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PYRANOSIDIC HOMOLOGATION: PART II: EXTENDING THE CARBOHYDRATE TEMPLATE VIA VICINAL (SECONDARY) HYDROXYLS

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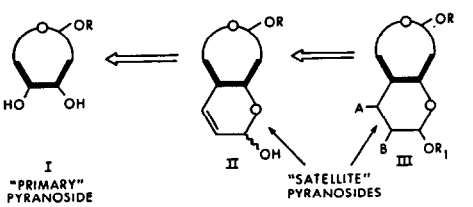
ABSTRACT: The oxirane ring of the dianhydro sugar (3b) is opened regioselectively by the dianion (4b), and reaction of the derived allylic alcohol (7b) with trifluoroacetic acid gives the oxa-cis-decalin (8b), which can be epoxidised selectively from the endo or exo face.

In the preceeding manuscript[1] we showed how the process of pyranosidic homologation could be applied via the C-4 and C-6 hydroxyl groups, and confirmed that the resulting bipyranose provided a secure template for controlled creation of multiple contiguous chiral centers. A secondary hydroxyl group on the sugar ring could conceivably also be a site for pyranosidic homologation via ring closure to a vicinal hydroxyl as in I⟶II Scheme 1. In this manuscript we outline a procedure for pyranosidic homologation via secondary sites on the pyranoside ring.

Scheme 1



The plan outlined in Scheme 1, regarding the functionalization in the satellite rings of II and III, is designed to take advantage of the sizeable body of knowledge on the reactions of unsaturated hexopyranose sugars.[2] Formation of II requires the attachment of a 3-carbon appendage to the pyranoside ring. An oxirane is a logical substrate for this purpose, but since ring-opening is predominantly trans-diaxial, the cyclization leading to II would have to be preceded by a conformational change. A 1,6-anhydro sugar emerged as the template of choice,

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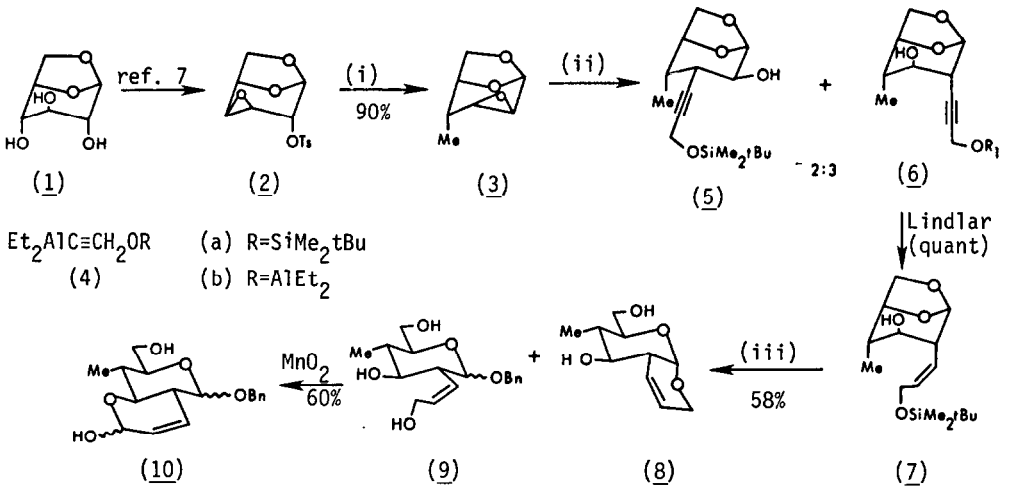
since the pyranoside moiety is held in the abnormal $^1C_4$ conformation,[3] from which it may be readily released by acid hydrolysis.

Scheme 2



(i) (a) MeMgCl/CuI/THF/NH_4Cl; (b) NaOMe/MeOH/$CHCl_3$; (ii) (4a) $PhCH_3$-THF/25°/16h; (iii) $PhCH_2OH/BF_3$/80°/2h.

The chemistry of levoglucosan (1) (1,6-anhydro-β-D-glucopyranose) has been studied extensively[4], and Czechoslovak workers[5] have developed excellent routes to the oxiranes (2)[6] and (3b).[7] Following their precedents for reaction with heteroatom nucleophiles, epoxide (2) was found to undergo copper(I) induced reaction with MeMgCl** to give a hydroxysulfonate from which epoxide (3a)≠ was obtained.

Ethynyl alanes[10] emerged as nucleophiles of choice for opening epoxide (3a). Reaction with the mono-anion (4a) went smoothly, but the product was, disappointingly, a 2:3 mixture of the regioisomers (5) and (6).≠ Lindlar reduction of the latter gave (7)≠ quantitatively but alcoholysis of (7) furnished (9)≠ a 9:1 mixture of 9 and 8≠.

Manganese dioxide oxidation of (9) could be made to stop at the hemiacetal (10), and with this accomplished, the desired pyranosidic homologation I⟶II had been realized. However the result was compromised (a) by the poor regioselectivity in the reaction (3), and (b) by the mixture of(9) and (8) obtained upon alcoholysis.

