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## Synthesis and Ring-Opening Polymerization of Bicyclic Lactones Containing a Tetrahydropyran Ring. 2,6-Dioxabicyclo[2.2.2]octan-3-one

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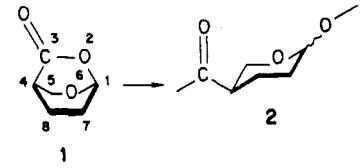
ABSTRACT: A new bicyclic lactone, 2,6-dioxabicyclo[2.2.2]octan-3-one (1), was synthesized from acrolein and dimethyl malonate via six reaction steps in an overall yield of 20%. Monomer 1 was polymerized with cationic and anionic initiators, among which boron trifluoride etherate was particularly effective, to give high molecular weight polyester 2 ($M_n \sim 1 \times 10^5$) at or below −60 °C. The polyester melted with decomposition at ca. 150 °C (DSC) and dissolved in chloroform, dichloromethane, γ-butyrolactone, and pyridine. A transparent film could be cast from a chloroform solution and its strips could be drawn to orient. $^1H$ and $^{13}C$ NMR analysis revealed that the polyester consisted of cis- and trans-2,5-linked tetrahydropyran rings, their proportions varying markedly depending on the reaction conditions. The mechanism of the ring-opening polymerization of 1 is discussed.

### Introduction

Ring-opening polymerization of bicyclic compounds containing two or more heteroatoms provides a useful method to synthesize a new class of specialty polymers possessing heterocyclic structures in their main chains. For example, a variety of stereoregular polysaccharides and their analogues have been prepared by cationic ring-opening polymerization of appropriate anhydrosugar derivatives (bicyclic acetals) followed by chemical modifications.[1-5] Furthermore, anionic polymerization of 8-oxa-6-azabicyclo[3.2.1]octan-7-one (bicyclic lactam) gave a polyamide containing tetrahydropyran rings, which was characterized by excellent permeability for water, and permselectivity for alkali metal ions and solutes of various sizes in aqueous solutions.[6,7] In contrast, cationic polymerization of 6,8-dioxabicyclo[3.2.1]octan-7-one (bicyclic lactone) having the same skeleton as that of the bicyclic lactam above yielded highly selectively 10-, 20-, and 25-membered cyclic oligoesters (macrolides) composed of alternating tetrahydropyran ring and ester moieties.[8-10] Among these, 20- and 25-membered macrolides act as ion carriers and can be regarded as model compounds for naturally occurring neutral ionophores.[11]

Bicyclic acetals, lactones, and lactams consisting of a bicyclo[3.2.1]octane skeleton are relatively easily prepared and there have been a number of publications concerning their polymerizations.[2,4,5] On the contrary, syntheses of bicyclic compounds containing a more strained bicyclo-[2.2.2]octane skeleton are in general difficult and therefore the studies dealing with the polymerization of heterobicyclic monomers of this type have been limited.[12-17]

In order to broaden the scope of the synthesis of specialty polymers by ring-opening polymerization of bicyclic monomers, it is desirable to explore convenient synthetic methods for strained bicyclic acetals, lactones, and lactams. As the first of a series of studies along this line, the present paper describes the synthesis of a new bicyclic lactone, 2,6-dioxabicyclo[2.2.2]octan-3-one (1) and its ring-opening polymerization to polyester 2 containing tetrahydropyran rings in the main chain.



1 2 (1)

### Results and Discussion

**Synthesis.** The synthesis of 2,6-dioxabicyclo[2.2.2]octan-3-one (1) was achieved through six reaction steps as illustrated in Scheme I: Dimethyl 4,4-dimethoxybutane-1,1-dicarboxylate (3) was prepared by the Michael addition of dimethyl malonate to acrolein followed by acetalization according to the procedure described by Hall

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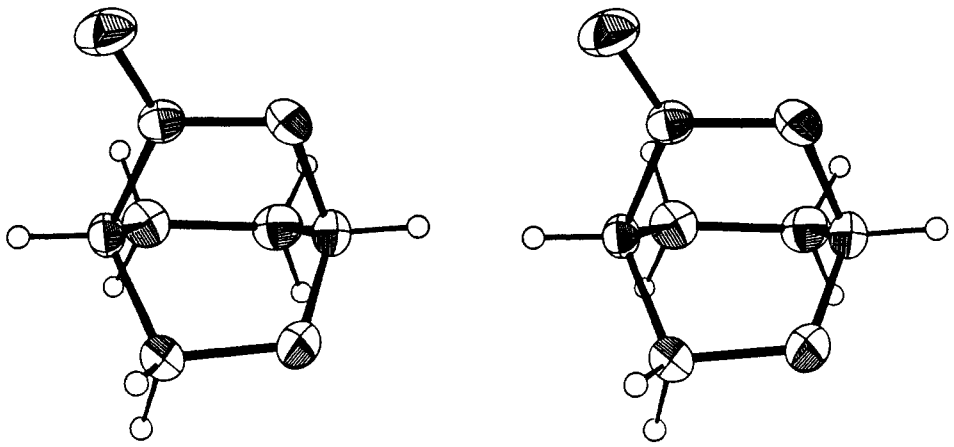
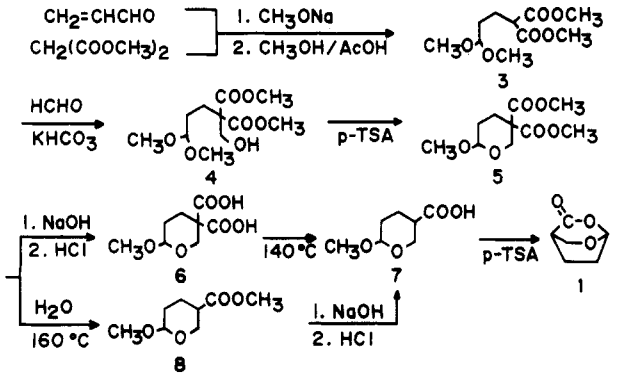


**Figure 1.** Stereodrawing of 2,6-dioxabicyclo[2.2.2]octan-3-one. The thermal ellipsoids are drawn at the 30% probability level.

