Enantiospecific syntheses of oxacyclodecanes from carvone via mild Lewis acid mediated etherification

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An efficient enantiospecific syntheses of oxatri-/tetra-cyclodecanes have been accomplished starting from (R)-carvone. A mild Lewis acid (BF$_3$·OEt$_2$) mediated intramolecular etherification is used as the key step. Structurally aesthetic tri- and tetracyclic ethers have been synthesized.

Keywords: (R)-Carvone, terpenes, cyclic ethers, Lewis acid, etherification

Monoterpenes (a 10-carbon containing compounds) are the simplest compounds of terpenes and can be obtained from combination of two isoprene molecules. They constitute acyclic, monocyclic, bicyclic and tricyclic structures. The chief source of them are plants, flowers, fruits, leaves and spices. Notably, monoterpenes are useful chiral auxiliaries, while their potential application has not been still properly explored. Though carbohydrates have been widely employed as chiral synthons, monoterpenes are essential starting materials in the enantioselective synthesis natural as well as unnatural products due to their ubiquitous nature. Monoterpenes are significant, as they are available as commercial chemicals. Further, unlike amino acids and carbohydrates, monoterpenes are found in both enantiomeric forms with limited stereocenters that helps to reduce unnecessary chemical reactions to dispose undesired chiral center(s). Furthermore, monoterpenes can be easily restructured into cyclic as well as acyclic fragments that permits implantation to the required carbocyclic cores of desired products. Since monoterpenes are chiral natural products, they are enantiomerically pure in nature. Thus, making use of monoterpenes to accomplish enantioselective total synthesis of natural and unnatural products is essential in the field of organic synthesis.

Xanthone based natural products are the chemical constituents of genus Garcinia (Figure 1). Most of Garcinia natural xanthones and their derivatives exhibit potent biological activities. These natural products in common possess oxatricyclo [4.3.1.0$^{3,7}$] decane part structure. To the best of our knowledge, very few reports exist on the synthesis of Garcinia xanthones; only a few research groups have attempted the synthesis of oxatricyclo [4.3.1.0$^{3,7}$] decane core.

In continuation to our research interest on the accomplishment of enantiomerically pure terpene natural products and chiron based approaches using commercially available chiral monoterpenes (R)-carvone, herein, we describe a synthetic strategy for the enantiospecific synthesis of oxatricyclo [4.3.1.0$^{3,7}$] decanes using mild Lewis acid (BF$_3$·OEt$_2$) promoted intramolecular etherification, as the key step.

It was intended that the tri- and tetra-cyclic ethers could be obtained from ketones through a stereoselective reduction of carbonyl group and acid catalyzed intramolecular etherification sequence (Scheme I). We envisioned that the suitably positioned double bond of isopropenyl moiety could be served as an ideal non-disposable electrophilic functional group for intramolecular nucleophilic addition of hydroxyl group, in the presence of suitable acid as promoter. The required ketones which in turn can be synthesized using the chiral starting material(s) (R)-carvone(s) 7.

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† Deceased on 20th January 2013.
To begin with, synthesis of enol ester 8a was planned for this study\(^9,10\), as depicted in Scheme IIa. Thus, generation of kinetic lithium enolate of (R)-carvone 7a with lithium hexamethyldisilazide (LiHMDS) in hexane and in situ double Michael addition with the Michael acceptor methyl methacrylate, delivered the bicyclic keto ester 6a in 70% yield, with high stereoselectivity (Scheme IIa). Stereoselective reduction of carbonyl group of 6a with NaBH\(_4\), afforded the exo-secondary alcohol 8a, in 91% yield. The stereoselective outcome of the reduction 6a can be explained on the basis of approaching the reducing agent (NaBH\(_4\)) from the less hindered exo-face of the ketone. To our delight, the intramolecular etherification reaction of 8a with 0.5 equiv of the Lewis acid \((\text{BF}_3 \cdot \text{OEt}_2)\), gave the expected tricyclic ether 5a, in excellent yield (Scheme IIa). On the other hand, reduction of both keto as well as ester groups of 6a with LiAlH\(_4\), furnished the diol 9a in 94% yield\(^11\). Thereafter, intramolecular etherification of the diol 9a in the presence of \(\text{BF}_3 \cdot \text{OEt}_2\), afforded the tricyclic ether 5c (Scheme IIb). Similarly, repetition of the above synthetic sequence with 6-methyl carvone 7b\(^12,13\), afforded the cyclic ethers 5b and 5d, in 90 and 94% yields, respectively (Scheme IIa and Scheme IIb).

