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The First Total Synthesis of (−)-Methyl Barbascoate

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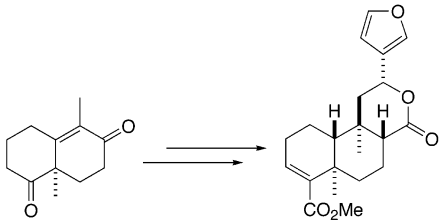
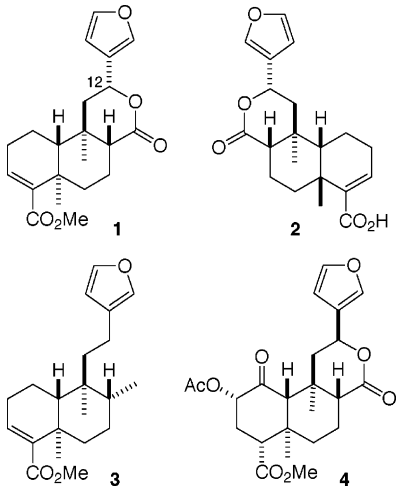


(–)-Methyl Barbascoate

The *neo-trans*-clerodane natural product, (−)-methyl barbascoate **1**, has been synthesized for the first time starting from the known ketone **6** derived from (*R*)-(−)-Wieland−Miescher ketone analogue **5**.

Clerodane diterpenoids constitute a large family of more than 800 compounds.[1] The structures of these family members incorporate *cis*- or *trans*-decalin rings with varying levels of oxygenation, often bearing pendant furan or lactone rings. These substituents have different stereochemical orientations. In addition, clerodanes exist in two *enantiomeric* series typified by methyl barbascoate **1**[2] and floribundic acid **2**.[3] The structural diversity and intriguing biological activities, such as insect anti feedant or antitumor activity, have stimulated the interest of many synthetic organic chemists, although significant synthetic challenges still surround a general approach to clerodane diterpenoids.[1]

In 1976, Wilson and co-workers reported the isolation of (−)-methyl barbascoate **1**[2] from the ethanol extract of *Croton californicus*, which is common in the Mohave Desert. Although the exact biological activity of **1** is unexplored, the powdered leaves were used traditionally as a pain reliever for rheumatism and the plant has been used by fishermen to stun fish. The relative stereostructure of **1** was determined by a single-crystal X-ray analysis, and the absolute stereochemistry was assigned by comparison with the CD spectra of (−)-methyl hardwickiate **3**. An interesting structural feature of **1** is that the lactone ring has an unusual boat conformation with an α-equatorial furan ring at C-12 (clerodane numbering).



Our ongoing program directed toward terpenoid synthesis starting from Wieland−Miescher ketone analogue **5**,[4] and the lack of successful total synthesis of clerodane natural products having a furo-lactone moiety, prompted us to investigate the total synthesis of (−)-methyl bar-

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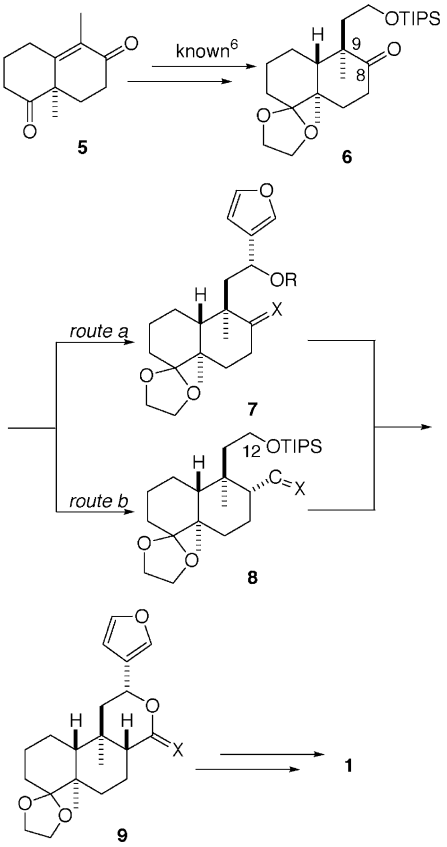
SCHEME 1. Synthetic Strategy



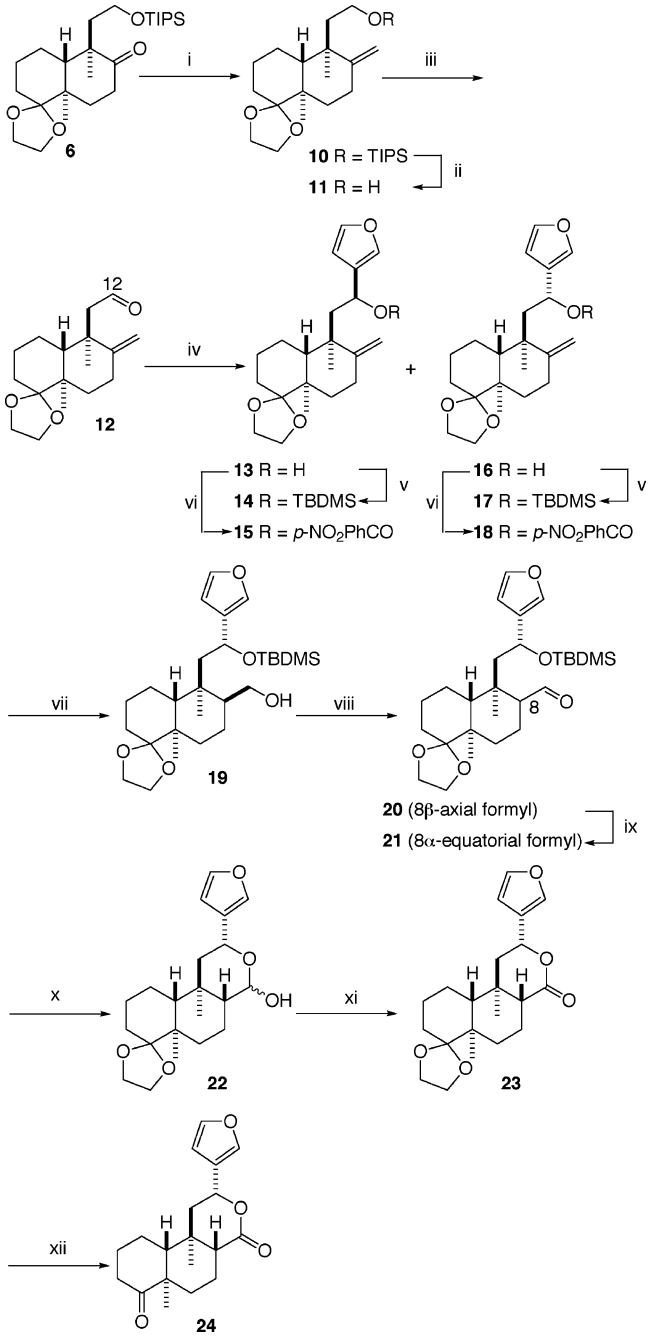
bascoate **1**. Our interest in the structural similarity of methyl barbascoate **1** to the hallucinogenic clerodane salvinorin A **4**[5] provided an additional stimulus for synthesizing **1**.

