A New Stereoselective and Convergent Approach to the Synthesis of Long-Chain Polypropionate Fragments

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Optically pure Diels–Alder adducts of 2,4-dimethylfuran and 1-cyanovinyl (1′*R*)- or (1′*S*)-camphanate are obtained readily. These 1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-1-yl derivatives can be converted with high stereoselectivity into polypropionate fragments such as (−)-(2*R*,3*R*,4*R*,5*S*)-5-(benzyloxy)-3-(isopropyloxy)-2,4-dimethylhept-6-enal ((−)-**16**) or (−)-(2*R*,2′*S*,3′*S*,4′*S*,5′*S*)-2-[4-(benzyloxy)tetrahydro-3,5-dimethyl-5-methoxyfur-2-yl]propanal ((−)-**20**). The latter underwent stereoselective cross-aldolization with the lithium enolate of (+)-(1*S*,4*S*,5*S*,6*S*)-6-*exo*-(benzyloxy)-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one ((+)-**9**) giving an aldol ((−)-**23**); like mode of aldolization) that can be converted into a polypropionate fragment containing nine contiguous stereogenic centers.

Introduction

A large variety of natural products of biological interest contain polypropionate fragments (chain with alternating hydroxy and methyl substituents).[1,2] Several methods and strategies have been developed to provide access to these systems which possess a high density of stereochemical information.[3] The control of the stereochemistry can rely on pericyclic reactions such as the Claisen rearrangement[4] or the Lewis acid-promoted hetero-Diels–Alder addition,[5] on aldol reactions[6] involving imide enolates,[7,8]boron enolates,[9] tin(II)enolates[10] or zirconium enolates,[11] on additions of crotylboronates to aldehydes,[12] on conjugate additions to butenolides,[13] on additions of vinyloxiranes,[14] or on using carbohydrates as starting materials.[15] Other approaches imply two-directional chain elongations and a "desymmetrization" process.[16] Many bicyclic systems with endocyclic double bonds or/and other functions react with high facial selectivity. This

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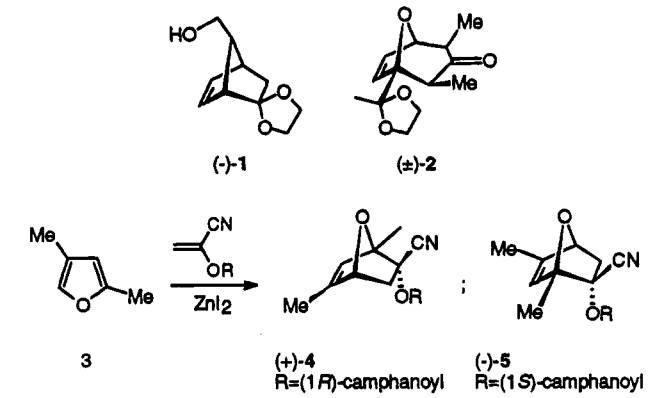
property has been exploited in a synthesis of methymycin starting from bicyclo[4.2.1]nona-2,4,7-triene.[17] The optically pure norbornenyl derivative (−)-**1** has been converted to thynolide,[18] and the racemic bicyclo[3.2.1]oct-6-ene system (±)-**2** derived from 2-acylfuran has been transformed into racemic Prelog−Djerassi lactonic acid.[19] More recently, 8-oxabicyclo[3.2.1]oct-6-ene[20] and 7-oxabicyclo[2.2.1]hept-5-ene derivatives[3a,21] were shown to undergo oxa ring openings via S_N2' reactions with polar metal alkyl reagents leading to the corresponding cyclohept-3-enols and cyclohex-3-enols, respectively, the ozonolysis of which provides polypropionate fragments in their racemic form[20,21] or with enantiomeric excesses approaching 52%.[22] These reports convinced us to disclose our progress on the use of optically pure 1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-one[23] in the highly stereoselective synthesis of polypropionate fragments with four and nine contiguous stereogenic centers. The chemistry developed was inspired from our work on the total synthesis of long-chain carbohydrates and analogues based on the "naked sugar" technology.[24]

Results and Discussion

Recently, we reported[23] that 2,4-dimethylfuran (**3**) obtained in three steps from acetone[25] adds to 1-cyanovinyl (1′*R*)-camphanate in the presence of ZnI_2 and gives, after two recrystallizations from EtOAc/hexane, the adduct (+)-**4** in 61% yield and a diastereomeric purity of 99.75:0.25. A new procedure has been developed which allows one to obtain (+)-**4** (and (−)-**5** starting with 1-cyanovinyl (1′*S*)-camphanate in 85% yield and an optical purity better than 95%. This diastereomeric excess can be improved to better than 99.5% by recrystallization.



Alkaline hydrolysis of (−)-**5** (KOH/H_2O, THF, 20 °C) followed by treatment with formaline (36% aqueous H_2CO) gave enone (−)-**6**, the absolute configuration (1*S*,4*S*) of which was given by its CD spectrum which was similar to that of the "naked sugar" (−)-(1*S*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2-one.[26] Treatment of (−)-**6** in trimethyl orthoformate with Montmorillonite (20 °C, 2 h) gave the corresponding dimethyl acetal which was submitted to hydroboration with $BH_3{\cdot}Me_2S$ followed with an oxidative workup with $NaBO_3{\cdot}4\ H_2O$.

This led to a mixture from which a 44% yield of pure alcohol (+)-**7** was isolated after flash chromatography (Scheme 1). The 400 MHz ^1H NMR spectrum of the crude reaction mixture suggested the presence of a regioisomeric alcohol, the yield of which never surpassed 8%. The same process applied to the racemic enone (±)-**6** derived from **3** and 1-cyanovinyl acetate led to the formation of (±)-**7** accompanied by less than 5% of regioisomeric alcohol. The *exo* face selectivity of the hydroboration was expected for steric reasons[27] and was confirmed by the observation of a typical vicinal coupling constant[28] between protons H_{exo}-C(5) and H-C(4) of 5.8 Hz in the ^1H NMR spectrum of (+)-**7**.

