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Asymmetric Hydrogenation of 3,5-Dioxoesters Catalyzed by Ru-binap Complex: A Short Step Asymmetric Synthesis of 6-Substituted 5,6-dihydro-2-pyrones

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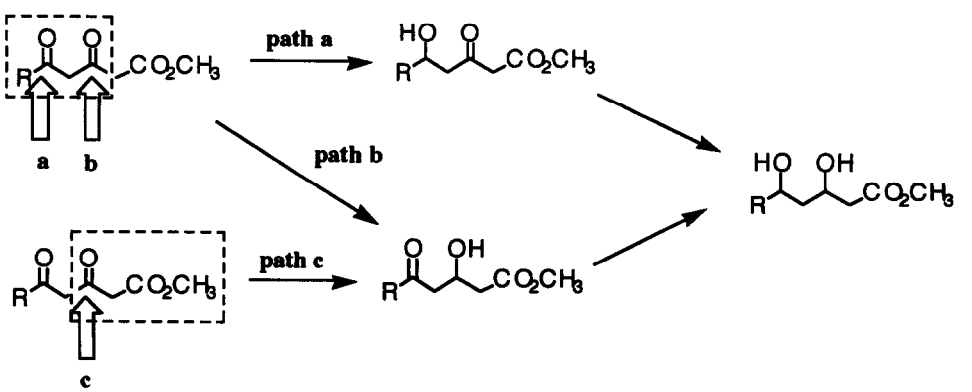
Key words: 3, 5-dioxoester; Ru-binap catalyst; asymmetric hydrogenation; asymmetric synthesis, lactone.

Abstract: Asymmetric hydrogenation of 3,5-dioxoesters **1a-c** using Ru_2Cl_4((*R*) or (*S*)-binap)$_2$(NEt_3) as the catalyst gave dominantly *anti* 3,5-dihydroxyesters **2**, which were then converted into unsaturated lactones **5a-b** (ca. 80% e.e.). The pathway of the hydrogenation reaction was also investigated by asymmetric hydrogenation of (*R*)- or (*S*)-5-hydroxy-3-oxoesters **8a-c**. It was revealed that the Ru-binap catalyzed hydrogenation of **1a-b** proceed dominantly via the β-diketone mode. A convenient asymmetric synthesis of hydroxylactone **3c** and unsaturated lactone **5c** was presented.

INTRODUCTION

It was demonstrated recently that the asymmetric hydrogenation of functionalized carbonyl compounds catalyzed by Ru-binap complexes (binap = (*R*)- or (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) affords the products having very high degree of enantiomeric excess, and that this provides a useful tool for asymmetric synthesis of hydroxy compounds.[1,2,3] In general, carbonyl compounds that involves an additional functional group, such as another keto group (α- or β-diketone) or an ester function (β-ketoester), for making secondary

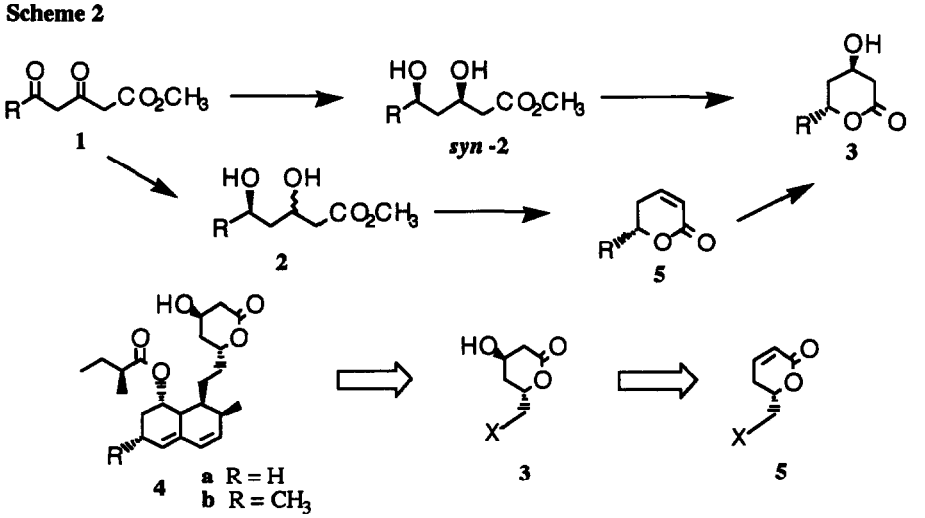
Scheme 1



interaction with the metal center effective, exhibit extremely high asymmetric induction upon the hydrogenation. It is of interest to clarify the stereochemical outcome of the hydrogenation of β,δ-diketoesters to give β,δ-dihydroxyesters, because the substrates involve partial structures of both β-diketone and β-ketoester in a molecule. As Scheme 1 shows, the initial hydrogenation step of β,δ-diketoesters could take place at the δ-carbonyl group in such a manner as β-diketone (path a). Otherwise, the substrate would be firstly hydrogenated with Ru-binap catalyst at the β-carbonyl group, acting either as a β-diketone (path b) or as a β-ketoester (path c). The hydrogenation of the remaining carbonyl group should be affected not only by the chiral catalyst but also by the chiral center formed in the preceding hydrogenation. The total hydrogenation of β,δ-diketoesters is, therefore, expected not to be simple.

If a highly enantio- and diastereoselective hydrogenation of 3,5-dioxoester **1** was successfully performed to give an enantiomerically pure *syn* 3,5-dihydroxyester **2**, it would provide a short and efficient access to a hydroxylactone **3**, the key building block for the synthesis of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, such as compactin **4a**[4] and mevinolin **4b**[5] (Scheme 2). These enzyme inhibitors and even more bioactive analogues have been the targets of intensive studies in organic synthesis.[6] Herein we describe the asymmetric hydrogenation of 3,5-dioxoesters **1** catalyzed by Ru-binap complex and a two step procedure of preparing 6-substituted 5,6-dihydro-2-pyrone **5** via the asymmetric hydrogenation of **1** and successive lactonization and dehydration of diastereomers of dihydroxyester **2**. Unsaturated lactones analogous to **5** have been employed for precursors of hydroxylactones as **3**.[6,7] A preliminary report for the asymmetric hydrogenation of 3,5-dioxohexanoate (**1**, R = CH_3) with Ru-binap catalyst has recently been published.[8]

Scheme 2



RESULTS AND DISCUSSION

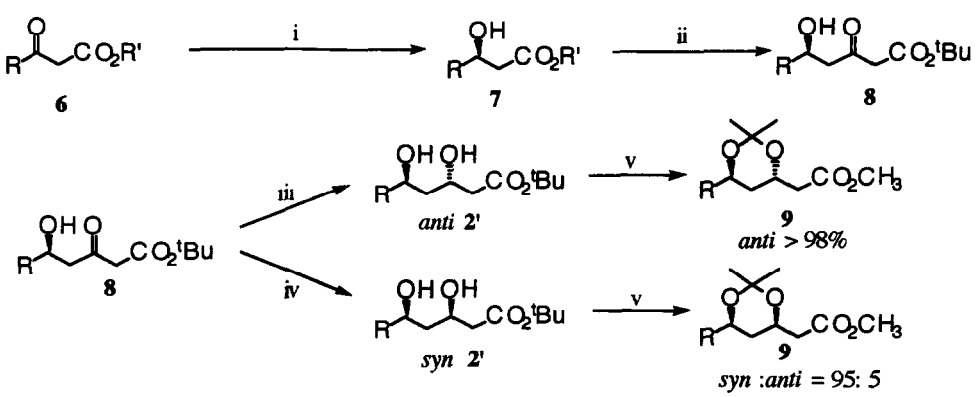
Preparation of authentic 3,5-dihydroxyesters

The hydrogenation of a 3,5-dioxoester **1** introduces two new chiral centers to the product in a single procedure. In order to investigate the stereoselectivity and reaction paths of the hydrogenation, we required the authentic *syn* and *anti* 3,5-dihydroxyesters. The dihydroxyesters having the distinct configurations were prepared by the known methods (Scheme 3). Firstly, β-ketoesters **6a-c** (**a**, R = CH_3; **b**, R = $CH_3CH_2CH_2$; **c**, R = $C_6H_5CH_2OCH_2$ (= $BnOCH_2$)) were transformed to the 3-hydroxyesters **7a-c** by Ru-binap catalyzed hydrogenations.[2] The enantiomeric excesses determination by HPLC employing the appropriate derivatives showed that **7a** and **7b** have equally 98 % e.e., while **7c** has 94% e.e., slightly lower than **7a** and **b**, presumably due to the steric and/or electronic effect of the benzyloxy group.

