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CHIRAL OXETANES FROM SUGAR LACTONES: SYNTHESIS OF DERIVATIVES OF 3,5-ANHYDRO-1,2-O-ISOPROPYLIDENE-α-D-GLUCURONIC ACID AND OF 3,5-ANHYDRO-1,2-O-ISOPROPYLIDENE-β-L-IDURONIC ACID

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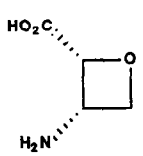
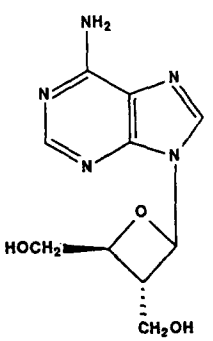
Ring contraction reactions of triflates of α-hydroxy-γ-lactones provide an approach to the synthesis of chiral polyfunctionalised oxetanes from sugars. Treatment of 1,2-O-isopropylidene-5-O-trifluoromethanesulphonyl-α-D-glucuronolactone with benzylamine or with potassium carbonate in methanol gave ring contraction reactions to form oxetanes in good yield.

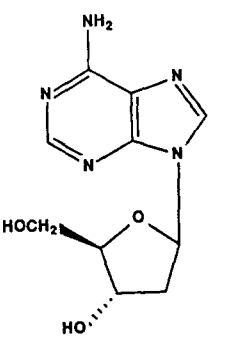
There are many naturally occurring oxetanes with interesting biological activity,[1] including oxetin, an antibiotic amino acid.[2,3] Recently, the novel nucleoside oxetanocin,[4,5] an isomer of 2'-deoxyadenosine which is active against Herpes simplex virus-II, has been isolated from bacteria. There is a rich and varied chemistry of the cheap and readily available glucuronolactone.[6] 1,2-O-Isopropylidene-5-O-trifluoromethanesulphonyl-α-D-glucuronolactone (1), prepared[7] in quantitative yield from the alcohol (2), is an easily manipulated compound[8] which is kinetically stable and may be recrystallised from ethanol. The lactone triflates (1) and (7) offer alternative sites for nucleophilic attack - either nucleophilic displacement of the triflate at C-5 or nucleophilic addition to the lactone carbonyl group. Nucleophilic displacements of the triflate from C-5 in (1) either by azide ion[9,10] or by trifluoroacetate ion[8] both take place under mild conditions in high yields to give, respectively, the ido azide (4) and the trifluoroacetate (5); none of these displacements at C-5 takes place when the corresponding mesylate (3) is subjected to similar treatment. Esterification of the ido alcohol (6) with triflic anhydride followed by treatment of the triflate (7) with sodium azide produces the gluco azide (8) in good yield.[9,10] This paper describes initial experiments on the ring contraction reactions of the lactone triflates (1) and (7) to highly substituted chiral oxetanes, arising from initial nucleophilic addition to the lactone carbonyl group.



oxetin

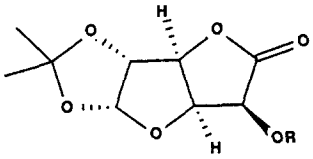


oxetanocin

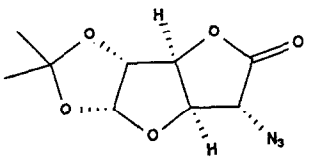


2'-deoxyadenosine

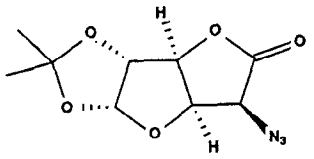
Treatment of the triflate of the protected glucuronolactone (1) with benzylamine in tetrahydrofuran at room temperature gave N-benzyl 3,5-anhydro-1,2-O-isopropylidene-α-D-glucuronamide (9),[11] m.p. 160°C, $[\alpha]_D^{20}$ -8.4° (c, 0.73 in $CHCl_3$) in 81% yield. Esterification of the iduronolactone (6) with triflic anhydride in the presence of pyridine at -40°C, followed by reaction of the resulting triflate (7) with benzylamine at room temperature also gave (9) in 70% overall yield. In the ring contraction of the glucuronolactone derivative, net overall retention of configuration of the stereochemistry at C-5 is observed, whereas the formation of (9) from the epimeric ido triflate proceeds with inversion at C-5. In neither reaction was any of the epimeric iduronamide (12) observed. Reaction of the mesylate (3) gave no oxetane products.



