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Ring Enlargement by Alkylated 3-Hydroxybutyrates: A Synthesis of (12*S*, 13*R*)-(–)-12-Methyl-13-tetradecanolide[1]

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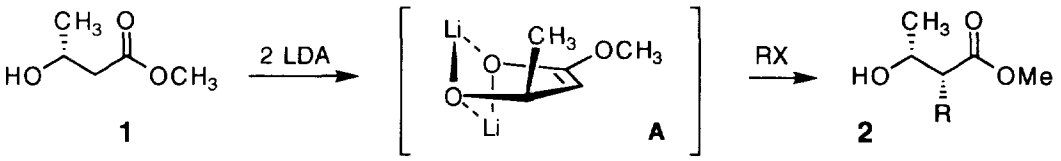
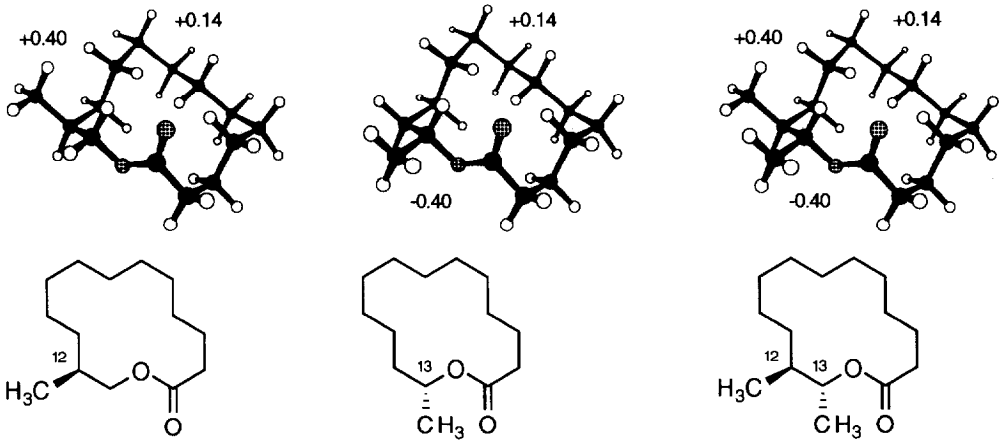
Abstract: TBS-protected iodo alkohols **6** were prepared *via* Fráter alkylation and applied in the synthesis of optically active macrolides **5** and **10**. By ring enlargement of cyclodecanone (**7**) the superposition molecule **5** of two macrocyclic odorants was synthesized and a conformationally fixed tricyclic macrolide **11** constructed.

Generating the dianion **A** by treatment with two equivalents of LDA effectively locks methyl (3*R*)-(–)-3-hydroxybutyrate (**1**) in an eclipsed conformation, where the lithium atoms are chelated with the lone electron pairs of the oxygens.[2] An electrophile approaching from the sterically less hindered side gives the *anti* diastereomer with high selectivity (Scheme 1). As a result, these Fráter alkylations[3,4] offer the opportunity of introducing additional substituents diastereoselectively in chiral building blocks derived from β-hydroxy esters. For instance, Mori *et al.* applied this strategy in their enantioselective synthesis of the potent antiulcerogen (+)-cassiol.[5]



Scheme 1. Fráter alkylation of methyl (3*R*)-(–)-3-hydroxybutyrate (**1**)

We became interested in the methylated 3-hydroxybutyrate **2a** as chiral building block for the synthesis of (12*S*,13*R*)-(–)-12-methyl-13-tetradecanolide (**5**), which we regarded as a superposition of (12*S*)-(–)-12-methyl-13-tridecanolide (**3**)[6] and (13*R*)-(–)-13-tetradecanolide (**4**),[7] macrocyclic odorants isolated from essential oils of *Umbelliferae*. (12*S*)-(–)-12-Methyl-13-tridecanolide (**3**) possesses a pronounced musk odor that differs from that of the enantiomer by its animalic character and camphoraceous aspects. In contrast, the musk note of (13*R*)-(–)-13-tetradecanolide (**4**) is weaker and woody aspects dominate. In our preceding paper[7] we attributed this effect to a steric hindrance of the 13-methyl group of **4** with the receptor for macrocyclic musk odorants. To support this suggestion, we had the idea of restraining the musk note of **3** by introducing the (13*R*)-methyl group of **4**. Thus, we wanted to synthesize a macrocyclic odorant that smells animalic but not musk-like (Scheme 2).



