Articles

Stereoselective Synthesis of Optically Active 2-Hydroxymandelic Acids and Esters via Friedel−Crafts Coordinated Reaction: Crystal Structure of Chiral Dichloro[2-(1-oxido-1-menthoxycarbonylmethyl)-4-methoxyphenoxido-*O*,*O*,*O*]titanium†

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Highly diastereoselective hydroxyalkylation of phenols with chiral glyoxylates was performed. Hydrolysis or reduction of the esters **3** afforded 2-hydroxymandelic acids **6** and diols **5** in high yields and enantiomeric pure form. Mechanistic evidence of chelation-controlled reaction comes from the crystal structure determination of titanium phenoxide complex **8**.

Introduction

Our results[1] on selective functionalization of phenolic systems promoted by the metal template complex of substrate and reagent with Lewis acid prompted us to investigate the possibility of stereocontrolled electrophilic aromatic substitution.

We have previously performed ortho hydroxyalkylation of phenols with good to excellent levels of stereochemical control using a chiral ketoester[1c] and chiral[1d,e] as well as achiral[1b] aldehydes.

This paper addresses regio- and stereocontrol in the synthesis of optically active 2-hydroxymandelic acids.

Mandelic acid and some derivatives are used as drugs[2] and are usually prepared as racemic mixtures by multistep syntheses.[3a] 2-Hydroxymandelic acid has recently received attention.[3b,c] The stereoselective syntheses reported give low values of diastereomeric excess and/or lacked general utility for preparation of 2-hydroxymandelic derivatives.[4]

Results and Discussion

The diastereoselective hydroxyalkylation of phenols **1** with chiral glyoxylates **2** leading to optically active 2-hydroxymandelic esters **3** and **4**,[5] and the removal of the chiral auxiliary, is described. New findings that relate to the mechanism of the *ortho*-coordinated alkylation of phenols as well as to the mechanism of diastereoselective reactions, like ene reactions,[4c,6] involving chiral glyoxylates in the presence of Lewis acids, are reported.

We first examined the model reaction of 3-*tert*-butylphenol (**1a**) with (−)-menthyl glyoxylate (**2i**). The different Lewis acids employed (Et_2AlCl, $EtAlCl_2$, EtMgBr, $InCl_3$, BCl_3, $SnCl_4$, and $TiCl_4$) affected both the yield and the diastereoselectivity; 2*S* diastereoisomer **3i** was favored. Titanium proved to be the most efficient metal promoter of the reaction for both stereocontrol (de 50%) and yield (53%), operating at −30 °C for 6 h.

Introduction of different chiral alcohols as titanium ligands ((−) and (+)-menthol, (−)-8-phenylmenthol, as well as (+)-diisopropyltartrate[7]) failed to significantly improve the diastereoselectivity.

Since the stereochemical outcome was unaffected by reaction time, whereas the yield was increased, the reactions were carried out for 20 h obtaining isomers **3i** and **4i** in good yields and about 50% de (Table 1, runs 1−4). The major isomers **3ia-d** were easily isolated by crystallization from hexane/dichloromethane.

† Dedicated to the memory of Professor Giuseppe Casnati on the 6th anniversary of his death.

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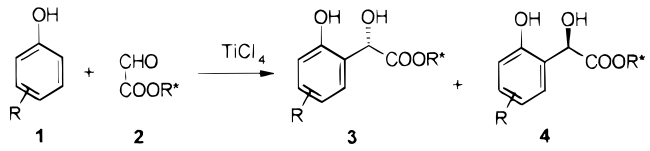
Table 1. Synthesis of 2-Hydroxymandelic Esters 3 and 4[a]



