Stereochemical Investigation on Asymmetrically Modified Raney Nickel Catalyst. Mode of Interaction between Modifying Reagent and Substrate in the Enantioface-differentiating Process

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The mode of enantioface-differentiating hydrogenation with asymmetrically modified Raney nickel (MRNi) was investigated by using various sorts of modifying reagents and substrates. The optical yields (O.Y.) of the hydrogenation of methyl acetoacetate over MRNi for different modifying reagents occured in the following order: $HO_2C\overset{OH}{C}H\overset{OH}{C}HCO_2H$ (O.Y. 85%) > $HO_2C\overset{OX}{C}H\overset{OH}{C}HCO_2H$, (X = CH_3–, and PhCO–) ≈ $HO_2CCH_2\overset{OH}{C}HCO_2H$ (O.Y. 61—65%) ≫ $HO_2C\overset{OX}{C}H\overset{OX}{C}HCO_2H$ (X = CH_3–, and PhCO) ≈ $CH_3\overset{OH}{C}H–\overset{OH}{C}HCO_2H$ (O.Y. 1—8%). The hydrogenation of various substrates of the structure, $R–\overset{Y}{C}–CH_2–\overset{O}{\overset{\|}{C}}–R'$, over tartaric acid-modified Raney nickel (TA–MRNi), gave high optical yields only when the substituent –Y functioned as a good hydrogen bond acceptor like a carbonyl group, and two pairs of hydrogen bondings between substrate and two hydroxyl groups of tartaric acid were available. As for the stereochemistry of the reaction in such a case, (*R,R*)-TA–MRNi always gave (*R*)-product in excess. Based on the stereochemistry of the reaction and the role of hydrogen bonds between modifying reagent and substrate, a stereochemical model is proposed to elucidate the mode of enantioface-differentiating hydrogenation of prochiral ketones over TA–MRNi.

It has been reported that the asymmetric modification of Raney nickel (RNi) with an aqueous solution of tartaric acid (TA) and NaBr gave an excellent catalyst (TA–NaBr–MRNi) for the enantioface-differentiating hydrogenation. The hydrogenation of methyl acetoacetate (MAA) over this catalyst gave methyl 3-hydroxybutyrate (MHB) in a quantitative chemical yield and almost 90% of optical yield. Studies on the development of the above-mentioned catalyst have made it clear that the enantioface-differentiating ability of the catalyst is governed by two major factors. The first one is the proportion of the number of enantioface-differentiating reaction sites (where the enantioface-differentiating hydrogenation of substrate takes place by the aid of modifying reagent) to the number of non-enantioface-differentiating sites (where the racemic product is produced because of the absence of the modifying reagent on the catalyst). Our recent study has shown that NaBr on the catalyst is specifically adsorbed on the non-enantioface-differentiating reaction sites, inhibiting the hydrogenation activity of these sites.[1] Thus, the hydrogenation of MAA over TA–NaBr–MRNi proceeded overwhelmingly at the enantioface-differentiating reaction sites in giving the product with a high optical purity. The second factor is the degree of the intrinsic enantioface-differentiating ability of the modifying reagent, which depends not only on the structural features but also on the mode of adsorption on the catalyst surface. Arguing from the structural features of TA and MAA, and the stereochemistry of the hydrogenation product, we have proposed a mode of interaction between TA and MAA at the enantioface-differentiating step of the hydrogenation.[2] In this paper, we wish to report the details on the mode of enantioface-differentiation process and the validity of the proposed stereochemical model, based on the following two series of investigations: 1) The hydrogenation of MAA over RNi modified with NaBr and the compound whose structure is analogous to TA, and 2) the hydrogenation of various prochiral ketones over TA–NaBr–MRNi.

Results

Hydrogenations of MAA over Various Sorts of MRNi. Several analogs of TA were prepared and their enantioface-differentiating abilities (e.d.a.) were evaluated from the optical yield of the hydrogenation of MAA over the MRNi prepared from TA-analogs and NaBr. The results are summarized in Table 1.

