Tetrahedron Letters, Vol. 34, No. 38, pp. 6115-6118, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

CYCLIC SULPHATES OF δ-LACTONES IN THE SYNTHESIS OF TETRAHYDROFURANS TETRAHYDROPYRANS AND CYCLOHEXANES

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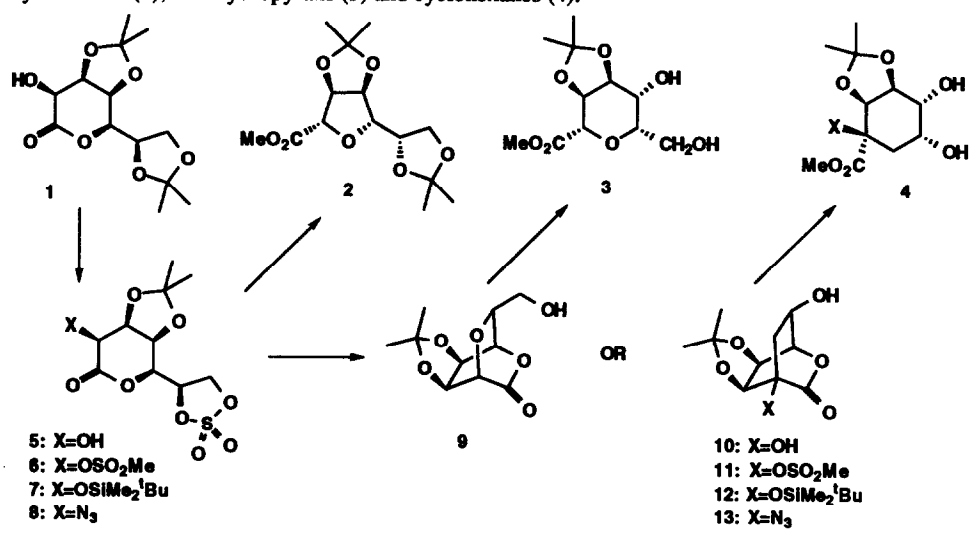
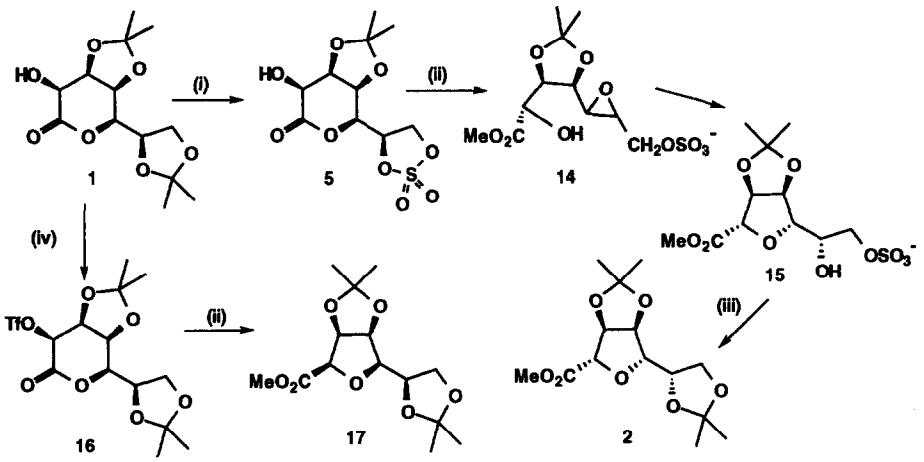
Abstract: Side-chain cyclic sulphates derived from a δ-lactone (1) provide easy access to complex tetrahydrofuran, tetrahydropyran and cyclohexane derivatives each with 5 adjacent chiral centres and at least 6 adjacent carbons bearing functional groups.

Sugar lactones provide a number of chiral pool constituents for the synthesis of a wide range of highly functionalised homochiral compounds by procedures that minimise the use of protecting groups.[1] The diacetonide (1), readily available on the kilogram scale by the cyanohydrin extension of diacetone mannose,[2,3] has been utilised in the synthesis of a diverse set of targets - most frequently by a strategy which involves nucleophilic substitution of a triflate at C-2 of the sugar lactone.[4] A different approach would be the removal of a proton from either the hydroxyl group or the carbon at C-2 to initiate intramolecular nucleophilic attack onto an electrophilic site in the side chain of the lactone. Cyclic sulphates[5] are powerful intermediates in carbohydrate[6] chemistry for the introduction of nucleophiles[7] since the cyclic sulphate moiety simultaneously activates one and protects another of two adjacent hydroxyl groups. This is particularly likely to be the case with sulphates, such as (5), where one of the cyclic sulphate groups is a primary and the other a secondary carbon; this structural feature should almost invariably lead to nucleophilic attack at the primary position by external nucleophiles but may allow choice of site of attack by internal nucleophiles. This paper describes the use of the cyclic side chain sulphates (5-8), easily derived from (1), in the synthesis of highly functionalised tetrahydrofurans (2), tetrahydropyrans (3) and cyclohexanes (4).



