Radical Cyclisation Reactions leading to Doubly Branched Carbohydrates and 6- and 8-Oxygenated 2,9-Dioxabicyclo[4.3.0]nonane Derivatives

Robert J. Ferrier,* Paul M. Petersen, and Mark A. Taylor

Department of Chemistry, Victoria University of Wellington, P.O. Box 600, Wellington, New Zealand

2,3-Dideoxy-α-D-*erythro*-hex-2-enopyranosyl derivatives having, separately, 2-halogenoethyl substituents at O-1 and O-4, on treatment with tri-n-butyltin hydride together with a radical promoter, gave products with tetrahydrofuranyl rings *cis*-fused to C-1, C-2 and C-3, C-4, *i.e.* with branched-points at C-2 and C-3, respectively, and similar reactions in the presence of methyl acrylate or allyltributyltin gave main products with the same bicyclic structures but with additional branch points at C-3 and C-2; when applied to a 2-bromo-1-methoxyethyl 2,3-dideoxyhex-2-enopyranoside and to a 2-bromoethyl 3-deoxyhex-2-enopyranoside the ring closure reactions afforded 8- and 6-oxygenated 2,9-dioxabicyclo[4.3.0]nonane derivatives.

We have found that compounds (**1**) and (**7**) readily cyclise to give the bicyclic products [(**2**), formed together with small amounts of the reduction product (**3**)] and the epimers (**8**), (**9**) (which are easily separated), and since our report was submitted other workers have described these ring closure reactions.[1] It was our intention to apply the radical reactions to the synthesis of doubly branched carbohydrates and to oxygenated analogues, and our findings on these matters are the subject of this Communication.

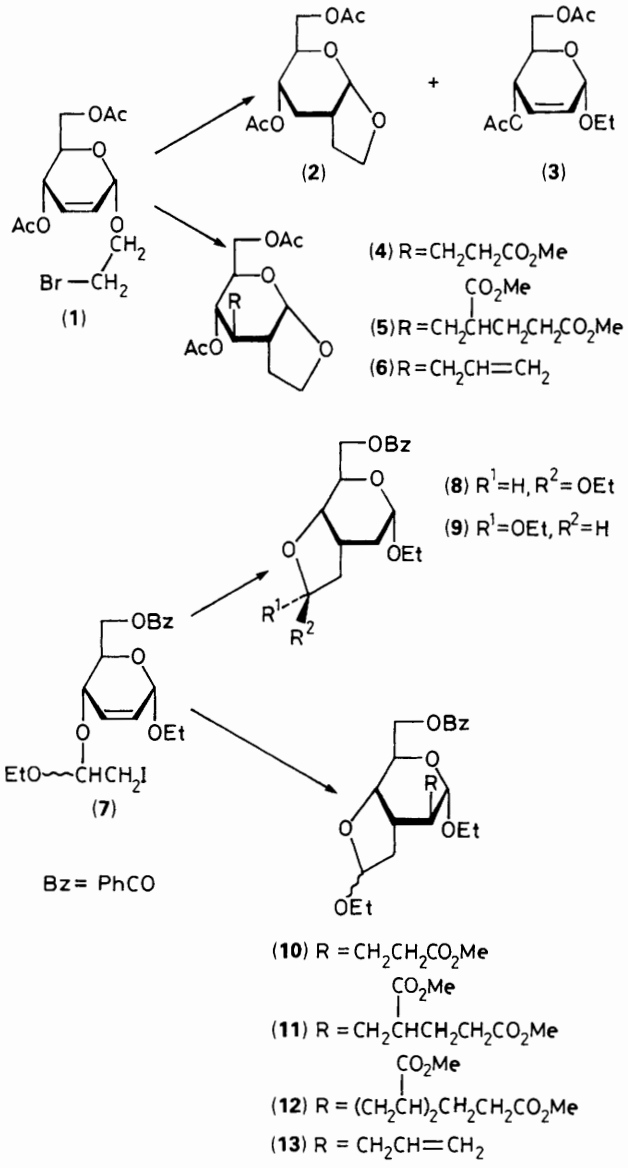
Several doubly branched carbohydrate compounds have been made by heterolytic processes involving sequential introduction of the branch points;[2] we find that radical procedures readily allow the concurrent establishment of two such centres. Application of the approach of Stork and Sher[3] to the reaction of compound (**1**) in benzene with tri-n-butyltin hydride together with azoisobutyronitrile (AIBN) in the presence of methyl acrylate (4 mol. equiv.) allowed the isolation of the doubly branched (**4**) in 53% yield (m.p. 56—58 °C, $[\alpha]_D$ + 55°) together with the product of trapping of two molecules of the ester (**5**, 7%) and that of reductive debromination (**3**, 28%). The D-*gluco*-configuration is assigned to the main product (**4**) on the basis of the many related *cis*-ring closures to have been reported[4] and the expected *trans*-relationship of the substituents at the two new chiral centres.[3] Values for $J_{3,4}$ and $J_{4,5}$ of 8.3 Hz in the ^{1}H n.m.r. spectrum of compound (**4**) confirm these expectations.

