)	5.04 (dt, $J = 5.0$, 3.9 Hz)
-OCH ₃	5.57 (d, $J = 1.1$ Hz)	5.60 (d, $J = 1.1$ Hz)
$\text{H}_2\text{C} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{O}$	2.80 (t, $J = 4.4$ Hz)	2.88 (t, $J = 4.4$ Hz)
	2.64 (dd, $J = 4.9$, 2.6 Hz)	2.75 (dd, $J = 4.8$, 2.5 Hz)
^{19}F	-72.77	-72.70
via ^1H NMR	10.8 : 1 (83% de)	
via ^{19}F NMR	11 : 1 (83% de)	16.9 : 1 (89% de)

Methyl 1-[[[(4S,5S)-2,2-Dimethyl-5-(pent-3-ynyl)-1,3-dioxolan-4-yl]methyl]-cyclohexa-2,5-diene-1-carboxylate (**19**)

To a stirred solution of benzoic acid (2.70 g, 22.1 mmol) in liquid NH_3 (150 ml, distilled from sodium) cooled to -49°C under N_2 was added lithium metal (0.43 g, 3.4 equivalents) until a blue color persisted. After 10 min, a solution of **13** (4.80 g, 18.4 mmol) in anhydrous ether (15 ml) was slowly introduced, and stirring was maintained for 45 min. After the addition of solid NH_4Cl (2.9 g) and evaporation of the NH_3 , the residue was taken up in water (60 ml) and ether (150 ml), and the separated aqueous phase was neutralized with 2 M HCl prior to ether extraction (5×60 ml). The combined organic phases were washed with brine (50 ml) and concentrated *in vacuo* to give 6.18 g of crude acid, which was dissolved in ether (50 ml) at 0°C and treated with diazomethane. After solvent evaporation, the residue was subjected to flash chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to provide 4.90 g (83%) of **19** as a colorless oil. IR (neat): 1 717, 1 434, 1 378, 1 279. ^1H NMR (200 MHz, CDCl_3): 5.81 (m, 4 H); 3.61 (s, 3 H); 3.60 (m, 2 H); 2.60 (m, 2 H); 2.22–2.15 (m, 2 H); 2.15–2.00 (m, 1 H); 1.79 (d, $J = 14.2$, 1 H); 1.72 (t, $J = 2.4$, 3 H); 1.65–1.50 (m, 2 H); 1.27 (s, 3 H); 1.24 (s, 3 H). ^{13}C NMR (50 MHz, CDCl_3): 174.5, 127.5, 126.7, 125.5, 125.2, 108.3, 79.8, 78.1, 76.9, 75.7, 52.0, 46.5, 43.2, 31.8, 27.1 (2 C); 25.8, 15.4, 3.3. FAB MS, m/z : (M^+) calculated: 319.19; found: 319.19. $[\alpha]_{\text{D}}^{20} -3.9$ (c 0.81, CHCl_3).

Methyl 1-[[[(4S,5S)-2,2-Dimethyl-5-(pent-3-ynyl)-1,3-dioxolan-4-yl]methyl]-4-oxo-cyclohexa-2,5-diene-1-carboxylate (**20**)

To a stirred solution of **19** (4.34 g, 13.6 mmol) in benzene (160 ml) were added successively at 5°C 16.4 g of Celite, 20.51 g (4 equivalents) of pyridinium dichromate, and 7.47 ml of *tert*-butylhydroperoxide (70% in water, 4 equivalents). The mixture was stirred for 8.5 h, diluted with water (350 ml), and filtered through a pad of silica gel. The solids were rinsed with ether (5×100 ml) and the filtrates were concentrated to leave a residue, purification of which by flash chromatography (elution with 30% ethyl acetate in petroleum ether) afforded 3.59 g (79%) of **20** as a colorless solid, m.p. $90.5\text{--}91^\circ\text{C}$ (from petroleum ether). IR (CHCl_3): 1 736, 1 668, 1 629, 1 220, 1 211. ^1H NMR (300 MHz, CDCl_3): 7.15–7.05 (m, 2 H); 6.33 (m, 2 H); 3.73 (s, 3 H); 3.71 (ddd, $J = 11.8$, 8.0, 6.0, 1 H); 3.59 (ddd, $J = 9.3$, 8.0, 2.2, 1 H); 2.29–2.19 (m, 2 H); 2.19 (dd, $J = 14.0$, 9.3, 1 H); 2.09 (dd, $J = 14.0$, 2.2, 1 H); 1.75 (t, $J = 2.5$, 3 H); 1.68–1.62 (m, 2 H); 1.33 (s, 3 H); 1.30 (s, 3 H). ^{13}C NMR (75 MHz, CDCl_3): 184.9, 170.3, 147.7, 147.6, 129.7, 129.6, 109.0, 79.6, 77.8, 76.8, 76.2, 53.6, 51.0, 41.8, 31.7, 27.1, 27.0, 15.3, 3.4. HR MS (EI), m/z : (M^+) calculated: 332.1624; found: 332.1624. $[\alpha]_{\text{D}}^{20} -39.4$ (c 0.78, CHCl_3). For $\text{C}_{19}\text{H}_{24}\text{O}_5$ (332.4) calculated: 68.66% C, 7.28% H; found: 68.36% C, 7.35% H.