After successfully demonstrating the Lewis acid (\(\text{BF}_3 \cdot \text{OEt}_2\)) mediated intramolecular etherification for the accomplishment of tri-cyclic ethers (5a-d, Scheme IIa and Scheme IIb), we turned our attention on the synthesis of cyclic ethers 5e and 5f (Scheme IIIa and Scheme IIIb). Thus, the bicyclic keto ester 6a was transformed into the homologated ester 12 using base hydrolysis, acid chloride formation, diazotization and photochemically induced
one carbon homologation protocol. Then, selective reduction of the ketone of keto ester 12 with NaBH₄ and BF₃·OEt₂ mediated etherification sequence, furnished the cyclic ether 5e (Scheme IIIa). Reduction of both ketone and ester groups of 12 with LiAlH₄, afforded the diol 14, which on catalytic BF₃·OEt₂ reaction, gave the cyclic ether 5f (Scheme IIIb).

Furthermore, to demonstrate the applicability of the strategy, next, we aimed at the synthesis of tetracyclic ethers. The bicyclic keto ester 6b was chosen for this study. Thus, base hydrolysis of the bicyclic keto ester 6b, gave the carboxylic acid 10b. Reaction of carboxylic acid 10b, with oxalyl chloride and subsequent diazotization, furnished the diazoketone 11b. Thereafter, the C-H insertion reaction of rhodium carbenoid 11b afforded the isotwistanedione 15b. Reduction of the diketone 15 with LiAlH₄, furnished the diol 16, with high stereoselectivity. The stereoselectivity in the reduction of diketone 15 was predicted based on the reason that the reducing agent (LiAlH₄) would approach the ketones from the less hindered exo-faces of the compound and thus,

Scheme II — Synthesis of tri-cyclic ethers 5a-d from (R)-carvones 7a-b

Scheme III — Synthesis of tri-cyclic ethers 5e-f from 6a
facilitate its hydride attack on the carbonyl groups from anti-position to the bulky moieties. Finally, BF$_3$·OEt$_2$ mediated intramolecular cyclization, gave the tetracyclic ether 5g, in near quantitative yield (Scheme IVa). Chemoselective mesylation of relatively less hindered hydroxyl group of the diol 16 led to the formation of 17. Final etherification of 17, gave the tetra-cyclic ether 5h in near quantitative yield (Scheme IVb).

In summary, we have established enantiospecific syntheses of oxatri-/tetra-cyclodecanes from chiral monoterpene (R)-carvone. A mild Lewis acid (BF$_3$·OEt$_2$) mediated intramolecular etherification was used as the key step. Structurally aesthetic tri- and tetracyclic ethers have been accomplished.

**Experimental Section**

Melting points were recorded on a Buchi M-560 apparatus and are uncorrected. IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were recorded on JEOL JNM k-300 spectrometer using a 1:1 mixture of CDCl$_3$ and CCl$_4$ as the solvent. The chemical shifts (δ, ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for $^1$H) or the central line (77.0 ppm) of CDCl$_3$ (for $^{13}$C). In the $^{13}$C NMR, the nature of carbons (C, CH, CH$_2$ and CH$_3$) was determined by recording the DEPT-135 spectra, and is given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer using electron spray ionization (ESI) mode. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and [α]$_D$ values are given in units of 10$^{-1}$ deg cm$^2$ g$^{-1}$. All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate or hexane and methylene chloride as eluents. Acme’s silica gel (100–200 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

(−)-Methyl(1R,2R,4S,5S,6S,8S)-5-hydroxy-8-isopropenyl-2,4,6-trimethyl-bicyclo[2.2.2]octane-2-carboxylate, 8b: To an ice cold, magnetically stirred solution of the keto ester 6b (100 mg, 0.38 mmol) in dry methanol (2 mL) was added NaBH$_4$ (43 mg, 1.14 mmol) and stirred for 1 h at the same temperature. The solvent was removed under reduced pressure and water (3 mL) was added to the residue followed by 3
N aqueous HCl (3 mL) and extracted with CH2Cl2 (3 × 5 mL). The combined CH2Cl2 extract was washed with brine and dried (anhdy. Na2SO4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:30 to 1:10) as eluent furnished the secondary alcohol 8b (81 mg, 80%) as oil. $[\alpha]_{D}^{27} +106.5$ (c 7.5, CHCl3). IR (neat): 3568, 2950, 2929, 2875, 1728, 1629, 1575, 1375, 1274, 1211, 1134, 1105, 889 cm⁻¹; ¹H NMR (300 MHz, CDCl3+CCl4): δ 4.98 (2 H, s, CH2=C), 3.66 (3 H, s, OCH3), 3.44 (1 H, m, CH-CH2), 2.30-2.00 (2 H, m), 2.00-1.60 (5 H, m), 1.86 (3 H, s, olefinic-CH), 1.60-1.10 (1 H, m), 1.30 (3 H, s) and 0.99 (3 H, s) [2 × tert-CH3]. 1.05 (3 H, d, $J= 7.2$ Hz, sec-CH3); ¹³C NMR (75 MHz, CDCl3+CCl4): δ 176.6 (C, O=C=O), 149.1 (C, C=CH2), 113.9 (CH2, CH=CH2), 113.9 (CH2, CH=CH2), 51.9 (CH3, O-CH3), 46.1 (C), 45.4 (2 C, CH, CH2), 39.7 (CH), 39.0 (C), 34.6 (CH2), 26.3 (CH3), 25.4 (CH), 23.8 (CH3), 21.5 (CH2), 13.3 (CH3); HRMS: $m/z$ Calcd for C16H26O3Na (M+Na): 289.1780. Found: 289.1790.