3
animalic musk odor, slightly camphoraceous

4
complex woody odor, weaker musk note

5
animalic cedarwood odor, camphoraceous aspects

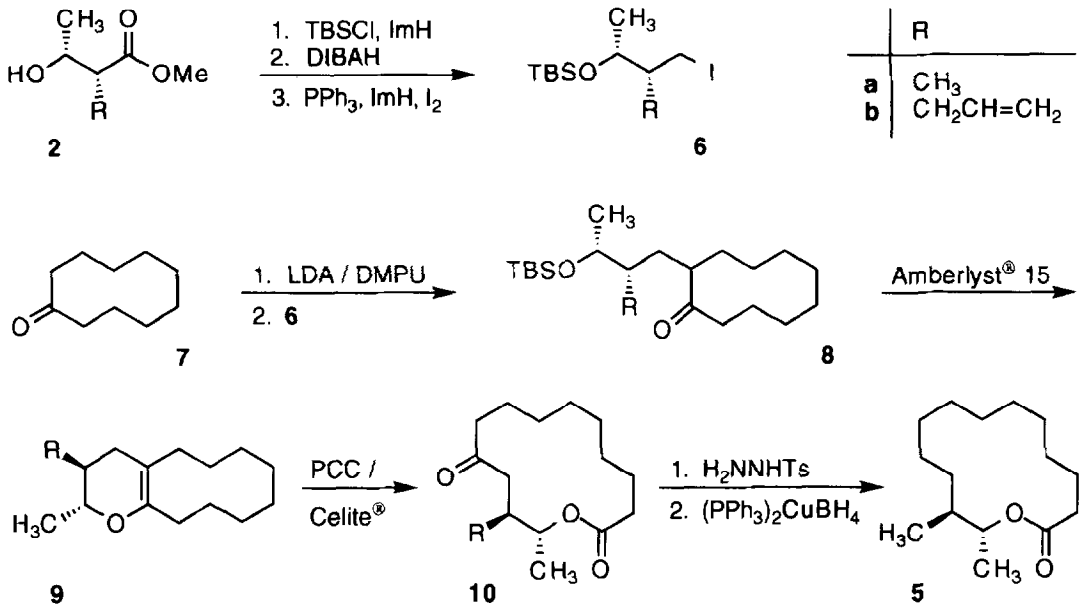
Scheme 2. (12*S*)-(−)-12-Methyl-13-tridecanolide (**3**), (13*R*)-(−)-13-tetradecanolide (**4**), and the superposition molecule (12*S*,13*R*)-(−)-12-methyl-13-tetradecanolide (**5**) with contributions to the Cotton effect assigned

Replacing the carcinogenic hexamethylphosphoric triamide of the original procedure[3] by 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU),[8] (3*R*)-(−)-3-hydroxybutyrate (**1**) was methylated in 69% yield with 94% de (^{1}H NMR of **5**) to give **2a**. Protection of the alkylated hydroxy ester **2a** by the *tert*-butyldimethylsilyl group (TBS), reduction with DIBAH, and iodination of the resulting hydroxy function with triphenylphosphine, imidazole (ImH) and iodine furnished the chiral building block **6a** in 54% overall yield. According to our standard sequence[7] cyclodecanone (**7**) was deprotonated by LDA / DMPU and alkylated with **6a** in 64% yield. Treatment of the alkylation product **8a** with Amberlyst® 15 in dichloromethane provided the cyclic enol ether **9a** in 71% yield (Scheme 3).

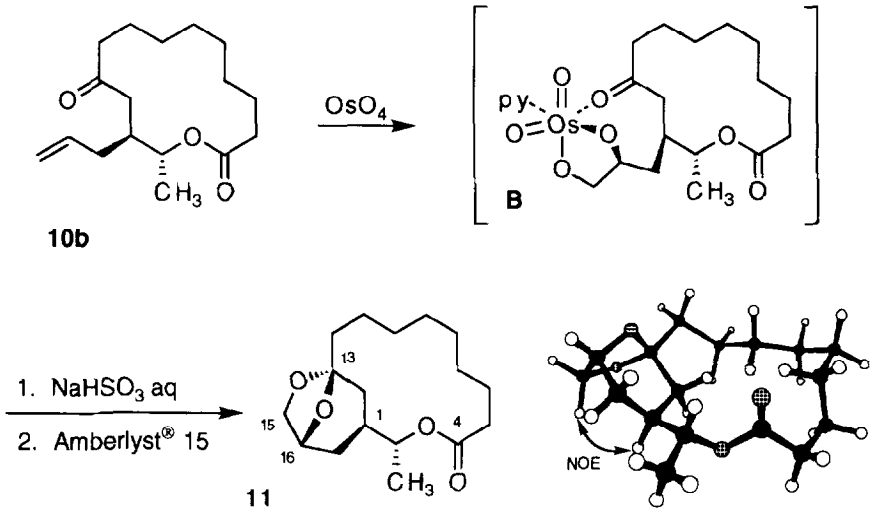
Due to competitive reactions initiated by oxidation of the C–H bond of the stereocenter cleavage of the enol ether double bond of 12-methyl-11-oxabicyclo[8.4.0]tetradec-1(10)-ene had been unsatisfactory.[7] Fortunately, the 12,13-dimethyl compound **9a** was less sensitive, and pyridinium chlorochromate (PCC) on Celite® as mild and selective reagent[9] afforded oxo lactone **10a** in 59% yield. The synthesis of **5** was completed by reduction of the tosylhydrazone of **10a** with bis(triphenylphosphine)copper(I) tetrahydridoborate,[10] which proceeded in 51% without isolation of the tosylhydrazone.

Superposition molecule **5** indeed completely lacks the musk note of **3**, although the animalic character and the camphoraceous aspects of **3** are markedly present. Instead of the musk odor **5** possesses a woody cedar-like note reminiscent of compound **4**. The overall impression is powdery, animalic, cedarwood-like, and slightly camphoraceous.