Benzylation of (+)-**7** following the method of Cernecki[29] afforded (+)-**8** (83%), the acidic hydrolysis (Nafion NR50)

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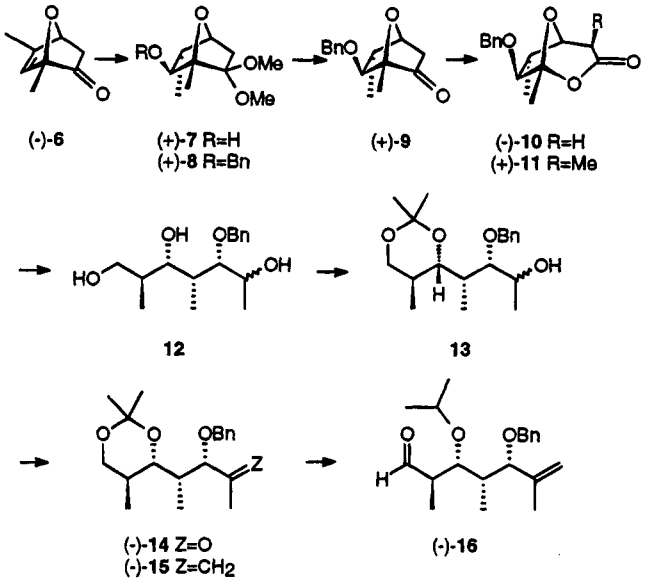
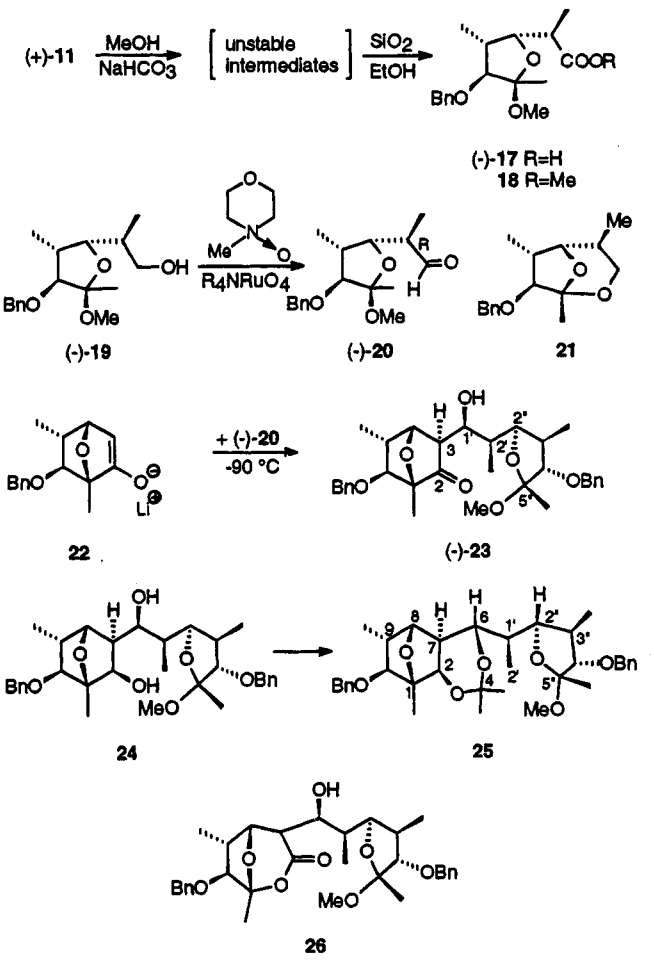
Scheme 1



Scheme 2



of which gave ketone (+)-**9** (92%). Baeyer–Villiger oxidation with *m*-CPBA and $NaHCO_3$ led to (−)-**10** (86%), the conjugate base of which obtained by treatment with $LiN(SiMe_3)_2$ reacted with CH_3I exclusively onto its *exo* face furnishing (+)-**11** (74%) ($^3J(H_{endo}$-C(4),H-C(5)) ≅ 0 Hz). Reduction of uronolactone (+)-**11** with $LiAlH_4/Et_2O$ gave a 1:1 mixture of diastereomeric triols **12** (88%), the treatment of which with dimethoxypropane and $SnCl_2$[30] afforded a mixture of alcohols **13** (70%). Oxidation with 4-methylmorpholine 4-oxide catalyzed with tetrapropylammonium perruthenate[31] generated the methyl ketone (−)-**14** (93%) which reacted with "Instant ylide" ($MePPh_3Br + NaNH_2$)[32] to give (−)-**15** (81%). Selective reduction of the acetonide with diisobutylaluminium hydride led to the corresponding primary alcohol, the oxidation of which[31] afforded aldehyde (−)-**16** (70%), a potentially useful polypropionate fragment containing four contiguous stereogenic centers and two alcoholic functions bearing two orthogonal protective groups. We have also prepared the polypropionate fragment (−)-**20** derived from (+)-**11** (Scheme 2) which is a methyl furanoside and have used it in a highly stereoselective cross-aldolization with the bicyclic ketone (+)-**9**. The treatment of (+)-**11** in MeOH and 1.3 equiv of $NaHCO_3$ at room temperature gave after flash chromatography the (methyl furanosid)-uronic acid (−)-**17**. The corresponding methyl ester **18** (85%) was obtained by treatment of (±)-**17** (derived from (±)-**7**) with CH_2N_2 in Et_2O.

Reduction of **18** with 1 equiv of DIBAH[33] gave a mixture of alcohol (±)-**19**, aldehyde (±)-**20**, and unreacted ester **18**. With 2 or 3 equiv of DIBAH, (±)-**19** was obtained in 94% yield. Treatment of (±)-**17** with $BH_3{\cdot}Me_2S$[34] also gave alcohol (±)-**19** with no trace of aldehyde (±)-**20**. Attempts to oxidize (±)-**19** into (±)-**20** with pyridinium chlorochromate (PCC)[35] with or without NaOAc led to mixtures of the desired aldehyde (±)-**20** and the 1,6-anhydrofuranose **21**. Similar deceiving results were obtained using pyridinium dichromate[36] and the Swern oxidation.[37] The Dess–Martin method[38] was more successful but with low reproducibility. We finally found that oxidation with *N*-methylmorpholine *N*-oxide in the presence of a catalytic amount of tetrapropylammonium perruthenate[31] furnished reproducibly (±)-**20** with a yield of 78%. The optically pure alcohol (−)-**19** was obtained in 56% yield (based on (+)-**11**) via $LiAlH_4$ reduction of the carboxylic acid (−)-**17** derived from (+)-**11**. Oxidation[31] of (−)-**19** led to (−)-**20** (80%). The lithium enolate **22** obtained by reaction of (+)-**9** with $(Me_3Si)_2NLi$ in THF added to aldehyde (−)-**20** at −90 °C and gave a single aldol (−)-**23** (by 400 MHz ^1H NMR spectrum of the crude reaction mixture) isolated in 60% yield together with some unreacted ketone (10–20%). The high *exo* face selectivity of the cross-aldolization of the bicyclic ketone (+)-**9** was expected.[24b] When run with the racemic derivatives **22** and (±)-**20**, a 7:1 mixture of (±)-**23** and a diastereomeric aldol was obtained, suggesting a stereochemical matching for the pairs (−)-**20**/(+)-**9** and (+)-**20**/(−)-**9** in their cross-aldolization. The structure of the minor aldol was not established. That of (±)-**23** was confirmed in the following way. Reduction of (±)-**23** with L-Selectride ($LiB[CH(Me)Et]_3H$) afforded the *exo*-alcohol **24** (81%) (absence of coupling between protons H_{endo}-C(3) and the bridgehead proton H-C(4) and ^3J(H-C(2),H-C(3)) = 6.8 Hz[28]). Treatment of **24** with dimethoxypropane and

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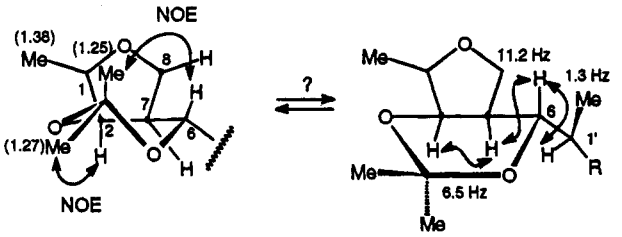

Figure 1.

