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ASYMMETRIC SYNTHESIS OF 3-HYDROXYACIDS FROM ALDEHYDE OR DIALKYL KETONE

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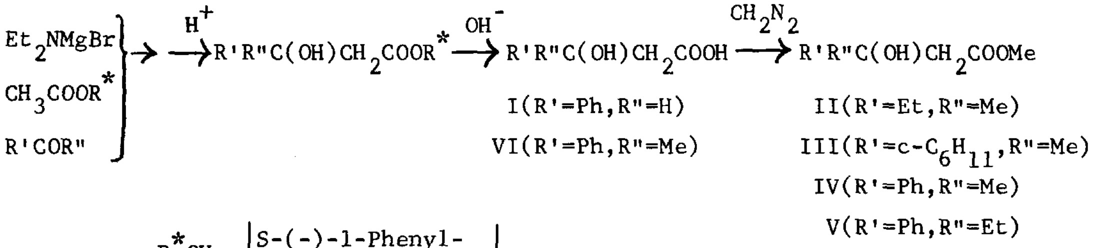
The asymmetric synthesis of 3-hydroxyacids from ketones and acetates by means of diethylaminomagnesium bromide($\mathrm{Et_2NMgBr}$) was applied to the synthesis of the substrates of the stereospecific hydrogenolysis by substituting alkyl aryl ketones[1] for diaryl ketones[2]. The high optical yields (93%) stimulated the systematic investigation of the reaction. As part of such studies, we wish to report the expansion of the reaction to an aldehyde (benzaldehyde) and dialkyl ketones (2-butanone and acetylcyclohexane). The reactions were carried out according to the literature[2] except the following esterification of the afforded 3-hydroxyacids with diazomethane in vitro in most cases. The absolute configuration of methyl 3-hydroxy-3-cyclohexylbutyrate(III) to be led from acetylcyclohexane was determined: S-(methyl 3-hydroxy-3-phenylbutyrate) (IV), b.p.$_{0.4}$104-105°, α_D^{26}10.01°(neat)[1], was hydrogenated on Rh-C to S-III, b.p.$_4$80-85°, α_D^{8}-2.06°(neat).

The scheme and the results of the reactions are shown in Table.

The reactions of S-(-)-1-phenylethyl, (-)-menthyl and (+)-bornyl acetates always predominantly resulted R-, S- and S-acids, respectively. Therefore the reactions of (-)-menthyl and (+)-bornyl acetates are 'normal' and 'abnormal', respectively, in view of the relation between the predominant enantiomers and the chirality of alcoholic α-carbons of acetates. Such relations between (-)-menthyl and (+)-bornyl derivatives were often observed.[3] It is interesting that the optical yields are higher in the 'normal' reactions than the 'abnormal' ones. These facts suggest that the chirality of the alcoholic α-carbon of the acetate is still one of the important factors in the asymmetric induction and that the other kinds of complexion of the transition states in addition to one shown by Sisido *et al*[2] have to be considered.

Table. The results of the asymmetric synthesis of 3-hydroxyacids: Yields, predominant enantiomers and the optical yields.



$$\left.\begin{array}{l}Et_2NMgBr\\ CH_3COOR^*\\ R'COR''\end{array}\right\}\rightarrow\xrightarrow{H^+}R'R''C(OH)CH_2COOR^*\xrightarrow{OH^-}R'R''C(OH)CH_2COOH\xrightarrow{CH_2N_2}R'R''C(OH)CH_2COOMe$$

I(R'=Ph,R"=H)
VI(R'=Ph,R"=Me)

II(R'=Et,R"=Me)
III(R'=c-C_6H_{11},R"=Me)
IV(R'=Ph,R"=Me)
V(R'=Ph,R"=Et)

R*OH / R'COR"	S-(-)-1-Phenyl-ethanol	(-)-Menthol	(+)-Borneol
Benzaldehyde	----	6 S-(-)-I 82	13 S-(-)-I 35
2-Butanone	----	30 (-)-II b	----
Acetylcyclohexane	50 R-(+)-III 17	30 S-(-)-III 66	50 S-(-)-III 0[a]
Acetophenone	18 R-(-)-IV 43	S-(+)-VI 93[1a] 28 S-(+)-IV 79	41 S-(+)-IV 24
Propiophenone[1b]	R-(-)-V 46	S-(+)-V 70	S-(+)-V 35

[a] $\alpha_D^{13}\pm0^\circ$(neat), $\alpha_{403}^{21}-0.41^\circ$(neat) and $\alpha_{362}^{21}-0.39^\circ$(neat). [b] $\alpha_D^{21}-0.25^\circ$(neat).

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