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RING CONTRACTION OF 3-DEOXY-2-O-TRIFLUOROMETHANESULPHONATES OF α-HYDROXY-γ-LACTONES TO OXETANES

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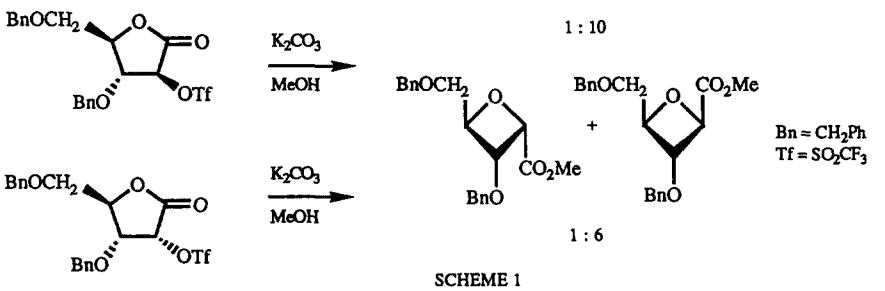
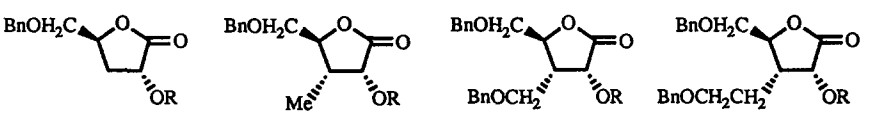
The ring contraction of α-triflates of 3-deoxy-1,4-lactones bearing hydrogen or alkyl substituents in the 3-position to methyl oxetane-2-carboxylates on treatment with potassium carbonate in methanol is described.

As well as in studies on the stability[1] of thromboxanes, the current interest in the synthesis of oxetanes[2,3] arises from the potent anti-viral activity of oxetane nucleosides including naturally occurring oxetanocin[4] and synthetic analogues such as norepioxetanocin.[5,6] Sugar γ–lactones bearing an α-trifluoromethanesulphonate (triflate) ester at C-2 and with an oxygen substituent at C-3 undergo ring contraction on treatment with potassium carbonate in methanol in good yields. Oxetane 2-carboxylates are formed in which the relationship of the C-3 oxygen substituent is predominantly *trans* to the carboxymethyl group, regardless of the relative stereochemistry of the C-2 and C-3 substituents in the starting lactone [Scheme 1].[7,8]

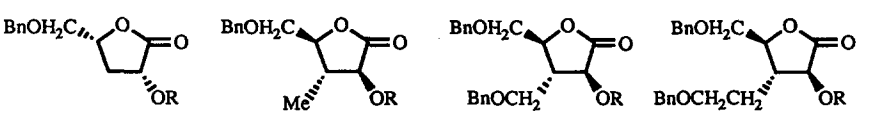


SCHEME 1

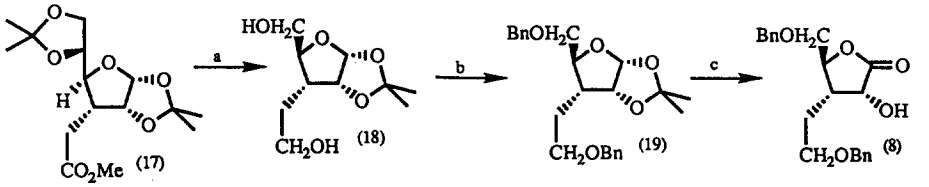
This paper reports the synthesis and ring contraction of γ-lactone triflates without an oxygen substituent at C-3 [(1) and (9)] and with carbon substituents at C-3 *cis* to the C-2 oxygen [(3), (5), (7)] and *trans* to the C-2 oxygen, [(11), (13) and (15)]. In marked contrast to the stereochemical course of the ring contraction of lactones with oxygen substituents at C-3, the major products invariably arise from ring contraction with inversion of configuration at C-2 of the sugar lactone.



