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PYRANOSIDIC HOMOLOGATION: PART I: EXTENDING THE CARBOHYDRATE TEMPLATE VIA C6 AND C4[1]

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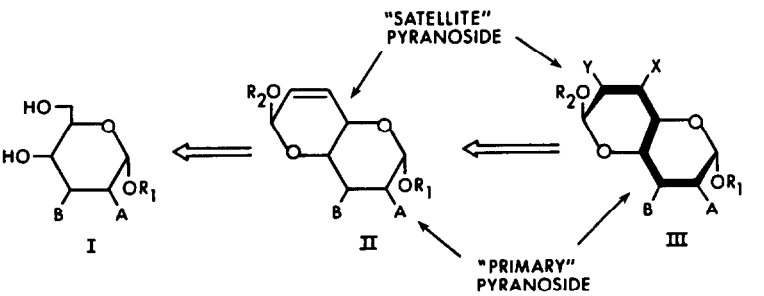
ABSTRACT: The aldehyde (6) reacts with ylid (3b) to give (7) as a 4:1 Z/E mixture which, upon methanolysis under catalysis by pyridinium p-toluenesulfonate (PPTS), affords the bispyranoside (5a) as single anomer.

The seco-acids of many macrolides may be regarded as "pseudo" long-chain sugars,[1] and hence they share many of the challenges posed by syntheses of "authentic" long-chain sugars[2,3,4] (i.e. carbon chain >6 members). In this and the accompanying[5] communication, we disclose some of our recent results which promise to provide a generalized approach to the synthesis of long-chain sugars, either "pseudo" or "authentic".

SCHEME 1



As a synthon for long-chain sugars, a hexopyranoside unit, e.g. I, is really very limited. Thus although there are five contiguous chiral centers, those at C-1 and C-5 are responsible for the attributes of the heterocyclic ring and therefore cannot suffer any tampering.

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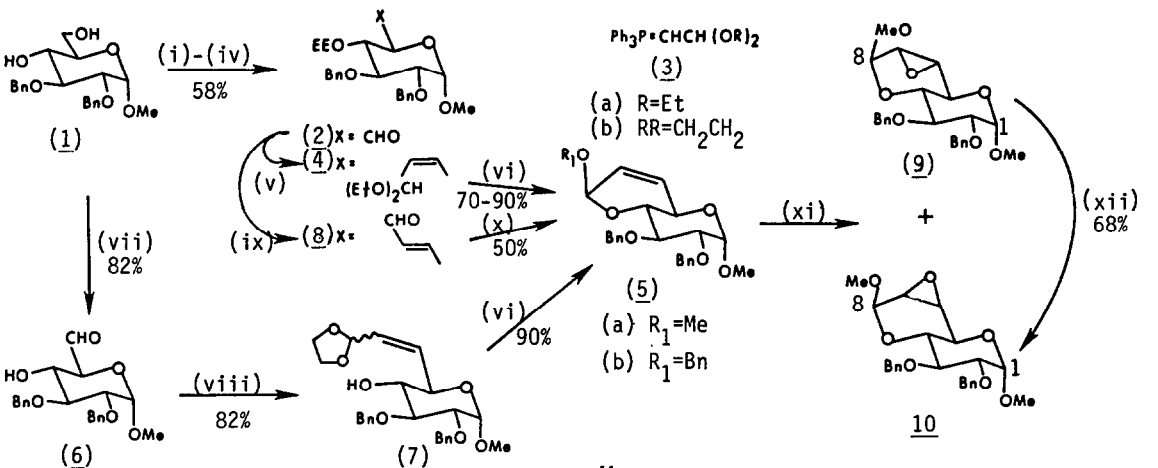
Stereocontrol at "off template" centers is normally marginal unless chelation can be invoked,[6] or a sigmatropic rearrangement can be engineered.[7] In view of these problems, only three of the "on template" sites (C-2, C-3, C-4) of I are available for chemical transformations, and so the maximum number of contiguous chiral centers which can be achieved is four assuming that the O-5 is preserved. This limitation could be overcome if hydroxyl groups of the sugar could be used for elaboration of other pyranoside rings.

