Total Synthesis of the Cytotoxic *Threo, Trans, Threo, Trans, Threo* Annonaceous Acetogenin Asimin and Its C-10 Epimer: Unambiguous Confirmation of Absolute Stereochemistry

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A convergent synthesis of asimin (**1**) and its C-10 epimer **33** is reported. The essential features of this synthesis include (a) the addition of an enantioenriched γ-OMOM allylic indium reagent to a core C-23 aldehyde precursor to install the C-24−C-34 segment with concomitant introduction of the C-24 and C-23 stereocenters; (b) the addition of an enantioenriched γ-OMOM allylic indium reagent to a core C-16 aldehyde to install the C-10−C-15 segment with formation of the C-15 and C-16 stereocenters, (c) the addition of a dialkyl zinc reagent, catalyzed by a chiral triflamide-Ti(O-*i*-Pr)$_4$ complex, to introduce the C-1−C-9 segment with creation of either the 10(*R*) or 10(*S*) stereocenters; and (d) aldol condensation of the foregoing C-1−C-34 segment with OTBS-protected lactic aldehyde to incorporate the C-35−C-37 butenolide segment. Removal of the three MOM protecting groups was achieved with aqueous HCl in THF. The 10(*R*) diastereomer was found to correspond to natural asimin.

The Annonaceous acetogenins comprise a widespread family of cytotoxic natural products with a remarkable range of biological activities.[1] Their novel and selective mode of action as inhibitors of oxidative phosphorylation offers a unique potential for these compounds as anticancer agents.[2] In fact, data from cell-culture bioassays against human tumor cell lines reveals nearly unbelievable levels of cytotoxicity, even against cells exhibiting multiple-drug resistance toward current chemotherapeutic agents.[3] For this reason, and by virtue of their extremely limited availability, these compounds have been targeted for total synthesis by a number of research groups.[4]

In 1994, McLaughlin and co-workers reported the isolation of three acetogenins, asimin (**1**), asiminacin (**2**), and asiminecin (**3**), from the stem back of the North American paw-paw tree, *Asimina triloba* Dunal,[5] which they identified as structural isomers of asimicin (**4**), a compound previously isolated from the same source.[6] All three of the new compounds showed extremely high potency against human tumor cell lines. The initial report depicted asimin as the C-10(*S*) isomer. However, in a subsequent paper the stereochemistry at C-10 was shown as *R*.[7] In that report, it was revealed that the assignment of configuration was based upon chemical shift differences of 0.06 Hz between the protons at C-4 and C-3 in the ^{1}H NMR spectra of the tris(2-methoxy-2-trifluoromethyl-2-phenylacetate) (MTPA) derivatives.[8] In view of the rather subtle basis for this assignment, and because of the high biological profile of these compounds, we undertook a total synthesis of both C-10 epimers of asimin along lines previously developed in our laboratory.[4c,9] Our synthesis started with alcohol **5**, which was converted to aldehyde **6** as previously described.[10] Addition of an allenylindium intermediate, generated in situ from the (*R*)-allylic stannane **7** and $InCl_3$, to aldehyde **6** of >95% ee afforded alcohol **8** (Scheme 1).[4c] This alcohol was "protected" as the tosylate derivative **9**. Upon stirring with 5% Pd−C under an atmosphere of hydrogen, tosylate **9** underwent hydrogenation of the double bond and concomitant hydrogenolysis of the benzyl ether. The resulting alcohol **10** was oxidized with PCC[11] to afford aldehyde **11** in high overall yield. Addition of the allylic indium reagent prepared by treatment of the (*S*)-allylic stannane **12** in situ with $InCl_3$ yielded the adduct **13**.[4c] The bis-tosylate **14** gave rise to the *threo, trans, threo, trans, threo* bis-tetrahydrofuran core unit **15** upon stirring with TBAF in THF. Hydrogenation/hydrogenolysis with H_2/Pd−C at one atmosphere afforded alcohol **16**, which was oxidized to the aldehyde **17** with PCC.[11]