Methyl (6S)-1-[[[(4S,5S)-2,2-Dimethyl-5-(pent-3-yn-1-yl)-1,3-dioxolan-4-yl]methyl]-6-[(*E*)-oct-6-en-1-yl]-4-oxocyclohex-2-ene-1-carboxylate (**21**)

A solution of **18b** (ref.¹⁵) (2.22 g, 9.32 mmol) in dry ether (20 ml) was blanketed with argon, cooled to -78°C , and treated with 1.7 M *tert*-butyllithium in pentane (11.3 ml). The white suspension was stirred for 1 h at -78°C and for 1 h at -10°C . A second three-necked flask was charged with copper(I) cyanide (774 mg, 8.64 mmol, previously dried for 2 days at $55\text{--}60^\circ\text{C}$ under high vacuum) and blanketed with argon. Dry THF (20 ml) was introduced and the suspension was cooled to -78°C prior to the addition of the organolithium solution *via* cannula. After 1 h each at -78 and -50°C , the reaction mixture was treated with boron

trifluoride etherate (1.63 ml, 12.9 mmol) followed by **20** (1.23 g, 3.70 mmol) dissolved in THF (20 ml). The latter addition was performed very slowly (45 min) in order to maintain a temperature at -78°C , then allowed to warm to -40°C during 2 h, at which point it was recooled to -78°C before being quenched with a 4 : 1 mixture of saturated NH_4Cl solution and aqueous ammonia (25 ml). The products were extracted into ether (4×25 ml) and the combined organic phases were washed with brine, dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 15% ethyl acetate in petroleum ether) furnished 1.49 g (91%) of **21** as a mixture of four isomers in a ratio of 60 : 12 : 16 : 12 (^1H NMR analysis). An aliquot fraction of these isomers (675 mg) was partially separated under medium-pressure conditions to yield 382 mg of **21a** and **21b**, alongside 120 mg of **21c** and **21d**, and 173 mg of a mixed fraction.

The major isomer of the **21a/21b** colorless oil mixture. ^1H NMR (300 MHz, CDCl_3): 7.14 (dd, $J = 10.4, 1.1, 1$ H); 5.97 (d, $J = 10.4, 1$ H); 5.32 (m, 2 H); 3.65 (s, 3 H); 3.62 (m, 2 H); 2.60 (dd, $J = 17.4, 4.8, 1$ H); 2.41 (dd, $J = 17.4, 5.0, 1$ H); 2.20 (m, 4 H); 2.04 (dd, $J = 14.4, 2.0, 1$ H); 1.85 (br s, 2 H); 1.68 (t, $J = 2.5, 3$ H); 1.66–1.55 (m, 5 H); 1.27 (s, 3 H); 1.26 (s, 3 H); 2.25–1.10 (series of m, 8 H). ^{13}C NMR (75 MHz, CDCl_3): 197.8, 173.2, 149.7, 131.1, 128.8, 124.6, 108.7, 80.0, 77.8, 76.7, 76.0, 51.9, 50.4, 41.3, 40.9, 37.8, 32.3, 31.8, 29.6, 29.2, 28.7, 27.0, 26.9, 26.8, 17.8, 15.2, 3.3. HR MS (EI), m/z : (M^+) calculated: 444.2876; found: 444.2878.

(5*R*)-4-[(4*S*,5*S*)-2,2-Dimethyl-5-(3-pentynyl)-1,3-dioxolan-4-yl]methyl]-5-[(*E*)-oct-6-en-1-yl]cyclohex-3-en-1-one (**22**)

Potassium *tert*-butoxide (19.26 g, 12 equivalents) was dissolved in anhydrous THF (200 ml), cooled to 0°C under argon, treated with water (0.50 ml, 2 equivalents), and stirred for 10 min. The **21** isomer mixture (6.36 g, 14.3 mmol) dissolved in dry THF (170 ml) was introduced over 15 min, followed by 20 min of stirring at 0°C and 4.5 h at room temperature. After being recooled to 0°C , the reaction mixture was quenched with ice, neutralized with 10% HCl, and extracted with ether (5×90 ml). The combined organic layers were washed with brine (80 ml), dried, and concentrated. The residue was heated at 105°C for 5–10 min and subjected to flash chromatography on silica gel. Elution with 15% ethyl acetate in petroleum ether led to the isolation of 2.82 g (51%) of **22** and 0.92 g (16%) of **23**.

Colorless oil **22**. IR (CHCl_3): 1 711, 1 380, 1 237. ^1H NMR (300 MHz, CDCl_3): 5.56 (dd, $J = 3.6, 3.6, 1$ H); 5.39 (m, 2 H); 3.85–3.70 (m, 2 H); 2.91 (br dd, $J = 12.8, 3.9, 1$ H); 2.80 (br d, $J = 12.8, 1$ H); 2.60 (dd, $J = 13.5, 5.6, 1$ H); 2.55 (m, 1 H); 2.47 (dd, $J = 13.5, 1.9, 1$ H); 2.40–2.25 (m, 4 H); 1.95 (m, 2 H); 1.76 (t, $J = 2.5, 3$ H); 1.75–1.70 (m, 2 H); 1.65 (m, 3 H); 1.39 (s, 3 H); 1.37 (s, 3 H); 1.35–1.20 (m, 8 H). ^{13}C NMR (75 MHz, CDCl_3): 210.8, 139.3, 131.4, 124.8, 120.4, 108.4, 79.0, 78.9, 78.3, 76.0, 43.6, 39.7, 39.6, 38.0, 33.4, 32.5, 32.4, 29.4, 29.1, 27.4, 27.2, 26.8, 17.9, 15.6, 3.5. HR MS (EI), m/z : (M^+) calculated: 386.2821; found: 386.2815. $[\alpha]_{\text{D}}^{20} +48.1$ (c 1.10, CHCl_3). For $\text{C}_{25}\text{H}_{39}\text{O}_3$ (387.6) calculated: 77.47% C, 10.14% H; found: 77.42% C, 9.97% H.

