DOI: 10.1002/ejoc.200900553

Vinyl Sulfone Modified Hex-3-enopyranosides: Novel Routes to C3–C4 and C4–C5 Cyclopropanated Pyranosides

Rahul Bhattacharya,[a] Debanjana Dey,[a] and Tanmaya Pathak*[a]

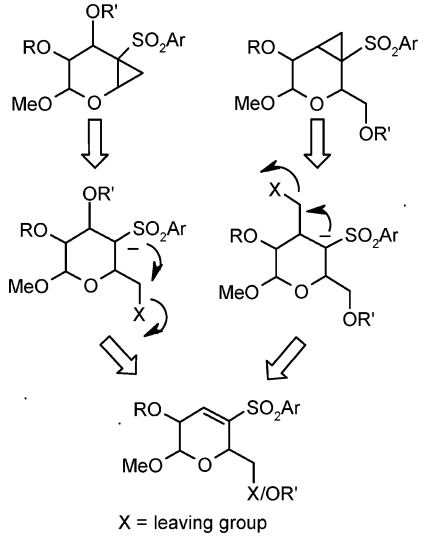
Keywords: Small-ring systems / Cyclization / Carbohydrates / Michael addition / Vinyl sulfone

In a departure from metal-based cyclopropanation reactions, 4-sulfonylhex-3-enopyranosides carrying a leaving group at either of the two γ-positions are used as efficient intermediates for the synthesis of C3–C4 and C4–C5 cyclopropanated pyranosides.

Introduction

Construction of cyclopropanes on carbohydrates has been identified as an important area of research in synthetic chemistry.[1] This particular combination offers a class of strained and reactive cyclopropanes embedded in chiral appendages. Development of strategies for the synthesis of this class of compounds is important, because in general, chemists have long been fascinated by the presence of cyclopropane subunits in a wide range of natural products and the usefulness of this strained cycloalkane in synthetic chemistry.[2] Moreover, barring a few reports, the large number of metal-mediated synthetic routes to cyclopropane-fused furanosyl[1–3] and pyranosyl[2,4] carbohydrates are based on the ritualistic use of glycals as starting materials. Although glycals are suitable intermediates for the synthesis of C1–C2 and C4–C5 cyclopropanated pyranosides, there is virtually no method available till today for the synthesis of C3–C4 cyclopropanated pyranosides.[1]

The attack of a nucleophile on the electron-deficient double bond of "3-halo-1-alkenylsulfone" was used about three decades back as an efficient strategy for the formation of cyclopropanes.[5] However, the strategy remained grossly underutilized mainly because of the unavailability of suitable vinyl sulfone based starting materials.[6] We realized the vast potential of suitably designed vinyl sulfone modified carbohydrates in the generation of a wide range of cyclopropanated carbohydrates.[7] We therefore opined that a 4-sulfonylhex-3-enopyranoside carrying a leaving group at the γ-position would be an effective intermediate for the synthesis of a new class of C4–C5 cyclopropanated pyranosides. We also envisaged that a suitably modified C3-branched chain sugar, easily synthesized from 4-sulfonylhex-3-enopyranoside, would be a useful intermediate for the preparation of otherwise inaccessible C3–C4 cyclopropanated pyranoside (Scheme 1). Moreover, the cyclopropane ring attached to an electron-withdrawing group like sulfone would be cleaved by electrophiles to afford new ionic intermediates[1b] useful for further synthetic manipulations. We therefore decided to synthesize and study the reaction patterns of 4-sulfonylhex-3-enopyranoside analogues **1** and **2** (Figure 1). It should be noted that barring the sole report on the cycloaddition reactions of a 4-sulfonylhex-3-enopyranoside, the strategy for the functionalization of the C3 carbon atom of a pyranoside ring of 4-sulfonylhex-3,4-enopyranosides for the generation of branched-chain sugars has not been explored at all.[8]



Scheme 1. Strategy for the synthesis of cyclopropanated pyranosides.

[a] Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India
Fax: +91-3222-282252
E-mail: tpathak@chem.iitkgp.ernet.in

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900553.

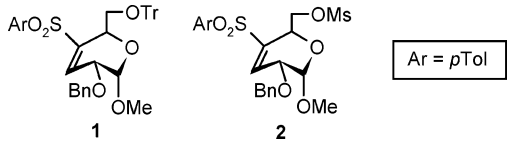
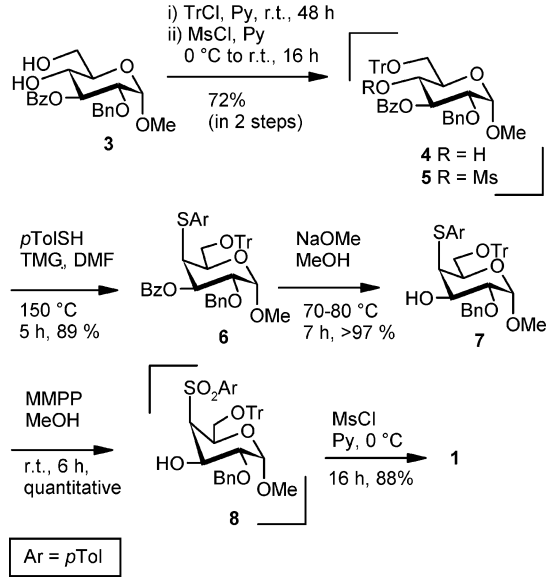


Figure 1. 4-Sulfonylhex-3-enopyranosides: the target molecules.

