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Radical Cyclization in Stereospecific Introduction of Chirality at 'Off Template Site' of 1,2-*O*-Isopropylidene-α-D-*xylo*-hexofuranose

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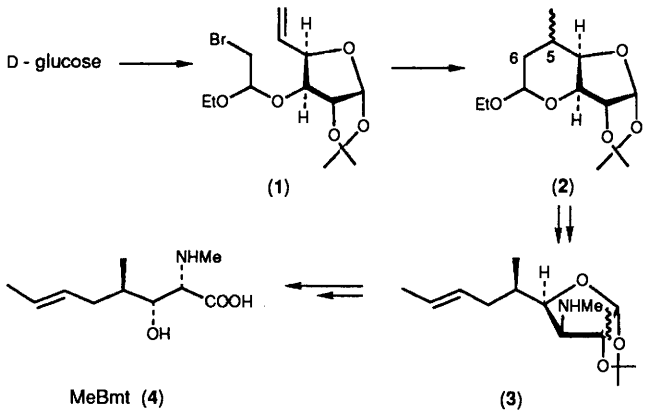
Bromoacetals derived from 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-ynofuranose (**9**) undergo facile free radical cyclization leading to the formation of olefinic acetals which are chemially manipulated to introduce either of the chiralities at C-5 of α-D-hexofuranose.

Free radical cyclizations are widely used for stereo- and regio-controlled C–C bond formation and their utility is well recognized[1] in natural product synthesis. We considered the possibility of using intramolecular cyclization of radicals derived from 'detachable' bromo acetals (**1**) to create chirality at a 'site' outside the furanose ring, obtainable from D-glucose, to prepare stereochemically defined (**2**), a useful precursor for the synthesis[2] of MeBmt (**4**)—an unusual amino acid present in the clinically used immunosuppressive agent cyclosporin[3] (Scheme 1). This requires the stereocontrolled creation of chirality at C-5 of 1,2-isopropylidene-α-D-*xylo*-hex-5-enofuranose during the C–C bond formation reaction. Earlier attempts[4] to induce an asymmetric centre at C-5, which falls 'outside' the furanose ring, have been partially successful. We describe here the stereospecific introduction of an asymmetric centre at C-5 of α-D-*xylo*-hexofuranose by demonstrating the synthesis of the chiral building blocks (**5**) and (**6**).



Scheme 1.

Central to our stereocontrolled operation was the expectation that the bromoacetals (**1**) and (**1a**) would undergo intramolecular radical cyclization to give a rigid tricyclic system in which the C-5 atom was an asymmetric centre. Thus, we prepared each of the two vital intermediates † (**9**) and (**10**), in a single operation from known[5] compound (**8**), by an efficient process recently described by us[6,7] (Scheme 2). The corresponding bromoacetals were prepared by a known procedure.[10]

The bromoacetal (**1**), when refluxed in toluene with Bu_3SnH in the presence of AIBN under standard conditions[10,11] afforded the cyclized products (**13**) and (**14**) (70%) which were not separable. However, since (**13**) could be hydrolysed preferentially with 0.8% H_2SO_4 in 95% aq. MeOH it could now be isolated, as its hydroxy aldehyde (30%). Hydrolysis followed by oxidation afforded the stereochemically pure lactone (28%), which was tentatively assigned as (**5**), $[\alpha]_D$ +4.31° (*c* 1.53, $CHCl_3$), m.p. 103–105 °C.