(−)-(1S,2S,3S,4R,5R,7R)-5-Hydroxymethyl-7-isopropenyl-1,3,5-trimethyl-bicyclo[2.2.2]octan-2-ol, 9b: To a cold (0 °C), magnetically stirred solution of the keto ester 6b (100 mg, 0.38 mmol) in dry ether (3 mL) was added LiAlH4 (43 mg, 1.14 mmol) and stirred for 1 h at RT. The reaction mixture was then diluted with ether (3 mL) and quenched with a few drops of water. The organic layer was separated and the aqueous phase was extracted with ether (3 × 4 mL). The combined organic layer was washed with brine and dried (anhdy. Na2SO4). Evaporation of the solvent furnished the diol 9b (86 mg, 95%) as oil. $[\alpha]_{D}^{27} +72.3$ (c 9.7, CHCl3). IR (neat): 3429, 2922, 2875, 1631, 1454, 1375, 1024, 887 cm⁻¹; ¹H NMR (300 MHz, CDCl3+CCl4): δ 5.02 and 5.00 (2 H, 2 × s, CH2=C), 3.45 and 3.23 (2 H, 2 × d, $J= 10.5$ Hz, CH2OH), 3.38 (1 H, dd, $J= 9.0$ and 1.8 Hz, CH-OH), 2.50-1.60 (7 H, m), 1.87 (3 H, s, olefinic-CH), 1.40-0.70 (2 H, m), 1.13 (3 H, s) and 0.96 (3 H, s) [2 × tert-CH3], 1.08 (3 H, d, $J= 7.2$ Hz, sec-CH3); ¹³C NMR (75 MHz, CDCl3+CCl4): δ 150.1 (C, C=CH2), 113.5 (CH2, CH=CH2), 76.8 (CH, CH-OH), 70.3 (CH3, CH2-CH2), 47.6 (CH2), 45.7 (CH), 38.9 (C), 37.4 (CH), 37.1 (C), 31.2 (CH), 25.9 (CH3), 25.4 (CH3), 24.1 (CH3), 22.4 (CH2), 13.5 (CH3); HRMS: $m/z$ Calcd for C18H26O3Na (M+Na): 261.1830. Found: 261.1828.

(−)-Methyl-2-[(IR,2S,4S,6S,8R)-8-isopropenyl-2,6-dimethyl-5-oxobicyclo[2.2.2]oct-2-yl]-acetate, 12

Step 1: Acid, 10a: A magnetically stirred solution of the keto ester 6a (1.0 g, 4 mmol) in methanol (5 mL) and 10% aqueous NaOH (5 mL) was refluxed for 8 h. The reaction mixture was cooled to RT and washed with CH2Cl2 (10 mL). Then, the aqueous layer was acidified with 3 N HCl and extracted with CH2Cl2 (3 × 10 mL). The CH2Cl2 extract was washed with brine and dried (anhdy. Na2SO4). Evaporation of the solvent furnished the acid 10a (870 mg, 92%) as sticky solid, which was recrystallized from a mixture of hexane and CH2Cl2.

Step 2: Acid chloride: To a magnetically stirred solution of the acid 10a (820 mg, 3.47 mmol) in dry benzene (3 mL) was added oxalyl chloride (6.95 mL, 0.61 mmol) and stirred for 2 h at RT. Evaporation of the solvent and excess oxalyl chloride under reduced pressure afforded the acid chloride, which was used immediately for the preparation of the diazoketone 11a.