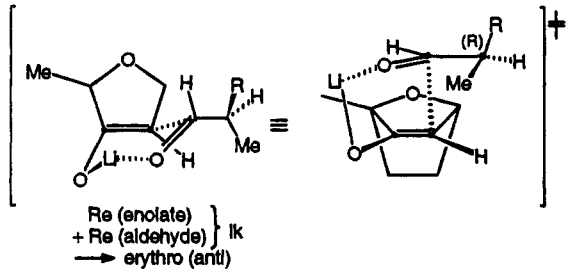

Figure 2.

p-TsOH gave the acetonide **25**, the structure of which was established by its 400 MHz ^{1}H NMR and NOESY spectra. As in the case of (+)-**9** → (−)-**10** the Baeyer–Villiger oxidation of ketone (±)-**23** with *m*-CPBA was regioselective and gave the uronolactone **26** (60%).

A vicinal coupling constant of 11.2 Hz was measured between H-C(6) and H-C(7) of the 3,5,11-trioxatricyclo-[6.2.1.0^{2,7}]undecane unit of acetonide **25**. This demonstrates the *trans* relative configuration for these protons. The ^{1}H NMR data were consistent also with the pseudo–chair and boat conformations or an equilibrium of these two conformations for the 1,3-dioxane unit of **25** (Figure 1). The NOESY spectrum displayed significant NOE between H-C(6) (δ_H = 4.07 ppm) and one of the methyl groups of the acetonide (δ_H = 1.25 ppm) and between H-C(2) (δ_H = 3.74 ppm) and the other methyl group (δ_H = 1.27 ppm) of the acetonide moiety. The same protons showed NOE's with the methyl group signals at δ_H = 0.81 (doublet, $H_3C(2')$) and 1.38 ppm (singlet, Me-C(1)), respectively. The observation of a relatively strong NOE between the signals attributed to Me-C(5″) (1.35 ppm) and H-C(2″) (4.08 ppm) of the tetrahydropyranyl system suggested the (*R*) configuration for that methyl furanoside.

As shown by Heathcock and co-workers[39] for related reactions, the *erythro* (or *anti*) relative configuration of C(1′) and C(3) in the aldol (−)-**23** was expected for steric reasons (lk mode[40]) in a "chelated transition state" (Figure 2). It is confirmed by our ^{1}H NMR data. The very good stereochemical matching between enolate **22** derived form (+)-**9** and aldehyde (−)-**20** is probably due to the fact that this nucleophilic addition follows the Cram[41] and Felkin–Anh models[42] (Figure 2) as already noted by Roush[43] for similar systems. It is not excluded that the minor aldol obtained on condensing the racemic enolate **22** to (±)-**20** results from the mismatched pairs in which the "*anti*-Cram" transition state must be reached for a "lk mode" of aldolization.

Conclusion

A new methodology for the synthesis of long-chain polypropionate fragments has been developed. It is based on the highly stereoselective reactions of the 1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives ("naked sugars of the second generation") which can be obtained readily in both their enantiomeric forms starting with 2,4-dimethylfuran and optically pure 1-cyanovinyl (1*S*)- and (1*R*)-camphanate. In this approach the chiral auxiliary is recovered at an early stage of the synthesis. The method is convergent since it allows one to condense polypropionate fragments possessing four contiguous stereogenic centers via highly stereoselective cross-aldolization with the lithium enolate of 7-oxabicyclo[2.2.1]-heptan-2-one derivatives. Work is underway in this laboratory to obtain other stereomeric polypropionate fragments and to apply them in the total synthesis of natural products and analogues of biological interest.

Experimental Section

General remarks, see ref 44. None of the procedures was optimized. 400 MHz ^{1}H NMR and 100.61 MHz ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer (Aspect X32/3 computer, 1.5 MBYTE maximum acquisition memory). *J* values are given in Hz.

m-Chloroperoxybenzoic acid (*m*-CPBA, 55%) was dissolved in CH_2Cl_2 and washed with saturated aqueous NaCl solution. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The resulting solid contained 70% *m*-CPBA. Column chromatography was performed on Merck silica gel (230–400 mesh).

(−)-(1*S*,2*R*,4*S*)-2-Cyano-1,5-dimethyl-7-oxabicyclo[2.2.1]-hept-5-en-2-yl (1′*S*)-Camphanate ((−)-5). 1-(Cyanovinyl)-(1′S)-camphanate (13.9 g, 55.8 mmol), 2,4-dimethylfuran (13.9 g, 144.2 mmol), and ZnI_2 (4.3 g, 13.5 mmol) were mixed in a 1 L flask protected from light. The flask was placed in a ultrasonic bath and sonicated for 24 h, the temperature reaching 55 °C. The semisolid residue was dissolved in a mixture of CH_2Cl_2 (350 mL), saturated aqueous NaCl solution (160 mL), and H_2O (160 mL) and then extracted with CH_2Cl_2. The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2, then AcOEt) yielded after washing with AcOEt/petroleum ether (7:3) 16.4 g (85%) of a white solid, de 95% (400 MHz ^{1}H NMR). Recrystallization from AcOEt/petroluem ether (7:3) gave 11.78 g (61%), de >99.5% of colorless prisms: mp 143–144 °C; IR (KBr) ν 3070–2800, 1785, 1760–1435, 1305, 1255, 1160, 1100, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.7 (q, ^4J = 1.6), 4.75 (d, ^3J = 4.6), 3 (dd, ^2J = 13.4, ^3J = 4.6), 2.41–2.34 (m), 2.06–1.9 (m, 2 H), 1.83 (d, ^4J = 1.6), 1.82 (s), 1.75 (d, ^2J = 13.4), 1.71–1.65 (m), 1.11, 1.03, 0.87 (3s); $[\alpha]^{25}_D$ = −89° (*c* = 1, $CHCl_3$).

(1*SR*,2*RS*,4*SR*)-2-*exo*-Cyano-1,5-dimethyl-7-oxabicyclo-[2.2.1]hept-5-en-2-yl Acetate. Into a 1 L flask were placed 1-cyanovinyl acetate (14 mL, 133.6 mmol), 2,4-dimethylfuran (6.53 g, 68 mmol), and ZnI_2 (2.17 g, 6.8 mmol). The flask was protected from light and the mixture stirred at 20 °C for 24 h. The semisolid residue was filtered on SiO_2 (CH_2Cl_2), and the solvent was evaporated under reduced pressure to give **3**, 11.3

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g (80%), as colorless crystals, mp 91 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.66 (q, ^4J = 1.7), 4.69 (d, ^3J = 4.8), 2.92 (dd, ^2J = 13.3, ^3J = 4.8), 2.05 (3 H, s), 1.85 (3 H, d, ^4J = 1.7), 1.76 (3 H, s), 1.70 (d, ^2J = 13.3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.2, 151.0, 127.3, 118.1, 89.5, 81.4, 76.5, 43.7, 20.6, 15.1, 12.6.

