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(*R*)-2,3-Cyclohexylideneglyceraldehyde: a versatile intermediate for sugar modified dideoxynucleosides

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Abstract: (*R*)-2,3-Cyclohexylideneglyceraldeyde **1** has been found to be a useful intermediate for the convenient synthesis of both *threo*- and *erythro*- forms of functionally rich 2-deoxypentofuranoses, possible precursors of sugar modified 2′,3′-dideoxynucleosides. This has been exemplified by the exploitation of its major allylation product **2b** for a short synthesis of **4** and **8** and subsequent transformation of **8** to *threo* 3-azido-2,3-dideoxypentofuranose **9**. © 1997 Elsevier Science Ltd

Recently, there has been considerable attention to the synthesis of 2′,3′-dideoxy nucleosides.[1–4] Many compounds of this class are found to be potent antitumor and antiviral agents[1–6] and some of them have subsequently been applied as chemotherapeutic agents such as AZT, ddC, ddI etc. Consequently, the synthetic analogues that are only minimally altered with respect to the corresponding natural nucleosides have become the topic of widespread physiological and pharmaceutical interest. The analogues, which possess the basic pentofuranose unit as present in the naturally occurring 2′-deoxynucleosides, the building blocks of DNA, are likely to interfere in DNA synthesis through interaction with the target enzymes either by competing with the natural substrates or by causing chain termination subsequent to their incorporation into DNA. In this endeavour, efforts have primarily been focused on chemical modification of the carbohydrate portion of the natural nucleosides to synthesise different 3′-substituted derivatives,[1–10] since the cellular kinases are known to be more tolerant of this change than the changes within the base moiety. An enhanced knowledge of structure–activity relationship of different 3′-modified-2′,3′-dideoxynucleosides is expected to produce new drugs with desirable bioactivity.

Among the established methodologies for the preparation of such compounds, the commonly used convergent approach involves condensation of the required sugar molecules with appropriate base. This in turn provides some opportunity for development of a simple synthesis of usefully functionalised pentofuranose intermediates which should be amenable for different functional and stereochemical modification with special attention at the 3′ position of the final deoxynucleoside.

In our ongoing progamme on the synthesis of biologically important compounds, we have reported a practical synthesis of homoallylic alcohols **2a** and **2b** *via* allylmetallation of (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde **1** of (D)-mannitol origin, both in anhydrous[11] and aqueous media.[12] These two diastereoalcohols, possessing diverse natures of stable functionalities, are found to be completely separable by ordinary column chromatography. Although the *anti*-alcohol **2b** has been formed predominantly in both cases, there is formation of an appreciable amount of *syn*-alcohol **2a** under anhydrous conditions.[11] In our earlier communication,[12] **2b** has been exploited to produce **3** in good yield in two steps. Ozonization of **3** at −78°C followed by reduction of the ozonide in the same pot directly afforded a functionalised 2-deoxypentofuranose **4** (Scheme 1). Compound **4** possesses a relatively stable -OTBDMS at C-*3* and hydrolysable -OBz at C-5. The wide difference in the nature of reactivity of these two protecting groups can facilitate selective manipulation at either of the positions.

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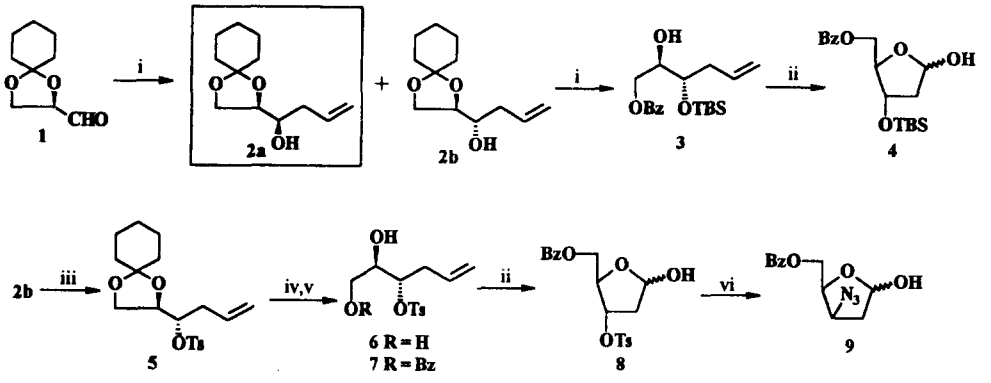

i) Ref. 12, ii) O_3; Ph_3P, iii) *p*-TsCl/py, iv) CF_3CO_2H/H_2O, v) PhCOCN/Triethylamine, vi) NaN_3/DMF/Δ

Scheme 1.

