Asymmetric Synthesis of (*R*)- and (*S*)-4-(Substituted Benzyl)dihydrofuran-2(3*H*)-ones: An Application of the Ruthenium–binap† Complex-catalysed Asymmetric Hydrogenation of Alkylidenesuccinic Acids

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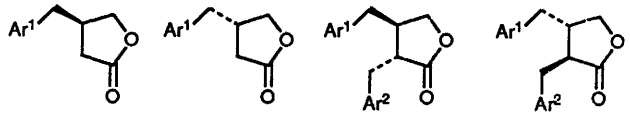
A concise synthesis of (*S*)- or (*R*)-4-(substituted benzyl)dihydrofuran-2(3*H*)-ones (**1**) with high enantiomeric purity is presented. (*S*)- or (*R*)-(Substituted benzyl)succinic acids (**6**) ≥97% enantiomeric excess) were first prepared by $Ru_2Cl_4[(R)$- or (*S*)-binap)$]_2(NEt_3)$ catalysed asymmetric hydrogenation of (substituted benzylidene)succinic acids. The diacids (**6**) were converted into (*R*)- or (*S*)-2-(substituted benzyl)butane-1,4-diols (**9**), and subsequent $RuH_2(PPh_3)_4$-catalysed dehydrogenative lactonization of (**9**) afforded the lactones (**1**) with complete retention of configuration at the chiral centre.

Lignans and neolignans have attracted considerable attention over the years because of their widespread occurrence in nature and their broad range of biological activities.[1–5] The wide variety of structures that lignans and neolignans assume presents interesting targets for organic synthesis.[3–5] In the past decade several elegant asymmetric syntheses of these compounds have been performed.[4–11] Retrosynthetic analysis indicates that 4-(substituted benzyl)dihydrofuran-2(3*H*)-ones (**1**), such as 4-(3,4-methylenedioxybenzyl)dihydrofuran-2(3*H*)-one, are key intermediates not only for preparing dibenzylbutyrolactone lignans (**2**), one of the representative families of lignans, but also for synthesizing other types of lignans which can be derived from dibenzylbutyrolactones themselves.[6–8,12]



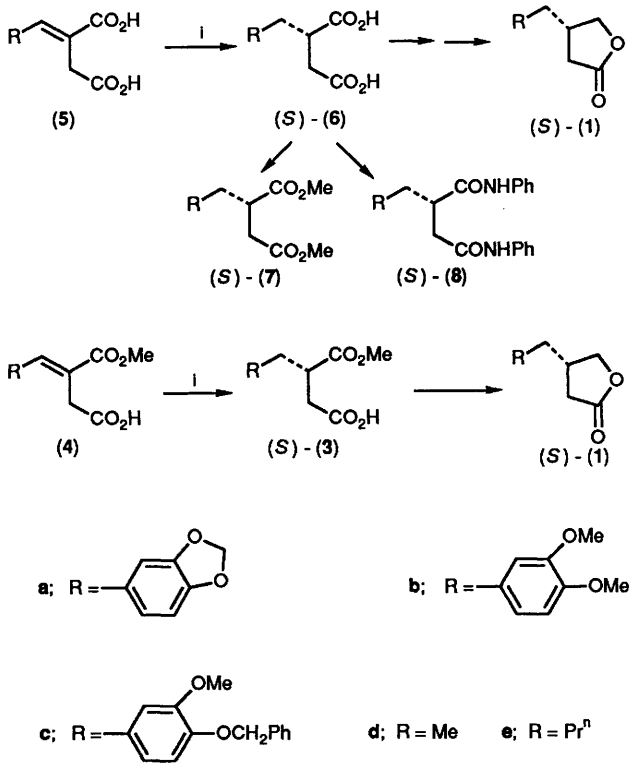
(*R*)-(**1**) (*S*)-(**1**) (*R,R*)-(**2**) (*S,S*)-(**2**)

In order to accomplish the asymmetric synthesis of a variety of lignans, enantiomerically pure substituted γ-butyrolactones (*R*)- and (*S*)-(**1**) have been used as the most versatile intermediates.[6a,7,8] Koga and collaborators prepared such starting compounds from (*S*)- or (*R*)-glutamic acid in several steps.[6a] Brown and co-workers succeeded in obtaining pure enantiomers of (**1a–c**) from optically resolved monoesters (**3a–c**) of (substituted benzyl)succinic acids.[8] Racemic compounds (**3**), (*RS*)-(**3**), were prepared in turn by hydrogenation of the benzylidene derivatives (**4**) (Scheme 1).

We have already reported that the asymmetric hydrogenation of benzylidenesuccinic acids gave α-benzylsuccinic acids of known absolute configuration.[13] In the present paper we describe a new extension of the previous work giving an easy access to (*S*)- or (*R*)-(**1a–c**) by applying the ruthenium–binap complex-catalysed asymmetric hydrogenation of alkylidenesuccinic acids (**5**) coupled with the $RuH_2(PPh_3)_4$ catalysed regioselective lactonization of 1,4-diols (**9**) (Scheme 2).

