nitrogen for 90 min. After cooling to room temperature, the solution was filtered and the solvent removed under reduced pressure. The brown residue was washed with a small volume of hexane–carbon tetrachloride (1:1) and then crystallized from carbon tetrachloride to give **19** as a yellow amorphous solid: 112 mg (48%); mp 96–97 °C; NMR δ 8.16–7.56 (m, 8), 6.45 (d, 1, H_8, $J_{8,9}$ = 8.2 Hz), 5.69 (dd, 1, H_{11}, $J_{10a,11e}$ = 4.4 Hz, $J_{10e,11e}$ = 4.4 Hz), 4.82 (m, 1, H_9, $J_{9a,10a}$ = 8.0 Hz, $J_{9a,10e}$ = 3.7 Hz), 3.17–2.56 (m, 2, $H_{10a,e}$), 2.30 (s, 3, CH_3CO_2); chemical ionization mass spectrum (methane), *m/e* (relative intensity) 391 (2), 389 (2), 361 (20), 359 (20), 333 (97), 331 (100), 311 (38), 252 (80), 57 (78).

8,9-Dihydro-8,9-epoxybenzo[*k*]fluoranthene (20). Sodium methoxide (250 mg, 5 mmol) was prepared by dissolving a sphere of sodium in dry methanol and evaporating under reduced pressure. Benzene was added, and the solvents were again evaporated. The dry sodium methoxide was suspended in dry THF (10 mL) under nitrogen at 0 °C. A solution of **19** (110 mg, 0.23 mmol) in THF (1 mL) was added to the methoxide and the reaction mixture was stirred at 0 °C overnight. Dry ether (20 mL) was added, and the solution was quickly washed with ice-cold water and then dried over potassium carbonate. The flask was wrapped with foil to keep the contents in the dark, and the solvents were removed under reduced pressure below 35 °C. The residue was dissolved in ether and precipitated by the addition of hexane, giving **20** as a yellow solid: 54 mg (84%); NMR δ 8.12 (s, 1, H_7), 8.0–7.55 (m, 7), 6.90 (d, 1, H_{11}, $J_{10,11}$ = 11.2 Hz), 6.46 (dd, 1, H_{10}, $J_{9,10}$ = 3.9 Hz), 4.61 (d, 1, H_8, $J_{8,9}$ = 3.7 Hz), 4.17 (m, 1, H_9); mass spectrum, *m/e* (relative intensity) 268 (M^+, 100), 239 (54), 213 (8); UV (THF) λ_{max} (ϵ) 418 nm (6700), 397 (7500), 380 (6800), 340 (6400), 302 (35 200), 272 (17 300), 240 (39 600); high-resolution mass spectrum, calcd for $C_{20}H_{12}O$ 268.0888, found 268.0874.

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Asymmetric Electrophilic Substitution on Phenols. 2. Enantio- and Diastereoselective Synthesis of *o*-Hydroxyatrolactic Esters[1]

Giovanni Casiraghi*

Dipartimento di Chimica dell'Università, I-07100 Sassari, Italy

Franca Bigi,* Giuseppe Casnati, Giovanni Sartori, and Paolo Soncini

Istituto di Chimica Organica dell'Università, I-43100 Parma, Italy

Giovanna Gasparri Fava and Marisa Ferrari Belicchi

Istituto di Chimica Generale and Centro di Studio per la Strutturistica Diffrattometrica del CNR, I-43100 Parma, Italy

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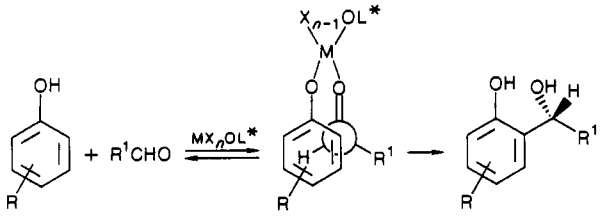
Both 2*R* and 2*S* stereoisomers of *o*-hydroxyatrolactic acid esters **3–5** are available with respective absolute configuration from phenols **1** and pyruvic acid esters **2** by using menthol only as a chiral inductor. Three asymmetric approaches were designed based on (a) single induction by chiral metal alkoxides, (b) single induction by chiral pyruvic esters, and (c) double induction by chiral pyruvic esters and chiral metal alkoxides. Route a furnished optically enriched enantiomers **3** with ee's ranging from 13% to 46%; route b furnished diastereomeric compounds **4** and **5** with 46–52% de; route c furnished diastereomeric compounds **4** and **5** with 36–88% de. The results have been incorporated into a mechanistic rationale involving a chelate transition state of the sort depicted in Figure 2.

The synthetic value of electrophilic aromatic substitution is widely recognized as a means of carbon–carbon bond construction leading to a variety of arylated compounds. Aiming at developing asymmetric versions of this reaction we have recently shown that chiral modified aluminum reagents promote enantioselective electrophilic substitution on phenols when reacted with prochiral carbonyl compounds.[2] In this special case the substitution reaction utilizes the chirality attached to the metal center to direct the carbonyl compound probably via a chelation-controlled transition state (Scheme 1), ultimately producing α-chiral nonracemic *o*-hydroxybenzyl alcohol derivatives.

In principle, according to this scheme, a second chiral procedure can be designed based on diastereoselective carbon–carbon bond formation by using carbonyl compounds incorporating suitable chiral centers, and, in addition, a double asymmetric approach can be developed which takes advantage from the combined use of the

Scheme I



chiralities in the reactant and promoter. In the present paper we describe a regio- and stereocontrolled entry to *o*-hydroxyatrolactic esters of either 2*R* or 2*S* configuration **3–5** by reaction of phenols **1** with pyruvic esters **2** by using three asymmetric techniques: (a) enantioselection using chiral metal alkoxides; (b) diastereoselection using chiral pyruvic esters; (c) double asymmetric induction using chiral metal alkoxides and chiral pyruvic esters.

Results and Discussion

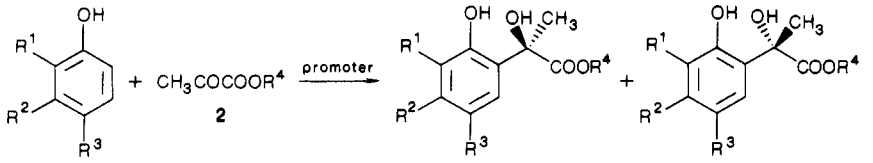
Enantioselection by Chiral Metal Alkoxides. First we investigated the reactions between 3-*tert*-butylphenol (**1a**) and ethyl pyruvate (**2a**) in the presence of chiral

(1) A preliminary paper of part of this work has been published: Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Soncini, P.; Gasparri Fava, G.; Ferrari Belicchi, M. *Tetrahedron Lett.* **1985**, *26*, 2021.

(2) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Gasparri Fava, G.; Ferrari Belicchi, M. *J. Org. Chem.* **1985**, *50*, 5018.