(−)-(1*S*,4*S*)-1,5-Dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-one ((−)-6). H_2O (145 mL) and KOH 3 N (13.4 mL, 40 mmol) were added to a stirred solution of (−)-**5** (7.26 g, 21 mmol) in THF (175 mL) at 20 °C. After 2 h, formaline (36% H_2CO in H_2O, 7.8 mL) was added. The solution was stirred for a further 30 min and then poured into a mixture of CH_2Cl_2 (180 mL) and H_2O−ice (85 mL). The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, washed with saturated aqueous NaCl solution, and dried ($MgSO_4$). The solvents were evaporated under reduced pressure (20 °C, 30 Torr) or distilled at atmospheric pressure to give 2.8 g (96%) of colorless oil: IR (film) ν 2980, 2940, 1750, 1630, 1440 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.68 (qd, ^4J = 1.8, ^5J = 0.6), 4.89 (d, ^3J = 4.3), 2.30 (dd, ^2J = 15.9, ^3J = 4.3, ^5J = 0.6), 1.92 (d, ^2J = 15.9), 1.89 (d, ^4J = 1.8), 1.48 (s); $[\alpha]^{25}_D$ = −781.5° (*c* = 0.91, $CHCl_3$).

(1*SR*,4*SR*)-1,5-Dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-one ((±)-6). MeONa 30% in MeOH (159 mL, 0.86 mol) was added to a stirred solution of (1*RS*,2*RS*,4*SR*)-2-*exo*-cyano-1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl acetate (18 g, 86.9 mmol) in MeOH (360 mL) at 20 °C. After 2 h formaline (30 mL) was added. The solution was stirred for a further 30 min and then poured into a mixture of CH_2Cl_2 and H_2O−ice. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, washed with saturated aqueous NaCl solution, and dried ($MgSO_4$). The solvents were evaporated under reduced pressure (20 °C, 30 Torr) or distilled at atmospheric pressure to give 10.64 g (89%) of a colorless oil.

(+)-(1*S*,4*S*,5*S*,6*S*)-6-*exo*-Hydroxy-2,2-dimethoxy-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptane ((+)-7). A solution of (−)-**6** (3.86 g, 27.94 mmol) in hexane (39 mL) was added to a stirred mixture of Montmorillonite (17 g) and trimethyl orthoformate (24.5 mL, 0.22 mmol). After being stirred at 20 °C for 2 h, the mixture was filtered and the Montmorillonite washed with EtOAc. The filtrate was washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution, dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil (4.9 g) which was immediately dissolved in dry ether (46 mL). The solution was cooled to −50 °C, and BH_3Me_2S complex (1.77 mL, 18.7 mmol) was added. The mixture was stirred at 20 °C for 2 h, and H_2O (18 mL) was added, followed by $NaBO_3{\cdot}4H_2O$ (8.61 g, 56 mmol). The mixture was stirred overnight and then extracted with EtOAc. The organic extracts were combined, washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash column chromatography (250 g SiO_2, EtOAc/light petroleum, 2:3) to give 2.45 g (44%) of colorless needles, mp 107−108 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.27 (t, ^3J = 5.8), 3.65 (dd, ^3J = 10, 2.8), 3.23, 3.20 (2s), 2.1−1.95 (m), 1.76 (d, ^2J = 12.9), 1.44 (s), 1.13 (d, ^3J = 7.2); $[\alpha]^{25}_D$ = +31.8° (*c* = 1, $CHCl_3$).

(1*SR*,4*SR*,5*SR*,6*SR*)-6-*exo*-Hydroxy-2,2-dimethoxy-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptane ((±)-7). Prepared according to the preceding procedure, starting with (±)-**6**. Colorless prisms: mp 72−73 °C. Anal. Calcd for $C_{10}H_{18}O$ (202.25): C, 59.39; H, 8.97. Found: C, 59.48; H, 9.13.

(+)-(1*S*,4*S*,5*S*,6*S*)-6-*exo*-(Benzyloxy)-2,2-dimethoxy-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptane ((+)-8). A solution of (+)-**7** (1.65 g, 8.16 mmol) in dry THF (12 mL) was added to a stirred suspension of NaH (60% in mineral oil, 1.3 g, 32 mmol) in dry THF (12 mL). Upon termination of H_2 evolution, Bu_4NI (0.29 g, 0.78 mmol) was added, followed by BnBr (3.5 mL, 29.5 mmol). The mixture was stirred overnight and then filtered. The filtrate was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by filtration on silica gel (Et_2O/light petroleum, 1/1) to give 1.99 g (83%) of an oil which crystallized from light petroleum as colorless needles, mp 66.5 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37−7.30 (m), 4.67 (d, ^2J = 12.2), 4.51 (d, ^2J = 12.2), 4.30 (t, ^3J = 5.7), 3.49 (d, ^3J = 3), 3.22 (s), 3.19 (s), 2.33−2.27 (m), 2.02 (ddd, ^2J = 12.8, ^3J = 5.7, ^4J = 1.4), 1.73 (d, ^2J = 12.8), 1.51 (s), 1.08 (d, ^3J = 7.3); $[\alpha]^{25}_D$ = +45.3° (*c* = 0.78, $CHCl_3$).

(1*SR*,4*SR*,5*SR*,6*SR*)-6-*exo*-(Benzyloxy)-2,2-dimethoxy-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptane ((±)-8). Prepared according to the preceding procedure starting with (±)-**7**. Colorless needles: mp 38−39 °C. Anal. Calcd for $C_{17}H_{24}O_4$ (292.37): C, 69.84; H, 8.27. Found: C, 69.95; H, 8.28.

(+)-(1*S*,4*S*,5*S*,6*S*)-6-*exo*-(Benzyloxy)-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one ((+)-9). Nafion NR50 (2.28 g) was added to a solution of (+)-**8** (3.94 g, 13.48 mmol) in acetone (40 mL) and H_2O (2.7 mL). The mixture was heated under reflux for 4 h and then filtered. The filtrate was diluted with EtOAc, washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and evaporated under reduced pressure and the residue purified by filtration on silica gel (Et_2O/light petroleum, 1:1) to give 3.06 g (92%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4−7.27 (m), 4.69 (t, ^3J = 5.7), 4.56 (2 H, s), 3.15 (d, ^3J = 3.3), 2.55−2.46 (m), 2.41 (ddd, ^2J = 17.7, ^3J = 5.7, ^4J = 1.6), 2.25 (d, ^2J = 17.7), 1.46 (s), 1.01 (d, ^3J = 7.3); $[\alpha]^{25}_D$ = +6.0° (*c* = 1.8; $CHCl_3$).