** While whis work was underway, reports from the laboratories of Kochetkov[8] and Ley[9] concerning the reactions of 1,6-anhydro sugar epoxides with carbon nucleophiles were published.

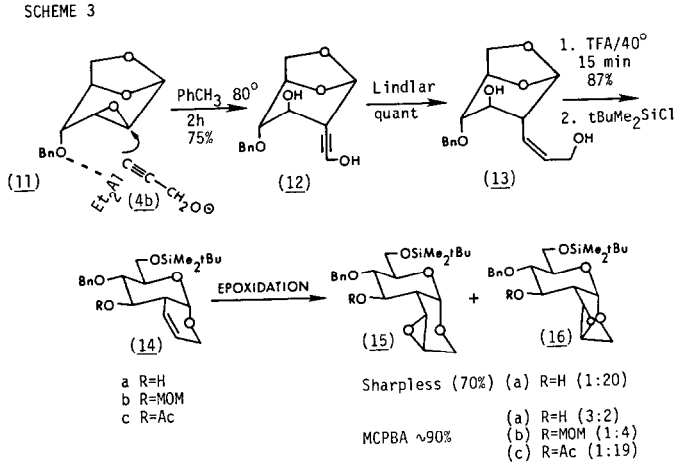
≠ This compound gave satisfactory spectroscopic data and elemental analysis or HRMS.

With respect to (a), the high tendency for reaction at C-3 of epoxide (3) is undoubtedly induced by the severe 1,3-interaction with the C-4-CH_3 which occurs during nucleophilic atack at C-2. By contrast the benzylated analogue (3b) would enjoy chelation to the incoming nucleophile, during the reaction as depicted in Scheme 3. Indeed the opening of epoxide (11) with the dianion (4b) was highly regiospecific, affording (12).[≠,11]

With respect to (b), a procedure for obtaining (10) exclusively is conceivable; however this would involve several steps and therefore contrasts with the one-step conversion (7)→(8)[12]. Indeed, as indicated in Scheme 3, we found with olefin (13) that use of neat trifluoroacetic acid afforded (14a) in 87% yield.

Although compounds (3) and (14) are structurally related to cis-decalins, the molecules are expected to be exceedingly immobile in view of the combined effects of four equatorial substituents, and the axial oxygen at C-1.[14] With the resulting clearly defined topology, the faces of the double bond of (14) should be readily differentiated. Indeed, as indicated in Scheme 3, reaction of the alcohol (14a) with Sharpless' reagent[15] afforded the endo-epoxide (15)[≠] predominantly. Facial selectivity in exo-epoxidation proved to be strongly dependent upon the protecting group of the homoallylic alcohol, as summarized in Scheme 3. However, use of the acetate (14c) led to the exo-product (16c)[≠] overwhelmingly.

SCHEME 3



For (15c): ^{1}H NMR (200 MHz) δ 7.25 (m, 5 H, φH), 5.55 (t, J = 10.0 Hz), 1H, H5), 4.65 (d, J = 3.5 Hz, 1 H, H1'), 4.62 (ABq, J = 12.0 Hz, Δδ = 0.15 ppm, 2 H, φCH_2), 4.10 (ABq, J = 12.5 Hz, Δδ = 0.35 ppm, 2 H, H1), 3.75 (m, 4 H), 3.20 (dd, J = 5.0, 4.0 Hz, 1 H, 43), 3.03 (d, J = 4.0 Hz, H2), 2.20 (ddd, J = 10.0, 5.0, 3.5 Hz, 1 H, H4), 1.92 (s, 3 H, Ac), 0.91 (s, 9 H, tBu), and 0.05 (s, 6H, $SiCH_3$); ^{13}C NMR (200 MHz) δ 169.3.

For (16c): ^{1}H NMR (200 MHz) δ 7.25 (m, 5 H, φH), 5.36 (dd, J = 11.0, 9.0 Hz, 1 H, H5) 4.84 (d, J = 3.0 Hz, 1 H, H1'), 4.62 (ABq, J_{AB} = 12.0 Hz, Δδ 0.10 ppm. 2 H, φCH_2), 4.18 (AB of ABX, J_{AB} = 13.0 Hz, Δδ = 0.30 ppm, J_{AX} = 0 Hz, J_{BX} = 3.0 Hz, 2 H, H1), 3.75 (m, 5 H), 3.19 (dd, J = 3.5, 3.0 Hz, 1 H, H2), 2.31 (bd, J = 11.0 Hz, 1 H, H4), 1.92 (s, 3 H, Ac), 0.90 (s, 9 H, tBu), 0.04 (2 X s, 6 H, $SiCH_3$);

The transformations in Schemes 2 and 3 indicate that the process of pyranosidic homologation can be carried out efficiently by partnership of an epoxide, e.g. (3), and a propargyl alcohol derivative. The prospect of an iterative process is therefore conceivable, in which a network of interlocking pyranosides is assembled, each being a valid template[15] in its own right. Such an array possesses a continuous carbon backbone with potential for rational creation of multiple contigous chiral centers.

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