# Approaches to the Synthesis of Bicyclomycin

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*Summary* 3-Acetoxy-1,4-dibenzyl-3-(3-methoxy-1-methyl-enepropyl)piperazine-2,5-dione (**4**) has been synthesized both *via* cyclization of *N*-benzyl-*N*-(*N*-benzylcarbamoyl-methyl)-5-methoxy-3-methylene-2-oxopentanamide (**10**)

and *via* cleavage of the epoxide ring of 4,7-dibenzyl-2-(2-methoxyethyl)-2-methyl-1-oxa-4,7-diazaspiro[2.5]-octane-5,8-dione (**12**); the hydroxy-compound (**2**) corresponding to (**4**) has been synthesized *via* cyclization of the (tetrahydropyran-2-yloxy)ethyl compound (**15**) corresponding to (**10**).

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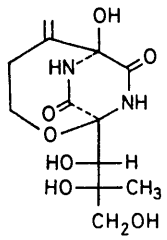
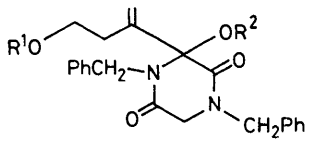
BICYCLOMYCIN (**1**), an antibiotic with a novel type of structure[1,2] and unusual antibacterial activity,[3] is produced by *Streptomyces sapporensis* and *S. aizunensis*.[4] Several recent synthetic approaches have not led to bicyclomycin itself,[2,5–7] but useful information has been gained for its eventual synthesis. We now report on our own approach, which also has not reached fruition, but which may contribute to the eventual solution of the problem.



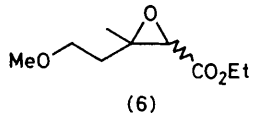
(1)



(2) $R^1$ = H, $R^2$ = Ac
(3) $R^1$ = Me, $R^2$ = H
(4) $R^1$ = Me, $R^2$ = Ac
(5) $R^1$ = THP, $R^2$ = Ac

THP = tetrahydropyran-2-yl

Our initial goal was the 3-hydroxypiperazine-2,5-dione derivative (**2**), which we hoped could be cyclized to the bridged bicyclic system of (**1**).† Previous synthetic approaches to (**1**) have involved either the manipulation of a pre-formed piperazine-2,5-dione ring system[2,6,7] or the construction of this system later in the synthesis.[5] The present approach has utilized both strategies.



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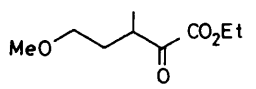

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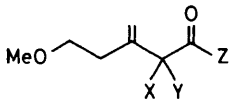
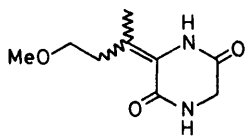


(8) X = OH, Y = H, Z = OEt
(9) X = OAc, Y = H,
Z = $N(CH_2Ph)CH_2CONHCH_2Ph$
(10) X,Y = O,
Z = $N(CH_2Ph)CH_2CONHCH_2Ph$

Treatment of 4-methoxybutan-2-one with ethyl chloroacetate and sodium ethoxide gave the glycidate (**6**)‡ as a mixture of *cis*- and *trans*-isomers, b.p. 93—98 °C (0·35 mmHg), which was converted into the butenoate (**8**), b.p. 55—65 °C (0·005 mmHg), by treatment with acetic anhydride and sulphuric acid[8] followed by ethanolysis of the acetate group with ethanolic hydrogen chloride and removal of the accompanying oxopentanoate (**7**) with Girard reagent T. Hydrolysis (aq. 25% NaOH) of the ester to the corresponding carboxylic acid, acetylation (MeCOCl) of the hydroxy-group, conversion (ClCOCOCl) into the acid chloride, and treatment with *NN'*-dibenzylglycinamide gave the amide (**9**). Hydrolysis (ethanolic KOH) of the acetate and oxidation of the resulting allylic alcohol group with activated $MnO_2$ gave the oxo-amide (**10**). Cyclization of (**10**) with magnesium isopropylcyclohexylamide (MICA)[9] gave the piperazine-2,5-dione (**3**) in 11% overall yield from (**6**).