(1) R=Tf (2) R=H (3) R=Tf (4) R=H (5) R=Tf (6) R=H (7) R=Tf (8) R=H



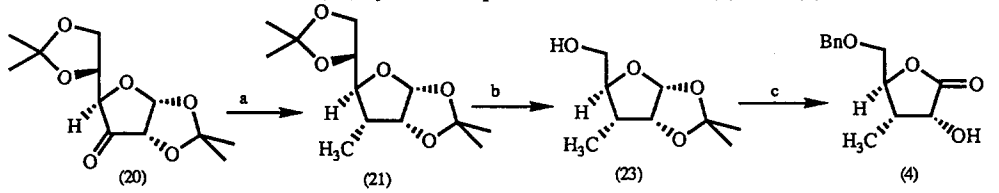
(9) R=Tf (10) R=H (11) R=Tf (12) R=H (13) R=Tf (14) R=H (15) R=Tf (16) R=H



a) aq. AcOH; then $NaIO_4$ / aq. EtOH; then $LiBH_4$ / THF; b) BnBr / NaH / DMF; c) aq. TFA; then Bz / aq. dioxan / barium benzoate

SCHEME 2

Synthesis of lactone triflates. The syntheses of the C-3 benzyloxymethyl substituted lactone triflates (5) and (13) are described in an accompanying paper.[9] The homologous lactones (8) and (16) were prepared [Scheme 2] from the ester (17), itself readily obtained from diacetone glucose in three steps and an overall yield of 76%.[10,11] Hydrolysis of the side-chain acetonide in (17), followed by periodate cleavage and subsequent reduction of the aldehydo-ester with lithium borohydride gave the branched diol (18), $[\alpha]_D^{20}$ +63.9° (c, 1.11)[12] [lit.[10] +72° (c, 1)], [77% yield over three steps]. Dibenzylation to (19) was followed by hydrolysis of the 1,2-acetonide with aqueous trifluoroacetic acid. Oxidation with bromine in buffered aqueous dioxane then gave the hydroxy lactone (8) in 77% yield over three steps $[\alpha]_D^{20}$ +17.4° (c, 1.33). The triflate ester (7) was formed quantitatively by treating (8) with triflic anhydride in the presence of pyridine in dichloromethane solution at -18°C. Treatment of the triflate (7) with sodium trifluoroacetate in dimethyl formamide followed by methanol afforded the epimeric lactone (16), [95% yield, $[\alpha]_D^{20}$ +9.0° (c, 1.0)]. This was converted to the triflate (15) by the same procedure used to form (7) from (8).



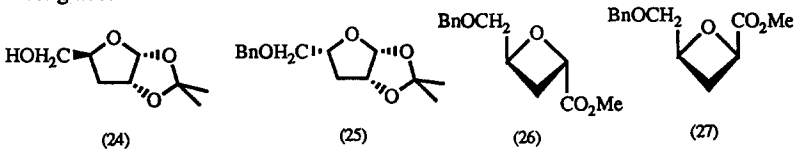
a) Me_3SiCH_2MgCl / Et_2O then NaH / THF / Reflux; then H_2 / Pd on C / EtOAc; b) aq. AcOH; then NaIQ / aq. EtOH; then $NaBH_4$ / EtOH; c) BnBr / NaH / DMF; then aq. TFA; then Bz / aq. dioxan / barium benzoate;

SCHEME 3

3-Deoxy-3-C-methyl-D-ribonolactone (4) was synthesised from the ketone (20) [Scheme 3]; Peterson methylenation of (20) by the reaction of the Grignard reagent derived from chloromethyltrimethylsilane gave an olefin which on hydrogenation gave exclusively the *allo* isomer (21) [73% over two steps], $[\alpha]_D^{20}$ +27.7° (c, 0.74) [Lit.[13] +35° (c, 1)]. Hydrolysis of the 5,6-acetonide in (21) followed by oxidative cleavage of the diol (22) and reduction of the resulting aldehyde with sodium borohydride afforded the methylribose (23) in 85% yield over three steps $[\alpha]_D^{20}$ +36.5° (c, 0.59 in chloroform). Subsequent benzylation, followed by hydrolysis and bromine oxidation gave (4) in 65% yield over three steps $[\alpha]_D^{20}$ +36.3° (c, 0.3). Esterification of (4) with triflic anhydride gave the triflate (3), m.p. 57-58°C, in 100% yield. Again, treatment with sodium trifluoroacetate resulted in clean nucleophilic displacement giving, after work-up with methanol, the inverted alcohol (12). This was readily converted to the triflate (11) by the aforementioned procedure.