The initial objective of this work was to induce sulphates such as (5) to cyclise by nucleophilic attack of an alkoxide - derived by removing a proton from the C-2 hydroxyl function - at the secondary carbon of the sulphate to give, after work up, an intermediate bicyclic lactone such as (9). Ring opening of (9) would provide access to fully substituted tetrahydropyrans such as (3); in principal, this strategy would produce short and convenient approach to the synthesis of C-glycosides. Accordingly, the sulphate (5) was prepared from (1) by selective hydrolysis of the side chain acetonide;[2] the resulting triol was then treated with thionyl chloride in pyridine and the cyclic sulphites oxidised by ruthenium(III) chloride and sodium periodate[8] in a mixture of carbon tetrachloride, acetonitrile and water to give the sulphate (5),[9] m.p. 141-144°C, $[\alpha]_D^{25}$ +74.4 (*c*, 1.0 in EtOH) in 52% yield [Scheme 1].[10] Treatment of the sulphate (5) with potassium carbonate in methanol gave a highly polar intermediate ionic sulphate which was treated directly with acetone in the presence of concentrated sulphuric acid to afford the tetrahydrofuran acetonide (2), an oil, $[\alpha]_D^{20}$ +24.6 (*c*, 1.3 in $CHCl_3$), in an overall yield of 76%.[11]

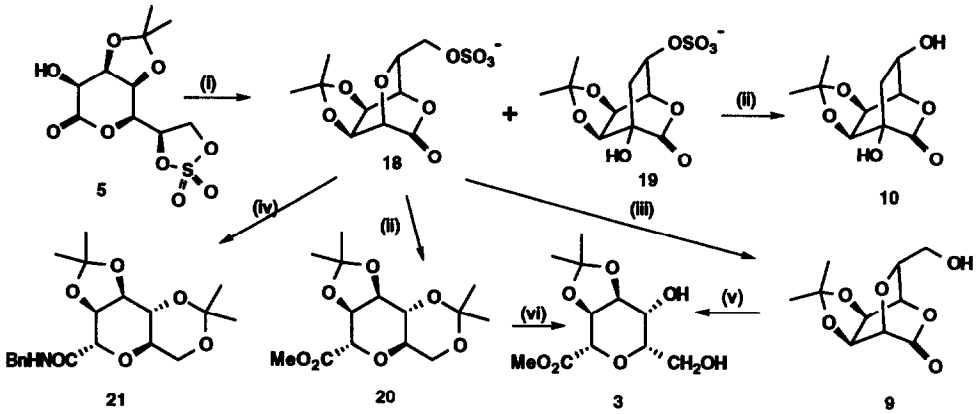


Scheme 1. Formation of tetrahydrofuran derivatives. (i) AcOH, H_2O; then $SOCl_2$, pyridine; then $RuCl_3$, $NaIO_4$, (ii) K_2CO_3, MeOH (iii) Me_2CO, conc. H_2SO_4 (iv) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2

A plausible rationale for the formation of (2) in this reaction is initial base-induced nucleophilic ring opening of the lactone by methanol to give an epoxide (14) derived from intramolecular nucleophilic attack by the C-5 hydroxyl group on the C-6 secondary carbon of the sulphate. The C-2 hydroxyl function in (14) then induces intramolecular ring opening of the epoxide to form the tetrahydrofuran (15). Subsequent reaction of (15) with acetone under acid conditions gives the readily isolated diacetonide (2); neither of the ionic sulphates (14) or (15) were characterised and it possible that the tetrahydrofuran ring is not formed until the step involving acid treatment.. The formation of tetrahydrofuran (2) from (1) involves overall inversion of configuration at C-5 and C-6 of the sugar; recently, it has been reported that treatment of the triflate (16), formed from (1) by esterification with triflic anhydride, with potassium carbonate in methanol afforded the tetrahydrofuran (17) in 81% yield.[12] Thus, these two complementary strategies for the formation of tetrahydrofurans from δ-lactones can give high yields of products with control of inversion at either C-2 or both C-5 and C-6 of the sugar lactone.

For the formation of a tetrahydropyran from (5), it is thus clearly necessary to avoid the possibility of nucleophilic ring opening by the base rather than removal of the proton from the C-2 hydroxyl group.