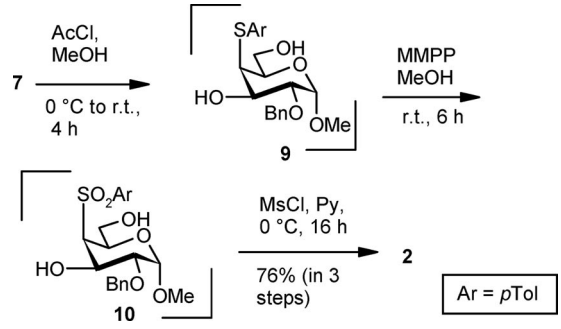
Results and Discussion

A retrosynthetic analysis of the route to **1** and **2** necessitated the introduction of the tolylthio group at the C4 position of a hexopyranosyl sugar. One of the easiest ways of forming a C–S bond would be the regioselective displacement of suitably oriented and protected sulfonates or regioselective ring opening of epoxides derived from carbohydrates. However, it is reported that ring-opening reactions at C3–C4 of epoxy sugars is not strictly regioselective.[9] Moreover, the retrosynthetic analysis also revealed that 4-thiopyranosides would be more easily accessible from 4-*O*-mesylates. Therefore, 4-*O*-mesylate **5** (Scheme 2) was used as a common starting material for the synthesis of both **1** and **2**. Thus, known diol **3**[10] was tritylated at room temperature by using trityl chloride and pyridine to afford **4** within 48 h (Scheme 2). Mesylation of **4** afforded required mesylate derivative **5** in 81% overall yield. Fully protected α-glucomesylate **5** was treated with *p*-thiocresol in DMF in the presence of 1,1,3,3-tetramethylguanidine (TMG) at 150–160 °C to afford galacto-derivative **6**, as expected[11] in 89% yield within 5 h. Treatment of compound **6** with methanolic NaOMe at reflux temperature for 7 h afforded compound **7** in 97% yield. The corresponding sulfone derivative **8** was generated in quantitative yield within 6 h at room temperature by oxidizing **7** with magnesium monoperoxyphthalate hexahydrate (MMPP) in MeOH. Compound **8** was subjected to an elimination reaction by using MsCl in pyridine at 0 to +4 °C to afford **1** in 88% yield (Scheme 2).



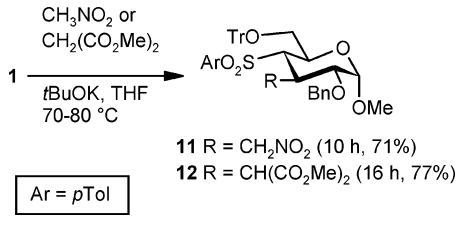
Scheme 2. Synthesis of 6-*O*-tritylated vinyl sulfone modified hex-4-enopyranoside **1**.

For the synthesis of vinyl sulfone **2**, compound **7** was detritylated within 4 h using AcCl in MeOH at room temperature to afford the diol **9** in high yield. Oxidation of the sulfide **9** produced the corresponding sulfone **10**, which was subjected to mesylation to get the desired vinyl sulfone **2** in 76% overall yield (Scheme 3). Identities of vinyl sulfones **1** and **2** were established on the basis of spectroscopic and analytical data. In both the cases the vinyl protons appeared at δ = 6.86–6.96.



Scheme 3. Synthesis of 6-*O*-mesylated vinyl sulfone-modifies hex-4-enopyranoside **2**.

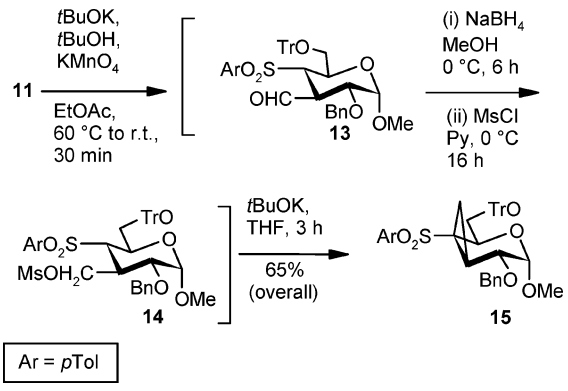
Compound **1**, upon reaction with nitromethane in the presence of *t*BuOK in THF at reflux temperature, generated a single compound **11** in 71% yield within 10 h. Dimethyl malonate, in contrast, under similar reaction conditions afforded compound **12** in 77% yield in 16 h (Scheme 4). Compounds **11** and **12** were identified as diequatorial products (see later), which are expected to form because these are thermodynamically more stable. Although it is difficult to pinpoint the exact reasons for the diastereoselectivity of the addition of nucleophiles to **1**, it may be argued that the incoming nucleophile added to C3 from a direction opposite to the disposition of the C2 OBn group; additionally, the bulky substituent at C3 preferred to orient itself at the equatorial position and thus among all other possibilities, the most stable products were formed. It should be noted that compounds **11** and **12** represent a special class of branched-chain sugars reported for the first time.[12]