**Scheme I**
**Synthetic Route of 2,6-Dioxabicyclo[2.2.2]octan-3-one**



et al.[15] Subsequent hydroxymethylation of **3** with formaldehyde in the presence of potassium hydrogen carbonate[18] gave nearly quantitatively dimethyl 1-hydroxy-5,5-dimethoxypentane-2,2-dicarboxylate (**4**). This compound readily underwent acid-catalyzed intramolecular cyclization in a dilute solution in benzene, aided by the favored six-membered-ring formation, to afford dimethyl 6-methoxytetrahydropyran-3,3-dicarboxylate (**5**). The tetrahydropyan derivative **3** was saponified to the free dicarboxylic acid (**6**), which was then decarboxylated in diglyme or dimethyl sulfoxide at 120–140 °C to give 6-methoxytetrahydropyran-3-carboxylic acid (**7**) as a stereoisomeric mixture (cis:trans = 2:3) in a quantitative yield. The carboxylic acid **7** was heated in a dilute solution in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid to give the desired bicyclic lactone **1**. The overall yield based on acrolein was approximately 20%.

An alternative, but less satisfactory, synthetic route involves the decarboxylation of **5** in the presence of sodium chloride and water in dimethyl sulfoxide,[19,20] followed by saponification of the resulting methyl 6-methoxytetrahydropyran-3-carboxylate (**8**) to **7**. The disadvantage of this route is that the decarboxylation of **5** requires higher temperature (160–170 °C) and longer reaction time (5–8 h) and that some side reactions are unavoidable. As a consequence, the yield of **8** was relatively low (~60%), although the reaction conditions remain to be optimized.

The bicyclic lactone **1** formed hygroscopic crystals melting at 69–71 °C. It was characterized by elemental analysis, mass, IR, $^1$H, and $^{13}$C NMR spectroscopy, and X-ray analysis. The bond lengths and bond angles of **1** are given in Table I. A stereodrawing of **1** is shown in Figure 1. The most interesting and important aspect of the molecular dimensions is the asymmetry of the tetrahydropyran ring, that is, the significant shortening of the C(1)–O(6) bond (1.390 Å) compared with the C(5)–O(6) bond (1.439 Å) (cf. the average C–O single bond, 1.43 Å). This shortening is attended by a lengthening of the C(1)–O(2) bond (1.458 Å).[21] A similar but less C–O bond shortening of tetrahydropyran rings was observed for cyclic oligomers of 6,8-dioxabicyclo[3.2.1]octan-7-one and interpreted in terms of the delocalization of the 2p lone-pair electrons on the oxygen atom.[22]

**Table I**
**Bond Lengths (Å) and Bond Angles (Deg) for 2,6-Dioxabicyclo[2.2.2]octan-3-one (1)[a]**

| | | | |
|---|---|---|---|
| **Bond Lengths** | | | |
| O(2)–C(1) | 1.458 (1) | C(1)–C(7) | 1.506 (1) |
| O(2)–C(3) | 1.345 (1) | C(3)–C(4) | 1.501 (1) |
| O(6)–C(1) | 1.390 (1) | C(4)–C(5) | 1.519 (1) |
| O(6)–C(5) | 1.439 (1) | C(4)–C(8) | 1.531 (1) |
| O(9)–C(3) | 1.196 (1) | C(7)–C(8) | 1.528 (1) |
| **Bond Angles** | | | |
| C(1)–O(2)–C(3) | 112.07 (6) | O(9)–C(3)–C(4) | 127.35 (8) |
| C(1)–O(6)–C(5) | 111.42 (6) | C(3)–C(4)–C(5) | 108.32 (7) |
| O(2)–C(1)–O(6) | 108.63 (7) | C(3)–C(4)–C(8) | 105.97 (7) |
| O(2)–C(1)–C(7) | 108.39 (7) | C(5)–C(4)–C(8) | 108.47 (7) |
| O(6)–C(1)–C(7) | 112.86 (8) | O(6)–C(5)–C(4) | 109.17 (6) |
| O(2)–C(3)–O(9) | 120.59 (8) | C(1)–C(7)–C(8) | 108.14 (7) |
| O(2)–C(3)–C(4) | 112.03 (6) | C(4)–C(8)–C(7) | 107.40 (7) |

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

**Polymerization.** The bicyclic lactone **1** consisting of a strained bicyclo[2.2.2]octane skelton is expected to show an enhanced polymerization reactivity. The polymerization of **1** was examined under a variety of conditions. Since this monomer was highly hygroscopic, a high-vacuum technique was employed for the polymerization. Some of the results of the polymerization of **1** are presented in Table II. Both cationic and anionic initiators were effective for the polymerization of **1**. Particularly, **1** was readily polymerized with boron trifluoride etherate at or below −60 °C to give high molecular weight polymers ($M_n$ ~ $1 \times 10^5$) in high yields. At higher temperatures or with stronger initiators, such as phosphorus pentafluoride, **1** afforded relatively low molecular weight polymers, presumably due to some chain-breaking reactions. The lactone **1** was polymerized also with anionic initiators, although higher temperature and longer reaction time were required.

The polymers obtained were white solids, soluble in chloroform, dichloromethane, γ-butyrolactone, and pyridine, and swelled in tetrahydrofuran and 1,4-dioxane. These polymers melted at ca. 150 °C with gradual decomposition (DSC). A transparent flexible film could be

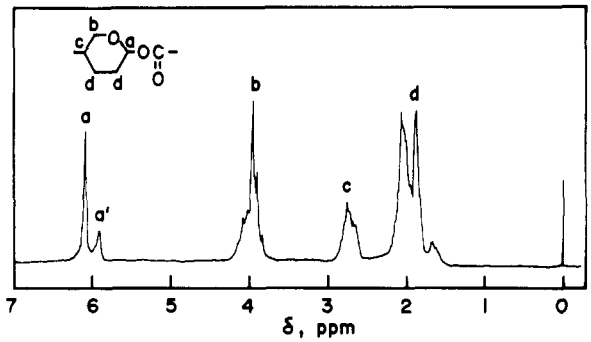



**Figure 2.** $^1$H NMR spectrum of poly(tetrahydropyran-5,2-diyloxycarbonyl) prepared at −60 °C with phosphorus pentafluoride as initiator. Solvent, $CDCl_3$; temperature, 50 °C; internal reference, tetramethylsilane; 200 MHz.