0022-3263/88/1953-1779$01.50/0

Table I. Enantioselective Synthesis of (*R*)- and (*S*)-Atrolactic Esters 3 Assisted by Chiral Metal Alkoxides[a]

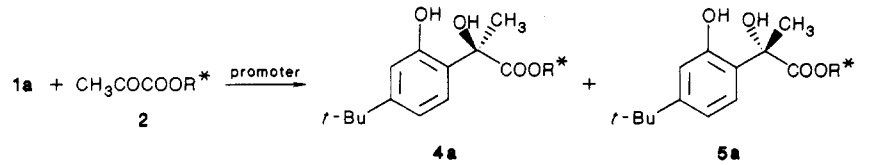


1 (*R*)-3 (*S*)-3

entry	1	R^1	R^2	R^3	2	R^4	promoter	product	yield, %[b]	ee, %[c] (confign)
1	**1a**	H	*t*-Bu	H	**2a**	Et	(−)-menthyl-O(Et)AlCl	**3aa**	59	39 (*R*)
2	**1a**	H	*t*-Bu	H	**2a**	Et	(−)-borneyl-O(Et)AlCl	**3aa**	11	3 (*R*)
3	**1a**	H	*t*-Bu	H	**2a**	Et	(+)-neomenthyl-O(Et)AlCl	**3aa**	48	8 (*S*)
4	**1a**	H	*t*-Bu	H	**2a**	Et	(−)-cinchonidinyl-O(Et)AlCl	**3aa**	16	4 (*R*)
5	**1a**	H	*t*-Bu	H	**2a**	Et	(+)-menthyl-$OTiCl_3$	**3aa**	62	2 (*R*)
6	**1a**	H	*t*-Bu	H	**2b**	*t*-Bu	(−)-menthyl-O(Et)AlCl	**3ab**	20	4 (*R*)
7	**1a**	H	*t*-Bu	H	**2c**	C_6H_{11}	(−)-menthyl-O(Et)AlCl	**3ac**	40	46 (*R*)
8	**1b**	H	H	H	**2a**	Et	(−)-menthyl-O(Et)AlCl	**3ba**	12	19 (*R*)
9	**1c**	H	Me	H	**2a**	Et	(−)-menthyl-O(Et)AlCl	**3ca**	39	23 (*R*)
10	**1d**	H	OMe	H	**2a**	Et	(−)-menthyl-O(Et)AlCl	**3da**	77	22 (*R*)
11	**1e**	H	H	Me	**2a**	Et	(−)-menthyl-O(Et)AlCl	**3ea**	20	21 (*R*)
12	**1f**	H	OCH_2O		**2a**	Et	(−)-menthyl-O(Et)AlCl	**3fa**	84	13 (*R*)
13	**1g**	$(CH{=}CH)_2$		H	**2a**	Et	(−)-menthyl-O(Et)AlCl	**3ga**	89	13 (*R*)

[a] Conditions: phenol 1, 10 mmol; alkoxide, 10 mmol; pyruvic ester 2, 10 mmol. At 17 ± 1 °C for 5 h. [b] Based on pure isolated compound. [c] Enantiomer excess was determined by ^1H NMR using $Eu(hfc)_3$. Configurational assignment, see text.

Table II. Diastereoselective Synthesis of (2*R*)- and (2*S*)-Atrolactic Esters 4 and 5 from 1a and Menthyl Pyruvates 2d and 2e[a]



4a 5a

entry	2	R*	promoter	temp, °C	products	yield, %[b]	ratio[c] 4:5	confign[d]
1	**2d**	(−)-menthyl	EtO(Et)AlCl	−20	**4ad + 5ad**	60	27:73	*S*
2	**2e**	(+)-menthyl	EtO(Et)AlCl	−20	**4ae + 5ae**	59	73:27	*R*
3	**2d**	(−)-menthyl	EtO(Et)AlCl	17	**4ad + 5ad**	63	36:64	*S*
4	**2d**	(−)-menthyl	$EtOTiCl_3$	−60	**4ad + 5ad**	64	24:76	*S*
5	**2e**	(+)-menthyl	$EtOTiCl_3$	−60	**4ae + 5ae**	65	75:25	*R*

[a] 1:2 mole ratio, 1:1. [b] Total yield of pure isolated compound. [c] Determined by reverse-phase HPLC. [d] Configuration at C(2) of the major diastereomer.

aluminum and titanium alkoxides leading to optically enriched (2*R*)- or (2*S*)-ethyl 2-hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)propionate (**3aa**). The reactions were carried out by adding **1a** and then **2a** to a preformed solution of the chiral alkoxide in anhydrous methylene chloride and allowing the resultant solution to react at ambient temperature. Aqueous acidic workup then furnished **3aa** and liberated the chiral alcohol auxiliary.

The results reported in Table I show that, in contrast to the efficiency of the menthol-based aluminum promoters (entry 1), the other employed alkoxides gave inferior enantioselection. It should be noted that the use of a chiral titanium-based alkoxide (entry 5) resulted in very low stereoselection probably due to the configurational instability of this metal center.[3] Also, the influence of the ester moiety in **2** on the enantioselection extent was examined. As it can be seen in entries 1, 6, and 7 there is not a regular variation of ee values by increasing the bulkiness of the ester group, the efficiency order being cyclohexyl > ethyl ≫ *tert*-butyl.

Of the several solvents tested, methylene chloride has proven to be the solvent of choice. Cooling from 20 to −20 °C did not improve the induction, but cooling below −20 °C caused the yield to drop markedly without significant stereoselection benefit. We extended the reaction to various phenols in order to evaluate the effect of the ring substituents on the asymmetric induction degree. As the results in entries 1 and 8–13 indicate high isolated yield were obtained with activated phenols **1d**, **1f**, and **1g**, but the ee values were in the unsatifactory range of 13–39%.

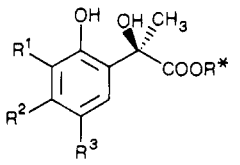
Diastereoselection by Chiral Pyruvic Esters. Since achiral pyruvates were characterized as efficient reagents for the preparation of racemic *o*-hydroxyatrolactic esters,[4] we next explored asymmetric induction by using pyruvic esters incorporating a suitable chiral moiety. For this phase of our investigation, we employed **1a** and (−)- and (+)-menthyl esters **2d** and **2e** in the presence of achiral aluminum and titanium alkoxides. The results are presented in Table II.

Pyruvic ester **2d**, when reacted in the presence of ethoxyethylaluminum chloride, produced a chromatographically separable mixture of the two diastereoisomers (2*R*)-**4ad** and (2*S*)-**5ad** in 60% total yield and a ratio of 27:73, favoring the 2*S* isomer, and this diastereofacial preference was observed also when ethoxytitanium tri-

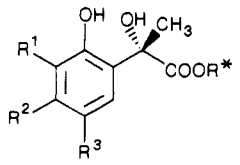
(3) Reetz, M. T.; Kyung, S. H.; Westermann, J. *Organometallics* **1984**, *3*, 1716. Reetz, M. T.; Kükenhöhner, T.; Weinig, P. *Tetrahedron Lett.* **1986**, *27*, 5711. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer Verlag: Berlin, 1986.

(4) Casiraghi, G.; Sartori, G.; Casnati, G.; Bigi, F. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1649. Citterio, A.; Gandolfi, M.; Piccolo, O.; Filippini, L.; Tinucci, L.; Valoto, E. *Synthesis* **1984**, 760.

Table III. Double Asymmetric Synthesis of (2*R*)- and (2*S*)-Atrolactic Esters 4 and 5[a]



4



5

entry	reactants	promoter	products	R^1	R^2	R^3	R*	yield, %[b]	ratio[c] 4:5	config[d]
1	**1a + 2d**	(+)-menthyl-O(Et)AlCl	**4ad + 5ad**	H	*t*-Bu	H	(−)-menthyl	58	22:78	*S*
2	**1a + 2d**	(−)-menthyl-O(Et)AlCl	**4ad + 5ad**	H	*t*-Bu	H	(−)-menthyl	56	40:60	*S*
3	**1a + 2d**	(−)-menthyl-$OTiCl_3$	**4ad + 5ad**	H	*t*-Bu	H	(−)-menthyl	65	12:88	*S*
4	**1a + 2d**	(+)-menthyl-$OTiCl_3$	**4ad + 5ad**	H	*t*-Bu	H	(−)-menthyl	64	27:73	*S*
5	**1a + 2e**	(+)-menthyl-$OTiCl_3$	**4ae + 5ae**	H	*t*-Bu	H	(+)-menthyl	66	87:13	*R*
6	**1g + 2e**	(+)-menthyl-$OTiCl_3$	**4ge + 5ge**	$(CH{=}CH)_2$		H	(+)-menthyl	86	93:7	*R*
7	**1g + 2d**	(−)-menthyl-$OTiCl_3$	**4gd + 5gd**	$(CH{=}CH)_2$		H	(−)-menthyl	85	6:94	*S*
8	**1f + 2e**	(+)-menthyl-$OTiCl_3$	**4fe + 5fe**	H	OCH_2O		(+)-menthyl	78	86:14	*R*
9	**1b + 2d**[e]	(−)-menthyl-$OTiCl_3$	**4bd + 5bd**	H	H	H	(−)-menthyl	41	27:73	*S*
10	**1h + 2d**[f]	(−)-menthyl-$OTiCl_3$	**4hd + 5hd**	*t*-Bu	H	H	(−)-menthyl	47	32:68	*S*

[a] Unless otherwise stated, Ti-based reactions were conducted at −60 °C and Al-based reactions at −20 °C. [b–d] See notes *b–d* for Table II. [e] At 20 °C. [f] At −20 °C.

chloride was used as promoter (24:76 ratio). As expected, the ester **2e** led to 2*R* stereoisomers preferentially as a consequence of the reversal of the reagent chirality.

