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SYNTHESES OF (±)- AND (−)-PENTENOMYCIN I

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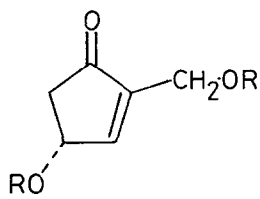
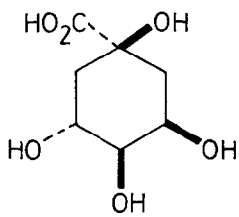
Summary: Syntheses of the cyclopentanoid antibiotic, (−)-pentenomycin I, from D-(−)-quinic acid are described; (±)-pentenomycin I is also prepared from 3-hydroxymethyl-2-methylfuran.

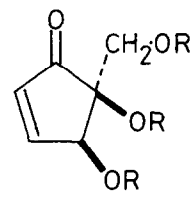
Recently, we described[1] syntheses of (±)-cyclopentenone (1a) from 3-hydroxymethyl-2-methylfuran and of (+)-cyclopentenone (1a) from D-quinic acid (2). We now illustrate the utility of compounds of type (1), as precursors of bioactive cyclopentanoid natural products, by describing their conversions into pentenomycin I (3a), an antibacterial antibiotic produced by Streptomyces eurythermus[2] and S.lavenduligriseus.[3]



(1)
a; R = H
b; R = $SiMe_2Bu^t$
c; R = CH_2Ph



(2)

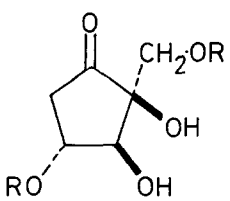


(3)
a; R = H
b; R = COMe

Treatment of (±)-diol (1a) with t-butyldimethylsilyl chloride and imidazole in N,N-dimethylformamide gave (±)-disilyl ether (1b) (40%), which was converted into (±)-diol (4a) (60%), m.p. 56-58°C by osmium(VIII) oxide in pyridine (employing a reductive work-up with $Na_2S_2O_5$). When left in a 1:1 mixture of 3M-hydrochloric acid and tetrahydrofuran, compound (4a) underwent hydrolysis of its silyl ether groups and elimination of water to give (±)-pentenomycin (3a) (54%) The spectroscopic properties of racemic pentenomycin (3a) and of derived triacetate (3b), m.p. 110-112°C, were identical to those published for the optically active compounds.[3,4]

Using a similar reaction sequence, diol (1a), $[\alpha]_D$ -50° (EtOH), was converted, via disilyl ether (1b), $[\alpha]_D$ +29° (EtOH), and diol (4a), m.p. 65-67°C, $[\alpha]_D$ -38° (EtOH), into pentenomycin (3a), $[\alpha]_D$ -11° (EtOH) [lit. -32° (EtOH)[2] and -27.4° (EtOH)[3]]. The foregoing result suggested that our synthetic sample of pentenomycin was either impure or partially racemic.

A crystalline derivative of natural pentenomycin I, which has been independently prepared by three groups, is triacetate (3b). However, whereas the melting points and spectroscopic properties of the samples are comparable, the quoted optical rotations are disparate {$[\alpha]_D$ -24° (EtOH),[4] -6.8° (EtOH),[3] and -8° (MeOH)[5]}. Our synthetic sample of pentenomycin triacetate, m.p. 112-113°C (lit.[4] 111-112°C), showed $[\alpha]_D$ -10° (EtOH).

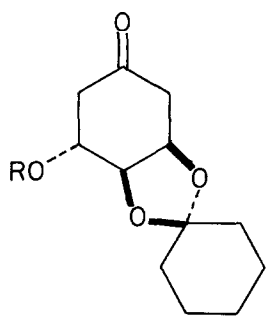


(4)

a; R = $SiMe_2Bu^t$

b; R = CH_2Ph

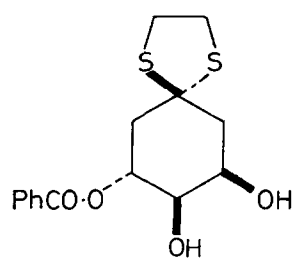
c; R = H



(5)

a; R = H

b; R = COPh

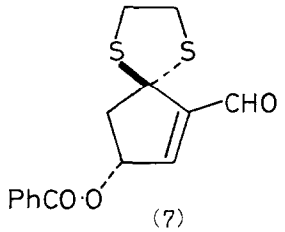


(6)

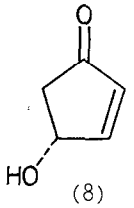
In view of the ambiguity concerning the "true" optical rotation of pentenomycin triacetate and the possibility that racemisation might have occurred during a number of steps in our reaction sequence, an alternative route to pentenomycin I was investigated.

