Tetrahedron Letters No. 41, pp 3955 - 3958.

0040-4039/78/1008-3955$02.00/0

AN APPROACH TO THE SYNTHESIS OF IONOPHORES RELATED TO A23187

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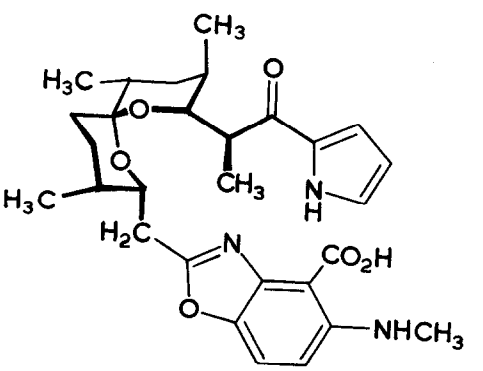
The antibiotic A23187 (1)[1] isolated from Streptomyces chartreusensis is an ionophore with a high specificity for divalent over monovalent cations. It has been widely used to study the movement of Ca^{II} and the consequences of Ca^{II} movement, both in biological[2] and non-biological[3] membrane systems. A23187 fails to show significant selectivity between Fe^{II} and Ca^{II} and its high in vivo toxicity [LD_{50} (mouse) 4.5 mg kg^{-1}] has been attributed to its ability to transport Ca^{II}.[4] A Fe^{II} specific ionophore would have potential clinical use in treating disorders arising from excess Fe^{II} in tissue, or failure to mobilise stored Fe^{II}. Analogues of A23187 may also find application as ion-selective electrodes for the measurement of concentration and movement of specific divalent cations.[3] With these aims in mind we have engaged in the synthesis of analogues of A23187. The recent communication of Evans et al[5] on their approach to A23187 prompts us to report our synthesis of the key intermediate 7 which incorporates the dioxaspiro[5.5]undecane ring with the stereochemistry of the natural ionophore 1.



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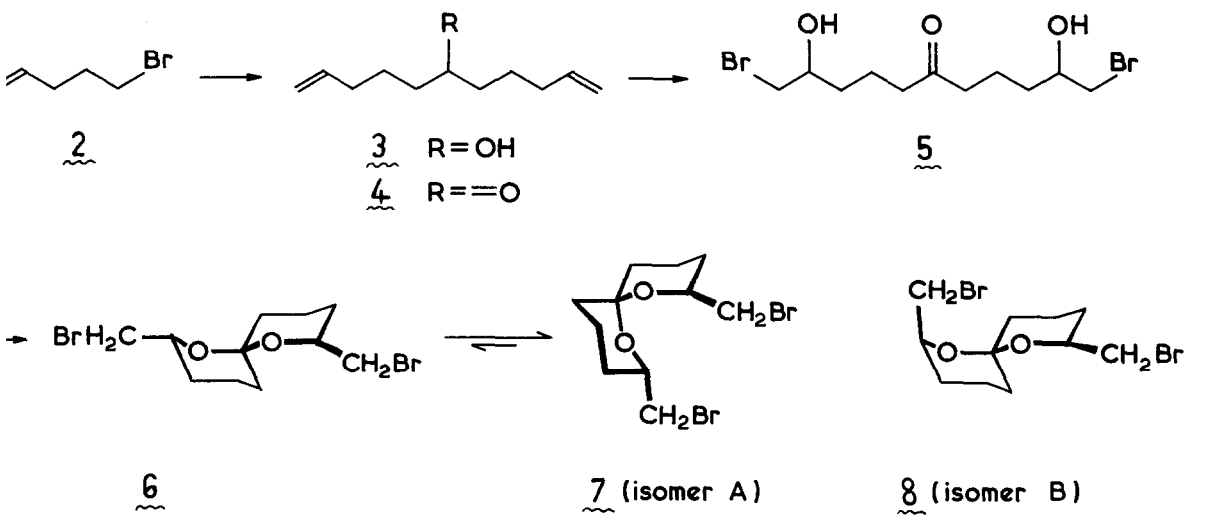
Dehydrative ring closure of a diastereoisomeric mixture of keto-diols of type 5 can theoretically give rise to three[6] stereoisomeric 2,8-disubstituted dioxaspirans of type 6, 7, and 8, where 7 has the stereochemistry of A23187. In acid medium, 6 and 7 will be in equilibrium. Examination of Dreiding molecular models shows that with the CH_2Br substituents equatorial, 7 will be free from the H-H interactions encountered in 6, and 7 would therefore be expected to be the energetically favoured diastereoisomer. This synthetic approach necessitates a mono-substitution of the symmetrical intermediate 7 since A23187 (1) is an unsymmetrically disubstituted dioxaspiran. It is therefore important to note that 7 (and 6, but not 8) has a C2-axis of symmetry because then the required mono-substitution step will lead to the same product, independent of which group is substituted. The proposed route via a linear diol of type 5 therefore seemed a rational one.

