Tetrahedron Letters, Vol.22, No.22, pp 2067 - 2070, 1981
Printed in Great Britain

0040-4039/81/222067-04$02.00/0

CARBOCYCLIC ANALOGS OF C-NUCLEOSIDES: A KEY INTERMEDIATE *VIA* A NOVEL AND EFFICIENT C-C RING SCISSION

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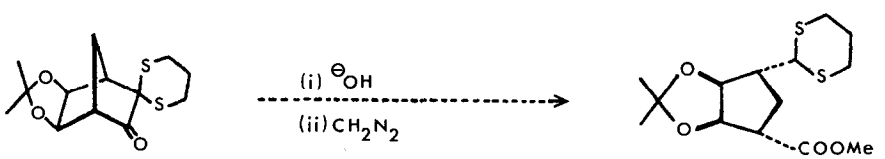
Abstract Treatment of hydroxymethylene ketone 6 with trimethylene dithiotosylate according to literature conditions,[3b] led to the novel C-C ring scission product 7 in high yield; also, the hydroxide-initiated cleavage[4] of 1 gave the β-elimination product 13 which underwent a highly stereospecific addition of diazomethane to provide 15.

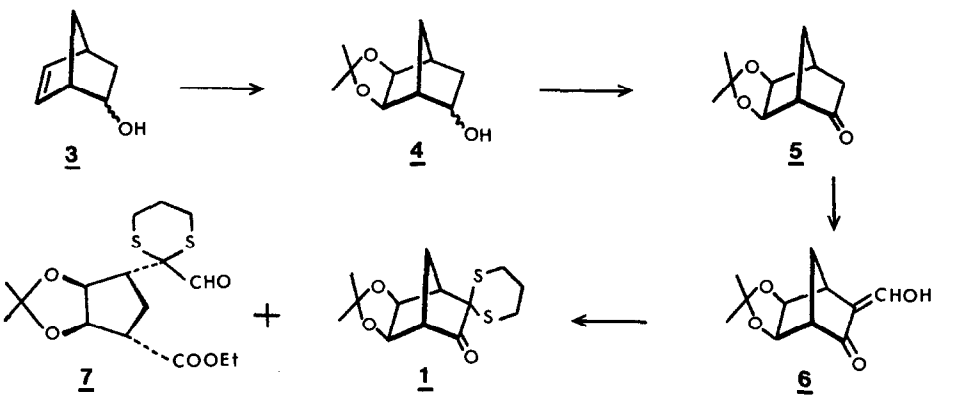
C-Glycosyl nucleosides comprise an important group of naturally-occurring substances represented by the broad spectrum antibiotics showdowmycin, pyrazomycin, formycins, and oxazinomycin (or minimicin).[1] Previously, we reported on a convenient route to carbocyclic analogs of conventional N-glycosyl nucleosides.[2] We here describe our progress towards a general route to carbocyclic C-nucleosides.

Of the several bicyclo[2.2.1]heptane systems which we considered as precursors, the α-diketone monothioketal 1 appeared to be the most appropriate. In addition to its possible availability from 3 by well-known procedures,[3] we envisioned that the hydroxide-initiated cleavage[4] of 1, followed by methylation of the resulting acid, should lead to 2. It seemed feasible that further modification of the dithian moiety[5] in 2 would allow synthesis of all the carbocyclic analogs of the above C-nucleoside antibiotics.