Step 3: Diazoketone, 11a: A solution of the acid chloride in dry ether (6 mL) was added drop wise to a cold (0 °C), magnetically stirred ethereal solution of diazomethane (excess, prepared from 2 g of N-nitroso-N-methylurea and 50 mL of 60% aqueous KOH solution and 50 mL of ether) and the reaction mixture was stirred at RT for 2 h. Careful evaporation of the excess diazomethane and solvent on water bath and rapid purification of the residue over a neutral alumina column using ethyl acetate-hexane (1:5) as eluent furnished the diazoketone 11a (831 mg, 90%) as yellow oil.

Step 4: Homologated Ester, 12: A solution of diazo ketone 11a (800 mg, 3.07 mmol) in methanol (100 mL) was placed in a pyrex photochemical reactor and irradiated with a Hanovia medium pressure mercury vapor lamp for 2 h. Evaporation of the solvent and purification of the photolysate on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the homologated ester 12 (600 mg, 74%) as oil. $[\alpha]_{D}^{25} +53.8$ (c 7.8, CHCl3). IR (neat): 2951, 1734, 1720, 1644, 1450, 1377, 1198, 1105, 1016, 895 cm⁻¹; ¹H NMR (300 MHz, CDCl3+CCl4): δ 4.70 and 4.69 (2 H, 2 × s, CH2=C), 3.65 (3 H, s,
CHCl₃). IR (neat): 3570, 2929, 2873, 1736, 1635, 2879, 1452, 1375, 1107, 1018, 887 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 4.98 and 4.91 (2 H, s, CH₂=C), 3.78 (1 H, dt, J = 13.8 and 4.2 Hz), 1.36 (1 H, dd, J = 13.8 and 4.2 Hz), 1.41 (1 H, dd, J = 13.8 and 4.2 Hz), 2.40-2.10 (3 H, m), 2.05-1.80 (2 H, m), 1.80-1.60 (2 H, m), 1.60-1.40 (4 H, m), 1.30-1.20 (1 H, m), 1.09 (3 H, s, tert-CH₃), 1.03 (3 H, s, tert-CH₃), 1.41 (1 H, dd, J = 13.8 and 4.2 Hz), 2.37 and 2.50 (2 H, 2 × d, J = 13.8 Hz, CH₂-C≡C), 2.40-2.10 (3 H, m), 1.96 (1 H, dd, J = 11.1, 9.3 and 1.8 Hz), 2.10-1.60 (3 H, m), 1.87 (3 H, s, olefinic-CH₃), 1.51 (1 H, dd, J = 13.8 and 4.2 Hz), 1.36 (1 H, dd, J = 13.8 and 1.8 Hz), 1.20 (3 H, s, tert-CH₃), 1.03 (3 H, d, J = 7.5 Hz, sec-CH₃). ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 172.2 (C, O-C=O), 150.7 (C, C=CH₂), 109.2 (CH₂, CH₂=CH₂), 72.5 (CH, CH-OH), 51.1 (CH₃, OCH₃), 46.1 (CH₂), 41.0 (CH), 40.6 (CH₂), 38.6 (CH), 35.8 (CH), 34.3 (C), 31.5 (CH), 27.2 (CH₃), 23.0 (CH₃), 20.1 (CH₂), 13.1 (CH₃); HRMS: m/z Calcd for C₁₆H₂₄O₃Na (M+Na): 287.1623. Found: 287.1622.

(−)-Methyl 2-[(IR,2S,4S,5S,6S,8R)-5-hydroxy-8-isopropenyl-2,6-dimethyl-bicyclo[2.2.2]oct-2-yl]acetate, 13: To an ice cold, magnetically stirred solution of the keto ester 12 (80 mg, 0.3 mmol) in dry methanol (3 mL) was added LiAlH₄ (93 mg, 2.44 mmol) and stirred for 1 h at RT. The reaction mixture was then diluted with ether (3 × 4 mL). The combined CH₂Cl₂ extract was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (2:3) as eluent furnished the diole 14 (199 mg, 98%) as colorless solid, which was recrystallized from a mixture of methanol and hexane. M.p.: 58-60 °C. [α]D₂⁰ = −113.9 (c 4.6, CHCl₃). IR (neat): 3421, 3070, 2947, 2869, 1631, 1452, 1375, 1045, 1045, 1016, 887, 739 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 5.03 (2 H, s, CH₂-C≡C), 3.61 (1 H, dd, J = 9.9 and 6.6 Hz, CH-OH), 3.08 (1 H, d, J = 5.4 Hz), 2.02-1.90 (4 H, m), 2.00-1.60 (2 H, m), 1.86 (3 H, s, olefinic-CH₃), 1.62 and 0.77 (2 H, 2 × d, J = 14.4 Hz), 1.30-0.90 (2 H, m), 1.07 (3 H, s), 1.04 (3 H, s) and 1.03 (3 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 150.0 (C, C=CH₂), 113.5 (CH₂, CH₂=CH₂), 109.1 (CH₂, CH₂=CH₂), 72.6 (CH, CH-OH), 59.2 (CH₂, CH₂-OH), 45.1 (CH₂), 41.7 (CH₂), 40.8 (CH), 38.8 (CH), 35.9 (CH), 33.2 (C), 31.0 (CH), 27.2 (CH₃), 23.0 (CH₃), 19.9 (CH₂), 13.2 (CH₃); HRMS: m/z Calcd for C₁₆H₂₄O₃Na (M+Na): 289.1830. Found: 289.1780. 

