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Late-Stage β-Epimerization. A Stereodivergent to Stereoconvergent Relay to the First Total Synthesis of (+)-Murolic Acid

Rodney A. Fernandes,*[a] Pradnya H. Patil,[a] and Asim K. Chowdhury[a]

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The first total synthesis of (+)-murolic acid is accomplished in 17 steps from ester **9** in 14.8 % overall yield. The key steps involve asymmetric dihydroxylation, orthoester Johnson–Claisen rearrangement and α-methylenation using Stiles reagent. A beneficial late stage β-epimerization reverted a stereodivergent relay to a stereoconvergent completion of an efficient synthesis of (+)-murolic acid.

Introduction

Naturally occurring plant glycosides have been known for a long time,[1] and the plant family of lichens has contributed to a few of them.[1] A few macrocyclic lipid glycosides have also been isolated.[1–3] The associated interesting bioactivities and the intriguing structural complexity in these molecules have provided the impetus towards developing new synthetic strategies for their chemical synthesis.[3] Rezanka et al.[4] isolated several new glycosides having murolic (**1**), protoconstipatic (**2**), and *allo*-murolic (**3**) acids as the aglycones and the oligosaccharide moiety made of one or two sugars (glucose and apiose or rhamnose or xylose or arabinose) linked through the C-18 hydroxy group of the aglycon (Figure 1). Five of these isolated glycosides **4a**–**e** have murolic acid (**1**) as the aglycon. Murolic acid belongs to the family of paraconic acids,[5] which constitute a small class of variously functionalized chiral γ-lactones. In addition to the presence of a $–CO_2H$ group at the β-position of the γ-butyrolactone ring, these compounds also bear an alkyl chain at the γ-carbon atom and either a methyl or a methylene group at the α-position. They display varied stereochemical relationships of substituents on the adjacent carbon atoms, and have been isolated from different species of *moss*, *lichens*, *fungi* and cultures of *Penicillium* sp.[6] In the past few years paraconic acids have been prominent synthetic targets due to their various pharmacological properties including antibacterial,[7] antifungal,[7b] antitumor,[8] and growth-regulating effects.[9] The activity arises mainly due to the α,β-unsaturated carbonyl system, which acts as a Michael acceptor to varied biological nucleophiles. A number of syntheses have been developed leading to these natural products either in racemic or enantiopure form using starting materials from the chiral pool, chiral auxiliaries, or by applying catalytic asymmetric methodologies.[5,10,11] In the course of our studies directed toward the enantioselective synthesis of paraconic acids[10,11] we became interested in the synthetically untouched molecule, murolic acid.

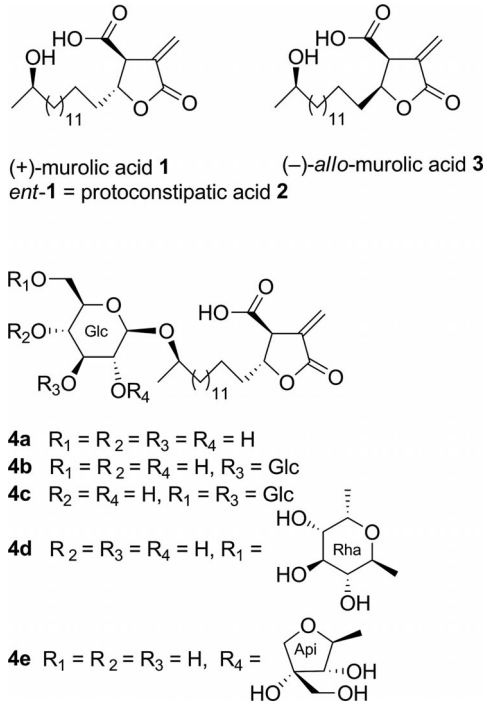

Figure 1. Structures of paraconic acids and murolic acid glycosides.

Herein, we report the first synthesis of (+)-murolic acid by utilizing asymmetric dihydroxylation,[12] orthoester Johnson–Claisen rearrangement,[13] and α-methylenation using Stiles reagent[14] as key steps. A beneficial late stage β-epimerization reverted the stereodivergent relay to a stereoconvergent first total synthesis of (+)-murolic acid.

[a] Department of Chemistry, Indian Institute of Technology Bombay,
Powai, Mumbai 400076, Maharashtra, India
E-mail: rfernand@chem.iitb.ac.in
http://www.chem.iitb.ac.in/~rfernand/default.htm

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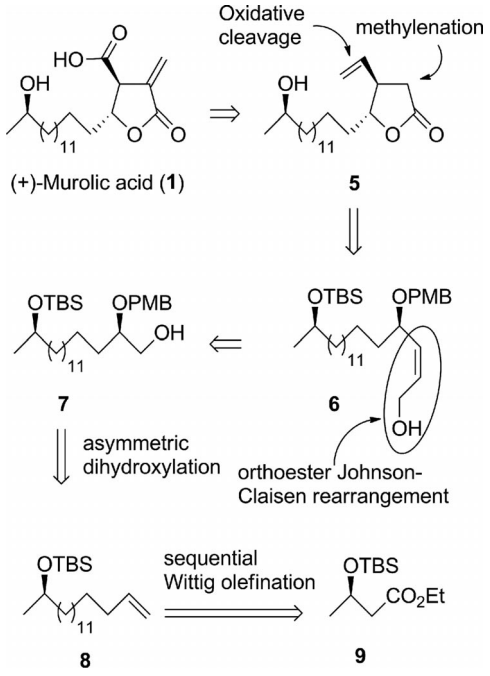
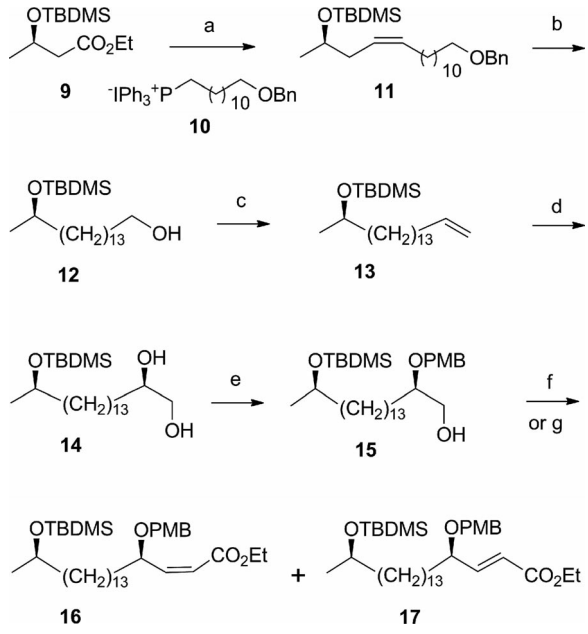
Results and Discussion