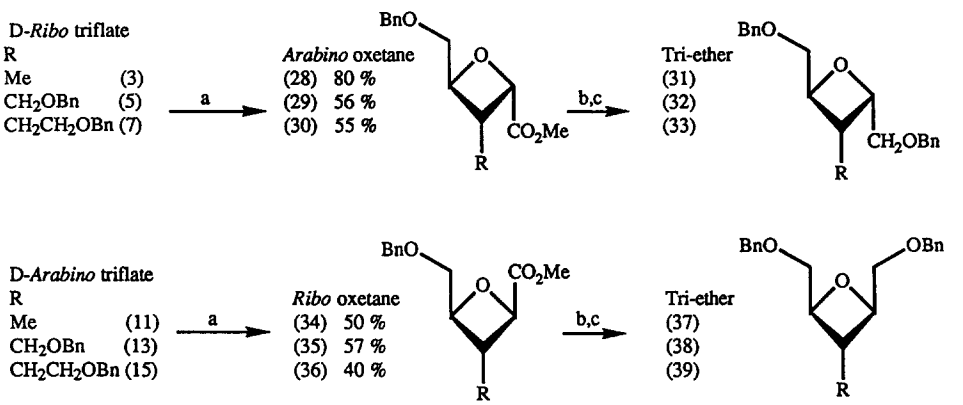
The synthesis of the 3-deoxylactone (2) involved protection of the primary alcohol (24)[14] by benzylation, followed by hydrolysis of the protecting acetonide and bromine oxidation of the resulting lactol to give (2) $[\alpha]_D^{20}$ +42.2° (c, 1.20) in overall 53% yield. Barium benzoate proved far superior to barium carbonate as a buffer for the bromine oxidation of all 3-deoxy lactols.[15] The triflate (1) could not be formed from (2) by the

usual procedure but an ether solution of (1) was formed by treatment of (2) in ether at -10°C with triflic anhydride and pyridine followed by filtration through anhydrous copper sulphate and a cotton wool plug. This lactone triflate (1) proved too unstable to purify and was therefore used immediately as the ether solution in the ring contraction studies below. Due to the instability of the triflate (1), the epimeric lactone (10) could not be prepared by displacement of triflate from (1) by trifluoroacetate. Accordingly (10), in which the triflate and benzyl ether functions are *cis* to each other, was prepared from (25);[16] acid hydrolysis of (25) followed by bromine oxidation of the resulting lactol gave the required lactone (10). All attempts to isolate the α-triflate ester (9) failed however, since it decomposed as it formed at -30°C. This ring contraction reaction could not therefore be investigated.



(24) (25) (26) (27)

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 moderate to good yield, by simple evaporation of the solvent and purification of the residue by flash chromatography. In each case, disappearance of starting material from the reaction was instantaneous at room temperature. Treatment of the ethereal solution of the triflate (1) under these conditions gave the ring contracted oxetane (26), $[\alpha]_D^{20}$ -52.5° (c, 1.25), in 35% yield; the low yield is partially due to the inherent instability of the triflate (1). The formation of the *trans*-isomer (26) requires an inversion of configuration at C-2 during the ring contraction; none of the *cis*-isomer (27) was isolated. The *trans*- stereochemistry is tentatively assigned on the basis of equilibrium n.O.e.studies.[17]



a) MeOH / K_2CO_3; b) $NaBH_4$ / EtOH; c) BnBr / NaH / THF.

