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STEREOSELECTIVITY IN CARBANIONIC ADDITIONS TO 2-PHENYLCYCLOHEXANONE

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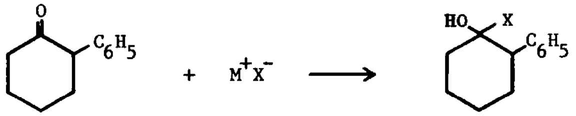
While some stereoselectivity is frequently found in the addition of secondary enolate anions to dissymmetric ketones,[1] complete stereospecificity has been rarely observed.[2] We describe herein the reactions of a graded series of carbanions with 2-phenylcyclohexanone in which progressive increases in stereoselectivity result until finally complete stereospecificity was realized, the product being formed with a single stereochemistry about three asymmetric centers.

When 2-phenylcyclohexanone (I) was treated with lithium acetylide,[3] a 1:1 mixture of the cis-trans isomers of the alcohol (II) was formed.



I

II, X = $-C\equiv CH$

III, X = $CH(CH_3)COOH$

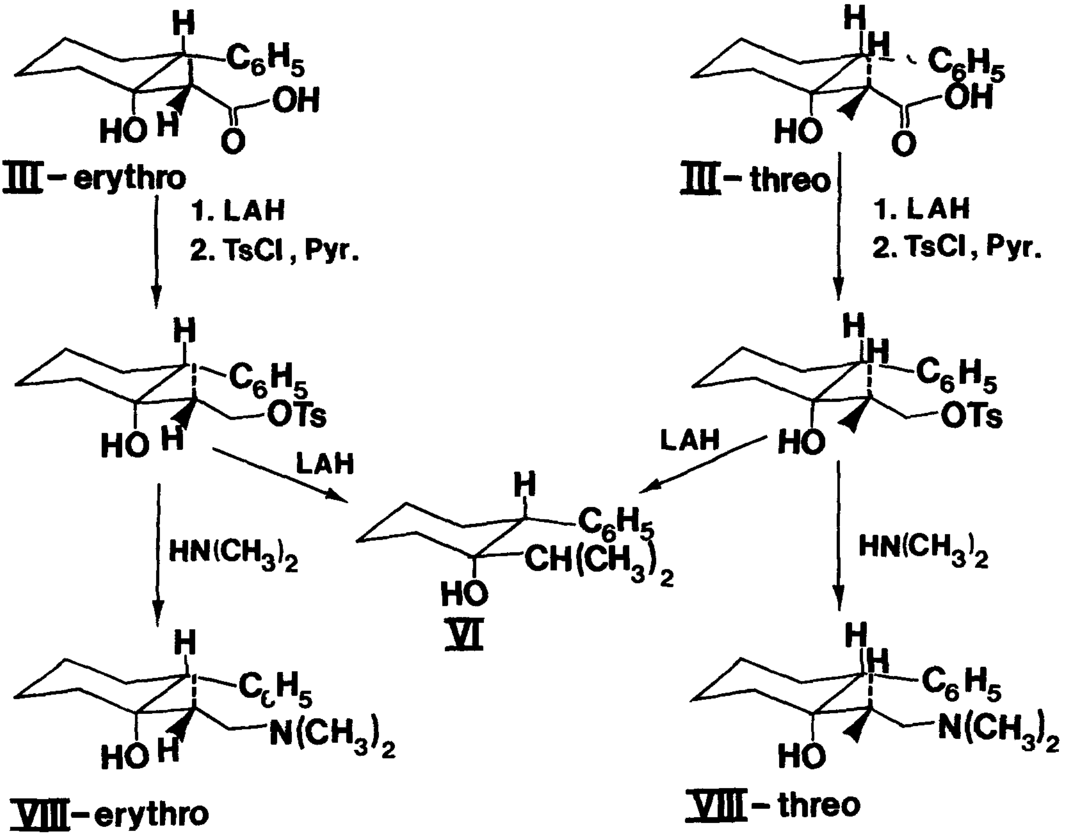
IV, X = $CH(CH_3)CON(CH_3)_2$

V, X = $CH(CH_3)COOC_2H_5$

With lithium 2-lithiopropionate [$LiCH(CH_3)COOLi$][4] stereoselectivity was observed both at the ring carbonyl center as well as in the side-chain, the products (III) not only being exclusively cis (vis-à-vis phenyl) but with a threo-erythro ratio of 3:1.[5] 2-Lithio-N,N-dimethyl propionamide[6] afforded even greater stereochemical control, the amides (IV) formed being cis with a threo-erythro ratio of 5:1. Finally, total stereospecificity was observed with ethyl-2-zincbromopropionate as reagent, the cis-threo material (V) being formed with no detectable quantity of erythro isomer present.[7,8]

The cis configuration of the hydroxy acids (III) was established via the reactions outlined in Scheme 1, both acids yielding the common reduction product, cis-2-phenyl-1-isopropylcyclohexanol (VI). The cis stereochemistry of this material was established by a lanthanide-induced chemical shift (LIS) experiment.[9] Upon treatment of (VI) with $Eu(fod)_3$ in $CDCl_3$, the 3H axial protons had a higher Δ value than the 2H benzylic proton, a fact only consistent with the cis-