(4*S*,5*R*)-4-[(4*S*,5*S*)-2,2-Dimethyl-5-(pent-3-yn-1-yl)-1,3-dioxolan-4-yl]methyl]-5-[(*E*)-oct-6-en-1-yl]cyclohex-2-en-1-one (**24**)

A solution of **22** (3.27 g, 8.46 mmol) was diluted under argon with 300 ml of methanol freshly distilled from magnesium methanolate. Sodium carbonate (30.5 mg, 3.4% equivalents) was introduced and the mixture was heated at 75°C for 13.5 h, cooled, and treated

with cold ethanolic NH_4Cl solution. After evaporation of the methanol, the residue was purified by flash chromatography (elution with 15% ethyl acetate in petroleum ether) and subsequent MPLC to give 1.51 g (46%) of **24** and 0.73 g (22%) of unreacted **22**.

Colorless oil **24**. IR (CHCl_3): 1 673, 1 227. ^1H NMR (300 MHz, CDCl_3): 6.93 (dd, $J = 10.2$, 3.5, 1 H); 5.97 (dd, $J = 10.2$, 1.9, 1 H); 5.39 (m, 2 H); 3.82–3.68 (m, 2 H); 2.58 (dd, $J = 16.4$, 4.3, 1 H); 2.48 (m, 1 H); 2.37–2.20 (m, 3 H); 2.20 (dd, $J = 16.4$, 9.9, 1 H); 1.94 (m, 3 H); 1.76 (t, $J = 2.5$, 3 H); 1.87–1.65 (m, 3 H); 1.62 (m, 3 H); 1.39 (s, 3 H); 1.32 (s, 3 H); 1.35–1.17 (m, 8 H). ^{13}C NMR (75 MHz, CDCl_3): 199.4, 152.5, 131.2, 128.4, 124.6, 108.4, 79.8, 78.0, 77.7, 75.9, 41.2, 39.1, 37.7, 35.5, 32.8, 32.3, 32.0, 29.3, 29.0, 27.2, 27.1, 26.1, 17.7, 15.3, 3.3. HR MS (EI), m/z : (M^+) calculated: 386.2821; found: 386.2806. $[\alpha]_{\text{D}}^{20}$ –1.6 (c 0.26, CHCl_3).

(1*S*,4*S*,5*R*)-4-[[[(4*S*,5*S*)-2,2-Dimethyl-5-(pent-3-yn-1-yl)-1,3-dioxolan-4-yl]methyl]-5-[(*E*)-oct-6-en-1-yl]cyclohex-2-en-1-ol (**25**)

A mixture of **24** (550 mg, 1.42 mmol) and cerium trichloride heptahydrate (583 mg, 1.1 equivalents) in methanol (8 ml) was cooled to 0 °C, treated with sodium borohydride (70 mg, 1.3 equivalents), stirred for 10 min, diluted with water (1 ml), and freed of methanol. Further dilution with water (12 ml) was followed by ether extraction (4 × 15 ml). The combined organic phases were washed with brine, dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 25% ethyl acetate in petroleum ether) gave 503 mg (91%) of colorless oil **25**. IR (CHCl_3): 3 364, 1 440, 1 378, 1 241. ^1H NMR (300 MHz, CDCl_3): 5.75 (ddd $J = 10.2$, 1.9, 1.9, 1 H); 5.67 (br d, $J = 10.2$, 1 H); 5.39 (m, 2 H); 4.20 (m, 1 H); 3.80 (ddd, $J = 9.9$, 8.0, 2.3, 1 H); 3.67 (dt, $J = 8.0$, 6.0, 1 H); 2.35–2.17 (m, 2 H); 2.16–2.00 (m, 2 H); 2.00–1.96 (m, 2 H); 1.76 (t, $J = 2.4$, 3 H); 1.78–1.50 (m, 8 H); 1.37 (s, 3 H); 1.36 (s, 3 H); 1.35–1.15 (m, 9 H) (OH not observed). ^{13}C NMR (75 MHz, CDCl_3): 131.7, 131.5, 130.9, 124.6, 108.3, 80.0, 78.3, 77.9, 75.9, 67.6, 38.4, 37.9, 37.3, 36.9, 33.0, 32.5, 32.2, 29.5, 29.4, 27.4, 27.3, 26.5, 17.9, 15.5, 3.5. HR MS (EI), m/z : (M^+) calculated: 388.2978; found: 388.2979. $[\alpha]_{\text{D}}^{20}$ –1.4 (c 0.29, CHCl_3).

(1*S*,4*S*,5*R*)-4-[[[(4*S*,5*S*)-2,2-Dimethyl-5-[(*E*)-pent-3-en-1-yl]-1,3-dioxolan-4-yl]methyl]-5-[(*E*)-oct-6-en-1-yl]cyclohex-2-en-1-ol (**26**)

To a solution of lithium (180 mg, 5 equivalents) in liquid ammonia (125 ml) was added a solution of **25** (1.98 g, 5.15 mmol) in THF (30 ml) *via* cannula during 15 min. After 30 min of stirring, the ammonia was evaporated in a flow of N_2 . The residue was taken up in ether (80 ml), and water (40 ml) was added slowly. The organic phase was washed with saturated NH_4Cl solution and brine, the aqueous phases were back-extracted with ether (5 × 40 ml), and the combined organic solutions were dried and concentrated. The residue was purified by flash chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to afford **26** (1.80 g, 89%) as a colorless oil. IR (CHCl_3): 3 600, 1 379, 1 371, 1 239. ^1H NMR (300 MHz, CDCl_3): 5.76 (dt, $J = 10.2$, 1.9, 1 H); 5.69 (br d, $J = 10.2$, 1 H); 5.44–5.38 (m, 4 H); 4.21 (m, 1 H); 3.74 (ddd, $J = 9.7$, 8.1, 2.1, 1 H); 3.57 (dt, $J = 7.5$, 4.9, 1 H); 2.20–2.00 (m, 4 H); 2.00–1.95 (br s, 2 H); 1.75 (ddd, $J = 13.8$, 9.9, 3.0, 1 H); 1.64 (m, 6 H); 1.62–1.50 (m, 5 H); 1.38 (s, 6 H); 1.38–1.20 (m, 8 H) (OH not observed). ^{13}C NMR (75 MHz, CDCl_3): 131.8, 131.5, 130.9, 130.4, 125.4, 124.6, 108.1, 80.7, 78.1, 67.6, 38.4, 37.9, 37.4, 36.9, 33.0, 32.6, 32.5, 29.5, 29.4, 29.0, 27.3 (2 C); 26.5, 17.9. HR MS (EI), m/z : (M^+) calculated: 390.3134; found: 390.3139. $[\alpha]_{\text{D}}^{20}$ –102.7 (c 1.405, CHCl_3). For $\text{C}_{25}\text{H}_{42}\text{O}_3$ (390.6) calculated: 76.87% C, 10.84% H; found: 77.00% C, 10.91% H.

