Synthesis of L-*ido*-Configured Six- and Seven-Membered Carba-Sugars

C. V. Ramana,* Siddhartha R. Chaudhuri, Mukund K. Gurjar

National Chemical Laboratory, Pune-411 008, India
Fax +91(20)25902629; E-mail: vr.chepuri@ncl.res.in

Received 6 September 2006; revised 13 November 2006

Abstract: Ring-closing olefin metathesis has been successfully applied to the modular construction of L-*ido*-configured six- and seven-membered carba-sugars.

Key words: allylations, carbocycles, carbohydrates, metathesis, radical reactions

L-Iduronic acid, one of the naturally available L-sugars, is the major component of the three glycosaminoglycans heparin, heparan sulfate, and dermatan sulfate. It is well established that low-molecular-weight heparin analogue **1**[1] (Figure 1) is a better anticoagulant than the heparin polymer that has been marketed[2] for several decades. The flexibility of the pyranose ring of L-iduronic acid to adopt either a chair $^4C_1/^1C_4$ or a $^2S_0$ skew boat conformation has been accentuated as a critical factor in the biology of heparin. Recently, Sinaÿ and co-workers[3] synthesized methylated antifactor Xa pentasaccharide **1** (Figure 1) containing three possible conformationally locked forms of L-iduronic acid and showed that the $^2S_0$-conformer plays a critical role in the activation of antithrombin by heparin and its analogues. The importance of conformationally flexible L-iduronic acid analogues as well as the greater metabolic stability and conformational flexibility of carba analogues of the sugars (carba- or pseudo-sugars) compared to their oxygen analogues motivated us to design a project on the synthesis of methylated antifactor Xa pentasaccharide analogues containing carba-L-iduronic acid (of varying ring sizes).

Several groups have reported the synthesis of six-membered L-*ido*-configured carba-sugars by a variety of methods.[4] However, synthetic efforts towards the selective construction of L-*ido*-configured medium-size carbacycles are scarce. Sinaÿ and co-workers[4h] reported the formation of an eight-membered carba-L-idose derivative as the minor product along with the corresponding major D-*gluco* analogue. Herein, we describe a flexible method for the synthesis of L-*ido*-configured carbacycles **2** and **3** (Figure 1) in which ring-closing metathesis (RCM) is the key reaction.

Our intended strategy was based on our observation[5] that radical allylation of 5-chloro-5-deoxy-1,2-isopropylidene-L-idofuranurono-6,3-lactone (**4**)[6] results in retention of configuration, exclusively giving **5** in 92% yield

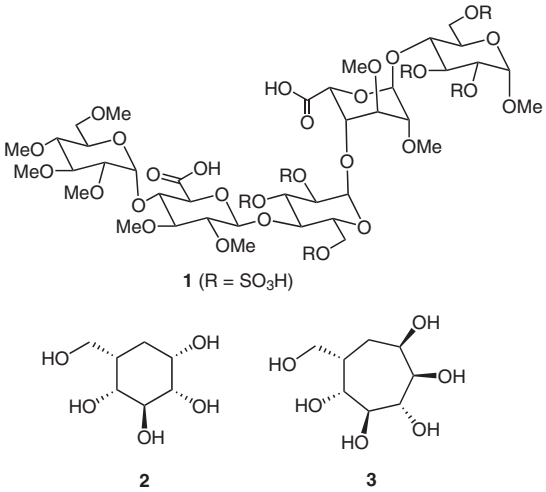


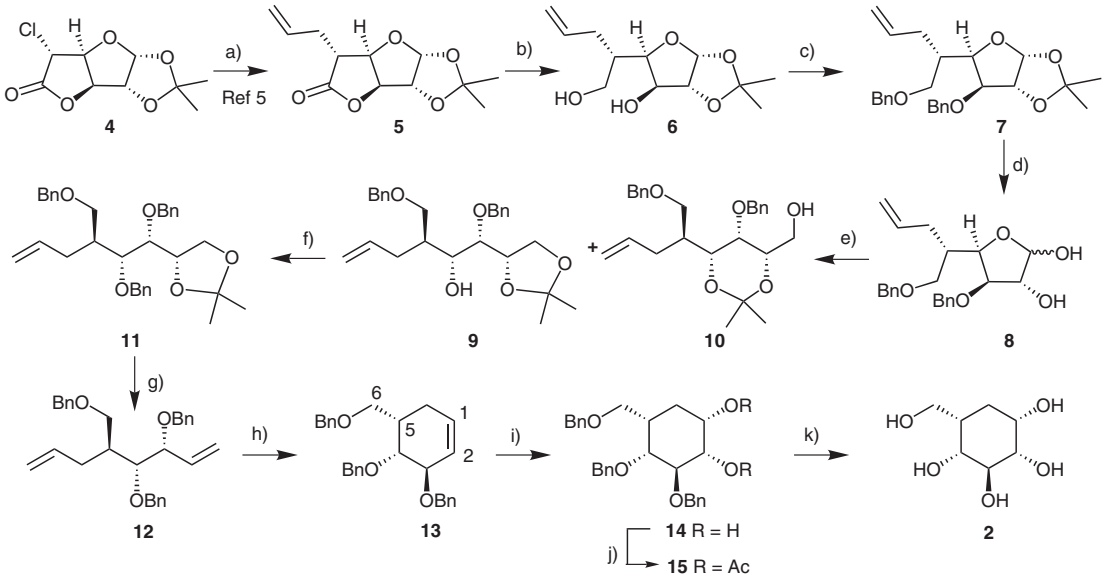
Figure 1 Antithrombin-binding synthetic pentasaccharide **1** and designed L-*ido*-configured carba-sugars **2** and **3**