All reactions involving the aluminum promoter were conducted at −20 °C in CH_2Cl_2 following a protocol consisting of the addition of **2** to a preformed solution of the phenolate. Lowering the reaction temperature was not profitable, the yield being negligible. With titanium reagents, optimum temperature was −60 °C under the standard conditions (premixing the phenol and $EtOTiCl_3$). In all cases higher reaction temperature caused a marked drop of facial selectivity.

Double Asymmetric Induction. As a third task we turned to double asymmetric synthesis[5] in order to solve the problem of controlling facial selectivity in a synthetically useful manner. At this point let us summarize some crucial results of the single asymmetric reactions we disclosed in the preceeding sections. For the representative reactions involving **1a**, we can observe that atrolactic esters of 2*R* configuration are preferentially formed with either (−)-menthol-based alkoxides (Table I, entry 1) or (+)-menthol-based pyruvates (Table II, entry 2) when aluminum is involved, while, with Ti-based addends, the same 2*R* compounds are the dominant products when (+)-menthol-based pyruvates are used (Table II, entry 5). Obviously, 2*S* derivatives can be preferentially produced by reverting the reactant chiralities.

With these results in hand, we hoped that a proper combination of the two involved chiralities in a matched sense would produce substantial benefit on the degree of asymmetric induction allowing a variety of ring-hydroxylated (2*R*)- and (2*S*)-atrolactic esters to be prepared at will and in a synthetically useful stereoselectivity. This was to be the case. Looking at the experiments involving **1a** conducted in the matched sense (Table III, entries 1, 3, and 5) one can first observe that matched pairs augment significantly the stereoselectivity intrinsic to chiral pyruvic esters even though the multiplicativity of stereoselectivities[5] is not very precise.

For example, the reaction in entry 1 (Al-based promoter), in which the two chiralities are acting in concert, gave rise to **4ad** and **5ad** in a ratio of 22:78, larger than the selectivities of either reactant. Examination of the data of entry 3 shows an unexpected pattern of selectivity. The diastereomeric ratio was 12:88 in favor of **5ad**, larger than the intrinsic selectivity of either **2d** (24:76) or Ti-based promoter (negligible induction). We do not have a solid rationale to advance for this deviation from the multiplicativity rule;[6] however, the observed selectivity is significant enough to be synthetically useful.

Entries 2 and 4 concern with two experiments conducted in the mismatched sense, being the two stereofacial selectivities of pyruvate and promoter counteracting each other. The expected products **4ad** and **5ad** resulted in a ratio smaller than the simple diastereoselectivity of **2d**.

By using this double asymmetric tactic and with a suitable combination of the reaction components we synthesized some atrolactic esters of both 2*R* and 2*S* configuration. The set of reactions (entries 6–10) demonstrates a predictable trend: 2*S* esters predominate when the (−)-menthyl-$OTiCl_3$/**2d** matched pair is used, while 2*R* esters are the major products with the (+)-menthyl-$OTiCl_3$/**2e** couple. Except for the less reactive phenols **1b** and **1h**, requiring higher reaction temperature (entries 9 and 10), all examples quoted show a synthetically interesting diastereoselection, leading to easily separable mixtures of diastereomeric esters **4** and **5**. In some instances, crystallization of crude reaction product was enough to furnish enantiomerically pure esters, as demonstrated for **5ad** and **4fe**. In any case, chromatography on a short silica gel column provided pure homochiral compounds.

Configurational Assignments and Auxiliary Removal. In order to assign the absolute configuration at the carbinol center of the new optically active compounds in this study we started with the unambiguous structural determination of **5ad** and **4fe** via single-crystal X-ray analysis. A stereoview of the two molecules is shown in Figure 1.

As can be seen from the stereoview, the chirality of the carbinol center in both the molecules is related to the stereodisposition of the three chiral centers of the menthyl moiety, which ultimately follows from the absolute configuration of the starting menthol auxiliary. Thus, the (−)-menthol-based compound **5ad** possess 2*S* absolute configuration (11*S* crystallographic numbering) and the (+)-menthol-based ester **4fe** 2*R* absolute configuration

(5) For recent reviews on this subject, see: Masamune, S. *Heterocycles* **1984**, *21*, 107. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(6) For a anomalous example of interactivity among chiral metal promoters and menthyl auxiliares, see: Danishefsky, S.; Bednarski, M. *J. Am. Chem. Soc.* **1983**, *105*, 6968.

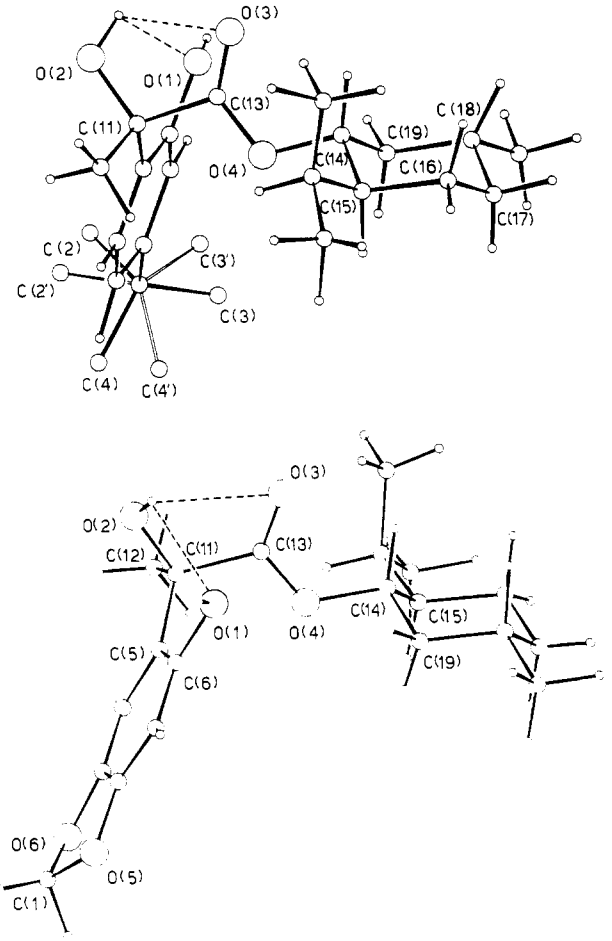


Figure 1. Computer-generated perspective view of the final X-ray models of **5ad** (top) and **4fe** (bottom).

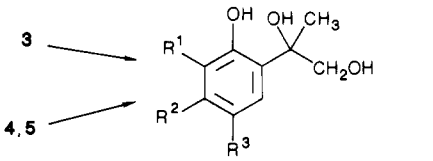
(11*R* crystallographic numbering).