(4S,5S)-2,2-Dimethyl-4-[[[(1S,4S,6R)-6-[(E)-oct-6-en-1-yl]-4-(vinylloxy)cyclohex-2-en-1-yl]-methyl]-5-[(E)-pent-3-en-1-yl]-1,3-dioxolane (**27**)

To a solution of **26** (1.80 g, 4.61 mmol) in ethyl vinyl ether (100 ml freshly distilled from sodium) cooled to 0 °C under argon was added triethylamine (0.71 ml, 1.1 equivalents) and mercuric trifluoroacetate (0.59 g, 0.3 equivalents). After one day of stirring at room temperature, additional $\text{Hg}(\text{OCOCF}_3)_2$ (0.59 g) was introduced, and this process was repeated a third time. The solvent was evaporated under reduced pressure, and the residue was taken up in 1 : 4 ether–petroleum ether (80 ml) and washed with 10% NaOH solution (40 ml) and brine (30 ml). The aqueous phases were extracted twice with the mixed solvent system, and the combined organic solutions were dried, concentrated, and purified by flash chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether). There were isolated 1.82 g (95%) of colorless oil **27**. IR (neat): 1 633, 1 609, 1 453, 1 369. ^1H NMR (300 MHz, CDCl_3): 6.37 (dd, $J = 14.2, 6.6$, 1 H); 5.83 (ddd, $J = 10.3, 2.1, 2.0$, 1 H); 5.73 (br d, $J = 10.3$, 1 H); 5.47–5.39 (m, 5 H); 4.38 (m, 1 H); 4.29 (dd, $J = 14.2, 1.6$, 1 H); 4.02 (dd, $J = 6.6, 1.6$, 1 H); 3.74 (m, 1 H); 3.57 (m, 1 H); 2.18–1.97 (m, 5 H); 1.80–1.20 (m, 14 H); 1.63 (br s, 6 H); 1.37 (s, 6 H). ^{13}C NMR (75 MHz, CDCl_3): 150.2, 144.1, 131.5, 130.4, 127.0, 125.4, 124.6, 108.1, 88.4, 80.7, 78.1, 74.4, 38.1, 37.5, 37.0, 33.7, 33.0, 32.6, 32.5, 29.5, 29.4, 29.0, 27.3 (2 C); 26.5, 17.9 (2 C). HR MS (EI), m/z : (M^+) calculated: 416.3290; found: 416.3294. $[\alpha]_{\text{D}}^{20} -91$ (c 0.025, CHCl_3). For $\text{C}_{27}\text{H}_{44}\text{O}_3$ (416.6) calculated: 77.84% C, 10.64% H; found: 77.98% C, 10.68% H.

(1S,5R,6S)-6-[[[(4S,5S)-2,2-Dimethyl-5-[(E)-pent-3-en-1-yl]-1,3-dioxolan-4-yl]methyl]-5-[(E)-oct-6-en-1-yl]cyclohex-2-en-1-acetaldehyde (**28**)

A sample of vinyl ether **27** (1.66 g, 4.00 mmol) was dissolved in freshly distilled xylenes, blanketed with argon, and heated for 5 h at 170 °C in a sealed glass vessel. The xylenes were evaporated under high vacuum and the residue was chromatographed on silica gel (elution with 5% ethyl acetate in petroleum ether) to afford 1.58 g (95%) of **28** as a colorless oil. IR (CHCl_3): 1 720, 1 380, 1 240. ^1H NMR (300 MHz, CDCl_3): 9.75 (m, 1 H); 5.67 (br d, $J = 9.8$, 1 H); 5.50 (br d, $J = 9.9$, 1 H); 5.45–5.37 (m, 4 H); 3.69 (dt, $J = 8.3, 2.8$, 1 H); 3.54 (dt, $J = 8.1, 5.0$, 1 H); 2.75 (m, 1 H); 2.66 (ddd, $J = 16.2, 4.9, 1.3$, 1 H); 2.38 (ddd, $J = 16.2, 7.8, 3.0$, 1 H); 2.22–2.01 (m, 3 H); 1.95 (m, 2 H); 1.72 (m, 1 H); 1.64 (m, 6 H); 1.60–1.40 (m, 6 H); 1.34 (s, 6 H); 1.35–1.20 (m, 8 H). ^{13}C NMR (75 MHz, CDCl_3): 203.2, 134.5, 130.5, 129.1, 126.3, 125.4, 124.7, 108.1, 80.8, 77.9, 48.7, 40.0, 36.1, 34.2, 33.8, 33.7, 32.6, 32.4, 29.6, 29.5, 29.1, 28.9, 27.3 (2 C); 26.7, 17.9 (2 C). HR MS (EI), m/z : (M^+) calculated: 416.3291; found: 416.3285. $[\alpha]_{\text{D}}^{24} -30.0$ (c 1.03, CHCl_3). For $\text{C}_{27}\text{H}_{44}\text{O}_3$ (416.6) calculated: 77.84% C, 10.64% H; found: 77.95% C, 10.57% H.

