Asymmetric Synthesis with Sugar Derivatives. V.[1,2] The Synthesis of α-Hydroxy Acids on Insoluble Polymer Supports

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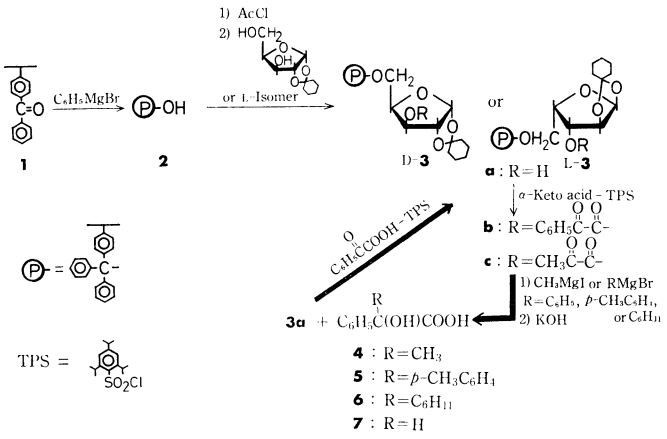
The styrene-2% divinylbenzene copolymer containing 1,2-*O*-cyclohexylidene-5-*O*-trityl-α-D- or -L-xylofuranose (D- or L-**3a**) was prepared. Asymmetric Grignard additions to benzoylformate (**3b**) and pyruvate (**3c**) were carried out using these polymers as chiral ester-components. Enantiomers of α-hydroxy acids, such as atrolactic acid (**4**) and 2-hydroxy-2-phenyl-2-(*p*-tolyl)acetic acid (**5**), were obtained in relatively good synthetic and optical yields, depending on the use of either D- or L-**3a**. The optical yields of **4** for the polymer were higher than those for a low-molecular-weight compound, 1,2-*O*-cyclohexylidene-5-*O*-trityl-α-D-xylofuranose (**8a**). It was shown that the polymer could be used repeatedly.

The application of the method[3] for the synthesis of polypeptides on polymer supports to asymmetric synthesis[4] seems to be very advantageous for the following reasons: (1) the isolation of a desired product from the reaction mixtures is very much simplified; (2) the polymer containing chiral groups which serve as a chiral environment for the asymmetric synthesis can be used repeatedly; and (3) the polymer chain may effect an increase in the stereoselectivities of the reagents.

Recently we have demonstrated[5] that sugar derivatives such as 1,2: 5,6-di-*O*-cyclohexylidene-α-D-glucofuranose can be used effectively as chiral alcohols for the asymmetric synthesis of atrolactic acid (2-hydroxy-2-phenylpropionic acid) (**4**)[6] by Grignard additions to the sugar-esters of benzoylformic acid, and that the increase in the steric bulkiness of a substituent on the C-4 of the furanose ring of gluco- or xylo-furanoside containing a 1,2-*O*-cyclohexylidene or -isopropylidene group causes the optical yield of the acid to increase. Therefore, the use of a cross-linked polystyrene-bound 1,2-*O*-cyclohexylidene-5-*O*-trityl-α-D- or -L-xylofuranose (D- or L-**3a**), which has a bigger substituent on the C-4 of the furanose ring, may be effected to increase the optical yield and provide a convenient method for the asymmetric synthesis.[7] In this paper we would like to report on the asymmetric synthesis of some α-hydroxy acids with insoluble-polymer supports, D- and L-**3a**, and on that with a low-molecular-weight compound, 1,2-*O*-cyclohexylidene-5-*O*-trityl-α-D-xylofuranose (**8a**).[8]



Scheme 1.

Results and Discussion

The polymer (**3a**) was prepared by a procedure similar to that reported earlier.[9] A commercially-available styrene-2% divinylbenzene copolymer (100—200 mesh) was converted into a 21 or 9 mol% benzoylated polymer (**1**) by the use of a limited amount of benzoyl chloride in the presence of aluminum chloride; hereafter, the polymers derived therefrom will be designated as P-21 or -9 respectively. The reaction of **1** with an excess of phenylmagnesium bromide gave a tritylated polymer (**2**) in an almost quantitative yield. On the treatment of **2** with an excess of acetyl chloride, followed by a reaction with 1,2-*O*-cyclohexylidene-α-D-[10] or -L-xylofuranose,[11] D- or L-**3a** was obtained in a 73—87% yield based on the amount of the trityl group in **2**; the remaining chloride was treated with absolute methanol. The hydrolysis of D-**3a** (P-21: 1.0 g) with an acid released ~0.9 mmol of 1,2-*O*-cyclohexylidene-α-D-xylofuranose, this value being very consistent with that calculated from the gain in weight.

