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A CONVENIENT ROUTE TO CARBOCYCLIC ANALOGS OF NUCLEOSIDES: (±) ARISTEROMYCIN**

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Stereocontrolled elaboration of cyclopentadiene-azomethine adducts 1[6] and 2[7] led to a short total synthesis of (±) aristeromycin. In the course of this work a novel zinc reduction (6/7→9) was observed. Also, ozonolysis of the gem-dihalo olefin 10 in methanol directly gave the methyl ester 12.

Since the first rational synthesis of the (±) carbocyclic analog of adenosine[1] and subsequent isolation of its (-) enantiomer the antifungal antibiotic aristeromycin[2a], the interest in this class of compounds has grown rapidly. The absolute configuration of aristeromycin[2b] bears a close relationship to that of the naturally occurring adenosine.

Early routes to carbocyclic nucleosides have been too lengthy[1,3] to allow rapid analog preparation. More recently however, Daluge and Vince in their continuing elegant studies on carbocyclic aminonucleosides[4] described an efficient route utilizing the known 2-azabicyclo [2.2.1] hept-5-ene-3-one[5]. They also reported a synthesis of carbocyclic arabinosyladenine with promising antiviral and antitumor activity[4].

The above work prompts us to submit our own general route to carbocyclic nucleosides exemplified in a total synthesis of (±) aristeromycin. To us the cycloadducts 1[6] and 2[7], available in excellent yields, offered many attractive opportunities for stereospecific reactions some of which we now describe.

Catalytic osmylation of 1 (endo:exo/2:1)[6] in a one-pot sequence[8] gave the acetonides 6 and 7 in over 60% yield. The assigned exo-configuration of the cis-diol 4 follows from the rule of exo-addition in related systems[1,9]. When the 6/7 mixture was refluxed with activated zinc powder in methanol for 30 minutes, interestingly the halogen free olefin 9[10] was obtained in 57% yield by chromatography. Isomers 6 (δ4.05, s, H_{3n}) and 7 (δ4.7, d, $J_{3x,4}$, 3.8 Hz, H_{3x}) when treated separately in the same manner gave an identical result.

Ozonolysis of 9 in methanol at -70° followed by reductive work-up with $NaBH_4$ in THF gave the crude 13 (not isolated) which was hydrolysed with methanolic sodium hydroxide to provide

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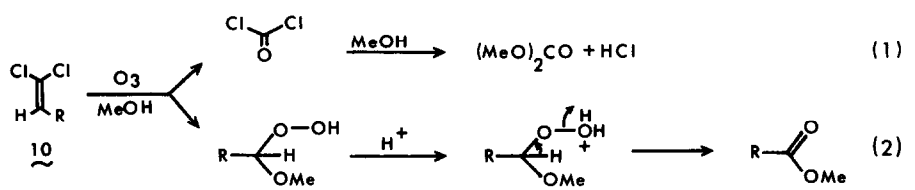
essentially pure amine 15[11]. It was further purified as its diacetate 16. By a standard three step sequence[12] the amine 15 was converted to 2',3'-isopropylidine (±) aristeromycin, m.p. 222-23° (methanol), (lit.[1], m.p. 216°), the acid hydrolysis (dil. H_2SO_4) of which gave (±) aristeromycin, m.p. 244-45° dec. (methanol), (lit. , m.p. 241-43° dec.), identical in its spectral properties and TLC behaviour to the natural antibiotic[13,14,15].

In an alternative sequence, the crystalline adduct 2[7] gave the exo-diol 5 (80% yield), m.p. 214-15°. It was converted to the acetonide 8, m.p. 176-77° in virtually quantitative yield. In practice the acetonide 8 was obtained directly from 2 as in the previous sequence. Treatment of 8 with activated zinc in methanol gave in this case the expected gem-dihalo olefin 10, m.p. 95-97° in over 90% yield[16].