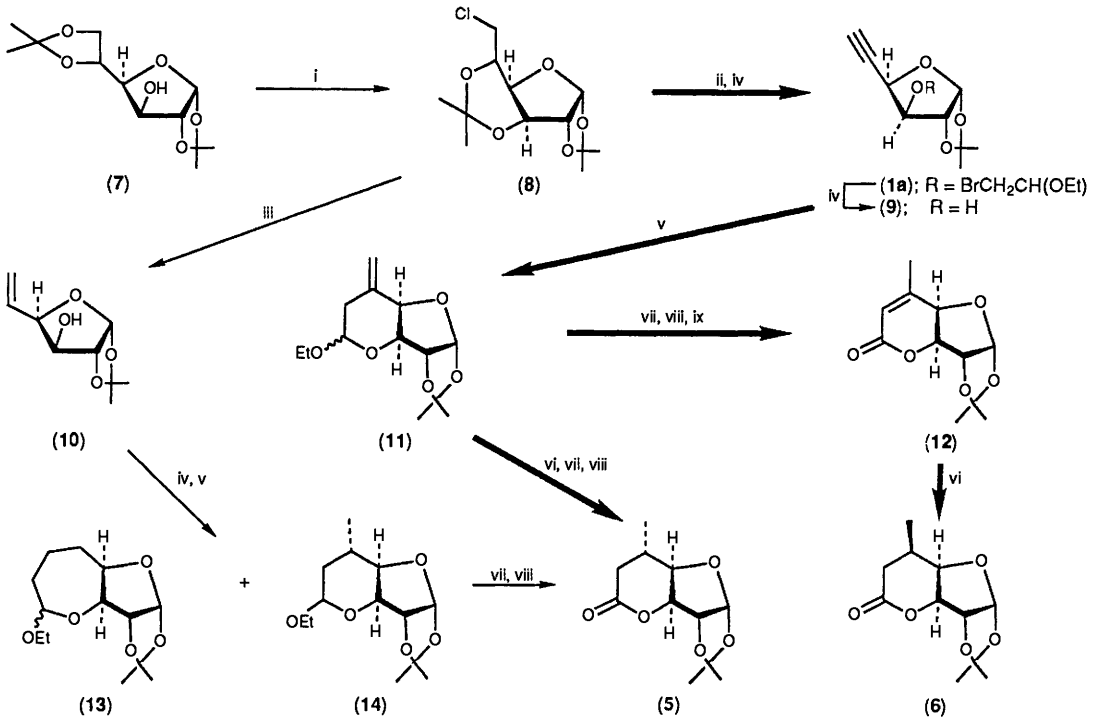
Compound (**5**), one of the desired lactones, was obtained only in poor yield since an unexpected seven-membered ring product (**13**) was also found in almost equal quantities; this proved to be a major problem. We addressed this issue by radical cyclization of the acetylenic bromoacetals (**1a**) to obtain a rigid tricyclic compound (**11**) the facial selectivity at trigonal centre C-5 of which was examined by means of hydrogenation. The hydrogenation of (**11**) over Rh–alumina was followed by hydrolysis and then by oxidation which furnished the lactone (**5**), as the sole product, identical with the lactone derived from the olefinic bromo acetals (**10**).

It is difficult to rationalize the origin of the high stereoselectivity during the hydrogenation step leading to (**5**). Inspection of a molecular model of (**11**) reveals that either of the isomers of (**2**) could be formed during the hydrogenation. In order to secure definitive proof for the correct sense of chirality at C-5, we hydrogenated the α,β-unsaturated lactone (**12**), having an endocyclic double bond [compound (**12**) was prepared from (**11**) by the sequence of reactions shown in Scheme 2]. Careful examination of a molecular model of (**12**) clearly indicated that hydrogenation would occur from the less congested 'α' side, *i.e.* from the convex face of the molecule, thereby creating the chirality of the C-5 methyl group as depicted in (**6**); this was indeed observed. Final structural support for (**6**) $[\alpha]_D$ −7.2° (*c* 0.83, $CHCl_3$) was derived from conversion of (**6**) *via* (**3**) into the stereochemically well established MeBmt (**4**) {m.p. 238.9° $[\alpha]_D$ +12.4° (*c* 0.32, H_2O, pH7, phosphate buffer) (lit.,[2b] m.p. 240 $[\alpha]_D$ +13° (*c* 0.46, phosphate buffer)} by an unambiguous route[12] in 19–21% overall yield from (**6**). As (**5**) and (**6**) are configurational isomers at C-5, the structure of the other lactone could now be assigned ‡ as (**5**).