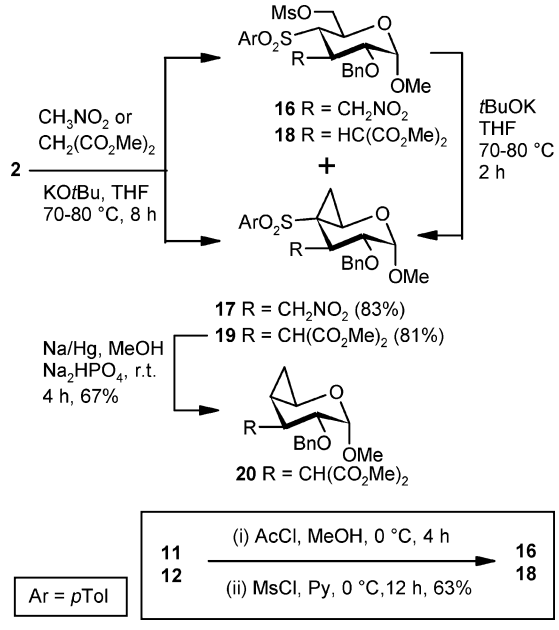
Scheme 4. C3 Branched-chain sugars from **1**.

In order to synthesize C3–C4 cyclopropanated pyranosides from branched-chain sugar **11**, it was subjected to a modified Nef carbonyl synthesis[13] to generate correspond-

ing aldehyde **13** (Scheme 5). The aldehyde was then reduced with $NaBH_4$ to the corresponding alcohol, and the alcohol was mesylated under standard conditions. Crude mesylate **14** was subjected to ring closure involving an intramolecular alkylation reaction in the presence of *t*BuOK dispersed in THF to afford compound **15** in 63% overall yield (Scheme 5). Attempted desulfonylation of **15** by using Mg/MeOH or Na/Hg generated inseparable mixtures. Compound **2**, upon reaction with nitromethane in the presence of *t*BuOK in THF at reflux temperature, generated a separable mixture of compounds **16** and **17** (Scheme 6). The mixture was separated over silica gel and compound **16** was treated with a suspension of *t*BuOK in THF for 2 h at room temperature to afford compound **17** in 83% combined yield. Similarly, dimethyl malonate in the presence of *t*BuOK in THF afforded compound **18** and **19**. Separation of the mixture over silica gel and treatment of compound **18** with *t*BuOK in THF afforded compound **19** in 81% combined yield. Compound **19**, upon treatment with Na/Hg in dry MeOH at room temperature, underwent desulfonylation to afford compound **20** in 67% yield (Scheme 6).[14] The structure of compound **17** was unambiguously confirmed by X-ray diffraction of the single crystals (Figure 2). Because **17** was formed via **16** we assigned the gluco configuration to the latter. Cyclopropane **19** and corresponding branched-chain sugar **18** were expected to follow the same reaction pattern (Scheme 6). Compounds **11** and **12** were identified unambiguously by converting them into **16** and **18**, respectively (Scheme 6; mixed ^{1}H NMR spectroscopy). It may be argued that cyclopropane ring formation for compounds **15**, **17** and **19** was possible only if the attack of the C4 carbanion took place from the β-face of the sugar ring.



Scheme 5. Synthesis of C3–C4 cyclopropanated pyranoside **15**.



Scheme 6. Synthesis of C4–C5 cyclopropanated pyranosides **17**, **19** and **20**.

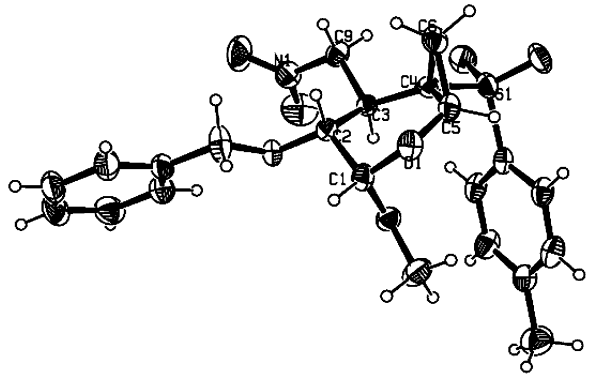


Figure 2. Crystal structure (ORTEP) of **17**.