The retrosynthetic analysis of (+)-murolic acid is highlighted in Scheme 1. The lactone **5** is an advanced intermediate featuring a β-vinyl bond as a masked group for generation of -CO_2H at the β-position with the active α-position available for methylenation. The synthesis of lactone **5** was visualized through orthoester Johnson–Claisen rearrangement of allyl alcohol **6**. The latter could be assembled through Wittig olefination of aldehyde from **7**. The terminal diol **7** was planned through asymmetric dihydroxylation of **8**, with the latter being accessed through sequential Wittig olefination of the aldehyde from **9**.



Scheme 1. Retrosynthesis of (+)-murolic acid (**1**).

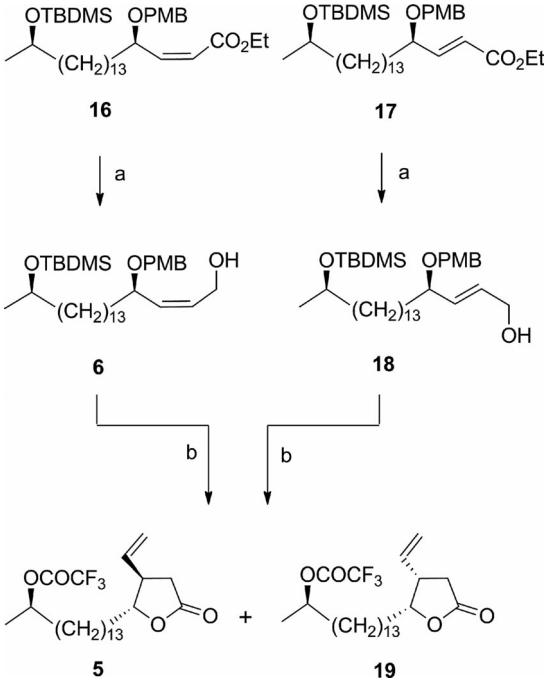
Accordingly, the forward synthesis was initiated from known compound **9**[15] (Scheme 2). DIBAL-H mediated reduction of the ester to the corresponding aldehyde and subsequent Wittig olefination with the requisite ylide from **10**[16] gave olefin **11** in 85% yield. Hydrogenation of **11** using Pearlman's catalyst in *i*PrOH solvent resulted in simultaneous reduction of the alkene bond and debenzylation, producing alcohol **12** in 65%yield. Performing the same reaction in EtOH gave **12** in 85% yield. Oxidation of the primary alcohol to aldehyde (Swern oxidation), followed by one-carbon Wittig olefination resulted in formation of terminal olefin **13** (86%).[17] The Sharpless asymmetric dihydroxylation of **13** using hydroquinidine (anthraquinone-1,4-diyl) diether [$(DHQD)_2AQN$] ligand[12b] provided the desired diol **14** in excellent yields (94%) and 95.5:4.5 *dr*.[18] The diol differentiation was manifested by following a standard procedure[19] by conversion into *p*-methoxybenzylidene (PMB) acetal, and DIBAL-H mediated reduction to deliver monoprotected PMB ether **15** (84%). Oxidation of the primary alcohol with Dess–Martin periodinane gave the corresponding aldehyde, and low-temperature Wittig olefination provided the mixture of α,β-unsaturated esters **16/17** (*Z*/*E* = 2.3:1). The mixture was efficiently separated by flash column chromatography to give **16** (68%) and **17** (29%). However, the same reaction using the Still–Gennari protocol delivered **16** in 81% and **17** in 7% isolated yields.[20]



Scheme 2. Synthesis of separable diastereomers **16** and **17**. *Reagents and conditions:* (a) i. DIBAL-H (1.2 equiv.), CH_2Cl_2, –78 °C, 1.5 h; ii. Wittig salt **10** (1.2 equiv.), *n*BuLi (1.2 equiv.), THF, –78 °C, 4 h, room temp., 6 h, 85%; (b) H_2, $Pd(OH)_2/C$, EtOH, balloon pressure, room temp., 2 h, 85%; (c) i. $(COCl)_2$ (1.5 equiv.), DMSO (3.0 equiv.), CH_2Cl_2, –78 °C, 10 min, alcohol **12**, 45 min, Et_3N (5.0 equiv.), CH_2Cl_2, –78 °C, 30 min, room temp., 1 h; ii. $Ph_3P^+MeI^-$(1.2 equiv.), *n*BuLi (1.2 equiv.), THF, 0 °C to room temp., 3 h, 86% (two steps); (d) $K_3Fe(CN)_6$ (3.0 equiv.), K_2CO_3 (3.0 equiv.), $(DHQD)_2AQN$ (1.12 mol-%), $K_2OsO_4{\cdot}2H_2O$ (0.4 mol-%), $MeSO_2NH_2$ (1.0 equiv.), *t*BuOH/H_2O (1:1), 0 °C, 24 h, 94%; (e) i. *p*-methoxy benzaldehyde dimethylacetal (2.0 equiv.), *p*TsOH·H_2O (cat.), benzene, room temp., 12 h; ii. DIBAL-H (3.0 equiv.), –78 °C, CH_2Cl_2, 3 h, 84% (two steps); (f) i. DMP (1.5 equiv.), CH_2Cl_2, room temp., 3 h; ii. $Ph_3P{=}CHCO_2Et$ (2.5 equiv.), MeOH, –40 °C to room temp., 24 h, **16** (68%), **17** (29%); (g) i. DMP (1.5 equiv.), CH_2Cl_2, room temp., 3 h; ii. $(CF_3CH_2O)_2POCH_2CO_2Et$ (1.1 equiv.), KHMDS (1.1 equiv.), 18-crown-6 (2.0 equiv.), THF, 0 °C, 15 min, then –78 °C, aldehyde from **15**, 2 h, **16** (81%), **17** (7%).