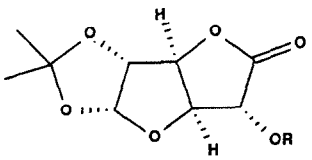
(1) R= SO_2CF_3
(2) R= H
(3) R= SO_2Me



(4)



(8)



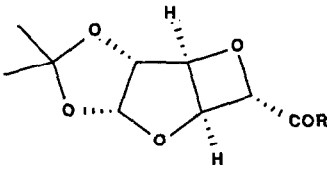
(5) R= $COCF_3$
(6) R= H
(7) R= SO_2CF_3

In contrast, when the glucuronolactone (1) was treated with potassium carbonate in methanol at room temperature for 20 min, a mixture of methyl 3,5-anhydro-1,2-O-isopropylidene-α-D-glucuronate, (10) m.p. 49-50°C, $[\alpha]_D^{20}$ -11° (c, 0.23 in $CHCl_3$) and methyl 3,5-anhydro-1,2-O-isopropylidene-β-L-iduronate, (13) m.p. 83-84°C, $[\alpha]_D^{20}$ +83° (c, 0.48 in $CHCl_3$) was isolated in a combined yield of 61% yield [ratio of (10) and (13) was 2:1]. When the epimeric triflate (7) was treated under similar conditions, the ratio of (10) to (13) was 9:1.

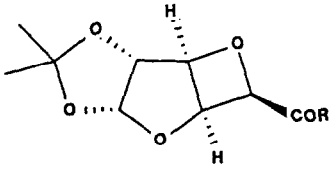
The overall retention of configuration at C-5 in the reaction of benzylamine with (1), and the epimeric mixture of esters obtained in the reaction of (1) with potassium carbonate in methanol indicates an epimerisation of C-5 either during the course of the reactions or after product formation.

When the methyl anhydroglucuronate (10) was reacted with benzylamine in methanol in the presence of sodium acetate for 2 h at room temperature, the benzylamide (9) was formed in 80% yield. When the epimeric iduronate (13) was treated under the same conditions for 41 h, N-benzyl 3,5-anhydro-1,2-O-isopropylidene-β-L-iduronamide, (12) m.p. 142-143°C, $[\alpha]_D^{20}$ +34° (c, 0.14 in $CHCl_3$) was obtained in 85% yield. The longer reaction time of the iduronate ester (13) with benzylamine may reflect the more sterically hindered carbonyl in (13) compared to the glucuronate (10). Also treatment of the glucuronate (10) with hydrazine hydrate in methanol in the presence of sodium acetate gave 3,5-anhydro-1,2-O-

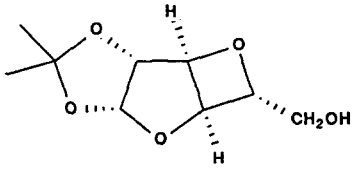
isopropylidene-α-D-glucuronic acid hydrazide (11), m.p. 170°C, $[\alpha]_D^{20}$ -58.4° (c, 0.32 in $CHCl_3$) in 79% yield; under the same conditions, the iduronate (13) led to the formation of 3,5-anhydro-1,2-O-isopropylidene-β-L-iduronic acid hydrazide (14), m.p. 118-121°C, $[\alpha]_D^{20}$ +147° (c, 0.14 in $CHCl_3$) in 67% yield. Reduction of (10) with lithium aluminium hydride gave only 3,5-anhydro-1,2-O-isopropylidene-α-D-glucose (15), m.p. 64-65°C, $[\alpha]_D^{20}$ +39° (c, 0.34 in $CHCl_3$) [lit.[12,13] m.p. 68-69°C, $[\alpha]_D^{20}$ +38.4° ($CHCl_3$)] in 91% yield; lithium aluminum hydride reduction of the epimeric (13) gave 3,5-anhydro-1,2-O-isopropylidene-β-L-idose (16), m.p. 46°C, $[\alpha]_D^{20}$ +50° (c, 0.34 in $CHCl_3$) [lit.[12,13] m.p. 49°C, $[\alpha]_D^{20}$ +53.2° ($CHCl_3$)] in 85% yield.



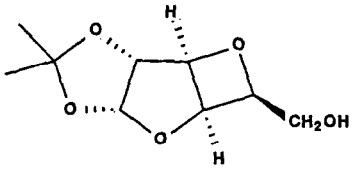
(9) R=NHCH$_2$Ph
(10) R=OMe
(11) R=NHNH$_2$



(12) R=NHCH$_2$Ph
(13) R=OMe
(14) R=NHNH$_2$



(15)



(16)

The above reactions show that the oxetane system is both chemically and configurationally stable to the reagents used in these transformations; no epimerisation was observed in the above reactions. Thus the overall retention of configuration found in the ring contraction of the glucuronolactone triflate (1) to the oxetanes (9) and (10) must arise from epimerisation prior to the formation of the oxetane ring and not by equilibration after the oxetane ring has been formed. The mechanism of this ring contraction is currently being studied to determine whether the initial triflates (1) and (7) interconvert during the reactions, or in some possible ring opened intermediate.