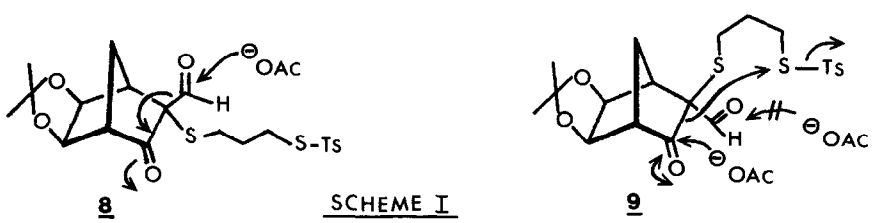


1 2

Oxidation of bicyclic alcohol 3 with a catalytic amount of OsO_4 and 30% H_2O_2 (*ca.* 3 equiv.) in acetone-ether-*t*-butanol,[6] followed by treatment with acetone/$MgSO_4$, afforded the *exo*-acetonide 4 which, upon further oxidation with Collins' reagent, provided ketone 5 (m.p. 74-76 °C; yield 80%). Hydroxymethylene derivative 6 was obtained in virtually quantitative yield by subsequent formylation with NaH/HCOOEt in benzene at room temperature (*ca.* 15 h.). When 6 was subjected to treatment with trimethylene dithiotosylate[7] and potassium acetate in refluxing ethanol (*ca.* 15 h.),[3b] the major product (*ca.* 80% yield)[8] was the interesting ring-scission product 7 rather than the anticipated α-diketone monothioketal 1 (m.p. 145-147 °C)[9] which was obtained in only 5 - 7% yield; separation of these compounds was readily effected by chromatography.

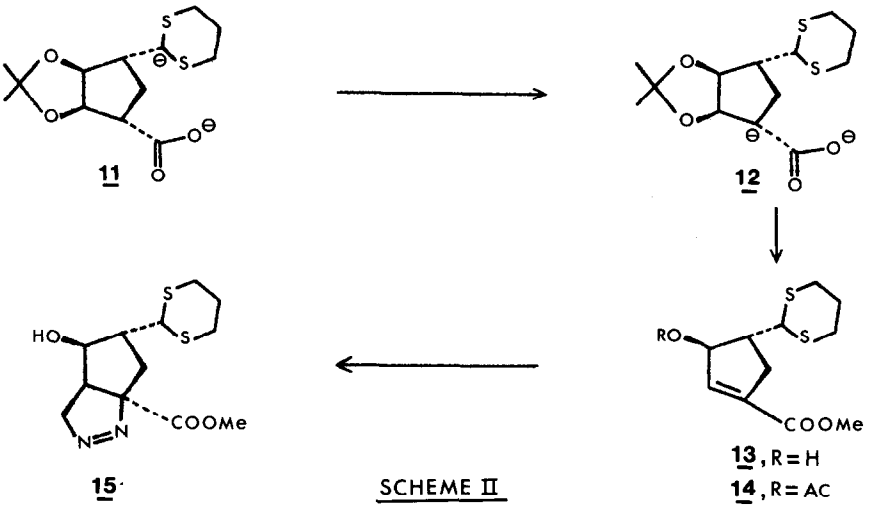


The preferential formation of 7 over 1 (Scheme I) merits comment. Intermediates 8 and 9 may be envisaged as being involved in this two-step displacement of *p*-toluenesulfinic acid (TS). Formation of 1 would be favored through intermediate 8 in which the *exo*-configuration of the formyl group would allow for easy access to attack by acetate anion as illustrated by the arrows. Although we have not isolated these postulated intermediates, it appears that the major one must be 9 wherein approach of the acetate anion to the *endo*-formyl group is so restricted that the unprecedented ring-scission product 7 is formed preferentially (*via* a mixed anhydride) by attack on the less electrophilic keto group.



SCHEME I

As may be seen from Scheme II, attempted cleavage of 1[10] with KOH/*t*-BuOH[4] followed by methylation did not lead to 2 as planned, but rather furnished the β-elimination product 13 (yield 40%).[11] Treatment of 7 under the same conditions also produced 13. Of particular interest is the fact that the conjugated addition of diazomethane to 13 occurred *syn* to the hydroxy group giving 15 (m.p. 103-105 °C; yield 90%) as the sole product. At the present time it is not clear if the presence of an allylic hydroxy group has any directing influence in this selective formation of 15 from 13.[12]



SCHEME II

The structure and stereochemistry of 15 were established unequivocally by single-crystal *X*-ray analysis. Crystals of 15 belong to the orthorhombic system, space group $Pna2_1$, with a = 7.813(3), b = 27.289(12), c = 6.779(3) Å, U = 1450 Å^3, Z = 4, $D_{calcd.}$ = 1.385 g cm^{-3}. One octant of intensity data to θ = 67°, recorded on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu-K_α radiation, λ = 1.5418 Å; θ-2θ scans), yielded 1237 statistically significant [$I > 2.0\sigma(I)$][13] reflections out of a total of 1307 independent intensity measurements. The structure was solved by direct methods by use of MULTAN.[14] Full-matrix least-squares adjustment of atomic positional and thermal (anisotropic C, N, O, S; isotropic H) parameters[15] converged at R = 0.039. A view of the solid-state conformation[16] is shown in the Figure. Bond lengths lie close to accepted values. Molecules of 15 are associated in the crystal by O-H...N hydrogen bonds (O...N = 2.80 Å)

In a future communication[17] we shall describe syntheses of some carbocyclic C-nucleosides utilizing 7 as a key intermediate. We shall also report on scope and extension of the C-C ring scission 6 → 7 with other anion stabilizing groups.[17,18]

ACKNOWLEDGEMENTS We thank Professor D. H. R. Barton and Dr. A. K. Ganguly for many stimulating discussions. Thanks are also due to Mr. R. Hovotny and Mr. P. Bartner for providing PMR and mass spectra.