This certainly confirms our supposition, but the Cotton effect of **5** expected to be negative like that of **4**[7] was found to be positive ($\Delta\varepsilon$ +0.14). By comparison of macrolides **3**, **4** and **5** the contribution of the 12-methyl group was derived as $\Delta\varepsilon$ +0.40. This Cotton effect cancels that of the 13-methyl group ($\Delta\varepsilon$ -0.40) to give the value for the ring atoms ($\Delta\varepsilon$ +0.14). By virtue of the X-ray crystal structure of 13-tridecanolide[11] and the observed chiroptical properties,[7] we assumed the shown conformation of **3** and **4** (Scheme 2) to be favored. In this conformation (Scheme 2) the 12-methyl group of **5** lies on a nodal plane and should not make any contribution



Scheme 3. Stereoselective syntheses of macrolides **5**, **10a** and **10b** by ring enlargement of cyclodecanone (**7**) with chiral building blocks **6**



Scheme 4. Diastereoselective dihydroxylation of **10b** and subsequent intramolecular ketalization to **11**

to the Cotton effect; either the quadrant rule[12] fails, or the contribution stems from an additional conformer. For clarification, we planned to fix C-12 in *gauche* conformation by construction of a tricyclic skeleton.

Intramolecular ketalization is an efficient access to molecules with fixed geometry like the aggregation pheromones (–)-frontalin[13] and (+)-*exo*-brevicomin.[14] To build up a dioxabicyclo[3.2.1]octane system we wanted to introduce an allyl group as synthetic equivalent for a 2,3-dihydroxypropyl fragment. Fráter alkylation of **1** by allyl bromide gave **2b** as starting material in 71% yield with 97% de (^{1}H NMR of **9b**). Following the same sequence, we converted **2b** into **6b** in 52% overall yield. Alkylation of cyclodecanone with the chiral building block **6b** gave in 67% yield **8b** that cyclized in 89% yield to **9b** upon treatment with Amberlyst® 15 in dichloromethane.

The enol ether double bond of **9b** was cleaved chemoselectively in the presence of the allyl group by PCC/Celite® to provide oxo lactone **10b** in 65% yield. Stoichiometric osmylation[15] of **10b** in ether / pyridine (py) and subsequent intramolecular ketalization catalyzed by Amberlyst® 15 afforded the tricyclic macrolide **11** with 94% de (^{1}H NMR of **11**) in 28% isolated yield (Scheme 4). The configuration of **11** was unambiguously established by the presence of a NOE between one methylene proton on C-15 (δ 3.86) and the methine on C-1 (δ 2.10). As predicted by the quadrant rule,[12] the observed Cotton effect of **11** was negative (Δε -0.16); accordingly, the contribution of the 12-methyl group of **5** is probably due to an additional conformer.[11]

The stereochemical course of this diastereoselective dihydroxylation was not influenced by asymmetric ligands, *i.e.* $(DHQD)_2$- or $(DHQ)_2$-PHAL.[16] Diastereoselective hydroxylation guided by a remote sulfoxide group[17] or sulfoximine group[18] had already been observed, and Weigel *et al.*[19] had suggested that a carbonyl group may disrupt asymmetric dihydroxylation. Therefore, osmate(VI) ester complex **B** (Scheme 4) might explain the observed diastereoselectivity of the dihydroxylation of **10b**.

In summary, the application of alkylated chiral building blocks **6** in our ring enlargement sequence[6,7] represents a facile and highly stereoselective method for the synthesis of (ω,ω-1)-disubstituted macrolides like **5**, **10a** and **10b**. A quaternary stereogenic center at carbon (ω-1) should be accessible by repeated Fráter alkylation.[5] Only recently, Yamamoto *et al.* synthesized (ω,ω-2)-disubstituted macrolides by ozonolysis of stereospecifically annulated cyclic enol ethers.[20] Both strategies of introducing two stereocenters by ring expansion broaden the synthetic access to medium and large ring lactones.[21]

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR-spectrometer. ^{1}H / ^{13}C NMR spectra (reference: TMS int) were taken in $CDCl_3$ on a Bruker AC 200 P and a Bruker AM 300, respectively. EI (70 eV) and CI (^{i}BuH) mass spectra were obtained on a Finnigan-MAT 8230 spectrometer. Column chromatography was performed on Baker Silicagel 30–60 μm and analytical TLC on Macherey-Nagel SIL G/UV_{254} plates. Melting points were determined on a Büchi 510 apparatus and are uncorrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium Ilse Beetz, D-96301 Kronach.

Fráter Alkylation of (3R)-(–)-3-Hydroxybutyrate (1)

General Procedure: To a soln of LDA [prepared under argon atmosphere by addition of *n*-butyllithium (124 mL of 1.6 M in *n*-hexane, 198 mmol) at –78 °C to a soln of diisopropylamine (26.0 mL, 198 mmol) in anhydrous THF (200 mL) and stirring at 0 °C for 30 min] cooled to –78 °C was added methyl (3*R*)-(–)-3-hydroxybutyrate (10 mL, 89.3 mmol; **1**) within 10 min. When the reaction temp dropped back to –78 °C the halide (98 mmol) and DMPU (30 mL, 248 mmol) was introduced. After stirring at –78 °C for another 15 min and at 0 °C for 45 min, the reaction mixture was poured into cold sat NH_4Cl aq (200 mL) and the aqueous layer extracted with Et_2O (3 × 200 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated to leave a residue, which was purified by distillation or column chromatography to give the alkylated β-hydroxy esters as clear, colorless liquids.