Results and Discussion

Asymmetric Hydrogenation of (Substituted Benzylidene)-succinic Acids (**5**).—The asymmetric hydrogenation of the benzylidene compounds (**5a–c**) was performed by using a



Scheme 1. *Reagents:* i, H_2, $Ru_2Cl_4[(R)$-binap$]_2(NEt_3)$, THF–EtOH (1:1), room temp., 48 h.

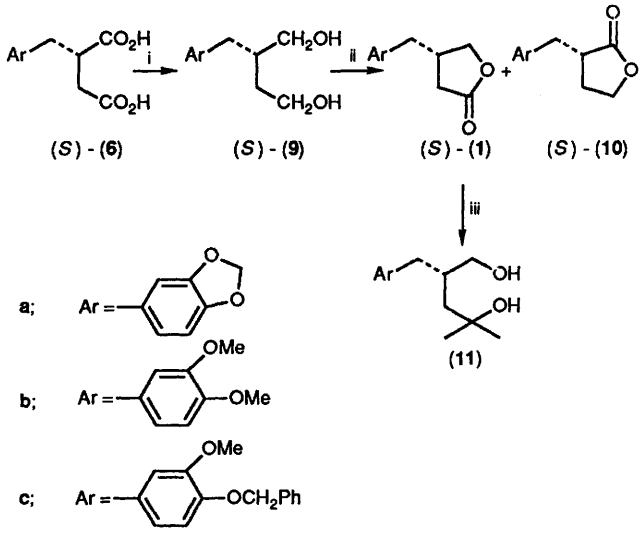
Ru–binap complex, $Ru_2Cl_4[(R)$-(+)- or (*S*)-(−)-binap$]_2$-(NEt_3),[13,14] as the catalyst under mild conditions (Scheme 1). The hydrogenations completed within 48 h, and (**6a–c**) were obtained in high yields. The hydrogenation products obtained by employing the Ru–[(*R*)-binap)] and –[(*S*)-binap] complex as the catalyst showed (−) and (+) optical rotation, respectively. Since the enantiomerically pure forms of (**6a–c**) have not been reported, the correlation between the rotation sign and the

† binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

Table. Asymmetric hydrogenation of (substituted benzylidene)succinic and alkylidenesuccinic acids with the Ru–binap catalyst and chiral HPLC parameters of the product derivatives.

Asymmetric hydrogenation[a]						Chiral HPLC parameters[f]		
Substrate	binap[b]	Product	% Yield	% E.e.	$[\alpha]_D$[c]	α	K_1'	R_s
(5a)	(*R*)	(*S*)-**(6a)**	91 (64)[d]	94 (98)[e]	−19.7°	1.63	2.07	2.96
(5a)	(*S*)	(*R*)-**(6a)**	(63)	(98)	+19.4°			
(5b)	(*R*)	(*S*)-**(6b)**	92 (67)	91 (97)	−22.0°	1.48	5.45	2.08
(5b)	(*S*)	(*R*)-**(6b)**	(65)	(98)	+21.4°			
(5c)	(*R*)	(*S*)-**(6c)**	91 (68)	92 (97)	−17.6°	1.52	8.43	1.94
(5c)	(*S*)	(*R*)-**(6c)**	(67)	(98)	+17.5°			
(5d)	(*R*)	(*S*)-**(6d)**	82	75		1.70	1.26	1.93
(5e)	(*R*)	(*S*)-**(6e)**	85	68		1.18	4.47	0.80

[a] Reaction conditions, see text. [b] The configuration of binap in the catalyst. [c] Data for the recrystallized samples. [d] Yields after two recrystallizations from ethyl acetate–hexane. [e] E.e.s of the recrystallized samples. [f] Data for the dimethyl esters (**7a–c**) and the dianilides (**7d** and **e**); see text. See ref. 15 for definitions of the chromatographic parameters.



Scheme 2. Preparation of (**1**) from (**6**). *Reagents:* i, $LiAlH_4$, THF; ii, $RuH_2(PPh_3)_4$, PhCH=CHCOMe; iii, MeLi.

absolute configuration has not been established yet for these diacids. We assigned the (−)- and (+)-isomers of (**6a–c**) the (*S*)- and (*R*)-configuration, respectively (*vide infra*). The direction of asymmetric induction observed here is in accord with that for the asymmetric hydrogenation of itaconic and benzylidenesuccinic acids catalysed by the Ru–binap catalysts.[13] The results are summarized in the Table.

The enantiomeric purities of (**6a–c**) were determined by HPLC analysis of the corresponding dimethyl esters (**7a–c**), which were found to be suitable for the HPLC analysis using a column of cellulose tris(3,5-dimethylphenylcarbamate).[15] For all diesters, the (*R*)-enantiomers were eluted faster than the antipodes. The chromatographic parameters are shown in the Table. The crude diacids had enantiomeric excesses (e.e.s) of >90% (see Table). Two recrystallizations from ethyl acetate–hexane improved the e.e.s of (**6a–c**) to 97% or higher. Thus, a simple approach to the pure enantiomers of (**6a–c**) has been realized.