Results and Discussion

Our synthetic strategy is outlined in Scheme 1. Known decalone **6**,[6] previously synthesized from optically pure **5**[7] during our total synthesis of clerodane antibiotics, was chosen as the starting material. Decalone **6** contains three of the five asymmetric centers in the target molecule **1** in addition to having requisite oxygenated functionalities for further transformations. The ready availability of decalone **6** in enantiomerically pure form stimulated three syntheses[8] from this method since our disclosure.[8] A major issue in our present synthetic study was how to install the furolactone moiety. To this end, two divergent routes were designed for introducing the furan containing side chain at C-9 and the carboxyl unit at C-8 (Scheme 1).

We initially pursued route a, which introduces a furan ring at the side chain (Scheme 2) prior to introduction of the (8*R*)-carboxy unit. Initial attempts to directly introduce various oxygenated carbon units at C-8 of decalin

SCHEME 2[a]



[a] Reagents and conditions: (i) Ph_3PCH_3 Br, NaHMDS, THF, reflux, 87%; (ii) TBAF, THF, quant.; (iii) SO_3-Pyr, DMSO, Et_3N, CH_2Cl_2, 88%; (iv) 3-furyllithium, *t*-BuLi, THF, −78 °C, 99% (**13**/**16** = 4:1); (v) TBDMSCl, imidazole, DMAP, DMF, 91%; (vi) DEAD, PPh_3, *p*-NO_2PhCO_2H, THF, rt, 66% (**15**/**18** = 3:2); (vii) BH_3-THF then H_2O_2, NaOH, 32%; (viii) PDC, AcONa, MS-4A,CH_2Cl_2, 76% in three steps; (xii) PPTS H_2O, acetone, reflux, 40%.

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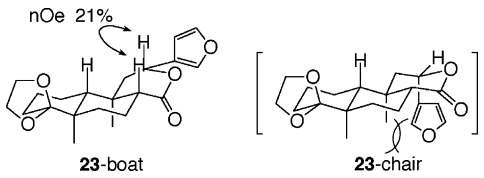

FIGURE 1. Key nOe assignments.

6 failed, presumably since C-8 is a sterically hindered *neo*-pentyl center. Fortunately, Wittig methylenation was successful with triphenylphosphonium bromide and sodium bistrimethylsilylamide (NaHMDS) giving the *exo*-methylene derivative **10** in 87% yield.

Deprotection of the TIPS ether of **10** with tetrabutylammonium fluoride (TBAF) proceeded quantitatively to give alcohol **11** which was oxidized by DMSO−SO_3/pyridine complex[9] to give aldehyde **12** in 88% yield. Addition of 3-furyllithium to the aldehyde **12** provided a 4:1 ratio of 12*S*- and 12*R*-alcohols **13** and **16** in 99% yield. The configuration of this newly introduced chiral center was assigned by converting the minor diastereomer into lactone **23** and observing key NOE enhancements (Figure 1). Since the minor 12*R* alcohol **16** is the desired compound, the 12*S*-alcohol **13** was inverted under Mitsunobu reaction conditions which formed the 12*S* and 12*R* *p*-nitrobenzoates **15** and **18** in a 2:3 ratio. Although the reaction proceeded mainly by an S_N1 process due to the electron-donating nature of the furan ring, a certain amount of the desired 12*R* derivative **18** predominated. Attempts to oxidize the 12*S*-alcohol **13**, followed by reduction, were not successful, since oxidation by Cr oxidants or under Swern conditions led only to decomposition and manganese dioxide oxidation was completely ineffective.

After protection of the 12*R* alcohol **16** as a TBDMS ether in 91% yield, hydroboration of the *exo*-methylene of TBDMS ether **17** proceeded solely from α-face of **17** to give alcohol **19** in 32% yield. Equatorial attack of BH_3 allows the nascent CH_2BH_2 group to avoid developing a gauche interaction with the axial CH_3 group. The yields were not improved with other hydroborating reagents although **17** was completely consumed. Pyridinium dichromate oxidation (PDC) of the resulting alcohol **19** gave in 79% yield aldehyde **20** that was equilibrated by treatment with sodium methoxide. Deprotecting the TBDMS ether present in **21**, with TBAF, resulted in spontaneous ring closure to furnish an inseparable diastereomeric mixture of hemiacetals **22**. PDC oxidation of **22** afforded lactone **23** in 75% yield from the aldehyde **20**. The relative stereochemistry and conformation of the lactone **23** was established by an nOe enhancement between 8*β*-H and 12*β*-H (Figure 1) together with the coupling constants of 12*β*-H (J = 11.2 and 6.6 Hz). Preliminary MM2 calculations indicate the boat conformation to be more stable than the chair conformation by 1.08 kcal/mol. Hydrolysis of the ketal present in **23** provided ketone **24** in 40% yield.

