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RING CONTRACTION REACTIONS OF 2-O-METHANESULFONATES OF α-HYDROXY-γ-LACTONES IN AQUEOUS MEDIUM TO OXETANE-2-CARBOXYLIC ACIDS: A CONVENIENT SYNTHESIS OF 3'-O-METHYLOXETANOCIN AND A FORMAL SYNTHESIS OF OXETANOCIN

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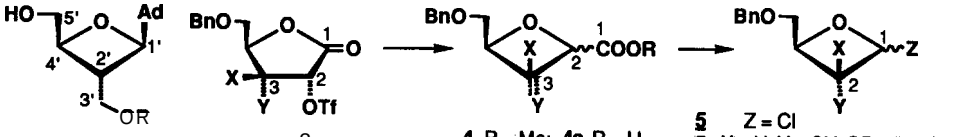
Abstract: Barton decarboxylative rearrangement[15] of thiohydroxamic ester 17 directly provided the key oxetanosyl-thiopyridyl glycosides **18** which were successfully coupled to N-benzoyladenine. A two-step ring contraction of the tosylate 7 to the oxetane-2carboxamide 23 is described. Attempted ring contraction of the triflate 24 gave the unexpected products 25 and 26. A ring expansion reaction (e.g. **14a** → 21a) was also observed.

Oxetanocin 1 , the first natural oxetanosyl-N-glycosie and its analogs show promising antiviral activities against HSV, humancytomegalovirus and HIV.[1,2] A number of elegant syntheses of 1 and other analogs have been reported.[3-6] In a versatile approach, the 2-O-triflate-γ-lactones 3 were ring contracted to oxetane-2-carboxylic esters 4 in the presence of anhydrous K_2CO_3/ methanol.[6] After hydrolysis the resulting acids 4a were then subjected to Barton decaboxylative chlorination[15] to provide unstable chlorooxetanes 5.[6b,7] Thus, in a "low yield" synthesis of 1 (Ad = adenine), the chlorooxetane 5a was converted to protected 1 and its a-anomer.[6b] For the success of the transformations 3 → 4, anhydrous conditions were found to be essential. It was also shown that under these conditions, the corresponding 2-0-mesylates provided virtually no oxetanes.[6a,b] *We now show that especially under aqueous hydrolytic conditions, ring contraction of such 2-O-mesylates is an efficient process culminating in an opportune synthesis* of 2 *and its anomer* **2a.**



1 R = H ; **2** R = Me

3

4 R = Me; **4a** R = H

[X = mostly H; Y = Subs. alkyls, heteroatoms etc.]

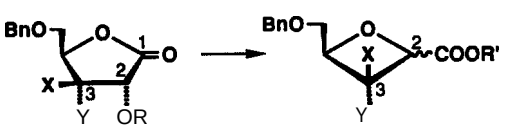
5 Z = Cl

5a X = H, Y = CH_2OBn, Z = Cl

5b X = H, Y = CH_2OBn, Z = SPh

The lactone substrates 6 - 11 and 24 were readily prepared from diacetone glucose according to published procedures.[6b,8] In initial experiments, when the mesylate 6 and the tosylate 7 were treated with anhydrous K_2CO_3 in methanol over 24-36 hours, the oxetane-2-methylesters 12b were isolated in -30% and 10% yields respectively (anomer ratio ~1:1); the unchanged lactones being the major components in these reactions.[9,10] This suggested that the poor leaving group ability of 0-mesylate and tosylate imposed an element of reversibility causing the intermediate oxy-anion to relactonize. In contrast, we found that treatment of the mesylates 6 and 8 – 11 in methanol with aqueous sodium hydroxide readily provided[11] the oxetane-2-carboxylic acids **12a** (80%),[12] **13a** (72%). 148 (56%) 158 (48%) and **16a** (35%). The predominant isomers in these reactions were derived from inversion of configuration at C-2 (5:1 for **12a** -14a and 3:2 for **15a** and 16a).[13,14] These oxetane-2-carboxylic acids were fully characterized as their methyl esters 12b – 16b.

