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A carbohydrate-based synthesis of fused bicyclic ethers by radical cyclization of epoxides using titanocene(III) chloride

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A carbohydrate-based synthesis of both *cis*- and *trans*-fused bicylic ethers has been achieved by radical cyclization of epoxides using a transition-metal radical source. Thus, 6-*exo* radical cyclizations of the carbohydrate derivatives using [bis(cyclopentadienyl)titanium(III)]chloride (Cp_2TiCl) as the radical source has resulted in corresponding *cis*- and *trans*-fused bicyclic ethers. While the *trans*-fused compound has allowed stereoselective radical cyclization, the *cis*-fused has ended up only in a mixture of isomers. The functionalities present in the bicyclic compounds are potential intermediates as multifunctional conformationally rigid scaffolds.

Keywords*:* Bicyclic ethers, carbohydrate, radical cyclization, epoxides, transition-metal

A large number of oxacyclic *cis* and *trans*-fused medium rings are used as important building blocks of many natural products, which show considerable biological activity. Synthesis of those conformationally flexible chiral medium ring ethers, the structural core of a large number of linearly condensed cyclic polyethers marine neurotoxins[1], has received considerable attention. *Cis*- and *trans*-fused bicyclic ethers *e.g.*, **I**, **II**, **III** and **IV** (**Figure 1**) constitute the prominent parts of various natural products, such as neonorhalichondrin B[2], neohomohalichondrin B[2], neoisohomohalichondrin B[2], azaspiracid[3], cimiracemoside A[4], malayamycin A[5] and many others. The potential of carbohydrate templates as a chiral pool has been investigated[6] thoroughly specially for the 5-hexynyl radical cyclizations. Comparatively, the 6-heptenyl and 6-heptynyl radical cyclizations onto carbohydrate scaffolds have been studied much less probably due to lack of stereoselectivity and the tendency of the intermediates to rearrange *via* [1,5]-hydrogen atom transfer[7]. In continuation of the study of the radical cyclization strategy for the total synthesis of natural products[8], herein is reported the synthesis of *cis*- and *trans*-fused bicyclic ethers by 6-*exo*-*trig* and 6-*exo*-*dig* radical cyclization of epoxides on sugar derivatives using titanocene(III) chloride (Cp_2TiCl) as the radical promoter[9].

Results and Discussion

The key radical precursors, epoxides **4a** and **7a** for the synthesis of *cis*-fused bicyclic ethers were prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1a** as shown in **Scheme I**. Thus, commercially available diacetone glucose **1a** was subjected to *O*-propargylation using NaH and propargyl bromide under N_2 at low temperature to furnish **2a** in 80% yield. Deprotection of the primary acetonide moiety[10] in compound **2a** with 75% AcOH followed by refluxing with PPh_3 in the presence of imidazole and iodine in dry toluene produced compound **3a** in 70% yield. The appearance of two doublets at δ 5.32 (J = 12.1 Hz) and at δ 5.45 (J = 17.3 Hz) and a multiplet at δ 5.89-5.97 in the ^{1}H NMR spectrum indicated the presence of three olefinic protons. Compound **3a** was subjected to epoxidation with 1.3 equivalent of *m*-CPBA in $CHCl_3$ to afford the epoxide **4a** in 60% yield as a mixture of two isomers in a ratio of 8:5. The ratio was determined from the two distinguishing doublets of the two isomers for the anomeric proton in the ^{1}H NMR spectrum which appeared at δ 5.91 (J = 3.6 Hz) for the major isomer and at δ 5.95 (J = 3.7 Hz) for the minor one. The major isomer **7a** was partly (30%) separated by preparative TLC. The minor isomer could not be obtained in pure form by chromatography and was always contaminated with the major isomer. On the other hand, the acetonide **2b**

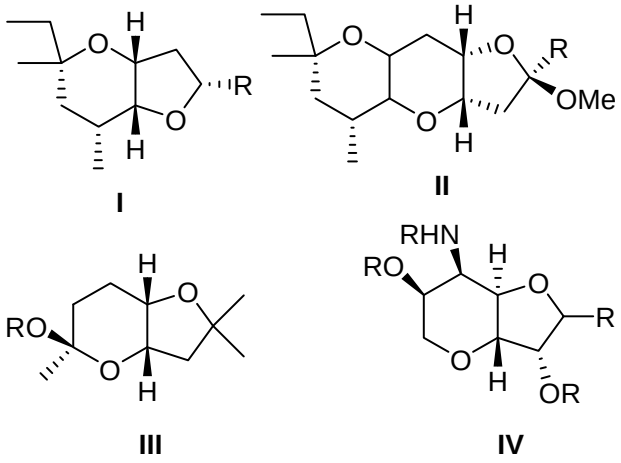
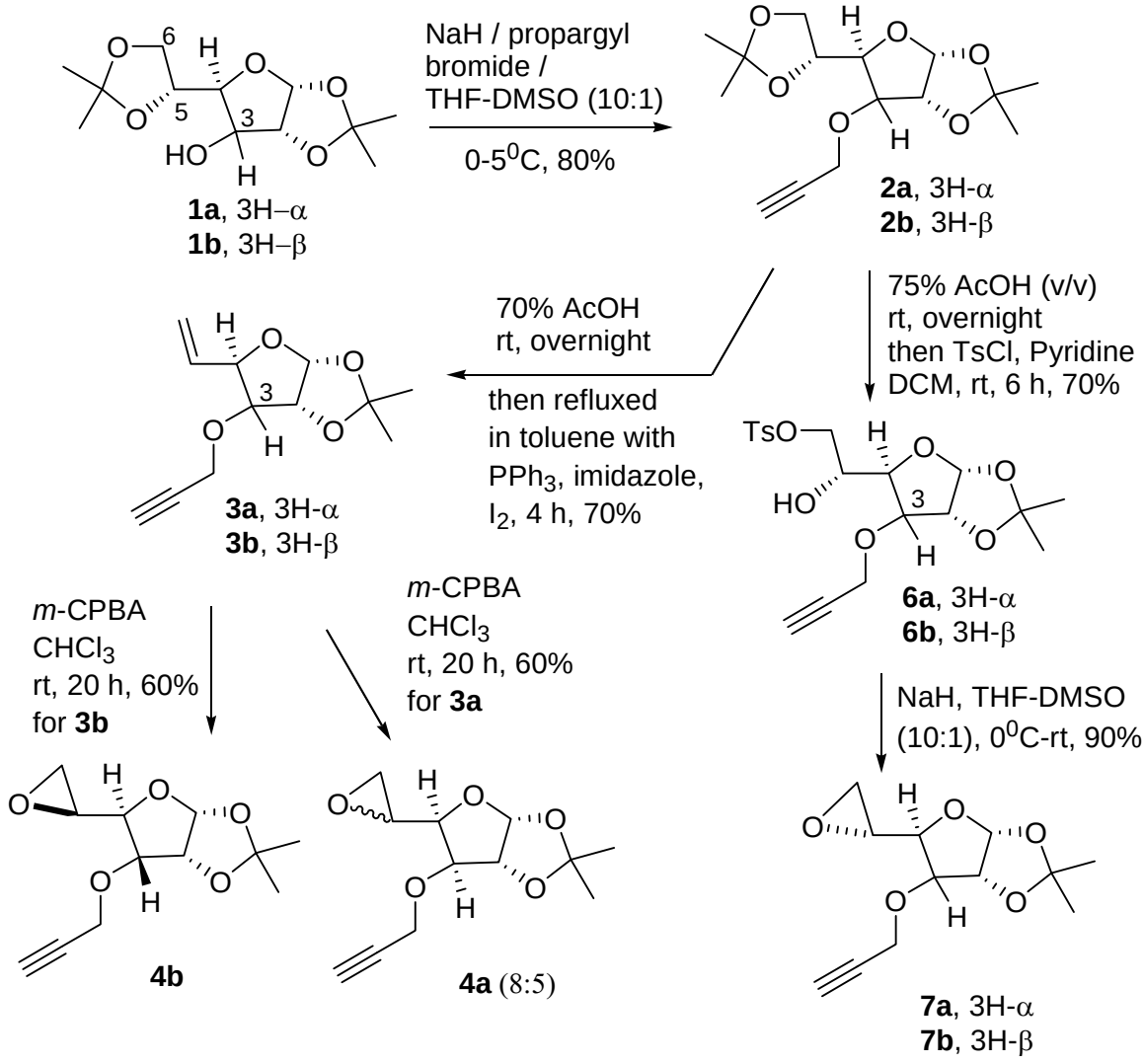