The polymer (**3a**) was easily esterified with an excess of benzoylformic acid[12] or pyruvic acid and 2,4,6-triisopropylbenzenesulfonyl chloride (TPS)[13] to give the polymer-bound benzoylformate (**3b**) or the corresponding pyruvate (**3c**) respectively in an almost quantitative yield. In these reactions every 100 styrene units, ~15 and ~7 in P-21 and -9 respectively, were derivatized to the ester functions. The polymers of the P-9 series were much more swelled than those of P-21 in a solvent such as tetrahydrofuran or benzene.

The polymer (**3b** or **c**) thus obtained was subjected to an asymmetric Grignard reaction, which was completed at room temperature. The complete detachment of the acid moiety was effected with a solution of potassium hydroxide at room temperature. The isolated free acids were almost pure, judging from their IR and NMR spectra and from tlc analyses. The results are summarized in Table 1.

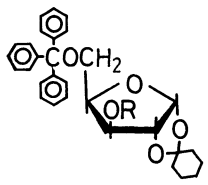
From the reaction of D- or L-**3b** (P-21) with methylmagnesium iodide, *R*-(—)- or *S*-(+)-**4**[14] was obtained respectively in a 65% (maximum) optical yield; the synthetic yields, based on the amount of the esters charged on the polymers, were also fairly high (Runs 1 and 5). Similar results were obtained in the case of

Table 1. Asymmetric synthesis of α-hydroxy acids

Run	Starting compound[a]	Grignard reagent	α-Hydroxy acid					Reaction condition[e]
			Product	Synthetic yield,[b] %	$[\alpha]_D^{20-25}$ (c 1, EtOH)	Optical yield,[c] %	Configuration[d]	
1	D-**3b** (P-21)	CH_3MgI	**4**	77	−24.6°	65	*R*	A D F
2	D-**3b** (P-21)	CH_3MgI	**4**	84	−24.2°	64	*R*	A D F
3	D-**3b** (P-21)	CH_3MgI	**4**	77	−24.0°	64	*R*	B D F
4	D-**3b** (P-9)	CH_3MgI	**4**	66	−22.8°	60	*R*	A D F
5	L-**3b** (P-21)	CH_3MgI	**4**	78	+22.8°	60	*S*	A D F
6	**8b**	CH_3MgI	**4**	68	−20.1°	53	*R*	A D F
7	**8b**	CH_3MgI	**4**	67	−20.0°	53	*R*	A C F
8	D-**3c** (P-9)	C_6H_5MgBr	**4**	18	+13.7°	36	*S*	A D F
9	**8c**	C_6H_5MgBr	**4**	21	+10.4°	28	*S*	A D F
10	D-**3b** (P-21)	*p*-$CH_3C_6H_4MgBr$	**5**	63	(−1.3°)[f]	52	(*S*)[g]	B D G
11	D-**3b** (P-9)	*p*-$CH_3C_6H_4MgBr$	**5**	53	(−1.4°)[f]	56	(*S*)[g]	A D G
12	L-**3b** (P-21)	*p*-$CH_3C_6H_4MgBr$	**5**	68	(+1.1°)[f]	44	(*R*)[g]	B D G
13	D-**3b** (P-21)	$C_6H_{11}MgBr$	**6**	45	−13.5°	60[h]	*R*	B E G

a) The symbols, P-21 and -9, are used for the polymers derived from 21 and 9 mol% benzoylated **1** respectively.
b) Calculated on the basis of the amount of the ester charged on the polymer.
c) Calculated on the basis of $[\alpha]_D^{13.8}$ −37.7° (*c* 3.35, EtOH), $[\alpha]_{546}^{20}$ +2.5° (*c* 5, EtOH), and $[\alpha]_D$ +22.6° (*c* 1.4, EtOH) for enantiomerically pure **4** (Ref. 6b), **5** (Ref. 16a), and **6** (Ref. 17) respectively.
d) See Refs. 14 and 17 for **4** and **6** respectively.
e) For details, see Experimental Section. The Grignard reagent was added during a period of 35 min at (A) 6—8 °C (bath) or (B) room temperature, and the mixture was then stirred at room temperature for (C) 0.5 hr, (D) 1 hr, or (E) 3 hr. The stirring in the saponification was done at room temperature for (F) 5 hr or (G) 17 hr.
f) $[\alpha]_{546}^{20-25}$ (*c* 5, EtOH).
g) The configuration was assigned temporarily on the basis of the Prelog rule: see Refs. 4a, pp. 50—83 and 6c.
h) This value is an optical purity (see Experimental Section).

