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A GENERAL STEREOCONTROLLED ROUTE TO CARBOCYCLIC C-NUCLEOSIDES: (±) CARBA-SHOWDOWMYCIN

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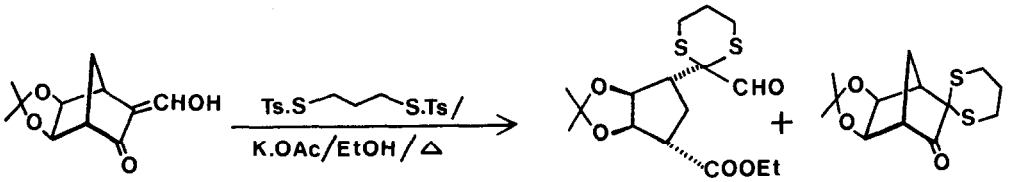
Abstract: Novel dithiotosylate-mediated C-C ring scission reactions 1→2 and 24→5 conveniently made available synthons towards a host of carbocyclic analogs of C-nucleosides. Unlike the past work,[4] no chemoselectivity problems arose in generation of 15.

The broad spectrum C-nucleoside antibiotics produced by several Streptomyces species continue to be of great synthetic interest.[1] Suitably protected α-ketoesters have been featured as key intermediates in the first elegant syntheses of showdowmycin,[2a-c] pyrazomycin[3] and their important relatives. The same strategy was effective in a previous route to the carbocyclic analogs 17 and 20.[4] However, lack of chemoselectivity in generation of an unstable α-ketoester of the type 15 affected the overall efficiency of this earlier route.

Our original plans were to transform the α-diketone monothioketal 3 to the 2-carbomethoxy 1,3-dithian 10 from which the α-ketoester 15 would be derived by oxidative hydrolysis.[6a,b] Availability of 2 from 1 in high yield,[5] offered a more attractive alternative since 2 contained the entire carbon framework that we sought in 10.



1 2 (~80%) 3 (~6%)

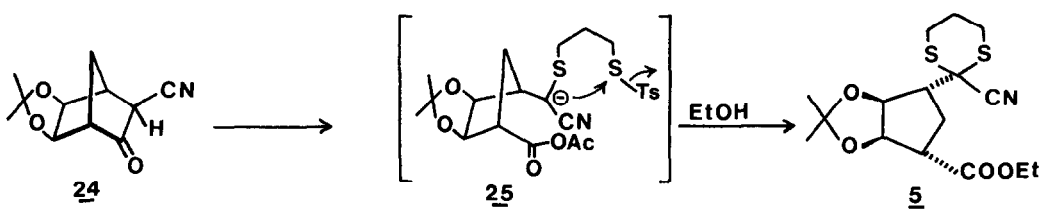
Direct oxidation of the formyl group in 2 appeared impractical due to the dithian moiety. Thus, treatment of 2 with $NH_2OH.HCl$ in pyridine (ca. 2 hrs.) followed by addition of mesyl chloride[7] gave (via 4), the nitrile 5, m.p. 108-110° in 87% yield.[8] Reduction of the carboethoxy group in 5 with $Ca(BH_4)_2$ generated in situ ($NaBH_4/CaCl_2$/THF, R.T.)[9] provided the alcohol 6, m.p. 81-83° in excellent yield (over 90%).

A minor more polar component often present in 6 was assigned the tautomeric imino-lactone[10] structure 13 (ν_{max} 1680 cm^{-1}); also 2D t.l.c. of 6 / 13 on silica gel showed 13 reverting to 6. This suggested that hydrolysis of the hindered and tertiary nitrile function should be relatively facile. Indeed, refluxing 6 with aqueous ethanolic NaOH (ca. 24 hrs.) afforded after work-up the acid 9, m.p. 189-190° in over 90% yield.[11] Methylation of crude 9 with diazomethane finally gave the desired methyl ester 10, m.p. 58-60° in overall 88% yield from 6. A shorter reflux period (ca. 12 hrs.) followed by CH_2N_2 treatment produced the amide 11 (20%) in addition to 10 (60%). Methyl ester 10 gave the THP ether 12 in virtually quantitative yield.