The configurational array of **4ad** and **5fe** was made sure by the above X-ray assignment of the corresponding diastereoisomers (2*S*)-**5ad** and (2*R*)-**4fe**, and the configuration of **4ae** and **5ae** was assigned on the basis of their rotation values in comparison with those of the corresponding enantiomers (2*S*)-**5ad** and (2*R*)-**4ad**. The absolute configuration of the other diastereomeric pairs **4** and **5** in Table III followed from ^{1}H NMR configurational correlation to the above assigned stereostructures. Since the signal due to the C-2 methyl at ca. δ 1.8 in the structure (2*R*)-**4ad** and its (2*S*)-**5ae** enantiomer appears consistently at lower field ($\Delta\delta$ 0.02) than that of the diastereomeric compound (2*S*)-**5ad** and its (2*R*)-**4ae** enantiomer we can confidentially assign 2*R* to **4ge** and 2*S* structure to **5ge**. As a consequence **5gd**, which is enantiomer of **4ge**, possesses the 2*S* configuration and **4gd**, which is enantiomer of **5ge**, possesses the 2*R* configuration. In a similar fashion we attributed the absolute configuration to compounds in entries 9 and 10 as shown in Table III. Furthermore, examination of TLC R_f values of our compounds corroborates this assignment, the R_f values being higher for compounds with the C-2 methyl resonating at higher field and vice versa.

The configurational assignment of enantiomers **3** in Table I was provided by chemical correlation to the corresponding diastereoisomers **4** and **5** according to Scheme II.

Thus, $LiAlH_4$ reduction of enantiomerically pure **5ad** gave rise to levorotatory diol **6a**, showing $[\alpha]_{546}$ −8.90° (*c* 1, EtOH). Instead , reduction of optically enriched (−)-**3aa** lead to dextrorotatory diol **6a** with $[\alpha]_{546}$ +4.01°, indicating that the parent esters **5ad** and (−)-**3aa** possess opposite

Scheme II[a]



6a: $R^1, R^3 = H$; $R^2 = t$-Bu
f: $R^1 = H$; R^2–$R^3 = OCH_2O$
g: R^1–$R^2 = (CH{=}CH)_2$; $R^3 = H$

[a] Conditions: $LiAlH_4$, ether, 0 °C, and then NH_4Cl/H_2O.

configuration at C-2 carbon. Since the configuration of **5ad** is 2*S* we thus assigned 2*R* configuration to (−)-**3aa**.

Reduction of (+)-**3ac** to (+)-**6a** yielded the 2*S* configuration to (+)-**3ac**; a similar reductive transformation yielded the 2*R* configuration to (+)-**3ga** via conversion of (2*S*)-**5gd** and (+)-**3ga** to (−)-**6g** and (+)-**6g**, respectively. Finally, convergent reduction of (2*R*)-**4fe** and (−)-**3fa** to the same diol (+)-**6f** ensured the 2*R* configurational assignment to (−)-**3fa**.

The $LiAlH_4$ reductive process giving 1,2-diols **6** was proven to be enantioconservative. Starting with optically pure menthyl esters **5ad**, **5gd**, and **4fe** we thus synthesized homochiral diols (2*S*)-**6a**, (2*S*)-**6g**, and (2*R*)-**6f** in 70–72% isolated yield.

As a final task we attempted to remove the menthol auxiliary by hydrolysis of diastereomeric esters. Optically pure (2*S*)-**5ad** was chosen as an example. The first attempt made by 10% aqueous NaOH was frustrated, owing to formation of an untractable reaction mixture. Fortunately, an alternative procedure by using *t*-BuOK in anhydrous diethyl ether containing 3.0 equiv of water[7] solved the problem, giving rise to the corresponding propanoic acid (2*S*)-**7a** in 40% isolated yield with concomitant recovery of menthol auxiliary. By this route, free acid (2*S*)-**7a** was obtained in an enantiomerically pure form as ascertained by $LiAlH_4$ reduction to pure alcohol (2*S*)-**6a**.

Conclusions

In summary, phenols undergo chemo- and regioselective carbon–carbon bond formation with pyruvic esters.[8] Both 2*R* and 2*S* stereoisomers of *o*-hydroxyatrolactic acid derivatives can be available merely by selecting the proper antipode of menthol[9] in the preparation of both the chiral alkoxide promoter and the pyruvate. By a synthetic point of view this process, in the double asymmetric version, fulfills the following requirements: (a) diastereomeric excess in the range 36–88%; (b) fairly good chemical yields; (c) commercailly available and inexpensive chiral auxiliaries; (d) the configuration of products is predictable. These factors, coupled with the ease of preparation of the starting chiral pyruvates and promoters, established the method as a useful technique for preparation of the title esters (and acids and diols therefrom) in an optically pure form. Mechanistically, the facial selectivity observed in this asymmetric electrophilic substitution with chiral py-

(7) Gassman, P. G.; Shenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.

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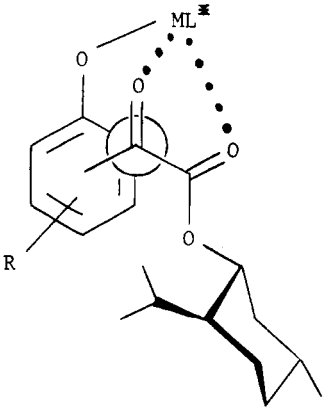

Figure 2. Staggered transition state for chelation-controlled metal-mediated reaction of (−)-menthyl pyruvate with a metal phenolate. The proximate phenolic ortho carbon approaches the carbonyl carbon along the less hindered trajectory (*si* face).

ruvic esters may be interpreted in terms of a metal-bound transition-state model as shown in Figure 2 (the view is along the forming bond) wherein chelation of the oxygen atoms by a metallic species M^{10} causes shielding of the *re* face of the substrate by the (−)-menthol substituent.

The incoming aromatic nucleus (ortho carbon only) tends to approach from the relatively unhindered *si* face, with the consequence that 2*S* chirality is induced. The additional presence of a chirality L* appended to the metal allows, if properly selected, improvement of the pyruvate diastereofacial bias with significant synthetic benefit.

Experimental Section

The instrumentation and procedures employed in ^{1}H NMR, IR, UV analysis, optical rotation, and CD measurements as well as description of calculation apparatus were given in our previous publication.[2] Electron impact mass spectra were obtained on a Finnigan 1020 instrument. Elemental analyses were obtained from Istituto di Chimica Farmaceutica dell'Università degli Studi di Parma, Italy.

Enantiomeric excesses were determined by direct method of ^{1}H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ [hfc = 3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]. Diastereomeric excesses were determined by HPLC on a Waters Associates liquid chromatograph using μ-Bondapak C_{18} columns with methanol/water solvent system. Ethyl pyruvate (**2a**) was from Merck. Pyruvic acid esters were prepared by the reported methods: **2b**,[11] **2c**,[12] **2d**,[12] **2e**.[12]

(*R*)-2-Hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)-propanoic Acid Ethyl Ester (3aa). Typical Procedure. To a solution of diethylaluminum chloride (10 mL of 1 M hexane solution) in anhydrous methylene chloride (10 mL) was added dropwise a solution of (−)-menthol (1.56 g, 10 mmol) in methylene chloride (15 mL) at 0 °C, while a stream of dry nitrogen was passed. After the mixture was stirred at room temperature for 20 min, 3-*tert*-butylphenol (**1a**) (1.50 g, 10 mmol) was added as a solution in 15 mL of methylene chloride. After additional 2 h at room temperature, pyruvic ester **2a** (1.16 g, 10 mmol) in methylene chloride (10 mL) was added dropwise with stirring. The reaction was stirred for 3 h and then quenched with an excess of an aqueous ammonium chloride solution and extracted with methylene chloride (3 × 100 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure, and **3aa** was separated from the residue by chromatography on silica gel using hexane/ethyl acetate (85:15): yield, 1.57 g (59%); oil; n^{13}_D 1.5135; $[\alpha]_{546}$ −0.204° (*c* 1, 95% ethanol); $[\theta]_{279}$ +3471 (*c* 6.8 × 10^{-3} M); MS, *m/z* (relative intensity) 266 (5, M), 193 (100),177 (12); IR ν_{max} (film) 3350, 2960, 1725, 1250, 1130, 940 cm^{-1}; UV λ_{max} 278 nm (ε 2527); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 1.31 (t, 3 H, *J* = 7.1 Hz), 1.82 (s, 3 H), 4.11 (br s, 1 H), 4.3 (m, 2 H), 6.86 (dd, 1 H, *J* = 8.1 and 2.0 Hz), 6.90 (d, 1 H, *J* = 2.0 Hz), 7.13 (d, 1 H, *J* = 8.1 Hz), 8.49 (br s, 1 H). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.53; H, 8.46.