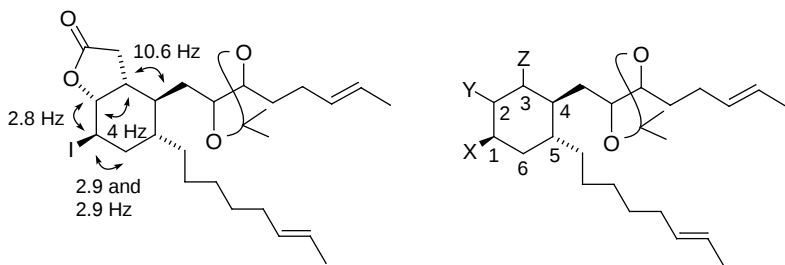
(1S,5R,6S)-6-[[[(4S,5S)-2,2-Dimethyl-5-[(E)-pent-3-en-1-yl]-1,3-dioxolan-4-yl]methyl]-5-[(E)-oct-6-en-1-yl]cyclohex-2-ene-1-acetic acid (**29**)

To a well stirred mixture of **28** (1.02 g, 2.45 mmol) in *tert*-butyl alcohol (24 ml) and 2-methyl-2-butene (8 ml) was added dropwise a solution of sodium chlorite (0.83 g, 3 equivalents) and sodium dihydrogen phosphate (0.90 g) in distilled water (10 ml). After 5 h at room temperature, brine (15 ml) was introduced, the solution was acidified with 1 M HCl (10 ml) prior to ether extraction (5 × 25 ml), and the combined organic phases were washed with brine (15 ml), dried, and concentrated. Purification of the residue by flash chromatog-

raphy on silica gel (elution with 15% ethyl acetate in petroleum ether) furnished 1.06 g (99%) of **29** as a colorless oil. IR (CHCl₃): 3 600–2 500, 1 707, 1 380. ¹H NMR (300 MHz, CDCl₃): 5.66 (br ddt, *J* = 10.2, 3.7, 2.0, 1 H); 5.56 (br d, *J* = 10.2, 1 H); 5.47–5.37 (m, 4 H); 3.72 (dt, *J* = 7.8, 4.7, 1 H); 3.54 (dt, *J* = 8.2, 5.4, 1 H); 2.66 (dd, *J* = 14.8, 5.4, 1 H); 2.56 (m, 1 H); 2.31 (dd, *J* = 14.8, 8.1, 1 H); 2.22–2.01 (m, 3 H); 1.95 (m, 2 H); 1.74 (br d, *J* = 18, 1 H); 1.64 (m, 6 H); 1.63–1.47 (m, 6 H); 1.36 (2 s, 6 H); 1.40–1.11 (m, 8 H). ¹³C NMR (75 MHz, CDCl₃): 178.4, 131.5, 130.5, 128.6, 126.0, 125.4, 124.7, 108.1, 80.8, 78.2, 39.4, 39.2, 36.4, 36.1, 35.0, 33.9, 32.6, 32.4, 29.6, 29.5, 29.0, 28.2, 27.3, 27.2, 27.1, 17.9 (2 C). HR MS (EI), *m/z*: (*M*⁺) calculated: 432.3240; found: 432.3251. [α]_D²⁵ –16.1 (c 1.45, CHCl₃).

(3*aR*,4*S*,5*R*,7*R*,6*aR*)-4-[[[(4*S*,5*S*)-2,2-Dimethyl-5-[(*E*)-pent-3-en-1-yl]-1,3-dioxolan-4-yl)methyl]-7-iodo-5-[(*E*)-oct-6-en-1-yl]-3*a*,4,5,6,7*a*-hexahydro-1-benzofuran-2(3*H*)-one (**30**)

A cold (–70 °C), magnetically stirred solution of **29** (42 mg, 0.10 mmol) in CH₂Cl₂ (0.5 ml) was added to *N*-iodosuccinimide (32 mg, 1.5 equivalents) dissolved in CH₂Cl₂ (1 ml). After 1 h at –70 °C and 2 h at room temperature, the solvent was evaporated and the residue was purified chromatographically on silica gel (elution with 10% ethyl acetate in petroleum ether). There were isolated 45 mg (79%) of **30** as a colorless oil. ¹H NMR (300 MHz, CDCl₃): 5.47–5.39 (m, 4 H); 4.79 (m, 1 H); 4.71 (m, 1 H); 3.67 (dt, *J* = 8.2, 3.3, 1 H); 3.54 (dt, *J* = 8.2, 6.0, 1 H); 3.00 (m, 1 H); 2.68 (dd, *J* = 17.1, 6.5, 1 H); 2.56 (d, *J* = 17.1, 1 H); 2.25–2.01 (m, 3 H); 1.97 (m, 2 H); 1.85 (m, 1 H); 1.64 (m, 6 H); 1.64–1.46 (m, 7 H); 1.38 (s, 3 H); 1.36 (s, 3 H); 1.40–1.15 (m, 8 H); for characteristic *J* values see Fig. 1. ¹³C NMR (75 MHz, CDCl₃): 176.5, 131.3, 130.3, 125.5, 124.8, 108.2, 83.1, 80.9, 77.1, 39.0, 37.8, 36.7, 34.2, 33.4, 32.5, 32.4, 32.0, 29.4, 29.2, 29.0, 27.3, 27.2, 27.1, 25.7, 17.9 (2 C). HR MS (EI), *m/z*: (*M*⁺) calculated: 558.2284; found: 558.2305. [α]_D²⁰ –0.84 (c 0.275, CHCl₃).



