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A NEW METHOD FOR STEREOSPECIFIC CIS HYDROXYLATION OF OLEFINS

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Summary: A new synthetic method is described for the cis-hydroxylation of olefins from either the less or more hindered π-face.

At present the cis hydroxylation of olefins at the least hindered π-face is most frequently accomplished by the use of the reagent osmium tetroxide, either in stoichiometric or catalytic amount.[1] The effectiveness and stereochemical selectivity of the osmylation of olefins and the very broad scope of the process usually outweigh the expense and hazards associated with this reagent. Various permanganate salts which have been employed are generally less satisfactory, despite recent improvements.[2,3] Prévost-Winstein-Woodward hydroxylation using bromine-silver acetate in wet acetic acid[4] finds occasional application in cases where overall cis hydroxylation at the more hindered π-face is required.

In a recent study which led to the total synthesis of the anti-complement agent K-76, we made the surprising observation that the oxidation of the 2,3-double bond in synthetic intermediate 1 produced mainly the $2\beta,3\beta$-diol rather than expected $2\alpha,3\alpha$-isomer (ratio > 10:1), apparently as a result of intervention of conformers in which the A ring or the A and B rings were of the twist boat type.[5] The PWW hydroxylation failed to produce either cis diol due to the occurrence of a carbon rearrangement reaction. In consequence, we embarked on the development of a new method for cis hydroxylation. This note reports on a practical and potentially very general process which has emerged as a result.

In general, trans 1,2-bromohydrins can be prepared readily from cyclohexenes by two stereochemically complementary routes: (1) reaction of the olefin with hypobromous acid which adds oxygen to the more hindered π-face and (2) peracid epoxidation followed by cleavage with HBr which adds oxygen to the less hindered face. This fact and the simplicity of preparation of bromohydrins make these substances attractive candidates for the generation of cis 1,2-diols. Our method for cis 1,2-diol formation from olefins, which proceeds via trans 1,2-bromohydrins, is first illustrated using cyclohexene.

Trans-2-bromocyclohexanol (available from cyclohexene in 99% yield by reaction with N-bromosuccinimide in dimethoxyethane-water at 0°C, 30 min and 20°C, 60 min) was converted to the cyanoacetate ester (2) by reaction with 4.5 equiv of cyanoacetic acid and 2.5 equiv of tosyl chloride in pyridine-methylene chloride[6] in 85% yield.[7] Reaction of 2 with a modest excess of sodium hydride in dry tetrahydrofuran (THF) at 0°C generated the enolate which upon stirring at 23°C for 24 hr underwent a clean internal nucleophilic displacement to form the cyanoketene

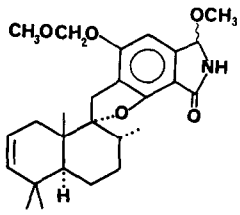
acetal 3 in 90% yield. Pmr peaks for 3 due to OCH (4.16 δ, m, 2H) and HCC≡N (3.76 δ, s, 1H) were characteristic. Stirring 3 in 5:1 THF-1 N hydrochloric acid at 23°C for 15 min produced the mono cyanoacetate of cis-cyclohexane-1,2-diol (4) in 100% yield, and this underwent cleavage using anhydrous potassium carbonate in methanol at 23°C for 15 min to afford after concentration and isolation pure cis-cyclohexane-1,2-diol (5) in 95% yield.

The conversion of the bicyclic olefin 6 to the corresponding 2α,3α-diol 8 illustrates a crucial application of the new methodology. The reaction of 6 with osmium tetroxide-pyridine at 23°C for 16 hr proceeds non-stereoselectively to give a 1:1 mixture of 8 and the stereoisomeric 2β,3β-diol. In the absence of pyridine or under various other conditions the hydroxylation is slow and even less satisfactory. In contrast, the bicyclic olefin undergoes epoxidation (m-chloroperbenzoic acid in methylene chloride) stereospecifically to give the 2α,3α-oxide in 95% yield, and this upon treatment with 4 equiv of hydrogen bromide in methylene chloride (0-10°C, 1 hr) is transformed into the bromohydrin 7 in 90% yield. The structure and stereochemistry are indicated by the pmr spectrum which shows HCBr at 4.30δ(m,1H). The bromohydrin was converted to the 2α,3α-diol 8 in 72.5% overall yield via the cyanoacetate route, essentially as outlined above for cis-cyclohexane-1,2-diol. Interestingly, cleavage of the intermediate cyanoketene acetal of diol 8 with THF-aqueous hydrochloric acid furnished specifically diol monocyanoacetate 9 (pmr peak due to $\underline{H}COCOCH_2CN$ at 4.985 δ (d, J = 2.5 Hz, 1H)) in 100% yield.

We are unaware of any other available methodology which is suitable for the stereospecific conversion of 6 to the 2α,3α-diol 8. Beyond that, it is evident that the cyanoacetate method is pleasingly practical for the reasons that: (1) it is easily carried out on either micro or molar scale, (2) it involves inexpensive reagents, (3) it carries little risk of major side reactions such as rearrangement, (4) in principle, it can be used for the cis hydroxylation of an olefin at either the more or less hindered π-face, and (5) it can lead to selectively monoprotected cis-1,2-diol derivatives.

With regard to this last point, it should be mentioned that the oxidation of 4 with pyridinium dichromate[8] in methylene chloride at 23°C for 24 hr affords cleanly keto ester 10 and, similarly, oxidation of 9 gives selectively keto ester 11.

Finally, we report that varients on the cyanoester method are also operable. For example, trans-2-bromo-cyclohexanol can be converted to cis-cyclohexane-1,2-diol by the sequence: (1) conversion to the mixed ethyl malonate ester (ethyl malonyl chloride, pyridine, 0°C, 1 hr, 70% yield); (2) cyclization of the bromo ester to ketene acetal (sodium hydride, THF, 90% yield); and (3) hydrolysis (92% yield).



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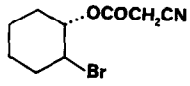

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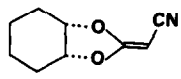

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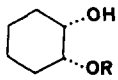
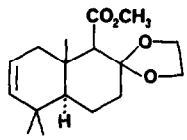


4, R = $COCH_2CN$

5, R = H



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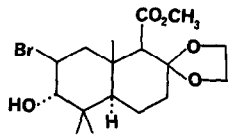

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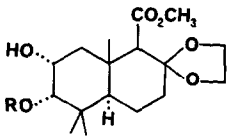
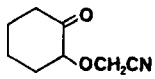


8, R=H

9, R=$COCH_2CN$



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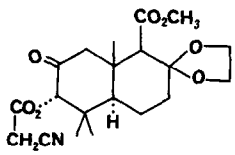

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We expect that the new methodology described herein will be of real value in synthesis.[9]

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7. Satisfactory spectral data were obtained for each isolated intermediate.

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