Treatment of (5) with sodium hydride in dimethylformamide gave a mixture of the bicyclic sulphates (18) and (19). The major product (18) was formed by nucleophilic attack by the alkoxide, derived from removal of the hydroxyl proton, at the secondary centre of the sulphate giving cyclisation by a 6-*exo*-tet process; the minor product (19) is also the result of a 6-*exo*-tet cyclisation by a carbanion derived from proton removal from C-2 of the lactone (5) closing onto the primary carbon of the sulphate [Scheme 2]. Reaction of the crude mixture of



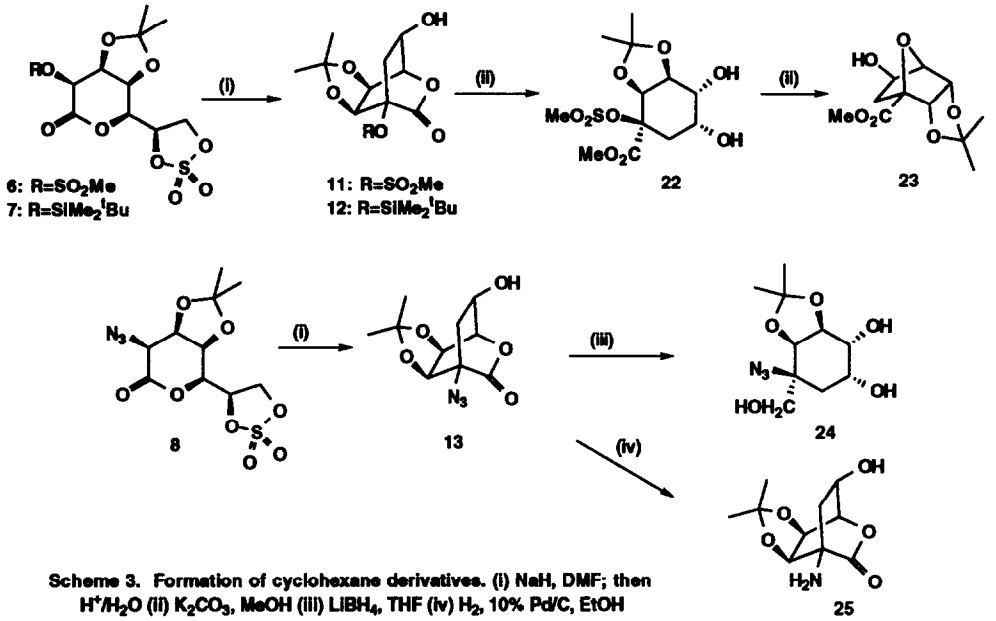
Scheme 2. Formation of tetrahydropyran derivatives. (i) NaH, DMF (ii) MeOH; then Me_2CO, conc. H_2SO_4 (iii) H^+/H_2O (iv) $PhCH_2NH_2$; then H^+/Me_2CO, $Me_2C(OMe)_2$ (v) K_2CO_3, MeOH (vi) AcOH, H_2O

(18) and (19) with methanol, and then acetone in the presence of acid gave a separable mixture of the tetrahydropyran diacetonide (20), m.p. 91-93 °C, $[\alpha]_D^{20}$ +40.0 (*c*, 0.69 in EtOAc) in 51% yield together with the easily crystallised carbocyclic lactone (10), m.p. 142-144°C, $[\alpha]_D^{20}$ +2.3 (*c*, 1.0 in MeCN) in 12% yield. If the crude mixture of (18) and (19) was treated with concentrated sulphuric acid and water, the bicyclic tetrahydropyran lactone (9), m.p. 101-103°C, $[\alpha]_D^{21}$ -42.5 (*c*, 4.4 in $CHCl_3$) could be isolated in 38% yield. The lactone (9) with potassium carbonate in methanol underwent ring opening to give the methyl ester (3), m.p. 132-144°C, $[\alpha]_D^{20}$ +67.5 (*c*, 1.0 in EtOH) in 88% yield; the same monoacetonide (3) was also formed by selective hydrolysis of the diacetonide (20) with aqueous acetic acid. The benzylamide (21) could be formed by treating the crude mixture of sulphates with benzylamine and then the reaction up with acetone and dimethoxypropane in the presence of acid to afford the tetrahydropyran (21), m.p. 81-83°C, $[\alpha]_D^{21}$ +15.4 (*c*, 1.0 in $CHCl_3$) in 53% yield.