Conclusions

We have established a new strategy for the synthesis of a hitherto unknown C3–C4 cyclopropanated pyranoside from new branched chain sugars. On the other hand, a C3-branched chain sugar was used to synthesize C4–C5 cyclopropanated pyranosides in one step. These diverse classes of cyclopropanated pyranosides were obtained from closely related vinyl sulfone modified carbohydrates. Additionally, this novel route also provides access to "acceptor" cyclopropanes ready to undergo further transformations.

Experimental Section

General Methods: All reactions were conducted under a N_2 atmosphere. Melting points were determined in open-end capillary tubes and are uncorrected. Carbohydrates and other fine chemicals were obtained from commercial suppliers and were used without purification. Solvents were dried and distilled following standard procedures. TLC was carried out on precoated plates (Merck silica gel 60, F_{254}) and the spots were visualized with UV light or by charring the plate dipped in 5% H_2SO_4/MeOH solution. Column chromatography was performed on silica gel (230–400 mesh). ^{1}H and ^{13}C NMR for most of the compounds were recorded at 200/400 and 50/100 MHz, respectively at 25 °C. DEPT experiments were carried out to identify the methylene carbon atoms. Optical rotations were recorded at 589 nm.

Methyl 2-*O*-Benzyl-3-*O*-benzoyl-4-deoxy-4-(4-methylphenyl)sulfanyl-6-*O*-triphenylmethyl-α-D-galactopyranoside 6: To a solution of

known compound **3** (4.2 g, 10.45 mmol) in dry pyridine (35 mL) was added trityl chloride (4.37 g, 15.7 mmol), and the reaction mixture was stirred at room temperature for 48 h under an atmosphere of N_2. The resulting solution was then cooled to 0 °C. To this cooled solution was added dropwise methanesulfonyl chloride (3.2 mL, 42 mmol) in dry pyridine (15 mL) at 0 °C. The mixture was left overnight at 4 °C. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (70 mL), and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The organic extracts were collected together, dried with anhydrous Na_2SO_4 and filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was purified over silica gel to yield white solid **5** (5.9 g, 72% over two steps). To a well-stirred solution of *p*-thiocresol (4.3 g, 34.63 mmol) and TMG (4.56 g, 36.36 mmol) in dry DMF (20 mL) was added a solution of compound **5** (5.0 g, 6.92 mmol) in dry DMF (10 mL), and the resulting solution was heated at 150–160 °C under an atmosphere of N_2 for a period of 6 h, cooled to room temperature and poured into saturated aqueous NaCl solution (80 mL). The mixture was extracted with EtOAc (3 × 30 mL). The EtOAc layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting syrup was purified over silica gel (EtOAc/petroleum ether, 1:3) to yield **6** (4.53 g, 89%). Colourless jelly. $[\alpha]_D^{30}$ = +46.2 (*c* = 0.625, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 3.34–3.39 (m, 1 H), 3.43 (s, 3 H), 3.56–3.59 (m, 1 H), 3.90–3.93 (m, 1 H), 4.08–4.15 (m, 2 H), 4.64–4.75 (m, 3 H), 5.47–5.52 (m, 1 H), 6.64 (d, *J* = 7.98 Hz, 2 H), 7.01 (d, *J* = 8.10 Hz, 2 H), 7.12–7.41 (m, 16 H), 7.43–7.52 (m, 8 H), 7.79–7.83 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.7, 54.3, 55.0, 64.6 (CH_2), 68.5, 72.8, 73.2 (CH_2), 74.7, 86.9, 98.4, 126.9, 127.6, 127.8, 128.2, 128.5, 129.2, 129.5, 129.6, 131.5, 132.0, 132.6, 136.4, 137.9, 143.8, 165.5 ppm. HRMS (ESI+): calcd. for $C_{47}H_{45}O_6S$ [M + H] 737.2937; found 737.2933.

Methyl 2-*O*-Benzyl-4-deoxy-4-(4-methylphenyl)sulfanyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (7): To a solution of **6** (4.0 g, 5.43 mmol) in MeOH (30 mL) was added NaOMe (0.3 g, 5.55 mmol), and the resulting solution was heated at reflux under an atmosphere of N_2 for 7 h, cooled to room temperature and the solvent was evaporated. The residue thus obtained was dissolved in EtOAc (30 mL). The organic layer was washed with saturated aqueous NH_4Cl solution (2 × 20 mL) and separated. The organic layer was then dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude **7** (1.63 g, 97%). Colourless jelly (eluent: EtOAc/petroleum ether, 1:3). $[\alpha]_D^{30}$ = +41.9 (*c* = 0.31, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 3.33 (s, 3 H), 3.38–3.52 (m, 2 H), 3.56–3.60 (m, 2 H), 3.90–3.92 (m, 1 H), 4.14–4.23 (m, 1 H), 4.60–4.76 (m, 3 H), 5.47–5.52 (m, 1 H), 6.99 (d, *J* = 7.97 Hz, 2 H), 7.21–7.47 (m, 22 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 55.1, 59.4, 64.4 (CH_2), 68.8, 69.1, 73.1 (CH_2), 78.5, 87.0, 98.1, 127.0, 127.1, 127.8, 127.9, 128.1, 128.4, 128.6, 129.7, 132.5, 137.1, 138.0, 143.8 ppm. HRMS (ESI+): calcd. for $C_{40}H_{41}O_5S$ [M + H] 633.2675; found 633.2673.