Among the compounds examined, only TA and 2-methyl-TA gave rise to more than 70% of e.d.a. (Entries 1 and 2). When one of the hydroxyl groups of TA was replaced by H–, benzoyloxyl or methoxyl group, appreciable decreases of e.d.a. were observed (Entries 3, 4, and 5). The e.d.a.'s of this type of compounds were around 65%. The replacement of one of the carboxyl groups of TA by a methyl group resulted in a complete loss of e.d.a. (Entry 6), even if vicinal hydroxyl groups existed. A drastic decrease in e.d.a. was also observed when both hydroxyl groups of TA were acylated or alkylated (Entries 7 and 8). These results clearly show that two hydroxyl groups and two carboxyl groups in TA were absolutely necessary functional groups for the effective enantioface-differentiation of MAA.

Hydrogenations of Prochiral Ketones over TA–NaBr–MRNi. In Table 2, the results of the hydrogenation of various prochiral ketones over TA–NaBr–MRNi are summarized.

In the series of the hydrogenations of methyl esters of α-, β-, γ-, and δ-keto acids (**1a**—**4a**) over TA–NaBr–MRNi, the excellent optical yield was obtained only with β-keto ester (Entry 2). Furthermore, the hydrogenation rate of **2a** was much faster than those of **1a**, **3a**, and **4a**. Although γ-keto ester (**3a**) was

Table 1. Degree of enantioface differentiaitng ability(e.d.a.) of TA and its analogues determined by hydrogenation of MAA[a)]

No.	Modifying reagent	e.d.a. of MRNi[b)] %	Configuration of product
1	(*R,R*)-TA(I)	83	*R*
2	(*2R,3R*) 2-Methyl-TA(II)	74	*R*
3	(*2R,3R*) *O*-Benzoyl-TA(III)	65	*R*
4	(*2R,3R*) *O*-Methyl-TA(IV)	68	*R*
5	(*S*) Malic acid(V)	61	*S*
6	(*2S,3R*) 2,3-Dihydroxybutyric acid(VI)	1.2	*S*
7	(*2R,3R*) *O,O'*-Dibenzoyl-TA(VII)	8	*R*
8	(*2R,3R*) *O,O'*-Dimethyl-TA(VIII)	0.2	*R*

a) MAA(100 mmol) in methyl propionate(23 ml) and acetic acid(0.2 ml) was subjected to hydrogenation over MRNi prepared from 1.6 g of Raney alloy at initial hydrogen pressure of 100 kg/cm^2 at 100 °C. b) Degree of e.d.a. was evaluated by the optical yield(%) of the reaction of MAA to MHB.

hydrogenated to **3b** in 40% optical yield, the hydrogenations of α- and δ-keto ester gave only racemic **1b** and **4b**, respectively (Entries 1 and 4).

It is interesting that the hydrogenations of simple ketone (**5a**) and γ-keto ester (**3a**) proceeded with almost the same optical yields but in opposite directions of enantioface-differentiation; that is, **3a** gave (*R*)-**3b** in excess, while **5a** gave (*S*)-**5b** in excess (Entries 3 and 5).

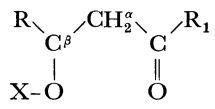
In the preceding paper, which dealt with the hydrogenation of **1a**—**4a** with various amino acid–MRNi's it was shown that the geometrical fitness of functional groups in the modifying reagent and substrate was an essential factor for giving high optical yield.[3)] It is thus expected that **2a** can enter a well-fitting interaction with TA, whereas other substrates (**1a**, **3a**, **4a**, and **5a**) cannot.

Two types of homologues of **2a**, that is, alkyl acetoacetates (**6a**—**9a**) and methyl alkanoylacetates (**10a**—**12a**) were found to be smoothly hydrogenated over TA–NaBr–MRNi in uniformly excellent optical yields (Entries 6—12).

