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Total Synthesis of (+)-Muconin

Takehiko Yoshimitsu,* Toshiyuki Makino, and Hiroto Nagaoka*

Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan

takey@my-pharm.ac.jp

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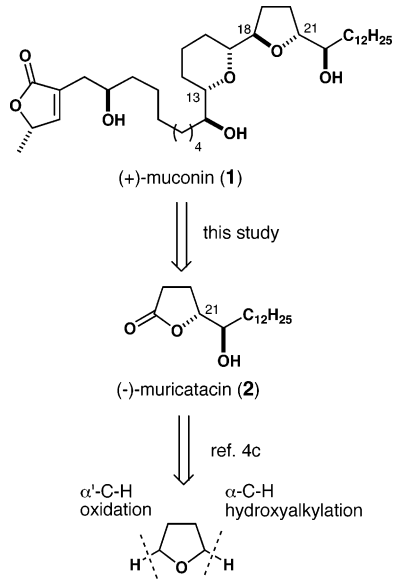
(+)-Muconin (**1**), isolated from the leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae), is a sequential THF/THP-possessing acetogenin that exhibits potent and selective in vitro cytotoxicity toward pancreatic and breast tumor cell lines. In this study, a new route was established for obtaining (+)-muconin (**1**) starting with (−)-muricatacin (**2**), a compound recently synthesized via the novel α-C−H hydroxyalkylation and α′-C−H oxidation of tetrahydrofuran.

Introduction

Annonaceous acetogenins constitute a class of bioactive polyketides that have been found to possess numerous biological properties which include antitumor, antimicrobial, immunosuppressive activity.[1] Among acetogenins possessing α-substituted tetrahydrofuran (THF) as a common structural motif, there is a group bearing an additional tetrahydropyran (THP) ring. (+)-Muconin (**1**), isolated from the leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae), is a sequential THF/THP-possessing acetogenin that exhibits potent and selective in vitro cytotoxicity toward pancreatic and breast tumor cell lines.[2] The biological significance and structural uniqueness of **1** have prompted intensive research to establish a route for its total synthesis, and consequently, three syntheses have been reported to date.[3] This study presents a new total synthesis of (+)-muconin (**1**) starting with (−)-muricatacin (**2**), the synthesis of which was recently carried out in our laboratory (Scheme 1).[4c,5]

SCHEME 1



Results and Discussion

In the course of devising new synthetic radical reactions,[4,6−8] we recently established the novel radical α-C−H hydroxyalkylation of THF as a means for prepar-

* Corresponding author.

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(5) Synthesis of complex acetogenins starting with muricatacin, for examples, see: (a) Tanaka, A.; Oritani, T. *J. Synth. Org. Chem., Jpn.* **1997**, 877. (b) Makabe, H.; Konno, H.; Tanimoto, H.; Tanaka, A.; Oritani, T. *Synposium Papers of the 38th Symposium on the Chemistry of Natural Products*; Sendai, Japan, 1996; p 265. (c) Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **1998** *54*, 6329. (d) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067. Also, see: (e) Szlosek, M.; Peyrat, J.-F.; Chaboche, C.; Franck, X.; Hocquemiller, R.; Figadére, B. *New J. Chem.* **2000**, *24*, 337.

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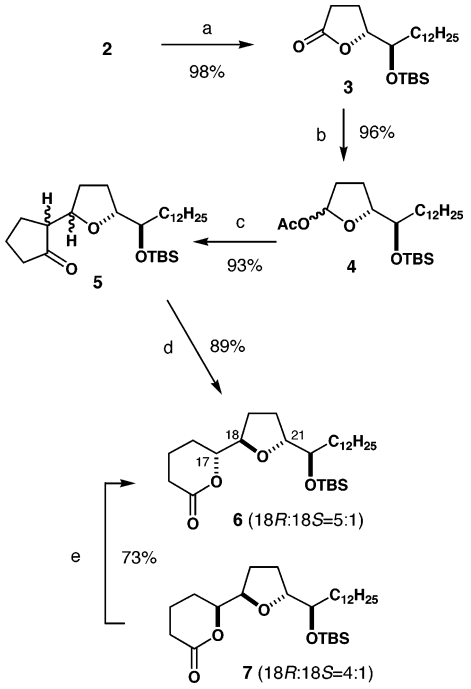
SCHEME 2[a]

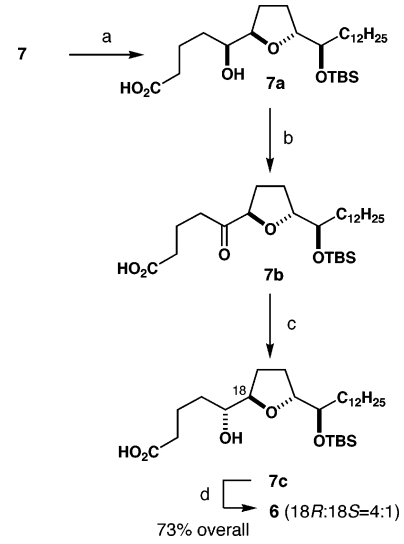


[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 98%; (b) DIBAL, CH_2Cl_2, −78 °C then Ac_2O, Et_3N, DMAP, −78 °C to rt, 96%; (c) 1-(trimethylsilyloxy)cyclopentene, $BF_3{\cdot}Et_2O$, propionitrile, −78 to −28 °C, 93%; (d) mCPBA, Na_2HPO_4, CH_2Cl_2, rt, 89% (**6**:**7** ca. 2:3); (e) see Scheme 3, 73% overall.

ing γ-hydroxyalkylated-γ-lactones.[4c] (−)-Muricatacin (**2**) thus obtained was initially converted to TBS ether **3** in 98% yield (Scheme 2). Silyl ether **3** was transformed to acetal **4** in 96% yield by a one-pot reduction/acetylation sequence.[9] The Lewis acid-catalyzed assembly of **4** with 1-(trimethylsilyloxy)cyclopentene produced an inseparable mixture of diastereomeric ketone **5** in 93% yield. Baeyer−Villiger oxidation of **5** with mCPBA under buffered condition provided δ-lactones **6** (18*R*:18*S* 5:1) and **7** (18*R*:18*S* 4:1) in 89% yield (**6**/**7** ca. 2:3). Lactone **7** was isomerized to **6** in 73% overall yield via four steps (Scheme 3): hydrolysis of lactone **7** followed by Dess−Martin oxidation provided ketone **7b** whose stereoselective reduction with L-Selectride and subsequent lactonization gave lactone **6** in good yield.