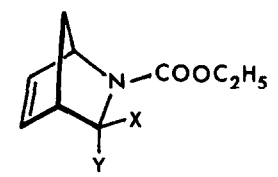
At the present time we do not have a satisfactory explanation for the anomalous reduction 6/7→9 under extremely mild conditions. The available experimental evidence rules out neither a direct reduction of the initially formed gem-dihalo olefin 9 (X=Cl), nor a possible recyclization and reduction of the same in two steps. The fact that 8 gave only the expected gem-dihalo olefin 10, may favor the latter mechanism since 8 would give a relatively more stable tosylamide anion which would therefore be more difficult to recyclize and reduce[17].

When 10 was ozonized in methanol at -70°, the crude product lost the acetonide protecting group. Re-acetonation followed by chromatography gave in 40% yield the methyl ester 12, m.p. 134-35° [18]. An analogous reaction (viz. formation of methyl ester) has been observed in the ozonolysis of vinyl monochlorides in methanol[19]. In the present example we propose in-situ generation of phosgene and its methanolysis as a possible source of acid responsible for both, removal of acetonide and collapse of the methyl hydroperoxide (equations 1 and 2). This reaction may apply to other gem-dihalo olefins as well.

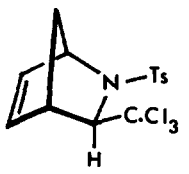


The gem-dihalo olefin 10 could be cleaved more efficiently by $RuO_4/NaIO_4$ reagent[20] in acetone: water (95:5). The resulting acid was treated with diazomethane to provide the methyl ester 12 in 92% yield from 10. $Ca(BH_4)_2$ reduction[21] ($NaBH_4/CaCl_2$/THF, R.T.) then gave the alcohol 14, m.p. 100-102° in 95% yield. Due to improved yields and high crystallinity of all compounds, we find this latter sequence more practical[23].

We shall report on the utility of the above intermediates including the related exo-epoxide 3[9] in a detailed communication.



1 a: X = C.Cl$_3$; Y = H;
b: X = H; Y = C.Cl$_3$



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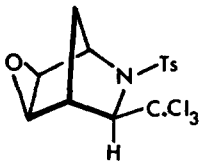
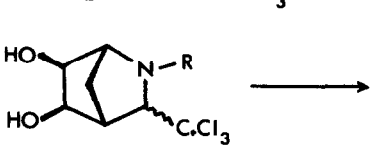
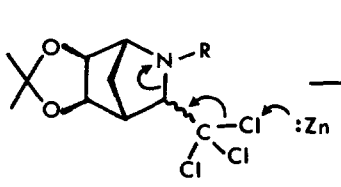


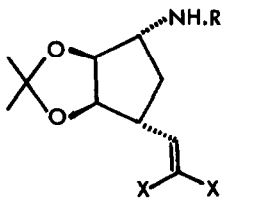
3



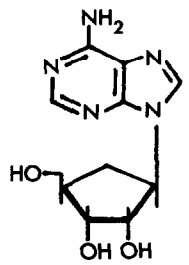
4 R = COOC$_2$H$_5$; C.Cl$_3$ = endo/exo
5 R = Ts; C.Cl$_3$ = exo



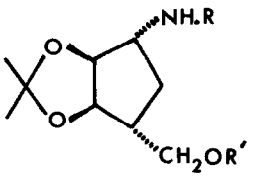
6 R = COOC$_2$H$_5$; C.Cl$_3$ = exo
7 R = COOC$_2$H$_5$; C.Cl$_3$ = endo
8 R = Ts; C.Cl$_3$ = exo



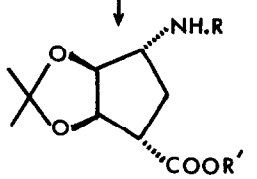
9 R = COOC$_2$H$_5$; X = H
10 R = Ts; X = Cl