Figure 1

was deprotected by 75% AcOH (v/v) followed by tosylation with *p*-toluenesulfonyl chloride and pyridine to afford the tosylate **6a** in 70% yield. Compound **6a** was then treated with NaH in THF-DMSO to furnish the pure epoxide **7a** in 90% yield.

Radical cyclization of the pure epoxide **7a** or the crude **4a** with Cp_2TiCl (Cp_2TiCl was prepared *in situ*[11] from commercially available Cp_2TiCl_2 and zinc dust in THF under argon) at RT furnished a mixture of the cyclized product **5a** and the reduced product **8a** (combined yield 95%) in a ratio of 5:4 (**Scheme II**). The ratio was determined from the two doublets for the anomeric proton in the ^{1}H NMR spectrum which appeared at δ 5.88 (J = 3.7 Hz) for the major compound **5a** and at δ 5.89 (J = 3.6 Hz) for the

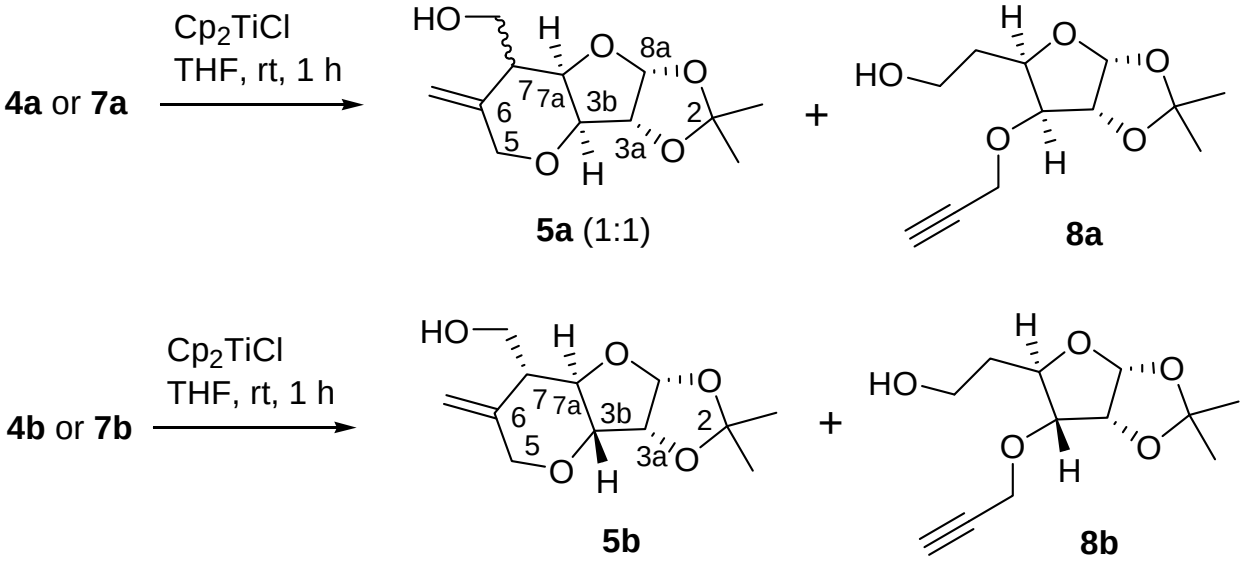


Scheme I

reduced product **8a**. Compound **5a** was separated (50%) from the mixture by HPLC as an inseparable mixture of two diastereomers in 1:1 ratio. The ratio of the two diastereomers was determined from the two separate multiplets for the proton at C-7 in ^{1}H NMR spectrum which appeared at δ 2.64-2.65 for one isomer and at δ 2.82-2.86 for the other. These two isomers could not be separated either by preparative TLC or by HPLC.