Then, **7a-c** were reacted with enolate of *t*-butyl acetate to give 5-hydroxy-3-oxoesters **8a-c** in 68-75% yields.[9] Finally, (*R*)-**8a** and -**8b** and (*S*)-**8c** were reduced with ($(CH_3)_4NHB(AcO)_3$)[10] to afford *anti* 3,5-dihydroxyesters (3*S*,5*R*)-**2'a** and -**2'b** , and (3*S*,5*S*)-**2'c**. (In order to distinguish the t-butyl esters of 3,5-dihydroxy acids from the corresponding methyl esters, the former will be referred hereafter as **2'**.) Alternatively, the reduction of the hydroxyketoesters **8a-c** by Narasaka's method ($Et_3B/NaBH_4$)[11] gave *syn* dihydroxyesters, (3*R*,5*R*)-**2'a** and -**2'b** and (3*R*,5*S*)-**2'c**, respectively, with sufficiently high diastereoselectivity.

The resulting diastereomers of 3,5-dihydroxyesters **2'a-c** were converted, respectively, into the acetonides *anti* **9a-c** (*anti* > 98%) and *syn* **9a-c** (*syn* = 95-98%). It has been demonstrated that the ^{13}C NMR characteristics of methyl groups of such acetonides are diagnostic to the relative stereochemistry of parent 1,3-diols.[12] These

Scheme 3



a, R = CH_3, R' = CH_3, **b**, R = C_3H_7, R' = Et; **c**, R = $BnOCH_2$, R' = ^tBu

i, Catalyst, Ru_2Cl_4((*R*)-binap)(NEt_3); H_2, 100 atm; solvent, MeOH; 50° C; 48 h. ii, AcOtBu / LDA.
iii, $(CH_3)_4NHB(AcO)_3$, CH_3CN, AcOH. iv, $Et_3B/NaBH_4$, THF-MeOH, -78°C, Ar;
v, $(CH_3)_2C(OCH_3)_2$, PTS, reflux 2h.

standard acetonides served for determining the diastereomer ratio of the hydrogenation products of **1** by means of GLC analysis. The acetonides *anti* and *syn* **9a-c** exhibited the ^{13}C NMR features expected for respective stereoisomers.

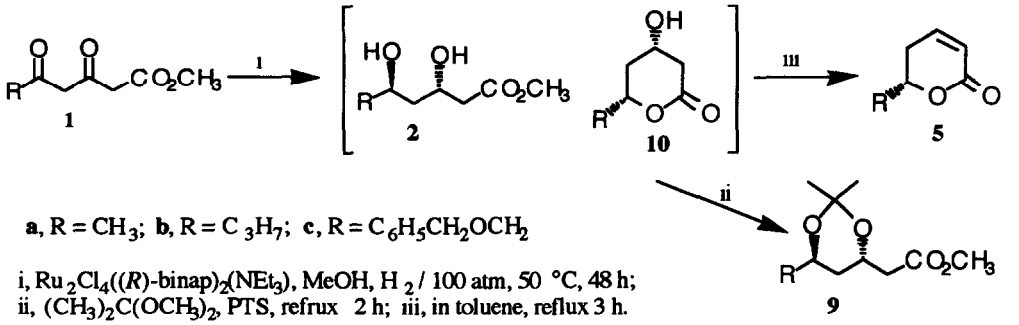
Ru-binap complex-catalyzed hydrogenation of 3,5-dioxoesters

In order to establish appropriate conditions for hydrogenation of 3,5-dioxoesters **1**, the hydrogenation of 3,5-dioxohexanoate **1a**, the simplest β,δ-diketoester, was examined under varied reaction conditions. We found a considerable temperature effect in the Ru-binap catalyzed hydrogenation of **1a**. At 25 °C, where β-ketoesters and β-diketones were found to be readily hydrogenated with Ru-binap catalyst (H_2 pressure, 100 atm; solvent, methanol; substrate/catalyst (as Ru) = 500; reaction time, 48 h),[2,3] no reaction took place, and a less than 5% conversion was obtained at 35 °C under the same conditions. In contrast, a complete hydrogenation of **1a** could be performed at 50 °C under above mentioned conditions. The GLC analysis of a reaction mixture at 50 °C showed that no substrate remained, and that dihydroxyhexanoate **2a** and hydroxylactone **10a** were recognized as the hydrogenated products. **10a** should be derived from **2a**, because the reaction medium is considerably acidic. The hydrogenation of other 3,5-dioxoesters **1b** and **1c** were also carried out in methanol with Ru_2Cl_4((*R*)-or (*S*)-binap)$_2$(NEt_3) (0.2 mol% as Ru) under 100 atm of hydrogen at 50° C for 48 h as the case of **1a**. The outline of Ru-(*R*)-binap catalyzed hydrogenation of 3,5-dioxoesters **1a-c** are given in Scheme 4 and Table 1. In Scheme 4, only the preferentially formed diastereomers of respective products are presented.

Small portions of the reaction mixtures from **1a-c** were treated, respectively, with 2,2-dimethoxypropane to give diastereomer mixtures of acetonides **9a-c**. The *anti* : *syn* ratios of **9a-c**, which should correspond to the overall diastereomer ratios of the hydrogenation products **2a-c**, were determined by the GLC analysis. Further, the whole reaction mixtures containing **2a-c** and **10a-c** were refluxed in toluene containing *p*-toluenesulfonic acid (PTS) for 2 h, and, after chromatographic purifications, the unsaturated lactones **5a-c** were obtained in 65-73% overall yield (see Scheme 4 and Table 1). The optical rotation of **5a** obtained by Ru_2Cl_4((*R*)-binap)$_2$(NEt_3) catalyzed hydrogenation was $[\alpha]_D^{26}$ -157.6°, indicating that the configuration at C-6 is dominantly (*R*) and that the optical purity of (*R*)-**5a** is 77 %[13] (lit. for (*S*)-**5a**, $[\alpha]_D^{24}$ +206°). The unsaturated lactones **5b** and **5c** possess similar optical purities as **5a** (Table 1). By similar procedures using Ru_2Cl_4((*S*)-binap)$_2$(NEt_3) as a catalyst, **1a-c** were converted in two steps to (*S*)-**5a** and -**5b** and (*R*)-**5c**, respectively, with comparable optical purities obtained with (*R*)-binap catalyst (Table 1).

The enantiomeric excesses of **5a-c** were determined for their amide derivatives by means of HPLC method (see Experimental). Since the enantiomeric purities of the lactones (*S*)-**5a**, (*S*)-**5b** and (*R*)-**5c** were 80, 80, and 70 %, respectively, it is apparent that the configuration at C-5 of 3,5-dihydroxyesters **2a** and **2b** (and that of acetonides **9a** and **9b**) is fairly controlled ((*S*) : (*R*) = 9 : 1), whereas the stereoselectivity at C-5 of **2c** is slightly lowered ((*R*) : (*S*) = 85 · 15 for **2c** and **9c**). The fact that the *anti* isomers are dominant among the diastereomers of **9a** and **9b** suggests that the stereocontrol for the hydrogenation of **1a** and **1b** is, as a whole, very similar to that found in the hydrogenation of β-diketones with Ru-binap catalyst.[3] However, it seems that, in the case of substrate **1c**, the benzyloxy group causes a significant substituent effect, which reduced both enantio- and diastereoselectivity of the hydrogenation.

Scheme 4



a, R = CH_3; **b**, R = C_3H_7; **c**, R = $C_6H_5CH_2OCH_2$

i, $Ru_2Cl_4((R)\text{-binap})_2(NEt_3)$, MeOH, H_2 / 100 atm, 50 °C, 48 h;
ii, $(CH_3)_2C(OCH_3)_2$, PTS, refrux 2 h; iii, in toluene, reflux 3 h.