Methyl (2R,3R)-(–)-3-hydroxy-2-methyl-butyrate (**2a**). Using methyl iodide, scale 44.7 mmol, yield 69% (4.09 g), bp 77–78 °C/10 Torr; $[\alpha]_D^{20}$ -32.9, $[\alpha]_{546}^{20}$ -38.9 (*c* 1.8, $CHCl_3$); for spectroscopic data of the corresponding ethyl ester, see ref.[3]

Methyl (2R,1'R)-(–)-2-(1'-hydroxyethyl)-allyl-acetate (**2b**). Using allyl bromide, scale 89.3 mmol, yield 71% (9.99 g), hR_f 40 (*n*-pentane:Et_2O, 1:1); $[\alpha]_D^{22}$ -8.7, $[\alpha]_{546}^{22}$ -10.0 (*c* 4.0, $CHCl_3$); for spectroscopic data of the corresponding ethyl ester, see ref.[3]

Preparation of the Chiral Building Blocks 6

General Procedure: See ref.[7]

(2R,3R)-(–)-(tert-Butyldimethyl)-(4-iodo-3-methylbut-2-oxy)-silane (**6a**). Scale 30.3 mmol, overall yield 54% (5.41 g), hR_f 64 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 835 (s, ν Si-OC), 774 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.07 / 0.09 (2s, 6H, SiMe_2), 0.89 (s, 9H, CMe_3), 0.96 (d, *J* = 6.8 Hz, 3H, 3-Me), 1.12 (d, *J* = 6.2 Hz, 3H, 1-H_3), 1.48 (qddd, *J* = 6.8, 6.4, 6.2 and 4.5 Hz, 1H, 3-H), 3.28 (dd, *J* = 9.5 and 6.4 Hz, 1H, 4-H_B, part of an AB system), 3.29 (dd, *J* = 9.5 and 4.5 Hz, 1H, 4-H_A, part of an AB system), 3.65 (qd, *J* = 6.2 and 6.2 Hz, 1H, 2-H);^{13}C NMR ($CDCl_3$, ppm) δ -4.62 / -4.10 (2q, SiMe_2), 14.27 (t, C-4), 17.11 (q, 3-*Me*), 18.02 (s, *C*Me_3), 20.52 (q, C-1), 25.92 (q, CMe_3), 42.60 (d, C-3), 71.31 (d, C-2); MS (CI, %) *m/z* 329 (100) [$M^{\oplus}$ + H], 313 (2) [$M^{\oplus}$ - CH_3], 271 (17) [$M^{\oplus}$ - C_4H_9], 201 (51) [$M^{\oplus}$ - I]; $[\alpha]_D^{20}$ -34.5, $[\alpha]_{546}^{20}$ -40.6 (*c* 0.9, $CHCl_3$).

(2R,3R)-(–)-(tert-Butyldimethyl)-(3-[iodomethyl]-hex-5-en-2-oxy)-silane (**6b**). Scale 45.0 mmol, overall yield 52% (8.24 g), hR_f 59 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 835 (s, ν Si-OC), 775 (s, ν O-Si-CH_3), 990 / 916 (m, δ =C-H oop), 1640 (w, ν C=C), 3076 (w, ν =C-H);^1H NMR ($CDCl_3$, ppm) δ 0.08 / 0.10 (2s, 6H, SiMe_2), 0.89 (s, 9H, CMe_3), 1.14 (d, *J* = 6.2 Hz, 3H, 1-H_3), 1.37 (dddt, *J* = 8.4, 6.0, 5.2 and 5.2 Hz, 1H, 3-H), 1.99 (dddt, *J* = 14.2, 8.7, 7.7 and 1.2 Hz, 1H, 4-H_b), 2.27 (dddt, *J* = 14.2, 6.5, 5.0 and 1.2 Hz, 1H, 4-H_a), 3.23 (dd, *J* = 9.7 and 5.2 Hz, 1H, CH_bI), 3.38 (dd, *J* = 9.7 and 5.2 Hz, 1H, CH_aI), 3.80 (qd, *J* = 6.2 and 6.0 Hz, 1H, 2-H), 5.07 (ddt, *J* = 10.1, 1.7 and 1.2 Hz, 1H, 6-H_{cis}), 5.13 (ddt, *J* = 17.0, 1.7 and 1.2 Hz, 1H, 6-H_{trans}), 5.70 (dddd, *J* = 17.0, 10.1, 7.8 and 6.5 Hz, 1H, 5-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.58 / -4.06 (q, SiMe_2), 11.22 (t, *C*H_2I), 17.91 (s, *C*Me_3), 20.48 (q, C-1), 25.88 (q, CMe_3), 34.45 (t, C-4), 47.03 (d, C-3), 69.57 (d, C-2), 116.99 (t, C-6), 135.91 (d, C-5); MS (CI, %) *m/z* 355 (55) [$M^{\oplus}$ + H], 339 (10) [$M^{\oplus}$ - CH_3], 297 (69) [$M^{\oplus}$ - C_4H_9], 227 (43) [$M^{\oplus}$ - I], 95 (100) [$C_7H_{11}^{\oplus}$]; $[\alpha]_D^{23}$ -29.5, $[\alpha]_{546}^{23}$ -35.1 (*c* 2.6, $CHCl_3$).