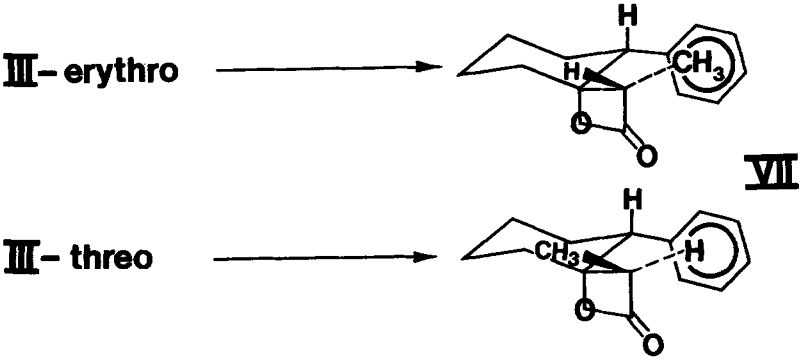
Scheme 1



configuration. The coupling constants between the 2H benzylic protons and the 3H protons indicate that the phenyl substituent is equatorial in every 2-phenylcyclohexanol compound we prepared, and no dynamic effects were observed for any derivative in the ambient temperature range.

The relative side-chain/hydroxyl stereochemistry of the pair of acids (III) was established as follows. Both acids were treated with ethyl chloroformate (and triethylamine) yielding the *spiro*-β-lactones (VII) (Scheme 2). One acid (the *threo*) formed the corresponding β-lactone (VII) under much milder conditions than the other, one forming derivative (VII) at room temperature in 2-3 hours, the other requiring heating at 80° for 8 hours. The *threo*-derived product also appeared to be more stable than its isomer.

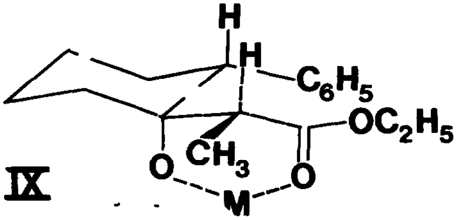
Scheme 2



The lactone derived from the erythro acid showed a chemical shift of the CH_3 group at τ9.25 ppm, this being markedly shielded relative to the CH_3 group in the isomeric (threo-derived) material which had a τ8.89 ppm. In the lactone derived from the erythro isomer, the methyl group is rigidly held in the shielding region of the adjacent aromatic ring.

The interrelationships of the ester (V) and the amides (IV) with the acids (III) were established by the following observations. Hydrolysis of (V) in refluxing aqueous methanolic sodium hydroxide gave exclusively the cis-threo acid (III), thereby establishing the cis-threo character of (V). The amides (IV) which could not be separated were reduced, using LAH, to the amino alcohols (VIII) which were separated. The amino alcohols obtained were then correlated with the corresponding cis-threo and cis-erythro acids by the sequence outlined in Scheme 1, the cis-threo acid, giving the cis-threo amino alcohol and so on.

Kinetic and steric factors alone do not give a satisfactory explanation of the stereospecificity achieved at the asymmetric center α to the ring when comparing the range of reagents bearing α-methyl groups, since both cis-erythro and cis-threo isomers may be obtained while maintaining minimum steric interactions, i.e., with α-methyl away from the phenyl. A possible explanation for the observed specificity is the involvement of an intermediate metal chelate (IX) whose formation should be maximally favored (in our work), using a zinc reagent.[1]



IX

Acknowledgment

We are indebted to Prof. T. Morrill of the Chemistry Department, Rochester Institute of Technology, for the LIS studies, which will be reported upon in more detail elsewhere.

References and Footnotes

1. See e.g. H. O. House, "Modern Synthetic Reactions," 2nd Edition, W. A. Benjamin, Inc., Menlo Park, California, 1972, pp. 671-682; M. W. Rathke, Organic Reactions, 22, 423 (1975).

2. Cf. M. Mousseron-Canet and Y. Beziot, Bull. Soc. chim. France, 2576 (1968).

3. Purchased from Foote Mineral Co., Exton, Pa., as an ethylenediamine complex.

4. P. E. Pfeffer, L. S. Silbert and J. M. Chirinko, Jr., J. Org. Chem., 37, 451 (1972).

5. Similar ring stereoselectivity was also observed in the reactions of isopropyl magnesium bromide with 2-methylcyclohexanone [*cis-trans* ratios of products being of the order of 98:2], J. Ficini and A. Maujean, Bull. Soc. chim. France, 219 (1971).

6. W. H. Puterbaugh and C. R. Hauser, J. Am. Chem. Soc., 75, 2415 (1953).

7. In the case of reactions leading to II and IV, the ketone (I) (0.8 equiv.) was slowly added to the organometallic reagent (1.1 equiv.) in THF or ether at ambient temperatures. In the reaction leading to III, the ketone was rapidly added to the organometallic compound in THF at -70°. The Reformatsky reaction leading to V was run with 1 equiv. of ketone, 1.1 equiv. of bromoester and 1.2 equiv. of freshly activated zinc dust in 1:1 benzene:toluene at 85°.

8. When 2-(alkyl-and/or alkoxy-aryl) cyclohexanones were used as substrates in the Reformatsky reaction with ethyl bromopropionate, again, total stereospecificity was observed.

9. The LIS experiments were performed at 60 MHz and 34°C, using $CDCl_3$ as solvent. The $Eu(fod)_3$/substrate ratios ranged from 0.041 to 0.890. All assignable Δ values were of the same magnitude as those obtained for model cyclohexanol derivatives. In that regard, see B. L. Shapiro, et. al., J. Am. Chem. Soc., 97, 542 (1975).