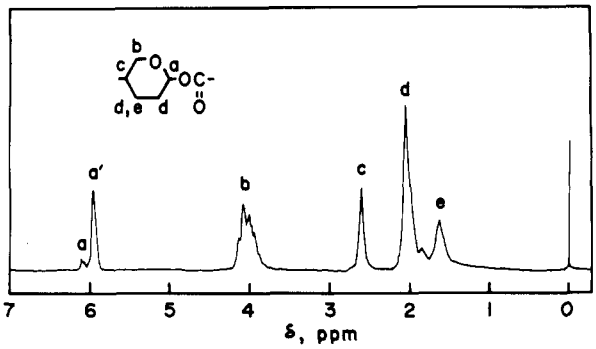
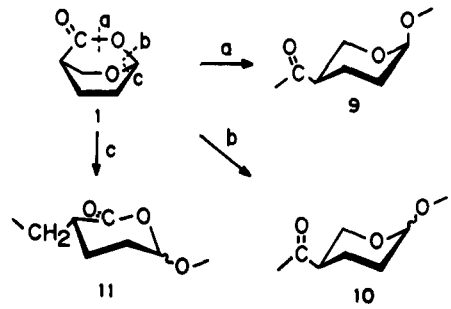



**Figure 3.** $^1$H NMR spectrum of poly(tetrahydropyran-5,2-diyloxycarbonyl) prepared at −90 °C with boron trifluoride etherate as initiator. Solvent, $CDCl_3$; temperature, 50 °C; internal reference, tetramethylsilane; 200 MHz.

**Scheme II**
**Possible Ring-Opening Modes of 2,6-Dioxabicyclo[2.2.2]octan-3-one in Cationic Polymerization**




cast from a chloroform solution of the polymer. Its strips could be drawn on a heated bar to orient.

**Structure and Stereochemistry.** There are three possible modes of bond cleavage when the bicyclic lactone 1 is polymerized (Scheme II). The first is the acyl-oxygen scission (a) of the ester linkage, leading to a cis-disubstituted tetrahydropyran ring (**9**). The second is the alkyl-oxygen scission (b) of the ester linkage, which gives a trans-disubstituted tetrahydropyran ring ($S_N2$ type reaction) or a mixture of cis- and trans-disubstituted tetrahydropyran rings ($S_N1$ type reaction) (**10**). The third is the C(1)–O(6) bond scission (c) giving rise to trans-disubstituted or a mixture of trans- and cis-disubstituted δ-lactone rings (**11**), depending on the types of reactions. Among these, the last mode of bond cleavage is less likely to take place, because the C(1)–O(6) bond (1.390 Å) is much shorter than the ordinary C–O bond and hence less reactive according to the recent theory of Kirby et al.[23]

$^1$H NMR spectra of the polymers obtained with phosphorus pentafluoride at −60 °C and with boron trifluoride etherate at −90 °C are shown in Figures 2 and 3, respectively, together with the assignments of the signals.

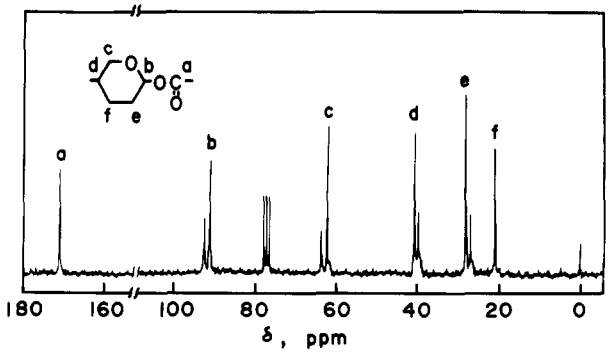



**Figure 4.** $^{13}$C NMR spectrum of poly(tetrahydropyran-5,2-diyloxycarbonyl) prepared at −60 °C with phosphorus pentafluoride as initiator. Solvent, $CDCl_3$; temperature, 50 °C; internal reference, tetramethylsilane; 50 MHz.

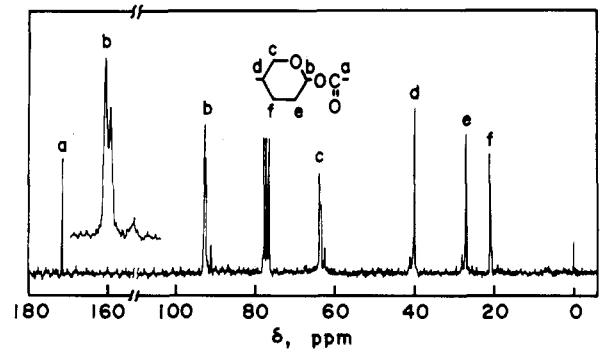
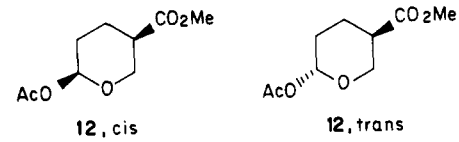



**Figure 5.** $^{13}$C NMR spectrum of poly(tetrahydropyran-5,2-diyloxycarbonyl) prepared at −90 °C with boron trifluoride etherate as initiator. Solvent, $CDCl_3$; temperature, 50 °C; internal reference, tetramethylsilane; 50 MHz.

There are noticeable differences between these two spectra, particularly in the acetal proton region: In figure 2, the lower field signal appearing at δ 6.1 is of stronger intensity than the higher field signal at δ 5.9. In contrast, in Figure 3, the lower field signal is of much weaker intensity than the higher field signal, suggesting that these two polymers are structurally different. In order to clarify the stereochemical structures of these polymers, cis and trans isomers of methyl 6-acetoxytetrahydropyran-3-carboxylate (**12**) were prepared as model compounds for the polymers and their $^1$H NMR data were compared with those of the polymers.




These model compounds[24] showed the acetal proton signals at δ 6.04 (cis isomer) and 5.85 (trans isomer), which were in good agreement with the corresponding chemical shifts of the polymers. Thus, the signal appearing at δ 6.1 is assignable to the acetal proton of the cis-disubstituted tetrahydropyran unit, while the signal at δ 5.9 is assignable to the acetal proton of the trans-disubstituted tetrahydropyran unit.