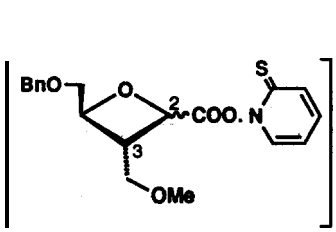
	X	Y	R
6	H	CH_2OMe	Ms
7	H	CH_2OMe	Ts
8	H	CH_2OBn	Ms
9	H	Me	Ms
10	H	OBn	Ms
11	OBn	H	Ms



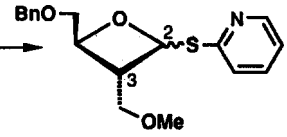
[Ms = SO_2Me; Ts = $SO_2C_6H_4Me$-p]

	X	Y	R'
12a	H	CH_2OMe	H
13a	H	CH_2OBn	H
14a	H	Me	H
15a	H	OBn	H
16a	OBn	H	H

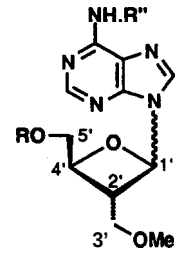
12b ---**16b** R' = Me



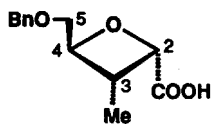
17



18a (1'-β)
18b (1'-α)

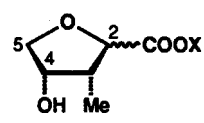


	R	R''	
19	Bn	CO.Ph	1'-α/β
20a	Bn	H	1'-β
20b	Bn	H	1'-α
2	H	H	1'-β
2a	H	H	1'-α



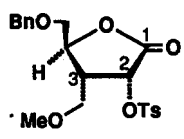
14a

dil. HCl
R.T.



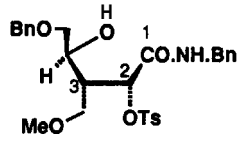
CH_2N_2 → 21a (X = H)
21b (X = Me)

Bn = $CH_2C_6H_5$
Ph = C_6H_5
Ts = $SO_2C_6H_4$ Me-p
Tf = SO_2CF_3



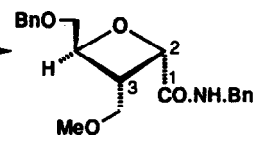
7

banzylamine
THF, R.T.

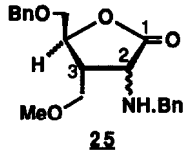


22

NaH
THF, R.T.

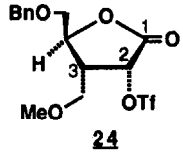


23
(major isomer)



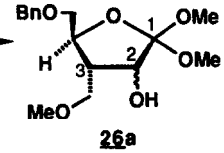
25

benzylamine
THF, R.T.

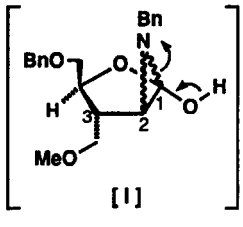


24

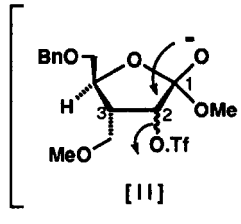
K_2CO_3/MeOH
anhydrous



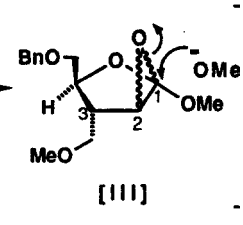
26a
26b



[I]



[II]



[III]

The carboxylic acid 12a was converted in a one-pot sequence to the thiohydroxamic ester 17 which was subjected to photolytic decarboxylatlve rearrangement[15,16] to provide thiipyrldyl glycosides 18a/b in 30% yield.[17] Coupling of 18a/b with N-benzoyladenine (4 equiv.) in DMF, in the presence of bromine (4 equiv.) and 4A molecular sieves,[18] led to protected nucleoslde (anomeric) mixture 19 in -60% yield. Removal of the N-benzoyl group (NaOMe, MeOH) provided easily separable[19] anomers 20a, m.p. 107-110° (H_1-α, d, $J_{1',2'}$ 5.9 Hz) and 20b, m.p. 134-136° (H_1-β, d, $J_{1',2'}$ 6.96 Hz) in over 90% yield (20a:20b, 2:3). Both isomers were debenzylated (Pd black, EtOH, ~quant. yield) to provide 3'-O-methyl oxetanosin 2, m.p. 203-205°, [a]D -14.3° ($CHCl_3$), and its l'-epimer 2a.[20] This also constitutes a formal synthesis of oxetanocin 1 since the oxetane-2- methyicarboxylate 13b[21] has been previously converted to 1.[6b]

We found that oxetane-2-carboxylic acids 12a – 16a on either prolonged storage or in contact with added acids undergo a ring expansion reaction (e.g. 14a → 21a; -30% yield).[22] Such furanosyl-C-glycosides could also be detected Immediately after some of the ring contraction reactions described above.[23] Ring expansion reactions of N-benzoyl oxetanocin diesters have been observed during transglycosidation attempts.[24] Formation of 218 appears to be a unusual example of a ring expansion reaction accompanying debenzylation. We have not studied these ring contraction reactions in the presence of other protecting groups.