Although the sequence assembles the carbocyclic framework, the unsatisfactory hydroboration of **16** and the low selectivity of the furyllithium addition to aldehyde **12** stimulated a focus on route b, where the 8α formyl group is introduced earlier (Scheme 3).

Hydroboration of the *exo*-methylene of **10** gave a 3.8:1 ratio of 8*β* and 8α alcohols **25** and **26** in 92% combined yield. PDC oxidation of the minor 8α-alcohol **26** led to 8α-aldehyde **28**, quantitatively. The configuration of C-8 was apparent from the coupling constants of the C-8 proton (*δ*. 2.6, J = 11.3, 4.3, and 2.3 Hz). On the other hand, PDC oxidation of the major 8*β*-alcohol **25**, followed by equilibration by sodium methoxide, provided 8α-aldehyde **28** in 85% yield for two steps. The aldehyde **28** was protected as an acetal with 2-ethyl-2-methyl-1,3-dioxolane in the presence of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid (PTSA) to give acetal **29** in 97% yield. Deprotection of the TIPS ether of **29** with TBAF in 97% yield followed by PDC oxidation of the resulting alcohol **30** provided aldehyde **31** in 91% yield. Addition of 3-furyllithium to the aldehyde **31** was accomplished in 86% yield to give 12*S* and 12*R*-alcohol **32** and **33** in a 2:3 ratio. Stereochemistry was established by the final transformation of **33** to methyl barbascoate **1**. The modest preference for **33** is in the opposite sense to the addition of 3-furyllithium to aldehyde **12** (Scheme 2). PM3 calculations locate the stable conformers of the aldehydes **12** and **31** as illustrated in Figure 2, where the *re* face is less congested in **12** and the *si* face is slightly more accessible in **31**. Addition of a Lewis acid such as $ZnCl_2$ or Ti(O*i*-Pr)$_4$ did not improve the selectivity.

Treatment of the acetal **33** with a catalytic amount of PTSA in aqueous acetone at 45 °C resulted in deprotection of the two acetals and concomitant formation of the hemi-acetal **34** which was oxidized with PDC to furnish lactone **24**.

Due to the sensitive nature of the furo-lactone moiety, a mild procedure was required for the introduction of an α,*β*-unsaturated ester moiety into **24**. Thus, final conversion to methyl barbascoate **1** was investigated by palladium-catalyzed carboxylation of enol triflate **35**, which was obtained from the decalone **24** by sequential treatment with NaHMDS and Comins' reagent [*N*-(5-chloro-2-pyridyl)triflimide].[10] In the presence of palladium acetate, 1,1′-bis(diphenylphosphino)ferocene (DPPF), and excess methanol[11] in DMF under an atmosphere of carbon monoxide the enol triflate **35** was successfully carboxylated to complete the total synthesis of (−)-methyl barbascoate **1**. Repeated addition of catalytic Pd(OAc)$_2$, DPPF, and excess MeOH was a key requirement for achieving a satisfactory yield. The spectral data (mp, NMR, IR, $[\alpha]_D$), including the sign and value of optical rotation were consonant with those previously reported, confirming the absolute stereochemistry of **1** assigned by Wilson et al. NOe enhancement between 8*β*-H and 12*β*-H (15%) together with the coupling constants of 12*β*-H (J = 9.8 and 7.6 Hz) indicated that the lactone ring of **1** has a boat conformation (Figure 3) not only in the solid state but also in solution. Presumably, steric hindrance between the furan at C-12 and the methyl group at C-9 forces the furan ring into equatorial orientation in a boat conformation.

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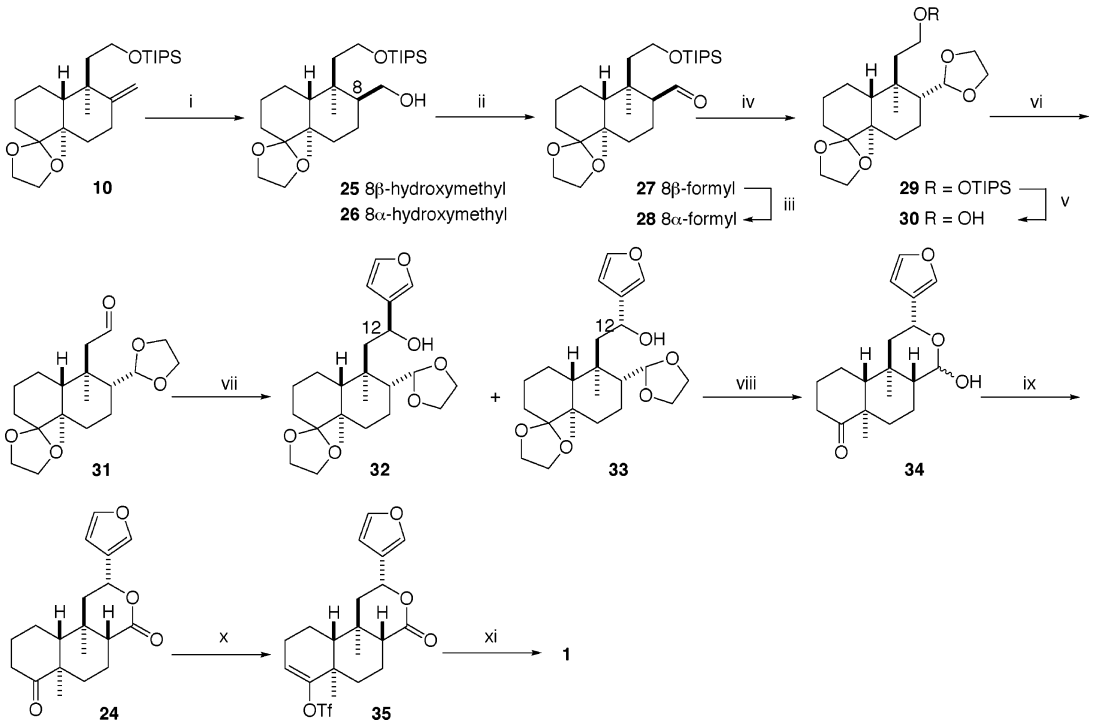
SCHEME 3[a]