Alkylation of Cyclodecanone (7) by Chiral Building Blocks 6

General Procedure: See ref.[7]

(2RS,2'S,3'R)-2-[3'-(tert-Butyldimethylsiloxy)-2',3'-dimethylprop-1'-yl]cyclodecan-1-one (**8a**). Scale 15.0 mmol, yield 64% (3.41 g), hR_f 20 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 836 (s, ν Si-OC), 1703 (s, ν C=O), 774 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.02 / 0.03 (2s, 6H, SiMe_2), 0.87 (s, 9H, CMe_3), 0.84 / 0.87 (2d, *J* = 6.7 / 6.5 Hz, 3H, 2'-Me), 1.02 / 1.03 (2d, *J* = 6.3 / 6.2 Hz, 3H, 4'-H_3), 1.19–1.87 (m, 17H, 1'-H_2, 2'-H and 3-H_2–9-H_2), 2.41– 2.77 (m, 3H, 2-H and 10-H_2), 3.58 / 3.63 (2qd, *J* = 6.3 / 6.2 and 4.5 / 4.6 Hz, 1H, 3'-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.73 / -4.32 (q, 2C, SiMe_2), 15.02 / 15.08 (q, 1C, 2'-Me), 18.08 (s, 1C, *C*Me_3), 19.60 / 19.70 (q, 1C, C-4'), 23.18 / 23.37 (t, 1C, C-9), 24.04 / 24.60 / 24.68 / 24.72 / 24.89 / 24.98 (t, 3C, C-4,-6,-7), 25.19 / 25.24 (t, 2C, C-5,-8), 25.91 (q, 3C, CMe_3), 29.82 / 32.10 (t, 1C, C-3), 36.18 / 37.00 (t, 1C, C-1'), 37.94 / 38.16 (d, 1C, C-2'), 40.37 (t, 1C, C-10), 50.07 / 51.27 (d, 1C, C-2), 71.98 / 72.15 (d, 1C, C-3'), 216.97 (s, 1C, C-1); MS (CI, %) *m/z* 355 (100) [$M^{\oplus}$ + H], 297 (13) [$M^{\oplus}$ - C_4H_9], 223 (30) [$M^{\oplus}$ - $C_6H_{15}OSi$].

(2RS,2'S,1''R)-2-{2'-[1''-(tert-Butyldimethylsiloxy)ethyl]-pent-4'-en-1'-yl}cyclodecan-1-one (**8b**). Scale 20.0 mmol, yield 67% (5.10 g), hR_f 17 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 836 (s, ν Si-OC), 775 (s, ν O-Si-CH_3), 1703 (s, ν C=O), 993 / 1004 / 910 (m, δ =C-H oop), 1640 (m, ν C=C), 3075 (w, ν =C-H); ^1H NMR ($CDCl_3$, ppm) δ 0.02 / 0.03 / 0.04 (3s, 6H, SiMe_2), 0.87 / 0.88 (2s, 9H, CMe_3), 1.04 / 1.05 (2d, *J* = 6.3 / 6.2 Hz, 3H, 2''-H_3), 1.15–2.00 (m, 18H, 1'-H_2, 2'-H, 3'-H_b and 3-H_2–9-H_2), 2.27 (m_c, 1H, 3'-H_a), 2.52 (m_c, 2H, 10-H_2), 2.73 / 2.75 (2ddd, *J* = 10.2 / 10.0, 5.7 / 5.9 and 3.7 Hz, 1H, 2-H), 3.81 / 3.82 (2dq, *J* = 12.6 and 6.2 / 6.3 Hz, 1H, 1''-H), 5.01 (m_c, 2H, 5'-H_2), 5.74 (ddt, *J* = 17.1, 10.1 and 7.2 Hz, 1H, 4'-H) / 5.75 (dddd, *J* = 17.4, 9.7, 7.8 and 6.7 Hz, 1H, 4'-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.83 / -4.79 / -4.31 (q, 2C, SiMe_2), 17.92 / 17.95 (s, 1C, *C*Me_3),

19.92 / 19.95 (q, 1C, C-2"), 23.09 / 23.21 (t, 1C, C-9), 24.11 / 24.26 / 24.64 / 24.64 / 24.92 / 24.95 / 25.08 / 25.36 (t, 4C, C-4–C-7), 25.80 (q, 3C, CMe_3), 30.44 (t, 1C, C-8), 31.34 (t, 1C, C-3'), 33.69 / 33.88 (t, 1C, C-3), 34.38 / 34.56 (t, 1C, C-1'), 40.16 / 40.43 (t, 1C, C-10), 42.81 / 43.00 (d, 1C, C-2'), 50.38 / 50.85 (d, 1C, C-2), 69.14 / 69.50 (d, 1C, C-1"), 115.70 (t, 1C, C-5'), 137.58 (d, 1C, C-4'), 216.40 / 216.50 (s, 1C, C-1); MS (CI, %) *m/z* 381 (36) [$M^{\oplus}$ + H], 365 (3) [$M^{\oplus}$ - CH_3], 323 (27) [$M^{\oplus}$ - C_4H_9], 249 (100) [$M^{\oplus}$ - $C_6H_{15}OSi$]; Anal calcd for $C_{23}H_{44}O_2Si$ (380.7), C 72.57, H 11.65; found C 72.65, H 11.68.