The most straightforward approach to the pure enantiomers of γ-butyrolactones (**1**) is that starting from the monoesters (**4**) *via* the homochiral hydrogenated monoester (**3**) (Scheme 1). Achiwa and collaborators have recently reported a successful example of such a conversion by using a rhodium catalyst.[16] The asymmetric hydrogenation of (**4a**) was also undertaken under similar conditions to those above employing the Ru–[(*R*)-binap] catalyst (Scheme 1). The hydrogenation was complete within 48 h to give the (*S*)-product, but the stereoselectivity in this case was not so high (64% e.e) as that found in the hydrogenation of the corresponding diacid (**5a**). A similar lowering of e.e.s in hydrogenations using esters instead of the parent diacids has previously been observed.[13] We considered, therefore, that if the above Ru–binap complex is used as the catalyst, it is difficult to obtain (**3a**) and other monoesters having satisfactorily high e.e.s. No further attempt to find a better catalyst precursor or appropriate reaction conditions for obtaining enantiomerically pure (**3a**) was made.

We also examined the possibility of obtaining enantiomerically pure alkylsuccinic acids by Ru–binap-catalysed hydrogenation. Some of these compounds have recently been prepared with high e.e.s utilizing a chiral auxiliary,[17] but these alkyl substituted acids have not previously been synthesized by asymmetric hydrogenation. The hydrogenation of (**5d**) and (**5e**) catalysed by the Ru–[(*R*)-binap] complex proceeded smoothly under the same reaction conditions as those for (**5a–c**) to give the corresponding alkylsuccinic acids (**6d**) and (**6e**) in good yields. The diacids (**6d**) and (**6e**) were converted into the dianilides (**8d**) and (**8e**), respectively, which were used for determining the enantiomeric purities of the parent diacids by the chiral HPLC method. The e.e. values of (**6d**) and (**6e**) and the chromatographic parameters of the dianilides were also summarized in the Table. In contrast with (**5a–c**), the asymmetric hydrogenation of (**5d**) and (**5e**) catalysed by the Ru–binap complex proceeded with only moderate enantioselectivities (65–75% e.e.). The reasons for these results are unclear at present. Efforts to obtain pure single enantiomers of alkylsuccinic acids by asymmetric hydrogenation are now in progress.

Preparation of 4-(*Substituted Benzyl*)*dihydrofuran*-2(3H)-*ones.*—We have reported previously that ruthenium complex-catalysed regioselective dehydrogenation of 2-substituted 1,4-diols in the presence of a hydrogen acceptor gave predominantly β-substituted-γ-butyrolactones. In addition, $RuH_2(PPh_3)_4$ was established as the most active and selective catalyst, which showed a high activity even at room temperature.[18] So, we investigated the exploitation of this dehydrogenative lactonization for preparing (**1**) from (**6**) *via* 1,4-diols (**9**) as shown in Scheme 2.

Recrystallized compounds (*S*)-(**6a–c**) (>97% e.e.) were reduced with $LiAlH_4$ in tetrahydrofuran (THF) under reflux, and the products were purified by flash column chromatography. (*S*)-(Substituted benzyl)butane-1,4-diols (*S*)-(**9a–c**) were obtained in satisfactory yields. The antipodal diols (*R*)-(**9a–c**) were also prepared. Compounds (*S*)-(**9a–c**) were lactonized almost quantitatively by dehydrogenation using $RuH_2(PPh_3)_4$

and 4-phenylbut-3-en-2-one as the catalyst and hydrogen acceptor, respectively (Scheme 2).[18] It would be expected that the products thus obtained would possibly contain two lactone regioisomers (**1a–c**) and (**10a–c**). GLC analysis of the products indicated that the isomers were regioselectively formed in a ratio of *ca.* 95:5, and 400 MHz ^{1}H NMR measurements confirmed the main products to be (**1a–c**). Several attempts to separate these regioisomers by usual chromatographic methods were unsuccessful. The lactonization of (*R*)-(**9a–c**) was also performed similarly.

Compounds (**1a–c**) derived from (−)-(**6a–c**) as above had (−) optical rotations without exception. Since compounds (−)-(**1a–c**) have been shown to have the (*S*)-configuration,[19,8a–c] compounds (−)-(**6a–c**) thus also have the (*S*) configurations as indicated in Scheme 2, and the stereochemistry in the asymmetric hydrogenation was established as given in Scheme 1. It should be noted that the absolute $[\alpha]_D$ values of (**1a–c**) obtained in this study were considerably smaller than those previously reported (see Experimental section).[8a–c] This could be ascribed either to partial racemization at the chiral carbon centres during the conversion from (**6**) to (**1**) (Scheme 2) or to contamination by the regioisomers. With a view to evaluate the enantiomeric purities of these lactones, both enantiomers of (**1a–c**) were converted into 2-(substituted benzyl)-4-methylpentane-1,4-diols (**11a–c**) by methyl-lithium and analysed by ^{1}H NMR spectroscopy in the presence of Eu(tfc)$_3$; [tfc = 2,2,2-trifluoro-1-hydroxyethylidene-(−)-camphorato],[20] but this gave no clear information with regard to the e.e.s of the lactones (**1a–c**).