In a two-step variant of the above ring contraction reactions, the tosylate 7 upon treatment with benzylamine in THF at room tempsrature cleanly gave the acyclic benzylamide 22. Treatment of 22 with NaH in THF at room temperature (-2.5 hrs.) led to oxetane-2-carboxamide 23 in overall 90% yield from 7 (anomer ratio 5:1; δ 5.04, d, $J_{2,3}$ 6.6 Hz, H_2-β, major isomer; δ 4.64, d, $J_{2,3}$ 6.0 Hz, H_2-α, minor isomer).

Reaction of the more reactive triflate 24 with benzylamine as above gave exclusively the a-aminobenzyl-y-lactone 25 rather than 23 – the ring contraction product.[25] Also, attempted ring contraction of 24 with K_2CO_3 in anhydrous methanol[26] dii not provide 12b but only the orthoesters 26a/b (-60% yield).[27] In view of ample precedents for ring contraction of closely related triflates,[6b] these anamolous results are inexplicable at this time.

Perhaps an 'aziridine-aminal' species such as [I] might be involved in the formation of 25 although direct nucleophilic displacement of the triflate group by benzylamine is a more plausible explaination. We propose an 'epoxy-acetal' species [III] as a possible intermediate in the formation of 26a/b. The tetrahedral intermediate [I I) may act as a common species for the well documented ring contraction reactions," as well as 26a/b via [I I). To the best of our knowledge, formation of 26a/b from 24 is a novel orlhoester forming reaction under basic conditions.

We are currently evaluating the scope and limitations of the above ring contraction reactions as well as the unusual transformations, 14a → 218 and 24 → 26a/b.[28]

Acknowledgements: We thank Sir Derek Barton. FRS, for stimulating discussions. We would also like to thank Dr. B. Pramanik and Mr. P. Banner for hllh resolution mass spectral data.

References and Notes:

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4. D. W. Norbeck and J. B. Kramer, *J. Am. Chem. Soc.*, 1988, 110, 7217.
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6. (a) G. N. Austin, G. W. J. Fleet, J. M. Peach, K. Prout and Jon C. Son, *Tetrahedron Lett.*, 1987, 28, 4741; (b) F. X. Wilson, G. W. J. Fleet, K. Vogt, Y. Wang, D. R. Wiiy, S. Choi, R. Storer, P. L. Meyers and C. J. Wallis, *ibid.*, 1990, 31, 6931.
7. These chlorooxetanes 5 were so unstable that it was found necessary to first convert them to thiophenyl glywsides 5b for purification; they were then regenerated back to chlorooxetanes for coupling with N- benzoyladenine just before use.[6b] The thiopyridylglycosides 18a/b used here were stable to chromatography and to storage at -10° under argon for several months.

8. E. M. Acton, R. M. Goerner, H. S. Uh, K. J. Ryan, D. W. Henry, C. E. Cass and G. A. LaPage, *J. Med. Chem.*, **1979**, 22, 518.

9. *Ail* new compounds were characterized by hiih resolution mass spectra, ^1H and ^{13}C NMR spectra. When necessary 2D (^1H-^1H) and 2D(^1H-^{13}C) COSY NMR spectra were obtained. Elemental analyses were obtained for crystalline compounds only. Yields refer to isolated products and have not been optimised. Selective spectral data is given here.

10. 6: ^1H NMR [400 MHz, $CDCl_3$] 82.95 (m, 1H), 3.25 (s, 3H), 3.35 (s, 3H), 3.55 (m, 3H), 3.75 (dd, J 10.8, 2.2 Hz. 1H), 4.55 (ABq J 12.1 Hz, 2H), 4.7 (s, broad, 1H), 5.68 (d, $J_{2,3}$ 9Hz, 1H), 7.2- 7.4 (m. 5H).
12b: ^1H NMR [$CDCl_3$] 84.9 (d, $J_{2,3}$ 6.0 Hz, 2α-H); 5.14 (d, $J_{2,3}$ 8.5 Hz, 2β-H). C_2-isomer ratio, ~1:1.

