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RING CONTRACTION OF 2-O-TRIFLUOROMETHANESULPHONATES OF α-HYDROXY-γ-LACTONES TO OXETANE CARBOXYLIC ESTERS

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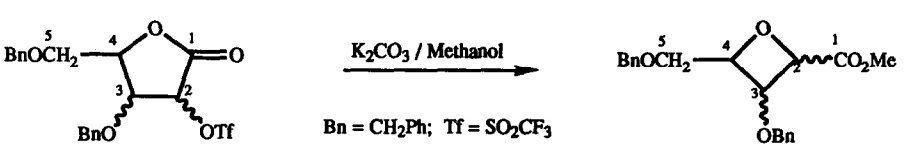
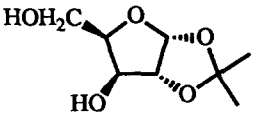
2-O-Trifluoromethanesulphonate esters of the four diastereomeric 3,5-di-O-benzyl-pentono-1,4-lactones gave, on treatment with potassium carbonate in methanol, efficient ring contraction to methyl oxetane-2-carboxylic esters. The stereochemistry at C-2 of the resulting oxetanes is determined largely by the configuration at C-3, rather than C-2, of the lactone.

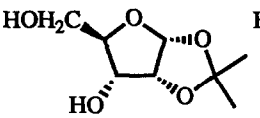
The isolation of oxetanocin from *Bacillus megaterium*,[1] and the activity of various oxetane containing nucleosides against Herpes simplex 2, human cytomegalovirus[2] and HIV,[3] have provided a stimulus for the investigation of the synthesis and reactivity of polyfunctionalised homochiral oxetanes. A diversity of approaches to oxetane formation in nucleoside syntheses has been reported. The oxetane ring of oxetanocin has been synthesised both by intramolecular nucleophilic attack of alkoxide on an acyclic mesylate[4] or epoxide[5] precursor, and from a ring contraction of a 2,3-diazoketone derived from adenosine.[6] Another approach has used the allyloxycarbanion-mediated ring closure of a glycidic ether onto an internal epoxide.[7] An asymmetric synthesis of oxetanes results from the boron trifluoride catalysed [2+2] cycloaddition of vinyl ethers with glyceraldehyde acetonide.[8] A synthesis of an oxetane nucloeoside was recently reported in which adenine displaced chloride from an α-chlorooxetane,[9] the latter being prepared from the corresponding oxetane-2-carboxylic acid by the Barton modification[10] of the Hunsdiecker reaction.[11] There is a single report of the ring contraction of α-triflates of γ-lactones to methyl oxetane-2-carboxylates induced by treatment with potassium carbonate in methanol.[12] As part of a programme to determine the viability of this strategy for the synthesis of oxetane nucleosides, this paper reports the synthesis of all four diastereomeric 3,5-di-O-benzyl-2-O-trifluoromethanesulphonyl-pentono-1,4-lactones and their efficient ring contractions to oxetane-2-carboxylic esters, and establishes the stereochemical features of the ring contraction.



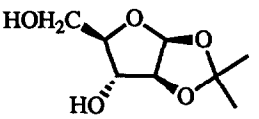
Synthesis of lactone triflates. In each case, the lactones were synthesised from 1,2-O-isopropylidene pentofuranose sugars. The D-xylo (1),[13] D-ribo (2),[14] D-arabino (3)[15] and L-lyxo (4)[16] diols were treated with benzyl bromide and sodium hydride in dimethyl formamide to give the