Chiral HPLC analysis showed that the enantiomers of the diol (**11c**) gave distinctly separate chromatographic peaks (α 1.32; K_1 1.55; R_s 0.96; hexane–isopropyl alcohol, 90:10; flow rate (0.5 cm^3/min), and that (**11c**) prepared by the reaction sequence in Scheme 2 had the same enantiomeric purity (97%) as that of the starting diacid (**6c**). This indicates that the lactone (**1c**) also has the same e.e. as (**6c**). Although similar chiral HPLC analyses of (**11a**) and (**11b**) showed no clear peak separations for the respective enantiomers, it may be concluded that the lactones (**1a–c**) obtained in the present study retained the enantiomeric purities of the starting (**6a–c**).

Experimental

M.p.s were determined on a Yanaco micro apparatus and are uncorrected. IR spectra were recorded on a Jasco IR-810 or a Hitachi 215 spectrophotometer for neat films otherwise noted. Optical rotations were measured on a Jasco DIP-360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were obtained on a Jeol JNM-GX 400 spectrometer using [$^2H_6$]acetone as solvent. Gas chromatographic analyses were performed on a Shimadzu GC-14A equipped with a fused silica capillary column (Shimadzu CDP1; 25 m) and a flame ionization detector. High performance liquid chromatography (HPLC) was carried out with a Jasco VIP-2 apparatus equipped with a Shimadzu SPC-7A UV spectrophotometric detector and a Shimadzu Chromatopac C-R5A, employing a commercially available chiral stationary phase column, Daicel Chemical Industries CHIRALCEL-OD [cellulose tris(3,5-dimethylphenylcarbamate; 0.46 cm (internal diameter); 25.0 cm (length)].

$Ru_2Cl_4[(R)\text{-}(+)$ or $(S)\text{-}(-)\text{-binap}]_2(NEt_3)$[13] and $RuH_2(PPh_3)_4$[21] were prepared according to literature methods. All solvents used in hydrogenation and lactonization reactions were dried, distilled, and stored under nitrogen.

(Substituted benzylidene)succinic acids (**5a**, **b**, and **c**) and the monoester (**4a**) were prepared by a general method.[8]

(3,4-Methylenedioxybenzylidene)succinic acid (**5a**) had m.p. 191–193 °C (lit.,[22] 190–194 °C) (Found: C, 57.85; H, 4.2. Calc. for $C_{12}H_{10}O_6$: C, 57.6; H, 4.0%); δ_H 7.81 (1 H, s, –CH=), 6.92–7.03 (3 H, m, ArH), 6.06 (2 H, s, OCH_2O), and 3.56 (2 H, s, CH_2CO_2H).

(3,4-Dimethoxybenzylidene)succinic acid (**5b**) had m.p. 172–173 °C (lit.,[22] 173–175 °C) (Found: C, 58.85; H, 5.3. Calc. for $C_{13}H_{14}O_6$: C, 58.6; H, 5.3%); δ_H 7.85 (s, 1 H, –CH=), 7.01–7.14 (m, 3 H, ArH), 3.85 (3 H, s, OMe), 3.84 (3 H, s, OMe), and 3.61 (s, 2 H, CH_2CO_2H).

(4-Benzyloxy-3-methoxybenzylidene)succinic acid (**5c**) had m.p. 184–185 °C (lit.,[23] 174–175 °C) (Found: C, 66.6; H, 5.4. Calc. for $C_{19}H_{18}O_6$: C, 66.6; H, 5.3%); δ_H 7.85 (1 H, s, –CH=), 7.32–7.51 (5 H, m, $PhCH_2O$), 7.03–7.16 (3 H, m, benzylidene ArH), 5.17 (2 H, s, $PhCH_2O$), 3.85 (3 H, s, OMe), and 3.60 (s, 2 H, CH_2CO_2H).

3-Methoxycarbonyl-4-(3,4-methylenedioxyphenyl)but-3-enoic acid (**4a**)[8a] had m.p. 138–140 °C; δ_H 7.76 (1 H, s, –CH=), 6.92–7.00 (3 H, m, ArH), 6.06 (2 H, s, OCH_2O), 3.77 (3 H, s, CO_2Me), and 3.55 (s, 2 H, CH_2CO_2H).

Ethylidenesuccinic acid (**5d**)[24] had m.p. 171.5–173 °C; δ_H 7.05 (1 H, q, *J* 7 Hz, –CH=), 3.37 (2 H, s, CH_2CO_2H), and 1.85 (3 H, d, *J* 7 Hz, Me).

n-Butylidenesuccinic acid (**5e**)[25] had m.p. 160–162 °C; δ_H 6.93–6.97 (1 H, t, *J* 8 Hz, –CH=), 3.36 (2 H, s, CH_2CO_2H), 2.23 (2 H, fortuitous q, *J* 8 Hz, CH_2CH_2CH=), 1.45–1.55 (2 H, m, $MeCH_2$), and 0.95 (3 H, t, *J* 7 Hz, Me).