D-**3b** (P-9) (Run 4).



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a: R = H

b: R = $C_6H_5\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-$

c: R = $CH_3\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-$

It was of interest to compare the optical yield for the polymer with that for a low-molecular-weight compound, 1,2-*O*-cyclohexylidene-3-*O*-benzoylformyl-5-*O*-trityl-α-D-xylofuranose (**8b**). Under similar conditions, **8b** gave *R*-(−)-**4** in a 53% optical yield (Runs 6 and 7); this yield was, as expected, clearly lower than that for the polymer. The observed difference can be explained by the difference in the steric bulkiness of the substituent on the C-4 of the furanose ring (*vide ante*).[5] In addition, the free rotation of the functionalized groups in the cross-linked polymer might be slightly restricted,[15] so that the α-keto carbonyl group in a favorable conformation is more susceptible to the attack by the Grignard reagent.

When D-**3c** (P-9) was treated with phenylmagnesium bromide the stereochemical result was reversed, and the synthetic and optical yields of *S*-(+)-**4** were much lower than those for D-**3b** (Run 8). It was assumed that, in this case, the ester-carbonyl group was very reactive and susceptible to attack by the Grignard reagent, resulting in release of the acid function from the polymer. Analogous results were observed in the case of 1,2-*O*-cyclohexylidene-3-*O*-pyruvinyl-5-*O*-trityl-α-D-xylofuranose (**8c**), but the optical yield was again lower than that for the polymer (Run 9). When D-**3c** (P-21) was used instead of P-9, the Grignard addition was incomplete even after a prolonged reaction time, presumably because of the difficult penetration of the reagent resulting from the poor ability of P-21 to swell in solvents.

The reaction of D- or L-**3b** with *p*-tolylmagnesium bromide gave, upon hydrolysis, (−)- or (+)-2-hydroxy-2-phenyl-2-(*p*-tolyl)acetic acid (**5**)[16] respectively (Runs 10—12). A difficulty was encountered when D-**3b** (P-21) was treated with cyclohexylmagnesium bromide, which has hydrogens on the beta carbon atom of the reagent. A large amount (~15%) of mandelic acid (**7**), besides 2-cyclohexyl-2-hydroxy-2-phenylacetic acid (**6**),[17] was produced by the Grignard reduction[18] of the α-keto carbonyl group with the β-hydrogen. Although attempts to purify these acids without changing their enantiomeric compositions as obtained from the asymmetric reaction were unsuccessful, relatively pure *R*-(−)-**6** could be isolated by a fractional precipitation (Run 13).[19]

One of the great advantages of the functional polymer is that the recovered **3a** can be utilized repeatedly. The polymer, D-**3b** (P-21), was subjected to re-cycled Grignard addition-saponification-esterification reactions for the asymmetric synthesis of *R*-(−)-**4** (Scheme 1). The results are summarized in Table 2. Even after the 6th repetition of the reactions, the polymer could

Table 2. Repetition of the asymmetric synthesis of *R*-(−)-atrolactic acid (**4**) with the polymer (D-**3b**)[a]

Repet.	Synthetic yield,[b] %	Optical yield,[c] %
1st	70	62
2nd	80	61
3rd	69	55
4th	78	54
5th	78	56
6th	81	58
7th	72	60

a) P-21: see footnote a in Table 1.
b) and c) See the corresponding footnotes in Table 1.

be used for the asymmetric synthesis without any loss of capability.

Although at present a detailed explanation of the steric course of the reaction cannot be offered,[20] some general tendencies of the direction of the attack of the Grignard reagent on the α-keto carbonyl group of the sugar-ester are apparent, as can be seen in Table 1.