Methyl 2-*O*-Benzyl-3,4-dideoxy-4-(4-methylphenyl)sulfonyl-6-*O*-triphenylmethyl-α-D-*erythro*-hex-3-enopyranoside (1): To a solution of compound **7** (3.8 g, 6.0 mmol) in MeOH (40 mL) was added MMPP (10.75 g, 21.74 mmol), and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was neutralized with saturated aqueous $NaHCO_3$ (70 mL). The mixture was extracted with EtOAc (3 × 30 mL). The organic layer was separated and dried with anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated to dryness under reduced pressure to yield **8** quantitatively (3.9 g). To a solution of **8** (3.0 g, 4.52 mmol) in dry pyridine (15 mL) was added methanesulfonyl chloride (1.0 mL, 13.6 mmol) in dry pyridine (5 mL) at 0 °C. The mixture was left overnight at 4 °C. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (70 mL), and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The organic extracts were collected together, dried with anhydrous Na_2SO_4 and filtered. Et_3N (5 mL) was added to the filtrate, and after 15 min the solvent was evaporated under reduced pressure. The resulting residue was purified over silica gel (EtOAc/petroleum ether, 1:3) to yield **1** (2.56 g, 88%). White solid. M.p. 132–134 °C. $[\alpha]_D^{30}$ = –18.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.19–3.23 (m, 1 H), 3.33 (s, 1 H), 3.50–3.54 (m, 1 H), 4.23–4.25 (m, 1 H), 4.30–4.31 (m, 1 H), 4.63 (d, *J* = 12.4 Hz, 1 H), 4.75 (d, *J* = 12.4 Hz, 1 H), 4.84 (d, *J* = 3.2 Hz, 1 H), 7.11 (d, *J* = 0.4 Hz, 1 H), 7.16–7.32 (m, 22 H), 7.33 (d, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 55.5, 64.3 (CH_2), 68.9, 71.9, 72.0 (CH_2), 86.7, 96.3, 126.9, 127.7, 127.9, 128.1, 128.2, 128.6 128.7, 129.6, 136.4, 137.0, 138.2, 138.9, 143.7, 144.2 ppm. HRMS (ESI+): calcd. for $C_{40}H_{39}O_6S$ [M + H]$^+$ 647.2467; found 647.2463.

Methyl 2-*O*-Benzyl-3,4-dideoxy-4-(4-methylphenyl)sulfonyl-6-*O*-mesyl-α-D-*erythro*-hex-3-enopyranoside (2): To a solution of compound **7** (3.8 g, 6.0 mmol) in MeOH (40 mL) at 0 °C was added acetyl chloride (0.1 mL, 1.40 mmol). The reaction mixture was stirred for 4 h (TLC) at ambient temperature. The volatile matters were evaporated under reduced pressure, and the residual reaction mixture was worked up in the usual way (see above) to yield **9**. To a solution of crude **9** in MeOH (40 mL) was added MMPP (10.75 g, 21.74 mmol). The reaction mixture was stirred for 6 h at ambient temperature and filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was neutralized with saturated aqueous $NaHCO_3$ (70 mL). The mixture was worked up in the usual way to yield **10**. Compound **10** was converted into **2** (2.21 g, 76%) by following the procedure described for the synthesis of **1**. Colourless jelly (eluent: EtOAc/petroleum ether, 1:3). $[\alpha]_D^{30}$ = –24.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 2.90 (s, 3 H), 3.21 (s, 3 H), 4.15–4.18 (m, 1 H), 4.21–4.22 (m, 1 H), 4.40–4.44 (m, 1 H), 4.51–4.57 (m, 2 H), 4.67 (d, *J* = 12.4 Hz, 1 H), 4.76 (d, *J* = 3.6 Hz, 1 H), 6.97 (s, 1 H), 7.05–7.38 (m, 7 H), 7.67 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 37.5, 55.9, 66.8, 69.5 (CH_2), 71.6, 72.2 (CH_2), 96.5, 127.8, 128.1, 128.3, 128.6, 130.0, 135.6, 136.1, 136.8, 140.0, 145.1 ppm. HRMS (ESI+): calcd. for $C_{22}H_{27}O_8S_2$ [M + H]$^+$ 483.1147; found 483.1143.