(S)-(−)-(3,4-*Methylenedioxybenzyl*)*succinic Acid*, (S)-(**6a**).—To a solution of (**5a**) (2.67 g) in a mixture of THF (30 cm^3) and ethanol (30 cm^3), $Ru_2Cl_4[(R)\text{-}(+)\text{-binap}_2](NEt_3)$ (0.11 g) and triethylamine (3 cm^3) were added. The mixture was stirred under hydrogen (initial pressure, 3 atm) at 35 °C for 48 h. The solvent was removed under reduced pressure, and then 1M aqueous NaOH (M = mol dm^{-3}) (50 cm^3) was added. After filtration, the aqueous layer was extracted with chloroform, and then acidified with 1M HCl to pH 1. The acidic aqueous layer was extracted (×3) with chloroform, and the dried organic phase was evaporated to give the *acid* (S)-(**6a**) with 94% e.e. as a solid in 91% yield (2.30 g). The crude product was recrystallized (×2) from ethyl acetate–hexane (1:1 v/v) to give white crystals, m.p. 128.8–129.5 °C; $[\alpha]_D^{22}$ −19.7° (*c* 1.4 in ethanol) (Found: C, 57.2; H, 4.8. $C_{12}H_{12}O_6$ requires C, 57.1; H, 4.8%); IR (KBr) ν_{max}/cm^{-1} 2 850 (OH) and 1 678 (C=O); δ_H 6.70–6.79 (3 H, m, ArH), 5.96 (2 H, s, OCH_2O), 3.02–3.06 (1 H, m, $ArCH_2CHCO_2H$), 2.98 (1 H, dd, ^2J 14, ^3J 7 Hz, $ArCH_2$), 2.79 (1 H, dd, ^2J 14, ^3J 8 Hz, $ArCH_2$), 2.62 (1 H, dd, ^2J 17, ^3J 9 Hz, $ArCH_2CHCH_2CO_2H$), and 2.42 (1 H, dd, ^2J 17, ^3J 5 Hz, $ArCH_2CHCH_2CO_2H$).

(S)-(−)-(3,4-*Dimethoxybenzyl*)*succinic Acid*, (S)-(**6b**).—A mixture of (**5b**) (2.67 g), $Ru_2Cl_4[(R)\text{-}(+)\text{-binap}]_2(NEt_3)$ (0.11 g), and NEt_3 (3 cm^3) in THF–ethanol (1:1 v/v; 60 cm^3) was stirred under hydrogen (initial pressure, 3 atm) at 35 °C for 48 h. Treatment as for (*S*)-(**6a**) gave the *acid* (S)-(**6b**) in 92% yield and 91% e.e. The pure enantiomer was obtained by recrystallization (×2) from ethyl acetate–hexane, m.p. 118.5–119 °C; $[\alpha]_D^{22}$ −22.0° (*c* 1.2 in ethanol) (Found: C, 58.0; H, 5.7. $C_{13}H_{16}O_6$ requires C, 58.2; H, 6.0%); IR (KBr) ν_{max}/cm^{-1} 2 940 (OH) and 1 678 (C=O); δ_H 6.74–6.88 (3 H, m, Ar), 3.79 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.04–3.09 (1 H, m, $ArCH_2CHCO_2H$), 3.01 (1 H, dd, ^2J 13, ^3J 6 Hz, $ArCH_2$), 2.78 (1 H, dd, ^2J 13, ^3J 8 Hz, $ArCH_2$), 2.62 (1 H, dd, ^2J 17, ^3J 9 Hz, $ArCH_2CHCH_2CO_2H$), and 2.41 (1 H, dd, ^2J 17, ^3J 5 Hz, $ArCH_2CHCH_2CO_2H$).

(S)-(−)-(4-*Benzyloxy*-3-*methoxybenzyl*)*succinic Acid*, (S)-(**6c**).—By similar procedures to those in the preparation of (*S*)-(**6a** and **b**), (**5c**) was converted into (*S*)-(**6c**) (92% e.e.) in 91% yield. The crude product was recrystallized (×2) from ethyl acetate–hexane to give the pure *acid* (S)-(**6c**), m.p. 148.5–149 °C;

$[\alpha]_D^{22}$ −17.6° (*c* 1.3 in ethanol) (Found: C, 66.2; H, 5.85. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.85%); IR (KBr) ν_{max}/cm^{-1} 3 000 (OH) and 1 660 (C=O); δ_H 7.30–7.49 (5 H, m, *Ph*CH_2O), 6.73–6.95 (3 H, m, benzyl ArH), 5.07 (2 H, s, PhCH_2O), 3.81 (3 H, s, OMe), 3.06–3.09 (1 H, m, ArCH_2C*H*CO_2H), 3.01 (1 H, dd, ^2J 13, ^3J 6 Hz, ArCH_2), 2.78 (1 H, dd, ^2J 13, ^3J 8 Hz, ArCH_2), 2.62 (1 H, dd, ^2J 17, ^3J 9 Hz, ArCH_2CHCH_2CO_2H), and 2.41 (1 H, dd, ^2J 17, ^3J 5 Hz, ArCH_2CHCH_2CO_2H).

The (*R*)-(+)-enantiomers of (**6a–c**) were obtained by similar procedures to those described for preparation of the corresponding antipodes, except for the use of Ru_2Cl_4[(*S*)-(−)-binap]$_2$(NEt_3) as the catalyst in place of the (*R*)-(+)-binap complex. The crude products were recrystallized twice from ethyl acetate–hexane to afford the pure (*R*)-(+)-isomers, which showed the same spectral data as those of the (*S*)-(−)-forms and gave satisfactory analytical data. The optical rotation data are given in the Table.