[a] Reagents and conditions: (i) BH_3−THF, THF then NaOH, H_2O_2, 92% (**25/26** = 3.8:1); (ii) PDC, AcONa, MS-4A,CH_2Cl_2, quant from **8**α isomer, 89% from **8**β isomer; (iii) MeONa, MeOH, rt, 95%; (iv) 2-ethyl-2-methyl-1,4-dioxolane, ethylene glycol, PTSA, 40 °C, 97%; (v) TBAF, THF, rt, 97%; (vi) PDC, AcONA, MS-4A, CH_2Cl_2, 91%; (vii) 3-furyllithium, *n*-BuLi, THF, −78 °C, 86% (**32/33** = 2:3); (viii) PTSA, H_2O, acetone, reflux, 70% (a mixture of 1:1 diastereomers); (ix) PDC, AcONa, MS-4A,CH_2Cl_2, rt, quant; (x) NaHMDS, Comins' reagent, −78 to −30 °C, 80%; (xi) $Pd(OAc)_2$, DPPF, *n*-Bu_3N, CO, MeOH, DMF, 90 °C, 86%.

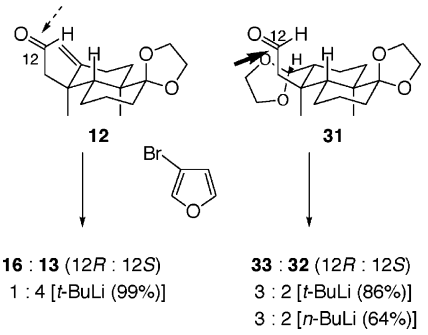


FIGURE 2. Stereochemistry of 3-furyllithium addition.

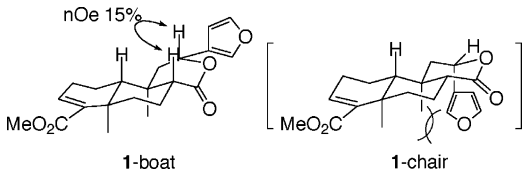


FIGURE 3. Conformation of methyl barbascoate **1**.

In summary, we have completed the first total synthesis of (−)-methyl barbascoate **1** (Scheme 3) in 12 steps from the known decalone **6**. The synthetic sequence is general and would be applicable to other furo-lactone clerodanes such as salvinorins.

Experimental Section

1-(2-((7*S*,11*S*)-7,11-Dimethyl-8-methylenespiro(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-7-yl)ethoxy)-1,1-bis(methylethyl)-2-methyl-1-silapropane (10). To a stirred suspension of methyltriphenylphosphonium bromide (427 mg, 1.19 mmol) in THF (6 mL) was added sodium bis(trimethylsilyl)amide (0.995 mL, 1.0 M solution in THF, 0.995 mmol) dropwise at 0 °C under nitrogen atmosphere. After being stirred for 30 min, a solution of silyl ether **6** (175 mg, 0.399 mmol) in THF (2 mL) was added. The resulting solution was stirred at 65 °C for 4 h. The reaction was quenched by addition of aq ammonium chloride. The product was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. MPLC purification of the residue (eluent: ethyl acetate/*n*-hexane = 1:6) provided methylene compound **10** (151 mg, 87%): $[\alpha]_D$ −16.3 (*c* 0.984, $CHCl_3$); IR (CCl_4) 3100, 2943, 2866, 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.03−1.10 (m, 21H), 1.12 (s, 3H), 1.22−1.54 (m, 5H), 1.56−1.72 (m, 4H), 1.73−1.84 (ddd, J = 9.5, 5.3, 3.2 Hz, 2H), 2.15 (dt like, 1H), 2.34 (m, 1H), 3.55−3.75 (m, 2H), 3.78−3.96 (m, 4H), 4.68 (s, 1H), 4.74 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0 (CH × 3), 17.8, 18.0 (CH_3 × 3), 21.4, 22.9, 23.8, 29.4, 30.3, 31.4, 41.5, 41.9, 43.3, 44.9, 59.5, 64.7, 65.1, 106.2, 113.2, 154.2. Anal. Calcd for $C_{26}H_{48}O_3Si$: C, 71.5; H, 11.1. Found: C, 71.3; H, 11.1.

((7*R*,8*S*,11*R*)-7-(2-(1,1-Bis(methylethyl)-2-methyl-1-silapropoxy)ethyl)-7,11-dimethylspiro(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-8-yl)methan-1-ol (25) and ((7*R*,8*R*,11*R*)-7-(2-(1,1-Bis(methylethyl)-2-methyl-1-silapropoxy)ethyl)-7,11-dimethylspiro(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-8-yl)methan-1-ol (26). To a stirred solution of methylene compound **10** (500 mg, 1.15 mmol) in THF (6 mL) was added borane−THF complex (2.7 mL, 1.04 M solution in THF, 2.86 mmol) at −78 °C under nitrogen atmosphere. After being stirred at room temperature for 1 h, 3 N aq sodium hydroxide (7.6 mL, 23 mmol) followed by hydrogen peroxide (2.6 mL, 30%, 23 mmol) were added at 0 °C. After the mixture was stirred for 6 h at room temperature, the reaction was quenched by addition of 1 N hydrochloric acid. The product

was extracted with ethyl acetate twice. The combined organic layer was washed with brine and evaporated to dryness. The residue was purified by MPLC (eluent: ethyl acetate/*n*-hexane = 1:3) to afford 8β-carbinol **25** (380 mg, 73%) and 8α-carbinol **26** (101 mg, 19%).