Experimental

The melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 instrument in KBr unless otherwise stated. The NMR spectra were obtained using a Model JNM-C-60 HL spectrometer (Japan Electronic Optics Laboratory Co.) with DSS as an internal standard. The chemical shifts are expressed in the δ values. The optical rotations were measured with a Perkin-Elmer Model 141 polarimeter and a 1 dm tube. The elemental analyses were performed by this Institute.

Thin-layer chromatography was accomplished on 2.5×10 cm plates coated with 0.25 mm layers of E. Merck GF-254 silica gel. The following products were detected on these plates: the sugar derivatives, by the use of a methanol–sulfuric acid–*p*-methoxybenzaldehyde (85: 10: 5, v/v) spray, followed by heating; the α-keto and hydroxy acids, under an UV light or by the use of a 0.1% methanolic methyl red spray, followed by heating. The following solvents were used as developers: chloroform or chloroform–methanol (9: 1) for the sugar derivatives; benzene–methanol–acetic acid (45: 8: 4) for the acids.

The polymers were dried over KOH–P_2O_5 at room temperature *in vacuo* overnight unless otherwise stated. The Grignard reagents were prepared by the reactions of magnesium and halides in ether. The crude acids obtained from the asymmetric reactions were identified by comparisons of their IR (in chloroform) and NMR spectra and thin-layer chromatograms with those of analytically-pure racemic samples which had been prepared from the reactions of methyl benzoylformate and Grignard reagents by the standard methods.

A styrene-2% divinylbenzene copolymer was purchased from the Protein Research Foundation (Minoo, Osaka).

The Benzoylated Polymer (1). To a stirred suspension of a styrene-2% divinylbenzene copolymer (100—200 mesh, 20.0 g, 0.19 mol of the phenyl group) in carbon disulfide (200 ml), we added benzoyl chloride (5.6 g, 39.8 mmol) at room temperature, and then added aluminum chloride (5.6 g) at 0—5 °C (bath). The mixture was stirred at 0—5 °C for 1 hr and at room temperature for 16 hr, and then stirred into a mixture of iced water (250 ml) and dioxane (250 ml). After the inorganic materials had been dissolved, the polymer was collected on a glass filter, washed successively with dioxane–water (500 ml, 1: 1), water (1 l), dioxane–water (500 ml, 1: 1), dioxane (400 ml), methanol (250 ml), and ether (500 ml), and then dried to give **1** (P-21). The yield was 24.1 g, which corresponded to 29.4 mmol of the benzoyl group, as judged by the increase in weight. Therefore, 21% of the starting phenyl groups were derivatized to the benzoyl groups. $\nu_{C=O}$, 1655 cm^{-1}.

Under similar conditions, **1** (P-9) was prepared using benzoyl chloride (3.0 g, 21.4 mmol) and aluminum chloride (3.0 g); the yield was 21.8 g (17.3 mmol of the benzoyl group).

The Tritylated Polymer (2). To a stirred suspension of **1** (P-21) (24.0 g, 38.4 mmol of the benzoyl group) in dry tetrahydrofuran (120 ml), we added a solution of phenylmagnesium bromide (78 mmol) in dry tetrahydrofuran (100 ml) at room temperature under a dry nitrogen atmosphere over a period of 30 min. After the completion of the addition, the mixture was stirred at room temperature for 18 hr and then refluxed gently for 6 hr. After the mixture had been cooled, it was stirred into iced 3 M HCl–acetic acid (500 ml, 1: 1). The polymer was collected on a glass filter, washed successively with 3 M HCl–acetic acid (500 ml, 1: 1), water (1 l), tetrahydrofuran–water (500 ml, 1: 1), dioxane–water (500 ml, 1: 1), dioxane (400 ml), methanol (400 ml), and ether (400 ml), and then dried to give **2** (P-21); the yield was 27.0 g (38.5 mmol of the trityl group). There was no carbonyl band detectable at 1655 cm^{-1}, indicating that the reaction had essentially been completed.

Under similar conditions, **2** (P-9) was prepared using **1** (P-9) (43.0 g, 35.3 mmol of the benzoyl group); the yield was 46.0 g, (38.5 mmol of the trityl group).