Reduction of **6** (18*R*:18*S* 5:1) with diisobutylaluminum hydride provided lactol **8**, the sodium alkoxide derivative of which subsequently underwent Wittig olefination with phosphonium compound **9**[10] to give olefin **10** in 83% yield (Scheme 4). Olefin **10** was oxidized with mCPBA to provide epoxide whose epoxide-opening with CSA gave tetrahydropyran **11** (39%) and **12** along with inseparable isomers (59%). The latter compounds comprised primarily of **12**, by isomerization and then chromatographic separation, gave the desired tetrahydropyran **11** as a single isomer. The pure compound **11** was thus obtained in 79% total yield from **10**. This isomerization was conducted as follows (Scheme 5): TPAP-NMO oxidation of **12** followed by epimerization at the C13 center and stereoselective

SCHEME 3[a]



[a] Reagents and conditions: (a) aq NaOH, MeOH, rt; (b) Dess−Martin periodinane, CH_2Cl_2, rt; (c) L-Selectride, THF, −78 °C; (d) PPTS, benzene, reflux, 73% overall.

reduction with $Zn(BH_4)_2$ yielded **11** favoring separable (12*S*)-isomer (12*S*:12*R* 23:1) in 68% overall yield from **12**. Protection of alcohol **11** as TBS ether **13** (98%), followed by hydrogenation of the benzyl ether with Pearlman's catalyst quantitatively provided alcohol **14**. Treatment of this alcohol with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine gave triflate **15** in 99% yield and subsequent reaction with a lithium enolate generated from the known α-thiophenyl γ-lactone **16**[11] provided lactone **17** in 86% yield. Thiophenyl lactone **17** was treated with mCPBA to give sulfoxide whose elimination afforded *O*-TBS muconin (**18**) in 97% overall yield. Removal of the TBS group of **18** with acetyl chloride in methanol furnished (+)-muconin (**1**) in 96% yield, whose spectroscopic and analytical data were consistent with those of the natural product[12] [[α]$_D$ +12.5 (*c* 0.80, $CHCl_3$); lit.[3a] [α]$_D$ +12.3 (*c* 0.80, $CHCl_3$); lit.[3d,e] [α]$_D$ +12.9 (*c* 0.21, $CHCl_3$); lit.[3b] [α]$_D$ +13.5 (*c* 0.28, $CHCl_3$)].

The total synthesis of (+)-muconin (**1**) starting with (−)-muricatacin (**2**) was thus successfully achieved. A chiral γ-lactone building block prepared via α-C−H functionalization of THF was used here for the synthesis of complex acetogenins. The present approach to (+)-muconin (**1**) facilitates the production of structural analogues useful for biological evaluation.

Experimental Section

(*R*)-Dihydo-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]furan-2(3*H*)-one (3). To a solution of (−)-muricatacin (**2**) (1.08 g, 3.80 mmol) in DMF (10 mL) were added imidazole (0.72 g, 10.6 mmol) and TBSCl (0.80 g, 5.32 mmol) at room temperature. After 10 h of stirring, the mixture was extracted with Et_2O and washed with H_2O and the extracts were dried over $MgSO_4$. Following solvent evaporation in vacuo, the residue was purified by silica gel chromatography (AcOEt/hexane 1:10) to give TBS ether **3** (1.49 g, 98%) as a colorless

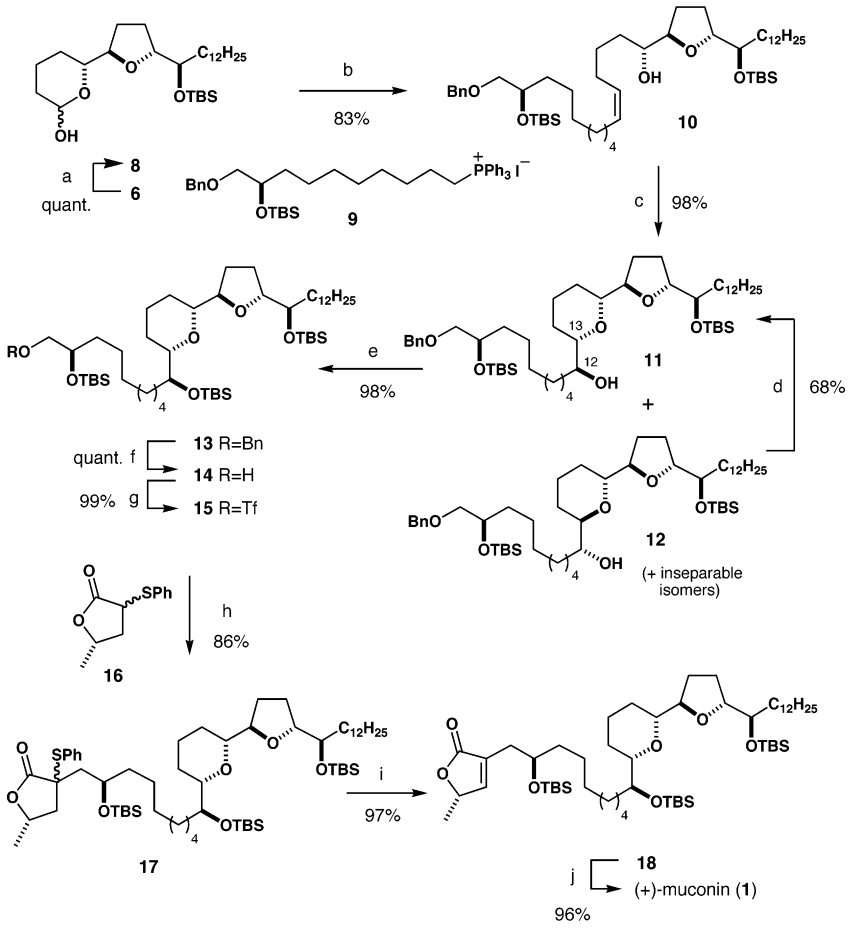
(9) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317.