Methyl 2-*O*-Benzyl-3,4-dideoxy-3-*C*-nitromethyl-4-(4-methylphenyl)sulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (11): To a suspension of 90% *t*BuOK (0.33 g, 2.94 mmol) in dry THF (5 mL) at 0 °C was added CH_3NO_2 (0.15 mL, ≈2.5 mmol), and the resulting solution was stirred for 15 min at that temperature under an atmosphere of N_2. A solution of **1** (0.33 g, 0.5 mmol) in dry THF (10 mL) was added dropwise to the reaction mixture. The resulting solution was then heated at reflux with continuous stirring under an atmosphere of N_2 for 10–16 h. The reaction mixture was cooled to room temperature, and the volatile matters were evaporated under reduced pressure. The residue obtained was triturated with EtOAc (30 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (3 × 30 mL) and separated. The organic layer was dried with anhydrous Na_2SO_4 and filtered, and the filtrate was evaporated under reduced pressure to get a residue. The crude residue was then purified by column chromatography over silica gel (EtOAc/petroleum ether, 1:4) to obtain **11** (0.26 g, 71%). White solid. M.p. 131–133 °C. $[\alpha]_D^{28}$ = +24.7 (*c* = 0.625, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 2.97–3.03 (m, 1 H), 3.17–3.21 (m, 1 H), 3.28 (s, 3 H), 3.50–3.53 (m, 1 H), 3.58–3.62 (m, 1 H), 3.96–4.02 (m, 1 H), 4.05–4.09 (m, 1 H), 4.56–4.66 (m, 3

H), 5.02–5.15 (m, 2 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.23–7.38 (m, 20 H), 7.45 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 34.7, 55.1, 59.7, 64.5 (CH_2), 66.5, 72.7 (CH_2), 73.8 (CH_2), 75.2, 86.6, 95.0, 127.0, 127.7, 128.2, 128.3, 128.4, 128.6, 128.7, 129.9, 135.2, 137.1, 143.7, 145.0 ppm. HRMS (ESI+): calcd. for $C_{41}H_{42}NO_8S$ $[M + H]^+$ 708.2631; found 708.2630.

Methyl 2-*O*-Benzyl-3,4-dideoxy-3-*C*-bis(methoxycarbonyl)methyl-4-(4-methylphenyl)sulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (12): Following the procedure described for the preparation of **11**, $H_2C(CO_2Me)_2$ (0.15 mL, ≈2.5 mmol) was treated with **1** (0.33 g, 0.5 mmol) to get compound **12** within 16 h (0.31 g, 77%). White solid (eluent: EtOAc/petroleum ether, 1:4). M.p. 112–114 °C. $[\alpha]_D^{28}$ = +31.2 (c = 0.625, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 3.15 (s, 3 H), 3.18–3.25 (m, 1 H), 3.42–3.46 (m, 1 H), 3.50 (s, 3 H), 3.58–3.60 (m, 1 H), 3.67 (s, 3 H), 3.75–3.84 (m, 1 H), 3.98–4.02 (m, 1 H), 4.39–4.43 (m, 1 H), 4.46–4.48 (m, 2 H), 4.54–4.60 (m, 2 H), 7.21–7.37 (m, 17 H), 7.40–7.48 (m, 5 H), 7.56 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 36.1, 49.5, 52.1, 52.3, 54.9, 61.6, 64.9 (CH_2), 66.9, 72.8 (CH_2), 74.7, 95.6, 126.9, 127.7, 127.8, 127.9, 128.2, 128.5, 129.0, 129.6, 134.9, 137.8, 143.9, 144.7, 168.8, 169.2 ppm. HRMS (ESI+): calcd. for $C_{45}H_{47}O_{10}S$ $[M + H]^+$ 779.9137; found 779.9136.

Methyl 2-*O*-Benzyl-3,4-dideoxy-3,4-cyclo-*C*-methylene-4-(4-methylphenyl)sulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (15): Compound **11** (0.71 g, 1 mmol) was dissolved in *t*BuOH (30 mL) at 60 °C. To the warm solution was added *t*BuOK (0.28 g, 2.5 mmol). The mixture was stirred under an atmosphere of N_2 for 20 min while cooling to room temperature and then ethyl acetate (75 mL) was added. This was immediately followed by an ice-cold solution of $KMnO_4$ (0.156 g, 1 mmol) in water (30 mL). The mixture was stirred vigorously for 20 min, and then the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure to get residue **13**. The crude residue was dissolved in ethanol (10 mL), cooled in an ice bath and sodium borohydride (2.5 equiv/mmol) was added; the solution was stirred for 16 h. Then the reaction mixture was poured into ice-cold water, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure to get a residue. The residue was then mesylated by using standard conditions, and the mesylate derivative was treated with *t*BuOK (0.34 g, 3.0 mmol) and THF (3 mL) for 3 h at room temperature to get a residue. The resulting residue was purified over silica gel (EtOAc/petroleum ether, 1:4) to afford **15** (0.43 g, 65%). Colourless jelly. $[\alpha]_D^{28}$ = +17.1 (c = 0.625, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.89–0.93 (m, 1 H), 1.53–1.57 (m, 1 H), 1.71–1.76 (m, 1 H), 2.42 (s, 3 H), 2.84–2.88 (m, 1 H), 3.00 (s, 3 H), 3.35–3.39 (m, 2 H), 4.20 (d, J = 7.2 Hz, 1 H), 4.49–4.59 (m, 3 H), 7.24–7.38 (m, 22 H), 7.52 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 11.8 (CH_2), 18.8, 20.9, 21.5, 54.9, 64.5, 65.1 (CH_2), 70.6 (CH_2), 72.2, 86.4, 94.4, 127.5, 128.0, 128.2, 128.3, 128.6, 128.7, 128.9, 129.9, 135.3, 138.5, 144.1, 144.9 ppm. HRMS (ESI+): calcd. for $C_{41}H_{41}O_6S$ $[M + H]^+$ 661.2624; found 661.2621.