Determination of Enantiomeric Purity of (**6a–c**).—To a methanol solution (2 cm^3) containing a small portion (*ca.* 10 mg) of either (*S*)-(−)- or of (*R*)-(+)-(**6a–c**), diazomethane was introduced for about 2 min. The solvent was removed under reduced pressure, and the residue taken up in hexane–isopropyl alcohol (90:10). The sample solutions of the dimethyl esters (**7a–c**) thus prepared were analysed by HPLC on a CHIRALCEL OD column: solvent, hexane–isopropyl alcohol (90:10); flow rate, 0.5 cm^3/min. The esters of the (*R*)-(−)-acids were eluted first in each case. The chromatographic parameters are given in the Table.

(S)-(−)-2-(3,4-*Methylenedioxybenzyl*)*butane*-1,4-*diol*, (*S*)-(**9a**).—The acid (*S*)-(**6a**) (1.01 g, 4 mmol) in dry THF (60 cm^3) was added dropwise to $LiAlH_4$ (0.33 g, 9 mmol) in dry THF (30 cm^3) under nitrogen during 30 min, and the mixture was refluxed for 1 h. Water (2 cm^3) was added followed by 5% aqueous HCl to pH 1, and the aqueous phase was extracted (×3) with chloroform. The combined organic layer was washed with water, dried (Na_2SO_4), and evaporated to dryness. Chromatography gave the pure *diol* (S)-(**9a**) (0.77 g, 85%) as a colourless oil, which crystallized on standing at room temperature, m.p. 63–64 °C; $[\alpha]_D^{22}$ −1.9° (*c* 1.1 in ethanol) (Found: C, 71.75; H, 7.7. $C_{12}H_{16}O_4$ requires C, 72.1; H, 7.65%); IR (KBr) ν_{max}/cm^{-1} 3 265 (OH); δ_H 6.65–6.75 (3 H, m, ArH), 5.94 (2 H, s, OCH_2O), 3.40–3.82 (4 H, m, HOCH_2CH_2CHCH_2OH), 2.87 (2 H, s, OH), 2.65 (1 H, dd, ^2J 14, ^3J 8 Hz, ArCH_2CH), 2.49 (1 H, dd, ^2J 14, ^3J 7 Hz, ArCH_2CH), 1.84–1.90 (1 H, m, C*H*CH_2OH), and 1.53–1.58 (2 H, m, CHC$H_2$$CH_2$OH).

(S)-(−)-2-(3,4-*Dimethoxybenzyl*)*butane*-1,4-*diol*, (S)-(**9b**).—By similar procedures as above, the diacid (*S*)-(**6b**) (1.07 g, 4 mmol) was allowed to react with $LiAlH_4$ (0.33 g, 9 mmol) in THF under nitrogen atmosphere. The diol (*S*)-(**9b**) (0.77 g, 80% yield) was obtained as a colourless oil after chromatographic purification; $[\alpha]_D^{22}$ −0.7° (*c* 1.2 in ethanol); IR (NaCl) ν_{max}/cm^{-1} 3 300 (OH); δ_H 6.70–6.85 (3 H, m, ArH), 3.78 (3 H, s, OMe), 3.76 (3 H, s, OMe), 3.40–3.75 (4 H, m, HOCH_2CH_2CHCH_2OH), 2.85 (2 H, s, OH), 2.65 (1 H, dd, ^2J 13, ^3J 7 Hz, ArCH_2CH), 2.49 (1 H, dd, ^2J 13, ^3J 7 Hz, ArCH_2CH), 1.85–1.95 (1 H, m, C*H*CH_2OH), and 1.54–1.60 (2 H, m, C$H_2$$CH_2$OH).

(S)-(−)-2-(4-*Benzyloxy*-3-*methoxybenzyl*)*butane*-1,4-*diol*, (S)-(**9c**).—The diol (*S*)-(**9c**) was prepared from (*S*)-(**6c**) in 77% yield as white crystals by procedures similar to those just described, m.p. 63–64 °C; $[\alpha]_D^{22}$ −0.8° (*c* 1.2 in ethanol) (Found: C, 64.3; H, 7.2. $C_{19}H_{24}O_4$ requires C, 64.1; H, 7.2%); IR (KBr) ν_{max}/cm^{-1} 3 240 (OH); δ_H 7.31–7.50 (5 H, m, *Ph*CH_2O), 6.69–6.93 (3 H, m, benzyl ArH), 5.07 (2 H, s, PhCH_2O), 3.81 (3 H, s, OMe), 3.42–3.80 (4 H, m, HOCH_2CH_2CHCH_2OH), 2.86 (2 H, s, OH), 2.66 (1 H, dd, ^2J 13, ^3J 7 Hz, ArCH_2CH), 2.50 (1 H, dd, ^2J 13, ^3J 7 Hz, ArCH_2CH), 1.85–1.95 (1 H, m, C*H*CH_2OH), and 1.54–1.60 (2 H, m, C$H_2$$CH_2$OH).