Acetylacetone (**13a**), in which one of the carbonyl groups takes the place of the ester carbonyl group of **2a**, was also found to be a good substrate.[4)] In this case, TA–NaBr–MRNi differentiates not only the enantioface of carbonyl group but also the one out of two carbonyl groups in **13a**. When the hydrogenation of **13a** is discontinued at 1.1 molar equivalent of hydrogen uptake, a mixture of **13b** and 2,4-pentanediol in a ratio of 91 to 9 was obtained. The optical yield of **13b** was 74%. (Entry 13). The complete hydrogenation of **13a** gave (*2R,4R*)-2,4-pentanediol of high optical purity.[5)]

The compounds, in which the ester group of **2a** was substituted with some other polar functional group such as $-SO_2CH_3$ (**14a**, **15a**),[6)] $-CH_2OH$ (**16a**),[7)] and $-CH_2OCH_3$ (**17a**) were found to be favorable substrates for the enantioface-differentiating hydrogenation with TA–NaBr–MRNi. As shown in Table 2 (Entries 14—17), the hydrogenation of these substrates over (*R,R*)-TA–NaBr–MRNi proceeded in reasonable optical yields in giving (*R*)-isomer in excess.

From the results mentioned above, it becomes evident that the essential factor for a good substrate is the presence of an oxygen atom bound to the β-carbon from the prochiral carbonyl group (to be hydrogenated as shown below).



Discussion

The rigorous enantioface-differentiating reaction over MRNi should be attained when the preadsorbed modifying reagent is well settled on the nickel surface and offers uniform chiral binding sites for the prochiral substrate approaching the nickel surface. The adsorbed substrates are uniformly orientated on the nickel surface with one side of enantiofaces by the aid of the well-fitting interaction between binding sites of modifying reagent and substrate.

According to the physicochemical studies[8)] on the mode of adsorption of modifying reagent on the nickel surface, a 2-hydroxyl carboxylic acid is coordinated to a surface nickel atom only through its carboxyl group dissociated as a carboxylate ion, while its hydroxyl group is essentially free from the surface metal.

In order to implant a modifying reagent and make it stationary on the surface of a catalyst, interactions may be required between modifying reagent and catalyst surface at more than two points. Thus, the presence of two carboxyl groups is expected to be one of the necessary conditions for a good modifying reagent. This consideration is compatible with the experimental results that the modifying reagent of high e.d.a. are limited to α-hydroxyl and α,β-dihydroxyl dicarboxylic acid.

The poor e.d.a.'s of *O,O'*-dibenzoyl- and *O,O'*-dimethyl-TA indicate that no effective interactions leading to the efficient enantioface-differentiation take place between modifying reagent and MAA, as a result of the absence of free hydroxyl groups in the modifying reagent. Although α-hydroxyl dicarboxylic acids (malic acid, *O*-benzoyl-TA, and *O*-methyl-TA) gave moderate e.d.a.'s, high e.d.a.'s (more than 70%) were exhibited only by using α,β-dihydroxyl dicarboxylic acid. Thus it is evident that two hydroxyl groups in a modi-

Table 2. Enantioface differentiating hydrogenation of various prochiral ketones with TA-NaBr-MRNi