*The Polymer-bound 1,2-O-Cyclohexylidene-α-*D*- or -*L*-Xylofuranose (*D*- or *L*-3a).* To a suspension of **2** (P-21) (13.0 g, 18.4 mmol of the trityl group) in dry benzene (80 ml), we added acetyl chloride (10 ml), after which the mixture was gently refluxed for 16 hr with stirring. After the mixture had been cooled, the polymer was collected on a glass filter in a dry-box, washed successively with dry benzene (200 ml) and dry ether (200 ml), and then dried. To a suspension of this polymer in a mixture of dry pyridine (15 ml) and dry benzene (80 ml), we then added 1,2-*O*-cyclohexylidene-α-D-[10] or -L-xylofuranose[11] (6.0 g, 26 mmol), after which the mixture was stirred at room temperature under a dry nitrogen atmosphere for 48 hr. In order to decompose the unreacted trityl chloride groups, absolute methanol (5 ml) was added and the mixture was stirred for another 24 hr. The polymer was collected on a glass filter, washed successively with benzene (100 ml), benzene–chloroform (200 ml, 1: 1), chloroform (200 ml), chloroform–tetrahydrofuran (100 ml, 1: 1), tetrahydrofuran (100 ml), tetrahydrofuran–water (100 ml, 1: 1), water (400 ml), water–dioxane (100 ml, 1: 1), dioxane (100 ml), dioxane-methanol (100 ml, 1: 1), methanol (200 ml), methanol–ether (100 ml, 1: 1), and ether (200 ml), and then dried to give **3a**. The yields of D- and L-**3a** (P-21) were 16.1 and 16.4 g, which corresponded to 14.6 and 16.0 mmol of the sugar respectively. Therefore, 80—87% of the trityl groups were converted into the sugar functions.

Under similar conditions, D-**3a** (P-9) was prepared using **2** (P-9) (45.0 g, 37.8 mmol of the trityl group), acetyl chloride (35 ml), and 1,2-*O*-cyclohexylidene-α-D-xylofuranose (31.1 g, 57 mmol); the yield was 50.8 g (27.4 mmol of the sugar).

The Acid Hydrolysis of the Polymer-bound Sugar (D-3a; P-21). Freshly-distilled dioxane was used in this experiment.

To a strirred suspension of D-**3a** (P-20) (1.0 g, 0.91 mmol of the sugar) in dioxane (5 ml), we added dioxane–8 M HCl

(5 ml, 100: 1, v/v) at room temperature under a nitrogen atmosphere over a period of 15 min, after which the mixture was stirred for 24 hr. The polymer was collected on a glass filter, washed successively with dioxane (20 ml), dioxane–water (20 ml, 1: 1), water (5 ml), dioxane–water (10 ml, 1: 1), dioxane (10 ml), methanol (20 ml), and ether (20 ml), and then dried. The weight of the recovered polymer was 807 mg.

The combined filtrate and washings were treated with Dowex-1, X-2 (OH^- form, 5 ml) for 5 min. The ion-exchange resin was removed by filtration and washed with successively with dioxane–water (20 ml, 1: 1) and water (30 ml). The combined filtrate and washings were then concentrated to dryness to give 1,2-*O*-cyclohexylidene-α-D-xylofuranose as a crystal (208 mg, 0.9 mmol), the spectral data of which were almost identical with those of an authentic sample.[10] No free D-xylose was detected by the tlc analysis.

The recovered polymer (747 mg) was further treated with dioxane–12 M HCl (5 ml, 100: 1, v/v) for 48 hr under conditions similar to those described above, thus giving 1.5 mg of 1,2-*O*-cyclohexylidene-α-D-xylofuranose. The IR spectrum of the resulting polymer showed that only a trace of the sugar function remained.

*The Polymer-bound Benzoylformate (**3b**).* To a stirred suspension of D-**3a** (P-21) (15.0 g, 14.7 mmol of the sugar) in a mixture of dry benzene (75 ml) and dry pyridine (25 ml), we added benzoylformic acid (3.76 g, 25 mmol), and then we added TPS (7.6 g, 25 mmol) at room temperature under a dry nitrogen atmosphere. After the mixture had been stirred for 5 hr, absolute methanol (2.5 ml) was added; the stirring was then continued for another hour. The polymer was collected on a glass filter, washed successively with pyridine (80 ml), pyridine–iced water (200 ml, 1: 1), water (1 l), dioxane–water (300 ml, 1:1), dioxane (300 ml), dioxane–methanol (300 ml, 1:1), methanol (200 ml), methanol–ether (200 ml, 1: 1), and ether (200 ml), and dried to give D-**3b** (P-21). The yield was 17.16 g, which corresponded to 16.4 mmol of the ester, as judged by the increase in weight. Therefore, the esterification had been essentially completed. $\nu_{C=O}$, 1740, 1691 cm^{-1}.