(Scheme 1); the required stereochemistry of L-*ido*-carbacycles is carried at C5 of **5**. Construction of another olefin of different length at the C1 terminal, followed by RCM should give the required medium-sized L-*ido*-configured carbacycles.[7]

As shown in Scheme 1, treatment of **5** with lithium aluminum hydride, benzylation, and deisopropylidenation gave lactol **8**. Upon treatment with sodium borohydride followed by the addition of 2,2-dimethoxypropane, **8** gave easily separable 1,2- and 2,4-isopropylidene derivatives **9** and **10**. Diene **12** was obtained in 61% overall yield from benzyl derivative **11** after a sequence of deisopropylidenation, dimesylation, and elimination,[8] without any purification of the intermediates. The key RCM reaction of **12** was quite facile when Grubbs' catalyst $[Ru(=CHPh)Cl_2(PCy_3)_2]$ was used, and afforded the pseudo-glycal **13** in excellent yield. Pseudo-glycal **13** is characterized by two peaks at δ 124.5 and 130.6 (C=C) in its ^{13}C NMR spectrum. In the ^1H NMR spectrum, the observed *J*(3,4) of 2.7 Hz indicated a pseudo-diequatorial relation between H–C3 and H–C4. The assigned L-*xylo* configuration of **13** was confirmed by its NOESY spectrum, where a weak NOE interaction was found between H–C3 and H–C6 and no NOE interaction between H–C3 and H–C5.

As observed with the carba-3,4,6-tri-*O*-benzyl-D-glucal,[9] dihydroxylation of **13** also occurred exclusively *anti* to the 3-OBn group, and the corresponding carba-β-L-idopyranose derivative **15** was obtained in good yield after acety-

SYNTHESIS 2007, No. 4, pp 0523–0528
Advanced online publication: 22.01.2007
DOI: 10.1055/s-2007-965899; Art ID: T13706SS

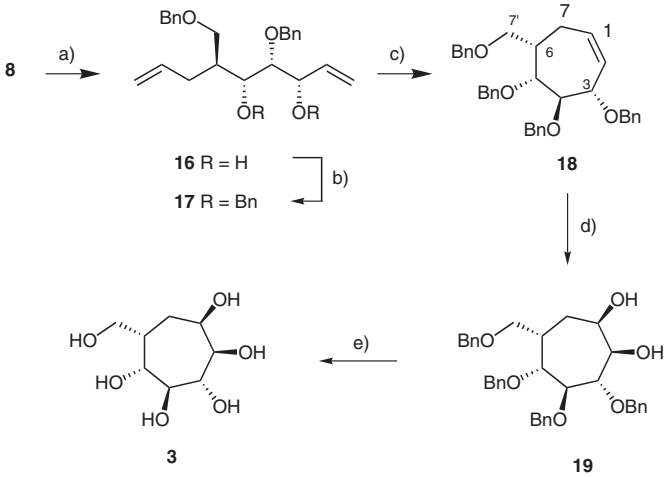


Scheme 1 *Reagents and conditions*: (a) $AllSnBu_3$, AIBN, benzene, reflux, 10 h, 92%; (b) LAH, THF, 0 °C to r.t., 1 h, 90%; (c) NaH, BnBr, DMF, 0 °C to r.t., 2 h, 88%; (d) 6 M HCl, THF–H_2O (5:1), 70 °C, 3 h, 74%; (e) i. $NaBH_4$, THF–H_2O (3:1), 0 °C, 10 min, ii. 2,2-dimethoxypropane, CH_2Cl_2, PTSA, r.t., 1 h, 65% (**9**), 14% (**10**); (f) NaH, BnBr, DMF, 0 °C to r.t., 3 h, 70%; (g) i. 0.8% H_2SO_4, MeOH, r.t., 5 h; ii. MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 0.5 h; iii. NaI, MEK, reflux, 6 h, 61% (3 steps); (h) [Ru(=CHPh)Cl_2(PCy_3)$_2$] (5 mol%), CH_2Cl_2, r.t., 6 h, 91%; (i) OsO_4, K_3[Fe(CN)$_6$], K_2CO_3, *t*-BuOH–H_2O (1:1), r.t.; (j) Ac_2O, py, r.t., 65% (two steps); (k) H_2,10% Pd/C, MeOH, 91%.

lation of the intermediate diol, whereas hydrogenation of the intermediate diol **14** provided the carba-β-L-idopyranose **2**.[10] The *trans*-diequatorial relation between H–C2 and H–C3 and between H–C3 and H–C4 and the $^1C_4$ conformation of diacetate **15** in acetone-d_6 solution was deduced from the observed coupling constants $J(2,3) = J(3,4) = 3.9$ Hz and $J(4,5) = 3.4$ Hz in the ^{1}H NMR spectrum.

After having gained easy access to carba-β-L-idopyranose, we next focused our attention on the synthesis of the corresponding seven-membered carbacycle. Treatment of **8** with excess methylene(triphenyl)phosphorane and subsequent benzylation and RCM provided cycloheptene derivative **18** (Scheme 2). The seven-membered carbacycle **18** is characterized by two peaks at δ 129.5 and 130.8 (C=C) in the ^{13}C NMR spectrum. The observed J(3,4) of 9.5 Hz and J(4,5) of 4.8 Hz indicate a diaxial relation between H–C3 and H–C4, and an axial–pseudoaxial relation between H–C4 and H–C5. The L-*ido* configuration assigned to **18** was confirmed by NOE experiments, where a strong NOE interaction was found between H–C3 and H–C5/H–C6.