As a modification of the above approach, **2b** was tosylated and subsequently deketalised to afford the diol **6** in good yield. Selective benzoylation at the primary hydroxyl group of **6** provided **7**. This was ozonised and then reduced *in situ* to afford the 2-deoxypentofuranose **8** in appreciable overall yield. Compound **8** is also a versatile functionalized molecule possessing a good leaving -OTos at C-3 in the presence of a hydrolysable -OBz at C-5. However, the tosylate **8** was found to be unstable on standing for long periods. Hence, it was immediately treated with sodium azide to produce the *threo* isomer of 3-azido dideoxypentofuranose **9** following a stereochemical inversion at C-3.

Thus, **2b** can be treated as a useful intermediate for the preparation of 2-deoxypentofuranoses **4** and **8** possessing a diverse nature of functionalities at C-3 and C-5. Both **4** and **8** have been produced as mixtures of α- and β-anomers whose separation has not been attempted by conventional chromatography. However, a report is available for successful conversion of the anomeric mixture of several pentofuranoses into the required β-anomer of the nucleosides *via* selective manipulation[1-4,10] of the hydroxyl group at C-5 or C-3. The azidation of tosylate **8** has been performed as a representative example with a view to establishing its utility. The spectral data of the resulting azide **9** are comparable with those of the corresponding (L)-pentofuranose derivative.[13] Hence, these two 2-deoxypentofuranoses are envisioned as the key intermediates in the total synthesis of a wide array of 3-substituted sugar modified nucleosides although substitution at C-3 should afford the *threo*-pentofuranosides. The corresponding *erythro*-isomers can be obtained either utilising **2a** following a similar reaction protocol or by appropriate double inversion[14] at C-3.

Thus, readily accessible **1** can be treated as a novel synthon for the preparation of a wide variety of both *erythro*- and *threo*- 3′-modified-2′,3′-dideoxynucleosides. Earlier the corresponding isopropylidene derivative of **1** has been utilised for a similar purpose after being subjected to Indium mediated allylation[15a] or Wittig olefination.[15b] But the instability of this derivative may cause difficulty in its utilisation. Moreover, neither of these two approaches mentioned the separation of the stereoisomers of the condensation products by conventional column chromatography. The advantage of our method is due to its being short and straightforward. Moreover, being comprised of a sequence of operationally simple reactions, it is practically viable. The easy preparation of substantial amounts of both **2a** and **2b** in stereochemically pure form and the availability of the enantiomer[16] of **1** appears to provide access to stereochemical flexibility of the resulting nucleosides.

Experimental

Chemicals used as starting materials are commercially available and were used without further purification unless otherwise mentioned. The IR spectra were recorded with a Perkin-Elmer spectropho-

tometer model 837. The PMR spectra were scanned with a Bruker AC-200 (200 MHz) instrument in $CDCl_3$. The optical rotations were measured with a Jasco DIP-360 polarimeter. The organic extracts were desiccated over Na_2SO_4.

*5-O-Benzoyl-3-O-*tert*-butyldimethylsilyl-2-deoxy-D-*erythro*-pentofuranose* **4**

To a stirred and cooled (−78°C) solution of **3** (350 mg, 1.0 mmol) in dichloromethane (50 ml), ozone was bubbled through until a blue colour remained. The excess of ozone was removed by flushing with argon. PPh_3 (288 mg, 1.1 mmol) was added to the mixture. The blue colour disappeared immediately. The solution was brought to room temperature, stirred for a further 5 h and concentrated under reduced pressure. The residue was chromatographed (silica gel, 0–20% EtOAc in petroleum ether) to afford **4** as the mixture of its α and β anomers. (279 mg, 79.2%). $[\alpha]_D^{24}$ +4.38 (c 0.96, $CHCl_3$), IR (film): 3418, 3071, 2857, 1715, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.07 and 0.10 (2s, 6H), 0.87 and 0.89 (2s, 9H), 2.0–2.2 (m, 2H, H-2), 3.2 (bs, 1H, OH), 4.1–4.3 (m, 2H, H-3 and H-4), 4.4–4.6 (m, 2H, H-5), 5.49 (m, 0.8 H, H-1β), 5.59 (m, 0.2 H, H-1α), 7.2–7.5 (m, 5 H). Anal. Calcd. for $C_{18}H_{28}O_5Si$: C 61.35, H 8.0; Found: C 61.50, H 7.83.