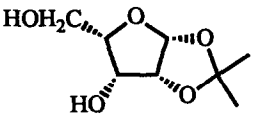
(1) D-xylo



(2) D-ribo

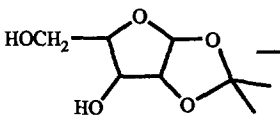


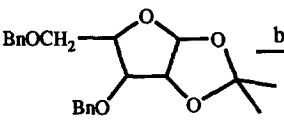
(3) D-arabino

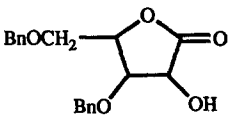


(4) L-lyxo

corresponding di-O-benzyl ethers (5)[17], (6),[18] (7) and (8) in good to excellent yields. Subsequent removal of the isopropylidene protecting group with aqueous trifluoroacetic acid, followed by oxidation of the resulting lactols with bromine in aqueous 1,4-dioxan containing a barium carbonate buffer, afforded the α-hydroxylactones (9), (10), (11) and (12) in yields between 66% and 77%. Esterification with trifluoromethanesulphonic anhydride in dichloromethane and pyridine gave the required 2-triflates (13) [92% yield], (14) [88% yield], (15) [95% yield] and (16) [95% yield]. The triflates were of varying stability and in general were subjected to ring contraction conditions immediately after purification by flash chromatography.



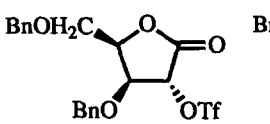




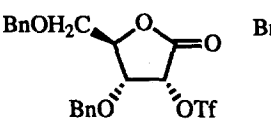
D-xylo	(1)	(5) 89%, -52.0 (c=1.0, $CHCl_3$)	(9) 66%, 70 +40.0 (c=1.00, $CHCl_3$)
D-ribo	(2)	(6) 94%, +84.5 (c=0.65, $CHCl_3$)	(10) 77%, 65-66, +27.6 (c=1.06, $CHCl_3$)
D-arabino	(3)	(7) 67%, +9.5 (c=1.2, $CHCl_3$)	(11) 75%, 85-86, +76.7 (c=0.31, $CHCl_3$)
L-lyxo	(4)	(8) 80%, -15.2 (c=0.85, $CHCl_3$)	(12) 76%, 130-33, +9.9 (c=0.79, MeOH)
		Yield, Optical Rotation / °	Yield, m.p./°C, Optical Rotation / °

a) NaH, BnBr in DMF; b) aqueous CF_3CO_2H c) Br_2, $BaCO_3$ in aqueous dioxan

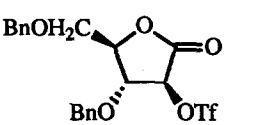
Ring contraction of lactone triflates to oxetane carboxylic esters. Treatment of the lactone triflates with a suspension of anhydrous potassium carbonate in dry methanol generally allowed the isolation of methyl oxetane-2-carboxylates, in good yield, by simple evaporation of the solvent and purification of the residue by flash chromatography. The protected triflate of L-lyxono-lactone (16) under these conditions gave exclusively the L-lyxo-oxetane (19) $[\alpha]_D^{20}$ +15.9° (c, 1.20 in CHCl3), in 80% yield; thus, in this case, the ring contraction occurs with ***retention*** of configuration at C-2 of the lactone. By contrast, D-xylono-lactone derivative (13) gave the D-lyxo-oxetane (17) $[\alpha]_D^{20}$ -17.9° (c, 1.0 in CHCl3), enantiomeric with the oxetane (19), in 79% yield. Both oxetanes (17) and (19) were spectroscopically identical,[19] save for the sign of the specific rotation; thus the contraction of lactone (13) occurs with complete ***inversion*** of configuration at C-2 of the lactone.