11. Typical procedure: A 10% methanolic solution of the mesylate was treated with aq. 1 N NaOH (3.5 equiv.) at R.T. After ~15 hrs. the reaction mixture was cooled (ii bath) and neutralized with 1 N HCl (3.5 equiv.). Evaporation of the solvents *in-vacuo* at 35-40°C followed by extraction of the residue with CH_2Cl_2 provided the crude product which was chromatographed on silica gel; eluent: 12 • 25% acetone in n-hexane followed by 25% methanol in CH_2Cl_2. Both isomers could be separated in this manner aithough mixtures were used for Barton decarboxylative rearrangement.[15]

12. **12a:** ^1H NMR [$CDCl_3$] 83.3 (m, 1H), 3.38 (s, 3H), 3.5 (dd, J ll.5, 1.5 Hz, 1H), 3.58 (m, 2H), 3.8 (dd, J 11.5, 2.6 Hz, 1H), 4.7 (ABq, J 12 Hz. 2H), 4.87 (m, 1H), 4.9 (d. $J_{2,3}$ 6.6 Hz, 2α-H, minor isomer), 7.3- 7.4 (m, 5H); δ 3.3 (s, 3H), 3.4 (m, 1H), 3.5 (m, 2H), 3.7 (m, 2H), 4.65 (ABq, J 12 Hz, 2H), 4.93 (m, 1H), 5.1 (d, J2.3 9 Hz. 2β–H, major isomer), 7.3- 7.4 (m, 5H).

13. For ^1H coupling constants in oxetanes, see: A. Balsamo, C. Ceccarelli, P. Crotti and F. Macchia, *J. Org. Chem.*, **1975**, 40, 473.

14. In the formation Of minor retention products, the available evidence neither rules out interconversion of lactone sulfonate esters nor epimerization at some latter stage. More detailed studies would be necessry lo fully understand these results.

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16. Thiohydroxamic ester 17 was prepared *in-situ* via *mixed* anhydride procedure by addition of isobutyrylchloroformate and N-methyl morpholine to a 10% solution oi **12a** in dry THF at -20°. After 5 minutes activation period a solution of N-hydroxy pyridinethione and triethylamine in dry THF was added. After stirring for -30 minutes, the reaction was allowed to warm lo room temperature and irradiated with 150 watts *tungsten* lamp for -60 minutes. Work-up by *extractive* isolation with *ethylacetate* provided the crude product, which was chromatographed on silica gel (eluent: 25% ethylacetate in n-hexane) to provide pure **18a** and **18b** in 30% combined yield. Some of the less polar fractions also contained the isobutyryl ester of the acid **12a** (-25%).

17. **18a:** ^1H NMR [$CDCl_3$] 63.2 (m, 1H0, 3.4 (s, 3H), 3.6 (dd, 2H), 3.75 (d, broad, 2H). 4.65 *(m.* 3H). 4.85 (m, 1H), 6.86 (d, $J_{1,2}$ 6.6 Hz. H_1-α, minor isomer), 7.0- 7.66 (m, 8H), 8.45 (m. 1H); **18b:** δ 3.38 (s, 3H), 3.6-3.8 (m. 4H). 4.65 (m, 3H), 4.85 (m, 1H), 6.88 (d. $J_{1\,2}$ 7.4 Hr. H_1-β, major Isomer), 7.0-7.6 (m. 8H), 8.45 (m, 1H).

18. S. Hanessbn, *K.* Sato, T. J. Liak, N. Oanh and *D. Dixit, J. Am. Chsm. Soc., 1984, 106, 6114; We* cordially thank Professor Hanessian for complete details of this procedure used originally for coupling of a thiophenyl glycoside with N-benzoyladenine.

19. Silica gel chromatography (TLC grade), eluent: 1% methanol in ethylacetate .

20. **2:** ^1H NMR [CD_3OD] *63.4* (s, 3H), 3.66 fd, J 5.2, 2H), 3.76 (dd, J 12.3 Hz, 1H), 3.9 (m, 2H), 4.68 (m. 1H), 6.5 (d, $J_{1',2'}$ 6.07, H_1-α, minor anomer), 8.2 (s, 1H) and 8.66 (s, 1H); 2a: δ 2.95 (s, 3H), 3.31-3.43 *(m,* 4H), 3.61 (m, 1H), 3.77 (dd, J 12.5, 3.8 Hz, 1H), 3.89 (dd, J 12.5, 2.9 Hz, 1H), 4.98 (m. 1H), 6.7 (d, $J_{1',2'}$ 6.88 Hz, H_1-β, major anomer), 8.2 (s, 1H), 8.46 (s, 1H).