(1*SR*,4*SR*,5*SR*,6*SR*)-6-*exo*-(Benzyloxy)-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one ((±)-9). Prepared according to the preceding procedure starting with (±)-**8**. Colorless needles: mp 58−59 °C. Anal. Calcd for $C_{15}H_{18}O_3$ (246.30): C, 73.15; H, 7.37. Found: C, 73.22; H, 7.25.

(−)-(1*S*,5*S*,6*S*,7*S*)-7-*exo*-(Benzyloxy)-1,6-*endo*-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-one ((−)-10). A mixture of *m*-chloroperoxybenzoic acid (3.1 g, 12.6 mmol) and $NaHCO_3$ (1.2 g, 14.3 mmol) in CH_2Cl_2 was added to a stirred solution of (+)-**9** (2.18 g, 8.87 mmol) in CH_2Cl_2 (100 mL). After being stirred overnight at 20 °C, the mixture was diluted with CH_2Cl_2 and then washed with saturated aqueous NaI solution, with saturated aqueous $Na_2S_2O_3$ solution, and finally with saturated aqueous NaCl solution. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc/light petroleum, 3:2) to give 2 g (86%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) 7.22−7.15 (m), 4.16 (2 H, s), 3.84 (t, ^3J = 6.9), 3.41 (d, ^3J = 3.8), 2.36 (dd, ^2J = 18.3, ^3J = 5.9), 2.08 (d, ^2J = 18.3), 2.20−2.04 (m), 1.71 (s), 0.57 (d, ^3J = 7.5); $[\alpha]^{25}_D$ = −30.1° (*c* = 0.68, $CHCl_3$).

(+)-(1*S*,4*R*,5*S*,6*S*,7*S*)-7-*exo*-(Benzyloxy)-1,4-*exo*,6-*endo*-trimethyl-2,8-dioxabicyclo[3.2.1]octan-3-one ((+)-11). A solution of BuLi 1.6 M in hexane (6.4 mL, 10.2 mmol) was added to a stirred solution of $(Me_3Si)_2NH$ (HMDS) (2.6 mL, 12.7 mmol) in anhydrous THF (15 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min and cooled to −78 °C and a solution of the (−)-**10** (2 g, 7.62 mmol) in dry THF (15 mL) was added. After the mixture was stirred at −78 °C for 30 min, MeI (2.4 mL, 38 mmol) was added and the mixture stirred for 2 h at −78 °C. The solution was poured into a saturated aqueous NH_4Cl solution (40 mL) at 0 °C and then extracted with EtOAc. The organic extracts were combined, washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, Et_2O/light petroleum, 1:1), to give 1.48 g (74%) of a colorless oil which crystallized on standing, colorless needles, mp 84−85 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38−7.31 (m), 4.6 (2 H, s), 4.28 (d, ^3J = 7.8), 3.63 (d, ^3J = 3.7), 2.60−2.50 (m), 2.59 (q, ^3J = 7.5), 1.70 (s), 1.43 (d, ^3J = 7.5), 1.1 (d, ^3J = 7.5); $[\alpha]^{25}_D$ = +58.6° (*c* = 0.88, $CHCl_3$).

(1*SR*,4*RS*,5*SR*,6*SR*,7*SR*)-7-*exo*-(Benzyloxy)-1,4-*exo*,6-*endo*-trimethyl-2,8-dioxabicyclo[3.2.1]octan-3-one ((±)-11). Prepared according to the preceding procedure starting with (±)-**10**. Colorless prisms: mp 61−62 °C. Anal. Calcd for $C_{16}H_{20}O_4$ (276.33): C, 69.55; H, 7.3. Found: C, 69.61; H, 7.30.

(2*S*,3*S*,4*R*,5*S*,6*R* and 6*S*)-5-(Benzyloxy)-2,4-dimethylheptane-1,3,6-triol (12). A saturated solution (7 mL) of $LiAlH_4$ in Et_2O (this solution was prepared by stirring 470 mg of $LiAlH_4$ in 12 mL of dry Et_2O) was added to a solution of (+)-**11** (504 mg, 1.82 mmol) in dry Et_2O (27 mL) at 0 °C. The mixture was warmed to 20 °C and stirred for 1 h. H_2O (0.5 mL) was added followed by Na_2SO_4. The resulting cake was filtered and rinsed with EtOAc. The solvent was evaporated

under reduced pressure to give 455 mg (88%) of a colorless oil. ^{1}H NMR showed that **12** is a 1:1 mixture of diastereoisomers: ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 137.9, 137.8, 128.4, 128.0, 127.8, 127.7, 87.1, 84.3, 78.0, 74.6, 73.1, 72.7, 69.1, 68.5, 68.3, 65.2, 37.0, 36.9, 36.6, 35.5, 21.1, 19.1, 13.8, 13.4, 9.1, 8.6.

(1′*R*,2′*S*,3′*R* and 3′*S*,4*S*,5*S*)-(1′,2′,3′,4,5)-4-[2′-(Benzyloxy)-3′-hydroxy-1′-methylbutyl]-2,2,5-trimethyl-1,3-dioxane (13). Dimethoxypropane (565 μL, 4.6 mmol) and $SnCl_2$ (84 mg, 0.44 mmol) were added to a stirred solution of **12** (380 mg, 1.34 mmol) in dioxane (6.5 mL) 20 °C. After being stirred for 1.5 h, the mixture was diluted with CH_2Cl_2, filtered, and washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified by flash column chromatography (SiO_2, Et_2O/light petroleum, 3:7) to give 302 mg (70%) of a colorless oil: ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 139.2, 139.1, 121.9–128.5, 99.0, 87.6, 85.6, 74.8, 74.4, 74.3, 73.8, 69.6, 66.9, 66.7, 36.3, 35.7, 31.2, 30.4, 30.3, 20.9, 20.3, 19.83, 19.78, 13.3, 12.0, 10.1.

(−)-(1′*R*,2′*S*,4*S*,5*S*)-4-[2′-(Benzyloxy)-3′-oxo-1′-methylbutyl]-2,2,5-trimethyl-1,3-dioxane ((−)-14). 4-Methylmorpholine 4-oxide monohydrate (329 mg, 2.43 mmol) was added to a stirred solution of **13** (518 mg, 1.61 mmol) in anhydrous CH_2Cl_2 (16 mL). After 5 min, molecular sieves (400 mg) were added. After the mixture was stirred for 15 min, tetrapropylammonium perruthenate (262 mg, 0.7 mmol) was added and the mixture stirred for another 15 min at 20 °C. The mixture was filtered on a column of Florisil (Et_2O/light petroleum, 1:4) to give 480 mg (93%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.30 (5 H, m), 4.53 (d, ^2J = 11.5), 4.45 (d, ^2J = 11.5), 3.72 (d, ^3J = 8), 3.68 (dd, ^3J = 5.1, ^2J = 11.6), 3.53–3.44 (2 H, m), 2.2–2.1 (m), 2.17 (3 H, s), 1.92–1.83 (m), 1.38, 1.34 (2s), 1.09 (3 H, d, ^3J = 6.9), 0.7 (3 H, d, ^3J = 6.7); $[\alpha]^{25}_D$ = −14.4° (c = 0.92, $CHCl_3$).