No.	Substrate	Reaction conditions[a] Substrate (mmol)	Solvent	Temp °C	Time h	Product(Configuration)	Chemical yield/%	Optical yield/%
1	Methyl pyruvate(**1a**)	110	MP[b]	100	36	Methyl lactate(**1b**) (*S*)	95	2
2	Methyl acetoacetate(**2a**)	100	MP	100	5	Methyl 3-hydroxybutyrate(**2b**) (*R*)	98	86
3	Methyl 4-oxopentanoate(**3a**)	88	MP	100	48	Methyl 4-hydroxypenanoate(**3b**) (*R*)		
						4-Pentanolide(**3c**) (*R*)	78[c]	38
4	Methyl 5-oxohexanoate(**4a**)	80	MP	100	48	Methyl-5-hydroxyhexanoate(**4b**)		
						5-Hexanolide(**4c**) (*R*/*S*)	74[c]	0
5	2-Hexanone(**5a**)	101	THF	100	48	2-Hexanol(**5b**) (*S*)	82	28
6	Ethyl acetoacetate(**6a**)	88	THF	85	5	Ethyl 2-hydroxybutyrate(**6b**) (*R*)	97	87
7	Isopropyl acetoacetate(**7a**)	80	THF	100	5	Isopropyl 3-hydroxybutyric acid(**7b**) (*R*)	95	88
8	Isobutyl acetoacetate(**8a**)	72	THF	100	5	Isobutyl 3-hydroxybutyrate(**8b**) (*R*)	95	88
9	Hexyl acetoacetate(**9a**)	62	THF	100	5	Hexyl 3-hydroxybutyrate(**9b**) (*R*)	96	88
10	Methyl 3-oxopentanoate(**10a**)	88	MP	100	5	Methyl 3-hydroxypentanoate(**10b**) (*R*)[g]	75	87
11	Methyl 4-methyl-3-oxopentanoate(**11a**)	80	MP	100	5	Methyl 3-hydroxy-4-methylpenatanoate(**11b**) (*R*)[g]	80	87
12	Methyl 3-oxotetradecanoate(**12a**)	39	MP	100	5	Methyl 3-hydroxytetradecanoate(**12b**) (*R*)	(79)[d]	86[17]
13	Acetylacetone(**13a**)	105	THF	100	—	4-Hydroxy-2-pentanone(**13b**) (*R*)	—	74[4]
14	1-Methylsulfonyl-2-butanone(**14a**)	56	THF	100	15	Methyl 2-hydroxybutyl sulfone(**14b**) (*R*)	96[e]	68[6]
15	1-Methylsulfonyl-2-heptanone(**15a**)	46	THF	100	15	Methyl 2-hydroxyheptyl sulfone(**15b**) (*R*)	93[e]	69[6]
16	4-Hydroxy-2-butanone(**16a**)	120	THF	85	14	1,3-Butanediol(**16b**) (*R*)	88	69[7]
17	4-Methoxy-2-butanone(**17a**)	102	THF	85	14	4-Methoxy-2-butanol(**17b**) (*R*)[f]	90	68

a) Substrate(amount listed in table) in solvent(23 ml) and AcOH(0.2 ml) was subjected to hydrogenation at initial hydrogen pressure of 100—120 kg/cm^2. b) Methyl propionate, c) Isoated yields of **3c** and **4c**, d) Isolated yield of 3-hydroxytetradecanoic acid obtained by the saponification of hydrogenation product. e) Evaluated from the weight of crude crystals obtained after the removal of solvent. f) The optical rotation of the sample was the same sign as that of 4-methoxy-2-butanol obtained by the reaction of (*R*)-1,3-butanediol with CH_3I and Ag_2O. g) The absolute configuration of (−)-**10b** and (−)-**11b** was estimated to be *R*, on the fact that all known (−)-methyl 3-hydroxyalkanoates have *R*-configuration.

Table 3. Analytical data of synthesized modifying reagent

No.	Compound	Configuration	Mp θ_m/°C	$[\alpha]_D^{20}$/° In this work	$[\alpha]_D^{20}$/° Literature	Found(%) C	Found(%) H	Calcd(%) C	Calcd(%) H	Ref.
1	2,3-Dihydroxy-2-methylbutanedioic acid	*2R,3R*	161	−5.61(*c* 3.2, H_2O)	−5.60	36.52	5.03	36.50	4.91	9
2	*O*-Benzoyltartaric acid	*R,R*	203	−6.4(*c* 1.16, EtOH)	−4.4	52.8	3.94	51.97	3.97	10
3	*O*-Methyltartaric acid	*R,R*	176	+47.2(*c* 2.5, H_2O)	+45.4(*c* 2, H_2O)	36.39	4.93	36.59	4.91	11
4	2,3-Dihydroxybutyric acid	*2S,3R*	109	−12.3(*c* 5, 1 M HCl)	−17.75(*c* 1, H_2O)	33.80	4.96	32.76	4.99	12
5	*O,O'*-Dibenzoyltartaric acid	*R,R*	84—87	−109.0(*c* 1.15, EtOH)	−125(*c* 1.13, EtOH)	57.61	4.15	57.45	4.29	13
6	*O,O'*-Dimethyltartaric acid	*R,R*	153—155	+74.3(*c* 8.8, H_2O)	+74.7(*c* 8.9, H_2O)	39.86	5.56	40.45	5.68	14