Under similar conditions, L-**3b** (P-21) (6.69 g, 5.23 mmol of the ester) and D-**3b** (P-9) (9.67 g, 5.1 mmol of the ester) were prepared starting from L-**3a** (P-21) (6.0 g, 5.88 mmol of the sugar) and D-**3a** (P-9) (9.0 g, 4.9 mmol of the sugar) respectively.

*The Polymer-bound Pyruvate (**3c**).* To a stirred suspension of D-**3a** (P-9) (9.0 g, 4.9 mmol of the sugar) in a mixture of dry benzene (60 ml) and dry pyridine (10 ml), we added freshly-distilled pyruvic acid (1.27 g, 14.7 mmol); we then added TPS (4.45 g, 14.7 mmol) at room temperature under a dry nitrogen atmosphere. The mixture was treated in a similar manner to that described for the synthesis of **3b**, giving D-**3c** (P-9). The yield was 9.38 g (5.4 mmol of the ester). $\nu_{C=O}$, 1760 (shoulder), 1734 cm^{-1}.

Analogously, D-**3c** (P-21) (14.98 g, 14.0 mmol of the ester) was prepared starting from D-**3a** (P-21) (14.0 g, 12.6 mmol of the sugar).

*1,2-O-Cyclohexylidene-5-O-trityl-α-D-xylofuranose (**8a**).* To a solution of 1,2-*O*-cyclohexylidene-α-D-xylofuranose[10] (23.0 g, 0.1 mol) in dry pyridine (100 ml), we added trityl chloride (32.3 g, 0.12 mol) at room temperature; the mixture was stirred for 1 hr and then allowed to stand at room temperature for 2 days. The mixture was poured into iced water (500 ml), and the undissolved materials were collected by decantation and dissolved in ether (600 ml). The ethereal solution was washed with water (2×100 ml) and dried over magnesium sulfate. The ether was then removed, and the pyridine was distilled by repeated co-evaporation with xylene. The residue was crystallized from benzene–*n*-hexane to afford **8a** (38.7 g, 82%). Further recrystallization gave an analytically pure sample: mp 145—147 °C; $[\alpha]_D^{25}$ −28.3° (*c* 1, EtOH); NMR (DMSO-d_6) 5.11 (d, 1H of the hydroxyl group on C-3).

Found: C, 76.45; H, 6.62%. Calcd for $C_{30}H_{32}O_5$: C, 76.24; H, 6.83%.

*3-O-Benzoylformyl-1,2-O-cyclohexylidene-5-O-trityl-α-D-xylofuranose (**8b**).* To a stirred solution of **8a** (4.7 g, 0.01 mol) in a mixture of dry pyridine (10 ml) and dry benzene (20 ml), we added benzoylformic acid (1.65 g, 0.011 mol); then we added TPS (3.34 g, 0.011 mol) at room temperature. After having been stirred for 3 hr, the mixture was stirred into iced water (100 ml) and then extracted with ether (300 ml). The extract was washed with water (2×50 ml) and dried over magnesium sulfate. The ether was then evaporated, and the pyridine was removed by repeated co-evaporation with toluene *in vacuo* to give a syrup, which was subsequently chromatographed on a silica gel column (100 g, 3.5×22 cm) packed with chloroform. Rapid elution (13 ml/min) was effected in order to avoid the decomposition of the product; 25 ml fractions were collected. Fractions 9—12 contained **8b** (3.5 g, 58%) slightly contaminated with impurities. Fractions 13—16 were combined, and the solvent was removed to give analytically pure **8b** (1.3 g, 22%) as a glass after drying over P_2O_5 at 100 °C *in vacuo* for 2 hr: $[\alpha]_D^{25}$ −23.1° (*c* 1, $CHCl_3$); $\nu_{C=O}$, 1740, 1695 cm^{-1}.

Found: C, 75.68; H, 5.92%. Calcd for $C_{38}H_{36}O_7$: C, 75.48; H, 6.00%.