Table 1. Asymmetric hydrogenation of 3,5- dioxoesters catalyzed by Ru-binap complexes[a]

Substrate	R[a]	Catalyst[b]	Conv. (%)[c]	*Anti* : *Syn*[d]	Configu.[e]	O.P. (%)[f]
1a	CH_3	(*R*)-**I**	100	80 :20	*R*	77
		(*S*)-**I**	100	81 : 19	*S*	78
1b	C_3H_7	(*R*)-**I**	100	78 :22	*R*	78
		(*S*)-**I**	100	76 : 24	*S*	81
1c	$BnOCH_2$	(*R*)-**I**	100	51 : 49	*S*	70
		(*S*)-**I**	100	50 : 50	*R*	71

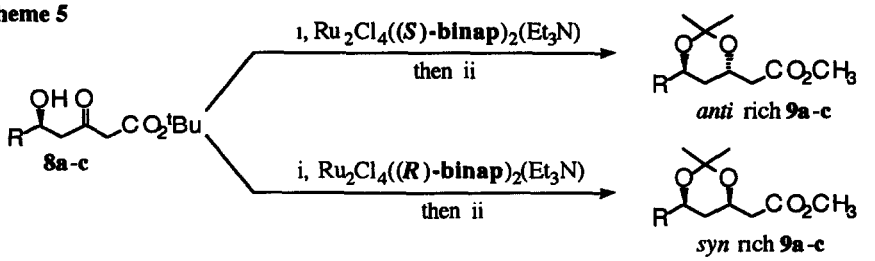
a, see Scheme 3. b, **I** refers to $Ru_2Cl_4(binap)_2(NEt_3)$; (*R*) and (*S*) show the configuration of binap used. c, Determined for reaction mixtures by GLC. d, Obtained by GLC for the acetonides **9a-c**. e, The configuration of unsaturated lactones **5a-c**. f, The optical purities of **5a-c**.

The ^1H NMR measurements of 3,5-dioxoesters **1a-c** indicated that these compounds exist almost exclusively in the enolate forms of their β-diketone moieties in solutions. Thus, a proton signal assignable to the enol part (OH..O) was found as a broad peak at lower field (δ ca. 15). In accord to this enolization, a singlet having one proton intensity, which should be ascribed to the signal at C-4, was found in the region δ 5.6-6.0. It is reasonably understood, therefore, that **1a-c** interact with the Ru species in similar manners with β-diketones to afford the hydrogenated products described above.

Asymmetric hydrogenation of 5-hydroxy-3-oxoesters with Ru-binap catalyst

Although it was revealed that the Ru-binap catalyzed hydrogenation of **1a-c** proceeds dominantly via the β-diketone mode and produces mainly the *anti* 3,5-dihydroxyesters, it is difficult to determine which carbonyl group of C-3 or C-5 in **1** is converted into a hydroxy group at the first stage of the total reaction, on the basis of hydrogenation results of diketoesters alone. With a view to solve this problem, the hydrogenation of *t*-butyl 5-hydroxy-3-oxoesters **8a-c** of known configuration was carried out under the same conditions employed for the hydrogenation of **1a-c** (Scheme 5 and Table 2). Thus, (*R*)-**8a** and -**8b** and (*S*)-**8c**, which assume the same relative configuration at C-5, were hydrogenated with Ru-(*S*)-binap complex to afford, after usual acetalization, *anti*-rich products with sufficient stereoselectivity. In contrast, with Ru-(*R*)-binap complex, the hydrogenation of (*R*)-**8a** and -**8b** and (*S*)-**8c** gives generally *syn*-rich mixtures of dihydroxyesters.

Scheme 5



i, H_2, 100 atm, 50 °C, methanol, 48 h. ii, 2,2-dimethoxypropane, PTS, reflux, 2 h.

Table 2. Asymmetric hydrogenation of t-butyl 5-substituted 5-hydroxy-3-oxohexanoate catalyzed by Ru-binap complex[a]

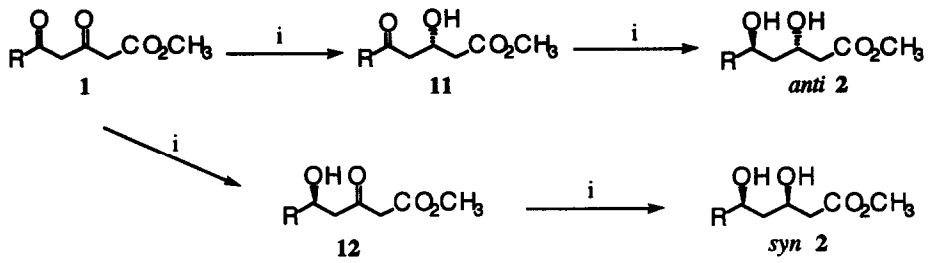
Substrate	R	Catalyst	Conversion (%)[b]	*Anti* : *Syn*[c]
(*R*)-**8a**	CH_3	(*S*)-**I**	100	95 : 5
		(*R*)-**I**	100	40 : 60
(*R*)-**8b**	C_3H_7	(*S*)-**I**	100	78 : 22
		(*R*)-**I**	100	43 : 57
(*S*)-**8c**	$PhCH_2OCH_2$	(*S*)-**I**	100	94 : 6
		(*R*)-**I**	100	18 : 82

a, see Scheme 4. b, Determined by GLC. c, Determined by GLC after converting the dihydroxy esters **2'a-c** to the corresponding dimethylacetals **9a-c**.

It should be noted that the stereochemical outcome in the hydrogenation of **8** is completely different from that observed in the direct hydrogenation of **1**. As described previously (Scheme 4, Table 1), the hydrogenation of **1a** and **1b** with Ru-(*R*)-binap complex should give preferentially the *anti* dihydroxy products **2a** and **2b** having (3*S*,5*R*) configuration. Under the same conditions, **1c** was converted into the *anti* product, (3*S*,5*S*)-**2c**. In contrast, the same *anti* enantiomers, (3*S*,5*R*)-**2'a** and -**2'b** and (3*S*,5*S*)-**2'c** were predominantly obtained, respectively, via the hydrogenation of (*R*)-**8a** and -**8b** and (*S*)-**8c** with Ru-(*S*)-binap complex, the antipode employed for the hydrogenation of **1a-c**. Alternatively, when the Ru-(*R*)-binap complex was used as a catalyst, the hydrogenation of (*R*)-**8a** and -**8b** gave dominantly the *syn* products (3*R*,5*R*)-**2'a** and -**2'b**, although the diastereoselectivity was only moderate (Scheme 5, Table 2). With the same Ru-(*R*)-binap catalyst, (*S*)-**8c** was transformed into the *syn* dihydroxyester, (3*R*,5*S*)-**2'c** with a considerably high diastereoselectivity (Table 2). These facts strongly indicate that the 5-hydroxy-3-oxoesters **8a-c** were not the main initial product in the hydrogenation of 3,5-dioxoesters **1a-c**.by the Ru-binap catalyst.

All of these results suggest that the hydrogenation of **1a** and **1b** proceeds via a reaction sequence shown in Scheme 6. We assume that, in Ru-(*R*)-binap catalyzed hydrogenation, **1a** and **1b** coordinate to a Ru-binap system predominantly with their 3,5-dicarbonyl moiety as described previously, and that the C-3 carbonyl group is at first selectively hydrogenated to give (*S*)-3-hydroxy-5-oxoesters, (*S*)-**11a** and -**11b** (path b in Scheme 1). The C-5 carbonyl group is subsequently hydrogenated to afford the dihydroxyester (3*S*,5*R*)-**2a** and -**2b** under an *anti* selective stereocontrol similar to the hydrogenation of β-diketones.[2]

Scheme 6 . A possible pathway for hydrogenation of 3,5-dioxoesters



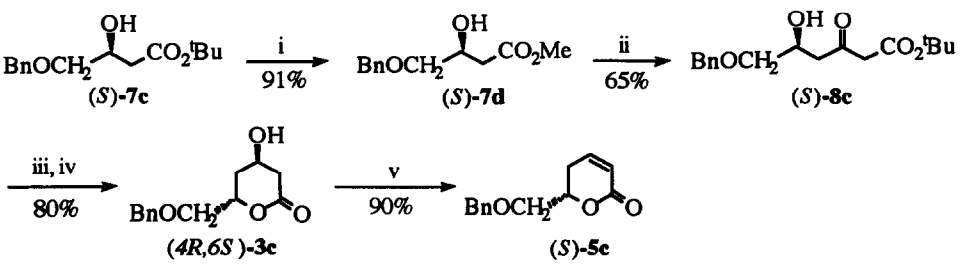
i, Ru_2Cl_4((*R*)-**binap**)$_2$(Et_3N), H_2/100 atm, 50 °C, 48 h, MeOH

It is possible that the hydrogenation of **1a** and **1b** with Ru-(*R*)-binap catalyst proceeds in small part under the control of C-3 carbonyl and ester carbonyl groups to give dominantly (*R*)-**11a** and -**11b** (path c in Scheme 1). The contamination of these 3-hydroxy-5-oxoesters should result in the formation of other diastereomers ((3*R*,5*S*) and (3*R*,5*R*)) of **2a** and **2b**, and the lower diastereoselectivity of **2a** and **2b** and lower e.e. values of lactone **5a** and **5b**, compared with the corresponding values for the hydrogenation of simple β-diketones by the same catalyst.