Alcohol **25**: $[\alpha]_D$ 0.32 (*c* 0.620, $CHCl_3$); IR (CCl_4) 3472, 2945, 2870, 1462, 1383 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)δ 0.75 (s, 3H), 1.04 (s, 3H), 1.06−1.13 (m, 21H), 1.19−1.91 (m, 13H), 2.11 (m, 1H), 3.34 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.58−3.99 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9 (CH × 3), 17.0, 18.0 (CH_3 × 3), 18.5, 20.1, 21.8, 22.8, 29.8, 30.5, 38.0, 40.6, 43.4, 44.2, 45.6, 59.5, 64.8, 65.2, 65.1, 113.2; *m/z* 454 (M^+, 3), 201 (71), 175 (100), 131 (27), 119 (27), 99 (100), 87 (36), 75 (31); HRMS *m/z* calcd for $C_{26}H_{50}O_4Si$ 454.3478, found 454.3478.

Alcohol **26**: $[\alpha]_D$ 16.2 (*c* 0.827, $CHCl_3$); IR (CCl_4) 3450, 2945, 2868, 1383, 1186 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.01−1.09 (m, 21H), 1.12 (s, 3H), 1.20−1.46 (m, 4H), 1.47−1.60 (m, 4H), 1.61−1.83 (m, 6H), 3.68−4.02 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9 (CH × 3), 17.8, 18.0 (CH_3 × 3), 18.5, 20.1, 21.3, 22.9, 23.8, 30.2, 37.1, 41.8, 43.5, 44.1, 44.2, 59.4, 60.7, 64.7, 65.1, 113.3. Anal. Calcd for $C_{26}H_{50}O_4Si$: C, 68.6; H, 11.0. Found: C, 68.3; H, 10.9.

(7*S*,8*S*,11*S*)-7-(2-(1,1-Bis(methylethyl)-2-methyl-1-silapropoxy)ethyl)-7,11-dimethylspiro(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-8-carbaldehyde (28). To a stirred suspension of pyridinium dichromate (147 mg, 0.392 mmol), sodium acetate (33 mg, 0.392 mmol), and anhydrous molecular sieves 4A powder (67 mg) in dichloromethane (1.2 mL) was added 8α-carbinol **26** (59 mg, 0.131 mmol) in dichloromethane (1.7 mL) at room temperature. After being stirred for 2 h, the organic layer was passed through silica gel short column with the aid of ethyl acetate. Evaporation of the solvents gave aldehyde **28** (60 mg, quant): $[\alpha]_D$ −15.1 (*c* 0.956, $CHCl_3$); IR (CCl_4) 2943, 2868, 1720, 1462, 1385 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)δ 0.91 (s, 3H), 1.01−1.12 (m, 24H), 1.19−1.85 (m, 13H), 2.61 (ddd, *J* = 11.3, 4.3, 2.3 Hz, 1H), 3.64−3.96 (m, 6H), 9.91 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9 (CH × 3), 16.8, 18.0 (CH_3 × 3), 18.2, 19.5, 19.8, 22.6, 28.7, 30.4, 38.3, 41.8, 43.1, 44.1, 55.6, 59.3, 64.8, 65.2, 112.9, 206.6; *m/z* 452 (M^+, 20%), 411 (23), 410 (88), 409 (80), 348 (24), 347 (83), 235 (100), 199 (29), 73 (68); HRMS *m/z* calcd for $C_{26}H_{48}O_4Si$ 452.3322, found 452.3328.

(7*S*,8*R*,11*S*)-7-(2-(1,1-Bis(methylethyl)-2-methyl-1-silapropoxy)ethyl)-7,11-dimethylspiro(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-8-carbaldehyde (27). To a stirred suspension of pyridinium dichromate (128 mg, 0.34 mmol), sodium acetate (29 mg, 0.34 mmol), and anhydrous molecular sieves 4A powder (58 mg, microwave dried) in dichloromethane (1 mL) was added 8β-carbinol **25** (52 mg, 0.113 mmol) in dichloromethane (1.5 mL) at room temperature. After being stirred for 2 h, the organic layer was passed through silica gel short column with the aid of ethyl acetate. Evaporation of the solvents and subsequent MPLC purification (eluent: ethyl acetate/*n*-hexane = 1:4) gave 8β-aldehyde **27** (46 mg, 89%): $[\alpha]_D$ 11.8 (*c* 0.985, $CHCl_3$); IR (CCl_4) 2943, 2868, 1716, 1464, 1383 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00−1.09 (m, 24H), 1.13 (s, 3H), 1.18−1.40 (m, 2H), 1.41−1.74 (m, 6H), 1.75−1.93 (m, 4H), 2.01 (dd, *J* = 11.9, 2.2 Hz, 1H), 3.69 (t, *J* = 7.1 Hz, 2H), 3.73−3.99 (m, 4H), 10.0 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9 (CH × 3), 17.0, 18.0 (CH_3 × 3), 19.8, 20.3, 21.0, 22.8, 25.5, 30.2, 36.8, 42.1, 43.4, 45.9, 54.0, 59.3, 64.8, 65.2, 113.0, 206.5; *m/z* 452 (M^+, 20), 411 (23), 410 (88), 409 (80), 348 (24), 347 (83), 235 (100), 199 (29), 173 (68); HRMS *m/z* calcd for $C_{26}H_{48}O_4Si$ 452.3322, found 452.3328.