$^{13}$C NMR spectra of the polymers prepared with phosphorus pentafluoride at −60 °C and with boron trifluoride etherate at −90 °C are presented in Figures 4 and 5, respectively. The assignments of the signals are given in the figures. In both spectra, there are two sets of signals b–e corresponding to the two configurationally different structural units.[25] The relative intensity of each signal pair

**Table II**
**Polymerization of 2,6-Dioxabicyclo[2.2.2]octan-3-one**

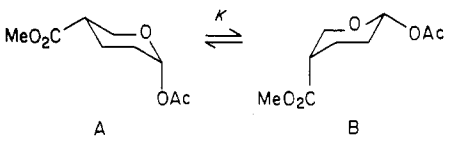
| monomer, g | solvent[a] (mL) | initiator (mol %) | temp, °C | time, min | yield,[b] % | $M_n \times 10^{-4}$ [c] | $M_w/M_n$ [c] | mp,[d] °C | cis:trans[e] |
|---|---|---|---|---|---|---|---|---|---|
| 0.64 | DCM (2.5) | $BF_3OEt_2$ (3) | 0 | 15 | 50 | 0.16 | 1.4 | | 76:24 |
| 0.64 | DCM (2.5) | $BF_3OEt_2$ (3) | −60 | 15 | 95 | 11 | 2.1 | 150–157 | 33:67 |
| 0.64 | DCM (4.5) | $BF_3OEt_2$ (1) | −90 | 10 | 12 | 3.3 | 2.5 | 141–154 | 11:89 |
| 0.64 | DCM (4.5) | $BF_3OEt_2$ (1) | −90 | 30 | 95 | 9.5 | 3.0 | 138–148 | 27:73 |
| 0.64 | DCM (4.5) | $BF_3OEt_2$ (3) | −90 | 24[f] | 93 | 9.9 | 2.5 | 144–156 | 30:70 |
| 0.64 | DCM (2.5) | $PF_5$ (2) | −60 | 15 | 87 | 1.4 | 3.8 | 146–155 | 75:25 |
| 0.64 | THF (5.5) | Li–BzPh[g] (0.8) | 0 | 67[f] | 37 | 0.56 | 3.0 | 153–159 | 42:58 |

[a] DCM, dichloromethane; THF, tetrahydrofuran. [b] Methanol-insoluble polymer. [c] By gel permeation chromatography (polystyrene standard). [d] With gradual decomposition; determined by differential scanning calorimetry. [e] Proportion of cis- and trans-2,5-linked tetrahydrofuran units determined by $^1H$ NMR peak area ratio of the corresponding acetal protons (cis, δ 6.1; trans, δ 5.9). [f] Hour. [g] Lithium benzophenone ketyl.

due to the respective carbons is similar to the relative intensity of the signal pair due to the acetal protons in Figures 2 and 3, respectively. In Table III, the $^{13}C$ NMR chemical shift data are compared with those of the model compounds **12**. These data also demonstrate that these polymers are composed of cis- and trans-disubstituted tetrahydropyran units, their proportion being dependent upon the reaction conditions.

Each of the cis- and trans-disubstituted tetrahydropyran units in the polymer chain is presumably in conformational equilibrium with its flipped structure. In order to estimate the conformational situation, the conformational free energy difference $\Delta G$ between each pair of the conformers was calculated for model compounds, *cis*- and *trans*-methyl 6-acetoxytetrahydropyran-3-carboxylate.[26] The numerical parameters of substituents in tetrahydropyrans used for the calculation are as follows (in kJ/mol): 3-$CO_2Me$, 2.47;[27] 6-OAc, −2.5.[28]

cis-isomer



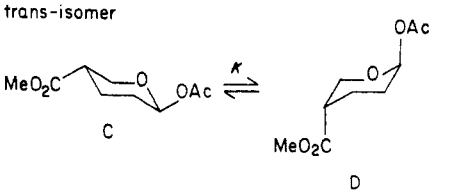

(2)

A B

$\Delta G = 4.98$ kJ/mol

$K = B/A = 12/88$

trans-isomer




(3)

C D

$\Delta G = 0.04$ kJ/mol

$K = D/C = 50/50$

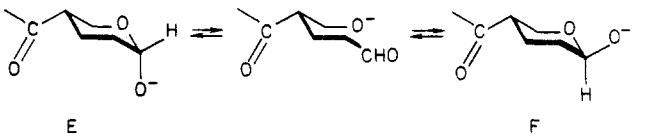
The calculation predicts that the cis-disubstituted tetrahydropyran unit in the polymer predominantly takes the conformation corresponding to A, whereas the trans-disubstituted tetrahydropyran unit exists as an equilibrium mixture of the two conformers corresponding to C and D.

The proportions of the cis- and trans-disubstituted tetrahydropyran units in the polymer determined by the relative peak areas of the acetal proton signals are listed in the last column of Table II. The cis/trans ratios varied from 11/89 to 76/24, depending on reaction conditions such as temperature, conversions, and initiators. The polymer having the lowest cis/trans ratio of 11/89 was obtained when the polymerization at −90 °C was terminated at low conversion. Even at −90 °C, the cis/trans ratios increased to 30/70 with increasing conversion and reaction time. The cis/trans ratios tend to increase with rising polymerization temperature.

When phosphorus pentafluoride was employed as an initiator at −60 °C, the cis/trans ratio of the polymer dramatically increased to as high as 75/25, in comparison with the cis/trans ratio of 30/70 of the polymer prepared with boron trifluoride etherate at the same temperature. According to the calculation described above, the free energy difference between the energetically favorable, respective conformers of the cis and trans isomers of methyl 6-acetoxytetrahydropyran-3-carboxylate is estimated to be 2.5 kJ/mol. This value, in combination with an entropy of mixing factor $R$ ln 2 favoring the trans isomer because of two equipopulated conformations, gives a cis/trans ratio of 67/33 at −60 °C. Taking uncertainty in the estimation of the free energy into account, the observed cis/trans ratio of 75/25 implies that even at −60 °C, a polymer composed of a nearly thermodynamically controlled equilibrium mixture of the cis- and trans-disubstituted tetrahydropyran units was produced in the presence of a strong initiator.