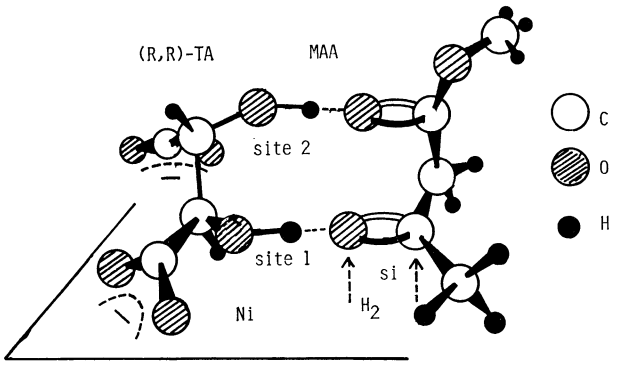


Fig. 1. Schematic representation of the interaction between (*R*,*R*)-TA and MAA on the MRNi.

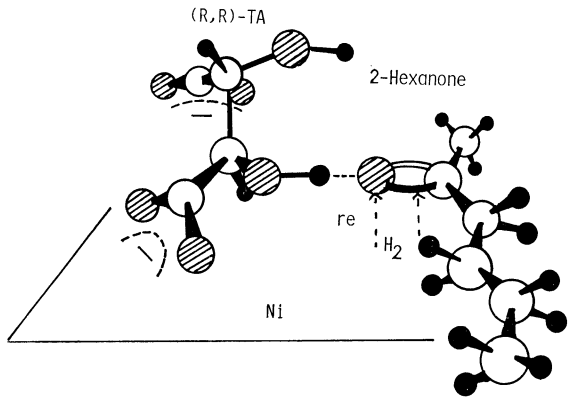


Fig. 2. Schematic representation of the interaction between (*R*,*R*)-TA and 2-hexanone on the MRNi.

fying reagent play an indispensable role in the enantioface-differentiation of MAA and analogs. Based on the hydrogen-bonding capacity between two hydroxyl groups in TA and two carbonyl groups in MAA, we have proposed the modes of co-adsorbed MAA and TA on the catalyst (Fig. 1).[5] When the mode of interaction is examined by a CPK model, it is expected that one of the hydroxyl groups of TA will come close to the catalyst surface (site 1), whereas the second hydroxyl group is somewhat remote from the surface (site 2).

If the adsorption of MAA takes place as shown in Fig. 1, the carbonyl group of MAA to be hydrogenated is fixed with site 1 and comes close to the surface of catalyst with its *si*-face facing to the catalyst. The MAA thus adsorbed is ready to be hydrogenated by the supply of activated hydrogen from the surface (*si*-face attack).

Thus, the hydrogenation of MAA over (*R*,*R*)-TA–NaBr–MRNi was expected to proceed predominantly by *si*-face attack.

As may be found in Fig. 1, the two hydroxyl groups of TA are arranged at a separation of around 2.5 Å and function as donors of the hydrogen bondings. Thus, it is predicted that not only MAA but also the compounds having two hydrogen bond acceptors arranged at a distance of around 2.5 Å, should be hydrogenated over TA–NaBr–MRNi in high optical yields. The good predictability of our stereochemical model is proved by the results summarized in Table 2. That is, all compounds satisfying the structural requirement shown in Fig. 1 were hydrogenated in high optical yields.

α-Keto ester (**1a**), which mostly exists in anti conformation, cannot make the interaction with TA through two hydrogen bonds. Even when it takes syn conformation its structure does not easily allow a well-fitting interaction with TA. Thus, the hydrogenation of **1a** was slow and gave an extremely poor optical yield.