*1,2-O-Cyclohexylidene-3-O-pyruvinyl-5-O-trityl-α-D-xylofuranose (**8c**).* To a stirred solution of **8a** (7.1 g, 15 mmol) in a mixture of dry pyridine (20 ml) and dry benzene (30 ml), we added freshly-distilled pyruvic acid (1.94 g, 22 mmol); following the subsequent addition of TPS (6.1 g, 20 mmol) at room temperature, the mixture was treated in a similar manner to that described for the synthesis of **8b**. The resulting syrup was crystallized from *n*-hexane–benzene to afford **8c** (4.5 g, 55%). Recrystallization from the same solvents gave an analytically pure sample: mp 149—152 °C; $[\alpha]_D^{25}$ −46.3° (*c* 1, $CHCl_3$); $\nu_{C=O}$, 1756, 1737 cm^{-1}.

Found: C, 73.20; H, 6.30%. Calcd for $C_{33}H_{34}O_7$: C, 73.04; H, 6.32%.

The Reaction Vessel for the Asymmetric Synthesis on the Polymer. The reaction vessel consisted of a three-necked flask (100 ml) fitted with a 2.5 cm medium-porosity fritted disk filter in the central part of the side of the flask. The tubing was led beyond the disk and sealed to a bore stopcock through which the solvents were removed under suction. A Grignard reagent which had been prepared in another three-necked flask (50 ml) was transferred directly into the above-mentioned flask through a tube fitted with a 1.3 cm rough-porosity fritted disk filter and a stopcock.

*Asymmetric Synthesis of Atrolactic Acid (**4**).* Some of the reaction conditions and results are presented in Tables 1 and 2.

(A) Synthesis on the polymer. To a stirred suspension of D- or L-**3b** (3—4 g, 2.1—2.5 mmol of the esters) in dry benzene (20—25 ml) in the reaction vessel, we added a solution of the Grignard reagent (6 mmol) in dry ether (18 ml) under a dry nitrogen atmosphere. After the reaction had been completed, the solvents were removed through the filter. The polymer was washed successively with a solution of ammonium chloride (10 g) in iced water–dioxane (200 ml, 1: 1), water (200 ml), dioxane–water (200 ml, 1: 1), dioxane (100 ml), dioxane–methanol (100 ml, 1: 1), and methanol (100 ml), and then dried over KOH–P_2O_5 at room tem-

perature *in vacuo* for 2—3 hr. The IR spectrum of the polymer showed the absence of the α-keto carbonyl group.

Freshly-distilled tetrahydrofuran was used in the next experiment. The polymer was swelled in tetrahydrofuran (15—25 ml), and then a solution of potassium hydroxide (600 mg, 11 mmol) in a tetrahydrofuran–methanol–water mixture (12 ml, 5: 5: 2) was added at room temperature under a nitrogen atmosphere over a period of 20 min. After the mixture had been stirred for 5 hr, the solvents were filtered; the polymer was then washed successively with tetrahydrofuran–methanol–water (100 ml, 20: 5: 2), water (50 ml), and tetrahydrofuran–water (100 ml). The resulting polymer could be used repeatedly; see (*B*). The combined filtrate and washings were concentrated to *ca.* 7 ml below 50 °C (bath) *in vacuo*. The residue was diluted with water (15 ml), and the undissolved material was removed by filtration through a Celite pad and washed with a small amount of water. The combined filtrate and washings were cooled, acidified with 12 M HCl (2 ml), and extracted with ether (3×100 ml). The ethereal extract was washed with water (10 ml) and dried over magnesium sulfate. The removal of the ether gave a slightly colored crystal, which was decolorized with active charcoal in water (20 ml). The water was removed *in vacuo*, and the crystalline residue was again dissolved in ethanol (15 ml). The solution was filtered through a Celite pad. The removal of the ethanol gave **4** as a colorless crystal, which was then dried over KOH–P_2O_5 at room temperature *in vacuo* for 20 min; yields, 52—308 mg.

(B) Repetition of the reactions. Under the same conditions as are described in (*A*), D-**3b** (P-20) (3.0 g, 2.5 mmol of the ester) was treated in the reaction vessel. The resulting polymer was washed with tetrahydrofuran (100 ml) and then stirred in a mixture of acetic acid–tetrahydrofuran–water (100 ml, 1: 95: 4) at room temperature for 30 min in order to remove the potassium hydroxide remaining in the polymer. After the solvents had been removed, the polymer was washed successively with tetrahydrofuran-water (100 ml, 19: 1), tetrahydrofuran–water (100 ml, 1: 1), tetrahydrofuran–pyridine (50 ml, 49: 1), tetrahydrofuran (100 ml), dioxane–methanol (50 ml, 1: 1), and methanol (100 ml), and then dried.