The *syn*-dihydroxylation reaction of **18** in the presence of osmium tetroxide and *N*-methylmorpholine *N*-oxide in a tetrahydrofuran–water mixture (1:1) at room temperature for five hours resulted in the formation of diol **19** (Scheme 2). Compound **19** was characterized by its ^{1}H NMR and ^{13}C NMR spectra and elemental analysis. Finally, hydrogenation of **19** over 10% palladium on carbon in methanol gave the polyhydroxylated seven-membered



Scheme 2 *Reagents and conditions*: (a) $Ph_3P{=}CH_2$, THF–Et_2O, –78 °C to r.t., 12 h, 77%; (b) NaH, BnBr, DMF, 0 °C to r.t., 6 h, 72%; (c) [Ru(=CHPh)Cl_2(PCy_3)$_2$] (5 mol%), CH_2Cl_2, r.t., 20 h, 87%; (d) OsO_4, NMO, THF–H_2O (1:1), r.t., 5 h, 91%; (e) H_2, 10% Pd/C, MeOH, 4 h, 92%.

carba-sugar **3** (Scheme 2). The ^{1}H NMR and ^{13}C NMR spectra and elemental analysis supported the assigned structure **3**.

To conclude, a simple approach for the synthesis of six- and seven-membered carbacycles was found from the easily available D-glucurono-6,3-lactone derived building block **4** through simple synthetic operations and ring-closing olefin metathesis as the key step. Experiments are in progress towards the synthesis of methylated antifactor Xa pentasaccharide analogues containing carba-L-iduronic acid.

Air- and/or moisture-sensitive reactions were carried out in anhyd solvents under an atmosphere of argon in oven-dried glassware. All anhyd solvents were distilled prior to use: THF and Et_2O from Na–benzophenone, CH_2Cl_2 from CaH_2, and MeOH from Mg cake. Commercial reagents were used without further purification. Column chromatography was carried out on Spectrochem silica gel (60–120 mesh). Optical rotations were determined on a Jasco DIP-370 digital polarimeter. ^{1}H and ^{13}C NMR spectroscopy measurements were carried out on Bruker AC 200 MHz or Bruker DRX 500 MHz spectrometers, and TMS was used as internal standard. Mass spectroscopy (EI, 70 eV, direct inlet system) was carried out on a Finnigan MAT-1020 spectrometer. Elemental analysis data were obtained on a Thermo Finnigan Flash EA 1112 Series CHNS Analyser.

5-*C*-Allyl-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranurono-6,3-lactone (5)

A soln of **4** (9.0 g, 38.4 mmol), $AllSnBu_3$ (12.9 mL, 42.2 mmol), and AIBN (25 mg) in benzene (75 mL) under argon was heated under reflux for 10 h and then concentrated. A sat. soln of KF in Et_2O was introduced, and the mixture was stirred vigorously for 4 h. The Et_2O layer was separated, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (silica gel, EtOAc–light PE, 1:9) gave **5** as a colorless oil.

Yield: 8.47 g (92%); $[\alpha]_D^{25}$ +70.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.50 (s, 3 H), 2.32 (dt, *J* = 8.0, 14.0 Hz, 1 H), 2.49 (dt, *J* = 6.0, 14.0 Hz, 1 H), 2.81 (dd, *J* = 6.0, 8.0 Hz, 1 H), 4.71 (d, *J* = 3.4 Hz, 1 H), 4.75 (d, *J* = 3.4 Hz, 1 H), 4.81 (d, *J* = 4.0 Hz, 1 H), 5.18 (d, *J* = 10.7 Hz, 1 H), 5.22 (d, *J* = 16.6 Hz, 1 H), 5.69–5.90 (m, 1 H), 5.94 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.9, 26.0, 31.6, 46.4, 81.7, 82.0, 83.7, 105.4, 111.8, 118.0, 132.8, 175.7.

MS (EI): *m*/*z* = 225 [M^+ – 15].

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.92; H, 6.75.

5-*C*-Allyl-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (6)

A suspension of LAH (1.26 g, 33.3 mmol) and **5** (8.0 g, 33.3 mmol) in THF (50 mL) was stirred at r.t. for 1 h. The excess LAH was quenched with a sat. soln of Na_2SO_4, the mixture was filtered, and the residue was thoroughly washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, EtOAc–light PE, 1:1); this gave **6** as a thick oil.

Yield: 7.32 g (90%); $[\alpha]_D^{25}$ −17.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.48 (s, 3 H), 1.95–2.18 (m, 2 H), 2.41–2.50 (m, 1 H), 3.20 (br s, 1 H), 3.49 (dd, *J* = 2.0, 10.5 Hz, 1 H), 3.78 (dd, *J* = 2.0, 10.5 Hz, 1 H), 3.91 (dd, *J* = 2.0, 8.8 Hz, 1 H), 4.14–4.24 (m, 1 H), 4.15 (d, *J* = 2.0 Hz, 1 H), 4.52 (d, *J* = 3.6 Hz, 1 H), 5.05 (br d, *J* = 10.2 Hz, 1 H), 5.07 (br d, *J* = 17.2 Hz, 1 H), 5.68–5.84 (m, 1 H), 5.88 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.8, 26.4, 33.0, 39.4, 61.2, 74.5, 82.7, 84.7, 103.6, 110.8, 116.7, 135.3.

MS (EI): *m*/*z* = 229 [M^+ – 15].

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.0; H, 8.25. Found: C, 58.81; H, 8.49.

5-*C*-Allyl-3,5-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (7)

Compound **6** (8.0 g, 32.8 mmol) in DMF (20 mL) was added to a stirred suspension of 60% NaH dispersion in oil (3.27 g, 82.0 mmol) in DMF (30 mL) at 0 °C. The resulting soln was stirred at r.t. for 30 min, and then BnBr (8.7 mL, 72.1 mmol) and TBAI (0.1 g, 0.27 mmol) were added. After 2 h, the reaction was quenched with ice-cold H_2O and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with H_2O (2 × 100 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (silica gel, EtOAc–light PE, 1:9) gave **7**.