Although there still remains some uncertainty as to the cationic polymerization mechanism, the propagation proceeds primarily through the $S_N2$ type alkyl-oxygen scission of the ester linkage of the growing oxonium ion at low temperatures to yield polyester consisting of the trans-2,5-linked tetrahydropyran rings. However, transacetalization, which converts the trans unit produced in this way to the more stable cis counterpart, inevitably occurs, thus making the structure of the polymer less regular in the polymerization after a relatively longer reaction time or at higher temperature. It seems less likely, but cannot be excluded, that concurrent $S_N1$ type propagation by the oxacarbenium ion giving both the cis and trans units becomes increasingly important with rising polymerization temperature to reduce the structural regularity of the polymer.

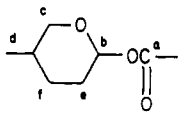
Finally, anionic polymerization of **1** should be briefly referred to. The polymerization initiated with lithium benzophenone ketyl gave a polymer having a cis/trans ratio of 42/58. The anionic polymerization conceivably involves an alkoxide growing ion; in other words, it proceeds through the acyl-oxygen scission of the ester linkage of the monomer. The formation of both cis and trans units can be interpreted in terms of anomerization at the growing chain end (eq 4). The cis alkoxide anion (E) producing a cis unit in a polymer chain can be converted through ring-chain equilibrium to the trans-alkoxide anion (F), which yields a trans unit by the addition of monomer.



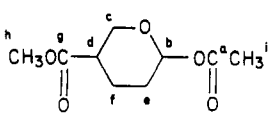

E F

(4)

**Table III**
**$^{13}C$ NMR Chemical Shift Data for Poly(tetrahydropyran-5,2-diyloxycarbonyl) and Its Model Compound[a]**




polymer




model compound

cis: g,δ172.75; h,δ51.90; i,δ20.86

trans: g,δ171.75; h,δ51.90; i,δ21.05

| | assignment (δ) | | | | | |
|---|---|---|---|---|---|---|
| | a | b | c | d | e | f |
| polymer[b] | | | | | | |
| cis unit | 170.48 | 91.21 | 62.25 | 40.59 | 27.82 | 20.85 |
| | | 92.67[c] | 63.41[c] | | | |
| trans unit | 170.48 | 92.96[c] | 63.78[c] | 39.64 | 26.70 | 20.85 |
| model compound[d] | | | | | | |
| cis isomer | 169.53 | 90.74 | 62.28 | 40.35 | 27.78 | 21.05 |
| trans isomer | 169.53 | 92.53 | 64.13 | 39.47 | 26.95 | 21.44 |

[a] Solvent, $CDCl_3$; internal reference, tetramethylsilane. [b] Prepared in dichloromethane at −60 °C with boron trifluoride etherate as the initiator. [c] The appearance of a pair of signals may be ascribable to the different di; l placements of the trans and cis units and/or to those of the D,L-enantiomeric units. [d] Methyl 6-acetoxytetrahydropyran-3-carboxylate.

An alternative explanation for formation of both cis and trans units is epimerization caused by hydrogen abstraction of the methine proton adjacent to the carbonyl group by alkoxide anions. However, such epimerization seems to be negligible, on the analogy of the finding that a polyester entirely consisting of cis-2,5-linked tetrahydropyran rings was formed in the anionic polymerization of 2,5-dioxabicyclo[2.2.2]octan-3-one under similar conditions or even at higher temperatures.[29]

The apparently lower anionic polymerizability of **1** will be discussed in a forthcoming paper dealing with anionic polymerization of 2,5-dioxabicyclo[2.2.2]octan-3-one.[29]

## Experimental Section

**General Method.** $^1H$ and $^{13}C$ NMR spectra were recorded on a JEOL JNM FX-200 spectrometer operating at 200 MHz ($^1H$) and 50 MHz ($^{13}C$), respectively, on solutions in deuteriochloroform and dimethyl-$d_6$ sulfoxide. Tetramethylsilane was used as the internal reference. IR spectra were measured on a Jasco A-3 spectrophotometer. Molecular weights of polymers were estimated by gel permeation chromatography (column, Shodex A 80M, 1 m; eluent, chloroform; polystyrene standard).

**Preparation of Dimethyl 1-Hydroxy-5,5-dimethoxypentane-2,2-dicarboxylate (4).** The hydroxymethylation of dimethyl 4,4-dimethoxybutane-1,1-dicarboxylate (**3**)[15] was carried out in a similar manner to that of diethyl malonate:[18] The diester **3** (23.4 g, 0.10 mol) was added dropwise to a mixture of formalin (8.1 mL, 0.10 mol) and potassium hydrogen carbonate (0.8 g, 8 mmol) over 20 min. The mixture was stirred at room temperature for 6 h until the starting ester was completely consumed (TLC). A saturated aqueous solution of ammonium sulfate (35 mL) was added to the reaction mixture. The mixture was then extracted with three 60-mL portions of ethyl ether, and the combined extracts were dried over anhydrous magnesium sulfate. The salt was filtered off and rotary evaporation of the solvent from the filtrate gave the product as a viscous oil: yield 95%; IR (neat) 3450 (ν(O–H)), 1730 (ν(C=O)), 1126 (ν(C–O–C)) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.36 (t, $J$ = 5.5 Hz, 1 H, H-5), 3.95 (s, 2 H, 2H-1), 3.76 (s, 6 H, $2OCH_3$), 3.32 (s, 6 H, $2COOCH_3$), 3.04 (s, 1 H, OH), 1.94–2.00 (m, 2 H, 2H-4), 1.55–1.66 (m, 2 H, 2H-3); $^{13}C$ NMR ($CDCl_3$) δ 107.86 (C=O), 104.00 (C-5), 64.21 (C-1), 59.16 (C-2), 52.86 ($OCH_3$), 52.49 ($COOCH_3$), 27.48 (C-4), 26.32 (C-3).