In the case of γ-keto ester (**3a**), the distance between two carbonyl groups is a little longer than that between hydroxyl groups in TA. Therefore, a well fitting interaction leading to a high optical yield is not expected. However, the flexible nature enables the substrate to make some two-point interactions with TA. Thus, the hydrogenation of **3a** over (*R*,*R*)-TA–NaBr–MRNi gave (*R*)-**3b** in excess with a moderate optical yield.

A flexible $CH_3OCCH_2CH_2CH_2-$ group in δ-keto ester (**4a**) behaves either as an acceptor of hydrogen bonding with its ester carbonyl, or as a simple hydrophobic alkyl chain. The almost negligible optical yield in the reaction of **4a** would be caused by the exsistence of the two opposite modes of adsorptions. One is the same adsorption mode as in **2a** or **3a** and gives the product of *si*-face attack. The other mode is caused by the repulsion of hydrophobic chain with the hydroxyl group of TA, as will be discussed shortly.

In the case of simple ketone (**5a**), the adsorption mode is determined only by the hydrophobic alkyl group. The proximity of the hydroxyl groups of TA on the catalyst is expected to form a highly hydrophilic region. When the carbonyl group of **5a** interacts with one of the hydroxy groups of TA (site 1), the other hydroxyl group of TA (site 2) should expel the large hydrophobic hydrocarbon residue of the substrate to the other side. Consequently, the mode of adsorption shown in Fig. 2, leading to the *re*-face attack in giving (*S*)-isomer in excess, is expected to be preferable for **5a**. Since this sort of differentiation originates from the repulsive force and the only one-point interaction between substrate and modifying reagent, the reaction rate and optical yield are expected to be less than those of β-keto ester. Thus, the stereochemistry and the slow rate of hydrogenation of **5a** were explained by the partial modification of the above-mentioned stereochemical model.

The data listed in Table 2 show that the substrate being hydrogenated at the higher rate gives always the higher optical yield. The result clearly shows that the some attractive force between modifying reagent and substrate leading to the rigorous stereocontrol also functions to increase the concentration of the substrate at the reaction site. That is, the enhancements of both optical yield and rate in the hydrogenation of β-keto esters over TA–MRNi must originate from the hydrogen bondings between the modifying reagent and the substrate on the catalyst surface.

Table 4. Hydrogenation products of various substrates over TA-NaBr-MNi

Substrate		Isolated product		Method for the determination of optical purity	Optically pure compound	
		Bp θ_b/°C(mmHg)	$[\alpha]_D^{20}$/°		$[\alpha]_D^{20}$/°	Configuration
1a	**1b**	60—61(35)	−0.16(neat)	A	−8.25(neat)	$S^{20)}$
2a	**2b**	70—71(20)	−19.0(neat)	A	−22.95(neat)	*R*
3a	**3c**	88—90(15)	+13.3(*c* 4, dioxane)	A	−35.1(*c* 4, dioxane)	$S^{21)}$
4a	**4c**	100—101(15)	0 (neat)	A	—	
5a	**5b**	134—136(760)	+3.24(neat)	A	+11.57(neat)	$S^{22)}$
6a	**6b**	80—81(20)	−13.8(*c* 10, ethanol)	B	—	
7a	**7b**	78—79(21)	−11.5(*c* 10, ethanol)	B	—	
8a	**8b**	101—103(20)	−10.9(*c* 10, ethanol)	B	—	
9a	**9b**	128—130(10)	−9.3(*c* 10, ethanol)	B	—	
10a	**10b**	80—82(17)	−12.6(*c* 5, ethanol)	C	—	
11a	**11b**	88—89(16)	−23.5(*c* 5, ethanol)	C	—	
17a	**17b**	52—53(15)	−20.6(*c* 10, ethanol)	C	—	

Experimental

The ^{1}H-NMR and IR spectra were taken with a JEOL-FX-100 spectrometer and a Shimadzu IR 27G spectrometer, respectively.

The optical rotation was measured with a Perkin Elmer 241 polarimeter. The GLC was carried out with a Shimadzu 6A-PF Gas Chromatography, using 3 m—5 mm o.d. glass column packed with 2% Silicone OV-17 on Chromosorb W. (OV-17), 5% Tween 80 on Shimalite W (TW 80), or 5% neopentyl glycol succinate on Chromosorb W (NPGS), at the stated temperature.