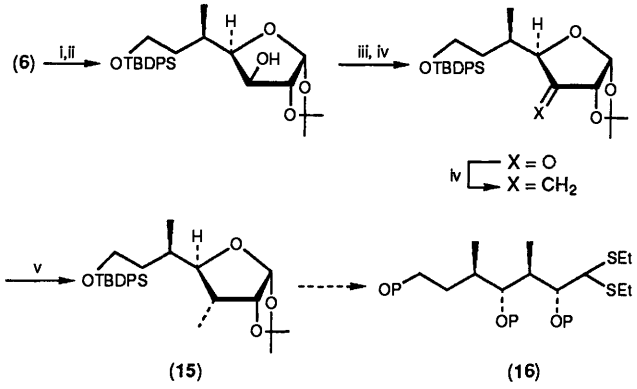
We have presented here an operationally novel approach (following route marked with heavy arrow in Scheme 2) for the stereospecific synthesis of two multifunctional chiral building

† Known procedures for the preparation of (**9**)[8] and (**10**)[9] are multistep ones and give a poor overall yield.

‡ ^1H NMR (300 MHz): (**5**) δ($CDCl_3$) 2.22 (dd, J_1, J_2 = 16.8, 4.9 Hz, 6-H), 2.41 (m, 5-H), 2.77 (dd, J_1, J_2 = 16.8, 5.4 Hz, 6′-H), 4.25 (dd, J_1 = J_2 = 3.3 Hz, 4-H), 4.72 (d, *J* 3.3 Hz, 2-H, 3-H), 5.95 (d, *J* 3.3 Hz, 1-H); (**6**) δ($CDCl_3$) 2.24 (m, 5-H), 2.43 (d, *J* 3.9 Hz, 6-H), 2.46 (d, *J* 1.5 Hz, 6′-H), 4.33 (dd, J_1, J_2 = 2.6, 2.3 Hz, 4-H), 4.67 (d, *J* 4 Hz, 2-H), 4.71 (d, *J* 2.6 Hz, 3-H), 5.92 (d, *J* 4 Hz, 1-H); (**5**) δ(C_6D_6) 1.67 (dd, J_1, J_2 = 16.5, 6 Hz, 6-H), 2.36 (dd, J_1, J_2 = 16.5, 5.2 Hz, 6′-H), (**6**) δ(C_6D_6) 2.02 (dd, J_1, J_2 = 17.5, 5.5 Hz, 6-H), and 2.15 (dd, J_1, J_2 = 17.5, 12.4 Hz, 6′-H).



Scheme 2. i, $Me_2\overset{+}{N}=CHCl\,Cl^-$, $Cl_2CHCHCl_2$ (75%); ii, $LiNH_2$ in Liq NH_3 (85%); iii, Zn, NaI, DMF (98%); iv, CH_2=CHOEt/NBS, CH_2Cl_2 (95%); v, Bu_3SnH, AIBN, toluene (70–80%); vi, H_2, Rh–Al_2O_3, EtOAc, 50 psi (95%); vii, 50% aq. AcOH, 50° (92%); viii, PCC, NaOAc, CH_2Cl_2 (88%); ix, DBU, CH_2Cl_2 (100%).



Scheme 3. i, LAH, ether; ii, TBDPSCl, Imidazole, DMF; iii, PDC, Ac_2O, CH_2Cl_2; iv, Ph_3P=CH_2; v, Pd–C, H_2.

blocks (**5**) and (**6**) and in the process introduced chirality at C-5 of D-glucose which is both rare and difficult to achieve. In addition, the chirons (**5**) and (**6**) both contained a rigid furanose ring which offers the preparation of stereochemically undisputed products in a highly predictive manner.[13] For instance, a 3-methyl group was introduced by the procedure of Rosenthal and Sprintz[14] to give (**15**) (Scheme 3) which could be opened to give (**16**) having methyl and hydroxy at alternative positions. Thus, this would pave the way to the synthesis of natural products derived *via* polypropionate pathways.[15]

Experimental

A typical experimental procedure for compound (**10**) is as follows. To a stirred heterogeneous mixture of zinc (260 mg, 4 mmol) and sodium iodide (906 mg, 6 mmol) in *N,N*-dimethylformamide (10 ml) was added (**8**) (834 mg, 3 mmol). The reaction mixture was refluxed for 2 h after which it was brought to room temperature, diluted with 5% aq. NH_4Cl (40 ml) and extracted with ether (3 × 25 ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated to give a single product (479 mg, 86% yield), identical in all respects with the known[9] compound (**10**).

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