In contrast to the cases of **1a** and **1b**, the Ru-(*R*)-binap catalyzed hydrogenation of **1c** showed no appreciable preference to the *anti* dihydroxyesters **2c**, although the unsaturated lactone **5c**, derived from **2c**, has a good enantiomeric purity (70 % e.e.; Table 1). We suppose that the asymmetric hydrogenation of **1c** could give firstly (*S*)-**12c** (via path a in Scheme 1) in comparable amount to (*S*)-**11c**, presumably due to the steric or/and electric effects of the benzyloxy group. The hydrogenation of (*S*)-**12c** with (*R*)-binap catalyst should afford the *syn* product with considerably high selectivity (Table 2). Thus, the concomitant formation of (*S*)-**12c** and -**11c** would result in the formation of the final product **2c** having rather low diastereoselectivity (*anti* : *syn* = ca. 50 : 50) by the subsequent hydrogenation. (see Tables 1 and 2; Scheme 6).

Preparation of Chiral 6-Substituted 4-Hydroxy-2-pyrone

Scheme 7



i, MeOH, H_2SO_4, reflux 5 h; ii, AcOtBu/LDA; iii, Et_3B/$NaBH_4$, THF-MeOH, -78°C, Ar;
iv, H^+; v, in toluene, PTS, reflux 2 h.

We have also established a chiral synthesis of (4*R*, 6*S*)-6-benzyloxymethyl-4-hydroxy-tetrahydro-2-pyrone **3c**, a key synthon for the lactone portion of compactin and mevinolin,[7] using hydroxyester **7c** as a starting material

(Scheme 7). (*S*)-**7c** was converted to (*S*)-**7d** by an ester exchange reaction, because the former does not react smoothly with the enolate of *t*-butyl acetate. It was ascertained that no racemization occurred during the ester exchange. **7d** was converted into the hydroxyketoester **8c** in 65% yield. **8c** was then stereoselectively reduced with $Et_3B/NaBH_4$ to afford, after lactonization, (4*R*,6*S*)-**3c** in 80% yield with 93% O.P.[7] (*S*)-**5c** having 94 % O.P.[7] was obtained in 43% overall yield from (*S*)-**7c**.

EXPERIMENTAL

General. All the solvents employed for preparing ruthenium complexes and for asymmetric hydrogenation were dried and distilled by conventional methods and stored under nitrogen. (*R*)- and (*S*)-Binap were presented by Takasago Research Institute Inc. $Ru_2Cl_4((R)\text{-binap})_2(NEt_3)$ and $Ru_2Cl_4((S)\text{-binap})_2(NEt_3)$ were prepared by the reported method[14].

Optical rotations were measured on a Jasco DIP-360 digital polarimeter. Gas chromatographic (GLC) analysis was performed with a Shimadzu GC-14A instrument equipped with a fused silica capillary column (Shimadzu CBP10, 25 m) and a flame ionization detector. High performance liquid chromatography (HPLC) was carried out with a Shimadzu SPD-6 apparatus equipped with a Shimadzu SPC-7A UV spectrometric detector and a Shimadzu Chromatopac CR-5A, employing chiral stationary phase columns Daicel Chiralcel-OD [Cellulose tris(3,5-dimethylphenylcarbamate; 0.46 cm, (internal diameter); 25.0 cm (length)]. IR spectra were measured on a Shimadzu FTIR-8100M spectrometer. ^1H and ^{13}C NMR spectra were measured with a JEOL JMN-GX 400 spectrometer.

Methyl 3,5-dioxohexanoate, 1a.[15] Dehydroacetic acid (25.0 g; 0.15 mol) was dissolved in 0.24 M methanol solution of $Mg(OMe)_2$ (500 cm^3). The mixture was refluxed for 8 h, and the solvent was removed under reduced pressure. The residue was acidified with 1 M HCl (500 cm^3) and extracted with ethyl acetate (3 × 100 cm^3). The combined organic layer was washed with water (3 × 50 cm^3), dried with Na_2SO_4 and concentrated. Methyl 3,5-dioxohexanoate was obtained by distillation in 75 % yield, bp: 90-92 °C (4 mmHg). ^1H NMR ($CDCl_3$, TMS), δ 2.08 (s, 3H, CH_3), 3.35 (s, 2H, 2-H), 3.75 (s, 3H, OCH_3), 5.62 (s, 1H, **4-H**), 15.11 (s, 1H). IR (NaCl) ν_{max} /cm^{-1}, 1750.

Methyl 3,5-dioxooctanoate 1b. Methyl 3,5-dioxooctanoate was prepared by the reported method[16] in 65%. ^1H NMR ($CDCl_3$, TMS), δ 0.96 (t, 3H, J = 7.3 Hz), 2.28 (t, 2H, J = 7.3 Hz), 3.36 (s, 2H), 3.75 (s, 3H, $-CO_2CH_3$), 5.60 (s, 1H), 15.14 (br, 1H). IR (NaCl) ν_{max} /cm^{-1} 1746.

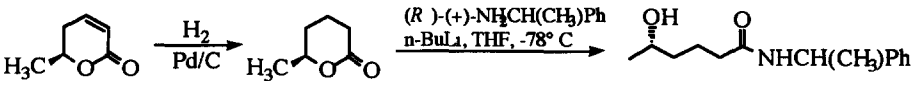
Methyl 6-benzyloxy-3,5-dioxohexanoate 1c. To a suspension of sodium hydride, (55 % mineral oil dispersion, 0.44 g, 10.0 mmol) in anhydrous tetrahydrofuran (25 cm^3), methyl acetoacetate (1.16 g, 10.0 mmol) was added dropwise at 0 °C under nitrogen atmosphere, and the mixture was stirred for further 10 min. A solution of n-butyllithium (1.65 M in hexane, 10.0 mmol) was added dropwise to the mixture, and this was stirred for 10 more min, and then ethyl benzyloxyacetate (5.0 mmol) was added in one portion. After ca. 20 min, the reaction was quenched with concentrated hydrochloric acid (pH 1). Water (10 cm^3) and ethyl ether (20 cm^3) were added, aqueous layer was separated and extracted with ether (2 × 20 cm^3). The combined organic layer was washed with saturated sodium bicarbonate solution (3 × 10 cm^3) and with saturated brine (3 x 10 cm^3), dried over sodium sulfate. After filtration and concentration, the residue was purified by column chromatography to give product in 62% yield. ^1H NMR ($CDCl_3$, TMS), δ 3.39 (s, 2H, **2-H**), 3.75 (s, 3H, CO_2CH_3), 4.10 (s, 2H, $BnOCH_2$), 4.60 (s, 2H, $PhCH_2$), 5.96 (s, 1H), 7.29-7.38 (m, 5H, **aromatic**), 15.12 (br, 1H). IR (NaCl) ν_{max} /cm^{-1} 1740.