(−)(7S,2R,3R,5S,6R,7S,9R)-9-Isopropenyl-1,3,6-trimethyltricyclo[4.3.1.0³,⁷]decane-2,5-diol, 16: To a cold (0 °C), magnetically stirred solution of the dione 15 (200 mg, 0.81 mmol) in dry ether (3 mL) was added LiAlH₄ (93 mg, 2.44 mmol) and stirred for 1 h at RT. The reaction mixture was then diluted with ether (5 mL) and quenched with a few drops of water. The organic layer was separated and the aqueous phase was extracted with ether (3 × 4 mL). The combined organic layer was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (2:3) as eluent furnished the diole 16 (199 mg, 98%) as colorless solid, which was recrystallized from a mixture of methanol and hexane. M.p.: 58-60 °C. [α]D₂⁰ = −131.0 (c 7.0, CHCl₃). IR (neat): 3377, 2925, 2879, 1452, 1377, 1107, 1018, 887 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 4.99 and 4.90 (2 H, 2 × s, CH₂-C≡C), 3.77 (1 H, dd, J = 9.3 and 3.3 Hz, CH-OH), 3.75-3.40 (2 H, m, CH₂-OH), 2.40-1.60 (8 H, m), 1.86 (3 H, s, olefinic-CH₃), 1.61 (2 H, t, J = 7.5 Hz), 1.41 (1 H, dd, J = 13.8 and 4.2 Hz), 1.35-1.20 (1 H, m), 1.09 (3 H, s, tert-CH₃), 1.01 (3 H, d, J = 7.2 Hz, sec-CH₃). ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 150.8 (C, C=CH₂), 109.1 (CH₂, CH₂=C), 72.6 (CH, CH-OH), 59.2 (CH₂, CH₂-OH), 45.1 (CH₂), 41.7 (CH₂), 40.8 (CH), 38.8 (CH), 35.9 (CH), 33.2 (C), 31.0 (CH), 27.2 (CH₃), 23.0 (CH₃), 19.9 (CH₂), 13.2 (CH₃); HRMS: m/z Calcd for C₁₆H₂₆O₃Na (M+Na): 287.1622. Found: 287.1622.
43.0 (C), 42.6 (CH₂), 37.5 (C), 26.1 (CH₃), 24.4 (CH₃), 24.1 (CH₃), 21.8 (CH₂), 20.8 (CH₃); HRMS: m/z Calcd for C₁₆H₂₀O₂Na (M+Na): 273.1830. Found: 273.1842.

(−)-(1S,2R,3S,5S,6R,7S,9R)-2-Hydroxy-9-isopropenyl-1,3,6-trimethyltricyclo[4.3.1.0³⁷]decan-5-yl-methanesulfonate, 17: To a cold (0 °C), magnetically stirred solution of the diol 16 (100 mg, 0.4 mmol) in pyridine (1 mL) and CH₂Cl₂ (1 mL) was added methanesulfonyl chloride (0.15 mL, 1.9 mmol) and the reaction mixture was stirred for 1 h at RT. It was then diluted with water (2 mL) and extracted with CH₂Cl₂ (3 × 3 mL). The organic layer was washed with 3 N aqueous HCl, saturated aqueous NaHCO₃ solution and brine, and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the ether 17 (128 mg, 98%) as colorless solid, which was recrystallized from a mixture of methanol and hexane.