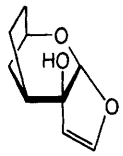
When allyltri-n-butyltin, which previously has afforded routes to allyl *C*-glycosides and allyl branched carbohydrates by radical mechanisms,[5] was used with AIBN to generate a radical from the carbon–bromine bond of compound (**1**), cyclisation occurred to give the previous adduct (**2**, 27%) together with the product of trapping of an allyl radical at C-3 (**6**, 56%), $[\alpha]_D$ + 26°, $J_{3,4} = J_{4,5}$ = 9.7 Hz.

The above approaches were essentially repeated using the iodoacetals (**7**) made by the use of ethyl vinyl ether together with *N*-iodosuccinimide,[3] and ring closure in the presence of methyl acrylate gave six products: the epimeric pairs of mono-, di-, and tri-acrylate adducts [(**10**) : (**11**) : (**12**), 45 : 28 : 27%, gas chromatographic, mass spectrometric determination]. Closure induced by use of allyltri-n-butyltin gave mixed epimers (**13**, 84%).

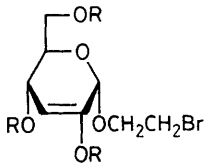
Some natural products, notably azadirachtin,[6] which exhibit insect antifeedant activity have furopyran structures related to those of compounds (**2**) and (**4**) but have an additional hydroxy group at the tertiary centre at C-6 of the dioxabicyclononane system and a double bond at C-7. Racemic compound (**14**), which represents a portion of the structure of azadirachtin, likewise is a potent antifeedant,[7] requiring the double bond[7] and the ethylene bridge[8] for full activity.

Because of current interest in pyranoid compounds with tertiary alcohol centres at C-2 (carbohydrate numbering) such as azadirachtin and the antimicrobial gorgonian metabolite bissetone,[9] we have examined briefly the radical cyclisation procedure as a means of generating the required tertiary centre and for introducing into the resulting furanoid rings functionality which could facilitate the production of unsaturated derivatives. Earlier studies have indicated that radical cyclisation reactions of the kind envisaged on the centres carrying oxygen atoms would proceed efficiently.[10]

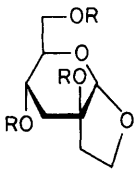




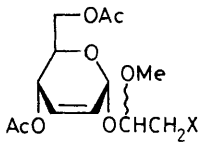
(14)



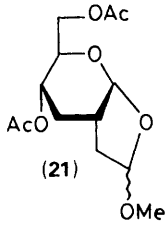
(15) R = Ac
(16) R = Bz



(17) R = Ac
(18) R = Bz



(19) X = Br
(20) X = HgOAc



(21)

Treatment of 2,3,4,6-tetra-*O*-acetyl- and -*O*-benzoyl-1,5-anhydro-D-*arabino*-hex-1-enitol ('tetra-*O*-acetyl- and -*O*-benzoyl-2-hydroxy-D-glucal') with 2-bromoethanol in benzene in the presence of boron trifluoride diethyl ether[11] gave the syrupy 2-bromoethyl glycosides (**15**, 95%, $[\alpha]_D$ + 78°) and (**16**, 95%, $[\alpha]_D$ + 62°) with good stereoselectivity ($\alpha:\beta$ > 10:1). These compounds reacted in refluxing benzene containing AIBN with tri-n-butyltin hydride to give, after chromatographic purification, the ring closed products (**17**, 55%, $[\alpha]_D$ +35°) and (**18**, 75%, $[\alpha]_D$ −22.5°) which were produced together with smaller amounts of the corresponding ethyl glycosides formed by reductive debromination. As anticipated, therefore, radical cyclisation on to the oxygenated sp^2 centres occurred without complication. The products gave analytical and n.m.r. data consistent with the assigned structures; the negative optical rotation of the α-compound (**18**) is noted with surprise.

For introduction of functionalisation at C-8 of the bicyclic system vinyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside was used. Previously this compound has been made as a syrup by elimination from the corresponding 2-(phenylselenenyl)ethyl glycoside[12] and by a photochemical procedure.[13] We obtained it crystalline, (m.p. 33—35 °C, but in only modest yield) from 2-bromoethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside by way of the 2-iodoethyl analogue which was treated with silver fluoride in pyridine, but have since found a more efficient procedure involving reaction of *S*-phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside with bis(formylmethyl)mercury.[14] The vinyl glycoside with equimolar amounts of *N*-bromosuccinimide or mercury(II) acetate in methanol gave the adducts (**19**) and (**20**) quantitatively and with complete regioselectivity because of the relative steric accessibility and electron rich character of the aglycone double bond. The adducts, on treatment with tri-n-butyltin hydride in the presence of AIBN, afforded mixed epimers (**21**) (96%, 1:0.6; 90%, 1:0.75, $[\alpha]_D$ +40°, respectively), the reaction of the bromo-compound (**19**) requiring heating in refluxing benzene, while that of the latter (**20**) proceeded in dichloromethane at room temperature.

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