**Preparation of Dimethyl 6-Methoxytetrahydropyran-3,3-dicarboxylate (5).** A solution of **4** (8.4 g, 0.032 mol) and *p*-toluenesulfonic acid (0.052 g, 0.27 mmol) in dry benzene (600 mL) was allowed to reflux through a Soxhlet extactor for 2 h. The Soxhlet thimble was charged with Type 4A molecular sieves (ca. 20 g). After the mixture was cooled to room temperature, anhydrous potassium carbonate (7 g, 0.05 mol) was added, and the mixture was stirred for 30 min. The mixture was filtered and the solvent was removed by a rotary evaporator. The residual amber oil was distilled under reduced pressure: yield 84%; bp 95–100 °C (1 mmHg); IR (neat) 1735 (ν(C=O)), 1120 (ν(C–O–C)) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.56 (t, $J$ = 3.2 Hz, 1 H, H-6), 4.16 (d, $J$ = 11.6 Hz, 1 H, H-2), 4.05 (d, $J$ = 11.6 Hz, 1 H, H-2), 3.78 (s, 3 H, $COOCH_3$), 3.73 (s, 3 H, $COOCH_3$), 3.38 (s, 3 H, $OCH_3$), 2.18–2.25 (m, 2 H, 2H-4), 1.61–1.96 (m, 2 H, 2H-5); $^{13}C$ NMR ($CDCl_3$) δ 169.92 (C=O), 98.39 (C-6), 62.52 (C-2), 55.02 ($OCH_3$), 53.41 (C-3), 52.68 ($COOCH_3$), 26.68 (C-4), 24.66 (C-5).

**Preparation of 6-Methoxytetrahydropyran-3,3-dicarboxylic Acid (6).** Dimethyl 6-methoxytetrahydropyran-3,3-dicarboxylate (**5**, 6.6 g, 0.028 mol) was added to a solution of sodium hydroxide (2.8 g, 0.07 mol) in water (10 mL), and the mixture was heated at 90 °C for 3 h. After the reaction mixture was cooled to 0 °C, 6 N hydrochloric acid (12 mL, 0.07 mol) was added to neutralize the solution. After salting out, the mixture was extracted with five 30-mL portions of ethyl ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and subjected to rotary evaporation. The residual white powder was recrystallized from a mixture of diethyl ether and acetone (3:1): yield 94%; mp (dec) 136–140 °C; IR (KBr) 2650, 2550 (ν(OH)), 1705 (ν(C=O)), 1120 (ν(C-O-C)) $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) δ 12.2–14.0 (br s, 2 H, 2COOH), 4.50 (t, $J$ = 3.3 Hz, 1 H, H-6), 3.98 (d, $J$ = 11.4 Hz, 1 H, H-2), 3.83 (d, $J$ = 11.4 Hz, 1 H, H-2), 3.27 (s, 3 H, $OCH_3$), 1.97–2.04 (m, 2 H, 2H-4), 1.48–1.78 (m, 2 H, 2H-5); $^{13}C$ NMR ($Me_2SO$-$d_6$) δ 170.52 (C=O), 97.98 (C-6), 62.78 (C-2), 54.28 ($OCH_3$), 32.37 (C-3), 26.41 (C-4), 24.42 (C-5).

**Preparation of a Stereoisomer Mixture of 6-Methoxytetrahydropyran-3-carboxylic Acid (7).** A solution of **6** (25.2 g, 0.12 mol) in diglyme (250 mL) was heated at 140 °C for 1.75 h. Removal of the solvent by a rotary evaporator gave **7** (cis and trans stereoisomer mixture) as a very viscous oil in a quantitative yield: IR ($CHCl_3$) 3650 (ν(OH)), 1705 (ν(C=O)), 1125 (ν(C–O–C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) cis isomer, δ 8.6–9.4 (br s, 1 H, OH), 4.64 (t, $J$ = 2.9 Hz, 1 H, H-6), 3.7–3.9 (m, 2 H, 2H-2), 3.38 (s, 3 H, $OCH_3$), 2.5–2.7 (m, 1 H, H-3), 1.4–2.2 (m, 4 H, 2H-4, 2H-5); trans isomer, δ 8.6–9.4 (br s, 1 H, OH), 4.50 (dd, $J$ = 2.7 Hz, $J$ = 5.4 Hz, 1 H, H-6), 4.09 (dd, $J$ = 3.9 Hz, $J$ = 11.5 Hz, 1 H, H-2), 3.7–3.9 (m, 1 H, H-2), 3.42 (s, 3 H, $OCH_3$), 2.5–2.7 (m, 1 H, H-3), 1.4–2.2 (m, 4 H, 2H-4, 2H-5); $^{13}C$ NMR ($CDCl_3$) cis isomer, δ 178.12 (C=O), 97.62 (C-6), 62.37 (C-2), 40.57 (C-3), 28.74 (C-5), 21.63 (C-4); trans isomer, δ 178.41 (C=O), 100.07 (C-6), 60.11 (C-2), 39.79 (C-3), 28.09 (C-5), 20.95 (C-4).

**Preparation of 2,6-Dioxabicyclo[2.2.2]octan-3-one (1).** A solution of **7** (2.7 g, 0.017 mol) and *p*-toluenesulfonic acid monohydrate (0.023 g, 0.12 mmol) in dry toluene (200 mL) was allowed to reflux through a Soxhlet extractor for 2 h. The Soxhlet thimble was charged with Type 4A molecular sieves (16 g). After the solution was cooled to room temperature, anhydrous potassium carbonate (5 g, 0.036 mol) was added to the solution, and the

mixture was stirred at room temperature for 30 min. The mixture was filtered and subjected to rotary evaporation to afford slightly yellow wax; yield 68%. Recrystallization from ethyl ether gave white crystals: mp 69 °C; IR (KBr) 1766 ($\nu$(C=O)) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.67 (s, 1 H, H-1), 4.13 (td, $J$ = 2.5 Hz, $J$ = 8.8 Hz, 1 H, H-5), 4.04 (dd, $J$ = 1.2 Hz, $J$ = 8.8 Hz, 1 H, H-5), 2.82 (br s, 1 H, H-4), 1.96–2.27 (m, 4 H, 2H-2, 2H-8); $^{13}$C NMR ($CDCl_3$) $\delta$ 172.13 (C=O), 97.30 (C-1), 66.67 (C-5), 36.56 (C-4), 26.89 (C-7), 20.49 (C-8); MS $m/e$ 128, 100, 84, 82, 72, 55, 43, 28. Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 56.38; H, 6.27. Triclinic space group $P\bar{1}$; $a$ = 5.924 (2) Å, $b$ = 6.775 Å, $c$ = 7.428 (2) Å, $\alpha$ = 82.70 (2)°, $\beta$ = 82.17 (2)°, $\gamma$ = 84.49 (2)°; $\rho$ = 1.46 g/cm$^3$.

