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The Stereo-differentiating (Asymmetric) Hydrogenation of the C=O Double Bond with a Modified Nickel Catalyst. XXXV. A Facile Method for the Preparation of Optically Pure β-Diols

Kazuhisa ITO, Tadao HARADA, and Akira TAI*

Institute for Protein Research, Osaka University, Yamada-kami, Suita, Osaka 565

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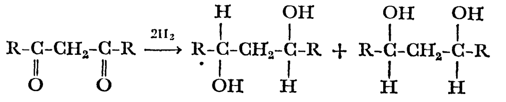
Synopsis. The hydrogenation of $RCOCH_2COR$ over a Raney nickel catalyst modified with a mixture of tartaric acid and NaBr gave (R*, R*)-$RCH(OH)CH_2CH(OH)R$ selectively with a high optical purity. The substrates with $R=CH_3$-, CH_3CH_2-, $CH_3CH_2CH_2$-, $CH_3(CH_2)_4CH_2$-, and Ph- were employed in this study. In all cases, the recrystallization of the hydrogenation product gave an optically pure (R*,R*)-isomer which was free from the (R*,S*)-isomer.

Optically pure β-diols and their derivatives are potentialy useful chiral compounds as chiral solvents, chiral ligands, and chemicals for the preparation of optically active compounds. Althgouh a small amount of (+)-(2S,4S)-2,4-pentanediol has been prepared by the tedious optical resolution,[1] no practical methods for the large-scale preparation of optically pure compounds have been reported.

In a previous communication, we have briefly reported that the Raney nickel catalyst (RNi) modified with a solution containing tartaric acid (TA) and NaBr (TA–NaBr–MRNi) is an excellent catalyst for the hydrogenation of acetylacetone (Ia) to 2,4-pentanediol (Ib), giving (2R*,4R*)-Ib selectively with a high optical purity.[2] The catalyst was also found to be effective for the hydrogenation of other symmetric β-diketones to a mixture of (R*,R*)- and (R*,S*)-diol.



$$R\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_2\text{-}\underset{\underset{O}{\|}}{C}\text{-}R \xrightarrow{2H_2} R\text{-}\overset{H}{\underset{OH}{C}}\text{-}CH_2\text{-}\overset{OH}{\underset{H}{C}}\text{-}R + R\text{-}\overset{OH}{\underset{H}{C}}\text{-}CH_2\text{-}\overset{OH}{\underset{H}{C}}\text{-}R$$

(R*,R*)-isomer (R*,S*)-isomer

$R=CH_3$-, acetylacetone (Ia) 2,4-pentanediol (Ib)
$R=CH_3CH_2$-, 3,5-heptanedioue (IIa) 3,5-heptanediol (IIb)
$R=CH_3CH_2CH_2$-, 4,6-nonanedione (IIIa) 4,6-nonanediol (IIIb)
$R=CH_3(CH_2)_4CH_2$-, 7,9-pentadecanedione (IVa) 7,9-pentadecanediol (IVb)
R=Ph-, dibenzoylmethane (Va) 1,3-diphenyl-1,3-propanediol (Vb)

The results are listed in Table 1. The major product, the (R*,R*)-isomer, can be separated from the (R*,S*)-isomer by the recrystallization of the reaction product. In all cases, the isolated (R*,R*)-isomer was found to be already optically pure. All substrates gave (−)-(R*,R*)-isomers in excess when (R,R)-TA–NaBr–MRNi was used.

As is found in the table, the ratio of the (R*,R*)-isomer to the (R*,S*)-isomer in the hydrogenation product is slightly decreased with an increase in the chain length of R in the substrate. Consequently, the isolation yield of the (R*,R*)-isomer decreases with the increase in the chain length of the substrate. However, the advantage of the present method is that optically pure β-diols are easily obtained by the recrystallization of the hydrogenation products. Furthermore, the preparation of TA–NaBr–MRNi is very simple, and the cost of the catalyst is negligibly low. Therefore, the present method would be easily applicable for the large-scale production of β-diols.

The optical purity of the (R*,R*)-isomers listed in Table 1 can be determined by means of the NMR of the diacetate derived from each diol. The chemical shifts for the acetyl group (singlet) of (−)- and (+)-diacetate were separated by 3 to 5 Hz in the presence of 2 molar eqivalents of $Eu(hfmc)_3$ to the acetate. In all cases, the signals of the diacetates derived from (+)-diols appeared at a high field.

The absolute configurations of the diols have not yet been determined except for the case of (−)-(2R,4R)-Ib. However, the configurations of the (−)-isomer can be expected to be (R,R) for the following reasons: 1) the lanthanid-induced shifts of all the (−)-diols in NMR show the same tendency as that of Ib, and 2) the analogues of the substrates thus far examined are hydrogenated to (−)-(R)-products over (R,R)-TA–NaBr–MRNi; *i.e.*, Ia, 4-hydroxy-2-butanone, and methyl acetoacetate are converted to (−)-(2R,4R)-Ib, (−)-(R)-1,3-butanediol,[3] and (−)-(R)-methyl 3-hydroxybutyrate[4] respectively.