Cyclization of Alkylation Products 8 to Enol Ethers 9

General Procedure: See ref.[7]

(12R,13S)-(+)-12,13-Dimethyl-11-oxabicyclo[8.4.0]-tetradec-1(10)-ene (**9a**). Scale 9.00 mmol, yield 71% (1.42 g), hR_f 16 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 1243 (s, ν C-O), 1674 (s, ν C=CO); ^1H NMR ($CDCl_3$, ppm) δ 0.93 (d, *J* = 6.4 Hz, 3H, 13-Me), 1.24 (d, *J* = 6.2 Hz, 3H, 12-Me), 1.31–1.72 (m, 14H, 3-H_2–8-H_2, 13-H and 14-H_b), including 1.58 (m_c, 1H, 13-H) and 1.63 (m_c, 1H, 14-H_b), 1.83 (m_c, 1H, 14-H_a), 1.97–2.23 (m, 2H, 2-H_2), 2.23–2.44 (m, 2H, 9-H_2), 3.47 (dq, *J* = 9.0 and 6.2 Hz, 1H, 12-H); ^{13}C NMR ($CDCl_3$, ppm) δ 17.89 (t, C-14), 19.13 (q, 12-Me), 20.17 / 20.85 (t, C-3,-8), 25.05 / 25.17 (t , C-5,-6), 26.31 / 26.55 (t, C-4,-7), 27.40 / 29.51 (t, C-2,-9), 32.87 (d, C-13), 33.52 (q, 13-Me), 76.03 (d, C-12), 105.54 (s, C-1), 147.20 (s, C-10); MS (EI, %) *m/z* 222 (42) [$M^{\oplus}$], 193 (32) [$M^{\oplus}$ - C_2H_5], 179 (100) [$M^{\oplus}$ - C_2H_3O] , 95 (45) [$C_7H_{11}^{\oplus}$]; $[\alpha]_D^{18}$ +79.4, $[\alpha]_{546}^{18}$ +93.8 (*c* 1.2, $CHCl_3$); Anal calcd for $C_{15}H_{26}O$ (222.4), C 81.02, H 11.79; found C 81.07, H 11.82.

(12R,13S)-(+)-13-Allyl-12-methyl-11-oxabicyclo[8.4.0]-tetradec-1(10)-ene (**9b**). Scale 11.8 mmol, yield 89% (2.61 g), hR_f 21 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 1245 (s, ν C-O), 912 / 994 (s, δ =C-H oop), 1674 (m, ν C=CO), 1640 (w, ν C=C), 3074 (w, ν =C-H); ^1H NMR ($CDCl_3$, ppm) δ 1.26 (d, *J* = 6.3 Hz, 3H, 12-Me), 1.34 – 1.72 (m, 14H, 3-H_2–8-H_2, 13-H and 14-H_b), 1.82–2.34 (m, 7H, 1'-,2-,9-H_2 and 14-H_a), 3.65 (dq, *J* = 6.9 and 6.3 Hz, 1H, 12-H), 5.02 (ddt, *J* = 10.2, 2.6 and 1.1 Hz, 1H, 3'-H_{cis}), 5.05 (ddt, *J* = 16.6, 2.6 and 1.1 Hz, 1H, 3'-H_{trans}), 5.79 (dddd, *J* = 16.6, 10.2, 7.7 and 6.5 Hz, 1H, 2'-H); minor diastereomer δ 1.16 (12-Me, 1.5%); ^{13}C NMR ($CDCl_3$, ppm) δ 19.19 (q, 12-Me), 20.25 / 20.86 (t, C-3,-8), 25.06 / 25.21 (t, C-5,-6), 26.27 / 26.55 (t, C-4,-7), 27.46 (t, C-2), 28.83 (t, C-14), 29.64 (t, C-9), 36.89 (t, C-1'), 37.80 (d, C-13), 73.96 (d, C-12), 104.88 (s, C-1), 116.30 (t, C-3'), 136.30 (d, C-2'), 146.57 (s, C-10); MS (EI, %) *m/z* 248 (55) [$M^{\oplus}$], 219 (25) [$M^{\oplus}$ - C_2H_5], 205 (100) [$M^{\oplus}$ - C_3H_7], 95 (84) [$C_7H_{11}^{\oplus}$]; $[\alpha]_D^{26}$ +72.0, $[\alpha]_{546}^{26}$ +85.1 (*c* 2.7, $CHCl_3$); Anal calcd for $C_{17}H_{28}O$ (248.4), C 82.20, H 11.36; found C 82.12, H 11.36.