The radical precursors **4b** and **7b** for the synthesis of *trans*-fused bicyclic ethers were prepared from the commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranoside **1b** following a reaction sequence similar to the one described above for **4a** (**Scheme I**). The epoxide protons in **4b** appeared at δ 2.81-2.89 (m, 2H) and at δ 3.14-3.17 (m, 1H) in the ^{1}H NMR spectrum. Unlike **4a**, compound **4b** (60%) was isolated as a single isomer. Probably, the epoxidation of **3b** occurred from the β-side as the α-side is more sterically hindered as compared to the β-side, by the isopropylidene and the propargyloxy groups. The other isomer of the epoxide **7b** was obtained by base treatment of the tosylate **6b** in 90% yield through **2b** following a reaction sequence similar to the one described for **7a**. The epoxide **4b** or **7b** on separate treatment with Cp_2TiCl in THF under argon afforded a mixture (88%) of the cyclized product **5b** and the reduced product **8b** in a ratio of 1:1 (**Scheme II**). The pure cyclized compound **5b** {$[\alpha]_D^{27.1}$, +18.7° (C = 0.48, $CHCl_3$)} was obtained in 50% yield by preparative TLC of the crude mixture. Although the stereochemical outcome of the 6-heptenyl radical cyclizations has been less studied[12] as compared to 5-hexenyl radicals[7,13], the stereochemistry at C-7 in **5b** can be predicted from the comparatively higher values of the coupling constants (J = 10.9, 9.3 Hz) of H-7a which appeared at δ 3.68 in the ^{1}H NMR spectrum. These higher values of J indicated the *trans*-relationship of this particular proton with both H-7 and H-3b. This stereochemistry can further be rationalized by invoking well-known conformational effects proposed by Beckwith[14] and Houk[15]. Two chair-like transition complexes **A** and **B** are possible for the intermediate radical generated from **4b** or **7b**. In the transition complex **A**, there is no 1,3-diaxial interaction between CH_2OTi (equatorial) and the axially oriented H_a and H_b (**Figure 2**). But in the transition complex **B**, there are severe interactions between CH_2OTi (axial) and the axially oriented H_a and H_b. So, the transition complex **A** is energetically more favored and the formation of **5b** is preferred over **5b´**. There may be some other factors that caused the exclusive formation of **5b**.

In case of the *cis* compound, 6-heptynyl radical can possess two distorted chair-like conformations **C** and **D** in the transition state generated from **4a** or **7a** (**Figure 3**). In both the conformers, very less interactions between CH_2OTi (axial or equatorial) and H_a or H_b (pseudo-axial) are observed and so their energy difference is minimum. Hence, both the isomers in **5a** are formed by radical cyclization of **4a** or **7a** in almost equal ratio. Reduced products **8a** and



Scheme II

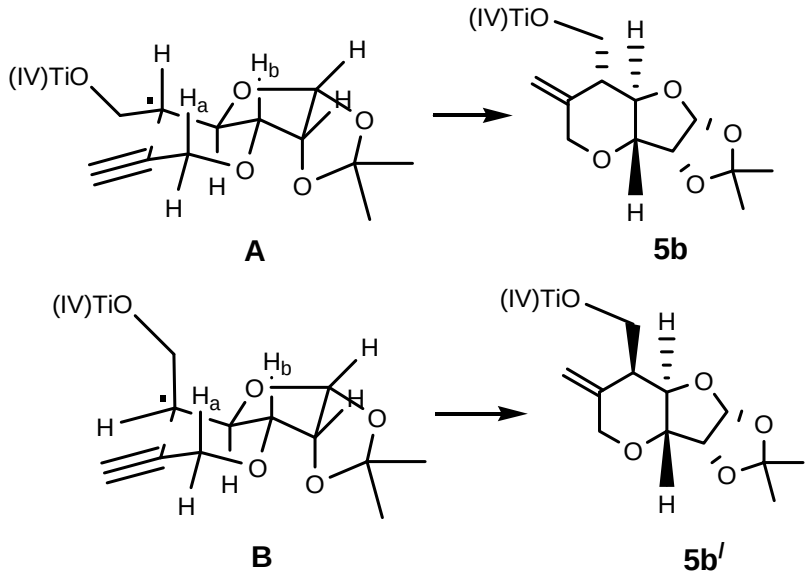


Figure 2

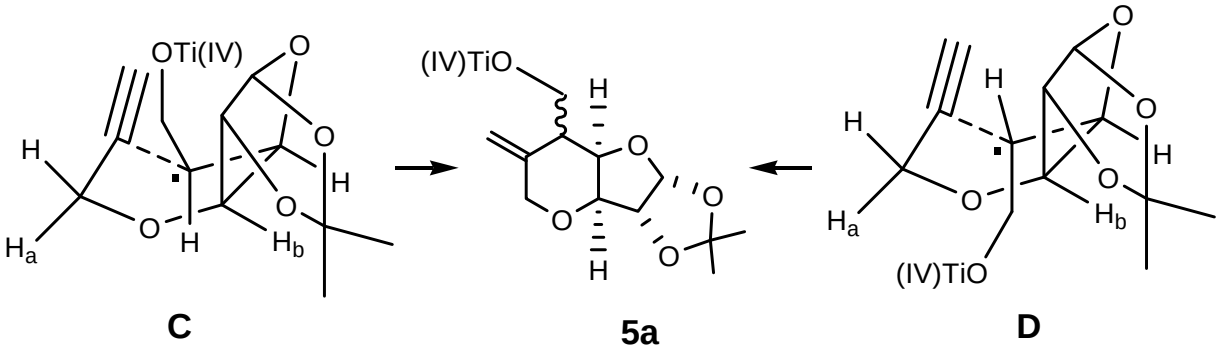


Figure 3

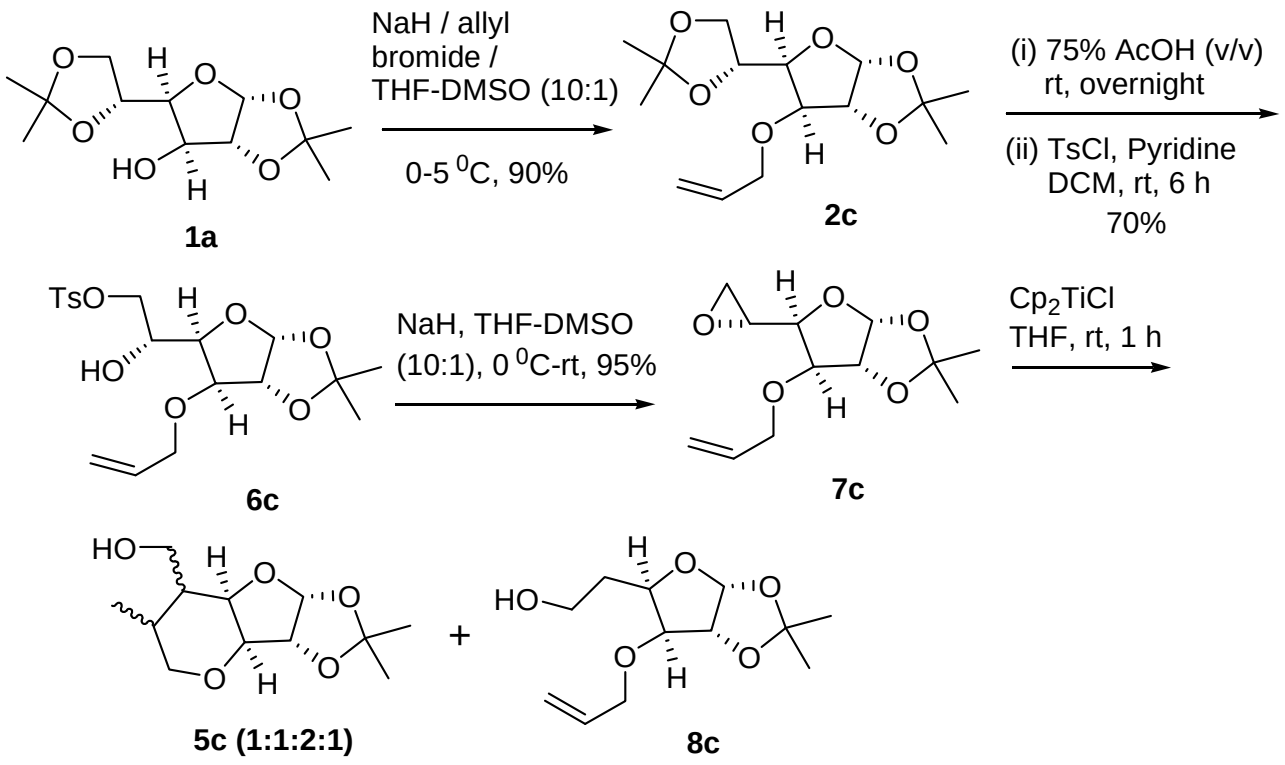
8b are probably derived from adventitious water in the reaction medium, thereby forming a water-solvated Cp_2TiCl complex and a hydrogen atom transfer process occurs from water to a carbon centered free radical forming the reduced products[16].