Epimerization of Aldehyde 27. Sodium hydride (240 mg, 55% in mineral oil, 5.5 mmol) was washed with *n*-hexane and dried in vacuo. To sodium hydride was added methanol (20 mL) at 0 °C under nitrogen atmosphere. To the solution was added a solution of 8β-aldehyde **27** (832 mg, 1.84 mmol) in methanol (30 mL) at 0 °C, and the resulting solution was stirred at room temperature for 4 h. The reaction was quenched by addition of aq. ammonium chloride and product was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Purification by column chromatography (eluent: ethyl acetate/*n*-hexane = 1:5) afforded 8α-aldehyde **28** (796 mg, 95%).

1-[2-((7*S*,8*R*,11*S*)-8-(1,3-Dioxolan-2-yl)-7,11-dimethylspiro(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-7-yl)ethoxy]-1,1-bis(methylethyl)-2-methyl-1-silapropane (29). A solution of 8α-aldehyde **28** (796 mg, 1.76 mmol), ethylene glycol (2 mL), and PTSA (17 mg, 0.088 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (5 mL) was stirred for 18 h at 40 °C under nitrogen atmosphere. The solution was diluted with ethyl acetate and washed with brine. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate/*n*-hexane = 1:7) gave ketal **29** (851 mg, 97%): $[\alpha]_D$ −5.65 (*c* 1.17, $CHCl_3$); IR (CCl_4) 2945, 2868, 1462, 1383, 1178 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.00−1.11 (m, 24H), 1.20−1.30 (m, 1H), 1.33−1.46 (m, 3H), 1.47−1.64 (m, 5H), 1.66−1.81 (m, 3H), 3.55−3.98 (m, 11H), 4.96 (d, *J* = 2.21 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0 (CH × 3), 16.6, 17.0, 18.0 (CH_3 × 3), 19.6, 20.2, 22.8, 29.6, 30.6, 37.6, 41.2, 43.5, 44.7, 45.9, 59.0, 64.2, 64.8, 65.1, 65.2, 104.2, 113.2, 206.6. Anal. Calcd for $C_{28}H_{52}O_5Si$: C, 67.7; H, 10.5. Found: C, 67.6; H, 10.4.

2-((7*S*,8*R*,11*S*)-8-(1,3-Dioxolan-2-yl)-7,11-dimethylspiro-(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-7-yl)ethan-1-ol (30). To a stirred solution of silyl ether **29** (179 mg, 0.36 mmol) in THF (4 mL) was added TBAF (469 μL, 1.0 M in THF, 0.469 mmol) at 0 °C under nitrogen atmosphere. After the mixture was stirred for 2.7 h, the reaction was quenched by addition of aq ammonium chloride. The product was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was purified by MPLC (eluent: ethyl acetate = 1) to provide alcohol **30** (119 mg, 97%): $[\alpha]_D$ 4.56 (*c* 0.613, $CHCl_3$); IR (CCl_4) 3520, 2953, 2882, 1383, 1049 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.05 (s, 3H), 1.19−1.58 (m, 9H), 1.59−1.82 (m, 5H), 1.89 (br s, 1H), 3.51−3.78 (m, 2H), 3.79−4.00 (m, 8H), 4.87 (d, *J* = 3.71 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 17.6, 19.5, 20.0, 22.8, 29.6, 30.5, 37.8, 41.0, 43.3, 44.6, 46.1, 58.6, 64.4, 64.7 (CH_2 × 3), 65.2, 104.5, 113.2; *m/z* 340 (M^+, 6), 263 (61), 177 (64), 150 (76), 73 (100); HRMS *m/z* calcd for $C_{19}H_{32}O_5$ 340.2250, found M^+, 340.2246.

2-((7*S*,8*R*,11*S*)-8-(1,3-Dioxolan-2-yl)-7,11-dimethylspiro-(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-7-yl)ethanal (31). To a stirred suspension of pyridinium dichromate (310 mg, 0.83 mmol), sodium acetate (69 mg, 0.83 mmol), and anhydrous molecular sieves 4A powder (100 mg, microwave dried) in dichloromethane (1.5 mL) was added alcohol **30** (94 mg, 0.28 mmol) in dichloromethane (2 mL) at room temperature. After being stirred for 2.5 h, the organic layer was passed through silica gel short column with the aid of ethyl acetate. Evaporation of the solvents and subsequent column chromatography (eluent: ethyl acetate/*n*-hexane = 1:1) gave aldehyde **31** (85 mg, 91%): IR (CCl_4) 2951, 2882, 1716, 1475, 1452, 1385 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.06 (s, 3H), 1.35−1.68 (m, 6H), 1.69−1.81 (m, 5H), 1.93 (m, 1H), 2.46 (dd, *J* = 15.6, 4.1 Hz, 1H), 2.76 (dd, *J* = 15.6, 2.2 Hz, 1H), 3.69−4.05 (8H, m), 4.89 (d, *J* = 4.8 Hz, 1H), 9.87 (dd, *J* = 4.1, 2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.2, 18.3, 20.0, 20.9, 22.4, 29.2, 30.2, 39.5, 43.4, 46.6, 47.3, 52.1, 64.4, 64.6, 64.7, 65.1, 104.8, 112.7, 203.7; *m/z* 338 (M^+, 5), 113 (8), 112 (11), 100 (10), 99 (100), 86 (10), 73 (24); HRMS *m/z* calcd for $C_{19}H_{30}O_5$ 338.2093, found 338.2088.

(1*R*)-2-((7*S*,8*R*,11*S*)-8-(1,3-Dioxolan-2-yl)-7,11-dimethylspiro(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-7-yl)-1-(3-furyl)ethan-1-ol (33) and (1*S*)-2-((7*S*,8*R*,11*S*)-8-(1,3-Dioxolan-2-yl)-7,11-dimethylspiro(1,3-dioxolane-2,7′-bicyclo[4.4.0]decane)-7-yl)-1-(3-furyl)ethan-1-ol (32). To a stirred solution of 3-bromofuran (39 μL, 0.43 mmol) in THF (1.0 mL) was added *t*-BuLi (556 μL, 1.45 M solution in *n*-pentane, 0.81 mmol) at −78 °C under nitrogen atmosphere.