(10) For preparation of this compound, see the Supporting Information.

(11) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991.

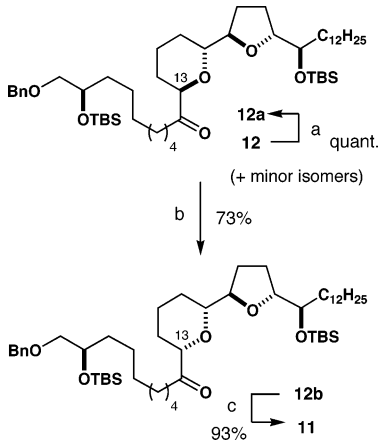
(12) For $^1H/^{13}C$ NMR spectra of synthetic and natural (+)-muconin, see the Supporting Information.

SCHEME 4[a]



[a] Reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C, quant.; (b) NaHMDS, THF, −78 °C then **9**, *n*-BuLi, THF, −78 °C to rt, 83% from **8**; (c) (i) mCPBA, CH_2Cl_2, rt, (ii) CSA, CH_2Cl_2, rt, **11** (39%), **12** (+ isomers) (59%); (d) see Scheme 5, 68% overall; (e) TBSCl, imidazole, DMF, rt, 98%; (f) $Pd(OH)_2$-C, H_2, AcOEt, rt, quant.; (g) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, 99%; (h) LiHMDS, **16**, HMPA, THF, −78 °C to rt, 86%; (i) (i) mCPBA, CH_2Cl_2, 0 °C, (ii) toluene, reflux, 97% overall; (j) cat. AcCl, MeOH, rt, 96%.

SCHEME 5[a]



[a] Reagents and conditions: (a) TPAP, NMO, 4AMS, MeCN, CH_2Cl_2, rt, quant.; (b) K_2CO_3, MeOH, THF, rt, then chromatographic separation, 73%; (c) $Zn(BH_4)_2$, CH_2Cl_2, −78 to 0 °C, **11** (93%), 12-*epi*-**11** (4%).

oil. $[\alpha]_D$ −19.9 (*c* 1.37, $CHCl_3$); IR (neat) ν_{max} 2926, 1784, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.48 (ddd, 1H, J = 7.7, 6.4, 4.6 Hz), 3.67 (dt, 1H, J = 6.4, 4.4 Hz), 2.63−2.39 (m, 2H), 2.20 (m, 1H), 2.03 (m, 1H), 1.59 (m, 1H), 1.46−1.23 (m, 21H), 0.93−0.84 (m, 12H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 81.6, 74.2, 32.7, 31.9, 29.74, 29.67, 29.64, 29.57, 29.54, 29.36, 28.6, 25.8, 25.3, 23.7, 22.7, 18.1, 14.1, −4.38, −4.41; HRMS (FAB) calcd for $C_{23}H_{47}O_3Si$ (MH^+) 399.3296, found 399.3288.

(*R*)-Tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-tridecyl]furan-2-yl Acetate (4). To a solution of **3** (0.96 g, 2.41 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added diisobutylaluminum hydride (0.93 M in hexane, 2.85 mL, 2.65 mmol). After 25 min of stirring, Et_3N (1.28 mL, 9.64 mmol), Ac_2O (0.45 mL, 4.82 mmol), and DMAP (294 mg, 2.41 mmol) were added and the mixture was allowed to warm to 0 °C over a period of 5 min. At room temperature, the mixture was stirred for 40 min, treated with H_2O, and filtered through a Celite pad. The filtrate was extracted with Et_2O and the extracts were dried over $MgSO_4$. Following solvent evaporation, the residue was purified by silica gel chromatography (AcOEt/hexane 1:6) to give acetate **4** (1.02 g, 96%) as a colorless oil. IR (neat) ν_{max} 2928, 1749, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.33−6.29 (m, 0.7H), 6.28−6.25 (m, 0.3H), 4.20 (dt, 0.7H, J = 7.7, 5.1 Hz), 3.99 (dt, 0.3H, J = 10.1, 6.4 Hz), 3.62 (m, 1H), 2.15−1.67 (m, 4H), 2.03 (s, 2.1H), 2.01 (s, 0.9H), 1.50−1.20 (m, 22H), 0.91−0.85 (m, 12H), 0.07 (s, 0.9H), 0.06 (s, 2.1H), 0.05 (s, 2.1H), 0.04 (s, 0.9H); HRMS (FAB) calcd for $C_{25}H_{50}O_4SiNa$ ($M + Na)^+$ 465.3378, found 465.3392.