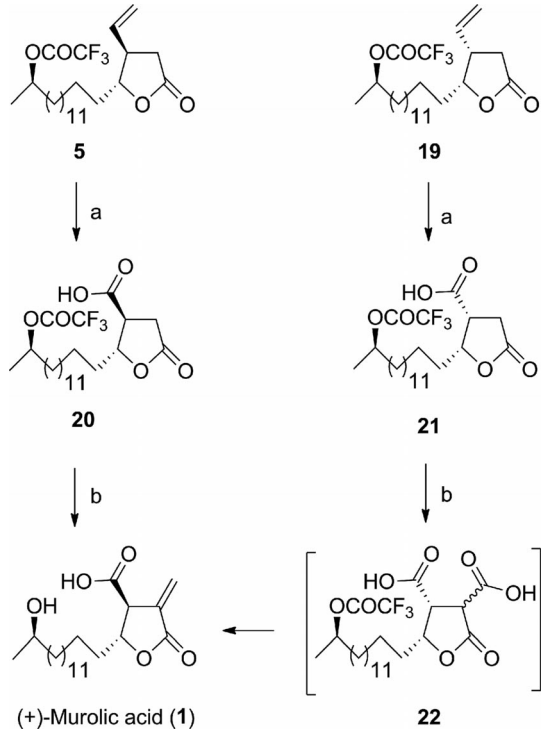
DIBAL-H mediated reduction of **16** and **17** provided primary allyl alcohols **6** (95%) and **18** (92%), respectively (Scheme 3). The lactone moiety was efficiently assembled by orthoester Johnson–Claisen rearrangement[13,11b] of allyl alcohol **6** with trimethylorthoacetate and catalytic propionic acid in toluene at reflux to deliver the γ,δ-unsaturated ester, which, upon one-pot lactonization using trifluoroacetic acid (TFA)-mediated debenzylation, gave *antilsyn* lactones **5/19** as a mixture in a ratio of 3.5:1.[21] The lactone diastereomers were efficiently separated by column chromatography to afford **5** (68%) and **19** (21%). Surprisingly, the unmasking of TBDSMS ether also occurred with concomitant trifluoromethyl acetate protection. This was

confirmed by the absence of signals arising from the TBDMS group in the ^{1}H NMR spectrum and also by the ^{19}F NMR spectra of **5** and **19**.[22] Similarly, *trans*-allyl alcohol **18** provided a mixture of **5**/**19**, albeit with a lower diastereoselectivity (1.3:1). These results are in agreement with our recent study.[11b]



Scheme 3. Synthesis of separable lactones **5** and **19**. *Reagents and conditions:* (a) i. DIBAL-H (2.5 equiv.), CH_2Cl_2, –20 °C, 2 h, room temp., 2 h, **6** (95%), **18** (92%); (b) i. $(MeO)_3CMe$ (10.0 equiv.), toluene, $EtCO_2H$ (cat.), reflux, 48 h; ii. TFA/CH_2Cl_2 (1:9), 0 °C to room temp., 12 h **5** (68%), **19** (21%) from **6**, **5** (48%), **19** (39%) from **18** (two steps).

Two-stage ozonolytic cleavage of the vinyl bond in **5** and subsequent Pinnick oxidation[23] efficiently generated the β-carboxylic acid group to provide **20** in 80% yield (Scheme 4). Finally, α-methylenation using Stiles reagent[14] followed by treatment with *N*-methylaniline and formaldehyde (with trifluoroacetate removal in situ), efficiently delivered (+)-murolic acid in 58% yield. Similar oxidation of the vinyl bond in **19** led to acid **21** (78%). The α-methylenation of compound **21** and trifluroacetate removal, astonishingly, gave (+)-murolic acid through epimerization of the β-CO_2H group in 46% yield. We believe the epimerization might be occurring at the diacid **22** stage through activation of the β-carbon center. This beneficial epimerization led to the same molecule, (+)-murolic acid. This is a remarkable feature that was previously unknown in paraconic acid synthesis.[10,11] Alternatively, after orthoester Johnson–Claisen rearrangement, the unseparated mixture of **5**/**19** (92%) was subjected to ozonolytic cleavage and oxidation to give the acid **20**/**21** in 79% yield. This mixture when subjected to final α-methylenation to give (+)-murolic acid, which was isolated in 54% yield. There was an excellent correlation of spectroscopic data between the synthetic material and natural isolate[4a,24] as well the optical rotation, synthetic material $[\alpha]_D^{25}$ = +10.5 (*c* = 0.12, $CHCl_3$) and natural isolate[4a] $[\alpha]_D^{24}$ = +11.2 (*c* = 0.14, $CHCl_3$).



Scheme 4. Synthesis of (+)-murolic acid (**1**). *Reagents and conditions:* (a) i. O_3, CH_2Cl_2, –78 °C, 20 min, then Me_2S, –78 °C, 2 h, room temp., 2 h; ii. $NaClO_2$ (2.3 equiv.), $NaH_2PO_4{\cdot}2H_2O$ (2.3 equiv.), cyclohexene (3.0 equiv.), *t*BuOH/H_2O (2:1), room temp., 12 h, **20** (80%), **21** (78%), (**20**/**21**, 79% from **5**/**19** mixture); (b) i. $MeOMgOCO_2Me$ (38.0 equiv.), DMF, 135 °C, 60 h; ii. CH_2O, *N*-methylaniline, AcOH, NaOAc, room temp., 2.5 h, (58% from **20**, 46% from **21**), (54% from **20**/**21** mixture).