The following ethyl esters, listed in Table I, were prepared in a similar way.

(*R*)-3ab: mp 76–77 °C; $[\alpha]_{546}$ −0.503° (*c* 1, 95% ethanol); $[\theta]_{278}$ +1113 (*c* 5.0 × 10^{-3} M); MS, *m/z* (relative intensity) 294 (9, M), 238 (19), 194 (100), 163 (10); IR ν_{max} (KBr) 3360, 2950, 1710, 1250, 940 cm^{-1}; UV λ_{max} 276 nm (ε 2560); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 1.50 (s, 9 H), 1.76 (s, 3 H), 4.26 (br s, 1 H), 6.86 (dd, 1 H), *J* = 8.3 and 1.8 Hz), 6.90 (d, 1 H, *J* = 1.8 Hz), 7.15 (d, 1 H, *J* = 8.3 Hz), 8.75 (br s, 1 H). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.29; H, 8.96.

(*R*)-3ac: oil; $[\alpha]_{546}$ +2.813° (*c* 0.7, 95% ethanol); $[\theta]_{279}$ +5023 (*c* 4.4 × 10^{-3} M); MS, *m/z* (relative intensity) 320 (2, M), 193 (100), 187 (16), 163 (10); IR ν_{max} (film) 3350, 2910, 1720, 1250, 940 cm^{-1}; UV λ_{max} 276 nm (ε 2647); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9 H), 1.2–2.0 (m, 10 H), 1.82 (s, 3 H), 4.19 (s, 1 H), 4.91 (s, 1 H), 6.86 (dd, 1 H, *J* = 8.1 and 2.0 Hz), 6.90 (d, 1 H, *J* = 2.0 Hz), 7.15 (d, 1 H, *J* = 8.1 Hz), 8.65 (s, 1 H). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.20; H, 9.00.

(*R*)-3ba: oil; $[\theta]_{275}$ +1388 (*c* 9.5 × 10^{-3} M); MS, *m/z* (relative intensity) 210 (2, M), 146 (26), 137 (71), 121 (100); IR ν_{max} (film) 3300, 1720, 1220, 940 cm^{-1}; UV λ_{max} 276 nm (ε 2228); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, *J* = 7.0 Hz), 1.85 (s, 3 H), 4.1–4.4 (m, 3 H), 6.8–7.3 (m, 4 H), 8.5 (br s, 1 H). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.81; H, 6.83.

(*R*)-3ca: oil; $[\alpha]_{546}$ −0.631° (*c* 1.1, 95% ethanol); $[\theta]_{277}$ +2242 (*c* 7.4 × 10^{-3} M); MS, *m/z* (relative intensity) 224 (5, M), 151 (100), 135 (14), 133 (14); IR ν_{max} (film) 3350, 2980, 1725, 1250, 950 cm^{-1}; UV λ_{max} 278 nm (ε 2231); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, *J* = 6.9 Hz), 1.82 (s, 3 H), 2.28 (s, 3 H), 4.14 (br s, 1 H), 4.2–4.4 (m, 2 H), 6.68 (d, 1 H, *J* = 8.0 Hz), 6.70 (s, 1 H), 6.71 (d, 1 H, *J* = 8.0 Hz), 8.42 (br s, 1 H). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.33.

(*R*)-3da: oil; n^{13}_D 1.5332; $[\alpha]_{546}$ −2.445° (*c* 1.1, 95% ethanol); $[\theta]_{280}$ +892 (*c* 7.6 × 10^{-3} M); MS, *m/z* (relative intensity) 240 (5, M), 168 (12), 167 (100), 155 (11); IR ν_{max} (film) 3300, 2980, 1730, 1260, 1130, 960 cm^{-1}; UV λ_{max} 278 nm (ε 2399); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, *J* = 7.0 Hz), 1.82 (s, 3 H), 3.78 (s, 3 H), 4.17 (br s, 1 H), 4.2–4.4 (m, 2 H), 6.3–7.2 (m, 3 H), 8.64 (s, 1 H). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.06; H, 6.61.

(*R*)-3ea: oil; n^{13}_D 1.5210; $[\alpha]_{546}$ −2.666° (*c* 1, 95% ethanol); $[\theta]_{284}$ +1309 (*c* 4.2 × 10^{-3} M); MS, *m/z* (relative intensity) 224 (12, M), 160 (14), 151 (100), 135 (30); IR ν_{max} (film) 3350, 2980, 1725, 1260, 1130, 940 cm^{-1}; UV λ_{max} 283 nm (ε 2240); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, *J* = 7.0 Hz), 1.82 (s, 3 H), 2.27 (s, 3 H), 4.17 (br s, 1 H), 4.31 (dq, 2 H, *J* = 7.0 and 2.7 Hz), 6.7–7.1 (m, 3 H), 8.20 (s, 1 H). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.33.

(*R*)-3fa: oil; n^{13}_D 1.5425; $[\alpha]_{546}$ −1.143° (*c* 1, 95% ethanol); $[\theta]_{301}$ +443 (*c* 3.4 × 10^{-3} M); MS, *m/z* (relative intensity) 254 (30, M), 190 (32), 181 (100), 165 (35); IR ν_{max} (film) 3350, 2980, 1725, 1260, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, *J* = 6.8 Hz), 1.78 (s, 3 H), 4.13 (br s, 1 H), 4.2–4.4 (m, 2 H), 5.91 (s, 2 H), 6.43 (s, 1 H) 6.73 (s, 1 H), 8.34 (br s, 1 H). Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.60; H, 5.69.

(*R*)-3ga: oil; $[\alpha]_{546}$ −10.0° (*c* 0.1, 95% ethanol); $[\theta]_{275}$ +1388 (*c* 4.8 × 10^{-3} M); MS, *m/z* (relative intensity) 260 (13, M), 240 (21), 214 (17), 196 (94), 186 (53), 171 (87), 168 (100), 139 (40), 115 (39); IR ν_{max} (film) 3300, 2950, 1720, 1250, 1120 cm^{-1}; UV λ_{max} 295 nm (ε 4929); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, *J* = 6.9 Hz), 1.94 (s, 3 H), 4.2–4.5 (m, 3 H), 7.2–8.4 (m, 6 H), 9.68 (s, 1 H). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.40; H, 6.14.

(2*R*)- and (2*S*)-2-Hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)propanoic Acid (−)-Menthyl Esters (4ad and 5ad). Al-Based Procedure. To a solution of diethylaluminum chloride (10 mL of 1M hexane solution) in anhydrous CH_2Cl_2 (10 mL) a solution of (+)-menthol (1.56 g, 10 mmol) in CH_2Cl_2 (15 mL) was added dropwise at −20 °C. After the mixture was stirred for 20 min, 3-*tert*-butylphenol (1.50 g, 10 mmol) was added as a solution in 15 mL of CH_2Cl_2. After additional 2 h at −20 °C, a solution

(10) For a recent discussion of regio- and stereocontrol by metal complex induced proximity effects, see: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(11) Raha, C. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 263.