(*R*)-Tetrahydro-6-[(2*RS*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]furan-2-yl]pyran-2-one (6) and (*S*)-Tetrahydro-6-[(2*RS*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]furan-2-yl]pyran-2-one (7). To a solution of acetate **4** (1.02 g, 2.31 mmol) in EtCN (60 mL)

at −78 °C were added 1-(trimethylsilyloxy)cyclopentene (0.61 mL, 3.46 mmol) and BF_3·Et_2O (0.21 mL, 2.31 mmol). The mixture, warmed to −28 °C over a period of 85 min, was treated with Et_3N (0.4 mL) and then extracted with Et_2O and washed with sat. $NaHCO_3$ and the extracts were dried over $MgSO_4$. Following solvent evaporation in vacuo, the residue was purified by silica gel chromatography (AcOEt/hexane 1:10) to give ketone **5** (1.00 g, 93%) as a colorless oil. To a solution of ketone **5** (1.00 g, 2.14 mmol) in CH_2Cl_2 (30 mL) at room temperature were added Na_2HPO_4 (0.911 g, 6.42 mmol) and mCPBA (0.712 g, 2.36 mmol). After 14.5 h of stirring, the mixture was treated with sat. $Na_2S_2O_3$, extracted with Et_2O, and washed with sat. $NaHCO_3$. The organics were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash chromatography (AcOEt/hexane 1:4) to afford lactones **6** (0.363 g, 35%; 18*R*:18*S* 5:1) and **7** (0.556 g, 54%; 18*R*:18*S* 4:1) as a colorless oil. **Threo lactone 6:** IR (neat) ν_{max} 2926, 1747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (m, 1H), 4.06−3.75 (m, 2H), 3.58 (m, 1H), 2.65−2.35 (m, 2H), 2.05−1.60 (m, 8H), 1.50−1.20 (m, 22H), 0.90−0.85 (m, 12H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, an asterisk indicates the minor (18*S*)-isomer) δ 171.4, 171.2*, 83.2*, 82.8, 81.43*, 81.37, 80.0, 79.6*, 74.9, 74.6*, 33.1, 33.0*, 31.9, 29.9, 29.8, 29.7, 29.61, 29.57, 29.56, 29.3, 27.62, 27.56, 27.2*, 27.0*, 25.9, 25.5, 25.3*, 24.6, 24.2*, 22.7, 18.6*, 18.5, 18.2, 14.1, −4.18*, −4.24, −4.6, −4.7*; HRMS (FAB) calcd for $C_{28}H_{55}O_4Si$ (MH^+) 483.3872, found 483.3872. **Erythro lactone 7**: IR (neat) ν_{max} 2930, 1747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, an asterisk indicates the minor (18*S*)-isomer) δ 4.30* (m), 4.15 (m, 1H), 3.96−3.83 (m, 2H), 3.55 (m, 1H), 2.65−2.39 (m, 2H), 2.19−1.56 (m, 8H), 1.45−1.20 (m, 22H), 0.89 (s, 9H), 0.91−0.85 (m, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, an asterisk indicates the minor (18*S*)-isomer) δ 171.2, 82.7, 82.6*, 82.4, 81.9*, 80.3, 80.1*, 75.1, 74.2*, 33.5*, 33.1, 31.8, 29.8, 29.7, 29.59, 29.56, 29.51, 29.50, 29.3, 28.9, 28.2*, 27.5, 26.3*, 25.9, 25.4, 25.3*, 24.92, 24.86*, 22.6, 18.2, 18.13, 18.09*, 14.0, −4.2, −4.3*, −4.6*, −4.7; HRMS (FAB) calcd for $C_{28}H_{55}O_4Si$ (MH^+) 483.3872, found 483.3860.

Isomerization of Lactone 7 to 6. To a solution of lactone **7** (1.00 g, 2.07 mmol) in MeOH (10 mL) at room temperature was added 20% aq NaOH (1.5 mL, 1.41 mmol). After 40 min of stirring, the mixture was concentrated in vacuo and the residue was acidified with 1 N HCl and extracted with CH_2Cl_2 and the extracts were dried over $MgSO_4$. Removal of the solvent in vacuo provided crude hydroxyl acid **7a** (1.03 g, quant.) for use in the following reaction without further purification. To a solution of crude acid **7a** (1.03 g, 2.06 mmol) in CH_2Cl_2 (20 mL) at room temperature was added Dess−Martin periodinane (1.04 g, 2.47 mmol). After 3 h of stirring, the mixture was treated with sat. $Na_2S_2O_3$ and extracted with Et_2O and the extracts were dried over $MgSO_4$. The solvent was removed in vacuo to give a residue whose purification by silica gel chromatography (MeOH/$CHCl_3$ 1:15) provided ketone **7b** (0.901 g, 88%) as a colorless oil. Ketone **7b** (0.901 g, 1.81 mmol) in THF (30 mL), cooled to −78 °C, was treated with L-Selectride (1.0 M in THF, 3.62 mL, 3.62 mmol) and stirred for 10 min. The mixture, warmed to 0 °C, was treated with sat. NH_4Cl and then extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give crude hydroxycarboxylic acid **7c** (0.895 g, 99%) as a colorless oil. To this acid **7c** (0.895 g, 1.79 mmol) in benzene (15 mL) was added PPTS (0.045 g, 0.18 mmol) at room temperature. After 14 h of stirring under reflux, the mixture was treated with sat. $NaHCO_3$ and extracted with Et_2O and the organics were dried over $MgSO_4$. After solvent removal in vacuo, the residue was purified by silica gel flash chromatography (AcOEt/hexane 1:4) to give lactones **6** (0.728 g, 84%) and **7** (0.034 g, 4%) as a colorless oil. **Keto acid 7b:** IR (neat) ν_{max} 2926, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.36−4.21 (m, 1H), 4.00 (m, 1H), 3.58 (m, 1H), 2.78−2.55 (m, 2H), 2.38 (t, 2H, J = 7.2 Hz), 2.27−1.55 (m, 6H), 1.55−1.20 (m, 23H), 0.91−0.84 (m, 12H), 0.08−0.04 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, an asterisk indictes the minor (18*S*)-isomer) δ 212.1, 211.7*, 179.2*, 179.1, 83.7*, 83.6, 83.4, 83.0*, 74.7, 74.3*, 37.4*, 36.7, 33.7*, 33.12, 33.08*, 33.01, 29.3, 29.0*, 27.4, 26.9*, 25.89, 25.86, 25.5, 25.3*, 22.6, 18.2, 18.1*, 18.0, 14.13, 14.06, −4.3, −4.4*, −4.6; HRMS (FAB) calcd for $C_{28}H_{55}O_5Si$ (MH^+) 499.3821, found 499.3835.