The C-1−C-9 side chain of asimin was introduced through addition of the organozinc reagent **18** to aldehyde **17** in the presence of Ti(O-*i*-Pr)$_4$ and the (*S,S*)-cyclohexanediamine bis-triflamide catalyst **19** (Scheme 2).[4c,12] The resulting adduct, alcohol **20** is presumed to be the 10*R* diastereomer based on a wealth of precedent.[12] Attempted assignment of C-10 absolute configuration through analysis of the ^{1}H NMR spectra of the (*R*)- and (*S*)-*O*-methyl mandelates was not successful owing to the absence of diagnostic peaks.[13] The MOM ether **21** was condensed with the TBS ether of (*S*)-lactic aldehyde **22** to afford, after treatment with TBAF, the γ-lactone adduct **23** as a mixture of C35 isomers.[4e,14] Exposure of the alcohol **23** to trifluoroacetic anhydride and triethylamine led to the butenolide **25** via the unisolated trifluoroacetate **24**. Cleavage of the MOM ethers was effected with aqueous HCl in THF. For comparison purposes, the triol **1** was converted to the (*S*)-MTPA ester **26**.[8] The ^{1}H NMR spectra of triol **1** and the (*S*)-ester **26** were identical to the corresponding spectra of asimin and its (*S*)-MTPA ester. The authentic (*R*)-MTPA ester showed several small differences in the ^{1}H NMR spectrum. In addition, the optical rotation of the triol **1** was in good agreement with the reported value.[5]

10(*S*)-Asimin (**33**) was prepared from aldehyde **17** by an identical sequence, except the triflamide **27** of (*R,R*)-1,2-cyclohexanediamine was used to catalyze the addition of the alkylzinc reagent **18** to aldehyde **17** (Scheme 3). The (*S*)-MTPA derivative **34** was subtly, but definitely different from the (*S*)-MTPA derivative **26** of the 10*R* alcohol **1**. In addition, the optical rotation was significantly lower for the 10*S* compound ($[\alpha]_D$ +22 for **1** and +16 for **33**). Interestingly, the ^{1}H NMR spectrum of the (*S*)-MTPA derivative **34** was virtually identical to that of the (*R*)-MTPA derivative of the 10*R* alcohol, indicating a pseudoenantiomeric relationship between these two derivatives. This finding

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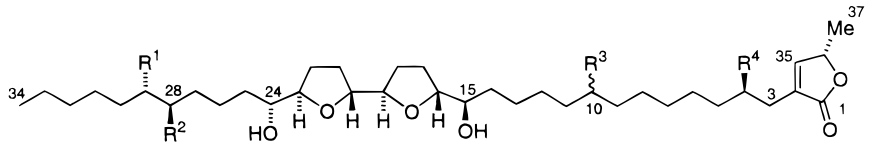
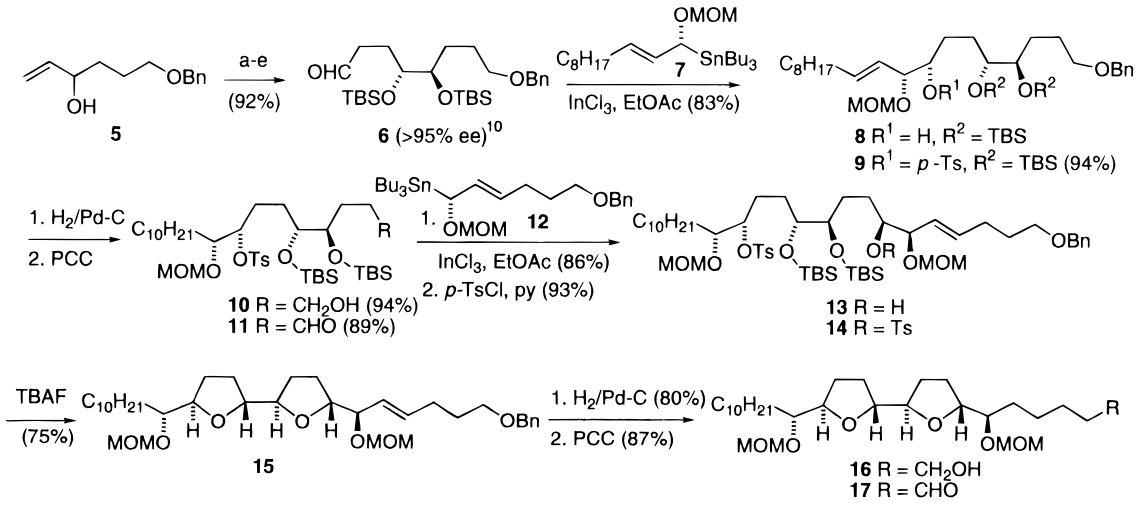


Asimin (**1**) $R^1 = R^2 = R^4 = H$; $R^3 = (R)$-OH
Asiminacin (**2**) $R^1 = R^3 = R^4 = H$; $R^2 = OH$
Asiminecin (**3**) $R^1 = OH$; $R^2 = R^3 = R^4 = H$
Asimicin (**4**) $R^1 = R^2 = R^3 = H$; $R^4 = OH$