On the other hand, epoxy allyl ether **7c**, prepared from **1a**, on radical cyclization reaction using Cp_2TiCl afforded the cyclized product **5c** as a mixture of four isomers in a ratio of 1:1:2:1 alongwith the reduced product **8c** (**Scheme III**). The ratio of the isomers in **5c** was determined from the relative intensity of the four distinguishable doublets of the CH_3 signal at C-6 in the ^{1}H NMR spectrum which appeared at δ 1.15 (J = 7.2 Hz), 1.06 (J = 7.2 Hz), 0.89 (J = 7.3 Hz) and 0.85 (J = 6.7 Hz). Compound **5c** (55%) was separated from the reduced product **8c** (20%) but the isomers of **5c** were inseparable by chromatographic methods including HPLC.

In conclusion, a carbohydrate-based synthesis of *cis*- and *trans*-fused bicyclic ethers has been achieved successfully involving 6-*exo* cyclizations of epoxy-alkynes or epoxy-alkenes using *bis*-(cyclopenta-dienyl)titanocene chloride as the radical initiator. While *trans*-fused carbohydrate derivatives allowed stereoselective radical cyclization, the *cis*-fused derivatives ended up only as a mixture of isomers. The functionalities present in the bicyclic compounds are potentially useful for the synthesis of multifunctional conformationally rigid scaffolds.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra



Scheme III

were recorded in $CDCl_3$ on 300 and 75 MHz spectrometer (Bruker) respectively and IR spectra were recorded using a Shimadzu FT IR-8300 instrument. Elemental analyses were performed using Hans Hoslli micro analyzer. High-resolution mass spectra were obtained using a Q-TOF Micro YA263 instrument. The optical rotations were measured on a Jasco P-1020 polarimeter using chloroform as solvent. Diethyl ether and tetrahydrofuran were dried over sodium and toluene was freshly distilled from calcium hydride. Dichloromethane was freshly distilled from phosphorus pentoxide. Pyridine was distilled over potassium hydroxide and chloroform was distilled over calcium chloride prior to use. Petroleum ether of boiling range 60-80°C and silica gel of 60-120 mesh were used for column chromatography.

1,2:5.6-Di-O-isopropylidene-3-O-propargyl-α-D-glucofuranose, 2a

To a magnetically stirred suspension of sodium hydride (800 mg, 60% dispersion, 20 mmol) in dry THF (2 mL) was added dropwise a solution of **1a** (2.60 g, 10 mmole) in dry THF: DMSO (10:1) (15 mL) at 0°C under nitrogen. After the evolution of hydrogen ceased (1 hr) a solution of propargyl bromide (1.55 g, 13 mmole) in dry THF (13 mL) was added dropwise at 0°C over 20 min. The reaction mixture was then stirred at RT for 8 hr and carefully decomposed with ice water. After removal of most of the solvent under reduced pressure, the resulting residue was extracted with diethyl ether (4 × 50 mL). The combined ether extracts were washed successively with water (2 × 10 mL), brine (1 × 10 mL) and finally dried (anhyd. Na_2SO_4). The solvent was removed under reduced pressure and the crude residue obtained was purified by column chromatography over silica gel (20% ethyl acetate in petroleum ether) to yield the propargyl ether **2a**[6k] (2.38 g, 80%). {$[\alpha]_D^{27.3}$-15.33° (C = 1.8, $CHCl_3$)}; IR (neat): 3271, 2987, 2937, 2895, 1456, 1373, 1255, 1217, 1164, 1116, 1080 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.46 (t, *J* = 2.4 Hz, 1H, C≡CH), 3.92-3.97 (m, 1H, H-5), 4.01-4.11 (m, 3H, H-3, H_2-6), 4.19-4.25 (m, 3H, H-4, OCH≡C), 4.59 (d, *J* = 3.6 Hz, 1H, H-2), 5.83 (d, *J* = 3.6 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 25.7 (CH_3), 26.6 (CH_3), 27.2 (2 CH_3), 58.5 (CH_2), 67.5 (CH_2), 72.9 (CH), 75.4 (CH), 79.6 (C), 81.4 (CH), 81.9 (CH), 83.2 (CH), 105.6 (CH), 109.4 (C),

112.2 (C); HRMS: Calcd. for $C_{15}H_{22}O_6$ (M^++ Na): 321.1314. Found *m/z* 321.1335.