(*Z*,1*R*,14*R*)-15-(Benzyloxy)-1-[(2*RS*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]furan-2-yl]-pentadec-5-en-1-ol (10). To a solution of **6** (0.754 g, 1.564 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added diisobutylaluminum hydride (0.93 M in hexane, 1.68 mL, 1.564 mmol). After 35 min of stirring, the mixture was treated with 28% NH_4OH and stirred at room temperature for 40 min. With Celite addition, the whole mixture was stirred at room temperature for 20 min and filtered. Solvent evaporation followed by purification of the residue by silica gel chromatography (AcOEt/hexane 1:4) afforded lactol **8** (0.749 g, quant.) as a colorless oil. To phosphonium iodide **9** (0.766 g, 1.00 mmol) in THF (8 mL) at −78 °C was added *n*-BuLi (1.58 M in hexane, 0.63 mL, 1.00 mmol) and the mixture was stirred for 10 min and then at 0 °C for 25 min. THF solution of the sodium alkoxide, prepared at −78 °C by addition of NaHMDS (1.0 M in THF, 0.48 mL, 0.48 mmol) to **8** (0.23 g, 0.476 mmol) in THF (4 mL), was added to the phosphorane solution over a period of 10 min. The mixture was stirred at −78 °C for 10 min and then at 0 °C for 10 min and finally for 20 min at room temperature. Following treatment with sat. NH_4Cl and extraction with Et_2O, the organics were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (AcOEt/hexane 1:15) to give olefin **10** (0.335 g, 83%) as a colorless oil. **Lactol 8:** IR (neat) ν_{max} 3420, 2926 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (br s, 0.55H), 4.75 (m, 0.45H), 4.10−3.30 (m, 4H), 3.05−2.42 (m, 1H), 1.95−1.20 (m, 32H), 0.88 (s, 9H), 1.00−0.85 (m, 3H), 0.11−0.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.3, 91.6, 82.0, 81.9, 81.2, 78.9, 74.6, 74.4, 71.5, 32.4, 32.03, 31.96, 31.8, 29.94, 29.90, 29.72, 29.68, 29.67, 29.62, 29.4, 28.34, 28.29, 27.1, 26.9, 26.6, 26.10, 26.08, 26.01, 26.00, 22.7, 21.8, 18.3, 18.2, 17.1, 14.2, −4.1, −4.2, −4.5; HRMS (FAB) calcd for $C_{28}H_{56}O_4SiNa$ $(M + Na)^+$ 507.3848, found 507.3864. **Olefin 10:** IR (neat) ν_{max} 3591, 3485, 2928, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, an asterisk indicates the minor (18*S*)-isomer) δ 7.37−7.23 (m, 5H), 5.42−5.28 (m, 2H), 4.52 (s, 2H), 3.95−3.73 (m, 3H), 3.58 (m, 1H), 3.42−3.33 (m, 3H), 2.65* (d, 0.16H, J = 5.3 Hz), 2.39 (d, 0.84H, J = 3.7 Hz), 2.10−1.15 (m, 46H), 0.92−0.80 (m, 21H), 0.10−0.00 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 130.2, 129.4, 128.3, 127.6, 127.4, 82.4, 82.3, 75.3, 74.9, 74.0, 73.3, 71.5, 34.7, 33.2, 33.0, 31.9, 29.9, 29.8, 29.68, 29.64, 29.60, 29.5, 29.4, 29.3, 28.6, 28.5, 27.3, 27.2, 26.0, 25.9, 25.7, 25.4, 25.2, 22.7, 18.3, 18.2, 14.1, −4.1, −4.3, −4.6, −4.7; HRMS (FAB) calcd for $C_{51}H_{97}O_5Si_2$ (MH^+) 845.6878, found 845.6893.

(1*S*,9*R*)-10-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-1-[(2*S*,6*R*)-tetrahydro-6-[(2*R*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]furan-2-yl]-2*H*-pyran-2-yl]decan-1-ol (11) and (1*R*,9*R*)-10-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-1-[(2*R*,6*R*)-tetrahydro-6-[(2*R*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]furan-2-yl]-2*H*-pyran-2-yl]decan-1-ol (12) + Isomers. To a solution of olefin **10** (0.80 g, 0.948 mmol) in CH_2Cl_2 (20 mL) at room temperature were added Na_2HPO_4 (0.296 g, 2.09 mmol) and mCPBA (0.315 g, 1.04 mmol). After 70 min of stirring, the mixture was treated with sat. $Na_2S_2O_3$ and extracted with Et_2O and the combined organics were washed with sat. $NaHCO_3$ and dried over $MgSO_4$. On solvent evaporation, the crude residue was subsequently used without purification. To a solution of epoxide (0.804 g, 0.935 mmol) in CH_2Cl_2 (20 mL) at room temperature was added CSA (0.011 g, 0.047 mmol). After 55 min of stirring, the mixture was extracted with Et_2O and washed with sat. $NaHCO_3$ and the organics were dried over $MgSO_4$. Following solvent evaporation in vacuo, the residue was purified by silica gel flash chromatography (Et_2O/hexane 1:6) to give alcohols **11** (0.312 g, 39%)