Yield: 12.23 g (88%); $[\alpha]_D^{25}$ –43.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.52 (s, 3 H), 2.15–2.37 (m, 2 H), 2.44–2.56 (m, 1 H), 3.27 (dd, *J* = 4.2, 9.3 Hz, 1 H), 3.36 (dd, *J* = 4.4, 9.3 Hz, 1 H), 3.80 (d, *J* = 2.9 Hz, 1 H), 4.11 (dd, *J* = 2.9, 9.3 Hz, 1 H), 4.28 (d, *J* = 11.7 Hz, 1 H), 4.32 (d, *J* = 12.2 Hz, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 4.57 (d, *J* = 3.9 Hz, 1 H), 4.58 (d, *J* = 11.7 Hz, 1 H), 5.01 (dd, *J* = 2.4, 9.8 Hz, 1 H), 5.05 (dd, *J* = 1.5, 17.1 Hz, 1 H), 5.71–5.85 (m, 1 H), 5.90 (d, *J* = 3.9 Hz, 1 H), 7.22–7.37 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.1, 26.6, 32.7, 37.1, 68.7, 71.2, 72.8, 80.5, 81.6, 81.8, 104.1, 110.8, 116.3, 127.2, 128.0, 136.2, 137.4, 138.3.

Anal. Calcd for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.33; H, 7.85.

5-*C*-Allyl-3,5-di-*O*-benzyl-5-deoxy-α/β-L-idofuranose (8)

A mixture of **7** (3.0 g, 7.1 mmol) and 6 M HCl (10 mL) in THF–H_2O (5:1, 30 mL) was heated at 70 °C for 3 h. The mixture was neutralized by the addition of solid $NaHCO_3$, filtered, and concentrated. The residue was partitioned between EtOAc and H_2O, and the organic layer was separated, washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (silica gel, EtOAc–light PE, 1:3) gave **8** as a thick oil.

Yield: 2.0 g (74%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.11–2.32 (m, 2 H), 2.41–2.51 (m, 1 H), 3.29–3.41 (m, 2 H), 3.48–3.56 (m, 2 H), 3.77–3.84 (m, 1 H), 4.12–4.61 (m, 6 H), 4.97–5.47 (m, 3 H), 5.70–5.92 (m, 1 H), 7.19–7.30 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.6, 32.8, 37.6, 38.4, 68.8, 69.0, 71.3, 71.8, 72.9, 74.5, 76.4, 77.3, 79.1, 82.1, 82.2, 83.6, 95.6, 102.7, 116.3, 116.4, 127.4, 127.5, 127.6, 128.0, 128.1, 128.3, 136.3, 136.5, 136.9, 137.6, 138.2.

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.67; H, 7.65.

Oct-7-en-4-ols 9 and 10

To a soln of **8** (2.0 g, 5.2 mmol) in THF–H_2O (3:1, 20 mL) at 0 °C was added $NaBH_4$ (0.2 g, 5.2 mmol) in portions. After 10 min, the solvent was removed and 1 M HCl (2 mL) was added; the mixture was extracted with EtOAc (3 × 30 mL), dried (Na_2SO_4), and concentrated. The residue was stirred with CH_2Cl_2 (10 mL), 2,2-dimethoxypropane (1.7 mL), and PTSA (30 mg). After 1 h, the mixture was neutralized with Et_3N and concentrated. The residue was partitioned between EtOAc and H_2O, the organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by column

chromatography (silica gel, EtOAc–light PE, 1:4); this gave **9** and **10** as colorless oils.

(2*S*,3*S*,4*R*,5*S*)-3-(Benzyloxy)-5-[(benzyloxy)methyl]-1,2-*O*-isopropylideneoct-7-en-4-ol (9)

Yield: 1.44 g (65%); $[\alpha]_D^{25}$ –21.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.44 (s, 3 H), 1.79–1.88 (m, 1 H), 2.08–2.18 (m, 1 H), 2.36–2.45 (m, 1 H), 3.24 (dd, *J* = 3.9, 9.6 Hz, 1 H), 3.33 (dd, *J* = 5.1, 9.6 Hz, 1 H), 3.39–3.45 (m, 1 H), 3.52 (dd, *J* = 1.4, 7.3 Hz, 1 H), 3.63 (t, *J* = 8.0 Hz, 1 H), 4.03 (dd, *J* = 6.6, 8.0 Hz, 1 H), 4.31–4.46 (m, 3 H), 4.58 (d, *J* = 11.7 Hz, 1 H), 4.88 (d, *J* = 11.2 Hz, 1 H), 4.97–5.02 (m, 2 H), 5.67–5.80 (m, 1 H), 7.24–7.34 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.6, 26.7, 32.2, 42.0, 66.2, 69.9, 72.5, 73.3, 73.6, 78.2, 79.5, 109.3, 116.3, 127.6–128.3, 137.1, 138.3, 138.6.

MS (EI): *m*/*z* = 426 [M$^+$].

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 72.95; H, 8.18.

(2*S*,3*S*,4*R*,5*S*)-3-(Benzyloxy)-5-[(benzyloxy)methyl]-2,4-*O*-isopropylideneoct-7-en-1-ol (10)

Yield: 0.32 g (14%); $[\alpha]_D^{25}$ –20.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 1.44 (s, 3 H), 2.04–2.09 (m, 1 H), 2.13–2.19 (m, 1 H), 2.43–2.50 (m, 1 H), 3.28–3.29 (m, 1 H), 3.30 (dd, *J* = 4.0, 9.5 Hz, 1 H), 3.34 (dd, *J* = 4.0, 9.5 Hz, 1 H), 3.55 (dd, *J* = 4.9, 11.1 Hz, 1 H), 3.73 (dd, *J* = 7.2, 11.1 Hz, 1 H), 3.80 (dd, *J* = 1.2, 9.1 Hz, 1 H), 3.89 (ddd, *J* = 1.2, 4.9, 7.2 Hz, 1 H), 4.35 (d, *J* = 12.1 Hz, 1 H), 4.45 (d, *J* = 12.1 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.57 (d, *J* = 11.9 Hz, 1 H), 4.95–5.02 (m, 2 H), 5.69–5.78 (m, 1 H), 7.22–7.35 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.8, 29.4, 31.3, 38.6, 62.1, 67.7, 70.5, 72.3, 72.8, 73.1, 73.8, 98.7, 116.1, 127.2, 127.5, 127.6, 127.9, 128.0, 136.6, 138.0, 138.2.