Methyl 2-*O*-Benzyl-4,6-cyclo-3-*C*-nitromethyl-4-(4-methylphenyl)-sulfonyl-3,4,6-trideoxy-α-D-glucopyranoside (17): Following the procedure described for the addition of C-nucleophiles to **1**, CH_3NO_2 (0.15 mL, ≈ 2.5 mmol) was treated with **2** (0.24 g, 0.5 mmol) to afford a mixture of two compounds within 8 h. The compound mixture was separated by column chromatography over silica gel and the desired cyclopropane derivative was preserved. The mesylate derivatives (slower moving compound by TLC) was then treated with a suspension of 90% *t*BuOK (0.17 g, 1.6 mmol) in dry THF (5 mL) at room temperature for 2 h under an atmosphere of N_2. The volatile matters were then evaporated under reduced pressure. The residue obtained in each case was triturated with EtOAc (30 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (3 × 30 mL) and separated. The organic layer was dried with anhydrous Na_2SO_4 and filtered, and the filtrate was evaporated under reduced pressure to get a residue. The crude residue obtained in each case was then purified over silica gel (EtOAc/petroleum ether, 1:4) and the pure product was combined with the previously obtained desired cyclopropane derivative to afford **17** (0.185 g, 83%). White crystalline solid. M.p. 141–143 °C $[\alpha]_D^{28}$ = +35.1 (c = 0.625, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07–1.10 (m, 1 H), 1.96–1.99 (m, 1 H), 2.48 (s, 3 H), 2.93 (s, 3 H), 3.20–3.26 (m, 2 H), 3.74–3.76 (m, 1 H), 4.24 (s, 1 H), 4.44–4.50 (m, 2 H), 4.54–4.59 (m, 1 H), 5.14–5.17 (m, 1 H), 7.21–7.34 (m, 5 H), 7.42 (d, J = 8.0 Hz, 2 H), 7.83 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (CH_2), 21.7, 32.3, 42.2, 51.5, 55.3, 72.9 (CH_2), 76.1 (CH_2), 77.2, 95.1, 128.1, 128.3, 128.4, 128.5, 129.8, 133.6, 136.7, 145.2 ppm. HRMS (ESI+): calcd. for $C_{22}H_{26}NO_7S$ $[M + H]^+$ 448.1430; found 448.1428.

Methyl 2-*O*-Benzyl-4,6-cyclo-3-*C*-bis(methoxycarbonyl)methyl-4-(4-methylphenyl)sulfonyl-3,4,6-trideoxy-α-D-glucopyranoside (19): Following the procedure described for the preparation of **17**, $H_2C(CO_2Me)_2$ (0.15 mL, ≈2.5 mmol) was treated with **2** (0.24 g, 0.5 mmol) to get compound **19** within 8 h. Yield: 0.21 g, 81%. Colourless jelly (eluent: EtOAc/petroleum ether, 1:4). $[\alpha]_D^{28}$ = +37.1 (c = 0.625, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.35 (m, 1 H), 1.86–1.89 (m, 1 H), 2.46 (s, 3 H), 3.02 (s, 3 H), 3.07 (s, 3 H), 3.46 (s, 3 H), 3.48–3.51 (m, 1 H), 3.77 (s, 3 H), 4.02–4.05 (m, 1 H), 4.22–4.33 (m, 3 H), 4.43–4.46 (m, 1 H), 4.58–4.62 (m, 2 H), 4.74–4.77 (m, 1 H), 7.19–7.29 (br. s, 5 H), 7.40 (d, J = 8.0 Hz, 2 H), 7.80 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 36.0, 37.6, 49.4, 52.4, 55.3, 61.4, 64.8, 71.1 (CH_2), 72.9 (CH_2), 74.4, 95.7, 128.0, 128.3, 128.5, 129.5, 130.0, 133.0, 137.4, 145.8, 168.8, 168.9 ppm. HRMS (ESI+): calcd. for $C_{26}H_{31}O_9S$ $[M + H]^+$ 519.1689; found 519.1682.