Asymmetric hydrogenation of **1a** was described as a representative. Under a flushing argon atmosphere, a solution of **1a** (1.0 g, 6.3 mmol) and $Ru_2Cl_4((S)\text{-binap})_2(NEt_3)$ (10 mg) in anhydrous methanol was placed in a 50 cm^3 stainless steel autoclave. Hydrogen was pressurized to 100 atm, and the solution was stirred at 50° C for 48 h. The GLC analysis showed that no substrate remained in the reaction mixture, and methyl 3,5-dihydroxyhexanoate **2a** and lactone **10a** (4-hydroxy-6-methyl-tetrahydro-2-pyrone, ^1H NMR ($CDCl_3$, TMS), δ 1.42 (d, 3H, CH_3), 1.60 (m, 1H, **5-H**), 2.28 (dddd, 1H, J = 13.7, 5.5, 3.1, 1.2 Hz, **5-H**), 2.46 (dd, 1H, J = 17.1, 7.6 Hz, **3-H**;), 2.89 (ddd, 1H, J = 17.1, 5.8, 1.2Hz, **3-H**), 3.41 (br, 1H, OH), 4.25 (m, 1H, **4-H**), 4.37 (m, 1H, **6-H**)) were obtained as a mixture. A small portion of the mixture was treated with 2,2-dimethoxypropane to give a diastereomer mixture of acetonide **9a**, the *anti* : *syn* ratio of which was determined to be 80 : 20 by GLC analysis.

6-Methyl-5,6-dihydro-2-pyrone ***5a***. The whole reaction mixture obtained as above, containing **2a** and **10a**, was evaporated and the residue dissolved in toluene containing PTS (3 mg), and the solution was heated under reflux for 2 h. After purification by a chromatography (silica gel; hexane/ethyl acetate, 4:1) lactone (*S*)-**5a** was obtained in 65 % overall yield. The optical rotation of (*S*)-**5a** was $[\alpha]_D^{26}$ +160.2° (c = 1.24, ethanol); optical purity, 78 % (lit.[13] for (*S*)-**5a**, $[\alpha]_D^{24}$ + 206° (c = 1, ethanol)). ^1H NMR ($CDCl_3$, TMS), δ 1.45 (d, 3H, CH_3; J = 6.4 Hz), 2.34 (m, 2H, **5-H**), 4.58 (m, 1H, **6-H**), 6.03 (ddd, 1H, J = 9.8, 2.7, 1.0 Hz, **3-H**), 6.80 (ddd, 1H, J = 9.8, 5.5, 2.8 Hz, **4-H**). IR (NaCl), ν_{max}/cm^{-1} 1715.

By similar procedures employing $Ru_2Cl_4((R)\text{-binap})_2(NEt_3)$ as the catalyst,.(*R*)-**5a** was obtained in 66% overall yield. $[\alpha]_D^{26}$ -157.6° (c = 1.06, ethanol), 77 % optical purity.

The enantiomeric excess of (*S*)-**5a** was determined as follows. (*S*)-**5a** was hydrogenated with Pd-C as a catalyst to the saturated lactone (*S*)-**13**, and then treated with anion of (*R*)-(+)-α-phenylethylamine to give the amide (*S,R*)-**14**. The diastereomer ratio of **14** ((*S,R*) : (*R,R*)) was determined by HPLC with a silica gel column (hexane/2-propanol = 85 : 5). The diastereomeric excess (80 %), which corresponds to the e.e. of (*S*)-**5a**, was almost same as the optical purity.

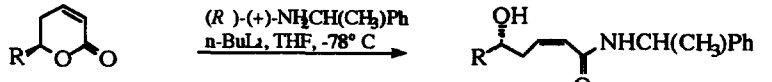


(*S*)-**5a** (*S*)-**13** (*S,R*)-**14**

6-Propyl-5,6-dihydro-2-pyrone ***5b***. By similar procedures described above, the asymmetric hydrogenation of **1b** was performed, employing $Ru_2Cl_4((R)\text{-binap})_2(NEt_3)$ as a catalyst. The subsequent treatments with PTS give (*R*)-6-propyl-5,6-dihydro-2-pyrone (*R*)-**5b** in 70% overall yield. $[\alpha]_D^{22}$ -107.2° (c = 1.2, $CHCl_3$), 81% optical purity (The O.P. was calculated based on the (*S*)-**5b** prepared from **7b** with 98% e.e., $[\alpha]_D^{22}$ +130.1° (c = 1.2, $CHCl_3$)). ^1H NMR ($CDCl_3$, TMS), δ 0.96 (t, 3H, J = 7.3 Hz, CH_3), 1.67-1.40 (m, 3H, $MeCH_2CH_2$), 1.80 (m, 1H, $EtCH_2$), 2.35 (m, 2H, **5-H**), 4.44 (m, 1H, **6-H**), 6.02 (m, 1H, **3-H**), 6.89 (dddd, 1H, J = 9.8, 5.5, 3.1 Hz, **4-H**). ^{13}C NMR ($CDCl_3$, TMS) δ 164.7, 145.1, 121.4, 77.8, 36.9, 29.4, 18.1, 13.8. IR (NaCl), ν_{max}/cm^{-1} 1721.

By the use of $Ru_2Cl_4((S)\text{-binap})_2(NEt_3)$ as the catalyst, the hydrogenation **1b** gave (*S*)-**5b** with $[\alpha]_D^{22}$ +103.6° (c = 1.0, $CHCl_3$), 78 % O.P.

The enantiomeric excess of (*S*)-**5b** was determined as follows. (*S*)-**5b** was treated with anion of (*R*)-(+)-α-phenylethylamine to give the amide **15b**. The diastereomer ratio of **15b** ((*S,R*) : (*R,R*)) was determined by HPLC with a silica gel column (hexane/2-propanol = 95 : 5, flow rate = 1.0 ml/min). The diastereomeric excess (80 %), which corresponds to the e.e. of (*S*)-**5b**, was almost the same to the optical purity.



(*S*)-**5** **b**, R = C_3H_7; **c**, R = $BnOCH_2$ (*S,R*)-**15**

6-Benzyloxymethyl-5,6-dihydro-2-pyrone **5c**. The hydrogenation of **1c** catalyzed by Ru_2Cl_4((*R*)-binap)$_2$(NEt_3) was carried out under similar conditions to those for the hydrogenation of **1a** to afford, after dehydration, (*S*)-6-benzyloxymethyl-5,6-dihydro-2-pyrone (*S*)-**5c** in 72% overall yield. $[\alpha]_D^{22}$ -81.7° (c = 1.1, $CHCl_3$) (lit.[7] .$[\alpha]_D^{27}$ -115.07° (c = 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, TMS), δ 2.40 (dddd, 1H, **5-H**, J = 18.6, 5.8, 4.3, 1.2 Hz), 2.57 (dddd, 1H, **5-H**, J = 18.6, 11.6, 2.8, 2.8 Hz), 3.70 (d, 2H, BnOC**H$_2$**, J = 4.9 Hz), 4.60 (m, overlap, 3H, **6-H** and Ph**CH$_2$**), 6.02 (ddd, 1H, **3-H**, J = 9.8, 2.8, 1.2 Hz), 6.90 (ddd, 1H, **4-H**, J = 9.8, 5.8, 2.8 Hz), 7.28-7.38 (m, 5H, **aromatic**). ^{13}C NMR ($CDCl_3$, TMS), δ 163.7, 144.9, 137.7, 128.5, 127.9, 127.7, 121.2, 76.6, 73.6, 70.8, 26.2. IR (NaCl), ν_{max} /cm^{-1} 1725.

(*R*)-**5c** was obtained in 73% yield, using Ru_2Cl_4((*S*)-binap)$_2$(NEt_3) as a catalyst. $[\alpha]_D^{22}$ +80.0° (c = 1, $CHCl_3$), 70 % O.P.

The enantiomeric excess of (*R*)-**5c** and (*S*)-**5c** were determined by similar procedures described above. (*R*) and (*S*)-**5c** were, respectively, converted to their (*R*)-(+)-α-phenylethylamide (*R,R*)-**15c** and (*S,R*)-**15c**. The diastereomer ratio was determined by HPLC with a Chiralcel OD column (hexane/2-propanol = 9 : 1, flow rate = 1.0 ml/min). The diastereomeric excesses (ca. 70 %), which correspond to the e.e.'s of **5c**, was almost same to the optical purity.