The enantiomers (*R*)-(**9a–c**) were obtained from (*R*)-(**6a–c**) by similar treatment with $LiAlH_4$ as just described. The spectral data of these products coincided with those of the corresponding (*S*)-isomers.

(S)-(−)-4-(3,4-*Methylenedioxybenzyl*)*dihydrofuran*-2(3H)-*one*, (S)-(**1a**).—To a solution of (*S*)-(**9a**) (0.45 g, 2 mmol) in toluene (10 cm^3), 4-phenylbut-3-en-2-one (0.59 g, 4 mmol) and $RuH_2(PPh_3)_4$ (93 mg, 0.08 mmol) were added under argon, and the mixture was stirred at 20 °C for 10 h. The solvent was removed on a rotary evaporator and the residue was distilled under reduced pressure (2–3 mmHg) on a Kugelrohr apparatus at 100 °C to remove excess of 4-phenylbut-3-en-2-one and its hydrogenated product. The residual dark blue oil was purified by column chromatography on silica gel to afford the furanone (**1a**) (0.33 g, 75% yield) as a colourless oil. GLC analysis showed contamination with the isomer (**10a**) [(**1a**):(**10a**) 96:4]; $[\alpha]_D^{22}$ −2.8° (*c* 1.1 in $CHCl_3$) {lit.,[8a,c] $[\alpha]_D$ −4.78° (*c* 1.7 in $CHCl_3$)}; IR (NaCl) ν_{max}/cm^{-1} 1 779 (lactone C=O); δ_H 6.70–6.80 (3 H, m, ArH), 5.96 (2 H, s, OCH_2O), 4.32 (1 H, dd, ^2J 9, ^3J 7 Hz, ArCH_2CHCH_2O), 4.01 (1 H, dd, ^2J 9, ^3J 6 Hz, ArCH_2CHCH_2O), 2.86–2.90 (1 H, m, C*H*CH_2O), 2.72–2.75 (2 H, m, ArCH_2), 2.54 (1 H, dd, ^2J 17, ^3J 8 Hz, CH_2CO), and 2.26 (1 H, dd, ^2J 17, ^3J 7 Hz, CH_2CO).

(S)-(−)-(3,4-*Dimethoxybenzyl*)*dihydrofuran*-2(3H)-*one*, (S)-(**1b**).—The diol (*S*)-(**9b**) (0.45 g, 2 mmol) was converted into (*S*)-(**1b**) by similar procedures to those just described, and after purification by column chromatography (*S*)-(**1b**) was obtained in 79% yield as a colourless oil. GLC analysis showed contamination with (**10b**) [(**1b**):(**10b**) 95:5]; $[\alpha]_D^{22}$ −3.2° (*c* 1.0 in $CHCl_3$) {lit.[8b] $[\alpha]_D$ −7.6° (*c* 2.7 in $CHCl_3$)}; IR (NaCl) ν_{max}/cm^{-1} 1 776 (lactone C=O); δ_H 6.75–6.89 (3 H, m, ArH), 4.30 (1 H, dd, ^2J 9, ^3J 7 Hz, ArCH_2CHCH_2O), 4.01 (1 H, dd, ^2J 9, ^3J 7 Hz, ArCH_2CHCH_2O), 3.80 (3 H, s, OMe), 3.78 (3 H, s, OMe), 2.89–2.92 (1 H, m, C*H*CH_2O), 2.73–2.75 (2 H, m, ArCH_2), 2.54 (1 H, dd, ^2J 17, ^3J 8 Hz, CH_2CO), and 2.27 (1 H, dd, ^2J 17, ^3J 8 Hz, CH_2CO).

(S)-(−)-4-(4-*Benzyloxy*-3-*methoxybenzyl*)-2-(3H)-*dihydrofuran*-2(3H)-*one*, (S)-(**1c**).—By procedures similar to those just described, the furanone (*S*)-(**1c**) containing a small amount of (**10c**) [(**1c**):(**10c**) 95:5] was obtained in crystalline form from (*S*)-(**7c**) in 81% yield, m.p. 73.0–74.5 °C; $[\alpha]_D^{22}$ −2.4° (*c* 1.2 in $CHCl_3$) (lit.[8c] for the antipode, $[\alpha]_D$ +4° in $CHCl_3$) (Found: C, 73.25; H, 6.4. Calc. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.45%); IR (KBr) ν_{max}/cm^{-1} 1 774 (lactone C=O); δ_H 7.28–7.50 (5 H, m, *Ph*CH_2O), 6.71–6.97 (3 H, m, benzyl ArH), 5.08 (2 H, s, PhCH_2O), 4.31 (1 H, dd, ^2J 9, ^3J 7 Hz, ArCH_2CHCH_2O), 4.02 (1 H, dd, ^2J 9, ^3J 7 Hz, ArCH_2CHCH_2O), 3.83 (3 H, s, MeO), 2.85–2.95 (1 H, m, C*H*CH_2O), 2.73–2.85 (2 H, m, ArCH_2), 2.54 (1 H, dd, ^2J 17, ^3J 8 Hz, CH_2CO), and 2.27 (1 H, dd, ^2J 17, ^3J 7 Hz, CH_2CO).