Oxidative Cleavage of the Cyclic Enol Ethers 9

General Procedure: See ref.[7]

(12S,13R)-(–)-12-Methyl-10-oxo-13-tetradecanolide (**10a**). Scale 3.84 mmol, yield 59% (575 mg), hR_f 48 (*n*-pentane:Et_2O, 4:1), mp 44.0–44.5 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 1718 (s, ν OC=O),1703 (s, ν C=O), 1260 (s, ν_{as} C-CO-O); ^1H NMR ($CDCl_3$, ppm) δ 0.95 (d, *J* = 6.6 Hz, 3H, 12-Me), 1.23 (d, *J* = 6.2 Hz, 3H, 14-H_3), 1.26–1.43 (m, 8H, 4-H_2–7-H_2), 1.60–1.71 (m, 4H, 3-,8-H_2), 2.15–2.24 (m, 2H, 11-H_b and 12-H), 2.29–2.39 (m, 4H, 2-,9-H_2), 2.74 (dd, *J* = 17.5 and 2.7 Hz, 1H, 11-H_a), 4.72 (dq, *J* = 9.1 and 6.2 Hz, 1H, 13-H); ^{13}C NMR ($CDCl_3$, ppm) δ 17.10 (q, 12-Me), 18.77 (q, C-14), 23.41 (t, C-8), 24.59 (t, C-3), 25.61 / 25.67 / 25.86 / 26.43 (t, C-4–C-7), 34.17 (d, C-12), 34.43 (t, C-2), 42.28 (t, C-11), 45.54 (t, C-9), 74.53 (d, C-13), 173.48 (s, C-1), 210.86 (s, C-10); MS (EI, %) *m/z* 254 (19) [$M^{\oplus}$], 239 (5) [$M^{\oplus}$ - CH_3],183 (57) [$M^{\oplus}$ - C_5H_{11}], 125 (44) [$M^{\oplus}$ - $C_8H_{17}O$], 112 (100) [$C_8H_{16}^{\oplus}$]; $[\alpha]_D^{19}$ -27.1, $[\alpha]_{546}^{19}$ -31.1 (*c* 2.4, $CHCl_3$); Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.82, H 10.35.

(12S,13R)-(–)-12-Allyl-10-oxo-13-tetradecanolide (**10b**). Scale 4.03 mmol, yield 65% (732 mg), hR_f 21 (*n*-pentane:Et_2O, 10:1); mp 39.0–39.5 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 1717 (s, ν OC=O), 1700 (s, ν C=O),1254 (m, ν_{as} C-CO-O), 910 (m, δ =C-H oop), 3081 (w, ν =C-H), 1640 (w, ν C=C); ^1H NMR ($CDCl_3$, ppm) δ 1.26 (d, *J* = 6.2 Hz, 3H, 14-H_3), 1.26–1.40 (m, 8H, 4-H_2–7-H_2), 1.59–1.72 (m, 4H, 3-,8-H_2), 2.09 (dddt, *J* = 14.7, 7.7, 7.1 and 1.4 Hz, 1H, 1'-H_b), 2.21 (dddt, *J* = 14.7, 6.4, 4.9, 7.1 and 1.4 Hz, 1H, 1'-H_a), 2.26–2.37 (m, 5H, 2-,9-H_2 and 12-H), 2.53 (dd, J = 18.1 and 6.2 Hz, 1H, 11-H_B, part of an AB system), 2.54 (dd, *J* = 18.1 and 4.8 Hz, 1H, 11-H_A, part of an AB system), 4.82 (dq, *J* = 8.3 and 6.2 Hz, 1H, 13-H), 5.03 (ddt, *J* = 17.4, 2.0 and 1.4 Hz, 1H, 3'-H_{trans}), 5.05 (ddt,

J = 9.7, 2.0 and 1.4 Hz, 1H, 3'-H_{cis}), 5.71 (dddd, J = 17.4, 9.7, 7.7 and 6.4 Hz, 1H, 2'-H); ^{13}C NMR ($CDCl_3$, ppm) δ 18.99 (q, C-14), 23.32 (t, C-8), 24.22 (t, C-3), 25.66 / 25.75 / 25.81 / 26.34 (t, C-4–C-7), 34.37 (t, C-2), 35.51 (t, C-1'), 38.07 (d, C-12), 42.04 (t, C-9), 42.26 (t, C-11), 73.06 (d, C-13), 117.48 (t, C-3'), 135.20 (d, C-2'), 173.12 (s, C-1), 210.23 (s, C-10); MS (EI, %) *m/z* 280 (49) [$M^{\oplus}$], 265 (17) [$M^{\oplus}$ - CH_3], 185 (46) [$M^{\oplus}$ - C_7H_{11}], 139 (42) [$C_9H_{15}O^{\oplus}$], 81 (100) [$C_5H_5O^{\oplus}$]; $[\alpha]_D^{28}$ -28.8, $[\alpha]_{546}^{28}$ -34.0 (*c* 1.2, $CHCl_3$); Anal calcd for $C_{17}H_{28}O_3$ (280.4), C 72.82, H 10.07; found C 72.91, H 10.00.

Chemoselective Carbonyl Reduction of 10a to 5

General Procedure: See ref.[7]