Oxidative hydrolysis of the dithioketal in 12 following literature conditions (NBS/$AgNO_3$/collidine/aq. 80% MeCN; R.T., pH 7)[6a] gave the desired α-ketoester 15 in poor yield (ca. 20%). When collidine was replaced with $CaCO_3$[12] (NBS/$CaCO_3$/95% aq. Me_2CO; 0°, pH 5-6, 10 min.), we obtained virtually homogenous 15 (t.l.c., PMR)[13] in quantitative yield. Wittig reaction of freshly prepared 15 with $Ph_3P{=}CH.CO.NH_2$[2b] gave the gummy maleimide 16 in 65% yield.[14] Deprotection of 16 with 4% aqueous trifluoroacetic acid then provided 17, m.p. 165-167°, identical in its spectral characteristics with published values for (±) carba-showdowmycin.[4] Acetylation with acetic-phosphoric anhydride gave the triacetate 18, m.p. 75-76°.

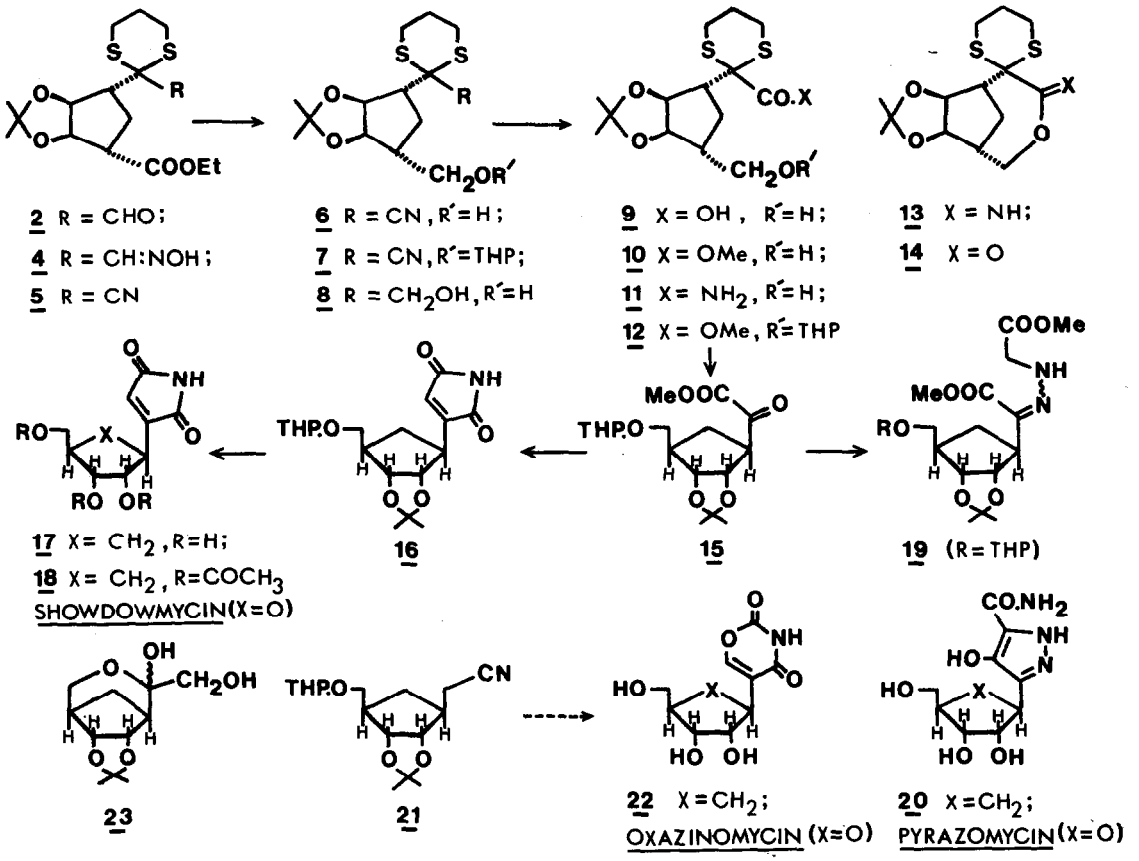
Treatment of 15 with ethyl hydrazinoacetate[3] gave the hydrazone 19 (E/Z; ~50:50) in 60% yield. Since an intermediate such as 19 (R=TBDMS) has been converted to (±) carba-pyrazomycin[4] 20, by a standard three-step sequence,[3] this may be considered as a synthesis of the latter in a formal sense.