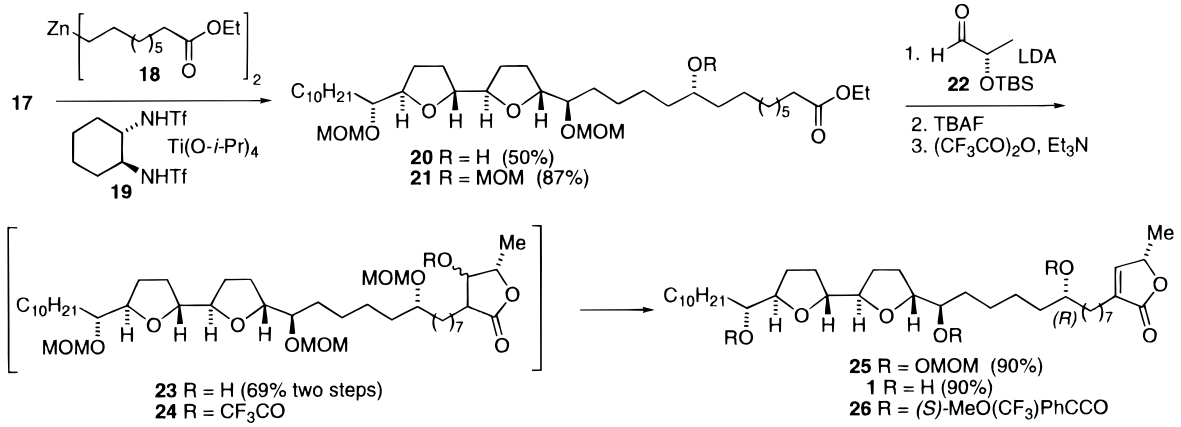
Figure 1. Representative members of the asimicin subgroup of Annonaceous acetogenins.

Scheme 1

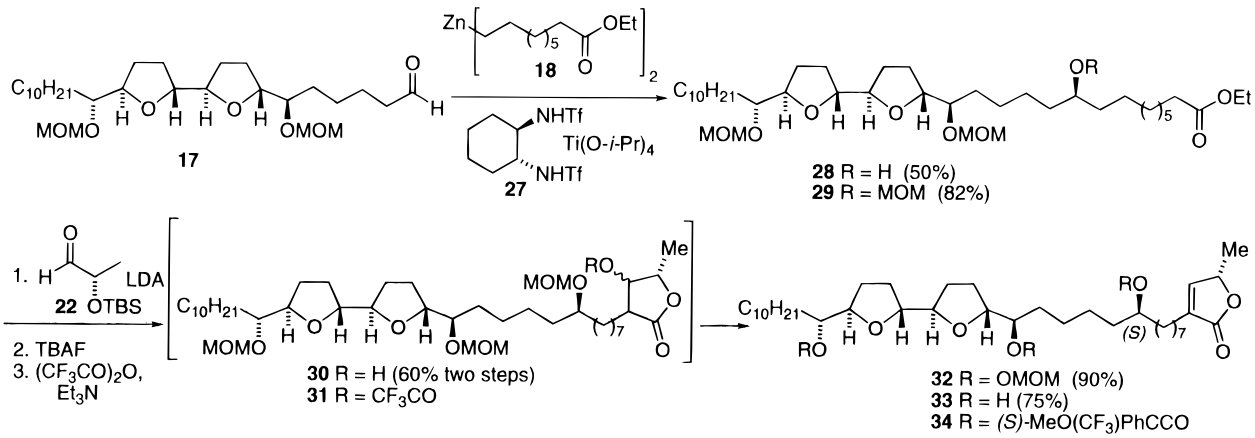


a) $(MeO)_3CMe$, $EtCO_2H$, heat (96%); b) AD-mix β (99%);c) MeONHMe•HCl, $AlMe_3$ (99%); d) TBSCl, Im (99%); e) DIBAL-H (99%)

Scheme 2



Scheme 3



is not surprising considering the ^{1}H NMR spectra of the diastereomeric alcohols **1** and **33** are identical.

On the basis of these results, the structure assigned to asimin (**1**) by McLaughlin and co-workers through analysis of the MTPA ester ^{1}H NMR chemical shift differences can be taken as correct.[7] A noteworthy feature of the present synthesis is the ability to "protect" the alcohol functions of adduct **8** as the tosylate **9** for later use in the bis-cyclization reaction **14** → **15**.

Experimental Section

General Experimental Procedures. NMR spectra were determined in $CDCl_3$ at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to TMS. FT−IR were taken on an Impact 410 spectrometer. Optical rotations were measured on a Perkin−Elmer 343 polarimeter. Kieselgel 60F_{254} plates were employed for TLC analyses. Si gel (200−400 mesh) was used for column chromatography. Reagents prepared according to literature procedures are footnoted. All other reagents were obtained from commercial sources. All reactions were performed under N_2 in oven-dried flasks. Elemental analyses were carried out by Atlantic Microlab, Inc. (Norcross, GA).