Asymmetric Hydrogenation of 3-Oxo Esters **6**

Methyl (R)- and (S)-3-hydroxybutanoate **7a**. A mixture of methyl acetoacetate **6a** (5 mmol) and Ru_2Cl_4((*R*)-binap)$_2$(NEt_3) (0.005 mmol as Ru) dissolved in methanol (10 cm^3) under a nitrogen atmosphere was placed in a 50 cm^3 stainless steel autoclave. After the atmosphere was replaced with hydrogen, hydrogen was pressurized to 100 atm, and the mixture was stirred at 30 °C for 48 h. The solvent was removed under reduced pressure, and the residue was distilled to give methyl (*R*)-3-hydroxybutanoate (*R*)-**7a** (yield 89 %). bp.29 °C/2.5 mmHg. $[\alpha]_D^{26}$ -24.2°(neat) ((*S*)-**7a**, $[\alpha]_D^{26}$ +24.1° (neat), was obtained with Ru_2Cl_4(*S*)-binap)$_2$(NEt_3)). ^{1}H NMR ($CDCl_3$, TMS), δ.1.23 (d, 3H, J = 6 Hz, **CH$_3$**CH(OH)-), 2.44 (dd, 1H, J = 16, 9 Hz, -**CH$_2$**CO_2Me), 2.50 (dd, 1H, J = 16, 4 Hz, -**CH$_2$**CO_2Me), 3.12 (s, br. 1H, -**OH**), 3.71 (s, 3H, -CO_2**CH$_3$**), 4.20 (m, 1H, -**CH**(OH)-). IR (NaCl), ν_{max} /cm^{-1} 3432, 1736.

The enantiomeric excess of **7a** was determined by HPLC after converting an aliquot of the product to the (*R*)-MTPA (MTPA = α-methoxy-α-trifluoromethylphenyl acetic acid) ester. A mixture of (*R*)- or (*S*)-**7a** (0.1 mmol), (*R*)-MTPA (0.1 mmol), DCC (0.11 mmol), and 4-dimethylaminopyridine (2 mg) dissolved in CH_2Cl_2 (5 cm^3) was stirred at room temperature for 20 h. White precipitate was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ solution and water, and dried over $MgSO_4$. After the solvent was removed, the crude residue was passed through a short column of silica gel (eluent, ether), and the ester-containing fractions were collected and concentrated. The sample solution containing an (*R*)-MTPA ester of **7a** was analyzed by an HPLC system equipped with a silica gel column, using hexane/2-propanol (99 : 1) as an eluent.

Ethyl (R) and (S)-3-hydroxyoctanoate **7b**. Ethyl 3-oxooctanoate was hydrogenated with Ru_2Cl_4((*R*)-binap)$_2$(NEt_3) to give ethyl (*R*)-3-hydroxyoctanoate, (*R*)-**7b**, in 85% yield. bp. 66 °C/2.5 mmHg. $[\alpha]_D^{26}$ -8.68° (neat) ((*S*)-**7b**, $[\alpha]_D^{26}$ +8.64° (neat), with Ru_2Cl_4((*S*)-binap)$_2$(NEt_3)). ^{1}H NMR ($CDCl_3$, TMS), δ 0.93 (t, 3H, J = 7.0 Hz, **CH$_3$**), 1.28 (t, 3H, J = 7.0 Hz, CO_2CH_2**CH$_3$**), 1.34-1.57 (m, 4H, **CH$_2$CH$_2$**), 2.40 (dd, 1H, **H-2**, J = 16.2, 8.9 Hz), 2.50 (dd, 1H, J = 16.2, 3.1 Hz, **H-2**), 4.02 (m, 1H, **H-3**), 3.06 (d, 1H, **OH**), 4.17 (q, 2H, J = 7.0 Hz, CO_2**CH$_2$**Me). IR (NaCl), ν_{max} /cm^{-1} 3449, 1736.

The enantiomeric excess of **7b** was determined as follows. (*R*) or (*S*)-**7b** (0.2 mmol) and phenyl isocyanate (0.3 mmol) were dissolved in THF (5 cm^3), and the mixture was stirred at 50 °C for 12 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel with ethyl acetate/hexane (4 : 1) as an eluent. The samples were analyzed by an HPLC system equipped with a Daicel Chiralcel OD column. Eluent, hexane/2-propanol (9 : 1), (α =1.65, k_R = 1.70, R_s = 2.61).

tert-Butyl (S)- and (R)-4-benzyloxy-3-hydroxybutanoate 7c. *tert*-Butyl 4-benzyloxy-3-oxobutanoate **6c** was prepared from ethyl benzyloxyacetate in 75 % yield by a similar method descried in preparation of **8**. ^{1}H NMR ($CDCl_3$, TMS), δ 1.44 (s, 9H, C(CH_3)$_3$), 3.45 (s, 2H, **2-H**), 4.17 (s,.2H, **4-H**), 4.59 (s, 2H, PhCH_2O-), 7.26-7.38 (m, 5H, **aromatic**). IR (NaCl), ν_{max} /cm^{-1} 1728.

Asymmetric hydrogenation of *tert*-Butyl 4-benzyloxy-3-oxobutanoate **6c** was carried out in a similar manner as that for **6a**. *tert*-Butyl (*S*)-4-benzyloxy-3-hydroxybutanoate, (*S*)-**7c**, was obtained with Ru_2Cl_4((*R*)-binap)$_2$(NEt_3). The product was purified by a column chromatography (ethyl acetate/hexane) in 85% yield. $[\alpha]_D^{22}$ +10.0° (neat); ^{1}H NMR ($CDCl_3$, TMS), δ 1.45 (s, 9H, -C(CH_3)$_3$), 2.55 (d, 2H, J = 6.4 Hz, BnOCH_2-), 3.13 (br, 1H, -OH), 3.46 (dd, 1H, J = 9.5, 5.8 Hz, **2-H**), 3.49 (dd, 1H, J = 9.5, 4.7 Hz, **2-H**), 4.19 (m, 1H, **3-H**), 4.56 (s, 2H, PhCH_2O-), 7.25-7.37 (m, 5H, **aromatic**). ^{13}C NMR ($CDCl_3$, TMS), δ 171.6, 138.0, 128.4, 127.7, 126.8, 81.2, 73.4, 73.2, 67.3, 39.3, 28.1. IR (NaCl), ν_{max} /cm^{-1} 3453, 1728.

(*R*)-**7c** was obtained by the use of Ru_2Cl_4((*S*)-binap)$_2$(NEt_3)) as the catalyst. $[\alpha]_D^{22}$ +9.6° (neat); $[\alpha]_D^{22}$ +12.1 (c, 1.3 $CHCl_3$)

tert-Butyl (*S*)- and (*R*)-4-benzyloxy-3-hydroxybutanoate, (*S*)- and (*R*)-**7c**, were converted to their (*R*)-MTPA esters by similar procedures to those for **7a** . The NMR measurements showed that (*S*)- and (*R*)-**7c** have 94% e.e.

Methyl 4-benzyloxy-3-hydroxybutanoate 7d. **7c** (1.0 g; 94 % e.e.) was dissolved in anhydrous methanol (50 cm^3) contained a few drops of conc. H_2SO_4. The solution was refluxed and the reaction was monitored by TLC until the ester exchange completed. The mixture was cooled to 0 °C, and ethyl ether (100 cm^3) and water (50 cm^3) were added. The aqueous layer was separated and extracted with ether (2 × 50 cm^3), and the combined organic layer was washed, successively, with 5% $NaHCO_3$ and water, and dried over Na_2SO_4. After filtration and concentration, the residue was purified by a column chromatography (ethyl acetate/hexane), and the oily product was obtained in 91 % yield. ^{1}H NMR ($CDCl_3$, TMS), δ 2.55 (d, 2H, J = 6.4 Hz, BnOCH_2-), 3.00 (br, 1H, **OH**), 3.47 (dd, 1H, J = 9.6, 5.9 Hz, **2-H**), 3.52 (dd, 1H, J = 9.6, 4.5 Hz, **2-H**), 3.69 (s, 3H, CO_2CH_3), 4.24 (m, 1H, **3-H**), 4.56 (s, 2H, PhCH_2O-), 7.26-7.38 (m, 5H, **aromatic**). ^{13}C NMR ($CDCl_3$, TMS), δ 172.5, 137.9, 128.5, 127.8, 127.7, 73.4, 73.1, 67.2, 51.8, 38.0. IR (NaCl), ν_{max} /cm^{-1} 3475, 1736.