(12S,13R)-(–)-12-Methyl-13-tetradecanolide (**5**). Scale 2.80 mmol, yield 51% (344 mg), hR_f 24 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1731 (s, ν OC=O),1216 / 1247 (m, ν_{as} C-CO-O); ^{1}H NMR ($CDCl_3$, ppm) δ 0.88 (d, J = 6.9 Hz, 3H, 12-Me), 1.21 (d, J = 6.2 Hz, 3H, 14-H_3), 1.24–1.47 (m, 16H, 4-H_2–11-H_2), 1.60 (m_c, 1H, 12-H), 1.62 (m_c, 1H, 3-H_b), 1.72 (m_c, 1H, 3-H_a), 2.30 (ddd, J = 14.4, 7.9 and 3.7 Hz, 1H, 2-H_b), 2.41 (ddd, J = 14.4, 9.5 and 3.7 Hz, 1H, 2-H_a), 4.64 (dq, J = 9.9 and 6.2 Hz, 1H, 13-H); minor diastereomer δ 4.95 (13-H, 3%); ^{13}C NMR ($CDCl_3$, ppm) δ 15.75 (q, 12-Me), 18.97 (q, C-14), 22.26 (t, C-11), 24.10 (t, C-3), 24.35 / 24.79 / 25.61 / 25.97 / 26.33 / 26.37 / 30.81 (t, C-4–C-10), 34.42 (t, C-2), 37.78 (d, C-12), 74.68 (d, C-13), 173.46 (s, C-1); MS (EI, %) *m/z* 240 (7) [$M^{\oplus}$], 222 (5) [$M^{\oplus}$ - H_2O], 211 (11) [$M^{\oplus}$ - CHO], 196 (76) [$M^{\oplus}$ - CO_2], 98 (60) [$C_7H_{14}^{\oplus}$], 70 (100) [$C_5H_{10}^{\oplus}$]; $[\alpha]_D^{19}$ -49.7, $[\alpha]_{546}^{19}$ -58.4 (*c* 2.0, $CHCl_3$); CD (MeCN) Δε +0.14 (212 nm); Anal calcd for $C_{15}H_{28}O_2$ (240.4), C 74.95, H 11.74; found C 75.00, H 11.67.

Diastereoselective Dihydroxylation of 10b and Ketalization to 11

Procedure: A soln of OsO_4 (300 mg, 1.18 mmol) in Et_2O (30 mL) was added to **10b** (280 mg, 1.00 mmol) in Et_2O (50 mL) containing pyridine (0.2 mL), and the mixture stirred at room temp for 3 h. The supernatant was decanted, the residue dissolved in dichloromethane (80 mL) and treated with 15% $NaHSO_3$ aq (80 mL, 115 mmol). After stirring at room temp for 14 h, the organic layer was separated and the aqueous extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried with Na_2SO_4, Amberlyst® 15 (1.0 g) was added, and the mixture was stirred at room temp for 1 h. The resin was filtered off, the filtrate concentrated under reduced pressure, and the residue purified by column chromatography to provide **11** (82 mg, 28%) as colorless crystals.

(1S,2R,13S,16R)-(+)-3,14,19-Trioxatricyclo[11.4.1.1^{13,16}]nonadecan-4-one (**11**). hR_f 17 (*n*-pentane:Et_2O, 4:1); mp 83.0 - 84.0 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 1726 (s, ν OC=O), 1055 / 1112 / 1183 / 1160 / 989 (s, ν C-O), 1254 (s, ν_{as} C-CO-O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.20 (d, J = 6.3 Hz, 3H, 2-Me), 1.33 (ddd, J = 12.9, 12.9 and 1.9 Hz, 1H, 18-H_b), 1.36–1.58 (m, 13H, 7-H_2–11-H_2, 17-H_2 and 12-H_b), 1.65 (m_c, 2H, 6-H_2), 1.87 (ddd, J = 14.1, 8.0 and 1.9 Hz, 1H, 12-H_a), 1.99 (dddd, J = 12.9, 5.6, 0.8 and 0.7 Hz, 1H, 18-H_a), 2.10 (ddddd, J = 12.9, 8.3, 5.7, 5.6 and 3.0 Hz, 1H, 1-H), 2.25 (ddd, J = 15.0, 10.5 and 3.7 Hz, 1H, 5-H_b), 2.50 (ddd, J = 15.0, 6.6 and 3.3 Hz, 1H, 5-H_a), 3.82 (ddd, J = 7.1, 4.8 and 1.1 Hz, 1H, 15-H_b), 3.86 (dd, J = 7.1 and 1.3 Hz, 1H, 15-H_a), 4.57 (ddd, J = 4.8, 3.0, 3.0 and 1.3 Hz, 1H, 16-H), 4.75 (dq, J = 8.3 and 6.3 Hz, 1H, 2-H); minor diastereomer δ 4.95 (2-H, 3%); ^{13}C NMR ($CDCl_3$, ppm) δ 18.27 (q, 2-Me), 21.72 (t, C-11), 25.01 (t, C-6), 26.11 / 26.44 / 26.70 / 26.82 (t, C-7–C-10), 31.72 (t, C-17), 34.49 (d, C-1), 35.15 / 35.54 / 36.00 (t, C-5,-12,-18), 68.46 (t, C-15), 73.77 / 73.98 (d, C-2,-16), 109.34 (s, C-13), 172.79 (s, C-4); MS (EI, %) *m/z* 296 (13) [$M^{\oplus}$], 266 (2) [$M^{\oplus}$ - CH_2O], 185 (39) [$M^{\oplus}$ - $C_6H_7O_2$], 139 (48) [$M^{\oplus}$ - $C_9H_{17}O_2$], 112 (100) [$C_8H_{16}^{\oplus}$]; $[\alpha]_D^{24}$ +40.3, $[\alpha]_{546}^{24}$ +48.0 (*c* 1.0, $CHCl_3$); CD (MeCN) Δε -0.16 (213 nm); Anal calcd for $C_{17}H_{28}O_4$ (296.4), C 68.89, H 9.52; found C 69.00, H 9.49.

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