*J*_{H1-H2} = 2.9 Hz (confirmed by irradiation of H3)
*J*_{H2-H3} = 4.0 Hz (confirmed by irradiation of H1)
*J*_{H3-H4} = 10.6 Hz (confirmed by irradiation of H2)
*J*_{H1-H6a} = 2.9 Hz (confirmed by irradiation of H3)
*J*_{H1-H6b} = 2.9 Hz (confirmed by irradiation of H3)
*J*_{H1-H3} ~ 1 Hz

FIG. 1
 Characteristic interaction constants (*J*) in ¹H NMR spectrum of lactone **30**

(1R,2S,3R,5S,6R)-2-[[[(4S,5S)-2,2-Dimethyl-5-[(E)-pent-3-en-1-yl]-1,3-dioxolan-4-yl]-methyl]-5,6-epoxy-3-[(E)-oct-6-en-1-yl]cyclohexane-1-acetaldehyde (**31**)

A solution of **30** (50 mg, 0.09 mmol) in CH_2Cl_2 (5 ml) was cooled to -78°C , treated with 1.0 M DIBAL-H (135 μl , 0.135 mmol), stirred for 90 min, and quenched with 3 : 1 water-acetic acid (1 ml). After 30 min of vigorous stirring, the reaction mixture was diluted with ether, washed with saturated NaHCO_3 solution and brine, dried, and evaporated. Flash chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) gave 45 mg (89%) of pure lactol as a clear oil. IR (neat): 3 415, 1 729, 1 453, 1 371. ^1H NMR (300 MHz, CDCl_3): 5.60 (m, 1 H); 5.48–5.39 (m, 4 H); 4.56 (m, 1 H); 4.50 (dd, $J = 4.5, 4.5$, 1 H); 3.68 (m, 1 H); 3.55 (m, 1 H); 2.85 (d, $J = 3.7$, 1 H); 2.60 (m, 1 H); 2.25–1.1 5 (series of m, 22 H); 1.65 (br s, 6 H); 1.37 (s, 6 H). ^{13}C NMR (75 MHz, CDCl_3): 131.4, 130.4, 125.5, 124.7, 108.1, 98.4, 81.7, 81.1, 77.9, 40.5, 40.3, 39.1, 36.4, 35.0, 34.5, 32.6, 32.5 (2 C); 29.9, 29.3, 29.1, 27.3, 27.2, 26.1, 17.9 (2 C). HR MS (EI), m/z : (M^+) calculated: 560.2363; found: 560.2332.

A solution of the above lactol (9.0 mg, 0.016 mmol) in CH_2Cl_2 (1 ml) was treated with methyl iodide (100 μl , 1.6 mmol) and silver(I) oxide (18.5 mg, 0.080 mmol), stirred for 2 h, filtered through a cotton plug, and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, elution with 10% ethyl acetate in hexanes) gave 5.4 mg (78%) of **31** as a colorless oil. IR (neat): 1 724, 1 453, 1 378, 1 238. ^1H NMR (300 MHz, CDCl_3): 9.88 (s, 1 H); 5.47–5.38 (m, 4 H); 3.59–3.52 (m, 2 H); 3.24 (dd, $J = 4.8, 4.3$, 1 H); 3.20 (dd, $J = 4.3, 1.5$, 1 H); 2.82 (dd, $J = 13.5, 1.3$, 1 H); 2.72 (dd, 8.4, 2.3, 1 H); 2.64 (m, 1 H); 2.17–2.06 (m, 3 H); 1.95 (m, 2 H); 1.64 (br s, 6 H); 1.60–1.05 (series of m, 15 H); 1.34 (s, 3 H); 1.32 (s, 3 H). ^{13}C NMR (75 MHz, CDCl_3): 202.5, 131.3, 130.3, 125.5, 124.8, 108.2, 80.8, 77.3, 56.0, 53.3, 46.0, 35.8, 34.6, 34.0, 32.5, 32.3, 30.5, 29.5, 29.4, 29.0, 28.7, 27.3, 27.2, 25.7, 17.9 (2 C). HR MS (EI), m/z : (M^+) calculated: 432.3240; found: 432.3218.

(1R,2S,3R,5S,6R)-2-[[[(4S,5S)-2,2-Dimethyl-5-[(E)-pent-3-en-1-yl]-1,3-dioxolan-4-yl]-methyl]-5,6-epoxy-3-[(E)-oct-6-en-1-yl]cyclohexane-1-ethanol (**32**)

Excess sodium borohydride was added to a solution of **31** (300 mg, 0.69 mmol) in methanol (10 ml) at 0°C . The reaction mixture was stirred for 10 min in the cold, diluted with ether, and washed with water. The resulting aqueous phase was extracted twice with ether, and the combined organic layers were washed with brine, dried, and concentrated. Flash chromatography of the residue (silica gel, elution with 20% ethyl acetate in hexanes) gave 282 mg (94%) of pure **32** as a clear oil. IR (neat): 3 452, 1 540, 1 378, 1 240. ^1H NMR (300 MHz, CDCl_3): 5.47–5.38 (m, 4 H); 3.79 (m, 2 H); 3.62–3.54 (m, 2 H); 3.27 (dd, $J = 4.9, 4.3$, 1 H); 3.21 (m, 1 H); 2.48 (m, 1 H); 2.19–1.83 (m, 9 H); 1.64 (br s, 6 H); 1.68–1.05 (series of m, 14 H); 1.37 (s, 3 H); 1.36 (s, 3 H). ^{13}C NMR (75 MHz, CDCl_3): 131.3, 130.3, 125.5, 124.7, 108.3, 80.8, 77.4, 60.3, 55.7, 53.7, 35.7, 34.8, 34.5, 33.4, 33.0, 32.5, 32.0, 30.0, 29.5, 29.4, 28.9, 28.8, 27.3, 27.1, 25.6, 17.9 (2 C). HR MS (EI), m/z : (M^+) calculated: 434.3396; found: 434.3401. $[\alpha]_{\text{D}}^{20} +23.9$ (c 1.8, CHCl_3). For $\text{C}_{27}\text{H}_{46}\text{O}_4$ (434.7) calculated: 74.61% C, 10.67% H; found: 74.48% C, 10.59% H.