All chemicals except those described below were obtained from commercial sources and were used without further purification.

Modifying Reagent. All modifying reagents employed in this study were synthesized by the reported methods. The physical and analytical data are listed in Table 3.

Substrate. Methyl pyruvate (**1a**):[3] bp 61—63 °C/13 mmHg (1 mmHg≈133.322 Pa), methyl 4-oxopentanoate (**3a**):[3] bp 76—78 °C/12 mmHg, methyl 5-oxohexanoate (**4a**):[3] bp 95—97 °C/15 mmHg, isopropyl acetoacetate (**7a**):[15] bp 82—84 °C/13 mmHg, isobutyl acetoacetate (**8a**):[15] bp 88—90 °C/19 mmHg, hexyl acetoacetate (**9a**):[15] bp 133—134 °C/24 mmHg, methyl 3-oxopentanoate (**10a**):[16] bp 68—71 °C/13 mmHg, methyl 4-methyl-3-oxopentanoate (**11a**):[16] bp 85—87 °C/22 mmHg, methyl 3-oxotetradecanoate (**12a**):[17] mp 30 °C, methyl 2-oxobutylsulfone (**14a**):[18] mp 44.0—44.5 °C, methyl 2-oxoheptylsulfone (**15a**):[18] mp 37—38 °C, 4-hydroxy-2-butanone (**16a**):[7] bp 56—58 °C, and 4-methoxy-2-butanone (**17a**):[19] bp 48—49 °C/20 mmHg were prepared by the reported methods.

MRNi. The modifying solution was prepared by dissolving 0.67 mol equivalent of modifying reagent and 10 g of NaBr in 100 ml of deionized water.

The solution was adjusted to pH 3.2 with 1 mol dm^{-3} NaOH. The Raney nickel prepared from 1.9 g of alloy (Kawaken Fine Chemical Co. Ni/Al=42/58) was subjected to modification at 100 °C by the method reported before.[1]

Hydrogenation. The hydrogenation was carried out in a 100 ml autoclave under 90—120 kg/cm^2 of initial hydrogen pressure at the conditions specified in Table 1 or 2 in the text.

Data listed in Entries 12, 13, 14, 15, and 16 in Table 2 are taken from our published papers. The details of isolation and determination of optical purity of each reaction product are described in the paper cited in Table 2.

The hydrogenation products of **1a**, **2a**, **5a** to **11a**, and **17a** in Table 2 were purified by fractional distillation. The hydrogenation products of **3a** and **4a**, mixture of ester of hydroxy acid and lactone, were converted to the corresponding lactone by refluxing in benzene with Amberlyst 15 for 3 h.[3] The resulting lactone was purified by fractional distillation.

The isolated hydrogenation products are listed in Table 4.

The optical purity of the reaction products was determined by three different methods, referred to as A, B, and C in Table 4.

(A) The optical purity was directly determined by polarimetry based on the published value of $[\alpha]_D^{20}$ for optically pure material.

(B) The optical purity of the hydrogenation product was evaluated from the optical purity of MHB derived from the hydrogenation product via saponification and the following esterification with CH_2N_2.

(C) The optical purity was determined by ^{1}H-NMR in the presence of Eu(hfmc)$_3$. In the case of **10b**, and **11b**, the difference of chemical shift for methyl proton of $-\overset{\overset{O}{\|}}{C}-O-CH_3$ (singlet) of (*S*) and (*R*)-isomers was 5.5 Hz when the spectra were measured with solution of **10b** or **11b** (10 mg) and Eu(hfmc)$_3$ (25 mg) in 400 μl of $CDCl_3$.

In the case of **17b**, the difference for methyl proton of (*R*) and (*S*)-isomer was 8 Hz in the spectra taken with a solution of **17b** (10 mg) and Eu(hfmc)$_3$ (5 mg) in 400 μl of $CDCl_3$.

The results are listed in Table 2.

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