The above sequence could be further refined as follows. Reaction of 1 with $CF_3CO.NH.OCOCF_3$[15] gave the β-ketonitrile 24, m.p. 111-113° (exclusively exo-CN), in over 80% yield.[16] When 24 was subjected to treatment with trimethylene di-p-toluenethiosulfonate



under exactly the same conditions as for 1,[5] the crystalline nitrile-ester 5 was the sole product isolated (75% yield). This obviated the need to separate 2 from 3 when only 5 was required.[17]

Desulfurization of 7 with Ra-Ni in ethanol produced 21 in 60% yield. We hope to utilize 21 for possible syntheses of (±) carbocyclic analogs of oxazinomycin[18] and 9-deazaadenosine.[19] In another set of transformations, $LiAlH_4$ reduction of 2 gave 8, m.p. 111-113° (90% yield), which upon oxidative hydrolysis with $HgCl_2/CaCO_3$[6a] afforded 23 in 75% yield. We shall report on the utility of these intermediates in a detailed communication.[20]



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References and Notes:

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8. PMR ($CDCl_3$): 1.28 (3H, t, J = 7Hz, $CH_2.CH_3$), 1.34 and 1.52 (6H, s, acetonide Me's), 4.22 (2H, q, J = 7Hz, $CH_2.CH_3$), 4.84 (2H, m, CH.O), 1.5-3.6 (10H, m); IR (nujol): 1730, 2225 cm^{-1}.
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11. In principle, oxidative hydrolysis of dithioketal in 14 should lead to a α-ketolactone of the type described earlier by Noyori et. al.[2c] We have not pursued this alternative approach in the present context.
12. We thank Dr. V. Girijavallabhan for this invaluable suggestion.
13. PMR ($CDCl_3$): 1.26 and 1.5 (6H, s, acetonide Me's), 2.5 (1H, m, CH.CO), 3.2-3.85 (4H, m, CH_2-O), 3.85 (3H, s, COOMe), 4.5 (2H, m, CH-O), 4.95 (1H, m, CH-O); IR (neat): 1750 cm^{-1}.
14. PMR ($CDCl_3$): 1.33 and 1.55 (6H, s, acetonide Me's), 1.65-3.3 (10H, m), 3.7 (4H, m, CH_2.O), 4.65 (3H, m, CH_2.O), 6.45 (1H, d, J = 1.5Hz, CH=C-).
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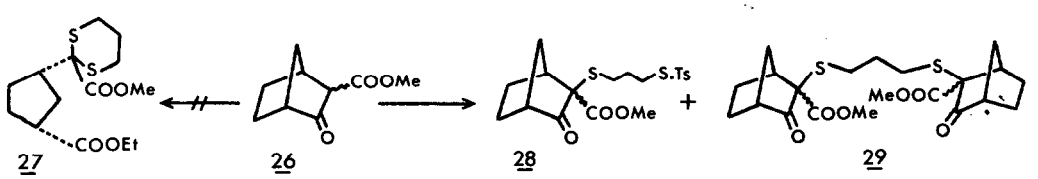
16. PMR ($CDCl_3$): 1.35 and 1.5 (6H, s, acetonide Me's), 1.7 and 2.3 (2H, bd, J = 12Hz, $H_{7's}$), 2.95 (1H, bs, H_1), 3.1 (1H, bs, H_4); 3.1 (1H, s, H_{2n}), 4.4 and 4.75 (2H, bd, CH-O); IR (nujol): 1770, 2250^{-1}.
17. In contrast, the β-ketoester 26 under the same conditions gave only 28 and 29. We attribute this failure to obtain 27 due to lack of relative anion stabilization of the primary ring scission product (e.g. 25). We thank Dr. Y.T. Liu for a generous gift of 26.



27 26 28 29

18. See e.g. the synthesis of oxazinomycin: S. DeBernardo and M. Weigele, J. Org. Chem., 42, 109 (1977).
19. M-I. Lim and R.S. Klein, Tetrahedron Letters, 25, (1981).
20. All new compounds described gave consistent spectroscopic data. Elemental analysis were obtained for crystalline compounds only. Yields refer to isolated products.

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