The α-triflates with carbon substituents at C-3 were relatively stable and easy to handle. Treatment of the *ribo*-triflates (3), (5) and (7) [in which the substituents at C-2 and C-3 are *cis*] with potassium carbonate in methanol resulted in ring contraction with predominant inversion of configuration to give the *arabino*-oxetane products (28) {contaminated by traces of C-2 isomer (34)}, (29) {$[\alpha]_D^{20}$ -7.74° (c, 2.3)}and (30) {$[\alpha]_D^{20}$ -15.8° (c, 0.94)} respectively. In each case a small (about 10%) quantity of the *ribo* -product, arising from overall retention of configuration at C-2, was observed by NMR spectroscopy. The ring contraction of the *arabino*-triflates (11), (13) and (15) under the same conditions also proceeded with almost exclusive inversion

of configuration at C-2 to give the *ribo*-oxetanes (34) {$[\alpha]_D^{20}$ +29.4° (c, 0.16)}, (35) {$[\alpha]_D^{20}$ +14.3° (c, 0.50)} and (36) {$[\alpha]_D^{20}$ 13.4° (c, 0.67)}, respectively with only traces of the *arabino*-oxetanes produced. The stereochemistry of the ring contracted methyl oxetane carboxylates was established by reduction of the esters with sodium or lithium borohydride to a primary alcohol, followed by benzylation to give oxetanes in which all the oxygen functions had been converted to benzyl ethers. Such treatment of the *arabino*-oxetanes (28), (29) and (30) gave the ethers (31) {$[\alpha]_D^{20}$ -0.9° (c, 0.59)}, (32) {$[\alpha]_D^{20}$ +11.0° (c, 1.27)}, and (33) {$[\alpha]_D^{20}$ -10.1° (c, 1.12)}, respectively, each of which was unsymmetrical as shown by the number of lines in their ^{13}C NMR spectra,[18] and their non-zero optical rotations. In contrast, the *ribo*-oxetanes (34), (35) and (36) gave the ethers (37), (38) and (39) respectively, each of which was symmetrical as shown by their zero optical rotations and by the number of lines in their ^{13}C NMR spectra.[19] Yields for the ring contractions to oxetanes were generally lower for C-3 alkyl substituted lactones than for lactones with C-3 oxygen substituents protected as ethers or acetals.[7,8] This reflects the greater tendency of these triflate lactones to eliminate rather than contract. α-Methoxy lactones were also significant by-products for the first time; in the case of C-3 alkyl lactone triflates there is no β-oxygen to inhibit S_N2 reactions. The contrast in the stereochemistry of the contraction of triflates with alkyl rather than oxygen substituents at C-3 may arise from the relatively easy ring closure of the intermediate hydroxy triflates to oxetanes. The S_N2 closure of the hydroxy triflates bearing oxygen substituents at C-3 will be relatively difficult and so the late transition state will reflect more strain between developing *cis*- carbomethoxy and oxygen substituents. This will allow a greater opportunity for epimerisation of the intermediate hydroxy triflate with C-3 oxygen, rather than carbon, substituents. The accompanying paper[9] describes attempts to prepare oxetanocin analogues from these alkyl oxetanes.[20]