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 73.15; H, 8.10.

(2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-[(benzyloxy)methyl]-1,2-*O*-isopropylideneoct-7-ene (11)

The benzylation of **9** (1.3 g, 3.1 mmol) was performed as described in the preparation of **7** above; used were NaH (0.14 g, 3.7 mmol), TBAI (0.1 g, 0.27 mmol), and BnBr (0.4 mL, 3.4 mmol) in DMF (10 mL); this gave **11** after purification by column chromatography (silica gel, EtOAc–light PE, 1:19) as a thick syrup.

Yield: 1.11 g (70%); $[\alpha]_D^{25}$ –7.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.45 (s, 3 H), 2.25 (m, 3 H), 3.37 (dd, *J* = 4.6, 9.6 Hz, 1 H), 3.49 (dd, *J* = 5.3, 9.6 Hz, 1 H), 3.54 (t, *J* = 5.3 Hz, 1 H), 3.66 (t, *J* = 8.0 Hz, 1 H), 3.73 (t, *J* = 4.6 Hz, 1 H), 3.85 (dd, *J* = 6.5, 8.0 Hz, 1 H), 4.26–4.36 (m, 2 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.55 (s, 2 H), 4.66 (d, *J* = 11.7 Hz, 1 H), 4.78 (d, *J* = 11.7 Hz, 1 H), 4.99 (br d, *J* = 10.2 Hz, 1 H), 5.04 (br d, *J* = 17.1 Hz, 1 H), 5.67–5.87 (m, 1 H), 7.22–7.40 (m, 15 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.6, 26.5, 31.7, 39.7, 66.0, 69.8, 72.8, 73.0, 73.8, 76.8, 78.6, 79.7, 108.9, 116.0, 127.3, 128.1, 137.2, 138.6.

MS (EI): *m*/*z* = 517 [M$^+$ + 1].

Anal. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80. Found: C, 76.94; H, 7.80.

(3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-[(benzyloxy)methyl]octa-1,7-diene (12)

A soln of **11** (1.0 g, 1.9 mmol) and 0.8% H_2SO_4 (2 mL) in MeOH (10 mL) was stirred at r.t. for 5 h, neutralized with solid $NaHCO_3$, filtered, and concentrated. The residue was partitioned between EtOAc and H_2O, and the organic layer was dried (Na_2SO_4) and concentrated. The crude diol was dissolved in CH_2Cl_2 (5 mL), and then Et_3N (0.6 mL, 4.5 mmol) and MsCl (0.3 mL, 3.7 mmol) were added. After 30 min, the mixture was partitioned between EtOAc and H_2O, and the organic layer was dried (Na_2SO_4) and concentrated. A mixture of the dimesylate (0.86 g) and NaI (1.2 g, 8.1 mmol) in MEK (10 mL) was heated under reflux for 6 h. The solvent was removed, the residue was partitioned between EtOAc and H_2O, and the organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (silica gel, EtOAc–light PE, 1:19) afforded **12** as a clear oil.

Yield: 0.51 g (61%, 3 steps); $[\alpha]_D^{25}$ +12.1 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.01–2.18 (m, 2 H), 2.25–2.38 (m, 1 H), 3.38–3.52 (m, 2 H), 3.87 (dd, *J* = 2.4, 6.8 Hz, 1 H), 4.08 (t, *J* = 7.3 Hz, 1 H), 4.37 (d, *J* = 12.2 Hz, 1 H), 4.42 (d, *J* = 11.2 Hz, 1 H), 4.47 (d, *J* = 12.2 Hz, 1 H), 4.58 (d, *J* = 11.2 Hz, 1 H), 4.67 (d, *J* = 11.7 Hz, 1 H), 4.93–5.07 (m, 3 H), 5.35 (dd, *J* = 2.3, 7.7 Hz, 1 H), 5.38 (dd, *J* = 2.3, 10.7 Hz, 1 H), 5.68–5.97 (m, 2 H), 7.34–7.40 (m, 15 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.6, 40.0, 70.0, 70.5, 72.9, 74.9, 80.8, 83.4, 115.5, 118.8, 127.2, 127.6, 128.2, 135.7, 137.4, 138.5, 139.3.

MS (EI): *m*/*z* = 351 [M$^+$ – Bn].

Anal. Calcd for $C_{30}H_{34}O_3$: C, 81.41; H, 7.74. Found: C, 81.65; H, 7.78.

(3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-[(benzyloxy)methyl]cyclohexene (13)

Compound **12** (0.2 g, 0.45 mmol) was dissolved in anhyd CH_2Cl_2 (20 mL) and the soln was degassed with argon. [Ru(=CHPh)$Cl_2(PCy_3)_2$] (18 mg, 5 mol%) was added and the mixture was stirred at r.t. for 6 h. The solvent was removed and the residue was purified by column chromatography (silica gel, EtOAc–light PE, 3:97); this gave **13** as a colorless syrup.