The concept of pyranosidic homologation therefore emerges as a protocol for achieving extended linear arrays through systems of interlocking pyranosides. An exemplification of the idea is outlined in Scheme 1 and it is reasonable to expect that the "satellite" rings of the bis-pyranosides II and III would be as good templates as the "primary" rings. Thus II and III would provide an eight-carbon chain with capability for six contiguous chiral centers. Notably: (a) the new glycosidic center OR_2 should be subject to the anomeric effect[8] (just like OR_1); (b) there are no "off-template" centers and so the stereocenters X and Y will be reliably created, and (c) proof of the orientations of X and Y would be simple NMR exercises.

Scheme 2



(1) $tBuMe_2SiCl$, Et_3N/CH_2Cl_2; (ii) ethyl vinyl ether, PPTS,[11] CH_2Cl_2; (iii) nBu_4NF, THF; (iv) Collin's reagent, CH_2Cl_2; (v) (3a), THF, 23° (70%); (vi) MeOH, PPTS[11] (0.1 equiv) reflux, 8h, (70%), or BnOH, PPTS, C_6H_6, reflux, 3h (90%); (vii) PhSMe, NCS, -10° CH_2Cl_2; (viii) (3b), DMSO/THF, 23°; (ix) Ph_3P=CHCHO (90%); (x) as in (vi)-4 days; (xi) (a) NBS, DME/H_2O (3:1), (b) NaH, DMF, 0°; (xii) (a) KOH, DMSO/H_2O (9:1) (b) NaH (1 equiv.), DMF, -40°, tosyl imidazole (1:1 equiv.); (c) NaH (1·1 equiv.), DMF, 0°-23°.

For (9): ^{1}H NMR (600 Mhz, $CDCl_3$): δ 3.23 (H6, br d $J_{6,7}$ = 3.5 Hz), 3.38 (H7, d, $J_{7,8}$ = 0) 3.42 (H4, dd, $J_{3,4}$ = 9.5 Hz), 3.43 (OCH_3, s), 3.45 (OCH_3, s), 3.48 (H2, dd, $J_{2,3}$ = 9.3 Hz), 3.67 (H5, br d $J_{5,6}$ < 1 Hz), 3.82 (H3, dd, $J_{3,4}$ = 9.5 Hz), 4.57 (H1, d, $J_{1,2}$ = 3.7 Hz), 4.73 ($PhCH_2$, AB, J=11.8 Hz), 4.85 ($PhCH_2$, AB, J=10.8 Hz), 4.90 (H8, s, $J_{7,8}$ = 0) and 7.34 (2 Ph, 10 H, m); $[\alpha]_D^{25}$ -1.36° (c-17.7 mg/1 ml, $CHCl_3$).

For (10): ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.39 (H6, d, $J_{6,7}$ = 4.4 Hz), 3.42 (OCH_3, s), 3.47 (H2, dd, $J_{2,3}$ = 9.5 Hz; H7, dd, $J_{7,8}$ = 2.9 Hz), 3.74 (H4, dd, $J_{4,5}$ = 9.5 Hz), 3.84 (H3, dd, $J_{3,4}$ = 9.6 Hz), 3.92 (H5, dd, $J_{5,6}$-1.2 Ha), 4.59 (H1, d, $J_{1,2}$ = 3.7 Hz) 4.89 (H8, d), 4.72 ($PhCH_2$, AB, J = 12.1 Hz), 4.83 ($PhCH_2$, AB, J = 11.4 Hz) and 7.7 (Ph, 10 H, m); $[\alpha]_D^{25}$ - 0.4° (C=15.9 mg/ml, $CHCl_3$).

The intermediacy of II is of paramount importance to the plan since the "satellite" ring is comparable to a 2,3-unsaturated pyranoside (i.e. a hex-2-enopyranoside), the enormous synthetic potential of which has been well catalogued.[9] Thus:

(d) the greater reactivity of the unsaturated moiety should permit the formation of the new glycosidic center, OR_2, without affecting OR_1. This differentiation would then allow selective access to either the "satellite" or the "primary" ring of II as required for further elaboration.