Conclusions

The first total synthesis of (+)-murolic acid has been accomplished. Notable features include asymmetric dihydroxylation of the terminal olefin, orthoester Johnson–Claisen rearrangement to install the lactone moiety, the use of the β-vinyl group for conversion into the CO_2H group, and α-methylenation using Stiles reagent. A beneficial late-stage β-epimerization reverted the stereodivergent strategy into a stereoconvergent relay leading to the completion of the first synthesis of (+)-murolic acid in 17 steps from **9** and overall yields of 14.8%.

Experimental Section

General Remarks: Anhydrous reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates; the spots were visualized either under a UV lamp or by staining with $KMnO_4$. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively, and the chemical shifts are based on the TMS peak (δ = 0.00 ppm) for ^{1}H NMR and the central $CDCl_3$ peak (δ = 77.00 ppm) in ^{13}C

NMR spectra. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates. High-resolution mass spectra were obtained by using positive electrospray ionization by TOF method.

(*R*,*Z*)-16-Benzyloxyhexadec-4-en-2-yloxy(*tert*-butyldimethyl)silane (11): To a stirred solution of ester **9** (2.2 g, 8.93 mmol) in anhydrous CH_2Cl_2 (50 mL) at –78 °C under an Ar atmosphere was added DIBAL-H (25 wt.-% in toluene, 6.1 mL, 10.71 mmol, 1.2 equiv.) over a period of 1 h. The reaction mixture was stirred at –78 °C for 1 h and then quenched with satd. aq. sodium potassium tartrate solution (20 mL). Stirring was continued for 1 h at room temp. and the aqueous layer was extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated to give the crude aldehyde (1.8 g), which was used for the next reaction without further purification. To a solution of Wittig salt **10**[16] (7.12 g, 10.71 mmol, 1.2 equiv.) in THF (20 mL) at 0 °C was added *n*BuLi (1.6 M in THF, 6.7 mL, 10.71 mmol, 1.2 equiv.). The reaction mixture was stirred for 30 min, then cooled to –78 °C and a solution of the above aldehyde (1.8 g) in THF (10 mL) was added slowly. The reaction mixture was warmed to room temp. over 12 h, then the reaction was quenched with satd. aq. NH_4Cl (15 mL) and THF was removed under reduced pressure. The aqueous layer was extracted with EtOAc (4× 20 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 19:1) to afford olefin **11** (3.50 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ = +1.7 (*c* = 0.66, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2927, 2855, 1463, 1361, 1255, 1100, 1005, 836, 774, 733, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.35–7.26 (m, 5 H), 5.47–5.33 (m, 2 H), 4.50 (s, 2 H), 3.83–3.76 (m, 1 H), 3.46 (t, *J* = 6.7 Hz, 2 H), 2.23–2.15 (m, 2 H), 2.06–1.97 (m, 2 H), 1.65–1.58 (m, 4 H), 1.35–1.26 (m, 14 H), 1.12 (d, *J* = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 133.8, 131.6, 128.3, 127.6, 127.4, 72.8, 70.5, 68.8, 37.5, 29.8, 29.7, 29.6, 29.5, 29.48, 29.3, 27.4, 26.2, 25.9, 23.4, 18.2, –4.6, – 4.7 ppm. HRMS (ESI^+): calcd. for $[C_{29}H_{52}O_2Si + K]^+$ 499.3368; found 499.3378.

(*R*)-15-*tert*-Butyldimethylsilyloxyhexadecan-1-ol (12): To a solution of olefin **11** (0.5 g, 1.085 mmol) in EtOH (10 mL) was added 10 wt.-% $Pd(OH)_2/C$ (50 mg) under an Ar atmosphere. The resulting reaction mixture was stirred at room temp. under a H_2 atmosphere (balloon pressure) for 2 h and then filtered through a pad of Celite and washed with EtOAc (2× 50 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to afford alcohol **12** (0.344 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ = –6.8 (*c* = 0.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3346, 2927, 2855, 1464, 1374, 1255, 1134, 1057, 836, 808, 774, 721, 663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.78–3.72 (m, 1 H), 3.64 (t, *J* = 6.6 Hz, 2 H), 1.59–1.53 (m, 6 H), 1.38–1.25 (m, 20 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.7, 63.1, 39.7, 32.8, 29.7, 29.64, 29.6, 29.59, 29.4, 25.9, 25.8, 25.7, 23.8, 18.2, –4.4, –4.7 ppm. HRMS (ESI^+): calcd. for $[C_{22}H_{48}O_2Si + Na]^+$ 395.3316; found 395.3310.

(*R*)-*tert*-Butyl(heptadec-16-en-2-yloxy)dimethylsilane (13): A solution of DMSO (0.29 mL, 4.03 mmol, 3.0 equiv.) in anhydrous CH_2Cl_2 (15 mL) was gradually added to a solution of oxalyl chloride (0.18 mL, 2.01 mmol, 1.5 equiv.) in CH_2Cl_2 (15 mL) at –78 °C over a period of 10 min. After stirring for 15 min, a solution of alcohol **12** (0.5 g, 1.34 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred for 45 min. Et_3N (0.94 mL, 6.70 mmol, 5 equiv.) was added and the mixture was stirred for 30 min. After warming to room temp. over 1 h, water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3× 50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated to give the crude aldehyde (0.497 g), which was used directly in the next reaction. To a slurry of methyltriphenylphosphonium iodide (0.651 g, 1.61 mmol, 1.2 equiv.) in THF (10 mL) at 0 °C was added *n*-BuLi (1.6 M in THF, 1.0 mL, 1.60 mmol, 1.2 equiv.). The mixture was stirred for 30 min, then a solution of the above aldehyde (0.497 g) in THF (10 mL) was added. After stirring for 3 h, the reaction mixture was quenched by adding satd. aq. NH_4Cl (3 mL) and extracted with EtOAc (3× 20 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc, 9:1) to provide **13** (0.425 g, 86%) as a colorless oil. $[\alpha]_D^{25}$ = –6.8 (*c* = 1.04, $CHCl_3$) {ref.[17] $[\alpha]_D^{22}$ = –8.0 (*c* = 20, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}$ = 2927, 2855, 2738, 1642, 1464, 1373, 1255, 1178, 1136, 1047, 910, 836, 806, 773, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.86–5.74 (m, 1 H), 5.02–4.89 (m, 2 H), 3.81–3.72 (m, 1 H), 2.11–2.01 (m, 2 H), 1.43–1.22 (m, 24 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 114.1, 68.7, 39.8, 33.8, 29.7, 29.68, 29.6, 29.5, 29.2, 29.0, 25.9, 25.8, 23.8, 18.2, –4.4, –4.7 ppm. HRMS (ESI^+): calcd. for $[C_{23}H_{48}OSi + H]^+$ 369.3554; found 369.3561.