Yield: 0.17 g (91%); $[\alpha]_D^{25}$ –77.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.08–2.16 (m, 2 H), 2.44 (dquin, *J* = 2.3, 6.8 Hz, 1 H), 3.51 (dd, *J* = 6.8, 9.1 Hz, 1 H), 3.66 (dd, *J* = 7.6, 9.1 Hz, 1 H), 3.89–3.96 (m, 2 H), 4.54 (s, 2 H), 4.56 (d, *J* = 12.2 Hz, 1 H), 4.59 (d, *J* = 11.9 Hz, 1 H), 4.64 (d, *J* = 11.9 Hz, 1 H), 4.67 (d, *J* = 12.2 Hz, 1 H), 5.79–5.87 (m, 1 H), 6.02 (dt, *J* = 3.4, 9.7 Hz, 1 H), 7.32–7.40 (m, 15 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.1, 34.4, 70.6, 71.1, 71.9, 72.4, 72.8, 75.5, 124.4, 127.3, 127.4, 127.5, 127.6, 128.1, 130.6, 138.6, 138.7.

MS (EI): *m*/*z* = 323 [M$^+$ – Bn].

Anal. Calcd for $C_{28}H_{30}O_3$: C, 81.13; H, 7.29. Found: C, 81.34; H, 7.50.

(1*S*,2*R*,3*S*,4*R*,5*S*)-1,2-Bis(acetoxy)-3,4-bis(benzyloxy)-5-[(benzyloxy)methyl]cyclohexane (15)

A soln of K_2CO_3 (99 mg, 0.72 mmol), $K_3Fe(CN)_6$ (0.23 g, 0.72 mmol), and 0.04 M OsO_4 in toluene (0.24 mL, 9.6 μmol) in *t*-BuOH–H_2O (1:1, 8 mL) was added to **13** (0.1 g, 0.24 mmol). After 12 h, the mixture was quenched with Na_2SO_3 and extracted with EtOAc, and the organic phase was dried (Na_2SO_4) and concentrated. The crude diol **14** was treated with Ac_2O (0.06 mL, 0.63 mmol) and Et_3N (0.11 mL, 0.83 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, EtOAc–light PE, 3:17); this gave **15** as a colorless oil.

Yield: 83 mg (65%); $[\alpha]_D^{25}$ –5.9 (*c* 1.1, $CHCl_3$).

^{1}H NMR (200 MHz, acetone-d_6): δ = 1.68 (dt, *J* = 3.9, 12.2 Hz, 1 H), 1.97 (s, 3 H), 2.02 (s, 3 H), 2.09–2.14 (m, 1 H), 2.40–2.55 (m, 1 H), 3.50 (dd, *J* = 6.8, 8.8 Hz, 1 H), 3.68 (dd, *J* = 7.9, 8.8 Hz, 1 H), 3.80 (t, *J* = 3.4 Hz, 1 H), 4.06 (t, *J* = 3.9 Hz, 1 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 4.51 (s, 2 H), 4.57 (d, *J* = 11.2 Hz, 1 H), 4.64 (d, *J* = 15.1 Hz, 1 H), 4.73 (d, *J* = 11.7 Hz, 1 H), 5.17 (dt, *J* = 3.9, 11.2 Hz, 1 H), 5.29 (t, *J* = 3.4 Hz, 1 H), 7.23–7.39 (m, 15 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8, 21.0, 24.2, 36.3, 69.3, 69.9, 70.5, 72.0, 72.8, 73.0, 73.6, 75.3, 127.5, 127.8, 128.2, 128.3, 137.8, 138.4, 170.1, 170.6.

Anal. Calcd for $C_{32}H_{36}O_7$: C, 72.16; H, 6.81. Found: C, 71.94; H, 6.86.

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(Hydroxymethyl)cyclohexane-1,2,3,4-tetrol (2)

A soln of crude **14** (50 mg, 0.11 mmol) in MeOH (5 mL) was hydrogenated in the presence of 10% Pd/C (10 mg) at r.t. After 4 h, the mixture was filtered through a pad of Celite, and concentrated.

Yield: 18 mg (91%); $[\alpha]_D^{25}$ +5.8 (*c* 1.5, MeOH) {Lit.[10] $[\alpha]_D^{25}$ +7.0 (*c* 1.5, MeOH)}.

^{1}H NMR (500 MHz, D_2O): δ = 1.68 (dt, *J* = 4.4, 13.5 Hz, 1 H), 1.75 (dt, *J* = 9.2, 13.5 Hz, 1 H), 2.08–2.18 (m, 1 H), 3.68 (dd, *J* = 6.4, 10.7 Hz, 1 H), 3.76 (dd, *J* = 6.6, 10.7 Hz, 1 H), 3.77 (t, *J* = 4.2 Hz, 1 H), 3.83 (t, *J* = 4.2 Hz, 1 H), 3.99 (t, *J* = 4.4 Hz, 2 H).

^{13}C NMR (50 MHz, D_2O–acetone-d_6): δ = 26.4, 38.5, 62.8, 68.2, 71.0, 71.5, 73.4.

Anal. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.44; H, 7.66.

(3*S*,4*R*,5*R*,6*S*)-4-(Benzyloxy)-6-[(benzyloxy)methyl]nona-1,8-diene-3,5-diol (16)

$Ph_3P{=}CH_2$ {prepared from $[PPh_3Me]I$ (2.1 g, 5.17 mmol) and 1.6 M *n*-BuLi (0.33 mL, 0.53 mmol)} was added dropwise to a soln of **8** (1.0 g, 2.6 mmol) in anhyd THF (10 mL) at –78 °C. After the mixture had stirred at r.t. for 12 h, it was quenched by the addition of a sat. aq soln of NH_4Cl. The two layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (silica gel, EtOAc–light PE, 1:4) furnished **16** as a colorless oil.