(−)-(1′*R*,2′*S*,4*S*,5*S*)-4-[2′-(Benzyloxy)-1′,3′-dimethylbut-3-enyl]-2,2,5-trimethyl-1,3-dioxane ((−)-15). THF (12 mL) was added to a stirred mixture of instant ylide (methyltriphenylphosphonium bromide and sodium amide, 1.58 g, 3.99 mmol). The suspension was stirred at 20 °C for 5 min and then cooled to −78 °C. A solution of (−)-**14** (406 mg, 1.27 mmol) in dry THF (7 mL) was then added at −78 °C and the solution was allowed to warm to 20 °C and stirred overnight. The mixture was poured into saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with saturated aqueous NaCl solution, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/light petroleum, 1:1) to give 326 mg (81%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.96–7.29 (5 H, m), 5.09 (br s), 4.96 (br s), 4.45 (d, ^2J = 11.4), 4.24 (d, ^2J = 11.4), 3.7 (d, ^3J = 10), 3.68 (dd, ^3J = 5.1, ^2J = 11.4), 3.47 (t, ^3J = 11.2, ^2J = 11.4), 3.35 (dd, ^3J = 1.6, 10.4), 1.95–1.82 (2 H, m), 1.69 (3 H, s), 1.34 (3 H, s), 1.31 (3 H, s), 1.09 (3 H, d, ^3J = 6.6), 0.67 (3 H, d, ^3J = 7.3); $[\alpha]^{25}_D$ = −23° (c = 0.8, $CHCl_3$).

(−)-(2*R*,3*R*,4*R*,5*S*)-5-(Benzyloxy)-3-(isopropyloxy)-2,4-dimethylhept-6-enal ((−)-16). A 1 M solution of DIBAH in toluene (2.9 mL, 2.9 mmol) was added to a solution of (−)-**15** (92 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) cooled to −78 °C. The solution was allowed to warm to 0 °C and stirred 2–5 h. The mixture was poured into 3 M aqueous NaOH solution (6 mL), extracted with CH_2Cl_2, washed with saturated aqueous NaCl solution, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (4 mL). 4-Methylmorpholine 4-oxide monohydrate (44 mg, 0.32 mmol) was added, followed, after 15 min, by tetrapropylammonium perruthenate (38 mg, 0.1 mmol). The mixture was stirred for another 15 min at 20 °C and then filtered on a column of Florisil (Et_2O/light petroleum, 1:4). The solvent was evaporated under reduced pressure to give 64 mg (70%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.7 (d, ^3J = 2.5), 7.35–7.30 (5 H, m), 5.1 (br s), 4.99 (br s), 4.54 (d, ^2J = 11.6), 4.19 (d, ^2J = 11.6), 3.72 (d, ^3J = 6.6), 3.71–3.53 (m, 2H), 2.6–2.52 (m), 1.93–1.83 (m), 1.57 (3 H, s), 1.12–1.01 (m, 12H); $[\alpha]^{25}_D$ = −80.8° (c = 0.8, $CHCl_3$).

(−)-(2*R*,2′*S*,3′*S*,4′*S*,5′*S*)-2-[4′-(Benzyloxy)tetrahydro-5′-methoxy-3′,5′-dimethylfur-2′-yl]propanoic Acid ((−)-17). $NaHCO_3$ (121 mg, 1.44 mmol) was added to a stirred solution of (+)-**11** (296 mg, 1.07 mmol) in MeOH (11 mL) at 20 °C. The mixture was stirred overnight and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (18 g SiO_2, EtOAc/MeOH) to give 293 mg (89%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.27 (m), 4.72 (d, ^2J = 12.1), 4.56 (d, ^2J = 12.1), 4.23 (dd, ^3J = 7.0, 9.4), 3.43 (d, ^3J = 4.5), 3.31 (s), 2.59 (dq, ^3J = 9.4, 6.9), 2.50–2.35 (m), 1.40 (s), 1.17 (d, ^3J = 6.9), 0.99 (d, ^3J = 7.3); $[\alpha]^{25}_D$ = −85.3° (c = 1.0, $CHCl_3$).

This acid should be stored in the freezer and used as soon as possible.

Methyl (2*RS*,2′*SR*,3′*SR*,4′*SR*,5′*SR*)-2-[4′-(Benzyloxy)-tetrahydro-3′5′-dimethyl-5′-methoxyfur-2′-yl]propanoate (18). CH_2N_2 in Et_2O was added to a stirred solution of the acid (±)-**17** (obtained according to the above procedure from (±)-**11**) (0.5 g, 1.64 mmol) in Et_2O (7 mL) at 20 °C until the yellow color persisted. A few drops of AcOH were then added to destroy the excess of CH_2N_2. The solvent was evaporated under reduced pressure to give 0.45 g (85%) of colorless prisms, mp 64–65 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.26 (m), 4.72 (d, ^2J = 12.1), 4.56 (d, ^2J = 12.1), 4.21 (dd, ^3J = 6.6, 9.7), 3.69 (s), 3.41 (d, ^3J = 4.5), 3.3 (s), 2.59 (dq, ^3J = 6.9, 9.7), 2.46–2.31 (m), 1.39 (s), 1.13 (d, ^3J = 6.9), 0.98 (d, ^3J = 7.2).

(−)-(2*R*,2′*S*,3′*S*,4′*S*,5′*S*)-2-[4-(Benzyloxy)tetrahydro-3,5-dimethyl-5-methoxyfur-2-yl]methylpropanol ((−)-19). From the lactone (−)-**11**: $NaHCO_3$ (92 mg, 41 mmol) was added to a stirred solution of (+)-**11** (223 mg, 0.81 mmol) in MeOH (8.5 mL) at 20 °C. The mixture was stirred overnight and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (14 g SiO_2, EtOAc/MeOH) to give (−)-**17** which was dissolved in dry ether (7 mL) and cooled to 0 °C. A 1 M solution of $LiAlH_4$ in Et_2O (1.3 mL, 1.3 mmol) was added, and the mixture was stirred at 20 °C for 1 h. Then H_2O (0.5 mL) and Na_2SO_4 were added. The mixture was filtered and the "cake" washed with EtOAc. The filtrate was evaporated under reduced pressure and purified by flash chromatography (SiO_2, Et_2O/light petroleum, 3:2) to give 132 mg (56%) colorless oil.