Alcohol 8. A solution of 1.07 g (4.84 mmol) of $InCl_3$ in 80.0 mL of EtOAc was sonicated for 20 min, and to it was added a solution of 2.10 g (4.24 mmol) of aldehyde **6**[4c] in 2.0 mL of EtOAc. The mixture was cooled to −78 °C, and to it was added a solution of 3.43 g (6.81 mmol) of stannane **7**[4c] in 2.0 mL of EtOAc. The reaction mixture was allowed to warm to room temperature (3 h), quenched with $NaHCO_3$, and extracted with ether. The ether extracts were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on Si gel (elution with 10% EtOAc in hexane) to afford 2.50 g (83%) of alcohol **8**: $[\alpha]^{25}_D$ −9.7 (*c* 0.66, $CHCl_3$); IR (film) 3484, 2916 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (5 H, m), 5.72 (1 H, dt, *J* = 6.9, 15.8 Hz), 5.38 (1 H, dd, *J* = 9.1, 15.8 Hz), 4.73 (1 H, d, *J* = 7.3 Hz), 4.56 (1 H, d, *J* = 7.3 Hz), 4.50 (2 H, s), 3.92 (1 H, m), 3.65 (1 H, m), 3.56 (2 H, m), 3.47 (2 H, t, *J* = 6.6 Hz), 3.37 (3 H, s), 2.06 (2 H, m), 1.94−1.12 (20 H, m), 0.88 (21 H, m), 0.05 (6 H, s), 0.04 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 137.5, 128.3, 127.5, 127.4, 124.8, 93.6, 80.4, 75.8, 75.4, 74.2, 72.7, 70.7, 55.4, 32.4, 31.9, 29.9, 29.4, 29.2, 29.1, 27.1, 26.7, 26.6, 25.8, 22.6, 18.0, 14.1, −4.1, −4.6; *anal.* C 67.57%, H 10.72%, calcd for $C_{40}H_{76}O_6Si_2$, C 67.74%, H 10.80%.

Tosylate 9. To a mixture of 1.00 g (1.41 mmol) of alcohol **8** in 2.0 mL of pyridine was added 1.60 g (8.4 mmol) of *p*-TsCl. The reaction mixture was stirred for 12 h, quenched with H_2O and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on Si gel (elution with 10% EtOAc in hexane) to afford 1.14 g (94%) of tosylate **9**: $[\alpha]^{25}_D$ −13.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (2 H, d, *J* = 8.5 Hz), 7.30 (7 H, m), 5.70 (1 H, dt, *J* = 6.1, 15.2 Hz), 5.20 (1 H, dd, *J* = 7.6, 15.4 Hz), 4.61 (1 H, d, *J* = 6.5 Hz), 4.50 (2 H, s), 4.45 (1 H, d, *J* = 6.5 Hz), 4.44 (1 H, m), 4.25 (1 H, m), 3.43 (4 H, m), 3.32 (3 H, s), 2.38 (3 H, s), 2.00 (2 H, m), 1.87−1.15 (20 H, m), 0.85 (21 H, m), 0.03 (6 H, s), 0.00 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.1, 138.6, 137.3, 134.5, 129.5, 128.3, 127.9, 127.6, 127.4, 124.7, 93.6, 86.0, 77.6, 75.4, 75.0, 72.8, 70.6, 55.4, 32.3, 31.8, 29.4, 29.2, 28.9, 27.0, 26.8, 26.5, 26.4, 26.0, 25.8, 25.7, 22.6, 21.5, 17.9, 14.1, −4.1, −4,6.

Alcohol 10. A mixture of 0.40 g (0.46 mmol) of tosylate **9** and 0.40 g of Pd−C (5%) in 6.0 mL of EtOAc was placed under one atmosphere of H_2 (balloon). The reaction mixture was stirred for 12 h and filtered through Celite. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography on Si gel (elution with 30% EtOAc in hexane) to afford 0.34 g (94%) of alcohol **10**: $[\alpha]^{25}_D$ +22.0 (*c* 0.50, $CHCl_3$); IR (film) 3493 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (2 H, d, *J* = 8.5 Hz), 7.31 (2 H, d, *J* = 8.5 Hz), 4.68 (1 H, d, *J* = 6.5 Hz), 4.58 (1 H, d, *J* = 6.5 Hz), 4.46 (1 H, m), 3.80 (1 H, m), 3.63 (2 H, m), 3.49 (1 H, m), 3.40 (1 H, m), 3.35 (3 H, s), 2.43 (3 H, s), 1.80−1.15 (26 H, m), 0.86 (21 H, m), 0.04 (6 H, s), 0.02 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.3, 134.3, 129.6, 127.9, 96.4, 85.8, 78.3, 77.6, 77.2, 76.6, 75.3, 75.0, 63.1, 55.7, 31.9, 31.4, 30.0, 29.6, 29.4, 29.3, 26.6, 26.3, 26.1, 25.8, 25.7, 25.6, 22.7, 21.6, 17.9, 16.9, 15.2, 14.1, −4.1, −4.2, −4.7.