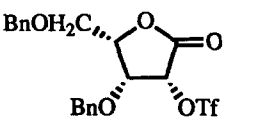
(13) D-xylono



(14) D-ribono



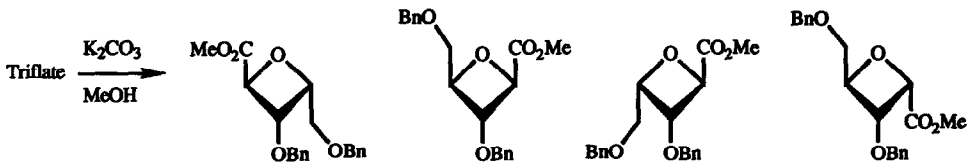
(15) D-arabinono



(16) L-lyxono

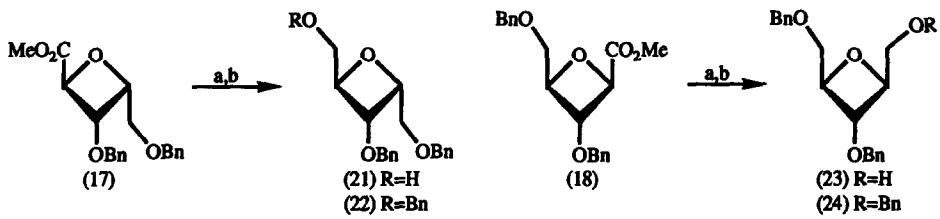
Retention of configuration at C-2 of the lactone was also found in the major product (18)[20] $[\alpha]_D^{20}$ +45.5° (c, 1.16 in CHCl3) [73% yield] from reaction of anhydrous potassium carbonate in dry methanol with the D-ribono-lactone triflate (14); a small amount (about 9%) of the arabino isomer (20)[21] arising from

inversion of configuration at C-2 of the lactone (14) was also formed in the course of the ring contraction. The D-arabinono-lactone (15) gave the same major ribo isomer (18), indicating predominant inversion of configuration of C-2 of the lactone during the ring contraction; only a trace of the minor epimer (20) was formed.



(13) D-xylono	79 %			
(14) D-ribono		73 %		~9%
(15) D-arabinono		70 %		Trace
(16) L-lyxono			~80 %	

The relative stereochemistry of oxetane carboxylic esters (17) and (18) was established by reduction to the primary alcohols (21) and (23) using sodium borohydride in ethanol; subsequent benzylation with sodium hydride and benzyl bromide in tetrahydrofuran gave the tribenzyl ethers (22) and (24) respectively. The 2,4-anhydro-D-lyxo isomer (22)[22] was shown to be lacking in symmetry both by the number of resonances - including three different doublets for the ring oxetane carbons - in its ^{13}C NMR spectrum and by its non-zero optical rotation. By contrast, the highly symmetric 2,4-anhydro-ribo isomer (24)[23] had only five non-benzenoid ^{13}C resonances and zero optical rotation.



a) $NaBH_4$/EtOH; b) NaH/ BnBr/THF

The major product in each ring contraction reaction has a *trans* -relationship between the C-2 and C-3 substituents of the oxetane. No incorporation of deuterium at C-2 of the methyl oxetane-2-carboxylates was observed when the oxetane methyl esters were stirred with potassium carbonate in d_4-methanol, so that the stereochemical course of the reaction is not a consequence of equilibration of the product oxetane esters. It is apparent in some, and may be so in all, cases that open chain 4-hydroxy-2-O-trifluoromethane sulphonate esters are intermediates; a plausible rationalisation[24] of the stereochemistry of the ring contraction is that the ring closure is an S_N2 displacement of triflate during which considerably greater unfavorable interactions develop when the substituents at C-2 and C-3 of the incipient oxetane are *cis*- rather than *trans*- to each other.