The enantiomers (*R*)-(**1a–c**) were obtained from (*S*)-(**9a–c**) by similar lactonization reactions, and characterized by spectroscopic measurements.

Determination of Enantiomeric Purity of (**1a–c**).—To a THF solution (2 cm^3) containing a small amount (*ca.* 15 mg) of (*S*)-(−)-or (*R*)-(+)-(**1a–c**), a hexane solution of methyl-lithium (1 cm^3; 0.98M) was added at −78 °C, and the reaction was continued at room temperature for 16 h. The mixture was acidified with 5% HCl and extracted with chloroform. The organic phase was dried, and evaporated under reduced

pressure. The residue was purified by flash column chromatography ($CHCl_3$–MeOH, 100:2 v/v) to give the pure diols (**11a–c**).

The 400 MHz ^1H NMR spectra of the diols (**11a–c**) were measured in $CDCl_3$ containing the chiral shift reagent $Eu(tfc)_3$ (15–30% molar proportion with respect to the diols).[20] The methyl singlets at δ *ca.* 1.16 and 1.24 in the absence of the $Eu(tfc)_3$ were shifted to lower fields on its addition. However, only poor splittings were detected in the key methyl signals for mixtures of enantiomers of (**11a–c**). The results indicated it to be difficult to evaluate the e.e.s of (**11a–c**) by this method.

The e.e. of the diol (**11c**) (97%) was determined by chiral HPLC analysis using a CHIRALCEL OD column, parameters: α 1.32; K_1' 1.55; R_s 0.96; eluant, hexane–isopropyl alcohol (90:10 v/v); flow rate, 0.5 cm^3/min. However, analyses of (**11a**) and (**11b**) exhibited no clear peak separations by the chiral HPLC method, despite several changes in the eluant composition and/or flow rate.

Asymmetric Hydrogenation of (**4a**).—3-Methoxycarbonyl-4-(3,4-methylenedioxyphenyl)but-3-enoic acid (**4a**) (1.32 g, 5 mmol) was hydrogenated and treated by procedures similar to those in the preparation of (**6a**). Owing to hydrolysis of the ester group during the work-up, (**6a**) with 64% e.e. was obtained as the product, in 90% yield (1.14 g), with ^1H NMR data identical with those given previously.

(S)-(−)-*Ethylsuccinic Acid* (**6d**) *and* (S)-(−)-n-Butylsuccinic Acid (**6e**).—By procedures similar to those in the preparation of (S)-(**6a–c**), the alkylsuccinic acids (**6d**) and (**6e**) were obtained.

The diacid (**5d**) (1.44 g, 10 mmol) was hydrogenated with $Ru_2Cl_4[(R)\text{-binap}]_2(NEt_3)$ as the catalyst to give (*S*)-(−)-ethylsuccinic acid (**6d**) (1.20 g, 82%); $[\alpha]_D^{22}$ −18.3° (*c* 1.5 in ethanol). Chiral HPLC analysis of its dianilide derivative (**8d**) indicated the e.e. of the product to be 75%. The dianilide derivatives (**8d** and **e**) were prepared as follows. To a THF solution (2 cm^3) containing (S)-(−)-(**6d** or **e**) (0.1 mmol), aniline (9.3 mg, 0.1 mmol), *N*,*N*′-dicyclohexylcarbodi-imide (23 mg, 0.11 mmol), 4-dimethylaminopyridine (2 mg), and acetonitrile (1 cm^3) were added, and the mixture was stirred at room temperature for 20 h. The precipitate was filtered off, and the filtrate was evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel with diethyl ether as an eluant. E.e. data and chromatographic parameters are shown in the Table. The diacid (**6d**) had δ_H 2.71–2.75 (1 H, m, $CHCO_2H$), 2.67 (1 H, dd, ^2J 16, ^3J 9 Hz, CH_2CO_2H), 2.44 (1 H, dd, ^2J 16, ^3J 5 Hz, CH_2CO_2H), 1.61–1.70 (2 H, m, $MeCH_2$), and 0.95 (3 H, t, *J* 7 Hz, $MeCH_2$).

(*S*)-(−)-n-Butylsuccinic acid (**6e**) was obtained by the hydrogenation of (**5e**) in 85% yield; $[\alpha]_D^{22}$ −24.4° (*c* 1.1 in ethanol); 68% e.e. by chiral HPLC analysis of the dianilide (**8e**); δ_H 2.75–2.82 (1 H, m, $CHCO_2H$), 2.66 (1 H, dd, ^2J 17, ^3J 9 Hz, CH_2CO_2H), 2.44 (1 H, dd, ^2J 17, ^3J 5 Hz, CH_2CO_2H), 1.58–1.60 (2 H, m, $Pr^nCH_2CHCO_2H$), 1.29–1.41 (4 H, m, $MeCH_2CH_2$), and 0.90 (3 H, t, *J* 7 Hz, Me).

Acknowledgements

This study was supported by Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, and Culture, Japan (No. 63607510, 01607002).

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Paper 9/04036F
Received 21*st September* 1989
Accepted 7*th December* 1989