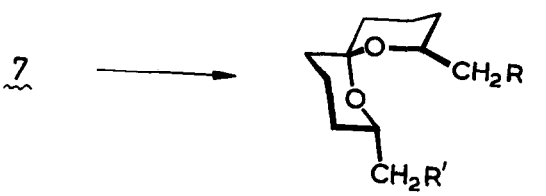
The key intermediate chosen was the dibromide 7. Treatment of an ethereal solution of the magnesium derivative of 5-bromopent-1-ene (2)[7] at 0 °C with methyl formate (0.5 equiv.) gave undeca-1,10-diene-6-ol (3)[8] (86 %, bp 67-68°/0.4 mm). Oxidation of 3 with Jones reagent in acetone (1h, 0-20 °C) yielded the ketone 4[8] (93 %, bp 94-96°/6 mm). Addition of HOBr across the olefinic bonds of 4 and subsequent dehydrative ring closure was effected by reaction of 4 with N-bromoacetamide (2.3 equiv.) in 4 % aqueous acetone (1h, 0 °C; 12 h, 20 °C), followed by addition of tosic acid (0.03 equiv., 2h, 20 °C). The isomeric mixture of 2,8-bis(bromomethyl)-1,7-dioxaspiro[5.5]undecanes (70 % yield from 4) was isolated by column chromatography [SiO_2, 5 % ethyl acetate-light petroleum (bp 40 - 60 °C)]. Hplc[9] examination showed the mixture to consist of two isomers, A and B (in order of elution), in the ratio 1·1 : 1. Isomer A could be obtained essentially pure, mp 117-120 °C, in 50 % yield



from 4 (assuming formation of an equimolar mixture of diastereoisomers of 5) by a single crystallisation from ether-light petroleum (bp 30-40 °). The analytical sample[8] formed blades, mp 124-125 °, from dichloromethane-light petroleum (bp 40-60 °). Isomer B[8] was readily obtained pure, m.p. 57 °, from ether-light petroleum (bp 30-40 °) by hplc[9] on the mother liquors left after the initial crystallisation of the chromatographed reaction mixture.

The ^{1}H-nmr spectrum [δ($CDCl_3$, 100 MHz) 3.8-4.1 (2H, m, methine H), 3.34 (4H, d, J 6Hz, CH_2Br), and 1.0-2.2 (12H, m, ring CH_2)], and the six-line proton decoupled ^{13}C-nmr spectrum [($CDCl_3$, ppm) 96.8, 69.1, 36.3, 34.8, 29.6, 18.4)] of isomer A clearly show that the molecule has a C2-axis of symmetry and is therefore either 6 or, if the above conclusions based on Dreiding models are correct, more likely the required dibromide 7. An x-ray crystallographic analysis of this isomer (following communication)[11] showed that it was indeed the required 2,8-bis(bromomethyl)-1,7-dioxaspiro[5.5]undecane (7).

In contrast to isomer A, isomer B had a complex ^{1}H-nmr spectrum [δ($CDCl_3$, 100 MHz) 4.1-4.4 (1H, m, methine H), 3.7-4.0 (1H, m, methine H), 3.50 (2H, d, J 7 Hz, CH_2Br), 3.34 (2H, d, J 6 Hz, CH_2Br), 1.0-2.4 (12 H, m, ring CH_2)] and a ten-line proton decoupled ^{13}C-nmr spectrum, consistent with structure 8. The combined yield (70 %) of the isomers A and B, and the ratio of the two isomers (1·1 : 1), confirms that isomer B must have structure 8.[10] Treatment of pure isomers A and B separately with aqueous acetone containing tosic acid (2h, 20 °) gave only pure starting material in each case.



9; R=Br, R'=CN
10; R=R'=CN

Reaction of the dibromide 7 with NaCN (1.0 equiv.) in DMF (3h, 80 °) gave, after column chromatography (SiO_2, 0-50 % ether-light petroleum (bp 30-40 °), in order of elution, the starting dibromide 7 (32 %), the mononitrile 9[8] (40 %, mp 87-88 °) and the dinitrile 10[8,12] (20 %, mp 102-103 °). The mononitrile 9 is an unsymmetrically substituted 1,7-dioxaspiran with the same stereochemistry as A23187. We are currently investigating methods for attaching suitable substituents to 9.

ACKNOWLEDGEMENTS

We would like to thank Dr. B.D. Gomperts, University College Hospital Medical School, for bringing the biological possibilities of A23187 analogues to our attention, and Mr. S. Corker for his expert work on the hplc separations. We are indebted to the Royal Society, the Science Research Council, and Syntex Corporation for financial support.

REFERENCES AND NOTES

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7. P. Gaubert, R.P. Linstead, and H.N. Rydon, J. Chem. Soc., 1971 (1937); F.B. La Forge, N. Green, and W.A. Gersdorff, J. Amer. Chem. Soc., 70, 3707 (1948); commercially available from Fluka AG.
8. The compound gave satisfactory spectral data and combustion analyses.
9. Performed on Partisil with 50 % pentane-dichloromethane as eluent.
10. The reasonable assumption being made that HOBr addition to 4 was non-stereospecific.
11. D.L. Hughes, Tetrahedron Lett., following communication.
12. The dinitrile 10 exhibited a seven-line proton decoupled ^{13}C-nmr spectrum, in accord with its C2-axis of symmetry.

(Received in UK 13 July 1978; accepted for publication 11 August 1978)