After the mixture was stirred at −78 °C for 1 h, a solution of aldehyde **31** (97 mg, 0.29 mmol) in THF (2 mL) was added, and the resulting solution was stirred at −78 °C for 2 h. The reaction was quenched by addition of aq ammonium chloride. After extraction with ethyl acetate twice, combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Column chromatography of the residue (eluent: ethyl aceate/dichloromethane = 1:3) afforded 12*R*-furano alcohol **33** (59 mg, 51%) and 12*S*-furano alcohol **32** (41 mg, 35%) as an amorphous powder.

(12*R*)-Furano alcohol **33**: $[\alpha]_D$ −13.99 (*c* 1.222, $CHCl_3$); IR (CCl_4) 3491, 2951, 2882, 1502, 1475, 1452, 1385 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.07 (s, 3H), 1.19−1.37 (m, 2H), 1.38−1.59 (m, 5H), 1.63−1.98 (m, 5H), 2.06 (dd, *J* = 16.1, 8.7 Hz, 1H), 2.23 (m, 1H), 3.31 (d, *J* = 5.1 Hz, 1H), 3.75−4.05 (m, 8H), 4.82 (br s, 1H), 4.83 (d, *J* = 5.7 Hz, 1H), 6.36 (m, 1H), 7.32−7.41 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.1, 18.9, 19.4, 20.0, 22.6, 29.6, 30.4, 38.3, 43.4, 43.8, 46.2, 46.6, 63.2, 64.2, 64.6, 64.8, 65.3, 105.3, 108.4, 113.2, 131.4, 138.1, 143; *m/z* 407 (28), 406 (M^+, 100), 345 (25), 344 (36), 295 (24), 293 (45); HRMS *m/z* calcd for $C_{23}H_{34}O_6$ 406.2355, found 406.2359.

(12*S*)-Furano alcohol **32**: $[\alpha]_D$ −10.7 (*c* 0.810, $CHCl_3$); IR (CCl_4) 3491, 2951, 2882, 1502, 1475, 1452, 1385 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.08 (s, 3H), 1.18−1.51 (m, 4H), 1.52−1.86 (m, 7H), 1.88−2.11 (m, 3H), 3.67−4.00 (m, 8H), 4.76 (d, *J* = 3.4 Hz, 1H), 4.91 (dd, *J* = 7.4, 2.9 Hz, 1H), 6.4 (m, 1H), 7.33−7.41 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 17.6, 19.0, 20.7, 22.7, 29.5, 30.7, 38.5, 43.5, 45.0, 45.9, 46.4, 63.6, 64.4, 64.8, 65.3, 104.6, 108.6, 113.5, 131.2, 138.4, 143.0; *m/z* 407 (18), 406 (74), 388 (26), 345 (21), 344 (35), 295 (22), 294 (23), 293 (100), 113 (25), 112 (30), 100 (22), 86 (29); HRMS *m/z* calcd for $C_{23}H_{34}O_6$ 406.2355, found 406.2345.

(7*S*,10*R*,11*S*,13*R*)-13-(3-Furyl)-11-hydroxy-1,7-dimethyl-12-oxatricyclo[8.4.0.0^{2,7}]tetradecan-6-one (34). A solution of (12*R*)-furano alcohol **33** (59 mg, 0.145 mmol) and PTSA (8.3 mg, 0.044 mmol) in acetone (4 mL) and water (263 μL, 15 mmol) was heated at 50 °C for 21 h. The product was extracted with ethyl acetate twice. The combined organic layer was washed with brine and evaporated to dryness. Column chromatography of the residue (eluent: ethyl aceate/dichloromethane = 1:5) afforded hemiacetal **34** (33 mg, 70%) as a 1:1 mixture of diastereomers as powder: mp 194 °C; $[\alpha]_D$ −27.6 (*c* 0.722, $CHCl_3$); IR (CCl_4) 3600, 3072, 2992, 2943, 2872, 1703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.16 (s, 3H), 1.35−1.60 (m, 5H), 1.61−1.73 (m, 4H), 1.74−1.92 (m, 2H), 2.05 (m, 1H), 2.21 (m, 1H), 2.58 (dt, *J* 13.8, 6.6 Hz, 1H), 3.01−3.26 (m, 1H), 4.92 (dd, *J* 7.9, 2.9 Hz, 1H), 5.04 (dd, *J* 10.4, 6.6 Hz, 1H), 6.39 (m, 1H), 7.33−7.44 (m, 2H)); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0, 19.4, 20.4, 26.2, 32.3, 35.7, 37.6, 46.5, 46.6, 49.0, 55.9, 62.3, 95.9, 96.0, 108.7, 127.2, 138.9, 143.3, 214.8; *m/z* 300 (18), 152 (33), 121 (24), 95 (31), 94 (100); HRMS *m/z* calcd for $C_{19}H_{24}O_3$ ($M^+ - H_2O$) 300.1725, found 300.1725.