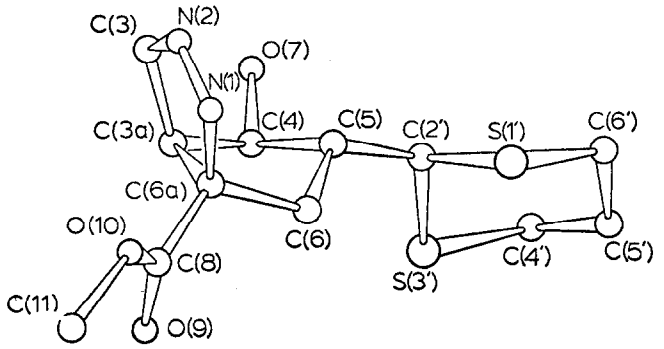


Figure. Structure and solid-state conformation of 15

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2. A. K. Saksena, Tetrahedron Letters, 133 (1980).
3. (a) J. C. A. Chivers and S. Smiles, J. Chem. Soc., 697 (1928); (b) R. B. Woodward, I. J. Patcher, and M. L. Schienbaum, J. Org. Chem., 36, 1137 (1971).
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7. For a convenient preparation of this reagent, see: P. P. Heaton, J. M. Midgley, and W. B. Whalley, J. C. S. Perkin Trans. 1, 1011 (1978).
8. PMR ($CHCl_3$): δ 1.26 (t, 3H, $C\underline{H}_3.CH_2$, J 6 Hz), 1.36 and 1.55 (s, 6H, acetonide Me groups), 1.22 (q, 2H, $CH_3.C\underline{H}_2$, J 6 Hz), 4.83 (m, 2H, C<u>H</u>.O), 9.3 (s, 1H, -C<u>H</u>O).
9. IR (nujol) 1730 cm^{-1}; oxime m.p. 165-166 °C.
10. We shall describe a more efficient preparation of 1 and its other reactions, as well as an alternative synthesis of 5 in a full paper, A. K. Ganguly, A. K. Saksena, and Y. T. Liu, manuscript in preparation.
11. PMR ($CHCl_3$): δ 3.75 (s, 3H, -COO$C\underline{H}_3$), 4.15 (d, 1H, -S-C<u>H</u>-S-), 5.0 (m, -C<u>H</u>OH), 6.65 (m, 1H, -C<u>H</u>=C<).
12. Results on conjugate addition of diazomethane to 14 are not available at the time of submission of this communication.
13. For details, see: R. W. Miller and A. T. McPhail, J. C. S. Perkin Trans. 2, 1527 (1979).
14. G. Germain, P. Main, and M. M. Woolfson, Acta Cryst., A27, 368 (1971).
15. Atomic co-ordinates for this work have been deposited with the Director of the Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.
16. Endocyclic torsion angles, ω(i-j) (σ range 0.3-0.5°) about bonds between atoms i and j are: N(1)-N(2) 0.8, N(1)-C(6a) 2.6, N(2)-C(3) -3.9, C(3)-C(3a) 5.0, C(3a)-C(6a) -4.6° in the dihydropyrazole ring; C(3a)-C(4) -25.5, C(3a)-C(6a) -1.5, C(4)-C(5) 43.0, C(5)-C(6) -43.7, C(6)-C(6a) 27.7° in the cyclopentane ring; S(1')-C(2') 66.0, S(1')-C(6') -61.6, C(2')-S(3') -64.3, S(3')-C(4') 59.4, C(4')-C(5') -63.8, C(5')-C(6') 64.8° in the dithian ring.
17. A. K. Saksena and A. K. Ganguly, manuscript in preparation.
18. All new compounds described gave spectroscopic data consistent with the assigned structures. Microanalyses were obtained only for crystalline compounds.

(Received in USA 24 February 1981)