It is noteworthy that no significant amounts of oxetanes are formed if the corresponding 2-O-methanesulphonate esters are treated under the same conditions; it is clear that the excellent triflate leaving

group is necessary for an S_N2 ring closure reaction to an oxetane to compete successfully with a number of other reactions. This work demonstrates that the contraction of triflates of sugar 1,4-lactones provides convenient and high yield access to highly functionalised homochiral oxetanes. These materials have been used in the synthesis of oxetane nucleosides including noroxetanocin[25] and the potent antiviral nucleoside,[26] norepioxetanocin.[27,28]

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18 Other than (20) which could not be completely purified away from its epimer (18), all new compounds reported in this paper have satisfactory microanalytical and spectroscopic data.
19 Data for (17): ^{1}H NMR ($CDCl_3$) δ (ppm) 3.82 (3H, s, Me), 3.93 (2H, abq, H-5, H-5'), 4.51-4.67 (5H, m, H-3, 2 x Ar-CH_2), 4.97-5.10 (2H, m, H-2, H-4), 7.28-7.42 (10H, m, Ar-H); ^{13}C NMR ($CDCl_3$) δ (ppm) 52.31 (q), 68.55 (t), 71.80 (t), 73.49 (t), 75.23 (d), 83.50 (d), 84.08 (d), 127.83 (d), 128.16 (d), 128.52 (d), 128.65 (d), 137.19 (s), 138.24 (s), 171.07 (s).
20 Data for (18): ^{1}H NMR (d-6 benzene) δ (ppm) 3.25 (3H, s, Me), 3.31, 3.37 (2H, 2 x dd, H-5, H-5', $J_{5,5'}$ 10.5 Hz, $J_{5,4}$ 3.9 Hz, $J_{5',4}$ 4.0 Hz), 4.28, 4.39 (2H, 2 x d, Ar-CH_2, $J_{H,H'}$ 12.1 Hz), 4.29 (2H, 2 x d, Ar'-CH_2, $J_{H,H'}$ 12 Hz), 4.58 (1H, dd, H-3, $J_{3,4}$ 4.7 Hz, $J_{2,3}$ 5.1 Hz), 3.72 (1H, dd, H-4), 4.99 (1H, d, H-2), 6.99-7.31 (10H, m, Ar-H); ^{13}C NMR ($CDCl_3$) δ (ppm) 52.13 (q), 69.89 (t), 71.63 (t), 73.51 (t), 76.43 (d), 81.8 (d), 85.84 (d), 127.73 (d), 128.11 (d), 128.49 (d), 128.64 (d), 137.22 (s), 137.90 (s).
21 ^{1}H NMR ($CDCl_3$) δ (ppm) for the ester methyl group in (20) was 3.84 compared with 3.76 for (18). The oxetane (20) is formed in small amounts and could not be separated completely from (18).
22 Data for (22): ^{13}C NMR ($CDCl_3$) δ (ppm) 69.15 (t), 70.63 (t), 72.07 (t), 73.58 (t), 73.77 (d), 82.16 (d), 86.91 (d), 127.89 (d), 128.04 (d), 128.29 (d), 128.52 (d), 128.61 (d), 137.91 (s), 138.32 (s), 138.42 (s); $[\alpha]_D^{20}$ +14.8° (c, 1.0 in $CHCl_3$).
23 Data for (24): ^{13}C NMR ($CDCl_3$) δ (ppm) 70.57 (t), 71.50 (t), 73.42 (t), 75.02 (d), 84.45 (d), 122.76 (d), 128.08 (d), 128.59 (d), 137.77 (s), 138.31 (s); $[\alpha]_D^{20}$ 0.0° (c, 0.63 in $CHCl_3$).
24 An alternative explanation in some, but not all, of these cases is that the starting lactone triflates interconvert under the conditions of the reaction.
25 F.X.Wilson, G.W.J.Fleet, D.R.Witty, K.Vogt, Y.Wang, R.Storer, P.L.Myers and C.J.Wallis, submitted for publication.
26 S. Nishiyama, T. Ohgiya, S. Yamamura, K. Kato, M. Nagai and T. Takita, *Tetrahedron Lett.*, 1990, **31**, 705.
27 Y. Wang, G.W.J.Fleet, R.Storer, P.L.Myers, C.J.Wallis, O. Doherty, D. J. Watkin, K.Vogt, D.R.Witty, F. X. Wilson and J. M. Peach, submitted for publication.

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