Aldehyde 11. To a mixture of 0.55 g (0.71 mmol) of alcohol **10** and 0.40 g of 4 Å molecular sieves in 6.0 mL of CH_2Cl_2 at 0 °C was added 0.50 g (2.30 mmol) of PCC. The reaction mixture was stirred at room temperature for 1 h, diluted with ether, and filtered through Celite. Solvent was removed under reduced pressure, and the residue was purified by column chromatography on Si gel (elution with 10% EtOAc in hexane) to afford 0.48 g (89%) of aldehyde **11**: $[\alpha]^{25}_D$ +22.0 (*c* 0.62, $CHCl_3$); IR (film) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.77 (1 H, s), 7.79 (2 H, d, *J* = 8.5 Hz), 7.31 (2 H, d, *J* = 8.5 Hz), 4.68 (1 H, d, *J* = 6.5 Hz), 4.59 (1 H, d, *J* = 6.5 Hz), 4.47 (1 H, m), 3.81 (1 H, m), 3.49 (1 H, m), 3.42 (1 H, m), 3.36 (3 H, s), 2.45 (2 H, m), 2.42 (3 H, s), 1.91−1.13 (24 H, m), 0.87 (21 H, m), 0.03 (6 H, s), 0.02 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.3, 144.4, 134.3, 129.7, 127.9, 96.4, 85.7, 78.4, 75.2, 74.2, 55.7, 41.1, 31.9, 31.5, 29.6, 29.4, 29.3, 26.6, 26.0, 25.7, 22.6, 21.5, 17.9, 14.1, −4.1, −4.7, −4.8; *anal.* C 62.33%, H 10.03%, calcd for $C_{40}H_{76}O_8SSi_2$, C 62.13%, H 9.91%.

Alcohol 13. The procedure for alcohol **8** was employed with 0.17 g (0.77 mmol) of $InCl_3$, 0.59 g (0.76 mmol) of aldehyde **11**, and 0.65 g (1.21 mmol) of stannane **12** in 8.0 mL of EtOAc. The crude product was purified by column chromatography on Si gel (elution with 15% EtOAc in hexane) to afford 0.67 g (86%) of alcohol **13**: $[\alpha]^{25}_D$ −7.1 (*c* 0.76, $CHCl_3$); IR (film) 3510 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (2 H, d, *J* = 8.5 Hz), 7.32 (7 H, m), 5.74 (1 H, dt, *J* = 6.5, 15.0 Hz), 5.41 (1 H, dd, *J* = 8.4, 15.4 Hz), 4.71 (1 H, d, *J* = 6.9 Hz), 4.67 (1 H, d, *J* = 6.9 Hz), 4.57 (1 H, d, *J* = 6.9 Hz), 4.55 (1 H, d, *J* = 6.9 Hz), 4.50 (2 H, s), 4.47 (3 H, m), 3.92 (1 H, m), 3.78 (1 H, m), 3.61 (1 H, m), 3.49 (3 H, m), 3.41 (1 H, m), 3.37 (3 H, s), 3.35 (3 H, s), 2.42 (3 H, s), 2.17 (2 H, m), 1.85−1.10 (28 H, m), 0.86(21 H, m), 0.02 (6 H, s), 0.00 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.2, 139.5, 136.5, 134.4, 129.6, 128.3, 127.8, 127.5, 127.4, 125.7, 96.3, 93.7, 85.7, 80.5, 78.3, 75.5, 75.4, 74.0, 72.8, 69.6, 55.6, 55.4, 31.8, 31.4, 29.8, 29.5, 29.4, 29.2, 29.1, 26.6, 26.2, 25.7, 22.6, 21.5, 17.9, 14.0, −4.1, −4.2, −4.7, −4.8.