The e.e. of **7d** was determined directly by HPLC with a Chiralcel OD column. Both (*R*)- and (*S*)-**7d** have 94% e.e. (eluent, hexane/2-propanol, 9 : 1; k_R = 3.23, α = 1.32, R_s = 2.00). This means that no racemization occurred in the ester exchange reaction.

Preparation of tert-Butyl 5-hydroxy-3-oxoesters 8

To a solution of LDA, prepared from diisopropylamine (7.07 g, 70 mmol) in anhydrous THF (100 cm^3) and n-butyllithium (1.66 M in haxane, 36 cm^3), *tert*-butyl acetate (6.97 g, 60 mmol) in THF (10 cm^3) was added at -78 °C. Then, the hydroxyester **7a**, **7b**, or **7d** (20 mmol) in THF (10 cm^3) was added dropwise at -78 °C. The mixture was stirred at -50 °C for 1.5 h, and, then, at -15 °C for 15 min. Ice-water (100 cm^3) was added to quench the reaction, and aqueous layer was extracted with ether (2 × 50 cm^3). The combined organic layer was washed with saturated $NaHCO_3$ (50 cm^3) and water (2 × 50 cm^3), and dried over anhydrous Na_2SO_4, and filtrated. The solvent was removed under reduced pressure, and the residue was purified by a flash chromatography (ethyl acetate-hexane) to afford **8**.

tert-Butyl (R)-5-hydroxy-3-oxohexanoate 8a. Yield 78%. ^{1}H NMR ($CDCl_3$, TMS), δ 1.21 (d, 3H, J = 6 Hz, -CH_3), 1.47 (s, 9H, -C(CH_3)$_3$), 2.64 (dd, 1H, J = 18, 9 Hz, **4-H**), 2.74 (dd, 1H, J = 18, 3 Hz, **4-H**), 2.92 (br. 1H, -**OH**), 3.38 (s, 2H, **2-H**), 4.26 (m, 1H, **5-H**). IR (NaCl), ν_{max} /cm^{-1} 3407, 1732, 1717..

tert-Butyl (R)- and (S)-5-hydroxy-3-oxooctanoate 8b. Yield 75%. ^{1}H NMR ($CDCl_3$, TMS), δ 0.93 (t, 3H, J = 7.0 Hz, CH_3), 1.31-1.54 (overlap, 4H, CH_2CH_2), 1.47 (s, 9H, C(CH_3)$_3$), 2.62 (dd, 1H, J = 17.4, 8.9 Hz, **4-H**), 2.73 (dd, 1H, J = 17.4, 2.7 Hz, **4-H**), 2.84 (br, 1H, **OH**), 3.38 (s, 2H, **2-H**), 4.08 (m, 1H, **5-H**). IR (NaCl), ν_{max} /cm^{-1} 3435, 1734, 1713.

tert-Butyl (S)- and (R)-6-benzyloxy-5-hydroxy-3-oxohexanoate ***8c***. Yield 65%. ^{1}H NMR ($CDCl_3$, TMS), δ 1.46 (s, 9H, C(**CH$_3$**)$_3$), 2.74 (d, 2H, J = 6.1 Hz, **6-H**), 3.39 (s, 2H, **2-H**), 3.45 (dd, 1H, J = 9.6, 6.1 Hz, **4-H**), 3.49 (dd, 1H, J = 9.6, 4.6 Hz, **4-H**), 4.28 (m, 1H, 5-H), 4.54 (s, 2H, PhC**H$_2$**O-), 7.27-7.37 (m, 5H, **aromatic**). IR (NaCl), ν_{max} /cm^{-1} 3453, 1734, 1717.

Selective Reduction of 5-Hydroxy-3-oxoesters ***8a-c****: Preparation of syn and anti Acetonides* ***9a-c***

(*R*) or (*S*)-5-hydroxy-3-oxoesters **8a-c** were selectively reduced by Naraska's method using triethylborane and $NaBH_4$.[11] After usual chromatographic purification, the reduced products *syn* **2'a-c** were dissolved in 2,2-dimethoxypropane and refluxed for 2 h in the presence of PTS. After usual work-up and chromatographic purification, the authentic *syn* acetals **9a-c** were obtained. The yield and analytical data were as follows.

*(4R,6R)-6-Methoxycarbonylmethyl-2,2,4-trimethyl-1,3-dioxolane, (R,R)-****9a***. Yield, 70 %. ^{1}H NMR ($CDCl_3$, TMS), δ 1.17 (d, 3H, J = 6.1 Hz, **CH$_3$**), 1.17 (overlap, 1H, **5-H**), 1.38 and 1.46 (s × 2, 3H × 2, C(**CH$_3$**)$_2$), 1.60 (m, 1H, **5-H**), 2.39 (dd, 1H, J = 15.6, 6.1 Hz, **CH$_2$**CO$_2$Me), 2.56 (dd, 1H; 15.6, 7.0 Hz, **CH$_2$**CO$_2$Me), 3.69 (s, 3H, CO$_2$**CH$_3$**), 4.01 (m, 1H, **4-H**), 4.31 (m, 1H, **6-H**). ^{13}C NMR ($CDCl_3$, TMS), δ 171.5, 98.8, 65.9, 64.9, 51.6, 41.3, 38.3, 30.2, 22.1, 19.8. IR (NaCl), ν_{max} /cm^{-1} 1744.

*(4R,6R)-6-Methoxycarbonylmethyl-2,2-dimethyl-4-propyl-1,3-dioxolane, (R,R)-****9b***. Yield, 73 %. ^{1}H NMR ($CDCl_3$, TMS), δ 0.91 (t, 3H, J = 7.0 Hz, CH$_2$**CH$_3$**), 1.16 (dd, 1H, J = 24.4, 11.6 Hz, **5-H**), 1.37 and 1.45 (s, 3H, C(**CH$_3$**)$_2$), 1.25-1.46 (overlap, 4H, **CH$_2$CH$_2$**), 1.60 (ddd, 1H, J =12.5, 2.4, 2.4 Hz, **5-H**), 2.38 (dd, 1H, J = 15.6, 6.4 Hz, **CH$_2$**CO$_2$Me), 2.55 (dd, 1H, J = 15.6, 6.9 Hz, **CH$_2$**CO$_2$Me), 3.69 (s, 3H, CO$_2$**CH$_3$**), 3.85 (m, 1H, **4-H**), 4.30 (m, 1H, **6-H**). ^{13}C NMR ($CDCl_3$, TMS), δ 171.5, 98.7, 68.5, 66.0, 51.6, 41.3, 38.5, 36.6, 30.2, 19.7, 18.1, 14.0. IR (NaCl), ν_{max} /cm^{-1} 1744.

*(4S,6R)-4-Benzyloxymethyl-6-methoxycarbonylmethyl-2,2-dimethyl-1,3-dioxolane, (S,R)-****9c***. Yield, 75 %. ^{1}H NMR ($CDCl_3$, TMS), δ 1.25 (dd, 1H, J = 24.4, 11.6 Hz, **5-H**), 1.48 and 1.40 (s × 2, 3H × 2, C(**CH$_3$**)$_2$), 1.63 (ddd, 1H, J = 12.8, 2.4, 2.4 Hz, **5-H**), 2.39 (dd, 1H, J = 15.6, 6.1 Hz, **CH$_2$**CO$_2$Me), 2.56 (dd, 1H, J = 15.6, 7.0 Hz, **CH$_2$**CO$_2$Me), 3.38 (dd, 1H, J = 10.1, 4.9 Hz, **CH$_2$**OBn), 3.50 (dd, 1H, J = 10.1, 5.8 Hz, **CH$_2$**OBn), 3.68 (s, 3H, -CO$_2$**CH$_3$**), 4.12 (m, 1H, **4-H**), 4.33 (m, 1H, **6-H**), 4.57 (dd, 2H, J = 22.6, 12.2 Hz, PhC**H$_2$**O-), 7.26-7.34 (m, 5H, **aromatic**). ^{13}C NMR ($CDCl_3$, TMS), δ 171.3, 138.2, 128.4, 127.7, 127.6, 98.9, 73.5, 73.4, 68.4, 65.6, 51.6, 41.3, 33.3, 30.0, 19.7. IR (NaCl), ν_{max} /cm^{-1} 1744.