(2R,3S)-3-Tosyloxy-5-hexene-1,2-diol **6**

To a cooled and well stirred solution of **2b** (5.3 g, 0.025 mole) in pyridine (30 ml) was added *p*-toluenesulphonyl chloride (5.0 g, 0.026 mole). The mixture was stirred overnight at ambient temperature and treated with water. It was extracted with ether. The organic extract was washed with dil. HCl, water, brine and dried. Solvent removal under reduced pressure afforded tosylate **5** in almost quantitative yield. The tosylate was mixed with 90% aqueous trifluoroacetic acid (25 ml), stirred for 4 h at 0°C and diluted with water. It was extracted with chloroform. The combined organic layer was washed thoroughly with water to make it acid free, then brine and then dried. Solvent removal under reduced pressure and chromatography of the residue (silica gel, 0–5% MeOH/chloroform) afforded pure **6** as viscous oil (5.7g, 80.6%); $[\alpha]_D^{24}$ +12.48 (c 1.50, $CHCl_3$); IR (film): 3500, 3073, 3005, 1363, 1175, 1096, 905 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.2–2.4 (m, 2H), 2.44 (s, 3H), 2.7 (bs, 2H, OH), 3.6–3.9 (m, 3H), 4.6–4.8 (m, 1H), 5.0–5.3 (m, 2H), 5.7–6.0 (m, 1H), 7.3–7.8 (m, 4H). Anal. Calcd. for $C_{13}H_{18}O_5S$: C 54.53, H 6.33; Found: C 54.69, H 6.14.

(2R,3S)-1-Benzoyloxy-3-tosyloxy-5-hexene-2-ol **7**

To a stirred and cooled (0°C) solution of **6** (2 g, 7 mmol) and triethylamine (0.3 ml, 2 mmol) in dichloromethane (20 ml) was added a solution of benzoyl cyanide (0.84 ml, 7 mmol) in dichloromethane (10 ml) over a period of 1 h. The mixture was stirred at 0°C for an additional 30 min and treated with water. The organic layer was separated and washed with water and then brine. Solvent removal under reduced pressure and column chromatography (silica gel, 0–15% EtOAc in petroleum ether) of the residue afforded pure **7** (2.25 g, 81.5%). $[\alpha]_D^{24}$ −4.4 (c 0.43, $CHCl_3$), IR (film): 3445, 3070, 3005, 1721, 1361, 1176 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.1–2.5 (m, 2H), 2.4 (s, 3H), 2.9 (bs, 1H, OH), 3.5–3.8 (m, 1H), 4.1–4.5 (m, 2H), 4.6–4.8 (m, 1H), 5.0–5.2 (m, 2H), 5.7–6.0 (m, 1H), 7.3–8.2 (m, 9H). Anal. Calcd. for $C_{20}H_{22}O_6S$: C 61.52, H 5.68; Found: C 61.73, H 5.84.

*5-O-Benzoyl-3-O-tosyl-2-deoxy-D-*erythro*-pentofuranose* **8**

Following a procedure similar to that for the preparation of **4**, **7** (600 mg, 1.53 mmol) was ozonised at −78° in dichloromethane (50 ml) and subsequently PPh_3 (421 mg, 1.6 mmol) was added. The solvent was removed under reduced pressure. The residue was chromatographed (silica gel, 0–20% EtOAc in petroleum ether) to afford **8** as a colourless oil as the mixture of its α and β anomers. (450 mg, 74.1%). The tosylate gradually darkened in colour due to decomposition on long standing and hence was immediately subjected to the next reaction. $[\alpha]_D^{24}$ −53.83 (c 1.9, $CHCl_3$), IR (film): 3418, 3071, 3045, 1721, 1365, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.0–2.5 (m, 2H, H-2), 2.37 and 2.39 (2s, 3H), 3.1 (bs, 1H, OH), 4.1–4.6 (m, 3H, H-4 and H-5), 4.9–5.2 (m, 1H, H-3), 5.5–5.7 (m, 1H, H-1), 7.3–8.2 (m, 9H). Anal. Calcd. for $C_{19}H_{20}O_7S$: C 58.15, H 5.14; Found: C 57.93, H 5.28.

*5-O-Benzoyl-3-azido-2-deoxy-D-*threo*-pentofuranose* **9**

8 (392 mg, 1 mmol) was heated in DMF (15 ml) with an excess of NaN_3 (137 mg, 2.1 mmol) at 80°C for 6 h. The solvent was removed *in vacuo*. The crude product was dissolved in dry ether from which the insoluble salt was filtered off. Ether was evaporated under reduced pressure, and the residue was chromatographed (silica gel column, 0–20% ether in petroleum ether) to afford pure **7** (189 mg, 68%) as clear oil. $[\alpha]_D^{24}$ −7.22 (c 1.05, $CHCl_3$), IR (film): 3438, 3071, 3045, 2953, 2103, 1721, 1605, 1452, 1274, 1026 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.8 (bs, 1H, OH), 2.0–2.4 (m, 2H, H-2), 3.9–4.6 (m, 4H, H-3, H-4 and H-5), 5.2–5.4 (m, 1H, H-1), 7.4–8.1 (m, 5H). Anal. Calcd. for $C_{12}H_{13}O_4N_3$: C 54.75, H 4.98, N 15.96; Found: C 54.93, H 4.83, N 15.69.

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