Bis-Tosylate 14. The procedure described for tosylate **9** was employed with 0.66 g (0.64 mmol) of alcohol **13**, 0.73 g (3.8 mmol) of *p*-TsCl, and 1.5 mL of pyridine. The crude product was purified by column chromatography on Si gel (elution with 10% EtOAc in hexane) to afford 0.70 g (93%) of bis-tosylate **14**: $[\alpha]^{25}_D$ −5.4 (*c* 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (4 H, d, *J* = 8.5 Hz), 7.31 (9 H, m), 5.71 (1 H, dt, *J* = 6.5, 15.4 Hz), 5.23 (1 H, dd, *J* = 8.4, 15.5 Hz), 4.66 (1 H, d, *J* = 6.7 Hz), 4.57 (1 H, d, *J* = 6.7 Hz), 4.55 (1 H, d, *J* = 6.7 Hz), 4.53 (2 H, m), 4.49 (2 H, s), 4.40 (1 H, d, *J* = 6.7 Hz), 4.19 (1 H, m), 3.75 (1 H, m), 3.47 (2 H, t, *J* = 6.1 Hz), 3.38 (2 H, m), 3.34 (3 H, s), 3.29 (3 H, s), 2.43 (3 H, s), 2.14 (2 H, m), 1.82−1.14 (28 H, m), 0.85 (21 H, m), 0.00 (12 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.2, 144.1, 138.5, 136.5, 134.6, 134.5, 129.6, 129.5, 128.3, 127.8, 127.5, 127.4, 125.2, 96.3, 93.5, 85.6, 85.4, 78.4, 75.3, 75.2, 72.8, 69.5, 65.8, 55.7, 55.4, 31.9, 31.5, 29.6, 29.4, 29.3, 29.0, 28.9, 27.2, 26.6, 26.3, 25.7, 22.6, 21.6, 17.8, 15.2, 14.1, −4.1, −4.2, −4.7.

Bis-THF Olefin 15. To a solution of 1.10 g (0.93 mmol) of bis-tosylate **14** in 15.0 mL of THF was added 4.6 mL (4.6 mmol) of TBAF (1.0 M in THF). The reaction mixture was stirred at 50 °C for 12 h, quenched with H_2O, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on Si gel (elution with 20% EtOAc in hexane) to afford 0.42 g (75%) of bis-THF olefin **15**: $[\alpha]^{25}_D$ −13.3 (*c* 0.67, $CHCl_3$); IR (film) 2925, 2855, 1457 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (5 H, m), 5.70 (1 H, dt, *J* = 6.9, 15.0 Hz), 5.35 (1 H, dd, *J* = 8.1, 15.4 Hz), 4.82 (1 H, d, *J* = 6.9 Hz), 4.68 (1 H, d, *J* = 6.9 Hz), 4.66 (1 H, d, *J* = 6.9 Hz), 4.58 (1 H, d, *J* = 6.9 Hz), 4.49 (2 H, s), 4.08−3.87 (6 H, m), 3.46 (2 H, t, *J* = 6.5 Hz), 3.39 (3 H, s),

3.37 (3 H, s), 2.15 (2 H, m), 2.00−1.15 (28 H, m), 0.88 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4, 134.8, 128.2, 127.4, 127.0, 96.6, 93.5, 81.6, 81.3, 81.2, 81.0, 79.4, 78.5, 72.8, 69.5, 55.5, 55.1, 31.8, 37.0, 29.7, 29.5, 29.2, 29.1, 28.9, 28.2, 28.0, 27.9, 25.5, 22.6, 14.0; *anal.* C 71.57%, H 9.85%, calcd for $C_{36}H_{60}O_7$, C 71.49%, H 10.00%.

Bis-THF Alcohol 16. The procedure described for alcohol **10** was employed with 0.41 g (0.68 mmol) of olefin **15** and 0.41 g of Pd−C (5%) in 5.0 mL of EtOAc. The product was purified by column chromatography on Si gel (elution with 40% EtOAc in hexane) to afford 0.28 g (80%) of bis-THF alcohol **16**: IR (film) 3475 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.84 (1 H, d, J = 6.9 Hz), 4.82 (1 H, d, J = 6.9 Hz), 4.67 (2 H, d, J = 6.9 Hz), 4.07−3.83 (4 H, m), 3.64 (2 H, m), 3.48 (2 H, m), 3.39 (3 H, s), 3.37 (3 H, s), 2.00−1.16 (34 H, m), 0.87 (3 H, t, J = 7.2 Hz).