21. **13b:** ^1H NMR [$CDCl_3$] S3.5 (m, 1H), 3.6 (dd, 2H), 3.67 (s, 3H), 3.69 (dd, 2H). 4.47 (dd, 3H), 4.65 (dd, 2H), 4.88 (m, 1 H), 6.14 (d, $J_{2,3}$ 8.8 Hz, H_2-β, major Isomer), 7.2-7.4 (m, 10H); minor isomer: δ 4.92 (d, $J_{2,3}$ 6.8 Hz, H_2-α).

22. **14b:** ^1H NMR [$CDCl_3$] δ 1.1, (d. 3H), 3.4 (m, 1H), 3.64 (dd, 2H), 3.8 (s, 3H), 4.45- 4.7 (m. 3H). 5.11 (d, $J_{2,3}$ 6.9 Hz, H_2-β), 7.2- 7.4 (m, 5H); signals at δ 1.3 (d, 3H). 2.94 *(m,* 1H), 3.7 (s, 3H) and 4.65 (d, $J_{2,3}$ 6.0 Hz, H_2-α) indicating the presence of -20% retention product (by integration).
21b: ^1H NMR [$CDCl_3$] δ 1.22 (d, 1.22 (d, J 7 Hz, 3H), 2.22 (m. broad, 1H), 2.29 *(m,* 1H), 3.76 (s, 3H), 3.92 (dd, J 10, 1 Hz, 1H), 4.12 (dd, J 10, 1H), 4.15 (d, J 10 Hz, 1H) and 4.28 (dd, 4, 4 Hz, 1H).

23. These observations appear to be related lo some recent examples of tetrahydrofuran cyclizations with concomitant debenzylations, see: H. Dahmlow. J. Mulzer, C. Seitz, A. Ft. Strecker and A. Kohlmann, *Tetrahedron Lett.*, **1992**, 33, 3607.

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25. **25:** ^{13}C NMR [$CDCl_3$] δ 176.8 (s), 139.8 (s), 137.8 (s), 126.5 (d), 128.3 (d), 127.9 (d), 127.8 (d), 127.2 (d), 127.1 (d), 76.8 d, C_4), 73.7 (t), 70.6 (t), 70.1 (t), 53.1 (l) and 44.3 (d, C3); ^1H NMR [$CDCl_3$] δ 2.47 (m, 1H), 3.26 (s. 3H), 3.41 (dd, 12,5 Hz, 1H) 3.43 (dd, J 11, 2 Hz, 1H), 3.50 (d, J 10, H_2), 3.6 (dd, J 11, 4 Hz, 1H), 3.77 (dd, J 11, 2 Hz, 1H), 3.94 (d, J 12, 1H), 4.0 (d, J 12, 1H), 4.55 (d, J 11 Hz, 1H), 4.58 (d. J 11 Hz, 1H). This data also ruled out the ring contracted oxetane-amide structure 23.

26. To a 10% solution of the triflate 24 in dry methanol was added K_2CO_3 (anhydrous; 6 equiv.) in one portion. The reaction mixture was stirred at room temperature for 30 minutes and filtered to remove solids. Evaporation of the fittrate *in-vacuo* and preparative TLC on silica gel (eluent: 40% ethylacetate in n-hexane) provided **26a** and 26b as colorless gums.

27. 24: ^1H NMR [$CDCl_3$] 62.95 (m, 1H), 3.35 (s, 3H), 3.54 (m, 3H). 3.75 (d, 1H), 4.55 (dd, 2H). 4.67 (s, broad, 1H), 5.78 (d, $J_{2,3}$ 8.8 Hz, 1H), 7.2- 7.4 (m, 5H).
26a: ^{13}C NMR [$CDCl_3$] δ 138.2 (s), 128.3 (d), 127.6 (d), 127.5 (d), 120.8 (s, C_1), 79.1 (d, C_4), 73.2 (t), 72.5 (d, C_2), 69.7 (t), 59.0 (q), 50.9 (q), 49.3 (q), and 44.0 (d, C_3); 26b: δ 137.8 (s), 128.4 (d), 127.7 (d), 119.3 (s. C_1), 77.8 (d, C_4), 73.9 (d, C_2), 73.5 (t), 72.4 (t), 71.8 (t), 58.9 (q), 50.0 (q), 49.5 (q) and 48.4 (d, C_3); Stereochemistry at C_2 in **26a:** δ H_3 2.45, δ C_3 44.0 (OH function is *cis to* H_3) end in 26b: δ H_2 2.30, δ C_3 48.4 (OH function is *trans* to H_3)
IR [neat, isomers **26a** and **26b**]: no carbonyl absorption.

28. A. K. S. would like to dedicate this contribution to his mentor, Dr. R. H. B. Gall.

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