Yield: 0.76 g (77%); $[\alpha]_D^{25}$ –16.1 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.83–1.99 (m, 1 H), 2.17 (dt, *J* = 8.2, 14.2 Hz, 1 H), 2.34–2.47 (m, 1 H), 2.68 (br s, 2 H), 3.45 (d, *J* = 4.9 Hz, 2 H), 3.59 (t, *J* = 4.1 Hz, 1 H), 3.81 (br t, *J* = 4.7 Hz, 1 H), 4.31 (br t, *J* = 4.6 Hz, 1 H), 4.45 (br s, 2 H), 4.65 (d, *J* = 11.3 Hz, 1 H), 4.76 (d, *J* = 11.3 Hz, 1 H), 5.03 (br d, *J* = 10.0, 1 H), 5.07 (br d, *J* = 17.3 Hz, 1 H), 5.25 (br dt, *J* = 1.4, 10.4 Hz, 1 H), 5.40 (br dt, *J* = 1.4, 17.3 Hz, 1 H), 5.69–6.02 (m, 2 H), 7.25–7.40 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.5, 41.7, 70.6, 73.0, 73.2, 73.7, 81.9, 116.0, 116.3, 127.6, 128.0, 128.4, 137.1, 138.2, 138.4.

MS (EI): *m*/*z* = 382 [M^+], 291 [M^+ – Bn].

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.11; H, 8.18.

(3*S*,4*R*,5*R*,6*S*)-3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]nona-1,8-diene (17)

The benzylation of **16** (0.51 g, 1.3 mmol) was performed as described in the preparation of **7** above; used were NaH (0.13 g, 3.3 mmol), TBAI (0.1 g, 0.27 mmol), and BnBr (0.3 mL, 2.9 mmol) in DMF (10 mL); this gave **17** after purification by column chromatography (silica gel, EtOAc–light PE, 1:19).

Yield: 0.54 g (72%); $[\alpha]_D^{25}$ +27.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.07–2.34 (m, 3 H), 3.39 (dd, *J* = 4.6, 9.0 Hz, 1 H), 3.49 (dd, *J* = 7.6, 9.0 Hz, 1 H), 3.72 (dd, *J* = 4.1, 7.0 Hz, 1 H), 4.01 (dd, *J* = 4.1, 7.5 Hz, 1 H), 4.10 (dd, *J* = 2.9, 7.0 Hz, 1 H), 4.38 (br d, *J* = 12.2 Hz, 2 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.58 (d, *J* = 11.7 Hz, 1 H), 4.66 (d, *J* = 11.7 Hz, 1 H), 4.74 (s, 2 H), 4.79 (d, *J* = 11.2 Hz, 1 H), 4.97 (br d, *J* = 10.2 Hz, 1 H), 5.02 (br d, *J* = 17.6 Hz, 1 H), 5.32 (br d, *J* = 16.6 Hz, 1 H), 5.33 (br d, *J* = 10.3 Hz, 1 H), 5.60–5.80 (m, 1 H), 5.89–6.07 (m, 1 H), 7.29–7.33 (m, 20 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.3, 39.6, 70.4, 70.6, 72.9, 74.2, 74.8, 78.9, 80.7, 83.0, 115.8, 118.5, 127.5, 128.2, 135.8, 137.6, 138.2, 138.7, 139.4.

MS (EI): *m*/*z* = 562 [M^+].

Anal. Calcd for $C_{38}H_{42}O_4$: C, 81.10; H, 7.52. Found: C, 81.40; H, 7.35.

(3*S*,4*R*,5*R*,6*S*)-3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]cycloheptene (18)

Compound **17** (0.4 g, 0.7 mmol) was dissolved in anhyd CH_2Cl_2 (30 mL) and the soln was degassed with argon. $[Ru(=CHPh)Cl_2(PCy_3)_2]$ (29 mg, 5 mol%) was added and the mixture was stirred at r.t. for 20 h. The solvent was removed and the residue was purified by column chromatography (silica gel, EtOAc–light PE, 1:49); this gave **18** as a colorless oil.

Yield: 0.33 g (87%); $[\alpha]_D^{25}$ +11.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.06–2.10 (m, 1 H), 2.30–2.37 (m, 1 H), 2.39–2.45 (m, 1 H), 3.41 (dd, *J* = 6.7, 8.8 Hz, 1 H), 3.55 (dd, *J* = 7.7, 8.8 Hz, 1 H), 3.84 (dd, *J* = 4.8, 9.5 Hz, 1 H), 4.0 (dd, *J* = 2.3, 4.8 Hz, 1 H), 4.41 (dt, *J* = 1.7, 9.5 Hz, 1 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.55 (d, *J* = 11.6 Hz, 1 H), 4.73 (d, *J* = 11.1 Hz, 1 H), 4.76 (s, 2 H), 4.80 (d, *J* = 11.6 Hz, 1 H), 4.98 (d, *J* = 11.1 Hz, 1 H), 5.71–5.78 (m, 2 H), 7.29–7.39 (m, 20 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.2, 38.4, 71.7, 72.9, 73.1, 74.3, 78.8, 81.5, 86.0, 127.3, 128.3, 129.5, 130.8, 138.4, 138.7, 138.9, 139.0.

MS (EI): *m*/*z* = 443 [M^+ – Bn].

Anal. Calcd for $C_{36}H_{38}O_4$: C, 80.87; H, 7.16. Found: C, 80.99; H, 7.27.

(1*R*,2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]cycloheptane-1,2-diol (19)

To a soln of **18** (30 mg, 56.17 μmol) in THF–H_2O (1:1, 2 mL) was added a 50 wt% soln of NMO in H_2O (0.04 mL, 0.17 mmol) and a 0.04 M soln of OsO_4 in toluene (0.06 mL, 2.24 μmol). After 5 h at r.t., the mixture was diluted with EtOAc (10 mL), washed with H_2O (2 × 5 mL) and sat. Na_2SO_3 (1 × 5 mL), dried (Na_2SO_4), and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, EtOAc–light PE, 1:4); this gave **19** as a clear liquid.