**Preparation of a Stereoisomer Mixture of Methyl 6-Methoxytetrahydropyran-3-carboxylate (8).** A mixture of **5** (4.50 g, 0.019 mol), sodium chloride (1.29 g, 0.022 mol), water (0.68 g, 0.038 mol), and dimethyl sulfoxide (20 mL) was heated in a 50-mL round-bottomed flask fitted with a condenser. The top of the condenser was connected to a trap containing an aqueous solution of barium hydroxide to monitor the evolution of carbon dioxide. The reaction mixture was heated at 160 °C for 6 h until the evolution of carbon dioxide almost ceased. The mixture was cooled to room temperature and poured into water (150 mL). After salting out, the aqueous solution was extracted with four 60-mL portions of ethyl ether. The combined ether extracts were washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and filtered. Rotary evaporation of the solvent gave an amber oil. It was distilled under reduced pressure to afford **8** as a transparent liquid: yield 57%; bp 65–70 °C (1.5 mmHg); IR (neat) 1738 ($\nu$(C=O)), 1125 ($\nu$(C–O–C)) cm$^{-1}$; $^1$H NMR ($CDCl_3$) cis isomer, $\delta$ 4.61 (dd, $J$ = 2.5 Hz, 1 H, H-6), 3.50–3.92 (m, 2 H, 2H-2), 3.68 (s, 3 H, $COOCH_3$), 3.36 (s, 3 H, $OCH_3$), 2.42–2.70 (m, 1 H, H-3), 1.4–2.2 (m, 4 H, 2H-4, 2H-5); trans isomer, $\delta$ 4.45 (dd, $J$ = 2.4 Hz, $J$ = 5.6 Hz, 1 H, H-6), 4.08 (dd, $J$ = 3.9 Hz, $J$ = 11.5 Hz, 1 H, H-2), 3.50–3.92 (m, 1 H, H-2), 3.71 (s, 3 H, $COOCH_3$), 3.42 (s, 3 H, $OCH_3$), 2.42–2.70 (m, 1 H, H-3), 1.4–2.2 (m, 4 H, 2H-4, 2H-5); $^{13}$C NMR ($CDCl_3$) cis isomer, $\delta$ 172.93 (C=O), 97.55 (C-6), 60.28 (C-2), 54.60 ($COOCH_3$), 51.57 ($OCH_3$), 40.91 (C-3), 28.91 (C-5), 21.15 (C-4); trans isomer, $\delta$ 173.10 (C=O), 100.39 (C-6), 63.07 (C-2), 55.38 ($COOCH_3$), 51.66 ($OCH_3$), 40.11 (C-3), 28.43 (C-5), 22.29 (C-4).

**Preparation of a Stereoisomer Mixture of Methyl 6-Acetoxytetrahydropyran-3-carboxylate (12).** A solution of 8 (1.99 g, 0.011 mol) and *p*-toluenesulfonic acid monohydrate (22.7 mg, 0.12 mmol) in dry toluene (200 mL) was refluxed for 2 h in a flask equipped with a Soxhlet extractor containing molecular sieves Type 4A in a thimble. After the solution was cooled to room temperature, sodium carbonate (10 g) was added and the mixture was stirred for 30 min. The solid was filtered off and the filtrate was subjected to rotary evaporation to afford methyl 3,4-dihydro-2*H*-pyran-3-carboxylate as a transparent liquid.

*p*-Toluenesulfonic acid monohydrate (26.4 mg, 0.14 mmol) was added to a solution of the dihydropyran derivative (1.03 g, 7.2 mmol) and acetic acid (0.434 g, 7.2 mmol) in benzene (10 mL), and the mixture was refluxed for 5 h. After the reaction mixture was cooled to room temperature, anhydrous potassium carbonate (6.6 g, 48 mmol) was added, and the mixture was stirred for 2 h. The mixture was filtered, and the solvent was removed by rotary evaporation. Subsequent column chromatographic separation of the residue (column, silica gel; eluent, 1:2 (v/v) *n*-hexane–ethyl acetate) gave **12** as transparent liquid: IR (neat) 1740 ($\nu$(C=O)), 1126 ($\nu$(C–O–C)) cm$^{-1}$; $^1$H NMR ($CDCl_3$) cis isomer, $\delta$ 6.04 (t, $J$ = 2.7 Hz, 1 H, H-2), 3.94 (dd, $J$ = 6.8 Hz, $J$ = 12.2 Hz, 1 H, H-6), 3.88 (dd, $J$ = 8.3 Hz, $J$ = 12.2 Hz, 1 H, H-6), 3.70 (s, 3 H, $OCH_3$), 2.70 (m, 1 H, H-5), 2.11 (s, 3 H, $COCH_3$), 2.12–1.53 (m, 4 H, 2H-3, 2H-4); trans isomer, $\delta$ 5.85 (dd, $J$ = 2.5 Hz, $J$ = 5.6 Hz, 1 H, H-2), 4.14 (dd, $J$ = 4.2 Hz, $J$ = 12.0 Hz, 1 H, H-6), 3.92 (dd, $J$ = 5.6 Hz, $J$ = 12.0 Hz, 1 H, H-6), 3.72 (s, 3 H, $OCH_3$), 2.60 (m, 1 H, H-5), 2.11 (s, 3 H, $COCH_3$), 2.12–1.53 (m, 4 H, 2H-3, 2H-4); $^{13}$C NMR ($CDCl_3$) data are given in Table III.

**Polymerization of 2,6-Dioxabicyclo[2.2.2]octan-3-one (1).** Cationic polymerization of **1** was carried out in dichloromethane at temperatures between −90 and 0 °C with boron trifluoride etherate and phosphorus pentafluoride as initiators. A high-vacuum technique was employed for the polymerization. After the polymerization was terminated by the addition of a small amount of pyridine, the reaction mixture was poured into a large volume of methanol to precipitate a polymer. It was purified by repeated reprecipitation from dichloromethane and methanol as a solvent–precipitant pair and dried under reduced pressure to a constant weight. Anionic polymerization of **1** was carried out in tetrahydrofuran at 0 °C by using lithium benzophenone ketyl as an initiator. After a specified time, a sufficient amount of acetic anhydride was added to the solution, and the resulting mixture was stirred at room temperature for several hours. The separation and purification of the polymer were similar to those described for the cationic polymerization: IR (film) 1738 ($\nu$(C=O)), 1125 ($\nu$(C–O–C)) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.12 (H-$2_{eq}$), 5.95 (H-$2_{ax}$), 3.8–4.2 (2H-6), 2.5–2.8 (H-5), 1.6–2.2 (2H-3, 2H-4); $^{13}$C NMR data are given in Table III. Anal. Calcd for $(C_6H_8O_3)_n$: C, 56.25; H, 6.29. Found: C, 56.28; H, 6.11.