(12) Matsumoto, K. *J. Org. Chem.* **1966**, *31*, 1956.

of pyruvic acid (–)-menthyl ester (**2d**) (2.26 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction solution was stirred for 24 h at –20 °C, then quenched with an excess of an aqueous ammonium chloride solution, and extracted with CH_2Cl_2 (3 × 100 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure, giving a solid residue. Crystallization from hexane afforded pure (2*S*)-**5ad**: 1.74 g (46%); colorless needles, mp 150–151 °C; $[\alpha]_{546}$ –80.7° (*c* 0.3, 95% ethanol); $[\theta]_{280}$ –11 728 (*c* 6.5 × 10^{-3} M); MS, *m/z* (relative intensity) 376 (14, M), 238 (21), 193 (100), 187 (16), 83 (12); IR ν_{max} (KBr) 3200, 2970, 1740, 1230, 1120, 940 cm^{-1}; UV λ_{max} 280 nm (ϵ 2625); ^1H NMR ($CDCl_3$) δ 0.76 (d, 3 H, *J* = 7.0 Hz), 0.89 (d, 3 H, *J* = 7.0 Hz), 1.90 (d, 3 H, *J* = 7.0 Hz), 1.28 (s, 9 H), 0.9–2.1 (m, 9 H), 1.80 (s, 3 H), 4.17 (s, 1 H), 4.80 (dt, 1 H, *J* = 10.5 and 4.4 Hz), 6.84 (dd, 1 H, *J* = 8.2 and 2.1 Hz), 6.90 (d, 1 H, *J* = 2.1 Hz), 7.13 (d, 1 H, *J* = 8.2 Hz), 8.55 (s, 1 H). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.19; H, 9.58.

The mother liquors from the above crystallization were evaporated under reduced pressure and the residue chromatographed on silica gel with hexane/ethyl acetate (95:5) as eluent to give the minor diastereoisomer (2*R*)-**4ad**: 0.44 g (12%); colorless crystals, mp 142–143 °C; $[\alpha]_{546}$ –56.9° (*c* 0.2, 95% ethanol); $[\theta]_{277}$ –18 571 (*c* 5.6 × 10^{-3} M); MS, *m/z* (relative intensity) 376 (3, M), 220 (12), 193 (100), 187 (19); IR ν_{max} (KBr) 3350, 2950, 1725, 1260, 1120, 950 cm^{-1}; UV λ_{max} 278 nm (ϵ 2730); ^1H NMR ($CDCl_3$) δ 0.52 (d, 3 H, *J* = 6.5 Hz), 0.65 (d, 3 H, *J* = 6.5 Hz), 0.91 (d, 3 H, *J* = 6.5 Hz), 0.7–2.5 (m, 9 H), 1.27 (s, 9 H), 1.82 (s, 3 H), 4.00 (s, 1 H), 4.65 (dt, 1 H, *J* = 10.5 and 4.4 Hz), 6.85 (dd, 1 H, *J* = 7.5 and 1.9 Hz), 6.88 (d, 1 H, *J* = 1.9 Hz), 7.15 (d, 1 H, *J* = 7.5 Hz), 8.22 (s, 1 H). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.22; H, 9.90.

(2*R*)- and (2*S*)-2-Hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)propanoic Acid (+)-Menthyl Esters (4ae and 5ae). Ti-Based Procedure. To a solution of titanium tetrachloride (1.0 g, 10 mmol) in CH_2Cl_2 (10 mL) was added a solution of (+)-menthol (1.56 g, 10 mmol) in CH_2Cl_2 (15 mL) at –60 °C. After the mixture was stirred for 20 min, 3-*tert*-butylphenol (**1a**) (1.50 g, 10 mmol) was added as a solution in 15 mL of CH_2Cl_2. After additional 2 h at –60 °C, a solution of pyruvic acid (+)-menthyl ester (**2e**) (2.26 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise, and the deep violet solution was stirred at –60 °C for 3 h. Workup as above furnished a solid residue, from which pure diastereomeric atrolactic esters **4ae** and **5ae** were separated and purified. (2*R*)-**4ae**: 2.11 g (56%); $[\alpha]_{546}$ +79.6° (*c* 0.6, 95% ethanol); ^1H NMR and IR spectral characteristics identical with those of its enantiomer (2*S*)-**5ad**. (2*S*)-**5ae**: 0.37 g (10%); $[\alpha]_{546}$ +55.8 (*c* 0.6, 95% ethanol); ^1H NMR and IR spectral characteristics identical with those of its enantiomer (2*R*)-**4ad**.

The following diastereomeric pairs of esters listed in Table III were prepared in a similar way.

(2*R*)-**4ge**: viscous oil; $[\alpha]_{546}$ +240.6° (*c* 0.8, 95% ethanol); $[\theta]_{326}$ –22 356 (*c* 7.9 × 10^{-4} M); IR ν_{max} (film) 3300, 2920, 1710, 1260, 1120, 940 cm^{-1}; UV ν_{max} 238 nm (ϵ 32 320), 298 (5020), 312 (4100); ^1H NMR ($CDCl_3$) δ 0.77 (d, 3 H, *J* = 6.9 Hz), 0.85 (d, 3 H, *J* = 6.7 Hz), 0.89 (d, 3 H, *J* = 6.9 Hz), 0.9–2.0 (m, 9 H), 1.89 (s, 3 H), 4.56 (br s, 1 H), 4.82 (dt, 1 H, *J* = 10.9 and 4.4 Hz), 7.2–8.4 (m, 6 H), 9.80 (br s, 1 H). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.51; H, 8.23.

(2*S*)-**5ge**: white solid, mp 135–136 °C; $[\alpha]_{589}$ –74.66° (*c* 0.6, 95% ethanol); MS, *m/z* (relative intensity) 370 (11, M), 232 (37), 214 (78), 196 (100), 187 (42), 168 (42), 139 (24); IR ν_{max} (KBr) 3420, 3240, 2920, 1710, 1270, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.42 (d, 3 H, *J* = 6.9 Hz), 0.48 (d, 3 H, *J* = 6.9 Hz), 0.91 (d, 3 H, *J* = 6.4 Hz), 0.9–2.1 (m, 9 H), 1.91 (s, 3 H), 4.30 (s, 1 H), 4.70 (dt, 1 H, *J* = 10.8 and 4.4 Hz), 7.2–8.4 (m, 6 H), 9.44 (s, 1 H). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.43; H, 8.24.

(2*R*)-**4gd**: mp 137–139 °C; $[\alpha]_{589}$ +75.1° (*c* 0.3, 95% ethanol) (lit.[13] mp 138–140 °C; $[\alpha]_D$ +74.16° (*c* 2.2, ethanol); ^1H NMR and IR spectral characteristics identical with those of its enantiomer (2*S*)-**5ge**.

(2*S*)-**5gd**: viscous oil; $[\alpha]_{546}$ –241.5° (*c* 0.8, 95% ethanol) (lit.[13] $[\alpha]_D$ –196.77° (*c* 2.04, ethanol); ^1H NMR and IR spectral characteristics identical with those of its enantiomer (2*R*)-**4ge**.

(13) Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Citterio, A. *Helv. Chim. Acta* **1984**, *67*, 739.

(2*R*)-**4fe**: colorless plates, mp 100–101 °C; $[\alpha]_{546}$ +44.8° (*c* 1, 95% ethanol); $[\theta]_{300}$ +2666 (*c* 8.2 × 10^{-4} M); MS, *m/z* (relative intensity) 364 (9, M), 226 (35), 208 (63), 190 (76), 181 (100), 162 (46), 138 (13); IR ν_{max} (KBr) 3470, 3180, 2930, 1730, 1250, 1120, 940 cm^{-1}; UV λ_{max} 301 nm (ϵ 5513); ^1H NMR ($CDCl_3$) δ 0.75 (d, 3 H, *J* = 6.9 Hz), 0.89 (d, 6 H, *J* = 6.8 Hz), 0.8–2.0 (m, 9 H), 1.76 (s, 3 H), 4.16 (br s, 1 H), 4.77 (dt, 1 H, *J* = 11.0 and 4.4 Hz), 5.88 (d, 1 H, *J* = 1.3 Hz), 5.90 (d, 1 H, *J* = 1.3 Hz), 6.42 (s, 1 H), 6.72 (s, 1 H), 8.36 (br s, 1 H). Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.88; H, 7.86.