M.p.: 88-90 °C. [α]D²⁵: −65.6 (c 8.8, CHCl₃). IR (neat): 3565, 2949, 2873, 1633, 1455, 1350, 1176, 1075, 956, 927, 810 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 4.96 and 4.94 (2 H, 2 × s, CH₂=C), 4.37 (1 H, dd, J = 9.6 and 6.3 Hz, CH-OMs), 3.07 (1 H, s), 2.92 (3 H, s, OMs), 2.80 (1 H, dd, J = 14.7 and 9.9 Hz), 2.10-1.60 (5 H, m), 1.79 (3 H, s, olefinic-CH₃), 1.53 and 0.85 (2 H, 2 × d, J = 14.1 Hz), 1.47 (1 H, dd, J = 14.7 and 6.3 Hz), 1.08 (3 H, s), 1.04 (3 H, s) and 0.96 (3 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 149.1 (C, C=CH₂), 114.0 (CH₃, CH₂=C), 87.1 (CH, CH-OMs), 87.0 (CH, CH-CH₂), 47.3 (CH₂), 46.5 (CH), 45.7 (CH), 43.5 (C), 43.3 (2C, C, CH₂), 38.1 (CH₃), 37.4 (C), 25.7 (CH₃), 24.0 (CH₃), 23.8 (CH₃), 21.4 (CH₃), 20.5 (CH₃); HRMS: m/z Calcd for C₁₆H₂₂O₃Na [(M+Na)-H₂O]: 275.1725. Found: 275.1740.

General procedure for intramolecular etherification reaction (GP)

To a cold (0 °C), magnetically stirred solution of the alcohol 8/9/13/14/16/17 (0.2 mmol) in dry CH₂Cl₂ (3 mL) was added a catalytic amount of BF₃·OEt₂ (0.1 mmol) and stirred for 30 min at the same temperature. Saturated aq. NaHCO₃ was added to the reaction mixture and the organic layer was extracted with CH₂Cl₂ (3 × 3 mL). It was then washed with brine, and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane as eluent furnished the ether 5 as oil/solid.

(−)-Methyl-(1R,2S,3S,6R,7S,9R)-2,5,5,9-tetramethyl-4-oxatricyclo[4.3.1.0³⁷]decan-9-carboxylate, 5a: GP was followed with alcohol 8a (50 mg, 0.2 mmol), CH₂Cl₂ (3 mL) and BF₃·OEt₂ (0.012 mL, 0.1 mmol). Purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the ether 5a (47 mg, 95%) as oil. [α]D²⁵: −73.3 (c 4.5, CHCl₃). IR (neat): 2925, 1732, 1456, 1375, 1265, 1221, 1117, 1063, 985, 964, 858, 814, 769 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCL₄): δ 3.82 (1 H, t, J = 11.7 Hz, CH-O), 3.59 (3 H, s, OCH₃), 2.60-2.30 (2 H, m), 1.80-1.50 (4 H, m), 1.50-1.20 (2 H, m), 1.21 (3 H, s), 1.17 (3 H, s) and 1.14 (3 H, s) [3 × tert-CH₃], 0.83 (3 H, d, J = 7.2 Hz, sec-CH₃); ¹³C NMR (75 MHz, CDC₁₃+CCL₄): δ 178.6 (C, C=O-C), 81.1 (C, C-O), 77.4 (CH₁, CH-O-CO), 51.8 (CH₃, OCH₃), 44.1 (C), 41.2 (CH), 37.3 (CH), 36.7 (2C, CH), 29.7 (CH₂), 27.9 (CH₃), 26.2 (CH₃), 24.1 (CH₃), 17.9 (CH₂), 13.9 (CH₃); HRMS: m/z Calcd for C₁₆H₂₂O₁NaNa (M+Na): 275.1623. Found: 275.1631.

(−)-Methyl-(1R,2S,3S,6R,7S,9R)-2,5,5,7,9-pentamethyl-4-oxatricyclo[4.3.1.0³⁷]decan-9-carboxylate, 5b: GP was followed with alcohol 8b (70 mg, 0.26 mmol), CH₂Cl₂ (3 mL), and BF₃·OEt₂ (0.02 mL, 0.13 mmol). Purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the ether 5b (63 mg, 90%) as oil. [α]D²⁶: −39.2 (c 5.0, CHCl₃). IR (neat): 2964, 2930, 2925, 1732, 1456, 1377, 1250, 1199, 1138, 1103, 982, 854 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCL₄): δ 3.62 (3 H, s, OCH₃), 3.53 (1 H, d, J = 6.6 Hz, CH-O), 2.60-2.30 (2 H, m), 2.00-1.70 (2 H, m), 1.65-1.00 (3 H, m), 1.35 (3 H, s), 1.27 (3 H, s), 1.20 (3 H, s) and 1.18 (3 H, s) [4 × tert-CH₃], 0.91 (3 H, d, J = 6.9 Hz, sec-CH₃); ¹³C NMR (75 MHz, CDC₁₃+CCL₄): δ 178.8 (C, C=O-C), 83.5 (CH₁, CH-O-CO), 81.6 (C, C-O), 51.8 (CH₃, OCH₃), 47.8 (CH), 46.0 (C), 43.0 (C), 38.2 (CH₂), 38.0 (CH), 37.3 (CH), 30.7 (CH₃), 28.3 (CH₃), 28.0 (CH₂), 26.3 (CH₃), 20.1 (CH₂), 15.0 (CH₃); HRMS: m/z Calcd for C₁₆H₂₂O₂NaNa (M+Na): 289.1780. Found: 289.1787.