(7*S*,10*R*,13*R*)-13-(3-Furyl)-1,7-dimethyl-12-oxatricyclo-[8.4.0.0^{2,7}]tetradecane-6,11-dione (24). To a stirred suspension of pyridinium dichromate (98 mg, 0.264 mmol), sodium acetate (22 mg, 0.264 mmol), and anhydrous molecular sieves 4A powder (40 mg, microwave dried) in dichloromethane (1 mL) was added hemiacetal **34** (28 mg, 0.088 mmol) in dichloromethane (1.5 mL) at room temperature. After the mixture was stirred for 6 h, the organic layer was passed through a silica gel short column with the aid of ethyl acetate. Evaporation of the solvents gave lactone **24** (29 mg, quantitative) as an amorphous solid: $[\alpha]_D$ 31.2 (*c* 0.686, $CHCl_3$); IR (CCl_4) 2945, 2868, 1759, 1712, 1103 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.06, (s, 3H), 1.10 (s, 3H), 1.33−1.78 (m, 7H), 1.79−2.01 (m, 3H), 2.04−2.32 (m, 2H), 2.44 (m, 1H), 2.61 (dt, *J* = 13.5, 6.5 Hz, 1H), 5.32 (dd, *J* = 10.2, 7.1 Hz, 1H), 6.41 (m, 1H), 7.38−7.52 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.0, 19.0, 21.2, 21.4, 26.2, 31.6, 37.4, 37.5, 45.3, 47.4, 48.8, 55.3, 69.9, 108.5, 124.3, 139.4, 143.6, 173.8, 213.6; *m/z* 316 (M^+, 56), 99 (72), 95 (66), 94 (100), 81 (55); HRMS *m/z* calcd for $C_{19}H_{24}O_4$ 316.1674, found 316.1683.

(7S,10*R*,13*R*)-13-(3-Furyl)-1,7-dimethyl-12-oxa-11-oxotricyclo[8.4.0.0^{2,7}]tetradec-5-en-6-yl (Trifluoromethyl)sulfonate (35). To a stirred solution of ketone **24** (34 mg, 0.11 mmol) in THF (2.0 mL) was added sodium bistrimethylsilylamide (434 mL, 1 M solution in THF, 0.43 mmol) at −78 °C under nitrogen atmosphere. After being stirred for 2 h, Comins's reagent (170 mg, 0.43 mmol) in THF (3.0 mL) was added. The resulting solution was stirred at −30 °C for 1.3 h. The reaction was quenched by addition of aq ammonium chloride. After extraction with ethyl acetate twice, combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Column chromatography of the residue (eluent: ethyl acetate/*n*-hexane = 1:3) provided enol triflate **35** (39 mg, 80%) as crystals: mp 125 °C; $[\alpha]_D$ −7.75 (*c* 0.774, $CHCl_3$); IR (CCl_4) 3038, 2255, 1746, 1410 and 1142 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.19 (s, 3H), 1.35−1.67 (m, 4H), 1.68−2.09 (m, 5H), 2.16−2.22 (m, 2H), 2.55 (dd, *J* = 11.7, 3.6 Hz, 1H), 5.36 (dd, *J* = 10.1, 7.5 Hz, 1H), 5.59 (dd, *J* = 4.7, 3.0 Hz, 1H), 6.42 (dd like, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.46 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1, 20.3, 22.0, 22.5, 26.4, 34.9, 38.7, 41.1, 47.1, 49.6, 55.6, 72.1, 110.6, 116.9, 126.5, 141.6, 145.8, 157.7, 175.7; *m/z* 448 (M^+, 21), 295 (17), 105 (18), 95 (30), 94 (100), 91 (21), 81 (26); HRMS *m/z* calcd for $C_{20}H_{23}F_3O_6S$ 448.1167, found 448.1165.

Methyl (7*S*,10*R*,13*R*)-13-(3-Furyl)-1,7-dimethyl-12-oxa-11-oxotricyclo[8.4.0.0^{2,7}]tetradec-5-ene-6-carboxylate (Methyl Barbascoate, 1). A solution of enol triflate **35** (51.5 mg, 0.155 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), *n*-Bu_3N (38 μL, 0.207 mmol), DPPF (3.8 mg, 0.007 mmol), and methanol (412 μL) in DMF (906 μL) was stirred under carbon monoxide atmosphere at 90 °C for 20 min. Extra MeOH (412 μL), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), and DPPF (3.8 mg, 0.007 mmol) were added, and stirring was continued for 20 min. Further MeOH (412 μL), $Pd(OAc)_2$ (3.8 mg, 0.007 mmol), and DPPF (3.8 mg, 0.007 mmol) were added, and stirring was continued for 23 min. After addition of ethyl acetate, the organic layer was passed through a silica gel short column and evaporated to dryness. The residue was purified by column by chromatography (eluent: ethyl acetate/*n*-hexane = 1:3) to provide methyl barbascoate **1** (35.4 mg, 86%) as crystals: mp 152 °C (lit.[2] mp 152−153 °C); $[\alpha]_D$ −73.6 (*c* 0.425, MeOH) (lit.[2] $[\alpha]_D$ −70); UV λ_{max} (MeOH) 211 nm (14,874); IR (CCl_4) 2991, 2949, 2860, 1759, 1720, 1242 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.28 (s, 3H), 1.45 (dd, *J* = 11.2, 3.1 Hz, 1H), 1.54−1.69 (m, 4H), 1.83−2.01 (m, 3H), 2.18−2.39 (m, 2H), 2.51 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.55 (dt, *J* = 13.1, 3.4 Hz, 1H), 3.70 (s, 3H), 5.34 (dd, *J* = 9.8, 7.6 Hz, 1H), 6.42 (m, 1H), 6.63 (dd, *J* = 4.0, 3.1 Hz, 1H), 7.42 (m, 1H), 7.45 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.3 (t), 18.4 (t), 20.5 (q), 20.7 (q), 27.0 (t), 34.4 (t), 36.9 (s), 37.2 (s), 45.5 (t), 47.8 (d), 51.3 (q), 53.8 (d), 70.0 (d), 108.5 (d), 124.6 (s), 137.1 (d), 139.4 (d), 141.0 (s), 143.7 (d), 167.2 (s), 174.2 (s); *m/z* 358 (M^+, 78), 205 (51), 107 (52), 105 (77), 96 (92), 91 (100); HRMS *m/z* calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1775.

Supporting Information Available: Experimental details of compounds **11**−**13**, **16**, **17**, **19**, and **21**−**23** and ^1H and ^{13}C NMR spectra of compounds **1**, **10**−**13**, **16**, **17**, and **19**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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