(2*R*,16*R*)-(*tert*-Butyldimethylsilyloxy)hepadecane-1,2-diol (14): To a mixture of $K_3Fe(CN)_6$ (2.68 g, 8.14 mmol, 3.0 equiv.), K_2CO_3 (1.125 g, 8.14 mmol, 3.0 equiv.), $MeSO_2NH_2$ (0.258 g, 2.71 mmol, 1.0 equiv.), $(DHQD)_2AQN$ (0.026 g, 0.03 mmol, 1.12 mol-%), and $K_2OsO_4{\cdot}2H_2O$ (4.0 mg, 0.01084 mmol, 0.4 mol-%) were added *t*BuOH (7 mL) and water (14 mL). The mixture was stirred for 5 min and cooled to 0 °C in an ice bath. To the cooled mixture, a solution of olefin **13** (1 g, 2.71 mmol) in *t*BuOH (7 mL) was added. The mixture was stirred at 0 °C for 24 h and then the reaction was quenched with solid Na_2SO_3 and the mixture was stirred for 30 min. The solution was extracted with EtOAc (3× 20 mL) and the combined organic layers were washed with 2 N KOH (10 mL), brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 1:1) to give **14** (1.027 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ = –9.9 (*c* = 0.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3392, 2929, 2855, 1465, 1374, 1254, 1187, 1134, 1067, 1006, 939, 836, 807, 720, 663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.80–3.62 (m, 3 H), 3.47–3.40 (m, 1 H), 2.02–1.98 (br. s, 1 H, OH), 1.86 (br. s, 1 H, OH), 1.59–1.21 (m, 26 H), 1.11 (d, *J* = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.3, 68.7, 66.6, 39.7, 33.0, 29.7, 29.6, 25.9, 25.8, 25.6, 23.8, 18.1, –4.5, –4.8 ppm. HRMS (ESI^+): calcd. for $[C_{23}H_{50}O_3Si + Na]^+$ 425.3421; found 425.3422. The diastereomeric ratio was determined to be 95.5:4.5 by conversion into tribenzoate and HPLC analysis.

(2*R*,16*R*)-16-(*tert*-Butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)heptadecan-1-ol (15): To a solution of diol **14** (1 g, 2.48 mmol) in anhydrous benzene (30 mL) were added *p*-methoxybenzaldehyde dimethylacetal (0.85 mL, 4.97 mmol, 2.0 equiv.) and $pTsOH{\cdot}H_2O$ (catalytic amount). The reaction mixture was stirred at room temp. for 12 h and then concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 19:1) to give the intermediate acetal (1.1 g) as a colorless oil, which was used in the next reaction.

To a solution of the above acetal (1.1 g, 2.11 mmol) in anhydrous CH_2Cl_2 (20 mL), at –78 °C under an Ar atmosphere, was added DIBAL-H (25 wt.-% in toluene, 3.6 mL, 6.32 mmol, 3.0 equiv.) over a period of 20 min. The mixture was stirred for 5 h, then the reaction was quenched with a satd. aq. sodium potassium tartrate solu-

tion (5 mL). Stirring was continued for 1 h at room temp., then the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to give **15** (1.09 g, 84% from **14**) as a colorless oil. $[\alpha]_D^{25}$ = –9.2 (*c* = 0.24, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3442, 2928, 2855, 1614, 1587, 1514, 1464, 1373, 1361, 1302, 1250, 1173, 1130, 1070, 1040, 880, 835, 808, 720, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.23 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 4.51 (d, *J* = 11.1 Hz, 1 H), 4.42 (d, *J* = 11.1 Hz, 1 H), 3.76 (s, 3 H), 3.75–3.74 (m, 1 H), 3.73–3.70 (m, 1 H), 3.48–3.41 (m, 2 H), 1.95 (br. s, 1 H, OH), 1.61–1.18 (m, 26 H), 1.07 (d, *J* = 6.0 Hz, 3 H), 0.84 (s, 9 H), 0.004 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 130.6, 129.4, 113.9, 79.5, 71.2, 68.7, 64.3, 55.3, 39.8, 30.8, 29.8, 29.7, 29.67, 29.6, 29.57, 25.9, 25.8, 25.4, 23.8, 18.2, –4.4, –4.7 ppm. HRMS (ESI^+): calcd. for $[C_{31}H_{58}O_4Si + Na]^+$ 545.3997; found 545.3996.

(4*R*,18*R*,*Z*)-Ethyl 18-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)nonadec-2-enoate (16) and (4*R*,18*R*,*E*)-Ethyl 18-(*tert*-Butyldimethylsilyoxy)-4-(4-methoxybenzyloxy)nonadec-2-enoate (17): To a solution of alcohol **15** (0.310 g, 0.592 mmol) in CH_2Cl_2 (35 mL) was added Dess–Martin periodinane (0.377 g, 0.889 mmol, 1.5 equiv.) in one portion, and the reaction was stirred at room temp. for 3 h. The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 19:1) to afford the aldehyde (0.3 g) as a colorless oil, which was immediately used in the next reaction.