(4S,5S)-4-[[[(1S,2R,3R,4S,6R)-3,4-Epoxy-2-{2-[(4-methoxybenzyl)oxy]ethyl}-6-[(E)-oct-6-en-1-yl]cyclohexyl)methyl]-2,2-dimethyl-5-[(E)-pent-3-en-1-yl]-1,3-dioxolane (**33**)

To a solution of **32** (125 mg, 0.288 mmol) in DMF (1 ml) was added 80% sodium hydride in oil (14 mg, 0.43 mmol) and 4-methoxybenzyl chloride (0.058 ml, 0.43 mmol). The reaction mixture was stirred for 36 h, diluted with ether, washed with water and brine, dried, and evaporated. Purification of the residue by flash chromatography on silica gel (elution with 4% ethyl acetate in CH₂Cl₂) provided 132 mg (83%) of **33** as a clear oil. IR (neat): 1 613, 1 513, 1 454, 1 368, 1 248. ¹H NMR (300 MHz, CDCl₃): 7.27 (d, *J* = 8.7, 2 H); 6.87 (d, *J* = 8.7, 2 H); 5.52–5.36 (m, 4 H); 4.49 (d, *J* = 11.5, 1 H); 4.43 (d, *J* = 11.5, 1 H); 3.80 (s, 3 H); 3.71–3.50 (m, 4 H); 3.19 (dd, *J* = 4.4, 4.4, 1 H); 3.14 (m, 1 H); 2.24–1.77 (series of m, 8 H); 1.64 (br s, 6 H); 1.69–1.10 (series of m, 15 H); 1.33 (s, 3 H); 1.32 (s, 3 H). ¹³C NMR (75 MHz, CDCl₃): 159.1, 131.4, 130.8, 130.4, 129.1 (2 C); 125.4, 124.7, 113.7 (2 C); 107.9, 80.9, 78.1, 72.4, 68.1, 55.4, 55.2, 52.9, 36.2, 35.9, 35.3, 33.4, 32.6, 32.5, 32.4, 31.2, 29.5, 29.4, 29.1, 28.5, 27.3, 27.2, 26.2, 17.0 (2 C). HR MS (EI), *m/z*: (*M*⁺) calculated: 554.3971; found: 554.3976. [α]_D²⁰ –12.0 (c 3.0, CHCl₃). For C₃₅H₅₄O₅ (554.8) calculated: 75.77% C, 9.81% H; found: 75.77% C, 9.86% H.

(2R,3R,4S,5R)-4-[[[(4S,5S)-2,2-Dimethyl-5-[(E)-pent-3-en-1-yl]-1,3-dioxolan-4-yl)methyl]-2-hydroxy-3-{2-[(4-methoxybenzyl)oxy]ethyl}-5-[(E)-oct-6-en-1-yl]cyclohexan-1-one (**34**)

Camphorsulfonic acid (51 mg, 0.22 mmol) was added to a solution of **33** (120 mg, 0.22 mmol) in 5 ml of 4 : 1 CH₂Cl₂–DMSO. The solution was stirred for 1.5 h, treated with triethylamine (0.5 ml), and 10 min later diluted with ether. The organic phase was washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (elution with 10% ethyl acetate in hexanes) yielded 65 mg (53%) of pure **34** as a clear oil. IR (neat): 3 486, 1 719, 1 514, 1 248. ¹H NMR (300 MHz, CDCl₃): 7.24 (d, *J* = 8.6, 2 H); 6.85 (d, *J* = 8.6, 2 H); 5.47–5.40 (m, 4 H); 4.41 (s, 2 H); 4.38 (m, 1 H); 3.79 (s, 3 H); 3.71 (ddd, *J* = 9.5, 7.7, 1.7, 1 H); 3.63 (d, *J* = 3.6, 1 H); 3.62–3.47 (m, 3 H); 2.61 (br d, *J* = 18.0, 1 H); 2.17–1.07 (series of m, 22 H); 1.65 (br s, 6 H); 1.37 (s, 3 H); 1.35 (s, 3 H). ¹³C NMR (75 MHz, CDCl₃): 212.2, 159.1, 131.3, 130.4, 129.2 (2 C); 125.5, 124.8, 113.7 (2 C); 108.1, 80.7, 78.0, 74.2, 72.4, 67.9, 55.2, 40.7, 40.0, 39.6, 37.8, 36.9, 34.8, 32.5, 30.5, 29.4, 29.3, 29.1, 29.0, 27.4, 27.3, 26.8, 17.9 (2 C). FAB MS, *m/z*: (*M*⁺) calculated: 570.39; found: 570.35.

tert-Butyl (5R,6S,7R,7aR)-6-[[[(4S,5S)-2,2-Dimethyl-5-[(E)-pent-3-en-1-yl]-1,3-dioxolan-4-yl)methyl]-7-{2-[(4-methoxybenzyl)oxy]ethyl}-5-[(E)-oct-6-en-1-yl]-2-oxo-4,5,6,7-tetrahydro-2*H*-1-benzofuran-3-propanoate (**36**)

A 0.5 M solution of **35** was prepared by adding oxalyl chloride (0.1 ml, 1.2 mmol) to the carboxylic acid (125 mg, 0.38 mmol) dissolved in dry benzene (10 ml). The solution was stirred for 9 h and concentrated. The acid chloride was taken up in CH₂Cl₂ (7.7 ml) and 4 ml of this solution (2.0 mmol) were added to a solution of **34** (60 mg, 0.10 mmol) and pyridine (0.025 ml, 3.0 mmol) in CH₂Cl₂ (10 ml) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h, diluted with ether, and washed with saturated NaHCO₃ solution and brine. The combined aqueous washings were extracted with ethyl acetate and the organic layers were dried and concentrated. Flash chromatography of the residue on silica gel (elution with 50% ethyl acetate in hexanes) gave the keto phosphonate (71 mg, 81%).