(2*S*)-**5fe**: colorless oil; IR ν_{max} (film) 3430, 3205, 2920, 1715, 1260, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (d, 3 H, *J* = 6.8 Hz), 0.72 (d, 3 H, *J* = 6.8 Hz), 0.91 (d, 3 H, *J* = 6.5 Hz), 0.9–2.1 (m, 9 H), 1.77 (s, 3 H), 4.12 (br s, 1 H), 4.68 (dt, 1 H, *J* = 10.7 and 4.4 Hz), 5.87 (m, 2 H), 6.40 (s, 1 H), 6.72 (s, 1 H), 8.17 (br s, 1 H). Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.80; H, 7.93.

(2*R*)-**4bd**: colorless solid, mp 107–110 °C; $[\alpha]_{546}$ –55.8° (*c* 0.7, 95% ethanol); MS, *m/z* (relative intensity) 320 (4, M), 182 (14), 137 (100), 121 (78); IR ν_{max} (KBr) 3260, 2930, 1710, 1265, 1140, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.56 (d, 3 H, *J* = 6.8 Hz), 0.68 (d, 3 H, *J* = 6.8 Hz), 0.91 (d, 3 H, *J* = 6.5 Hz), 0.9–2.1 (m, 9 H), 1.83 (s, 3 H), 4.07 (s, 1 H), 4.69 (dt, 1 H, *J* = 10.9 and 4.4 Hz), 6.8–7.0 (m, 2 H), 7.1–7.3 (m, 2 H), 8.30 (s, 1 H). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.36; H, 8.93.

(2*S*)-**5bd**: colorless oil; $[\alpha]_{546}$ –78.9° (*c* 0.9, 95% ethanol); $[\theta]_{280}$ –10 866 (*c* 1.4 × 10^{-3} M); MS, *m/z* (relative intensity) 320 (3, M), 182 (14), 137 (100), 121 (20); IR ν_{max} (film) 3360, 2920, 1710, 1275, 1130, 760 cm^{-1}; UV λ_{max} 274 nm (ϵ 2375); ^1H NMR ($CDCl_3$) δ 0.76 (d, 3 H, *J* = 6.9 Hz), 0.89 (d, 6 H, *J* = 6.8 Hz), 0.9–2.1 (m, 9 H), 1.82 (s, 3 H), 4.21 (br s, 1 H), 4.80 (dt, 1 H, *J* = 10.7 and 4.4 Hz), 6.8–7.0 (m, 2 H), 7.1–7.3 (m, 2 H), 8.56 (br s, 1 H). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.41; H, 9.03.

(2*R*)-**4hd**: colorless oil; $[\alpha]_{546}$ –5.0° (*c* 0.6, 95% ethanol); IR ν_{max} (film) 3320, 2920, 1715, 1260, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55 (d, 3 H, *J* = 6.9 Hz), 0.64 (d, 3 H, *J* = 6.9 Hz), 0.90 (d, 3 H, *J* = 6.5 Hz), 1.38 (s, 9 H), 0.9–2.0 (m, 9 H), 1.84 (s, 3 H), 3.96 (br s, 1 H), 4.71 (dt, 1 H, *J* = 10.6 and 4.4 Hz), 6.79 (t, 1 H, *J* = 7.8 Hz), 7.08 (dd, 1 H, *J* = 7.8 and 1.5 Hz), 7.22 (dd, 1 H, *J* = 7.8 and 1.7 Hz), 8.37 (s, 1 H). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.27; H, 9.91.

(2*S*)-**5hd**: colorless oil; $[\alpha]_{546}$ –76.2° (*c* 0.17, 95% ethanol); $[\theta]_{281}$ –9177 (*c* 1.7 × 10^{-3} M); MS, *m/z* (relative intensity) 376 (4, M), 237 (17), 193 (100), 177 (55); IR ν_{max} (film) 3320, 2870, 1720, 1255, 1100 cm^{-1}; UV λ_{max} 277 nm (ϵ 1710); ^1H NMR ($CDCl_3$) δ 0.75 (d, 3 H, *J* = 6.9 Hz), 0.86 (d, 3 H, *J* = 6.4 Hz), 0.87 (d, 3 H, *J* = 6.9 Hz), 1.39 (s, 9 H), 1.83 (s, 3 H), 0.9–2.0 (m, 9 H), 4.06 (s, 1 H), 4.78 (dt, 1 H, *J* = 11.0 and 4.6 Hz), 6.79 (t, 1 H, *J* = 7.7 Hz), 7.08 (dd, 1 H, *J* = 7.8 and 1.7 Hz), 7.24 (dd, 1 H, *J* = 7.8 and 1.7 Hz), 8.4 (s, 1 H). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.51; H, 9.77.

(2*S*)-2-(2-Hydroxy-4-*tert*-butylphenyl)-1,2-dihydroxypropane (6a). To a slurry of $LiAlH_4$ (0.76 g, 20 mmol) in diethyl ether (100 mL) was added dropwise a solution of (2*S*)-**5ad** (3.76 g, 10 mmol) in diethyl ether (100 mL) under stirring at 0 °C. The resulting mixture was stirred at 0 °C for 3 h and then quenched with a saturated aqueous solution of NH_4Cl and extracted with diethyl ether (3 × 100 mL). After drying (Na_2SO_4) the solvent was removed under reduced pressure and the residue chromatographed over a silica gel column by using a hexane/ethyl acetate (85:15) solvent system, giving pure (2*S*)-**6a**: 1.60 g (71%); mp 116–118 °C; $[\alpha]_{546}$ –8.36° (*c* 0.4, 95% ethanol); MS, *m/z* (relative intensity) 224 (9, M), 206 (32), 193 (100), 177 (98), 163 (22), 115 (29); IR ν_{max} (KBr) 2440, 3330, 3070, 2960, 1230, 1120, 930 cm^{-1}; UV λ_{max} 278 nm (ϵ 2318); ^1H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 1.60 (s, 3 H), 1.98 (br s, 1 H), 3.47 (br s, 1 H), 3.59 (d, 1 H, *J* = 11.2 Hz), 3.90 (d, 1 H, *J* = 11.2 Hz), 6.8–7.0 (m, 3 H), 9.0 (br s, 1 H). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.90; H, 9.13.

The following diols were prepared in a similar way:

(2*S*)-**6g**: by reduction of (2*S*)-**5gd**; 1.57 g (72%); white solid, mp 112–113 °C; $[\alpha]_{546}$ –28.8° (*c* 1.6, 95% ethanol); MS, *m/z* (relative intensity) 218 (6, M), 200 (42), 182 (100), 170 (35), 152 (85), 141 (64), 115 (68); IR ν_{max} (KBr) 3400, 2900, 1570, 1380, 1300, 1020, 800 cm^{-1}; UV λ_{max} 297 nm (ϵ 3868); ^1H NMR ($CDCl_3$) δ 1.63 (br s, 1 H), 1.67 (s, 3 H), 3.64 (br s, 1 H), 3.69 (d, 1 H, *J* = 11.3

Hz), 4.07 (d, 1 H, J = 11.3 Hz), 7.0–8.4 (m, 6 H), 8.75 (br s, 1 H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.60; H, 6.43.

(2*R*)-6f: by reduction of (2*R*)-**4fe**; 1.48 g (70%); colorless crystals, mp 68–70 °C; $[\alpha]_{546}$ +6.74° (c 0.36, 95% ethanol); $[\theta]_{297}$ +2797 (c 5.2 × 10^{-3} M); MS, m/z (relative intensity) 212 (7, M), 194 (32), 176 (36), 165 (100); IR ν_{max} (KBr) 3490, 3180, 1490, 1175, 1040 cm^{-1}; UV λ_{max} 300 nm (ϵ 5312); ^1H NMR ($CDCl_3$) δ 1.56 (s, 3 H), 3.55 (d, 1 H, J = 11.3 Hz), 3.60 (br s, 1 H), 3.92 (d, 1 H, J = 11.3 Hz), 5.87 (s, 2 H), 6.42 (s, 1 H), 6.50 (s, 1 H), 8.99 (br s, 1 H). Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.51; H, 5.83.