as a single isomer and **12** along with inseparable minor isomers (0.475 g, 59%) as a colorless oil. **Alcohol 11:** $[\alpha]_D$ +10.1 (*c* 0.57, $CHCl_3$); IR (neat) ν_{max} 3580, 3468, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.52 (s, 2H), 3.92−3.77 (m, 3H), 3.55 (m, 1H), 3.41 (m, 1H), 3.39 (dd, 1H, *J* = 9.8, 5.6 Hz), 3.36 (dd, 1H, *J* = 9.5, 5.4 Hz), 3.30 (ddd, 1H, *J* = 11.2, 5.4, 1.7 Hz), 3.16 (ddd, 1H, *J* = 11.2, 6.8, 1.5 Hz), 1.93−1.83 (m, 3H), 1.73−1.19 (m, 43H), 0.92−0.85 (m, 21H), 0.88 (m, 21H), 0.11 (s, 3H), 0.07 (s, 3H), 0.055 (s, 3H), 0.047 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.2, 127.5, 127.3, 82.7, 81.2, 80.8, 80.2, 75.3, 74.9, 74.2, 73.3, 71.6, 34.8, 33.0, 32.7, 32.0, 29.9, 29.8, 29.73, 29.70, 29.67, 29.63, 29.4, 28.2, 27.9, 27.3, 27.2, 26.1, 26.0, 25.6, 25.5, 25.3, 23.1, 22.7, 18.4, 18.3, 14.2, −3.9, −4.2, −4.6, −4.7; HRMS (FAB) calcd for $C_{51}H_{97}O_6Si_2$ (MH^+) 861.6827, found 861.6830. **Alcohol 12 (+ inseparable minor isomers):** ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 4.52 (s, 2H), 4.07−3.27 (m, 7H), 3.39 (dd, 1H, *J* = 9.5, 5.5 Hz), 3.35 (dd, 1H, *J* = 9.7, 5.5 Hz), 1.95−1.20 (m, 47H, including OH), 0.88 (s, 18H), 0.92−0.80 (m, 3H), 0.10−0.02 (m, 12H).

Isomerization of 12 to 11. To a solution of alcohol **12** along with minor diastereomeric alcohols (0.395 g, 0.459 mmol) in MeCN−CH_2Cl_2 (2:1 v/v, 15 mL) at room temperature were added 4AMS (0.23 g), NMO (0.081 g, 0.689 mmol), and TPAP (8.1 mg, 0.023 mmol). After 2 h of stirring, the mixture was concentrated in vacuo to give the residue whose purification by silica gel chromatography (AcOEt/hexane 1:6) afforded ketone **12a** (0.349 g, quant.) as a colorless oil. Ketone **12a**, dissolved in MeOH−THF (5:2 v/v, 14 mL), was treated with K_2CO_3 (0.19 g, 1.38 mmol) at room temperature. After 5 h of stirring, the mixture was concentrated in vacuo, extracted with Et_2O, and washed with sat. NH_4Cl. The extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash chromatography (AcOEt/hexane 1:20) to afford ketone **12b** (0.29 g, 73%) as a colorless oil. To ketone **12b** (0.28 g, 0.326 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added $Zn(BH_4)_2$ (0.14 M in hexane, 2.76 mL, 0.386 mmol). The mixture was stirred for 15 min, then at 0 °C for 45 min, extracted with Et_2O, and washed with sat. NH_4Cl and the extracts were dried over $MgSO_4$. Following solvent evaporation, purification of the residue by silica gel flash chromatography (AcOEt/hexane 1:10) provided alcohols **11** (0.26 g, 93%) and 12-*epi*-**11** (0.011 g, 4%) as a colorless oil. **Ketone 12b:** $[\alpha]_D$ −7.4 (*c* 1.86, $CHCl_3$); IR (neat) ν_{max} 2928, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.52 (s, 2H), 3.98−3.90 (m, 2H), 3.85−3.74 (m, 2H), 3.59 (m, 1H), 3.43−3.28 (m, 3H), 2.60 (dd, 2H, *J* = 7.6, 7.1 Hz), 2.00−1.20 (m, 44H), 0.93−0.84 (m, 21H), 0.09 (s, 3H), 0.07 (s, 3H), 0.053 (s, 3H), 0.046 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 138.4, 128.2, 127.5, 127.3, 83.1, 82.7, 81.1, 80.3, 75.1, 74.9, 73.3, 71.5, 37.8, 34.8, 32.8, 32.0, 29.9, 29.71, 29.68, 29.67, 29.57, 29.4, 28.11, 28.06, 27.7, 26.8, 26.1, 26.0, 25.7, 25.3, 23.2, 23.0, 22.7, 18.3, 18.2, 14.2, −4.0, −4.3, −4.63, −4.65; HRMS (FAB) calcd for $C_{51}H_{94}O_6Si_2$ (MH^+) 859.6671, found 859.6653.

(1*R*,9*R*)-10-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-1-[(2*S*,6*R*)-tetrahydro-6-[(2*R*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyl dimethylsilyloxy)tridecyl]furan-2-yl]-2*H*-pyran-2-yl]decan-1-ol (12-*epi*-11): $[\alpha]_D$ +13.4 (*c* 0.69, $CHCl_3$); IR (neat) ν_{max} 3450, 2928, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 4.52 (s, 2H), 3.93−3.77 (m, 3H), 3.68 (m, 1H), 3.57 (m, 1H), 3.42−3.28 (m, 4H), 1.95−1.20 (m, 46H), 0.93−0.80 (m, 21H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.2, 127.5, 127.3, 82.5, 81.4, 80.5, 79.9, 75.1, 74.9, 73.35, 73.28, 71.6, 34.8, 32.8, 32.0, 31.7, 29.9, 29.81, 29.76, 29.73, 29.70, 29.67, 29.62, 29.4, 28.3, 27.7, 27.4, 26.09, 26.06, 26.04, 25.97, 25.7, 25.3, 24.0, 23.0, 22.7, 18.4, 18.3, 14.2, −4.0, −4.2, −4.6, −4.7; HRMS (FAB) calcd for $C_{51}H_{97}O_6Si_2$ (MH^+) 861.6827, found 861.6808.