1,2:5.6-Di-*O*-isopropylidene-3-*O*-propargyl-α-D-allofuranose, 2b

Compound **2b** was prepared from **1b** (1.3 g, 5 mmole) in 80% yield as a crystalline solid, m.p. 110-12°C following the same procedure described for compound **2a**. IR (KBr): 3435, 3230, 2987, 2925, 2881, 2110, 1492, 1463, 1450, 1373, 1340, 1265, 1240, 1203, 1168, 1147, 1082 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.48 (t, *J* = 2.3 Hz, 1H, C≡CH), 3.95-4.05 (m, 2H, H_2-6), 4.08 (dd, *J* = 8.7, 3.1 Hz, 1H, H-3), 4.14 (dd, *J* = 8.7, 4.2 Hz, 1H, H-4), 4.34 (dd, *J* = 15.9, 2.5 Hz, 2H, O-CH_2C≡C), 4.37 (m, 1H, H-5), 4.71 (t, *J* = 3.9 Hz, 1H, H-2), 5.79 (d, *J* = 3.6 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 25.1 (CH_3), 26.2 (CH_3), 26.4 (CH_3), 26.7 (CH_3), 57.3 (CH_2), 65.0 (CH_2), 74.7 (CH), 75.3 (CH), 76.8 (CH), 77.8 (CH), 79.1 (C), 103.7 (CH), 109.6 (C), and 112.9 (C); HRMS: Calcd. for $C_{15}H_{22}O_6$ (M^++ Na): 321.1314. Found *m/z* 321.1307.

1,2:5.6-Di-*O*-isopropylidene-3-*O*-allyl-α-D-glucofuranose, 2c

Compound **2c**[17] was prepared from **1a** (2.0 g, 7.6 mmole) and allyl bromide (1.1 g, 9.12 mmole) in 90% yield following the same procedure described for compound **2a**. IR (neat): 2987, 2935, 2893, 1456, 1373, 1253, 1217 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.94 (d, *J* = 2.9 Hz, 1H, H-3), 3.96-4.16 (m, 5H, H-3, H-4, H-5, H_2-6), 4.28-4.32 (m, 1H, H-5), 4.53 (d, *J* = 3.6 Hz, 1H, H-2), 5.19 (dd, *J* = 10.4, 1.5 Hz, 1H, =CH), 5.30 (dd, *J* = 15.7, 1.5 Hz, 1H, =CH), 5.84-5.92 (m, 2H, =CH, H-1); ^{13}C NMR ($CDCl_3$): δ 25.1 (CH_3), 26.0 (CH_3), 26.6 (2 CH_3), 67.0 (CH), 70.9 (CH_2), 72.2 (CH_2), 80.9 (CH), 81.2 (CH), 82.5 (CH), 104.9 (CH), 108.6 (C), 111.4 (C), 116.9 (=CH_2), and 133.9 (=CH); HRMS: Calcd. for $C_{15}H_{24}O_6$ (M^++ Na): 323.1471. Found *m/z* 323.1497.

5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-*xylo*-hex-5-enofuranose, 3a

A solution of **2a** (1.50 g, 5 mmole) was stirred overnight with 75% aqueous acetic acid (v/v) (20 mL) at RT. Then, acetic acid was removed under reduced pressure (bath temperature: 40°C) using dry toluene (3 × 40 mL) and the viscous residue obtained was dissolved in dry toluene (100 mL) and heated under reflux with imidazole (1.02 g, 15 mmole) and PPh_3 (3.93 g, 15 mmole) while I_2 (3.3 g, 13 mmole) was added to the boiling mixture in small portions over a period of 1hr. The refluxing was continued for an additional 3 hr and then the resulting mixture was cooled to RT and extracted with toluene (5 × 20 mL). The combined organic layer was successively washed with 10% aqueous NaOH solution (3 × 10 mL), water (3 × 10 mL), brine (1 × 10 mL) and finally dried (anhyd. Na_2SO_4). Solvent was evaporated under reduced pressure to afford a viscous liquid, which was purified by column chromatography over silica gel (10% ethyl acetate in petroleum ether) to obtain **3a** (789 mg, 70%). {$[\alpha]_D^{27.3}$-19.6° (C = 0.30, $CHCl_3$)}; IR (neat): 3273, 2987, 2935, 2862, 1454, 1431, 1379, 1352, 1255, 1217, 1164, 1080 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.45 (t, *J* = 2.4 Hz, 1H, C≡CH), 4.05 (d, *J* = 3.1 Hz, 1H, H-3), 4.21 (d, *J* = 2.4 Hz, 2H, OCH_2C≡), 4.64 (d, *J* = 3.8 Hz, 1H, H-2), 4.63-4.68 (m, 1H, H-4), 5.32 (d, *J* = 12.1 Hz, 1H, H-6), 5.45 (d, *J* = 17.3 Hz, 1H, H-6), 5.89-5.97 (m, 1H, H-5), 5.92 (d, *J* = 3.6 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 26.5 (CH_3), 27.1 (CH_3), 58.0 (CH_2), 75.4 (CH), 79.3 (C), 81.4 (CH), 83.1 (CH), 83.3 (CH), 105.07 (CH), 112.0 (C), 119.5 (=CH_2), and 132.1 (=CH); HRMS: Calcd. for $C_{12}H_{16}O_4$ (M^++ Na): 247.0947. Found *m/z* 247.0964.

5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-*ribo*-hex-5-enofuranose, 3b

Compound **3b** was prepared from **2b** (1.5 g, 5 mmole) in 70% yield following the same procedure described for compound **3a**. {$[\alpha]_D^{25.3}$+65.8° (C = 3.4, $CHCl_3$)}; IR (neat): 3265, 2989, 2935, 2117, 1649, 1454, 1375, 1217, 1168, 1132, 1095 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.47 (t, *J* = 2.3 Hz, 1H, C≡CH), 3.77 (dd, *J* = 8.9, 4.2 Hz, 1H, H-3), 4.30 (ddd, *J* = 16.2, 3.2, 2.3 Hz, 2H, OCH_2C≡), 4.41 (dd, *J* = 8.9, 7.0 Hz, 1H, H-4), 4.68 (t, *J* = 4.0 Hz, 1H, H-2), 5.27 (dt, *J* = 10.4, 1.1 Hz, 1H, H-6), 5.44 (d, *J* = 17.2 Hz, 1H, H-6), 5.78 (d, *J* = 3.6 Hz, 1H, H-1), 5.8-5.91 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 26.3 (CH_3), 26.5 (CH_3), 57.5 (CH_2), 75.4 (CH), 77.3 (CH), 78.7 (CH), 78.8 (C), 81.0 (CH), 103.6 (CH), 112.9 (C), 119.0 (=CH_2) and 134.4 (=CH); Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.02; H, 7.13%.