Yield: 29 mg (91%); $[\alpha]_D^{25}$ –47.9 (*c* 2.7, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42–1.47 (m, 1 H), 1.80–1.87 (m, 1 H), 2.29–2.35 (m, 1 H), 2.44 (br s, 1 H), 3.09 (s, 1 H), 3.20–3.27 (m, 2 H), 3.74 (dd, *J* = 2.2, 6.7 Hz, 1 H), 3.78 (dd, *J* = 1.4, 9.6 Hz, 1 H), 3.88–3.90 (m, 1 H), 3.92 (dd, *J* = 6.7, 9.6 Hz, 1 H), 4.03 (dd, *J* = 1.4, 5.5 Hz, 1 H), 4.24 (d, *J* = 11.5 Hz, 1 H), 4.26, 4.40 (2d, *J* = 11.9 Hz, 2 H), 4.51, 4.52 (2d, *J* = 11.5 Hz, 2 H), 4.54, 4.57 (2d, *J* = 11.9 Hz, 2 H), 4.82 (d, *J* = 11.5 Hz, 1 H), 7.14–7.26 (m, 20 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.0, 32.4, 69.6, 71.4, 72.1, 72.2, 72.4, 72.5, 75.3, 75.7, 80.3, 83.3, 127.4–128.6, 137.9, 138.0, 138.3, 138.5.

Anal. Calcd for $C_{36}H_{40}O_6$: C, 76.03; H, 7.09. Found: C, 76.17; H, 7.22.

(1*R*,2*R*,3*S*,4*S*,5*R*,6*S*)-6-(Hydroxymethyl)cycloheptane-1,2,3,4,5-pentol (3)

Compound **3** was obtained by the hydrogenation of **19** (20 mg, 35.2 μmol) with 10% Pd/C in MeOH (2 mL), by the same method as that described above for the synthesis of **2** .

Yield: 6.7 mg (92%); $[\alpha]_D^{25}$ –96.3 (*c* 0.7, MeOH).

^{1}H NMR (200 MHz, D_2O): δ = 1.60–1.94 (m, 2 H), 2.07–2.27 (m, 1 H), 3.51–3.90 (m, 5 H), 4.01–4.09 (m, 1 H), 4.16–4.25 (m, 1 H).

^{13}C NMR (50 MHz, D_2O–acetone-d_6): δ = 27.6, 34.5, 64.4, 69.7, 71.8, 73.4, 74.5, 78.4.

Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.87; H, 7.58.

Acknowledgment

S.R.C. is grateful to CSIR (New Delhi) for the award of a research fellowship.

References

(1) (a) Capila, I.; Linhardt, R. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 390. (b) Fareed, J.; Hoppensteadt, D. A.; Bick, R. L. *Semin. Thromb. Hemost.* **2000**, *26*, 5. (c) Linhardt, R. J.; Gunay, N. S. *Semin. Thromb. Hemost.* **1999**, *25*, 5.

(2) Witczak, Z. J.; Nieforth, K. A. *Carbohydrates in Drug Design*; Marcel Dekker: New York, **1997**.

(3) (a) Mallet, J.-M.; Esnault, J.; Driguez, P.-A.; Duchaussoy, P.; Sizun, P.; Hérault, J.-P.; Herbert, J.-M.; Petitou, M.; Sinaÿ, P. *Angew. Chem. Int. Ed.* **2001**, *40*, 1670. (b) Das, S. K.; Mallet, J.-M.; Esnault, J.; Driguez, P.-A.; Duchaussoy, P.; Herault, J.-P.; Herbert, J.-M.; Petitou, M.; Sinaÿ, P. *Chem. Eur. J.* **2001**, *7*, 4821.

(4) (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455. (b) Ogawa, S.; Ara, M.; Kondoh, T.; Saitoh, M.; Masuda, R.; Toyokuni, T.; Suami, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1121. (c) Ogawa, S.; Tsukiboshi, Y.; Iwasawa, Y.; Suami, T. *Carbohydr. Res.* **1985**, *136*, 77. (d) Blattner, R.; Ferrier, R. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1008. (e) Paulsen, H.; von Deyn, W. *Liebigs Ann. Chem.* **1987**, 125. (f) Barton, D. H. R.; Géro, S. D.; Cléophax, J.; Machado, A. S.; Quiclet-Sire, B. *J. Chem. Soc., Chem. Commun.* **1988**, 1184. (g) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625. (h) Dalko, P. I.; Sinaÿ, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 773. (i) Sollogoub, M.; Pearce, A. J.; Hérault, A.; Sinaÿ, P. *Tetrahedron: Asymmetry* **2000**, *11*, 283. (j) Trotter, N. S.; Larsen, D. S.; Stoodley, R. J.; Brooker, S. *Tetrahedron Lett.* **2000**, *41*, 8957.

(5) Gurjar, M. K.; Chaudhuri, S. R. *Tetrahedron Lett.* **2002**, *43*, 2435.

(6) Parolis, H. *Carbohydr. Res.* **1983**, *114*, 21.

(7) (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3013. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. For a latest comprehensive review on the utilization of RCM in carbohydrate chemistry, see: (c) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519.

(8) (a) Manna, S.; Jacques, Y. P.; Falck, J. R. *Tetrahedron Lett.* **1986**, *27*, 2679. (b) Gurjar, M. K.; Patil, V. J.; Pawar, S. M. *Carbohydr. Res.* **1987**, *165*, 313.

(9) Sudha, A. V. R. L.; Nagarajan, M. *Chem. Commun.* **1998**, 925.

(10) Barton, D. H. R.; Géro, S. D.; Cléophax, J.; Machado, A. S.; Quiclet-Sire, B. *J. Chem. Soc., Chem. Commun.* **1988**, 1184.