The formation of a small amount of the carbocyclic product (10) by treatment of (5) with sodium hydride indicated that higher yields of carbocycles should be formed if the free hydroxyl group in (5) was protected and thereby removing the competing reaction of the formation of tetrahydropyrans. Accordingly the mesylate sulphate (6), m.p. 161-164°C, $[\alpha]_D^{20}$ +45.1 (*c*, 1.0 in EtOAc), was treated with sodium hydride in dimethyl formamide and the reaction worked up with concentrated sulphuric acid and water to afford the bicyclic lactone (11), m.p. 222-224°C, $[\alpha]_D^{20}$ +12.2 (*c*, 1.0 in EtOAc) in 69% yield [Scheme 3]; similar treatment of the silyl protected sulphate (7) afforded the carbocyclic lactone (12), m.p. 111-113°C, $[\alpha]_D^{20}$ +13.9 (*c*, 1.0 in $CHCl_3$), in 45% yield. Similarly, the azidosulphate (8) under the same conditions gave the bicyclic azidolactone (13), as an oil, $[\alpha]_D^{20}$ +52.7 (*c*, 1.0 in $CHCl_3$), in 59% yield.

The use of such carbocyclic lactones as intermediates is illustrated by the treatment of the lactone mesylate (11) with potassium carbonate in methanol which resulted in initial ring opening to (22) followed by spontaneous cyclisation under the reaction conditions to give the bicyclic tetrahydrofuran (23), m.p. 136-

138°C, $[\alpha]_D^{20}$ +67.4 (*c*, 1.0 in $CHCl_3$), in 66% yield. Further examples are the reduction of the azidolactone (13) by (a) lithium borohydride in tetrahydrofuran to give the azidocyclohexantriol (24), m.p. 90-92°C, $[\alpha]_D^{22}$ +53.1 (*c*, 1.0 in EtOAc) in 76% yield, and (b) hydrogen in the presence of palladium in ethanol to give the aminolactone (25), m.p. 173-175°C, $[\alpha]_D^{21}$ +8.4 (*c*, 1.0 in EtOH) in quantitative yield.



Scheme 3. Formation of cyclohexane derivatives. (i) NaH, DMF; then H^+/H_2O (ii) K_2CO_3, MeOH (iii) $LiBH_4$, THF (iv) H_2, 10% Pd/C, EtOH

If the types of reaction illustrated for the sulphates derived from the heptonolactone (1) were found to be general, these procedures would provide simple and short routes to a range of complex synthetic targets; many of the intermediates reported here would allow easy access to sugar analogues which may have interesting biological properties.[13]

REFERENCES

1. Fleet, G. W. J., *Plenarias 23 Reunion Bienal de la Socieded Espanola de Quimica*, (Ed. San Feliciano, A., Grande, M., and Casado, J., Universidad de Salamanca) pp. 73-88, 1991.
2. Beacham, A. R., Bruce, I., Choi, S., Doherty, O., Fairbanks, A. J., Fleet, G. W. J., Skead, B. M., Peach, J. M., Saunders, J., Watkin, D. J., *Tetrahedron: Asymm.*, 1991, **2**, 883.
3. Fleet, G. W. J., Bruce, I., Girdhar, A., Haraldsson, M., Peach, J. M., Watkin, D. J., *Tetrahedron*, 1990, **46**, 19.
4. Burton, J. W., Son, J. C., Fairbanks, A. J., Taylor, H., Watkin, D. J., Winchester, B. G., Fleet, G. W. J., accompanying paper and references therein.
5. Lohray, B. B., *Synthesis*, **1992**, 1035.
6. Gomez, A. Z., Valverde, S., Fraser-Reid, B., *J. Chem. Soc., Chem. Commun.*, **1991**, 1207.
7. Lohray, B. B., Ahuja, J. R., *J. Chem. Soc., Chem. Commun.*, **1991**, 95; Kim, B. M., Sharpless, K. B., *Tetrahedron Lett.*, 1990, **31**, 4317;
8. Lowe, G., Salamone, S. J., *J. Chem. Soc., Chem. Commun.*, **1984**, 466; Lowe, G., Salamone, S. J., Jones, R. H., *J. Chem. Soc., Chem. Commun.*, **1983**, 266; Gao, Y., Sharpless, K. B., *J. Am. Chem. Soc.*, 1988, **110**, 7538.
9. None of the intermediate ionic sulphates have been fully characterised; spectroscopic and microanalytical data consistent with the proposed structures have been obtained for all other new compounds reported in this paper. The structures of (9) (11) and (20) were established by single crystal X-ray crystallographic analysis.
10. The relatively low yield of (5) from the triol is probably due to reaction of the C-2 hydroxyl with thionyl chloride but 5g amounts of (5) are readily available by this route.
11. The stereochemistry in (2) was determined by degradation and other chemical studies.
12. Choi, S. S., Myerscough, P. M., Fairbanks, A. J., Skead, B. M., Bichard, C. J. F., Mantell, S. J., Fleet, G. W. J., Saunders, J., Brown, D., *J. Chem. Soc., Chem. Commun.*, **1992**, 1605.
13. A SERC CASE award (to BMS) with Glaxo Group Research Limited is gratefully acknowledged.

(Received in UK 7 June 1993; accepted 23 July 1993)