D-(−)-Quinic acid (2) was converted into cyclohexanone (5a), m.p. 110-113°C (lit. 98°C), $[\alpha]_D$ +120° (EtOH) [lit. +103° ($CHCl_3$)], in 55% overall yield by the literature procedure.[6] Treatment of derived benzoate (5b) (95%), m.p. 131-133°C, $[\alpha]_D$ +80° (EtOH), with ethane-1,2-dithiol and boron trifluoride etherate in dichloromethane gave diol (6)[7] (90%), m.p. 115-117°C, $[\alpha]_D$ +17° (EtOAc), which was converted into cyclopentene-carbaldehyde (7)[8] (72%), m.p. 93-94°C, $[\alpha]_D$ +280° ($CHCl_3$), by sequential reactions with lead(IV) acetate in dichloromethane and pyrrolidinium acetate in benzene. The optical purity of compound (7) was established by its transformation [deformylation with $(Ph_3P)_3RhCl$ in acetonitrile,[9] debenzoylation by methanolic NaOMe, and dethioacetalisation with copper(II) oxide-copper(II) chloride in aqueous acetone[10]] into cyclopentenone (8), $[\alpha]_D$ +84° (MeOH) [lit.[11] +82° (MeOH)].

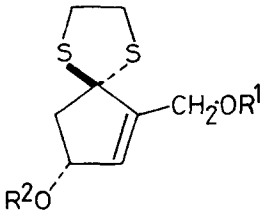
Lithium aluminium hydride in tetrahydrofuran effected the conversion of compound (7) into diol (9a) (90%), m.p. 106-108°C, $[\alpha]_D$ +100° (EtOH). That no racemisation had occurred in this reaction was inferred by the observation that alcohol (9b), $[\alpha]_D$ +179° ($CHCl_3$), prepared from aldehyde (7) by reduction with sodium cyanoborohydride in acetic acid, gave diol (9a), $[\alpha]_D$ +101° (EtOH), on treatment with methanolic sodium methoxide. The optical purity of alcohol (9b) was confirmed by its transformation into aldehyde (7), $[\alpha]_D$ +274° ($CHCl_3$), with manganese dioxide in dichloromethane.



(7)



(8)



(9)

a; $R^1 = R^2 = H$

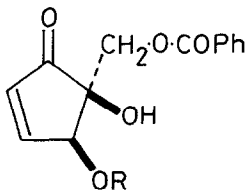
b; $R^1 = H$, $R^2 = COPh$

c; $R^1 = R^2 = CH_2Ph$

Dibenzyl ether (9c), $[\alpha]_D$ +56° (EtOH), prepared in 77% yield from diol (9b) by treatment with benzyl bromide-sodium hydride in tetrahydrofuran, was converted into cyclopentenone (1c) (86%), $[\alpha]_D$ +23° (EtOH), by the action of copper(II) oxide-copper(II) chloride in aqueous acetone. Hydroxylation of cyclopentenone (1c) (OsO_4 in pyridine followed by $Na_2S_2O_5$ work-up) afforded diol (4b) (77%), $[\alpha]_D$ -48° (EtOH), as a single diastereoisomer on the basis of 360 MHz ^{1}H- and 20 MHz ^{13}C-n.m.r. spectroscopy. Treatment of ether (4b) with hydrogen-palladium gave tetrol (4c) (72%), $[\alpha]_D$ -56° (EtOH), which, with dilute hydrochloric acid, was transformed into pentenomycin (3a) (84%), $[\alpha]_D$ -17° (EtOH), and thence into pentenomycin triacetate (3b), m.p. 112-114°C, $[\alpha]_D$ -8° (EtOH) and -6° (MeOH).

That ether (4b) was enantiomerically pure was rigorously established by chemical means, using Mosher's procedure.[12] Thus, cyclopentenone (10a), $[\alpha]_D$ +7° (EtOH), obtained from ether (4b) by treatment with dilute hydrochloric acid, reacted with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride to give ester (10b), $[\alpha]_D$ +43° (EtOH); 90 MHz ^{1}H- and 85 MHz ^{19}F-n.m.r. spectroscopy convincingly demonstrated the enantiomeric homogeneity of the sample.[13]

Finally, since pentenomycin (3a) was shown to be optically stable under the acidic conditions required for its formation, it may be inferred that the synthesis via cyclopentenecarbaldehyde (7) is subject to high enantiocontrol.



(10)

a; R = H

b; R = CO—C(Ph)(OMe)—CF3

Syntheses of (±)- and (−)- pentenomycin (3a), from cyclopent-2-en-1-one[14] and D-glucose,[15] respectively, have been reported.

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References and Footnotes

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