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PROSTAGLANDIN IX.[1] A SIMPLE SYNTHESIS OF OPTICALLY ACTIVE 11-DEOXYPROSTAGLANDINS

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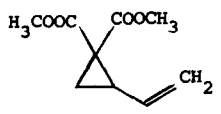
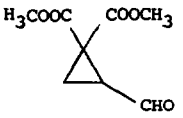
Optically active 11-deoxyprostaglandins have been obtained i) by selective hydrogenation of PGA_2 derived from the gorgonian Plexaura homomala,[2] ii) by dehydration of natural PGE followed by selective hydrogenation[2] and iii) by the use of optically active organometallic reagents.[3] These methods appeared unattractive for the large scale preparation of the title compounds.

Recently we reported a short synthesis of (±)-11-deoxyprostaglandins.[4] The key step (IV → V) in this synthesis involves a stereospecific opening of the cyclopropane ring. In the present communication, advantage has been taken of this stereospecificity for the preparation of optically active 11-deoxyprostaglandins. The process is characterized by readily available starting materials and by manipulative simplicity. As an example we give the syntheses of (-)-11-deoxy PGE_1 (VI) and (-)-15-epi-11-deoxy PGE_1 (VII) both belonging to the natural series.

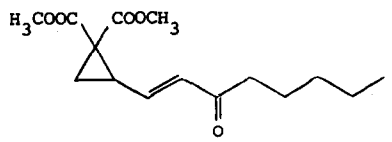
(±)-2-Vinylcyclopropane-1,1-dicarboxylic acid[5] was resolved via the monobrucine salt. The (-)-acid was esterified with diazomethane to I, $[\alpha]_D$ -54.7°,[6] which was ozonized with MeOH at -75° and the ozonide decomposed with dimethyl sulfide to give II, $[\alpha]_D$ -142.7°. II was successively transformed[7] to III, $[\alpha]_D$ -87.8° and to a mixture of epimeric alcohols, IV, $[\alpha]_D$ -60.8°. The tetrahydropyranyl ether of IV was condensed[7] with $HC(COOCH_3)_2(CH_2)_6COOCH_3$ and the protecting group removed[7] to yield the mixture of epimeric alcohols, V, $[\alpha]_D$ -8.9°. Hydrolysis[7] of V followed by chromatographic separation afforded 11-deoxy PGE_1 (VI), m. 95-97° (lit.[3] 95-96°), $[\alpha]_D$ -51.8° (lit.[3] -51.0°, $CHCl_3$) and 15-epi-11-deoxy PGE_1 (VII), $[\alpha]_D$ -52.9° both belonging to the natural series.



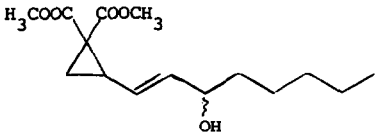
I



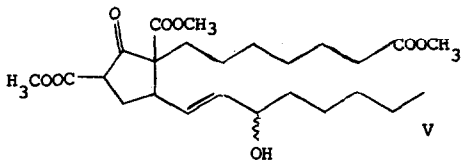
II



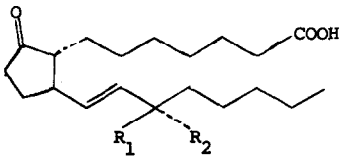
III



IV



V



VI, R_1 = H, R_2 = OH

VII, R_1 = OH, R_2 = H

The fact that the specific rotation of VI agrees with the value reported for 11-deoxy PGE_1 indicates that the opening of the cyclopropane ring of IV to form V has been completely stereospecific[8] and that the newly formed asymmetric centre at C_{12} (prostaglandin numbering) in V is optically pure. Since decarbomethoxylative hydrolysis of V to VI and VII creates a trans C_8-C_{12} junction in VI and VII, the C_8 centre in the latter two compounds is also optically pure.

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References

1) Paper VIII, N.A. Abraham, J. Chem. Soc. Comm., submitted

2) F.H. Lincoln et al, J. Org. Chem., 38, 951(1973)

3) C.J. Sih et al, Tetrahedron Letters, 2435(1972) and A.F. Kluge et al, J. Amer. Chem. Soc., 94, 9256(1972).

4) N.A. Abraham, Tetrahedron Letters, 451(1973)

5) This compound was prepared as described by R.W. Kierstead et al, J. Chem. Soc., 3610(1952) except that 1,4-dibromo-2-butene was replaced by 1,4-dichloro-2-butene.

6) S. Danishefsky and G. Rovnyak, J. Chem. Soc. Comm., 821(1972). These authors report a value of 55.2° for the (+)-ester. The rotations were taken in CCl_4 (c=1) for I to V and in $CHCl_3$ (c=1) for VI and VII.

7) Under conditions described in reference 4, which also gives the yield.

8) We have no experimental proof, at this stage, to show whether this stereospecificity occurs with complete retention or with complete inversion. Pyrrolidine is reported to open the cyclopropane ring in I with clean inversion. See reference 6.