Although the proton NMR of the ido- and gluco- oxetanes are quite distinctive, it is not possible to determine the stereochemistry of the oxetane ring by coupling constants in ^{1}H NMR. The stereochemical assignments in this paper are based on the reduction of methyl esters (10) and (13) to the known anhydrosugars (15) and (16) and by a crystal structure[14] of N-benzyl 3,5-anhydro-1,2-O-isopropylidene-α-D-glucuronamide (9) (Figure).

The scope amd limitations of the ring contraction of lactone triflates to give chiral oxetanes is currently being evaluated, in particular in relation to the synthesis of oxetanocin and C-nucleoside analogues thereof; initial experiments indicate that this procedure may provide a flexible approach to the synthesis of highly substituted and functionalised chiral oxetanes.[15,16]

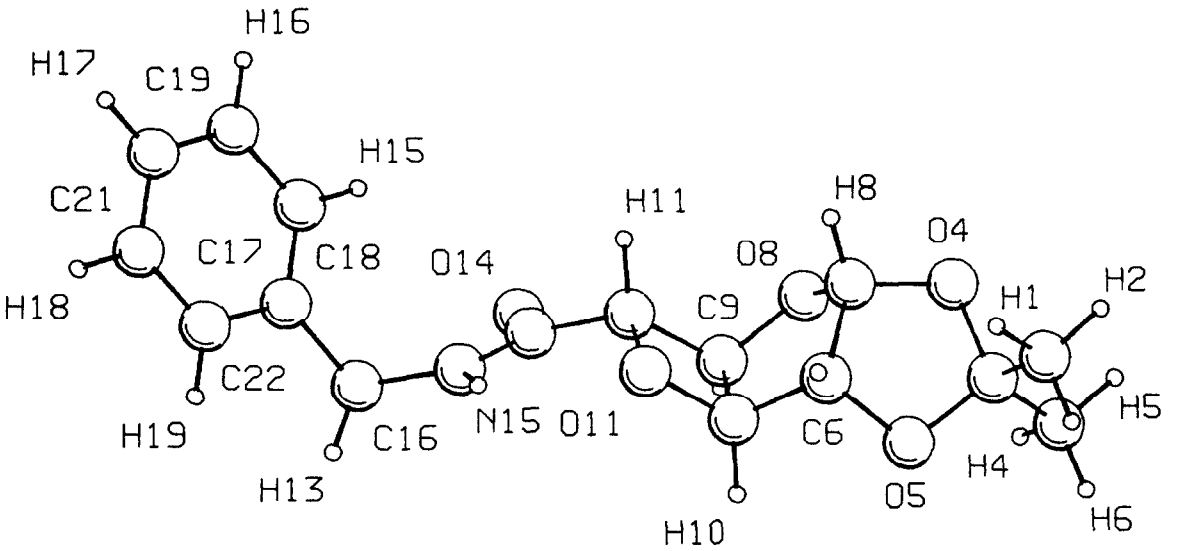


Figure. Crystal Structure of N-Benzyl 3,5-Anhydro-1,2-O-isopropylidene-α-D-glucuronamide (9)

REFERENCES
1. S. Searles in Comprehensive Heterocyclic Chemistry, (ed. W. Lwowski), Vol. 7, p. 363 Pergamon, Oxford, 1984.
2. S. Omura, M. Murata, N. Imamura, Y. Iwai and H. Tanaka, J. Antibiot., 1984, 37, 1324.
3. Y. Kawahata, S. Takatsuto, N. Ikekawa, M. Murata and S. Omura, Chem. Pharm. Bull., 1986, 34, 3102.
4. N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii and T. Takita, J. Antibiot., 1986, 39, 1623.
5. H. Nakamura, S. Hasegawa, N. Shimada, A. Fujii, T. Takita and Y. Iitaka, J. Antibiot., 1986, 39, 1626.
6. K. Dax and H. Weidmann, Adv. Carbohydr. Chem. Biochem., 1976, 33, 189.
7. B. P. Bashyal, H.-F. Chow, L. E. Fellows and G. W. J. Fleet, Tetrahedron, 1987, 43, 415.
8. R. Cauk, H. Honig, J. Nimpf and H. Weidmann, Tetrahedron Lett., 1980, 21, 2135.
9. B. P. Bashyal, H.-F. Chow and G. W. J. Fleet, Tetrahedron, 1987, 43, 423.
10. B. P. Bashyal, H.-F. Chow and G. W. J. Fleet, Tetrahedron Lett., 1986, 27, 3205.
11. All new compounds in this paper have satisfactory microanalytical data and spectra consistent with the structures reported.
12. J. G. Buchanan and E. M. Oakes, Tetrahedron Lett., 1964, 2013.
13. J. G. Buchanan and E. M. Oakes, Carbohydr. Res., 1965, 1, 242.
14. The details of the crystal struture of (9) will be given in a full paper.
15. An SERC post-doctoral fellowship (to JCS) is gratefully acknowledged.
16. We are very grateful to Dr. Peter Myers of Glaxo Group Research for help in this project.

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