Bis-THF Aldehyde 17. To a mixture of 0.023 g (0.04 mmol) of alcohol **16** and 0.020 g of 4 Å molecular sieves in 1.0 mL of CH_2Cl_2 at 0 °C was added 0.020 g (0.09 mmol) of PCC. The reaction mixture was stirred at room temperature for 1 h, quenched with ether, and filtered through Celite. Solvent was removed under reduced pressure, and the residue was purified by column chromatography on Si gel (elution with 25% EtOAc in hexane) to afford 0.020 g (87%) of bis-THF aldehyde **17**: $[\alpha]^{25}_D$ +42.8 (c 0.96, $CHCl_3$); IR (film) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.76 (1 H, s), 4.82 (1 H, d, J = 6.9 Hz), 4.81 (1 H, d, J = 6.9 Hz), 4.67 (1 H, d, J = 6.9 Hz), 4.65 (1 H, d, J = 6.9 Hz), 4.00 (2 H, m), 3.91 (2 H, m), 3.48 (2 H, m), 3.39 (3 H, s), 3.38 (3 H, s), 2.44 (2 H, dt, J = 1.5, 7.3 Hz), 2.00−1.16 (32 H, m), 0.87 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.4, 96.7, 96.6, 81.7, 81.5, 81.3, 81.2, 81.1, 79.4, 79.2, 55.6, 43.7, 31.8, 31.1, 30.8, 29.7, 29.5, 29.2, 28.2, 25.5, 25.1, 22.6, 22.1, 14.0; *anal.* C 67.44%, H 10.79%, calcd for $C_{29}H_{54}O_7$, C 67.67% H 10.57%.

Hydroxy Ester 20. The previously described procedure[4c] was employed with 0.66 g (0.13 mmol) of aldehyde **17** resulting in 0.045 g (50%) of alcohol **20**: $[\alpha]^{25}_D$ +26.7 (c 0.38, $CHCl_3$); IR (film) 3501, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.82 (1 H, d, J = 6.9 Hz), 4.81 (1 H, d, J = 6.9 Hz), 4.67 (2 H, d, J = 6.9 Hz), 4.12 (2 H, q, J = 7.0 Hz), 4.00 (2 H, m), 3.91 (2 H, m), 3.57 (1 H, m), 3.47 (2 H, m), 3.39 (6 H, s), 2.28 (2 H, t, J = 7.3 Hz), 2.00−1.17 (51 H, m), 0.88 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 96.6, 81.7, 81.6, 81.1, 79.4, 79.3, 71.7, 60.0, 55.6, 37.4, 37.3, 36.5, 34.3, 31.8, 31.1, 31.0, 30.0, 29.7, 29.5, 29.3, 29.2, 29.1, 29.0, 28.2, 25.7, 25.6, 25.5, 24.9, 22.6, 14.2, 14.0; *anal.* C 68.63%, H 10.94%, calcd for $C_{40}H_{76}O_9$, C 68.53%, H 10.93%.

(*R*)-Mandelate: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (5 H, m), 4.89 (1 H, m), 4.82 (1 H, d, J = 6.9 Hz), 4.78 (1 H, d, J = 6.9 Hz), 4.73 (1 H, s), 4.67 (1 H, d, J = 6.9 Hz), 4.61 (1 H, d, J = 6.9 Hz), 4.12 (2 H, q, J = 7.5 Hz), 3.94 (5 H, m), 3.47 (1 H, m), 3.41 (3 H, s), 3.39 (3 H, s), 3.36 (3 H, s), 2.28 (2 H, t, J = 7.7 Hz), 2.00−1.00 (49 H, m), 0.88 (3 H, t, J = 7.2 Hz).

(*S*)-Mandelate: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (5 H, m), 4.89 (1 H, m), 4.82 (1 H, d, J = 6.9 Hz), 4.82 (1 H, d, J = 6.9 Hz), 4.81 (1 H, d, J = 6.9 Hz), 4.73 (1 H, s), 4.67 (1 H, d, J = 6.9 Hz), 4.65 (1 H, d, J = 6.9 Hz), 4.13 (2 H, q, J = 7.5 Hz), 3.99 (2 H, m), 3.91 (2 H, m), 3.46 (2 H, m), 3.41 (3 H, s), 3.39 (3 H, s), 3.38 (3 H, s), 2.27 (2 H, t, J = 7.7 Hz), 2.00−0.96 (49 H, m), 0.88 (3 H, t, J = 7.2 Hz).

MOM Ether 21. To a mixture of 0.036 g (0.05 mmol) of alcohol **20** and 0.10 mL (0.4 mmol) of *i*-Pr_2NEt in 0.50 mL of CH_2Cl_2 at 0 °C was added 0.02 mL (0.2 mmol) of MOMCl. The reaction mixture was stirred for 12 h, quenched with H_2O, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on Si gel (elution with 20% EtOAc in hexane) to afford 0.033 g (87%) of MOM ether **21**: $[\alpha]^{25}_D$ +33.5 (c 0.25, $CHCl_3$); IR (film) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.82 (2 H, d, J = 6.9 Hz), 4.66 (2 H, d, J = 6.9 Hz), 4.64 (2 H, s), 4.12 (2 H, q, J = 6.9 Hz), 4.00 (2 H, m), 3.91 (2 H, m), 3.48 (3 H, m), 3.39 (6 H, s), 3.37 (3 H, s), 2.28 (2 H, t, J = 7.2 Hz), 2.00−1.15 (51 H, m), 0.88 (2 H, t, J = 7.2 Hz).