The above intermediate (80 mg, 0.080 mmol) was dissolved in dry THF (10 ml), cooled to -78°C , and treated with 0.10 ml of 1.0 M lithium hexamethyldisilazide (1.0 mmol). The cooling bath was removed and the reaction mixture was stirred for 8 h, diluted with ether, washed with 1 M HCl and brine, dried, and concentrated. Purification of the residue by flash chromatography on silica gel (elution with 20% ethyl acetate in hexanes) yielded **36** (48 mg, 83%) as a colorless oil. IR (neat): 1 748, 1 732, 1 682, 1 614, 1 514, 1 454, 1 367. ^1H NMR (300 MHz, CDCl_3): 7.22 (d, $J = 8.6$, 2 H); 6.84 (d, $J = 8.6$, 2 H); 5.50–5.37 (m, 4 H); 4.92 (d, $J = 6.6$, 1 H); 4.38 (s, 2 H); 3.78 (s, 3 H); 3.69 (ddd, $J = 7.8$, 7.8, 3.1, 1 H); 3.56 (m, 1 H); 3.44 (m, 2 H); 2.68 (dd, $J = 17.0$, 5.1, 1 H); 2.52–2.36 (m, 5 H); 2.17–1.93 (m, 4 H); 1.83–1.09 (series of m, 17 H); 1.65 (s, 3 H); 1.64 (s, 3 H); 1.36 (s, 3 H); 1.35 (s, 3 H). ^{13}C NMR (75 MHz, CDCl_3): 174.2, 171.8, 161.5, 159.0, 131.3, 130.5, 130.3, 129.1, 125.5, 124.7, 124.6, 113.7, 108.1, 80.6, 80.4, 79.4, 78.7, 72.4, 68.7, 55.2, 40.6, 38.3, 38.1, 34.9, 32.9, 32.5, 32.4, 29.4 (2 C); 29.1, 29.0, 28.7, 28.0 (3 C); 27.7, 27.4, 27.3, 27.2, 18.9, 17.9 (2 C). FAB MS, m/z : (M^+) calculated: 722.48; found: 722.45.

tert-Butyl (3*S*,5*R*,6*S*,7*R*)-3-[(*tert*-Butyloxycarbonyl)methyl]-6-[[4*S*,5*S*)-2,2-dimethyl-5-[(*E*)-pent-3-en-1-yl]-1,3-dioxolan-4-yl]methyl]-7-[2-(4-methoxybenzyloxy)ethyl]-5-[(*E*)-oct-6-en-1-yl]-2-oxo-2,3,4,5,6,7-hexahydro-1-benzofuran-3-propanoate (**37**) and *tert*-Butyl (3*R*,5*R*,6*S*,7*R*)-3-[(*tert*-Butyloxycarbonyl)methyl]-6-[[4*S*,5*S*)-2,2-dimethyl-5-[(*E*)-pent-3-en-1-yl]-1,3-dioxolan-4-yl]methyl]-7-[2-(4-methoxybenzyloxy)ethyl]-5-[(*E*)-oct-6-en-1-yl]-2-oxo-2,3,4,5,6,7-hexahydro-1-benzofuran-3-propanoate (**38**)

A solution of 0.5 M potassium hexamethyldisilazide in toluene (0.04 ml, 0.2 mmol) was added to a solution of **36** (10 mg, 0.014 mmol) in DMF (1 ml) at -40°C . The reaction mixture was stirred at this temperature for 20 min, treated with *tert*-butyl bromoacetate (0.007 ml, 0.047 mmol), warmed slowly to 20°C during 1.5 h, quenched with water, and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (elution with 10% ethyl acetate in hexanes) to give **37** and **38** as a 2 : 1 mixture of diastereomers (8 mg, 69%). IR (neat): 1 798, 1 732, 1 614, 1 514, 1 455. ^1H NMR (300 MHz, CDCl_3): 7.25 (d, $J = 8.6$, 2 H); 6.86 (d, $J = 8.6$, 2 H); 5.40 (m, 4 H); 4.43 (s, 2 H); 3.80 (s, 3 H); 3.64–3.46 (m, 4 H); 2.77 (d, $J = 15.4$, 0.66 H); 2.76 (d, $J = 15.7$, 0.33 H); 2.53 (m, 1 H); 2.46 (d, $J = 15.7$, 0.33 H); 2.43 (d, $J = 15.4$, 0.66 H); 2.15–1.16 (series of m, 28 H); 1.63 (br s, 6 H); 1.41 (s, 5.9 H); 1.40 (s, 3.1 H); 1.39 (s, 3.1 H); 1.37 (s, 5.9 H); 1.33 (s, 3 H); 1.31 (s, 3 H). ^{13}C NMR (75 MHz, CDCl_3): 180.2, 171.6, 168.4, 159.1, 151.6, 131.4, 130.6, 130.4, 129.2 (2 C); 125.3, 124.8, 113.7 (2 C); 112.2, 108.1, 81.4, 80.8, 80.7, 78.2, 77.2, 68.2, 55.2, 50.1, 41.4, 39.7, 37.1, 35.6, 34.1, 33.9, 32.6, 32.3, 31.4, 30.6, 29.9, 29.5, 29.4, 29.3, 29.2, 28.0 (3 C); 27.9 (3 C); 27.5, 27.4, 27.3, 27.2, 22.0, 17.9 (2 C). FAB MS, m/z : (M^+) calculated: 836.54; found: 836.69.

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