The polymer was then swelled in benzene (15 ml). To this suspension we added, successively, pyridine (3 ml), benzoylformic acid (750 mg, 5.0 mmol), and TPS (1.5 g, 5.0 mmol), after which the mixture was treated under the conditions described for the synthesis of **3b**. The resulting polymer was again subjected to the Grignard addition, and the subsequent reactions were repeated.

The yields were 288—336 mg. The IR and NMR spectra of **4** from the 1st and 7th runs were identical with those of an analytically pure racemic sample.

(C) Synthesis with low-molecular-weight compounds. **8b** (1.21 g, 2.0 mmol) or **8c** (1.25 g, 2.3 mmol) was treated under the conditions described in (*A*), except for the following conditions: (1) The Grignard adduct was hydrolyzed with a solution of ammonium chloride (10 g) in cold water (100 ml), and the resulting ester was extracted with ether (3×100 ml). The extract was then dried over magnesium sulfate, and the ether was removed. (2) The ester of **4** was completely hydrolyzed in methanol (15 ml) with a solution of potassium hydroxide in a mixture of methanol (6 ml) and water (3 ml). The concentrated reaction mixture was then diluted with water (20 ml) and extracted with chloroform (4×100 ml). The water layer was concentrated to *ca.* 10 ml and acidified. (3) In the case of **8c**, the crude product (**4**) was placed in a solution of sodium bicarbonate (300 mg) in water (15 ml), after which the mixture was extracted with ether (100 ml). The extract was washed with water (5 ml). The combined water layer was then acidified to give **4**.

The yields were 221—226 and 82 mg from **8b** and **c** respectively.

*Asymmetric Synthesis of 2-Hydroxy-2-phenyl-2-(*p*-tolyl)acetic Acid (5).* Some of the reaction conditions and results are listed in Table 1. To a stirred suspension of D-**3b** (P-21) (3.0 g, 2.64 mmol of the ester), L-**3b** (P-21) (3.0 g, 2.34 mmol of the ester), or D-**3b** (P-9) (4.0 g, 2.4 mmol of the ester) in dry benzene (20—25 ml) in the reaction vessel, we added a solution of *p*-tolylmagnesium bromide (6 mmol) in dry ether (18 ml) over a period of 35 min under a dry nitrogen atmosphere. The polymer was treated in a manner similar to that described for the synthesis of **4**, except that after the hydrolysis with potassium hydroxide, the diluted solution with water (15 ml) was decolorized at this stage. The crude **5** was crystallized on standing at room temperature over KOH–P_2O_5 for 1—2 days; the yields were 310—394 mg.

Asymmetric Synthesis of 2-Cyclohexyl-2-hydroxy-2-phenylacetic Acid (6). Some of the reaction conditions and results are listed in the Table 1. To a stirred suspension of D-**3b** (P-21) (4.0 g, 3.8 mmol of the ester) in dry benzene (30 ml) in the reaction vessel, we added a solution of cyclohexylmagnesium bromide (11.4 mmol) in dry ether (25 ml) over a period of 35 min under a dry nitrogen atmosphere. The polymer was treated in a manner similar to that described for the synthesis of **5**, thus yielding the crude product (593 mg) as a syrup. Its NMR spectrum and thin-layer chromatogram showed the presence of **7** (~15%) and small amounts of benzoylformic acid and impurities, besides **6**.

In order to remove these undesirable acids, which were highly soluble in water, a carborundum[21] column (100 mesh, 2.8×19 cm) packed with cold water was used. A crude sample (530 mg) was dissolved in a small amount of ethanol, and the solution was put on the top of the column. After a few ml of water had been eluted, a few ml of cold water was added. The carborundum steeped with the ethanolic solution was stirred with a spatula so that the water-insoluble **6** could be precipitated. The column was then washed with cold water (125 ml), and the **6** was eluted with ethanol. The subsequent evaporation of the solvents gave a syrup, which was then decolorized with active charcoal in aqueous ethanol. The removal of the solvents afforded crystalline **6** (355 mg) after drying over KOH–P_2O_5 at room temperature for 2 days. Although a small amount of **6** was eluted while the column was being washed with water, **6** obtained was free from the water-soluble acids, judging from NMR spectroscopy and tlc analysis.

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