Preparation of 6-deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-5,6-oxyranyl-α-D-glucofuranose 7a, from 3a

To a magnetically stirred solution of **3a** (1.12 g, 5 mmole) in chloroform (50 mL), *m*-CPBA (70%, 1.6 g, 6.5 mmole) was added and the resulting mixture was stirred under nitrogen for 20 hr. The organic layer was diluted with $CHCl_3$ (50 mL) and washed successively with saturated aqueous solution of sodium sulfite (2 × 10 mL), sodium bicarbonate (2 × 10 mL), water (2 × 10 mL), brine (10 mL) and finally dried (anhyd. Na_2SO_4). The solvent was removed under reduced pressure to obtain **4a** (720 mg, 60%) as a mixture of two isomers in a ratio of 8:5 which on preparative TLC (15% ethyl acetate in petroleum ether) afforded pure epoxide **7a** (360 mg, 30%). $\{[\alpha]_D^{26.6}$-51.3° (C = 1.35, $CHCl_3$)}; IR (neat): 3273, 2989, 2935, 1733, 1456, 1375, 1353, 1253, 1217, 1164, 1110, 1080 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.49 (t, *J* = 2.3 Hz, 1H, C≡CH), 2.77 (dd, *J* = 5.1, 2.6 Hz, 1H, H-6), 2.89 (dd, *J* = 4.9, 3.9 Hz, 1H, H-6), 3.20-3.24 (m, 1H, H-5), 3.76 (dd, *J* = 7.05, 3.1 Hz, 1H, H-4), 4.19 (d, *J* = 3.1 Hz, 1H, H-3), 4.28 (d, *J* = 2.9 Hz, 2H, OCH_2C≡C), 4.65 (d, *J* = 3.6 Hz, 1H, H-2), 5.91 (d, *J* = 3.6 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 26.6 (CH_3), 27.2 (CH_3), 47.3 (CH_2), 48.5 (CH), 58.4 (CH_2), 75.7 (CH), 79.3 (C), 81.6 (CH), 82.2 (CH), 83.0 (CH), 105.7 (CH), 112.4 (C); HRMS: Calcd. for $C_{12}H_{16}O_5$ (M^++ Na): 263.0896. Found *m/z* 263.0854.

The minor isomer, which could not be separated by usual chromatographic methods, always contaminated the major isomer.

6-Deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-5,6-oxyranyl-α-D-allofuranose, 4b

Compound **4b** was prepared from **3b** (1.12 g, 5 mmole) in 60% yield following the same procedure described for compound **4a**. $\{[\alpha]_D^{27}$ +70.1° (C = 0.59, $CHCl_3$)}; IR (neat): 3267, 2987, 2925, 2854, 2185, 1726, 1454, 1375, 1317, 1253, 1217, 1166, 1126, 1095 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.51 (t, *J* = 2.1 Hz, 1H, C≡CH), 2.81-2.89 (m, 2H, H_2-6), 3.14-3.17 (m, 1H, H-5), 3.96-4.06 (m, 2H, H-3; H-4), 4.34 (dd, *J* = 8.8, 3.9 Hz, 2H, OCH_2C≡C), 4.69 (t, *J* = 3.6 Hz, 1H, H-2), 5.75 (d, *J* = 3.5 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 26.30 (CH_3), 26.6 (CH_3), 44.1 (CH_2), 50.8 (CH), 57.7 (CH_2), 75.6 (CH), 77.0 (CH), 77.1 (CH), 78.5 (C), 104.1 (CH), 113.2 (C); Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.12; H, 6.35%.

1,2-*O*-isopropylidene-3-*O*-propargyl-6-*O*-tosyl-α-D-glucofuranose, 6a

A solution of **2a** (1.50 g, 5 mmole) was stirred overnight with 75% aqueous acetic acid (v/v) (20 mL) at RT. Then, acetic acid was removed under reduced pressure (bath temperature: 40°C) using dry toluene (3 × 40 mL) and the viscous residue obtained was dissolved in dichloromethane (25 mL). The solution was stirred at RT with *p*-toluenesulphonyl chloride (1.1 g, 5.5 mmole) and pyridine (1 mL) for 6 hr. After decomposition with dilute HCl the reaction mixture was extracted with diethyl ether (2 × 50 mL). The ether layer was washed successively with water (2 × 10 mL), brine (1 × 10 mL) and finally dried (anhyd. Na_2SO_4). Solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography over silica gel (20% ethyl acetate in petroleum ether) to afford **6a** (1.45 g, 70%) as a viscous oil. $\{[\alpha]_D^{24.5}$-27.9° (C = 2.08, $CHCl_3$)}; IR (neat): 3500, 3282, 2989, 2937, 2110, 1598,1454, 1359, 1217 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.44 (s, 3H, Ar-CH_3), 2.51 (t, *J* = 2.3 Hz, 1H, C≡CH), 4.02-4.34 (m, 7H, OCH_2C≡C, H-3, H-4, H-5, H_2-6), 4.60 (d, *J* = 3.6 Hz, 1H, H-2), 5.84 (d, *J* = 3.6 Hz, 1H, H-1), 7.35 (d, *J* = 8.1 Hz, 2H, ArH), 7.80 (d, *J* = 8.1 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 21.6 ($ArCH_3$), 26.2 (CH_3), 26.7 (CH_3), 57.7 (CH_2), 67.0 (CH), 72.2 (CH_2), 75.5 (CH), 78.9 (CH), 79.1 (C), 81.3 (CH), 82.0 (CH), 105.2 (CH), 112.1 (C), 128.05 (2 ArCH), 129.9 (2 ArCH), 132.6 (C), 144.9 (C); HRMS: Calcd. for $C_{19}H_{24}O_8S$ (M^++ Na): 435.1090. Found *m/z* 435.1039.

1,2-*O*-isopropylidene-3-*O*-propargyl-6-*O*-tosyl-α-D-allofuranose, 6b

Compound **6b** was prepared from **2b** (1.00 g, 3.33 mmole) as a viscous oil in 72% yield following the same procedure described for compound **6a**. $\{[\alpha]_D^{25.1}$ +75.2° (C = 1.3, $CHCl_3$)}; IR (neat): 3510, 3305, 3018, 2983, 2935, 2117, 1598,1450, 1373, 1215 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.45 (s, 3H, $ArCH_3$), 2.48 (t, *J* = 2.4 Hz, 1H, C≡CH), 3.97 (dd, *J* = 9.0, 3.6 Hz, 1H, H-3), 4.04-4.29 (m, 6H, H-4, H-5, H_2-6, OCH_2C≡C), 4.68 (t, *J* = 3.9 Hz, 1H, H-2), 5.75 (d, *J* = 3.65 Hz, 1H, H-1), 7.34 (d, *J* = 8.3 Hz, 2H, 2 ArH), 7.80 (d, *J* = 8.3 Hz, 2H, 2 ArH); ^{13}C NMR ($CDCl_3$): δ 21.6 ($ArCH_3$), 26.5 (CH_3), 26.7 (CH_3), 57.2 (CH_2), 69.2 (CH), 70.5 (CH_2), 76.1 (CH), 76.3 (CH), 77.2 (CH), 77.5 (CH), 78.6 (C), 104.2 (CH), 113.4 (C), 128.1 (2 ArC), 129.9 (2 ArC),

132.7 (C), 145.0 (C); HRMS: Calcd. for $C_{19}H_{24}O_8S$ (M^++ Na): 435.1090. Found *m/z* 435.1030.