(1*S*,9*R*)-10-(Benzyloxy)-1-[(2*S*,6*R*)-tetrahydro-6-[(2*R*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]-furan-2-yl]-2*H*-pyran-2-yl]-1,9-bis(*tert*-butyldimethylsilyloxy)decane (13). To a solution of alcohol **11** (0.50 g, 0.582 mmol) in DMF (10 mL) at room temperature were added imidazole (0.095 g, 1.40 mmol) and TBSCl (0.106 g, 0.70 mmol). After 10 h of stirring, the mixture was extracted with Et_2O, washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (AcOEt/hexane 1:30) to afford TBS ether **13** (0.56 g, 98%) as a colorless oil. $[\alpha]_D$ +2.6 (*c* 1.44, $CHCl_3$); IR (neat) ν_{max} 2928, 1464, 1252, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.52 (s, 2H), 3.92−3.77 (m, 3H), 3.63 (m, 1H), 3.56 (m, 1H), 3.42−3.24 (m, 4H), 1.92−1.18 (m, 46H), 0.92−0.85 (m, 30H), 0.09 (s, 3H), 0.06−0.01 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.2, 127.5, 127.3, 82.4, 81.1, 80.7, 80.2, 75.2, 74.9, 74.4, 73.3, 71.6, 34.8, 32.8, 32.0, 31.9, 30.0, 29.90, 29.88, 29.75, 29.71, 29.69, 29.4, 27.9, 27.7, 27.0, 26.1, 26.02, 25.99, 25.8, 25.3, 25.1, 23.4, 22.8, 18.4, 18.2, 14.2, −4.0, −4.15, −4.24, −4.5, −4.6, −4.7; HRMS (FAB) calcd for $C_{57}H_{111}O_6Si_3$ (MH^+) 975.7692, found 975.7685.

(2*R*,10*S*)-10-[(2*S*,6*R*)-Tetrahydro-6-[(2*R*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]furan-2-yl]-2*H*-pyran-2-yl]-2,10-bis(*tert*-butyldimethylsilyloxy)decan-1-ol (14). To a solution of **13** (0.186 g, 0.190 mmol) in AcOEt (9 mL) was added $Pd(OH)_2$-C (20 wt %, 19 mg) at room temperature. After 100 min of stirring under hydrogen atmosphere, the mixture was filtered through a Celite pad and then concentrated in vacuo to give sufficiently pure alcohol **14** (0.17 g, quant.) as a colorless oil. $[\alpha]_D$ −4.9 (*c* 1.07, $CHCl_3$); IR (neat) ν_{max} 3479, 2928, 1462, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, D_2O exchange) δ 3.93−3.82 (m, 2H), 3.72 (m, 1H), 3.62 (m, 1H), 3.58−3.50 (m, 2H), 3.42 (dd, 1H, *J* = 10.8, 5.3 Hz), 3.33−3.23 (m, 2H), 1.93−1.17 (m, 46H), 0.92−0.82 (m, 30H), 0.10−0.02 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.4, 81.1, 80.6, 80.2, 75.2, 74.3, 73.0, 66.3, 34.0, 32.7, 31.9, 31.8, 29.9, 29.83, 29.78, 29.68, 29.64, 29.62, 29.60, 29.3, 27.8, 27.6, 27.0, 26.1, 25.9, 25.8, 25.7, 25.3, 25.0, 23.3, 22.7, 18.3, 18.2, 18.1, 14.1, −4.1, −4.3, −4.4, −4.58, −4.63, −4.8; HRMS (FAB) calcd for $C_{50}H_{105}O_6Si_3$ (MH^+) 885.7223, found 885.7224.

(2*R*,10*S*)-10-[(2*S*,6*R*)-Tetrahydro-6-[(2*R*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]furan-2-yl]-2*H*-pyran-2-yl]-2,10-bis(*tert*-butyldimethylsilyloxy)decyl Trifluoromethanesulfonate (15). To a solution of alcohol **14** (0.17 g, 0.19 mmol) in CH_2Cl_2 (8 mL) at −78 °C were added 2,6-lutidine (0.068 mL, 0.583 mmol) and Tf_2O (0.039 mL, 0.232 mmol). The mixture was stirred for 5 min, then at room temperature for 5 min, extracted with Et_2O, and washed with sat. $NaHCO_3$. The extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (AcOEt/hexane 1:30) to afford triflate **15** (0.191 g, 99%) as a colorless oil. $[\alpha]_D$ −4.2 (*c* 1.09, $CHCl_3$); IR (neat) ν_{max} 2930, 1418, 1211, 1148, 953 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38 (dd, 1H, *J* = 9.9, 3.9 Hz), 4.31 (dd, 1H, *J* = 9.9, 6.4 Hz), 3.98−3.80 (m, 3H), 3.63 (m, 1H), 3.55 (m, 1H), 3.35−3.22 (m, 2H), 1.92−1.17 (m, 46H), 0.92−0.80 (m, 30H), 0.10−0.02 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.8, 116.5, 82.4, 81.1, 80.6, 80.3, 79.4, 75.2, 74.3, 69.9, 33.8, 32.7, 31.9, 31.8, 29.83, 29.82, 29.69, 29.64, 29.63, 29.59, 29.5, 29.4, 27.9, 27.6, 27.0, 26.1, 25.9, 25.71, 25.67, 25.0, 24.8, 23.3, 22.7, 18.3, 18.2, 18.0, 14.1, −4.1, −4.3, −4.6, −4.73, −4.76, −4.82; HRMS (FAB) calcd for $C_{51}H_{103}O_8F_3Si_3SNa$ (M + Na)$^+$ 1039.6535, found 1039.6545.