(−)-(1R,2S,3S,6R,7S,9R)-(2,5,5,9-Tetramethyl-4-oxatricyclo[4.3.1.0³⁷]decan-9-yl)-methanol, 5c: GP was followed with the diol 9a (50 mg, 0.22 mmol), CH₂Cl₂ (3 mL) and BF₃·OEt₂ (0.014 mL, 0.11 mmol). Purification of the residue over a silica gel column using ethyl acetate-hexane (1:3) as eluent furnished the ether 5c (46 mg, 93%) as oil. [α]D²⁶: −88.0 (c 4.5, CHCl₃). IR (neat): 3427, 2925, 2871, 1454, 1261,
1124, 1037, 983, 881, 810 cm⁻¹; 1H NMR (300 MHz, CDCl₃+CCl₄): δ 3.80 (1 H, t, J = 6.0 Hz, CH-O), 3.40 and 3.20 (2 H, 2 × d, J = 10.8 Hz), 3.22 (1 H, br s, OH), 2.42 (1 H, s), 2.60-2.00 (1 H, m), 1.84 (1 H, quintet, J = 6.6 Hz), 1.90-1.40 (5 H, m), 1.24 (3 H, s), 1.17 (3 H, s) and 1.03 (3 H, s) [3 × tert-CH₃]; HRMS: m/z Calcd for C₁₄H₂₄O₂Na (M+Na): 261.1830. Found: 261.1836.

(-)(IR,2S,3S,6R,7S,9R)-(2,5,5,7,9-Pentamethyl-4-oxatricyclo[4.3.1.0³,7]dec-9-yl)-ethanol, 5f: GP was followed with the secondary alcohol 14 (70 mg, 0.29 mmol), CH₂Cl₂ (3 mL) and BF₃·OEt₂ (0.013 mL, 0.15 mmol). Purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the ether 5f (66 mg, 94%) as colorless solid, which was recrystallized from a mixture of methanol and hexane. M.p.: 58-60 °C. [α]D²⁶ = +61.0 (c 4.8, CHCl₃). IR (neat): 3421, 2954, 2923, 2875, 1458, 1377, 1024, 974, 867 cm⁻¹; 1H NMR (300 MHz, CDCl₃+CCl₄): δ 3.49 and 3.19 (2 H, 2 × d, J = 7.5 Hz, CH₂-OH), 3.45 (1 H, d, J = 12.0 Hz, CH-O), 2.21 (1 H, br s, OH), 2.20-1.95 (1 H, m), 2.00-1.70 (2 H, m), 1.70-1.50 (1 H, m), 1.50-0.98 (3 H, m), 1.36 (3 H, s), 1.29 (3 H, s), 1.13 (3 H, s) and 1.04 (3 H, s) [4 × tert-CH₃]; 13C NMR (75 MHz, CDCl₃+CCl₄): δ 84.4 (CH, CH-OH), 82.1 (C-C), 70.3 (CH₂, CH₂-OH), 47.9 (CH), 42.9 (C-O), 40.7 (CH₂), 35.9 (C), 35.3 (CH), 33.2 (CH), 30.7 (CH₂), 28.6 (CH₃), 28.4 (CH₃), 25.9 (CH₃), 20.8 (CH₂), 14.8 (CH₃); HRMS: m/z Calcd for C₁₅H₂₆O₃Na (M+Na): 289.1830. Found: 289.1834.