Alternatively, 5-hydroxy-3oxoesters **8a-c** were reduced stereoselectively by the Evans's method[10] to give *anti* dihydroxyesters **2'a-c**. Successive treatments of *anti* **2'a-c** with 2,2-dimethoxypropane afforded the *anti* acetonides **9a-c**.

*(4R,6S)-6-Methoxycarbonylmethyl-2,2,4-trimethyl-1,3-dioxolane, (R,S)-****9a***. Yield, 69 %. ^{1}H NMR ($CDCl_3$, TMS), δ 1.20 (d, 3H, J = 6.4 Hz, **CH$_3$**), 1.26 (m, 1H, **5-H**), 1.35 and 1.37 (s × 2, 3H × 2, C(**CH$_3$**)$_2$), 1.66 (m, 1H, **5-H**), 2.44 (dd, 1H, J = 15.6, 5.5 Hz, **CH$_2$**CO$_2$Me), 2.55 (dd, 1H, J = 15.6, 8.2 Hz, **CH$_2$**CO$_2$Me), 3.69 (s, 3H, CO$_2$**CH$_3$**), 3.97 (m, 1H, **4-H**), 4.28 (m, 1H, **6-H**). ^{13}C NMR ($CDCl_3$, TMS), d 171.4, 100.4, 63.4, 62.6, 51.6, 40.6, 39.3, 24.8, 21.6. IR (NaCl), ν_{max} /cm^{-1} 1740.

*(4R,6S)-6-Methoxycarbonylmethyl-2,2-dimethyl-4-propyl-1,3-dioxolane, (R,S)-****9b***. Yield, 70 %. ^{1}H NMR ($CDCl_3$, TMS), δ 0.91(t, 3H, J = 7.0 Hz, CH$_2$**CH$_3$**), 1.33 and 1.36 (s × 2, 3H × 2, C(**CH$_3$**)$_2$), 1.25-1.50 (overlap, 5H, **CH$_2$CH$_2$**, and **5-H**), 1.63 (m, 1H, **5-H**), 2.44 (dd, 1H, J = 15.6, 5.2 Hz, **CH$_2$**CO$_2$Me), 2.55 (dd, 1H, J = 15.6, 8.2Hz, **CH$_2$**CO$_2$Me), 3.69 (s, 3H, CO$_2$**CH$_3$**), 3.78 (m, 1H, **4-H**), 4.27 (m, 1H, **6-H**). ^{13}C NMR ($CDCl_3$, TMS), δ 171.5, 100.5, 66.2, 63.4, 51.6, 40.7, 38.0, 37.9, 24.7, 24.5, 18.6, 13.9. IR (NaCl), ν_{max} /cm^{-1} 1740.

*(4S,6S)-4-Benzyloxymethyl-6-methoxycarbonylmethyl-2,2-dimethyl-1,3-dioxolane, (S,S)-****9c***. Yield, 72 %. ^{1}H NMR ($CDCl_3$, TMS), δ 1.25 (dd, 1H, J = 24.4, 11.6 Hz, **5-H**), 1.40 and 1.48 (s × 2, 3H × 2, C(**CH$_3$**)$_2$), 1.63 (ddd, 1H, J = 12.8, 2.4, 2.4 Hz, **5-H**), 2.39 (dd, 1H, J = 15.6, 6.1 Hz, CH$_2$CO$_2$Me), 2.56 (dd, 1H, J = 15.6, 7.0 Hz,

CH_2CO_2Me), 3.38 (dd, 1H, J = 10.1, 4.9 Hz, CH_2OBn), 3.50 (dd, 1H, J = 10.1, 5.8 Hz, CH_2OBn), 3.68 (s, 3H, $-CO_2CH_3$), 4.12 (m, 1H, **4-H**), 4.33 (m, 1H, **6-H**), 4.57 (dd, 2H, J = 22.6, 12.2 Hz, $PhCH_2O$-), 7.26-7.34 (m, 5H, **aromatic**). ^{13}C NMR ($CDCl_3$, TMS), δ 171.4, 138.3, 128.3, 127.7, 127.6, 100.8, 73.4, 72.7, 72.6, 66.1, 51.6, 40.5 34.2, 24.7. IR (NaCl) ν_{max} /cm^{-1} 1740.

Asymmetric Hydrogenation of 3-Hydroxy-5-oxoesters ***8a-c*** *Catalyzed by Ru-binap Complex*

The hydrogenation of (*R*)-**8a-c** or (*S*)-**8a-c** were performed by following procedures: The substrate (0.5 mmol) dissolved in anhydrous methanol (10 cm^3) was added to Ru_2Cl_4((*R*)- or (*S*)-binap)$_2$(NEt_3) (0.001 mmol) under nitrogen atmosphere. After the atmosphere was replaced with hydrogen, hydrogen was pressurized to 100 atm, and the reaction was continued at 50 °C for 48 h. The solvent was removed, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give a mixture of 3,5-dihydroxyester **2'** and hydroxylactone **10**. The stereoselectivities for the hydrogenation at C-3 of **8a-c** were determined by GLC, after converting the mixture of **2'** and **10** into a diastereomer mixture of acetonides **9**, in a similar manner for the hydrogenation of **1**. The results were summarized in Table 2.

(4S,6S)-4-Hydroxy-6-benzyloxymethyl-2-pyrone (4S,6S)-3c. To a THF-MeOH (10 cm^3; 4:1) solution of triethylborane (1 M, 1.1 cm^3 in hexane) and (*S*)-**8c** (0.51 g, 1 mmol) was introduced a small amount of air (3 cm^3), and the solution was stirred for 2 h at room temperature under an argon atmosphere. Then, the solution was cooled to -78 °C, and solid $NaBH_4$ (1.1 mmol) was added in one portion. The mixture was stirred for 6 h, and a mixture of 31% H_2O_2 (5 cm^3), phosphate buffer (pH 6.88, 10 cm^3) and methanol (15 cm^3)was added. Almost all the organic solvent was removed under reduced pressure, and the residual aqueous solution was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated. To the residue was added conc. HCl (1 μl) in MeOH (4 cm^3) and evaporated. This procedures was repeated five times to completely decompose the remaining boric acid ester of diols. Then, the oily residue was chromatographed on silica gel (hexane/ethyl acetate, 4 : 1) to afforded lactone **3c** in 80% yield. $[\alpha]_D^{22}$ +6.12° (c, 1.04, $CHCl_3$) (lit.[7], $[\alpha]_D^{22}$ +6.59°). ^1H NMR ($CDCl_3$, TMS), δ 1.95 (dd, 2H, J = 9.3, 6.5 Hz), 2.17 (s, 1H, OH), 2.60 (dd, 1H, J = 17.7, 3.2 Hz, **3-H**), 2.68 (dd, 1H, J = 17.7, 4.6 Hz, **3-H**), 3.60 (dd, 1H, J = 10.7, 4.3 Hz, $BnOCH_2$), 3.69 (dd, 1H, J = 10.7, 3.7 Hz, $BnOCH_2$), 4.38 (m, 1H, **4-H**), 4.57 (dd, 2H, J = 15.9, 11.9 Hz, $PhCH_2O$), 4.86 (m, 1H, **6-H**), 7.26-7.37 (m, 5H, **aromatic**).

(S)-6-Benzyloxymethyl-5,6-dihydro-2-pyrone (S)-5c. **3c** (100 mg) dissolved in toluene (5 cm^3) was refluxed in the presence of PTS for 2 h. To the mixture, toluene (5 cm^3) and 5% $NaHCO_3$ (5 cm^3) were added and the organic layer was separated, washed with water (2 × 5 cm^3), and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by a flash chromatography. (*S*)-**5c** was obtained as colorless oil in 90 % yield. $[\alpha]_D^{22}$ -108.1° (c, 1.11, $CHCl_3$) (lit.[7], $[\alpha]_D^{22}$ -115°).

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