Methyl 2-*O*-Benzyl-4,6-cyclo-3-*C*-bis(methoxycarbonyl)methyl-3,4,6-trideoxy-α-D-glucopyranoside (20): Compound **19** (0.2 g, 0.4 mmol) was desulfonylated at room temperature by using Na/Hg (6%)[7b] in MeOH in 4 h to afford **20** (0.095 g, 67%). Colourless jelly (eluent: EtOAc/petroleum ether, 1:4). $[\alpha]_D^{28}$ = +34.8 (c = 0.625, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.30–0.33 (m, 1 H), 0.55–0.58 (m, 1 H), 1.46–1.50 (m, 1 H), 3.13–3.15 (m, 1 H), 3.32–3.39 (m, 2 H), 3.41 (s, 3 H), 3.58 (s, 3 H), 3.64 (d, J = 6.4 Hz, 1 H), 3.69 (s, 3 H), 4.39 (s, 1 H), 4.50 (s, 2 H), 7.28–7.36 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.81 (CH_2), 14.8, 33.1, 47.3, 52.2, 53.6, 55.5, 72.5 (CH_2), 76.4, 95.8, 127.8, 128.1, 128.3, 137.8, 168.8, 169.1 ppm. HRMS (ESI+): calcd. for $C_{19}H_{25}O_7$ $[M + H]^+$ 365.1600; found 365.1601.

CCDC-732518 (for **17**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for new compounds.

Acknowledgments

T.P. thanks the Department of Science and Technology (DST), New Delhi for financial support. R.B. and D.D. thank the Council

for Scientific and Industrial Research, New Delhi for a fellowship. DST is also thanked for creation of the 400 MHz facility under the IRPHA (Intensification of Research in High Priority Areas) program and DST-FIST (Fund for Improvement of Science and Technology Infrastructure) for the single-crystal X-ray facility.

[1] a) G. S. Cousins, J. O. Hoberg, *Chem. Soc. Rev.* **2000**, *29*, 165–174; b) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321–347.

[2] a) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050; b) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196; c) O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597–2632.

[3] a) J. S. Brimacombe, M. E. Evans, E. J. Forbes, A. B. Foster, J. M. Webber, *Carbohydr. Res.* **1967**, *4*, 239–243; b) T. Sasaki, K. Minamoto, H. Suzuki, *J. Org. Chem.* **1973**, *38*, 598–607; c) M. Kawana, H. Kuzuhara, *Synthesis* **1995**, *5*, 544–552; d) J. Gagneron, G. Gosselin, C. Mathe, *J. Org. Chem.* **2005**, *70*, 6891–6897; e) P. Besada, D. H. Shin, S. Costanzi, H. Ko, C. Mathe, J. Gagneron, G. Gosselin, S. Maddileti, T. K. Harden, K. A. Jacobson, *J. Med. Chem.* **2006**, *49*, 5532–5543; f) I. Nowak, J. F. Cannon, M. J. Robins, *J. Org. Chem.* **2007**, *72*, 532–537.

[4] S. A. Testero, R. A. Spanevello, *Carbohydr. Res.* **2006**, *341*, 1057–1760.

[5] J. J. Eisch, J. E. Galle, *J. Org. Chem.* **1979**, *44*, 3277–3279.

[6] a) D. Gravel, C. Leboeuf, *Can. J. Chem.* **1982**, *60*, 574–587; b) K. Ogura, T. Iihama, K. Takahashi, H. Iida, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3347–3348; c) J. Zindel, A. de Meijere, *Synthesis* **1994**, *2*, 190–194; d) D. B. Reddy, M. R. Sarma, A. S. Reddy, N. S. Reddy, *Ind. J. Chem. B* **2000**, *39B*, 901–903; e) V. Padmavathi, M. R. Sarma, K. V. Reddy, A. Padmaja, D. B. Reddy, *Het. Chem.* **2003**, *14*, 155–159.

[7] a) I. Das, T. K. Pal, T. Pathak, *J. Org. Chem.* **2007**, *72*, 9181–9189; b) A. K. Atta, T. Pathak, *J. Org. Chem.* **2009**, *74*, 2710–2717.

[8] C. W. Holzapfel, T. L. van der Merwe, *Tetrahedron Lett.* **1996**, *37*, 2303–2306.

[9] N. R. Williams, *Adv. Carbohydr. Chem. Biochem.* **1970**, *25*, 109–179.

[10] D. E. Ward, B. F. Kaller, *J. Org. Chem.* **1994**, *59*, 4230–4238.

[11] a) F. W. Lichtenthaler, P. Heidel, *J. Org. Chem.* **1974**, *39*, 1457–1462; b) O. Varela, D. Cicero, R. M. de Lederkremer, *J. Org. Chem.* **1989**, *54*, 1884–1890.

[12] For selected references on branched-chain sugars, see: I. Das, T. K. Pal, C. G. Suresh, T. Pathak, *J. Org. Chem.* **2007**, *72*, 5523–5533 and references cited therein.

[13] N. Kornblum, A. S. Erickson, W. J. Kelly, B. Henggeler, *J. Org. Chem.* **1982**, *47*, 4534–4538.

[14] It is expected that other nucleophiles would also trigger this type of cyclopropanation reaction, see ref.[7a]

Received: May 19, 2009
Published Online: September 3, 2009