REFERENCES

1. A. J. Kirby, H. Ryder and V. Matassa, *J. Chem. Soc., Perkin Trans. 2*, 1990, 825.
2. R. Hambalek and G. Just, *Tetrahedron Lett.*, 1990, **31**, 4691.
3. S. Nishiyama, S. Yamamura, K. Kato, T. Takita and Y. Terada, *Tetrahedron Lett.*, 1990, **31**, 4777.
4. N. Shimada, S. Harada, T. Tomisawa, A. Fujii and T. Takita, *J. Antibiot.*, 1986, **39**, 1623.; Y. Nishiyama, N. Yamamoto, Y. Yamada, N. Fujioka, N. Shimada and K. Takahashi, *J. Antibiot.*, 1989, **42**, 1308; H. Hoshino, N. Shimizu, N. Shimada, T. Takita and T. Takeuchi, *J. Antibiot.*, 1987, **40**, 1078.
5. S. Nishiyama, T. Ohgiya, S. Yamamura, K. Kato, M. Nagai and T. Takita, *Tetrahedron Lett.*, 1990, **31**, 705.
6 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, *Tetrahedron: Asymm.*, 1990, **1**, 527.
7. G. W. J. Fleet, G. N. Austin, J. M. Peach, K. Prout and J. C. Son, *Tetrahedron Lett.*, 1987, **28**, 4741.
8. D.R.Witty, G.W.J.Fleet, K.Vogt, F.X.Wilson, Y Wang, R.Storer, P.L.Myers,C.J.Wallis, *Tetrahedron Lett.*, 1990, **31**, 4787.
9. F.X.Wilson, K.Vogt, G.W.J.Fleet, D.R.Witty, Y. Wang, R.Storer, P.L.Myers and C.J.Wallis, accompanying paper·
10. A. Rosenthal and L.B. Nguyen, *J. Org. Chem.*, 1969, **34**, 1029.
11. G.W.J. Fleet, C.J. Mathews, J.A. Seijas, M.P.V. Tato, P.D. Baird, D. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1067.
12. All specific rotations in this paper were determined in chloroform as a solvent; all new compounds in this paper had consistent spectral data and satisfactory CHN microanalyses were obtained for: (3) (4) (5) (6) (8) (12) (14) (16) (19) (21) (23) (24) (25) (26) (28) (29) (30) (32) (33) (34) (35) (36) (37) (38).
13. Y. Oikawa, T. Nishi, H. Yonemitsu, *Tetrahedron Lett.*, 1983, **24**, 1987.
14. O.V. Nair and A.K. Sinhababu, *J. Org. Chem.*, 1978, **43**, 5013.
15. C.S. Hudson and H.S. Isbell, *J. Am. Chem. Soc.*, 1929, **51**, 2225.
16. O.Dahlmar, P.J. Garegg, H. Mayer and S.Schramek, *Acta. Chem. Scand. Ser. B*, 1986, **40**, 15.
17. ^1H n.O.e data (d_6-benzene): irradiate δ2.35 (H-3α): δ2.55 +19%, δ4.75 +6%, δ4.90 +3%; irradiate δ2.55 (H-3β): δ2.35 +18.5%, δ3.2 (H,H'-5) +3%, δ4.9 +6%; irradiate δ4.75 (H-4): δ2.35 +7%, δ3.2 +5%; irradiate δ4.90 (H-2): δ2.55 +6.5%.
18. ^{13}C ($CDCl_3$) data for *arabino* ethers: (31) δ 12.45 (*q*, Me), 32.84 (d, C-3), 70.32, 72.55, 73.51 (3t, C-1, C-5, 2 x $ArCH_2$), 79.96, 83.30 (2d, C-2, C-4); 127.74, 127.87, 128.46 (3d, Ar), 138.31, 138.49 (2s, Ar); (32) 138.23, 138.31, 138.48 (3s, Ph), 128.38, 128.04, 127.73 (3d, Ar), 82.15 (d, C-2), 79.24 (d,C-4), 73.52, 73.16, 72.65, 70.61, 68.13 (5t, C-1, C-3', C-5, 3 x $ArCH_2$), 38.21 (d, C-3); (33) δ 27.99 (t, C-3'), 36.14 (d, C-3), 68.63, 70.50, 72.76, 72.98, 73.20, 73.44 (6t, C-1, C-3", C-5, 3 x $ArCH_2$), 79.68, 85.46 (2d, C-2, C-4), 127.65, 127.75, 127.86, 128.50 (4d, Ph), 138.32, 138.42, 138.57 (3s, Ph)
19. ^{13}C ($CDCl_3$) data for *ribo* ethers: (37) δ 16.72 (q, Me), 33.81 (d, C-3), 72.77, 73.38 (2t, 3 x $ArCH_2$), 84.70 (d, C-2, C-4), 127.06, 128.48 (2d, Ar), 138.49 (s, Ar); (38) δ 138.31, 138.49, (2s, Ph), 128.45, 127.65 (2d Ph), 80.36 (d, C-2, C-4), 78.34, 73.06, 72.72, 70.11 (4t, C-1, C-3', C-5, 3 x $ArCH_2$), 38.73 (d, C-3); (39) δ 32.31 (t, C-3'), 36.94 (d, C-3), 68.29, 72.83, 72.99, 73.31 (4t, C-1, C-3", C-5, 3 x $ArCH_2$), 83.39 (d, C-2, C-4), 127.61, 127.72, 128.42 (3d, Ph), 138.39, 138.53 (2s, Ph).

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