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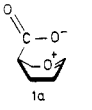
(21) This is an example of the anomeric effect (Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: New York, 1983; p 54. The shortening of the C(1)–O(6) bond and the lengthening of the C(1)–O(2) bond are reasonably explained by the double bond–no bond resonance (**1a**) or its quantum-mechanical equivalent.



**1a**

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(24) The model compounds were obtained as a 1:~2 mixture of cis and trans stereoisomers. Although the $^1$H and $^{13}$C NMR spectra of the model compounds were taken without separating the components, the assignment of the peaks was achieved as follows: The cis isomer is an equatorial–axial conformer, whereas the trans isomer is a mixture of diequatorial and diaxial conformers (see eq 2 and 3). Taking this into account, the anomeric carbon should be upfield in the cis isomer, because the $\alpha_{ax}$ effect is in general smaller than the $\alpha_{eq}$ effect. The anomeric carbon signals appeared at $\delta$ 92.54 and 90.73 with an intensity ratio of ~2:1. Therefore, the proportion of the stereoisomers was determined to be cis:trans = 1:~2 and all the other signals were readily assigned. As for the $^1$H NMR signals, the all-equatorial anomeric proton in the cis isomer should be downfield of the "mixed" anomeric proton in the

trans isomer. In fact, the anomeric proton signals appeared at δ 6.04 (triplet) and 5.85 (doublet–doublet) with an intensity ratio of 1:~2. Therefore the former signal was definitely assigned to the anomeric proton in the cis isomer and the latter signal to that in the trans isomer.

(25) As clearly shown in the expanded spectrum in Figure 5, the lower peaks of signals b and c are split into two peaks of different intensities. Presumably, such splittings arise from the different diad placements of the cis and trans units and/or from those of the D,L-enantiomeric monomeric units in a polymer chain. Okada, M.; Sumitomo, H.; Komada, H. *Macromolecules* **1979**, *12*, 395. Okada, M.; Sumitomo, H.; Sumi, A. *Macromolecules* **1982**, *15*, 1238.

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# Selective Step-Growth Phenol–Aldehyde Polymerization. 4.[1] Regio-, Enantio-, and Diastereocontrolled Entry to Chiral Nonracemic All-Ortho Novolacs

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ABSTRACT: The enantiodifferentiating reaction of substituted phenols with racemic α-substituted 2-hydroxybenzyl alcohols assisted by chiralized aluminum chlorides provides a viable entry into optically active binuclear phenolic compounds. The ethylmagnesium bromide promoted condensation of optically active dimers with *rac*-α-methyl-2-hydroxybenzyl alcohol then produces optically active trimers threospecifically (>95% diastereomeric excess) with virtually complete chirality transfer from the existing chiral bridge to the newly created one. A chelate mechanism involving the intermediacy of prochiral *o*-quinone methides is suggested to account for the regio-, enantio-, and diastereoselective reaction behavior.

## Introduction

There exists an intense interest in the synthesis of well-defined, molecularly uniform oligonuclear phenolic compounds due to their occurrence in important synthetic resins and unique structural features.[3]

The previous paper of this series[1,4] described highly regiocontrolled syntheses of linear all-ortho methylene- and alkylidene-bridged polyphenols exploiting the use of nontransition metal complexes as organizing agents and selectivity factors. We now report a study directed toward the synthesis of optically active low molecular weight oligomers related to novolacs by using chirally modified organometallic promoters as a source of chirality.[5,6]

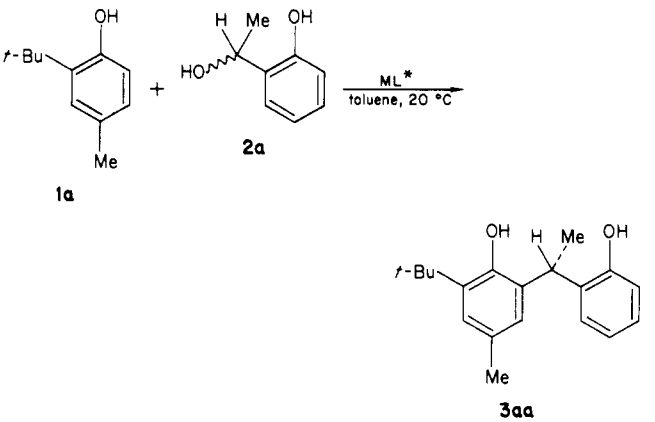
## Results and Discussion

**Preliminary Experiments.** The asymmetric benzylation reaction in Scheme I leading to substituted binuclear compound **3aa** was chosen as a model for the preliminary optimization experiments.

The reaction was carried out under varied conditions by using aluminum(III) or titanium(IV) organometallics chiralized by suitable optically active ligands. In favorable instances, a fairly good chirality transfer from the chiral environment of the metallic promoter to the newly created chiral bridge occurred. Selected results are summarized in Table I.

Inspection of the data in Table I reveals a substantial ligand effect upon the asymmetric induction. Among tested aluminum auxiliaries (runs 1–11), (–)-menthol gave the best asymmetric induction, producing levorotatory **3aa** as the sole reaction product with 28% enantiomeric excess (enantiomer ratio, 64:36), and, as expected, an equal and opposite bias in favor of dextrorotatory **3aa** was observed by using the (+)-menthol-based organometallic.

**Scheme I**[a]




[a] ML* = the metal with its chiral environment.

Precise observance of the following reaction protocol is required to obtain good enantiocontrol. (a) In situ preparation of the chiralized promoter via ligand-exchange reaction between diethylaluminum chloride and the selected optically active auxiliary; (b) equilibration (30 min) and then addition of the phenol **1a**; (c) equilibration (30 min) and then addition of **2a**. Changing the sequence order by reversing (b) and (c) steps or conducting them simultaneously gave inferior results as far as the chemical and optical yield is concerned.

In a second set of experiments (runs 12–14), titanium(IV)-based chiralized promoters were investigated. Only

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