(+)-(IR,2S,3S,6R,7S,9R)-2,5,5,7,9-Tetramethyl-4-oxatricyclo[4.3.1.0³,7]dec-9-yl)-acetate, 5e: GP was followed with the secondary alcohol 13 (60 mg, 0.22 mmol), CH₂Cl₂ (3 mL) and BF₃·OEt₂ (0.014 mL, 0.11 mmol). Purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the ether 5e (58 mg, 97%) as oil. [α]D²⁶ = +8.57 (c 2.8, CHCl₃). IR (neat): 3421, 2925, 1452, 1377, 1252, 1128, 1043, 1020, 899 cm⁻¹; 1H NMR (300 MHz, CDCl₃+CCl₄): δ 3.61 (1 H, dd, J = 9.3 and 8.1 Hz, CH-OH), 3.18 (1 H, s, CH-OH), 1.97 (1 H, dd, J = 13.8 and 9.9 Hz), 1.85 (1 H, dd, J = 13.8 and 5.1 Hz), 1.80-1.55 (5 H, m), 1.38 (3 H, s), 1.30 (3 H, s), 1.26 (3 H, s), 1.03 (3 H, s) and 0.95 (3 H, s) [5 × tert-CH₃]; 13C NMR (75 MHz, CDCl₃+CCl₄): δ 93.0 (CH, Hz, CH₂-C=O), 1.90 (1 H, quintet, J = 6.9 Hz), 1.85-1.60 (3 H, m), 1.52 (2 H, d, J = 3.0 Hz), 1.28 (3 H, s), 1.21 (3 H, s) and 1.12 (3 H, s) [3 × tert-CH₃]; 1.00 (1 H, br s), 0.92 (3 H, d, J = 7.2 Hz, sec-CH₃); 13C NMR (75 MHz, CDCl₃+CCl₄): δ 172.3 (C, O-C=O), 81.5 (C, C-O), 78.3 (CH, CH-OH), 51.0 (CH₃, OCH₃), 45.6 (CH₂), 40.6 (CH), 38.8 (CH), 36.8 (CH), 33.5 (CH), 33.0 (C), 32.9 (CH₂), 29.6 (CH₃), 27.4 (CH₂), 24.2 (CH₃), 18.9 (CH₂), 13.8 (CH₃); HRMS: m/z Calcd for C₁₂H₂₀O₂Na (M+Na): 289.1830. Found: 289.1834.

(+)-2[(IR,2S,3S,6R,7S,9R)-2,5,5,7,9-Tetramethyl-4-oxatricyclo[4.3.1.0³,7]dec-9-yl]-ethanol, 5f: GP was followed with the secondary alcohol 14 (70 mg, 0.29 mmol), CH₂Cl₂ (3 mL) and BF₃·OEt₂ (0.014 mL, 0.15 mmol). Purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the ether 5f (66 mg, 94%) as oil. [α]D²⁶ = -89.4 (c 6.4, CHCl₃). IR (neat): 3396, 2925, 1454, 1373, 1261, 1126, 1051, 985, 962, 885, 812 cm⁻¹; 1H NMR (300 MHz, CDCl₃+CCl₄): δ 3.89 (1 H, t, J = 3.0 Hz, CH-OH), 3.62 (2 H, s, CH₂-OH), 3.20 (1 H, br s, OH), 2.44 (1 H, br s), 1.97 (1 H, quintet, J = 6.9 Hz), 1.90-1.35 (8 H, m), 1.28 (3 H, s), 1.21 (3 H, s) and 1.02 (3 H, s) [3 × tert-CH₃]; 0.92 (3 H, d, J = 6.9 Hz, sec-CH₃); 13C NMR (75 MHz, CDCl₃+CCl₄): δ 81.7 (C, C-O), 78.4 (CH, CH-OH), 59.3 (CH₃, CH₂-OH), 44.5 (CH₂), 41.0 (CH), 38.5 (CH), 36.9 (CH), 34.0 (CH₂), 32.9 (CH), 31.7 (C), 29.6 (CH₃), 27.4 (CH₂), 24.1 (CH₃), 18.9 (CH₂), 13.9 (CH₃); HRMS: m/z Calcd for C₁₂H₂₀O₂Na (M+Na): 261.1830. Found: 261.1836.
CH-O), 81.7 (C, C-O), 77.5 (CH, CH-OH), 50.1 (CH), 47.1 (CH2), 45.0 (C), 44.6 (C), 44.3 (CH), 42.2 (C), 35.1 (CH2), 30.8 (CH3), 28.6 (CH3), 28.4 (CH3), 23.6 (CH3), 23.5 (CH3), 20.5 (CH3); HRMS: m/z Calcd for C16H20O2Na (M+Na) 273.1830. Found: 273.1848.

(+)-[IR,3S,4S,7R,9S,10R,12S]-13,6,3,6,10-pentamethyl-5-oxatetracyclo[7.3.0.03,7.04,10.01,9]dodecan-12-yl-methanesulfonate, 5h: GP was followed with the methanesulfonate, 5h.

References

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