Experimental

The ^{1}H-NMR and IR spectra were taken with a JELO FX-100 spectrometer and a Shimadzu IR 27G spectrometer respectively. The optical rotation was measured with a Perkin Elmer 241 polarimeter. The analytical GLC was carried out with a Shimadzu GC 4A-PF gas chromatograph, using a 3 m—5 mm o.d. glass column packed with 15% Ucon 50 HB-2000 on Chromosorb W (Ucon) or 2% Silicone OV-17 on Chromosorb W (OV-17) at the stated temperature. The preparative GLC was carried out with a Shimadzu 3A instrument using a 6 m—6 mm o.d. stainless column packed with OV-17. The preparative TLC was carried out on a Silicagel F plate (Merck Co.) with a solvent of ether/hexane=1/1.

All the chemicals except those listed below were obtained from commercial sources. 3,5-Heptanedione (IIa), 4,6-nonanedione (IIIa), and 7,9-pentadecanedione (IVa) were prepared from an appropriate ester, $RCOOCH_3$, and the 2-alkanones, CH_3COR, by a previously reported method.[5] The physical constants of the products were identical with those previously reported.[5] The GLC analysis indicated that the purity of each compound was more than 97%.

The preparation of TA–NaBr–MRNi and the hydrogenation of each substrate were carried out by a procedure reported before.[2]

Determination of the Ratio of Diastereomers in the Hydrogenation Product. The hydrogenation products of Ia and IIa were directly subjected to the GLC (Ucon) analysis. The GLC data (retention time and column temperature) are as follows: (2R*,4R*)-Ib, 170 min/80 °C; (2R*,4S*)-Ib, 159 min/80 °C; (3R*,5R*)-IIb, 109 min/120 °C; (3R*,5S*)-IIb, 99.6 min/120 °C. The GLC analyses of the hydrogenation products of IIIa to Va were carried out after the products had been converted to its trimethylsilyl (TMS) ether. A 0.1-g portion of the sample was treated with 0.2 ml each

TABLE 1. HYDROGENATIONS OF β-DIKETONES OVER (*R*,*R*)-TA–NaBr–MRNi[a]

Substrate	Proportion of diastereomers (%) in the hydrogenation product		Isolation of (R^*, R^*)-diol from the hydrogenation product	
	(R^*, R^*)-diol	(R^*, S^*)-diol	Yield/%	$[\alpha]^{20}_{D}$ of diol
Ia	87	13	65 (57)	−54.5 (+53.6)
IIa	80	20	30 (25)	−39.1 (+39.0)
IIIa	85	15	11 (13)	−21.4 (+21.2)
IVa	80	20	21 (20)	−10.8 (+11.1)
Va	77	23	20 (23)	−72.7 (+72.3)

a) Figures in parenthese show the results of (*S*,*S*)-TA–NaBr–MRNi.

of $(CH_3)_3SiCl$ and $(CH_3)_3Si–NH–Si(CH_3)_3$ in 20 ml of pyridine at 90 °C for 10 min. After the removal of volatiles under reduced pressure at 90 °C, the residue was mixed with 1 ml of hexane and then centrifuged. The TMS ether in the supernatant was subjected to GLC analysis. The GLC data (retention time, packings of column, and column temperature) are as follows: ($4R^*$,$6R^*$)-TMS-IIIb, 58.4 min/Ucon/150 °C; ($4R^*$,$6S^*$)-TMS-IIIb, 54.4 min/Ucon/150 °C; ($7R^*$,$9R^*$)-TMS-IVb, 89.6 min/Ucon/150 °C; ($7R^*$,$9S^*$)-TMS-IVb, 83.6 min/Ucon/150 °C; ($1R^*$,$3R^*$)-TMS-Vb, 122 min/OV-17/140 °C; ($1R^*$,$3S^*$)-TMS-Vb, 116 min/OV-17/140 °C. The ratio of the diastereomers was evaluated from the ratio of the peak areas of the GLC.

Isolation of the (R,R*)-Isomers from the Hydrogenation Product.* *(−)-(2R,4R)-2,4-Pentanediol (Ib)*: A 9-g portion of the hydrogenation product of Ia over (*R*,*R*)-TA–NaBr–MRNi was dissolved in 10 ml of ether, after which the solution was cooled at −50 °C for 1 h. The crystals precipitated from the solution were taken out and recrystallized from 10 ml of ether at −5 °C to give 5 g of (*2R*,*4R*)-Ib (bp 111—113 °C/19 mmHg; mp 50.5 °C). The analytical GLC (Ucon, 120 °C) showed a single peak. The crystals were too hygroscopic for the elemental analysis to be performed with a completely dried sample. The results of a partially dried sample were as follows; Found: C, 56.50; H, 11.70%. Calcd for $C_5H_{12}O_2\cdot(0.1\ H_2O)$: C, 56.70; H, 11.62%. The NMR and IR spectra of the sample were consistent with the structure of Ib. The optical rotation of the sample was as follows; $[\alpha]^{20}_{D}$ −53.7° (*c* 10, ethanol), $[\alpha]^{25}_{D}$ −41.2° (*c* 10, $CHCl_3$) (lit,[1] −41.3° ($CHCl_3$, *c* not stated)). As a large-scale preparation, the hydrogenation of 200 g of Ia over 26 g of (*R*,*R*)-TA–NaBr–MRNi was carried out in an autoclave with a capacity of 2000 ml. From the hydrogenation products, 131 g of (*2R*,*4R*)-Ib was obtained.