1,2-*O*-isopropylidene-3-*O*-allyl-6-*O*-tosyl-α-D-glucofuranose, 6c

Compound **6c** was prepared from **2c** (300 mg, 1 mmole) and allyl bromide (158 mg, 1.3 mmole) in 60% yield following the same procedure described for compound **6a**. {$[\alpha]_D^{24.7}$-26.5° (C = 3.12, $CHCl_3$)}; IR (neat): 3510, 2987, 2937, 1598, 1454, 1359, 1217, 1190, 1176 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.45 (s, 3H, $ArCH_3$), 4.03-4.19 (m, 5H, H-3, H-4, H-5, H_2-6), 4.28 (dd, *J* = 9.9, 2.4 Hz, 2H, $OCH_2C{\equiv}C$), 4.54 (d, *J* = 3.6 Hz, 1H, H-2), 5.22 (dd, *J* = 10.2, 1.5 Hz, 1H, $=CH_2$), 5.29 (dt, *J* = 17.4, 1.5 Hz, 1H, $=CH_2$), 5.85-5.90 (m, 1H, =CH), 5.86 (d, *J* = 3.6 Hz, H-1), 7.35 (d, *J* = 8.1 Hz, 2H, 2 ArCH), 7.80 (d, *J* = 8.1 Hz, 2H, 2 ArCH); ^{13}C NMR ($CDCl_3$): δ 21.54 ($ArCH_3$), 26.10 (CH_3), 26.65 (CH_3), 67.12 (CH_2), 71.15 (CH), 72.33 (CH_2), 79.05 (CH), 81.60 (CH), 82.00 (CH), 104.99 (CH), 111.80 (C), 117.98 ($=CH_2$), 127.95 (2 ArCH), 129.84 (2 ArCH), 132.37 (ArC), 133.56 (=CH), 144.92 (ArC); HRMS: Calcd. for $C_{19}H_{26}O_8S$ (M^++ Na): 437.1246. Found *m/z* 437.1230.

6-Deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-5,6-oxyranyl-α-D-glucofuranose 7a, from 6a

To a magnetically stirred suspension of sodium hydride (0.10 g, 60% dispersion, 2.4 mmole) in dry THF (2 mL) was added dropwise a solution of 6a (0.50 g, 1.2 mmole) in dry THF-DMSO (10:1) (7 mL) at 0°C under nitrogen. Then it was stirred at RT for 8 hr and carefully decomposed with ice water. After removal of the solvent under reduced pressure the resulting residue was extracted with diethyl ether (4 × 50 mL). The combined ether extract was washed successively with water (2 × 10 mL), brine (1 × 10 mL) and finally dried (anhyd. Na_2SO_4). The solvent was removed under reduced pressure and the crude residue was purified by column chromatography over silica gel (20% ethyl acetate-petroleum ether) to furnish 7a (0.26 g, 90%) as a viscous oil.

6-Deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-5,6-oxyranyl-α-D-allofuranose, 7b

Compound **7b** was prepared from **6b** (0.30 g, 0.72 mmole) as a viscous oil in 88% yield following the same procedure described for compound **7a**. {$[\alpha]_D^{26.8}$ +101.3° (C = 0.39, $CHCl_3$)}; IR (neat): 3305,3018, 2995, 1384, 1375, 1215,1101, 1028 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.36 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.52 (t, *J* = 2.4 Hz, 1H, C≡CH), 2.83-2.86 (m, 2H, H_2-6), 3.25 (dd, *J* = 6.7, 3.2 Hz, 1H, H-5), 3.94 (dd, *J* = 8.8, 4.4 Hz, 1H, H-3), 4.18 (dd, *J* = 8.8, 3.1 Hz, 1H, H-4), 4.32 (dd, *J* = 16.1, 2.3 Hz, 2H, $OCH_2C{\equiv}C$), 4.69 (t, *J* = 4.1 Hz, 1H, H-2), 5.80 (d, *J* = 3.7 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 25.5 (CH_3), 25.8 (CH_3), 43.4 (CH_2), 49.5 (CH), 56.1 (CH_2), 74.8 (CH), 75.4 (CH), 76.3 (CH), 76.6 (CH), 77.7 (C), 103.0 (CH) and 112.2 (C); HRMS: Calcd. for $C_{12}H_{16}O_5$ (M^++ Na): 263.0896. Found 263.0845.

6-Deoxy-1,2-*O*-isopropylidene-3-*O*-allyl-5,6-oxyranyl-α-D-glucofuranose, 7c

Compound **7c** was prepared from **6c** (250 mg, 0.60 mmole) in 95% yield following the same procedure described for compound **7a**. {$[\alpha]_D^{25}$-58.2° (C = 4.54, $CHCl_3$)}; IR (neat): 2962, 2931, 2852, 1726, 1461, 1375, 1257, 1217, 1164 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.74 -2.76 (m, 1H, H-6), 2.88-2.90 (m, 1H, H-6), 3.22-3.26 (m, 1H, H-5), 3.71 (dd, *J* = 7.2, 3.1 Hz, 1H, H-4), 4.00 (d, *J* = 3.1 Hz, 1H, H-3), 4.06-4.20 (m, 2H, $OCH_2C{\equiv}C$), 4.58 (d, *J* = 3.6 Hz, 1H, H-2), 5.20 (dd, *J* = 10.5, 1.5 Hz, 1H, $=CH_2$), 5.31 (dt, *J* = 15.9, 1.5 Hz, 1H, $=CH_2$), 5.84-5.93 (m, 1H, =CH), 5.92 (d, *J* = 3.6 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 26.1 (CH_3), 26.7 (CH_3), 46.8 (CH_2), 47.9 (CH), 71.2 (CH_2), 81.6 (CH), 81.7 (CH), 82.7 (CH), 105.2 (CH), 111.8 (C), 117.5 ($=CH_2$), 133.7 (=CH); HRMS: Calcd. for $C_{12}H_{18}O_5$ (M^++ H): 243.1227. Found *m/z* 243.1234.