(*S*)-Dihydro-3-[(2*R*,10*S*)-10-[(2*S*,6*R*)-tetrahydro-6-[(2*R*,5*R*)-tetrahydro-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-tridecyl]furan-2-yl]-2*H*-pyran-2-yl]-2,10-bis(*tert*-butyldimethylsilyloxy)decyl]-5-methyl-3-(phenylthio)furan-2(3*H*)-one (17). To a solution of LiHMDS (1.0 M in THF, 0.364 mL, 0.364 mmol) in THF at −78 °C was added lactone **16** (0.076 g, 0.364 mmol) in THF (2 mL). The mixture was stirred for 10 min, then at 0 °C for 7 min, and again cooled to −78 °C. After 11 min of stirring, HMPA (1.2 mL) was added and then after 6 min, triflate **15** (0.191 g, 0.188 mmol) in THF (2.8 mL) was added. After 10 min, the mixture was allowed to warm to 0 °C over a period of 15 min, then stirred at room temperature for 10 min, extracted with Et_2O, and washed with sat. NH_4-

Cl, and the organics were dried over $MgSO_4$. With solvent evaporation, the residue was purified by silica gel flash chromatography (Et_2O/hexane 1:10) to give lactone **17** (0.175 g, 86%) as a colorless oil. IR (neat) ν_{max} 2928, 1771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59−7.51 (m, 2H), 7.44−7.29 (m, 3H), 4.55 (m, 1H), 4.25 (m, 0.5H), 3.93−3.79 (m, 2.5H), 3.62 (m, 1H), 3.53 (m, 1H), 3.35−3.20 (m, 2H), 3.05 (m, 0.5H), 2.45 (dd, 0.5H, J = 13.9, 10.3 Hz), 2.31 (dd, 0.5H, J = 13.8, 5.5 Hz), 2.12−1.18 (m, 51.5H), 0.91−0.85 (m, 30H), 0.16−0.02 (m, 18H); HRMS (FAB) calcd for $C_{61}H_{114}O_7Si_3SNa$ $(M + Na)^+$ 1097.7495, found 1097.7513.

***O*-TBS-muconin (18).** To a solution of lactone **17** (0.092 g, 0.086 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added mCPBA (0.026 g, 0.086 mmol). After 20 min of stirring, Me_2S was added and the mixture was extracted with Et_2O and washed with sat. $Na_2S_2O_3$ and with sat. $NaHCO_3$. The organics were dried over $MgSO_4$. Following solvent evaporation, the crude sulfoxide (0.093 g, quant.) was used for subsequent reaction without purification. The sulfoxide (0.093 g, 0.086 mmol) in toluene (4 mL) was heated under reflux for 30 min and then concentrated in vacuo to give the residue whose purification by silica gel chromatography (AcOEt/hexane 1:7) afforded *O*-TBS-muconin (**18**) (0.080 g, 97%) as a colorless oil. $[\alpha]_D$ +5.2 (*c* 1.33, $CHCl_3$); IR (neat) ν_{max} 2930, 1761, 1252, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (br d, 1H, J = 1.5 Hz), 5.00 (ddd, 1H, J = 13.8, 6.8, 1.5 Hz), 4.00−3.82 (m, 3H), 3.62 (m, 1H), 3.55 (m, 1H), 3.35−3.23 (m, 2H), 2.45−2.40 (m, 2H), 1.92−1.18 (m, 46H), 1.42 (d, 3H, J = 6.8 Hz), 0.92−0.83 (m, 30H), 0.10−0.02 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 151.3, 130.9, 82.4, 81.1, 80.6, 80.2, 77.4, 75.1, 74.3, 70.2, 37.0, 32.73, 32.66, 31.90, 31.85, 29.9, 29.8, 29.73, 29.66, 29.63, 29.59, 29.3, 27.8, 27.6, 26.9, 26.0, 25.93, 25.86, 25.7, 25.1, 25.0, 23.3, 22.7, 19.0, 18.3, 18.1, 18.0, 14.1, −4.1, −4.3, −4.46, −4.49, −4.6, −4.8; HRMS (FAB) calcd for $C_{55}H_{109}O_7Si_3$ (MH^+) 965.7485, found 965.7449.

(+)-Muconin (1). To a solution of *O*-TBS-muconin **18** (0.150 g, 0.156 mmol) in MeOH (3 mL) was added 5% AcCl in MeOH (3 mL) at room temperature. After 30 min of stirring, the mixture was diluted with CH_2Cl_2, treated with $NaHCO_3$ (solid), and filtered through a Celite pad. With solvent evaporation, the residue was purified by column chromatography (AcOEt as eluent) on silica gel (prewashed with MeOH) to provide (+)-muconin (**1**) (0.094 g, 96%) as a colorless oil. (This compound was noted to undergo partial solidification with refrigeration (−38 °C) to give a low-melting waxy solid.) $[\alpha]_D$ +12.5 (*c* 0.80, $CHCl_3$); IR (neat) ν_{max} 3416, 2956, 2855, 1753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, 1H, J = 1.2 Hz), 5.05 (dq, 1H, J = 6.7, 1.2 Hz), 3.88 (m, 1H), 3.84 (m, 1H), 3.80 (m, 1H), 3.43 (m, 1H), 3.38 (m, 1H), 3.31 (m, 1H), 3.16 (m, 1H), 2.52 (m, 1H), 2.39 (dd, 1H, J = 15.3, 8.2 Hz), 2.30 (br s, 1H, OH), 1.98−1.87 (m, 3H), 1.78−1.23 (m, 45H, including 2 × OH), 1.43 (d, 3H, J = 6.7 Hz), 0.87 (t, 3H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 151.7, 131.1, 82.8, 81.2, 80.9, 80.0, 77.9, 74.1, 74.0, 69.9, 37.3, 33.4, 33.2, 32.5, 31.9, 29.7, 29.62, 29.60, 29.59, 29.56, 29.4, 29.3, 28.3, 28.2, 27.1, 27.0, 25.6, 25.5, 25.2, 22.9, 22.6, 19.1, 14.0; HRMS (FAB) calcd for $C_{37}H_{67}O_7$ (MH^+) 623.4889, found 623.4878.

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Supporting Information Available: Experimental procedures for the preparation of phosphonium reagent **9**; characterization data along with $^1H/^{13}C$ NMR spectra of new compounds and (+)-muconin (**1**); and determination of the stereochemistry of compounds **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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