(−)-(3R,5R*)-3,5-Heptanediol (IIb)*: A 9 g portion of the hydrogenation product of IIa over (*R*,*R*)-TA–NaBr–MRNi was dissolved in 20 ml of ether, after which the solution was cooled at −50 °C for 3 h. The crystals thus precipitated were separated from the supernatant solution by decantation at −50 °C. Two successive recrystallizations of the crystals from 20-ml portions of ether at −10 °C gave optically pure (−)-($3R^*$,$5R^*$)-IIb in a yield of 2.7 g (30% based on the crude product) (bp 110 °C/12 mmHg; mp 52—53 °C; Found: C, 62.64; H, 12.21%. Calcd for $C_7H_{16}O_2\cdot(0.1\ H_2O)$: C, 62.73; H, 12.18%, $[\alpha]^{20}_{D}$ −39.1° (*c* 10, ethanol)). The analytical GLC (Ucon, 120 °C) showed a single peak. The NMR and IR spectra of the sample were consistent with the structure of IIb.

(−)-(4R,6R*)-4,6-Nonanediol (IIIb)*: A solution of 9 g of the hydrogenation product of IIIa over (*R*,*R*)-TA–NaBr–MRNi in 20 ml of ether was kept overnight at −50 °C. The crystals thus precipitated were taken out by filtration in a cold room. Three successive recrystallizations from 20 ml of ether at −10 °C gave 1.4 g of an optically pure (−)-($4R^*$,$6R^*$)-IIIb (16% based on the crude product); mp 58—59 °C; Found: C, 67.05; H, 12.56%. Calcd for $C_9H_{20}O_2\cdot(0.05\ H_2O)$: C, 67.07; H, 12.57%, $[\alpha]^{20}_{D}$ −21.4° (*c* 10, ethanol). The NMR and IR spectra of the sample were consistent with the structure of IIIb.

(−)-(7R,9R*)-7,9-Pentadecanediol (IVb)*: A solution of 9 g of the hydrogenation product of IVa over (*R*,*R*)-TA–NaBr–MRNi in 20 ml in 20 ml of ethyl acetate was allowed to stand at −50 °C for 1 h. The crystals thus precipitated were taken out at −50 °C and recrystallized three times from 20 ml of ethyl acetate at 5 °C to give 1.9 g of optically pure (−)-($7R^*$,$9R^*$)-IVb (21% based on the crude product); mp 73—74 °C, Found: C, 72.89; H, 13.10%. Calcd for $C_{15}H_{32}O_2$ $(0.05\ H_2O)$: C, 73.17; H, 13.18%, $[\alpha]^{20}_{D}$ −10.8° (*c* 10, ethanol). The NMR and IR of the sample were consistent with the structure of IVb.

(−)-(1R,3R*)-1,3-Diphenyl-1,3-propanediol (Vb)*: A solution of 9 g of the hydrogenation product of Va over (*R*,*R*)-TA–NaBr–MRNi in 10 ml of ethyl acetate was allowed to stand at −10 °C overnight. The crystals thus precipitated were separated by filtration and then recrystallized three times from 20 ml of (ether/ethyl acetate) = (8/2) to give 1.8 g of optically pure (−)-($1R^*$,$3R^*$)-Vb (20% based on the crude product); mp 145—147 °C; Found: C, 78.40; H, 7.21%. Calcd for $C_{15}H_{16}O_2\cdot(0.05\ H_2O)$: C, 78.30; H, 7.45%, $[\alpha]^{20}_{D}$ −72.7° (*c* 10, ethanol). The NMR and IR spectra of the sample were consistent with the structure of Vb.

Determination of the Optical Purity of the Purified Sample. The optical purities of the purified diols were determined by means of NMR after the diols had been converted to diacetates. Into a solution of 0.5 g of diol in 5 ml of pyridine were added 2 ml of acetic anhydride. The solution was heated at 60 °C for 3 h and then worked up in the usual manner to give the crude diacetate of the diol. The purification of the diacetate was carried out by either preparative GLC (diacetates of Ib and IIb) or preparative TLC (diacetates of IIIb, IVb, and Vb). The NMR spectra were measured with a solution of diacetate (10 mg) and Eu(hfmc)$_3$ (2 molar equvalents to the acetate) in $CDCl_3$ (0.4 ml) at 50 °C. None of the diacetates derived from purified products showed any detectable signal of the antipode.

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