run	phenol	R	aldehyde	R*	major compd	*T* (°C)	time (h)	% total yield	**3:4**[c]
1	**1a**	3-Bu^t	**2i**	(−)-menthyl	**3ia**	−30	20	82[b]	75:25
2	**1b**	4-OMe	**2i**	(−)-menthyl	**3ib**	−30	20	80[b]	75:25
3	**1c**	H	**2i**	(−)-menthyl	**3ic**	−30	20	77[b]	74:26
4	**1d**	4-Bu^t	**2i**	(−)-menthyl	**3id**	−30	20	78[b]	76:24
5	**1a**	3-Bu^t	**2j**	(−)-8-Ph-menthyl	**3ja**	20	6	95	97:3
6	**1b**	4-OMe	**2j**	(−)-8-Ph-menthyl	**3jb**	20	6	97	97:3
7	**1e**	4-Cl	**2j**	(−)-8-Ph-menthyl	**3je**	20	6	62	97:3

[a] All reactions were carried out in a ratio of phenol/glyoxylate/Lewis acid = 1:1:1 in CH_2Cl_2. [b] The use of aldehyde **2i** in the hydrate form or 0.5 equiv of Lewis acid gave slightly lower yields. [c] The diastereomeric excesses were determined by HPLC (see Experimental Section).

Diastereoselectivity was significantly improved by the use of (−)-8-phenylmenthyl glyoxylate **2j**[6,8,9] (Table 1, runs 5−7).

Titanium tetrachloride is the most efficient promoter for this reaction, of the Lewis acids examined. Indeed, the reaction of 3-*tert*-butylphenol (**3a**) and glyoxylate **2j** in the presence of $TiCl_4$ gave the product **3ja** in essentially quantitative yield and with excellent diastereoselectivity even at room temperature.[10] The temperature decrease (down to −60 °C) affected the yield more markedly than the stereoselectivity. Thus, the reaction was extended to activated and weakly deactivated phenols at room temperature, providing 2-hydroxymandelic esters **3j** with high diastereoselection (94%) and good yields (62−97%).

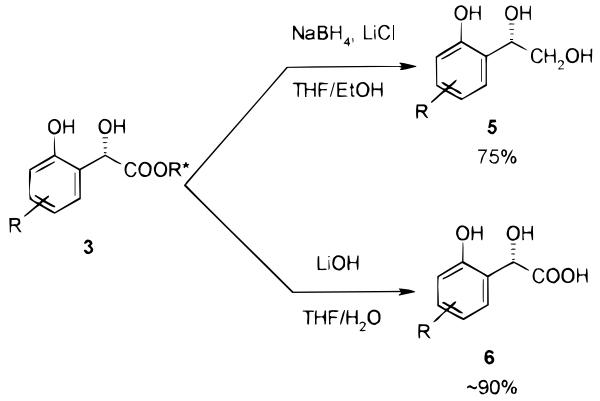
As far as absolute configuration of the new chiral carbon is concerned, the assignment of *S* configuration was made at C-2 of the major diastereoisomers **3ia**−**d** on the basis of ^{1}H NMR studies.[5,11]

This attribution is confirmed by the crystal structure of compound **4ic**, which has the *R* configuration at C-2.[12] The *S* configuration at C-2 of the isomer **3ja** was attributed on the basis of chemical correlation with compound **3ia**. Convergent reduction of (2*S*)-**3ia** and **3ja** to the same diol (−)-1-(2-hydroxy-4-*tert*-butylphenyl)-1,2-dihydroxyethane (**5a**) confirmed the 2*S* attribution of **3ja**.[13]

It is noteworthy that reduction with $NaBH_4$/LiCl[14] opens the way to the synthesis of optically pure polyhydric alcohols, which represent useful chiral ligands.

Finally, we have removed of the chiral auxiliary by hydrolysis of the esters **3** and **4** to give the corresponding acids **6** (Scheme 1). The diastereomer (2*S*)-**3ic**, easily purified by crystallization, was chosen as an example, since (*S*)-2-hydroxymandelic acid is reported to be dextrorotatory.[15]

Scheme 1. Removal of the Chiral Auxiliary



Unlike other hydroxy acids, e.g., 4-hydroxymandelic acid, the isolation of 2-hydroxymandelic acid is difficult, as recently stated[3c] and witnessed by conflicting analytical data.[15,16]

The hydrolysis was accomplished using LiOH in THF/H_2O,[17] which gave (+)-(*S*)-2-hydroxymandelic acid **6c** in high yield (92%) with concomitant recovery of (−)-menthol auxiliary. By this route, **3ia** afforded the corresponding acid (+)−(S)-**6a** in 90% yield.