Methyl 2,3-di-O-benzyl-α-D-glucopyranoside, (1) was converted into the aldehyde (2)≠ whose reaction with $Ph_3P{=}CHCH(OEt_2)$ (3a)[10] was virtually instantaneous, giving alkene (4)predominantly. Methanolysis of (4) proceeded best in the presence of a catalytic amount of pyridinium p-toluenesulfonate[11] (PPTS) to afford the enoside (5a)≠ (77%) whose NMR parameters were in complete agreement with those observed for normal alkyl α-D-hex-2-enopyranosides.[9] There was no evidence for the corresponding equatorial anomer.

In keeping with requirement (d) above, it is noted that (4) also reacted smoothly with benzyl alcohol and PPTS[11]; however in this case approximately 5% of the equatorial anomer of (5b) was obtained.

The route (1)→(2)→(4)→(5a) was nevertheless compromised by the number of steps required to go from (1) to (2). Painstaking experimentation showed (a) that selective oxidation of (1) to (6) could be readily accomplished using thioanisole, n-chlorosuccinimide (NCS) and ethyl diisopropylamine, and (b) that the ethylene acetal $Ph_3P{=}CH\overline{CHOCH_2CH_2O}$ was easier to prepare and handle thereby facilitating the formation of (7).≠ Gratifyingly, the fact that (7) was a 4:1 mixture of cis and trans isomers proved to be of no consequence, since methanolysis of the mixture furnished (5a) in 90% yield.

The last observation prompted us to examine the enal (8) obtained as a 9:1 E/Z mixture by reaction of (6) with $Ph_3P{=}CHCHO$, in the hope that the trans- isomer would also lead to (5a) upon acid catalysed methanolysis.** Unfortunately, this was only partially successful, since the optimum yield was 50%. Irradiation led to poorer yields.

We have established that the "satellite" enoside of (5a) is indeed a reliable template. Thus treatment of enoside (5a) with N-bromosuccinimide (NBS) in dimethoxyethane (DME) and water (3:1) followed by sodium hydride, provided epoxides (9) and (10) (9:1) in 70% overall yield. The sterochemistry of the two epoxides was confirmed by hydrolysis of the major isomer (9) with potassium hydroxide in dimethyl sulfoxide (DMSO) at 100°. The resulting diol was converted to the minor epoxide (10) using standard procedures.

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

** The ideas was to irradiate (8) in acidified methanol in the hope of trapping the minor component of the photoequilibrium as the acetal (5a). Since (5a) was indeed obtained, albeit in low yield, the reaction was assumed to have been successful! However, efforts to optimize the yield soon showed that the irradiation was superfluous. The specific effect of Grieco's acid on this transformation, suggests conjugate addition of pyridine to the enal occurs first, followed by formation of the hemiacetal, glycosylation, and then β-elimination of pyridine then to give (5a).

2,3-Anhydrohexopyranosides have been featured widely in carbohydrate syntheses,[13,14] and so the ready obtainment of (9) and (10) is significant. Further importance of (9) and (10) follows from the fact that in the accompanying manuscript,[5] the oxirane ring is shown to be a key synthon for pyranosidic homologation. Thus, further homologation on the "satellite" ring of (9) or (10) is conceivable thereby making the process essentially iterative.

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1. For example, the seco-acid of erythronolide, in sugar parlance, is 2,4,7,8,10, 14,15-heptadeoxy-2,4,6,8,10,12-hexa-C-methyl-D-erythro-L-ido- pentadec-9-ulosonic acid. We are indebted to Professor Derek Horton of Ohio State University for verifying this name.
2. For example, long-chain sugars occur in the antibiotics hikizimycin (11 carbons),[3a] tunicamycin (11 carbons)[3b] and apramycin (8 carbons).[3c]
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