[(3a*R*,3b*S*,7a*R*,8a*R*)-2,2-dimethyl-6-methylenehexahydro-3b*H*-[1,3]dioxolo[4,5]furo[3,2-b]pyran-7-yl]methanol, 5a

A solution of Cp_2TiCl_2 (523 mg, 2.1 mmole) in dry THF (26 mL) was stirred with activated Zn dust (458 mg, 7 mmole) for 1 hr under argon. The resulting green solution was then added dropwise to a stirred solution of the crude epoxide **4a** (240 mg, 1 mmole) or the pure epoxide **7a** (240 mg, 1 mmole) in dry THF (25 mL) under argon over 10 min. The reaction mixture was stirred for an additional 1 hr and then quenched with saturated aq. NaH_2PO_4 (10 mL). After 15 min, most of the THF was removed under reduced pressure and the resulting residue was extracted with diethyl ether (4 × 25 mL). The combined ether extract was washed successively with water (1 × 10 mL), brine (1 × 10 mL) and finally dried (anhyd. Na_2SO_4). After removal of solvent the crude material obtained was purified by column chromatography over silica

gel (20% ethyl acetate in petroleum ether) to obtain a mixture (230 mg, 95%) of the cyclized product **5a** and the reduced product **8a** in a ratio of 5:4. The pure cyclized material **5a** (120 mg, 50%) and the pure reduced product **8a** (48 mg, 20%) were separated from the mixture by preparative TLC (10% ethyl acetate in petroleum ether). The remaining portion extracted from the TLC plate (50 mg, 20%) was a mixture of **5a** and **8a**. Pure cyclized product **5a** was found to be a mixture of two isomers in a ratio of 1:1. The two isomers could not be separated by preparative TLC or by HPLC. The spectral and analytical data of crude **5a**: IR (neat): 3444, 3080, 2985, 2923, 2850, 1778, 1728, 1658, 1454, 1375, 1296, 1244, 1215, 1164, 1087 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.64-2.65 (m, 1H, H-7 for one isomer), 2.82-2.86 (m, 1H, H-7 for another isomer), 3.69-3.81 (m, 2H, CH_2O), 3.91-4.18 (bunch of multiplets, 4H, H-3b, H-7a, H_2-5), 4.46 (d, *J* = 3.7 Hz, 1/2H, H-3a for one isomer), 4.49 (d, *J* = 3.78 Hz, 1/2H, H-3a for another isomer), 5.03 (d, *J* = 2.1 Hz, 1/2H, CH=C for one isomer), 5.07 (d, *J* =2.1 Hz, 1/2H, CH=C for another isomer), 5.11 (s, 1H, CH=C), 5.88 (d, *J* = 3.7 Hz, 1/2H, H-8a for one isomer), 5.89 (d, *J* = 3.6 Hz, 1/2H, H-8a for another isomer); ^{13}C NMR ($CDCl_3$): δ 25.6 (CH_3), 28.7 (CH_3), 40.6 (CH), 43.4 (CH), 60.5 (CH_2), 62.0 (CH_2), 67.0 (CH_2), 70.6 (CH_2), 78.9 (CH), 82.2 (CH), 83.9 (CH), 103.5 (CH), 104.2 (CH), 110.9 (C), 114 (CH_2), 138.8 (C); HRMS: Calcd. for $C_{12}H_{18}O_5$ (M^++ Na): 265.1052. Found *m/z* 265.1051.

[(3a*R*,3b*R*,7*R*,7a*R*,8a*R*)-2,2-dimethyl-6-methylenehexahydro-3b*H*-[1,3]dioxolo[4,5]furo[3,2-b]pyran-7-yl]methanol, 5b

Compound **4b** or **7b** (240 mg, 1 mmole) under similar radical cyclization conditions as described for **5a** afforded a mixture of compound **5b** and the reduced product **8b** (1:1) (211 mg, 88%) which was partly separated by preparative TLC (10% ethyl acetate in petroleum ether) to furnish **5b** (120 mg, 50%) and the reduced product **8b** (49 mg, 20%). The remaining portion extracted from the TLC plate (43 mg, 17%) was a mixture of **5b** and **8b**. The spectral and analytical data of **5b**: {$[\alpha]_D^{27.1}$+18.7° (C = 0.48, $CHCl_3$)}; IR (neat): 3489, 2923, 2852, 1724, 1649, 1454, 1375, 1303, 1245, 1215, 1170, 1151, 1128, 1078, 1062 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.49-2.56 (m, 1H, H-7), 3.34 (dd, *J* = 9.3, 4.0 Hz, 1H, H-3b), 3.68 (dd, *J* = 10.9, 9.3 Hz, 1H, H-7a), 3.98 (d, *J* = 6.5 Hz, 2H, CH_2O), 4.24 (dd, *J* = 12.5 Hz, 2H, H_2-5), 4.66 (t, *J* = 3.8 Hz, 1H, H-3a), 4.97 (d, *J* = 1.9 Hz, 1H, CH=C), 5.13 (s, 1H, CH=C), 5.85 (d, *J* = 3.4 Hz, 1H, H-8a); ^{13}C NMR ($CDCl_3$): δ 27.9 (CH_3), 28.1 (CH_3), 31.6 (CH), 49.9 (CH), 64.7 (CH_2), 76.8 (CH_2), 78.1 (CH), 79.3 (CH), 83.7 (CH), 107.3 (C), 115.2 (CH_2), 130.6 (C). Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.36; H, 7.41%.

(2,2,6-Trimethyl-hexahydro-1,3,4,8-tetraoxa-cyclopenta[a] inden-7-yl)-methanol, 5c

Compound **7c** (120 mg, 0.51 mmole) under similar radical cyclization conditions as described for **5a** afforded a mixture of compound **5c** and the reduced product **8c** (1:1) (105 mg, 88%) which was partly separated by preparative TLC (10% ethyl acetate in petroleum ether) to furnish **5c** (36 mg, 30%) and pure reduced product **8b** (25 mg, 20%). The remaining portion extracted from the TLC plate (43 mg, 35%) was a mixture of **5b** and **8b**. Compound **5c** was found to be a mixture of four isomers in a ratio of 1:1:2:1 (^1H NMR), which could not be separated by usual chromatographic methods including HPLC. Only four distinguishable doublets of the CH_3 signals at C-6 for four isomers appeared at δ 1.15 (d, *J* = 7.2 Hz), 1.06 (d, *J* = 7.2 Hz), 0.89 (d, *J* = 7.3 Hz) and 0.85 (d, *J* = 6.7 Hz) respectively in ^1H NMR spectrum. HRMS: Calcd. for [$C_{12}H_{20}O_5$ + H^+) 245.1389. Found *m/z* 245.1342.

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