(2*S*)-2-Hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)-propanoic Acid (7a). To a suspension of t-BuOK (2.46 g, 22 mmol) in anhydrous diethyl ether (20 mL) water (0.12 mL, 6.7 mmol) was added at 0 °C under stirring. After 5 min, a solution of (2*S*)-**5ad** (0.93 g, 2.5 mmol) in diethyl ether (20 mL) was added, and the mixture was stirred at ambient temperture overnight. The reaction mixture was quenched with water and the organic layer separated. The aqueous phase was further extracted with ether and separated. The aqueous layer was passed through an acidic Dowex ion-exchange column and the resin was then washed with methanol. The combined water and methanol solutions were evaporated under reduced pressure, giving a solid residue consisting of crude **7a**, which was purified by chromatography (silica gel; benzene/methanol/saturated aqueous NH_4OH, 28:57:14). By this procedure pure **7a** ammonium carboxylate was obtained, from which the free acid was liberated by treating a methanol/water solution with a Dowex acidic resin: 0.24 g (40%); colorless solid, mp 108 °C; $[\alpha]_{546}$ +31.7° (c 0.35, 95% ethanol); MS, m/z (relative intensity) 238 (1, M), 220 (10), 187 (38), 177 (100); IR ν_{max} (KBr) 3260, 2950, 1732, 1123 cm^{-1}; UV λ_{max} 280 nm (ϵ 2417); ^1H NMR ($CDCl_3$) δ 1.26 (s, 9 H), 1.83 (s, 3 H), 6.25 (br s, 3 H), 6.88 (s, 1 H), 6.90 (d, 1 H, J = 8.2 Hz), 7.23 (d, 1 H, J = 8.2 Hz). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53, H, 7.61. Found: C, 65.36, H, 7.85.

Crystal Structure Determination of Compounds (2*S*)-5ad and (2*R*)-4fe. The crystal data for (2*S*)-**5ad** as well as atomic coordinates and bond lengths were reported in the preliminary paper.[1]

Crystal Data for (2*R*)-4fe: $C_{20}H_{28}O_6$, M_r 364.4; colorless thin plates; orthorhombic space group $P2_12_12_1$ (from systematic absences and structural analysis); cell dimensions, a = 6.839 (1) Å, b = 13.954 (2) Å, c = 20.658 (3) Å; V = 1971.4 (5) Å^3, Z = 4, (Cu Kα)λ = 1.541 78 Å, μ = 7.0 cm^{-1}, D_c = 1.228 g cm^{-3}, $F(000)$ = 784; crystal size, 0.26 × 0.26 × 0.06 mm; 2196 reflections measured, 1382 with $I > 2\sigma(I)$ used in refinement of 235 parameters, $(\Delta\rho)_{max}$ = 0.09, $(\Delta\rho)_{min}$ = −0.12, max 2θ = 140°. Intensity data were collected at room temperature using Ni-filtered Cu Kα radiation and ω–2θ scan technique. The intensity of a standard reflection was measured every 50 reflections to check the stability of the crystal and the electronics. No absorption correction was applied. The structure was solved by direct methods, using the program SHELX-76[14] and refined by full-matrix least-squares cycles with initially isotropic and then anisotropic thermal parameters.

The hydrogen atoms were located from a difference Fourier synthesis but not refined. The final conventional R index was 0.0455 (observed reflections only). Scattering factors for C, H, and O were taken from ref 15, and both the real and imaginary components of anomalous dispersion were included.

The molecular structures and numbering schemes of (2*S*)-**5ad** and (2*R*)-**4fe** compounds are shown in Figure 1.

The absolute stereochemistries were defined by the known configurations of the menthyl moieties. The cyclohexane rings are in the chair form for both compounds, with the methyl and isopropyl groups equatorial. In (2*R*)-**4fe** the benzene ring of the benzodioxolane group is not quite planar, but it presents a rather flattened twist-boat conformation as appear from puckering amplitudes (θ = 96.6°; ψ = −41.3°). For the dioxolane ring the ψ value (179°) corresponds to envelope conformation with mirror plane through vertex C(1).

In (2*S*)-**5ad** and (2*R*)-**4fe** the mean values for the bond distances in the benzene rings are 1.39 (2) and 1.38 (1) Å, respectively; for C–C single bonds they are 1.54 (2) and 1.52 (1) Å, and the corresponding angle means are 120.0 (1.1)° and 120.0 (6)° and 109.5 (1.1)° and 110.0 (6)°, in agreement with previous X-ray investigations.[16,17] In (2*R*)-**4fe** the O(2) atom forms, as in (2*S*)-**5ad**, a three center (bifurcated) intramolecular H-bond (O(2)H-(O2)···O(3) = 2.637 (6) Å, O(2)H(O2)···O(1) = 2.848 (6) Å) and an intermolecular H-bond (O(1)H(O1)···O(2) ($^1/_2 + x$, $^3/_2 - y$, $-z$) = 2.732 (6) Å) determines the formation of helicoidal chains (Figure S1, supplementary material) running around the screw axis parallel to [100]. For both compounds, the connection between the chains is ensured by Van der Waals contacts. Some selected distances and torsion angles are compared for (2*S*)-**5ad** and (2*R*)-**4fe**: C(11)–O(2) = 1.44 (1) and 1.43 (1) Å; C(13)–O(3) = 1.20 (1) and 1.20 (1) Å; C(13)–O(4) = 1.32 (1) and 1.33 (1) Å; O(2)–C(11)–C-(13)–O(3) = 5.4 (1.5)° and −4.0 (9)°; C(12)–C(11)–C(13)–O(3) = −108.3 (1.2)° and 109.5 (7)°.

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Registry No. **1a**, 585-34-2; **1b**, 108-95-2; **1c**, 108-39-4; **1d**, 150-19-6; **1e**, 106-44-5; **1f**, 533-31-3; **1g**, 90-15-3; **1h**, 88-18-6; **2a**, 617-35-6; **2b**, 76849-54-2; **2c**, 6963-43-5; **2d**, 951-98-4; **2e**, 93059-38-2; (*R*)-**3aa**, 100990-38-3; (*S*)-**3aa**, 100990-37-2; (*R*)-**3ab**, 113322-76-2; (*R*)-**3ac**, 113351-81-8; (*R*)-**3ba**, 113322-77-3; (*R*)-**3ca**, 113322-78-4; (*R*)-**3da**, 113322-79-5; (*R*)-**3ea**, 113322-80-8; (*R*)-**3fa**, 113322-81-9; (*R*)-**3ga**, 113322-82-0; **4ad**, 100990-39-4; **4ae**, 100993-15-5; **4ge**, 113322-83-1; **4gd**, 91044-37-0; **4fe**, 100990-41-8; **4bd**, 113322-85-3; **4hd**, 113322-87-5; **5ad**, 100993-14-4; **5ae**, 100990-40-7; **5ge**, 113322-84-2; **5gd**, 91044-38-1; **5fe**, 100990-42-9; **5bd**, 113322-86-4; **5hd**, 113322-88-6; (*S*)-**6a**, 113322-89-7; (*R*)-**6f**, 113322-91-1; (*S*)-**6g**, 113322-90-0; (*S*)-**7a**, 113322-92-2.

Supplementary Material Available: Bond lengths and angles, final atomic coordinates, and thermal parameters with their estimated standard deviations for compound (2*R*)-**4fe** and Figure S 1, showing molecular packing of (2*R*)-**4fe** and (2*S*)-**5ad** (3 pages). Ordering information is given on any current masthead page. The observed and calculated structure factors can be obtained from G.G.F. on request.

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