Lactone 23. To LDA prepared from 0.07 mL (0.18 mmol) of BuLi (2.5 M in hexane) and 0.03 mL (0.22 mmol) of *i*-Pr_2-NH in 0.50 mL of THF at −78 °C was added a solution of 0.031 g (0.04 mmol) of ester **21** in 0.30 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, and to it was added a solution of 0.016 g (0.08 mmol) of aldehyde **22** in 0.30 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, quenched with NH_4Cl, and diluted with ether. The aqueous layer was extracted with ether, and the combined extracts were dried over $MgSO_4$. Solvent was removed under reduced pressure, and to the residue was added 1.0 mL of THF followed by 0.15 mL (0.15 mmol) of TBAF (1.0 M in THF). The reaction mixture was stirred for 1 h, quenched with H_2O, and extracted with ether. The extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on Si gel (elution with 40% EtOAc in hexane) to afford 0.022 g (69%) of lactone **23**: IR (film) 3432, 1771 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.82 (2 H, d, J = 6.9 Hz), 4.66 (2 H, d, J = 6.9 Hz), 4.63 (2 H, s), 4.18 (1 H, m), 4.00 (2 H, m), 3.91 (2 H, m), 3.48 (3 H, m), 3.39 (6 H, s), 3.37 (3 H, s), 2.56 (1 H, m), 2.00−1.14 (51 H, m,), 0.88 (3 H, t, J = 7.2 Hz).

Butenolide 25. To a mixture of 0.019 g (0.02 mmol) of alcohol **23** and 0.10 mL (0.2 mmol) of Et_3N in 2.0 mL of CH_2Cl_2 at 0 °C was added 0.02 mL (0.08 mmol) of $(CF_3CO)_2O$. The reaction mixture was stirred at room temperature for 20 h, quenched with $NaHCO_3$, and extracted with ether. The extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on Si gel (elution with 20% EtOAc in hexane) to afford 0.017 g (90%) of butenolide **25**: IR (film) 1754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (1 H, s), 4.99 (1 H, m), 4.82 (2 H, d, J = 6.9 Hz), 4.66 (2 H, d, J = 6.9 Hz), 4.63 (2 H, s), 4.00 (2 H, m), 3.90 (2 H, m), 3.48 (3 H, m), 3.39 (6 H, s), 3.37 (3 H, s), 2.26 (2 H, t, J = 7.5 Hz), 2.00−1.12 (46 H, m), 1.40 (3 H, d, J = 6.9 Hz), 0.88 (3 H, t, J = 7.2 Hz).

Asimin (1). A mixture of 0.014 g (0.02 mmol) of butenolide **25** in 1.50 mL of 6 M HCl−THF−MeOH (1:2:2) was stirred for 12 h, quenched with H_2O, and extracted with ether. The ether extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on Si gel (elution with 80% of EtOAc in hexane) to afford 0.010 g (90%) of asimin (**1**): $[\alpha]^{25}_D$ +22.0 (c 0.45, $CHCl_3$), lit.[5] +26.0 (c 0.10, $CHCl_3$); IR (film) 3459, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (1 H, s), 4.99 (1 H, m), 3.86 (4 H, m), 3.58 (1 H, m), 3.39 (2 H, m), 2.26 (2 H, t, J = 7.6 Hz), 2.12−1.07 (46 H, m), 1.40 (3 H, d, J = 6.9 Hz), 0.87 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 148.8, 134.3, 83.2, 83.0, 81.8, 74.1, 74.0, 71.8, 37.4, 33.4, 33.3, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.0, 27.4, 25.7, 25.6, 25.1, 22.7, 19.2, 14.1.

Tri-(*S*)-Mosher Ester (26). ^{1}H NMR ($CDCl_3$, 300 MHz) (diagnostic peaks are italicized) δ *5.00 (4 H, m)*, 3.94 (2 H, m), 3.78 (2 H, m), *3.54 (6 H, s), 3.52 (3 H, s),* 2.26 (2 H, t, J = 7.7 Hz), 2.00−1.00 (46 H, m), 1.40 (3 H, d, J = 6.5 Hz), 0.88 (3 H, t, J = 6.5 Hz).

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Supporting Information Available: ^{1}H NMR spectra for all new compounds and experimental procedures for **17**−**34**. This information is available free of charge on the World Wide Web at http://pubs.acs.org.

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