From the methyl uronate **18**: A solution of DIBAH 1 M in toluene (21 mL, 21 mmol) was added to a stirred solution of **18** (1.66 g, 5.15 mmol) in anhydrous CH_2Cl_2 at −78 °C. The mixture was stirred at −78 °C for 3.5 h, and MeOH (9 mL) was added, followed by potassium sodium tartrate (25% in H_2O, 49 mL). After being stirred for 2 h, the mixture was extracted with EtOAc, and the extracts were combined, washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, Et_2O/light petroleum, 3:2) to give 1.26 g (83%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.26 (m), 4.71 (d, ^2J = 12.1), 4.55 (d, ^2J = 12.1), 3.95 (dd, $^3J_{H2'H3'}$ = 6.1, $^3J_{H2'H2}$ = 10.2), 3.63 (dd, ^2J = 11, ^3J = 8.2), 3.53 (dd, ^2J = 11, ^3J = 3.5), 3.39 (d, ^3J = 3.3), 3.35 (3 H, s), 2.4–2.25 (m), 1.95–1.85 (m), 1.42 (3 H, s), 1.0 (3H, d, ^3J = 7.3), 0.79 (3 H, d, ^3J = 6.8); $[\alpha]^{25}_D$ = −36.7° (c = 0.97, $CHCl_3$).

N.B.: Flash column chromatography was carried out on Merck (230–400 mesh). Attempts to purify alcohol (−)-**19** on any other kind of silica gel led to formation of the bicyclic acetal **21**. Furthermore, alcohol (−)-**19** must be stored at low temperature (−20 °C) to avoid this transformation.

(−)-(2*R*,2′*S*,3′*S*,4′*S*,5′*S*)-2-[4′-(Benzyloxy)tetrahydro-3′,5′-dimethyl-5′-methoxyfur-2′-yl]propanal ((−)-20). Methylmorpholine 4-oxide monohydrate (199 mg, 0.86 mmol) was added to a stirred solution of (−)-**19** (127 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (15 mL). After 5 min molecular sieves (152 mg) were added. After the mixture was stirred for 15 min, tetrapropylammonium perruthenate (12.6 mg, 0.035 mmol) was added and the mixture stirred for another 15 min at 20 °C. The mixture was filtered on Florisil and the "cake" washed with EtOAc (100 mL). The filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Et_2O/light petroleum, 3:7) to give 100 mg (80%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.71 (d, ^3J = 2.9), 7.37–7.29 (m), 4.74 (d, ^2J = 12), 4.57 (d, ^2J =

12), 4.21 (dd, ^3J = 7.0, 8.8), 3.40 (d, ^3J = 5.1), 3.32 (s), 2.54–2.44 (2 H, m), 1.40 (s), 1.07 (3 H, d, ^3J = 6.8), 1.02 (3 H, d, ^3J = 7.3); $[\alpha]^{25}_D$ = −127° (*c* = 0.77, $CHCl_3$).

(−)-(1*S*,1′*S*,2′*S*,2″*S*,3*R*,3″*S*,4*R*,4″*S*,5*S*,5″*R*,6*S*)-6-*exo*-(Benzyloxy)-3-*exo*-[2′-[4″-(benzyloxy)-2″,3″,4″,5″-tetrahydro-5″-methoxy-3″,5″-dimethylfur-2″-yl]-1′-hydroxypropyl]-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one ((−)-23). BuLi 1.6 M in THF (390 L, 0.02 mmol) was added to a solution of HMDS (136 μL, 0.65 mmol) in anhydrous THF (3 mL), stirred at 0 °C. After being stirred at 0 °C for 30 min, the mixture was cooled to −70 °C and a solution of (+)-**9** (146 mg, 0.59 mmol) in anhydrous THF (3 mL) was added dropwise. The mixture was stirred at −70 °C for 1 h and then cooled to −90 °C. A solution of (−)-**20** (232 mg, 0.79 mmol) in anhydrous THF (3 mL) was then added slowly at −90 °C. After being stirred at this temperature for 3 h, the mixture was added via a cannula to a solution of AcOH (120 μL) in MeOH (10 mL) which had been precooled to −90 °C. The cool bath was removed and the mixture warmed to 20 °C. The solvent was evaporated under reduced pressure and the residue purified by flash column chromatography (SiO_2, Et_2O/light petroleum then, Et_2O) to give 190 mg, 60%, and some starting ketone was also recovered (10–20%). (−)-**23**: colorless needles, mp 122–123 °C; ^{1}H NMR (250 MHz, $CDCl_3$, coupling constants measured under selective signal irradiations conditions) δ 7.39–7.28 (10 H, m), 4.72 (d, ^2J = 12.2), 4.57 (d, ^2J = 12.2), 4.57 (2 H, s), 4.42 (d, ^3JH$_4$H$_5$ = 5.9), 4.19 (dt, ^3JH$_1$′H$_3$ = 8.8, ^3JH$_1$′OH = ^3JH$_1$′H$_2$′ = 2.6), 4.12 (dd, ^3JH$_2$″H$_3$″ = 6.4, ^3JH$_2$′H$_2$″ = 9.5), 3.39 (d, ^3JH$_4$″H$_3$″ = 3.7), 3.32 (3H, s), 3.19 (d, ^3JH$_5$H$_6$ = 3.6), 2.81 (d, ^3JOHH$_1$′ = 2.6), 2.48 (ddq, ^3JH$_5$H$_4$ = 5.9, ^3JH$_5$H$_6$ = 3.7, ^3JHMe = 7.3), 2.41 (d, ^3JH$_1$′H$_3$ = 8.8), 2.34 (ddq, ^3JH$_3$″H$_4$″ = 3.7, ^3JH$_3$″H$_2$″ = 6.3, ^3JH$_3$″Me = 7.4), 1.86 (ddq, ^3JH$_2$′H$_2$″ = 9.5, ^3JH$_2$′H$_1$′ = 2.6, ^3JHMe = 6.8), 1.48 (3 H, s), 1.39 (3 H, s), 1.04 (3 H, d, ^3J = 7.3), 0.99 (3 H, d, ^3J = 7.4), 0.82 (3 H, d, ^3J = 6.8); $[\alpha]^{25}_D$ = −92.8° (*c* = 0.9, $CHCl_3$).