To a solution of the above aldehyde (0.3 g) in MeOH (10 mL) at –40 °C was added (carbethoxymethylene)triphenylphosphorane (0.502 g, 1.44 mmol, 2.5 equiv.). The reaction mixture was stirred at –40 °C for 5 h, then warmed to room temp. and stirred for 12 h and then concentrated. To the residue was added petroleum ether to precipitate $Ph_3P{=}O$. The white solid was filtered and washed with petroleum ether. The filtrate was concentrated and the residue was purified by flash silica gel column chromatography (petroleum ether/EtOAc, 19:1) to afford **16** (0.238 g, 68% from **15**) as a colorless oil. Further elution gave **17** (0.102 g, 29% from **15**) as a colorless oil.

Compound 16: $[\alpha]_D^{25}$ = –2.9 (*c* = 0.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2927, 2855, 1722, 1646, 1614, 1587, 1514, 1464, 1410, 1387, 1302, 1249, 1186, 1132, 1083, 1039, 834, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.24 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.19–6.13 (m, 1 H), 5.90–5.85 (m, 1 H), 5.02–4.97 (m, 1 H), 4.46 (d, *J* = 11.3 Hz, 1 H), 4.33 (d, *J* = 11.3 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.80 (s, 3 H), 3.79–3.72 (m, 1 H), 1.52–1.22 (m, 29 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 0.85 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 159.1, 151.4, 130.6, 129.4, 120.9, 113.6, 74.7, 70.9, 68.6, 60.1, 55.2, 39.7, 35.0, 29.7, 29.64, 29.6, 29.59, 29.57, 29.5, 25.9, 25.8, 25.2, 23.8, 18.1, 14.2, –4.5, –4.8 ppm. HRMS (ESI^+): calcd. for $[C_{35}H_{62}O_5Si + Na]^+$ 613.4259; found 613.4264.

Compound 17: $[\alpha]_D^{25}$ = +2.6 (*c* = 0.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2928, 2855, 1723, 1614, 1514, 1465, 1370, 1298, 1251, 1173, 1092, 1040, 985, 836, 771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 6.87–6.82 (m, 1 H), 6.02–5.97 (m, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.29 (d, *J* = 11.4 Hz, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 3.93–3.88 (m, 1 H), 3.81 (s, 3 H), 3.79–3.73 (m, 1 H), 1.31 (t, *J* = 7.14 Hz, 3 H), 1.42–1.22 (m, 26 H), 1.12 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 159.2, 148.7, 130.2, 129.3, 121.8, 113.7, 77.7, 70.6, 68.6, 60.4, 55.2, 39.7, 34.9, 29.67, 29.63, 29.6, 29.57, 29.5, 29.45, 25.9, 25.8, 25.1, 23.8, 18.1, 14.3, –4.5, –4.8 ppm. HRMS (ESI^+): calcd. for $[C_{35}H_{62}O_5Si + Na]^+$ 613.4259; found 613.4256.

Preparation of 16 and 17 by using the Still–Gennari Procedure:[20] To a solution of alcohol **15** (0.14 g, 0.267 mmol) in CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (0.17 g, 0.4 mmol, 1.5 equiv.) in one portion and the reaction was stirred at room temp. for 3 h. The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 19:1) to afford the aldehyde (0.138 g) as a colorless oil, which was immediately used in the next reaction.

To a solution of freshly prepared ethyl bis(2,2,2-trifluoroethyl)-phosphonoacetate[20b] (0.0976 g, 0.294 mmol, 1.1 equiv.) and 18-crown-6 (0.141 g, 0.534 mmol, 2.0 equiv.) in anhydrous THF (7 mL) at 0 °C was added KHMDS (1M in THF, 0.3 mL, 0.3 mmol, 1.1 equiv.) and the reaction mixture was stirred for 15 min. It was then cooled to –78 °C and a solution of the above aldehyde (0.138 g) in THF (1 mL) was added. The mixture was stirred for 2 h, then the reaction was quenched with satd. aq. NH_4Cl. The solution was extracted with Et_2O (3× 15 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc, 19:1) to afford **16** (0.128 g, 81% from **15**) as a colorless oil. Further elution gave **17** (0.011 g, 7% from **15**) as a colorless oil. Data for **16** and **17** were the same as detailed above.

(4*R*,18*R*,*Z*)-18-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)nonadec-2-en-1-ol (6): To a solution of ester **16** (0.35 g, 0.592 mmol) in CH_2Cl_2 (20 mL) at –20 °C was added DIBAL-H (25 wt.-% in toluene, 0.85 mL, 1.48 mmol, 2.5 equiv.). The mixture was stirred for 2 h, then warmed to room temp. and the reaction was quenched with satd. aq. sodium potassium tartrate solution and the mixture was stirred for 2 h. The solution was extracted with CH_2Cl_2 (3× 20 mL) and the combined organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc, 7:3) to afford **6** (0.309 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ = +10.3 (*c* = 0.46, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 3000, 2928, 2855, 1613, 1587, 1514, 1464, 1373, 1361, 1302, 1173, 1134, 1039, 940, 835, 809, 721, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.25 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.83–5.76 (m, 1 H), 5.50–5.44 (m, 1 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 4.29 (d, *J* = 11.5 Hz, 1 H), 4.25–4.17 (m, 1 H), 4.16–4.03 (m, 2 H), 3.80 (s, 3 H), 3.80–3.74 (m, 1 H), 1.35–1.25 (m, 26 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 133.3, 131.4, 130.5, 129.3, 113.7, 73.8, 69.7, 68.7, 58.7, 55.2, 39.7, 35.5, 29.7, 29.63, 29.6, 29.55, 29.5, 25.9, 25.8, 25.3, 23.8, 18.1, –4.5, –4.8 ppm. HRMS (ESI+): calcd. for $[C_{33}H_{60}O_4Si + Na]^+$ 571.4153; found 571.4151.