(±) ARISTEROMYCIN



13 R = COOC$_2$H$_5$; R′ = H
14 R = Ts; R′ = H
15 R = R′ = H
16 R = R′ = CO.CH$_3$



11 R = Ts; R′ = H
12 R = Ts; R′ = CH$_3$

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10. IR (neat) 3300 cm^{-1}. PMR ($CDCl_3$) δ 1.27 (t,3H, J 7Hz, $CH_2.CH_3$), 1.3 and 1.5 (s, 6H, acetonide CH_3), 4.14 (q, 2H, J 7Hz, $CH_2.CH_3$), 4.5 (m, 2H, C<u>H</u>.O), 4.8 (d, broad, N<u>H</u>.COOEt), 5.0 (m, 1H, J_{cis} 10 Hz, $H\diagup C{=}C\diagdown^{H}_{\underline{H}}$), 5.24 (m, 1H, J_{trans} 16 Hz, $H\diagup C{=}C\diagdown^{H}_{\underline{H}}$), 5.65-6.2 (8 lines, J_{vic} 6 Hz, CH.C<u>H</u>=).
11. PMR ($CDCl_3$) δ 1.3 and 1.5 (s, 6H, acetonide CH_3), 2.45 (m, 3H, C<u>H</u>.CH_2OH, CH.C<u>H</u>$_2$CH), 3.35-3.75 (m, 6H, O<u>H</u>, N<u>H</u>$_2$, C<u>H</u>.OH), 4.25 (d, broad, 1H, CH_2.O), 4.75 (d, broad, 1H, C<u>H</u>.O).
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13. PMR (DMSO-d_6) δ1.5-2.5 (m, 3H, H_4, and 2$H_{6'}$), 3.5 (m, 2H, CH_2.OH), 3.85 (m, 1H, H_2, or $H_{3'}$), 4.3 (m, 1H, H_2, or $H_{3'}$), 4.4-4.9 (m, 4H, $H_{1'}$, 3O<u>H</u>), 7.14 (s, broad, N<u>H</u>$_2$), 8.1 and 8.18 (s, 2H, purine ring 2H's).
14. We thank Dr. Ueyanagi of Takeda Industries for kindly supplying an authentic sample of natural aristeromycin for comparison.
15. The m.p.'s and PMR's reported by Holy[3] for (±) aristeromycin (255-56°) and its 2',3'-acetonide (over 260°) do not correspond with ours and Shealy and Clayton's[1]. Numerous other inconsistencies were also noted in the experimental data. We hope to discuss these in a future communication.
16. PMR ($CDCl_3$) δ 1.22 and 1.45 (s, 6H, acetonide CH_3), 2.46 (s, 3H, aromatic CH_3) 3.4-3.8 (m, 1H, C<u>H</u>.NH.Ts), 4.4 (m, 2H,C<u>H</u>.O), 5.2 (d, broad, 1H, N<u>H</u>.Ts), 5.85 (d, 1H, J 9Hz, C<u>H</u>=C.Cl_2), 7.35 (d, 2H, aromatic), 7.85 (d, 2H, aromatic).
17. To our knowledge C-N ring scission reactions by such Boord type elimination have not been reported on these 2-azabicyclo [2.2.1] systems[22].
18. PMR ($CDCl_3$) δ 1.25 and 1.43 (s, 6H, acetonide CH_3), 2.45 (s, 3H, aromatic CH_3), 3.0 (m, broad, 1H, C<u>H</u>.COOMe), 3.75 (s, 3H, COOC<u>H</u>$_3$), 3.5-3.9 (m, 1H, C<u>H</u>.NH.Ts), 4.55 (d, 1H, C<u>H</u>-O-), 4.8 (d, 1H, C<u>H</u>-O-), 5.75 (d, broad, 1H, CH-N<u>H</u>.Ts).
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22. For a base-promoted elimination reaction of 2 see: J.J. Eisch and A.F. Noels, J.O.C., 41, 1461, (1976), and references cited therein.
23. All new compounds described gave spectroscopic data consistent with the assigned structures. Elemental analyses were obtained only for crystalline compounds.

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