(1*RS*,1′*RS* or 1′SR,2′RS or 2′*SR*,2″*RS*,3*SR*,3″*RS*,4*SR*,-4″*RS*,5*RS*,5″*SR*,6*RS*)-6-*exo*-(Benzyloxy)-3-*exo*-[2′-[4″-(benzyloxy)-2″,3″,4″,5″-tetrahydro-5″-methoxy-3″,5″-dimethylfur-2″-yl]-1′-hydroxypropyl]-1,5-*endo*-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one (minor racemic aldol). Prepared according to the procedure described for the synthesis of (−)-**23**. Purification by flash column chromatography gave 70% of (±)-**23** (mp 130–131 °C) and a second fraction containing 10% of an isomeric aldol, colorless oil: IR (film) ν 3480, 3000–2800, 1750, 1450 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) (toluene, 250 MHz, coupling constants measured under selective signal irradiation conditions) δ 7.3–6.98 (10 H, m), 4.84 (d, ^3JH$_4$H$_5$ = 5.8), 4.55 (d, ^2J = 11.7), 4.37 (dd, ^3JH$_1$′H$_3$ = 9.7, ^3JH$_1$′H$_2$′ = 1.7), 4.23 (d, ^2J = 11.7), 4.22 (1 H, d, ^2J = 12.1), 4.14 (d, ^2J = 12.1), 4.1 (brt, ^3JH$_2$′H$_2$″ = 6.2, ^4JH$_2$″H$_3$″ = 7.7), 3.28 (d, ^3J = 6.3), 3.16 (s), 2.97 (d, ^3J = 3.6), 2.51 (q), 2.45 (d, ^3J = 9.7), 2.37–2.3 (m), 2.25 (dt, ^3JH$_2$′H$_1$′ = 1.7, ^3JH$_2$′H$_2$″ = 6.2, ^3JHMe = 6.9), 1.52, 1.23 (2s), 1.09 (d, ^3J = 6.9), 0.94 (d, ^3J = 7.3), 0.71 (d, ^3J = 7.3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.8, 138.1, 137.7, 128.4–127.5, 103.1, 91.2, 91.1, 85.6, 81.1, 80.1, 72.9, 72, 69.6, 50.8, 48.6, 45.4, 40.1, 34.8, 21.4, 14.3, 13.7, 11.2, 10.7.

(1*RS*,1′*RS*,2*SR*,2′*RS*,2″*RS*,3*SR*,3″*RS*,4*RS*,4″*RS*,5*SR*,-5″*SR*,6*RS*)-6-*exo*-(Benzyloxy)-3-*exo*-[2′-[4″-(benzyloxy)-2″,3″,4″,5″-tetrahydro-5″-methoxy-3″,5″-dimethylfur-2″-yl]-1′-hydroxypropyl]-1,5-*endo*-dimethyl-7-oxabicyclo-[2.2.1]heptan-2-*exo*-ol ((±)-24). L-Selectride 1 M in THF (120 L, 0.12 mmol) was added to a solution of (±)-**23** (33.5 mg, 0.06 mmol) in dry THF (1 mL) cooled to −78 °C. After being stirred at −78 °C for 3 h, the mixture was warmed to 0 °C and stirred for 1.5 h. Aqueous NaOH 3 M (0.3 mL) and then 30% H_2O_2 (0.3 mL) were added. After being stirred overnight, the mixture was extracted with EtOAc, washed with saturated aqueous NaCl solution, and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure to give 27 mg (81%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$, D_2O shake, coupling constants measured under selective irradiations conditions) δ 7.37–7.3 (10 H, m), 4.73 (d, ^2J = 11.9), 4.6 (d, ^2J = 11.9), 4.59 (d, ^2J = 12.2), 4.51 (d, ^2J = 12.2), 4.2 (dd, ^3JH$_1$′H$_3$ = 10.9, ^3JH$_1$′H$_2$′ = 1.8), 4.1 (t, ^3JH$_2$″H$_3$″ = 7.5, ^3JH$_2$′H$_2$″ = 7), 3.96 (d, ^3JH$_4$H$_5$ = 5.3), 3.81 (d, ^3JH$_2$H$_3$ = 6.8), 3.45 (d, ^3JH$_4$′H$_3$″ = 5.9), 3.32 (s), 2.95 (d, ^3JH$_5$H$_6$ = 3.9), 2.52–2.44 (m, ^3JH$_3$″H$_2$″ = 7.5, ^3JH$_3$″H$_4$″ = 6), 2.31 (dd, ^3JH$_1$′H$_3$ = 10.9, ^3JH$_3$H$_2$ = 6.8), 2.18–2.11 (m), 1.85 (pentxd, ^3JH$_2$′H$_2$″ = ^3JH$_2$′Me = 7, ^3JH$_2$′H$_1$′ = 1.9), 1.53, 1.41 (2s), 1.03 (6 H, d, ^3J = 7.2), 0.92 (d, ^3J = 7).

(1*RS*,1′*SR*,2*SR*,2″*RS*,3″*RS*,4″*RS*,5″*SR*,6*RS*,7*RS*,8*SR*,9*SR*,-10*RS*)-10-*exo*-(Benzyloxy)-6-endo-[1′-[4″-(benzyloxy)-2″,3″,4″,5″-tetrahydro-5″-methoxy-3″,5″-dimethylfuran-2″-yl]ethyl]-1,4,4,9-endo-tetramethyl-3,5,11-trioxatricyclo-[6.2.1.0^{2,7}]undecane ((±)-25). *p*-Toluenesulfonic acid (3 mg, 0.015 mmol) was added to a stirred solution of (±)-**24** (24.7 mg, 0.045 mmol) in dimethoxypropane (1 mL). After being stirred for 2 h at 25 °C, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give 24 mg (90%) of a colorless oil: ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.38–7.25 (10 H, m), 4.67 (d, ^2J = 12), 4.6 (d, ^2J = 12.2), 4.54 (d, ^2J = 12), 4.50 (d, ^2J = 12.2), 4.08 (dd, ^3J = 11.8, 5.1), 4.07 (dd, ^3J = 11.2, 1.3); 3.89 (d, ^3J = 5.2), 3.74 (d, ^3J = 6.5), 3.59 (br s), 3.22 (3 H, s), 3.09 (d, ^3J = 4), 2.34 (dd, ^3J = 6.5, 11.2), 2.30 (m), 2.08 (m), 1.80 (m), 1.38 (3 H, s), 1.35 (3 H, s), 1.27 (3 H, s), 1.25 (3 H, s), 1.08 (3 H, d, ^3J = 7.1), 1.03 (3 H, d, ^3J = 7.4), 0.81 (3 H, d, ^3J = 7.4); ^{13}C NMR (100.6 MHz, CD_3COCD_3) δ 139.9, 139.6, 129.0, 128.9, 128.2, 128.1, 128.0, 127.9, 109.5, 99.7, 92.4, 91.0, 88.1, 81.7, 79.3, 73.9, 72.2, 71.6, 67.0, 48.3, 47.1, 43.3, 42.3, 39.7, 35.3, 30.3, 30.1, 29.9, 29.7, 29.5, 29.3, 29.1, 27.4, 26.5, 24.8, 18.0, 13.9, 12.5, 11.7, 9.2, 8.5; MS (CI NH_3) *m*/*z* 551 (8), 550 (20), 549 (18), 492 (6), 491 (6), 108 (6), 92 (11), 91 (100), 90 (5).

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Supplementary Material Available: IR, assigned ^{1}H NMR spectra, ^{13}C NMR, and MS spectral data as well as elemental analyses of most of the new compounds including (−)-**5**, (−)-**6**, (+)-**7**, (+)-**8**, (+)-**9**, (−)-**10**, (+)-**11**, **12**, **13**, (−)-**14**, (−)-**15**, (−)-**16**, (−)-**17**, **18**, (−)-**19**, (−)-**20**, (−)-**23**, (±)-**24**. ^{1}H NMR and NOESY ^{1}H NMR spectra of (±)-**25** (10 pages). This material is contained in libraries on microfiches, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.