This piperazinedione was also obtained by the following route. Treatment of the glycidate (**6**) with toluene-*p*-sulphonic acid in boiling benzene gave a mixture of the corresponding 2-hydroxy $\Delta^3$-unsaturated esters§ which was hydrogenated (Pt) to give a 2 : 1 mixture of ethyl 2-hydroxy-5-methoxy-3-methylpentanoate and ethyl 2-hydroxy-3-methylpentanoate. This was oxidized with Jones reagent to give a mixture of the corresponding oxo-esters from which the oxopentanoate (**7**), b.p. 55—57 °C (0·015 mmHg), was separated by distillation. Reaction of (**7**) with chloroacetamide and $H_2SO_4$ in boiling benzene followed by cyclization with ethanolic $NH_3$[11] gave the *Z*- and *E*-isomers of the piperazine-2,5-dione (**11**), m.p. 157—158 and 211—212 °C,



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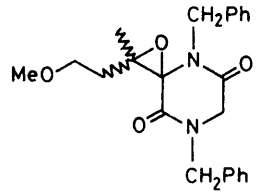


(12)

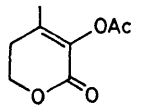
respectively. Dibenzylation (benzyl bromide, $Ag_2O$)[12] of the individual isomers of (**11**) followed by oxidation (*m*-$ClC_6H_4CO_3H$) gave the corresponding epoxides (**12**), m.p. 127—128 and 112—113 °C, respectively. Treatment of the epoxide *Z*-(**12**) with MICA[9] gave the piperazinedione (**3**) in 6% overall yield from (**6**). Attempted chromatography ($SiO_2$) of (**3**) led to partial ring opening to give a 1 : 1 mixture of (**3**) and (**10**). Acetylation ($Ac_2O$, 4-$Me_2NC_5H_4N$, $Et_3N$)[13] of (**3**) gave its acetyl derivative (**4**) which could be purified by chromatography ($SiO_2$). Interestingly, reaction of (**3**) with iodotrimethylsilane gave *E*-(**11**).

Attempted demethylation of (**4**) with iodotrimethylsilane was unsuccessful and attention was turned to demethylation of the intermediate (**9**) in the first synthetic route.

† It is noteworthy that the work of Nakatsuka *et al.*[6] suggests that the trihydroxyisobutyl side chain of (**1**) can be introduced at a late stage in the synthesis.

‡ Compounds (**2**)—(**16**) have spectroscopic data in accord with the structures assigned.

§ It has been reported[10] that treatment of ethyl 3,3-dimethyl- and 3-ethyl-3-methyl-glycidate with toluene-*p*-sulphonic acid in toluene at 80—85 °C gives the corresponding α-oxo-esters. Under our conditions we find that both (**6**) and ethyl 3,3-dimethylglycidate give the corresponding 2-hydroxy $\Delta^3$-unsaturated esters as the major products.



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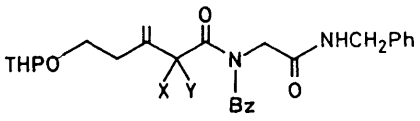
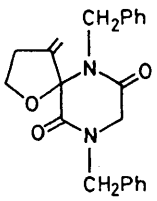


(14) X = OAc, Y = H

(15) X,Y = O



(16)

Reaction of this with iodotrimethylsilane resulted in concomitant demethylation and amide cleavage to give the dihydropyrone (**13**), but reaction with methylthiotrimethylsilane[14] led to demethylation without amide cleavage, and the resulting hydroxy-compound was treated with tetrahydropyran-2-yl t-butyl ether and hydrochloric acid[15] to give the tetrahydropyranyl derivative (**14**). This was converted into the oxo-compound (**15**) as in the preparation of (**10**). Treatment of (**15**) with MICA[9] followed by direct acetylation ($Ac_2O$) of the magnesium derivative of the cyclized product gave the piperazine-2,5-dione (**5**). This on treatment with aqueous acetic acid in tetrahydrofuran gave the desired hydroxy-compound (**2**) [overall yield from (**9**) 11%] together with the spiro-compound (**16**) in a 3 : 1 ratio.¶

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¶ *Cf.* the formation of analogous products from (**1**)[2] and in other synthetic approaches to (**1**).[2,6]

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