(4*R*,18*R*,*E*)-18-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)nonadec-2-en-1-ol (18): Prepared from **17** (0.035 g, 0.059 mmol) by a procedure similar to that described for **6**, to afford **18** (0.030 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ = +12.7 (*c* = 0.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 2995, 2927, 2855, 1613, 1586, 1514, 1464, 1376, 1298, 1250, 1173, 1070, 1039, 974, 836, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 5.84–5.77 (m, 1 H), 5.64–5.57 (m, 1 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 4.29 (d, *J* = 11.5 Hz, 1 H), 4.21–4.17 (m, 2 H), 3.79 (s, 3 H), 3.80–3.73 (m, 2 H), 1.69–1.24 (m, 26 H), 1.11 (d, *J* = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 132.5, 131.6, 130.8, 129.3, 113.7, 79.1, 69.8, 68.7, 63.0, 55.2, 39.7, 35.6, 29.7, 29.65, 29.6, 29.58, 29.5, 25.9, 25.8, 25.4, 23.8,

18.2, –4.5, –4.7 ppm. HRMS (ESI+): calcd. for $[C_{33}H_{60}O_4Si + Na]^+$ 571.4153; found 571.4148.

(*R*)-15-[(2*R*,3*R*)-5-Oxo-3-vinyltetrahydrofuran-2-yl]pentadecan-2-yl 2,2,2-Trifluoroacetate (5) and (*R*)-15-[(2*R*,3*S*)-5-Oxo-3-vinyltetrahydrofuran-2-yl]pentadecan-2-yl 2,2,2-Trifluroacetate (19): To a solution of allyl alcohol **6** (0.82 g, 1.49 mmol) in toluene (20 mL) was added trimethylorthoacetate (1.9 mL, 14.94 mmol, 10.0 equiv.) and propionic acid (cat.). The reaction mixture was heated to reflux for 48 h, cooled, and concentrated. The residue was dissolved in CH_2Cl_2 (7 mL), trifluoroacetic acid (1.15 mL, 14.94 mmol, 10.0 equiv.) was added at 0 °C and the mixture was stirred for 12 h, then concentrated under reduced pressure and the residue was purified by column chromatography (petroleum ether/EtOAc, 9:1) to provide the mixture of lactones **5/19** (0.597 g, 92%) as a colorless oil. Analysis of the mixture by ^{1}H NMR spectroscopy indicated an *anti*/*syn* ratio of 3.5:1. The mixture was separated by flash column chromatography (petroleum ether/EtOAc, 9:1) to give **5** (0.441 g, 68%) as a colorless oil. Further elution gave **19** (0.136 g, 21%) as a colorless oil.

Compound 5: $[\alpha]_D^{25}$ = +38.3 (*c* = 0.18, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2929, 2856, 1778, 1546, 1512, 1466, 1439, 1381, 1323, 1171, 929, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.76–5.67 (m, 1 H), 5.20–5.17 (m, 2 H), 5.16–5.07 (m, 1 H), 4.16–4.11 (m, 1 H), 2.80–2.65 (m, 2 H), 2.46 (dd, *J* = 17.2, 10.5 Hz, 1 H), 1.73–1.50 (m, 4 H), 1.34 (d, *J* = 6.3 Hz, 3 H), 1.41–1.20 (m, 22 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 156.8 (q), 135.7, 117.8, 114.5 (q), 84.7, 76.5, 46.3, 35.3, 35.2, 33.5, 29.55, 29.52, 29.45, 29.35, 29.28, 29.26, 29.2, 29.1, 25.61, 25.56, 24.9, 19.3 ppm. ^{19}F NMR: δ = –75.4 ppm. HRMS (ESI+): calcd. for $[C_{23}H_{37}O_4F_3 + H]^+$ 435.2722; found 435.2716.

Compound 19: $[\alpha]_D^{25}$ = +35.8 (*c* = 0.22, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2928, 2856, 1783, 1501, 1466, 1384, 1338, 1170, 1119, 924, 777, 724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.80–5.71 (m, 1 H), 5.20–5.18 (m, 2 H), 5.16–5.07 (m, 1 H), 4.52–4.45 (m, 1 H), 3.19–3.11 (m, 1 H), 2.70 (dd, *J* = 17.4, 8.1 Hz, 1 H), 2.44 (dd, *J* = 17.4, 5.6 Hz, 1 H), 1.72–1.47 (m, 6 H), 1.34 (d, *J* = 6.3 Hz, 3 H), 1.39–1.21 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 157.0 (q), 133.9, 117.9, 114.5 (q), 83.2, 76.5, 43.0, 35.3, 34.6, 30.7, 29.5, 29.46, 29.4, 29.36, 29.3, 29.27, 29.2, 29.1, 25.6, 25.58, 24.9, 19.3 ppm. ^{19}F NMR: δ = –75.4 ppm. HRMS (ESI+): calcd. for $[C_{23}H_{37}O_4F_3 + H]^+$ 435.2722; found 435.2711.

(2*R*,3*R*)-5-Oxo-2-[(*R*)-14-(2,2,2-trifluroacetoxy)pentadecyl]tetrahydrofuran-3-carboxylic Acid (20): A solution of vinyl lactone **5** (0.120 g, 0.276 mmol) in CH_2Cl_2 (25 mL) was cooled to –78 °C and a stream of O_3/O_2 was bubbled through the reaction mixture until the blue color of unreacted O_3 appeared. The reaction mixture was quenched with Me_2S (0.6 mL) and stirred for 1 h at –78 °C and for 2 h at room temp. The mixture was concentrated to give the crude aldehyde (0.120 g), which was used directly for the next reaction. The crude aldehyde was dissolved in *t*BuOH (3 mL) and cyclohexene (68 mg, 0.828 mmol, 3.0 equiv.) and a solution of sodium chlorite (57.4 mg, 0.635 mmol, 2.3 equiv.) and sodium dihydrogenphosphate (99 mg, 0.635 mmol, 2.3 equiv.) in water (1.5 mL) were added dropwise over 10 min. The resulting mixture was stirred at room temp. for 12 h, then the reaction was quenched with satd. aq. NH_4Cl. *t*BuOH was removed under vacuo, the aqueous layer was extracted with EtOAc (3× 10 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc, 1:9) to afford **20** (100 mg, 80%) as a white solid (m.p. 114–116 °C); $[\alpha]_D^{25}$ = +13.5 (*c* = 0.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3402, 2920, 2852, 1783, 1750, 1723, 1646, 1472, 1380, 1336, 1238, 1191, 1168, 1043, 1026, 967, 869, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.13–5.06 (m, 1 H), 4.64–4.58 (m, 1 H), 3.13–3.06 (m, 1 H), 2.94 (dd, *J* = 17.9, 8.4 Hz, 1 H), 2.81 (dd, *J* = 17.9, 9.6 Hz, 1 H), 1.83–1.41 (m, 4 H), 1.34 (d, *J* = 6.3 Hz, 3 H), 1.35–1.25 (m, 22 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 174.9, 157.4 (q), 114.8 (q), 82.1, 76.8, 45.6, 35.5, 32.0, 29.84, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 25.3, 25.2, 19.6 ppm. ^{19}F NMR: δ = –75.4 ppm. HRMS (ESI+): calcd. for $[C_{22}H_{35}O_6F_3 + Na]^+$ 475.2278; found 475.2277.

(2*R*,3*S*)-5-Oxo-2-[(*R*)-14-(2,2,2-trifluroacetoxy)pentadecyl]tetrahydrofuran-3-carboxylic Acid (21): The title compound was prepared from **19** (0.090 g, 0.207 mmol) by a procedure similar to that described for the conversion of **5** into **20** to afford **21** (0.073 g, 78%) as a white solid (m.p. 103–105 °C); $[\alpha]_D^{25}$ = +32.9 (*c* = 0.08, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3499, 3016, 2928, 2855, 1780, 1737, 1550, 1468, 1384, 1301, 1170, 1034, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.14–5.06 (m, 1 H), 4.70–4.61 (m, 1 H), 3.50–3.44 (m, 1 H), 2.91 (dd, *J* = 17.6, 5.3 Hz, 1 H), 2.70 (dd, *J* = 17.6, 8.6 Hz, 1 H), 1.74–1.51 (m, 4 H), 1.35 (d, *J* = 6.3 Hz, 3 H), 1.45–1.19 (m, 22 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 174.7, 157.1 (q), 114.5 (q), 80.4, 76.6, 42.5, 35.3, 31.9, 31.8, 31.2, 29.6, 29.5, 29.46, 29.4, 29.3, 29.27, 29.1, 25.8, 24.9, 19.4 ppm. ^{19}F NMR: δ = –75.4 ppm. HRMS (ESI+): calcd. for $[C_{22}H_{35}O_6F_3 + Na]^+$ 475.2278; found 475.2280.

(2*R*,3*S*)-2-[(*R*)-14-Hydroxypentadecyl]-4-methylene-5-oxotetrahydrofuran-3-carboxylic Acid [(+)-Murolic Acid; 1]: Stiles reagent[14] (2 M in DMF, 3.0 mL, 6.0 mmol, 39.0 equiv.) was added under an Ar atmosphere to **20** (70 mg, 0.155 mmol) and the solution was stirred at 135 °C for 60 h. After cooling, the mixture was acidified with dropwise addition of cold 10% HCl (30 mL) at 0 °C, then CH_2Cl_2 (50 mL) was added and the mixture was stirred for 0.5 h. The aqueous layer was extracted with EtOAc (4× 50 mL), then the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was treated with 4 mL of a freshly prepared stock solution [HOAc (20 mL), 37% formaldehyde in water (15 mL), *N*-methylaniline (5.2 mL) and NaOAc (0.6 g)] and the mixture was stirred for 3 h at room temp. Acidic brine solution (40 mL, containing 4 mL concd. aqueous HCl) was added and the aqueous layer was extracted with Et_2O (5× 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc/acetic acid, 1:9:0.2) to provide **1** (33 mg, 58%) as white solid (m.p. 106–108 °C; ref.[4a] 112.5 °C); $[\alpha]_D^{25}$ = +10.5 (*c* = 0.12, $CHCl_3$) {ref.[4a] $[\alpha]_D^{24}$ = +11.2 (*c* = 0.14, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3446, 2919, 2851, 1745, 1717, 1663, 1515, 1470, 1404, 1255, 1131, 1022, 965, 928, 815, 718 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 6.40 (d, *J* = 3.0 Hz, 1 H), 6.01 (d, *J* = 2.7 Hz, 1 H), 4.81 (dt, *J* = 7.1, 5.9 Hz, 1 H), 3.86–3.75 (m, 1 H), 3.64–3.58 (m, 1 H), 1.78–1.68 (m, 2 H), 1.65–1.26 (m, 24 H), 1.19 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 168.5, 132.8, 125.5, 79.0, 68.6, 49.7, 39.0, 35.6, 29.7, 29.5, 29.44, 29.4, 29.38, 29.3, 29.2, 29.18, 29.0, 25.6, 24.7, 23.2 ppm. HRMS (ESI+): calcd. for $[C_{21}H_{36}O_5 + H]^+$ 369.2642; found 369.2634.

(+)-Murolic Acid (1) from a Mixture of 20/21: Prepared from **20/21** (50 mg, 0.111 mmol) by a procedure similar to that described for the conversion of **20** into **1** to afford **1** (0.073 g, 54%) as a white solid. $[\alpha]_D^{25}$ = +10.3 (*c* = 0.05, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): Preparation and characterization of precursors; ^{1}H, ^{13}C, ^{19}F NMR spectra; comparison of spectral data of synthetic material with natural isolate.

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