We have checked the enantiomeric purity of the acid (+)−(*S*)-**6c** as well as of the diol **5a** via the de's of their Mosher derivatives[18] (see Experimental Section) and by HPLC chiral separation.[19] The hydrolysis and reduction procedures do not cause any racemization of the compounds.

The ^{1}H NMR spectra of the esters **3** and **4** exhibit an interesting feature. The benzylic methine signal in (−)-8-phenylmenthyl esters **3j** and **4j** is shielded in comparison with values observed for the corresponding (−)-

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(13) The stereochemical outcome is in agreement with the preferred *si*-face attack of the reagent **2j**.

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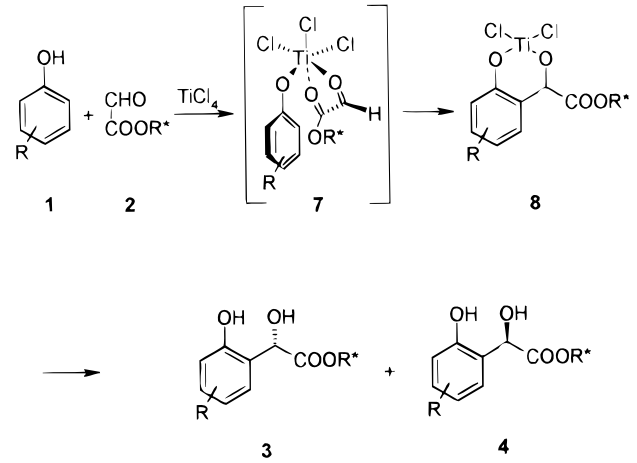
Scheme 2. Reaction Mechanism



menthyl derivatives **3i** and **4i**. In particular, significant upfield shifts are observed for the (2*S*)-**3j** isomers, being $\Delta\delta \sim 1.1$ ppm. These strong shieldings suggest a proximity to the phenyl group, as has been observed for similar compounds.[20] This is probably due to $\pi-\pi$ interaction between the phenyl moiety and the ester.[21]

Concerning the mechanism, on the basis of a large number of synthetic results,[1] NMR study[22] and more recently X-ray structure of a complex between phenoxymagnesium bromide and *p*-isopropylbenzaldehyde,[23] we have proposed the formation of an "oriented complex" between the reagent and the substrate (**7**), in which the metal plays a fundamental role, that accounts for the high *ortho* regioselectivity (Scheme 2). To rationalize the stereochemical outcome of the present reaction, we suggest that the reagent **2** coordinates the metal with both carbonyl groups, recognizing that nonbonded interactions are important for efficient chirality transfer. Other authors[6,9a] presented a chelation mechanism for reactions involving chiral glyoxylates and Lewis acids, which can account for the absolute stereochemistry of the products. However, there is no direct evidence for this chelation, except a photophysical study.[24] Here, we present the X-ray structure of a complex obtained as dark red crystals from the reaction mixture of 4-methoxyphenol (**1c**) and (−)-menthylglyoxylate (**2i**), carried out in the presence of $TiCl_4$ at room temperature in $Cl_2C{=}CCl_2$ as solvent.

The reaction of $TiCl_4$ with 4-methoxyphenol proceeded with spontaneous evolution of HCl to give the metal phenoxide that reacted with the glyoxylate **2i**.

The structure of the titanium complex **8** (Scheme 2, R = 4-OCH_3, R* = (−)-menthyl) is shown in Figure 1.[25] The complex exists in the solid state as a dimer in which both the diastereoisomers **3ic** and **4ic** are present. The titanium atoms show octahedral coordination with three

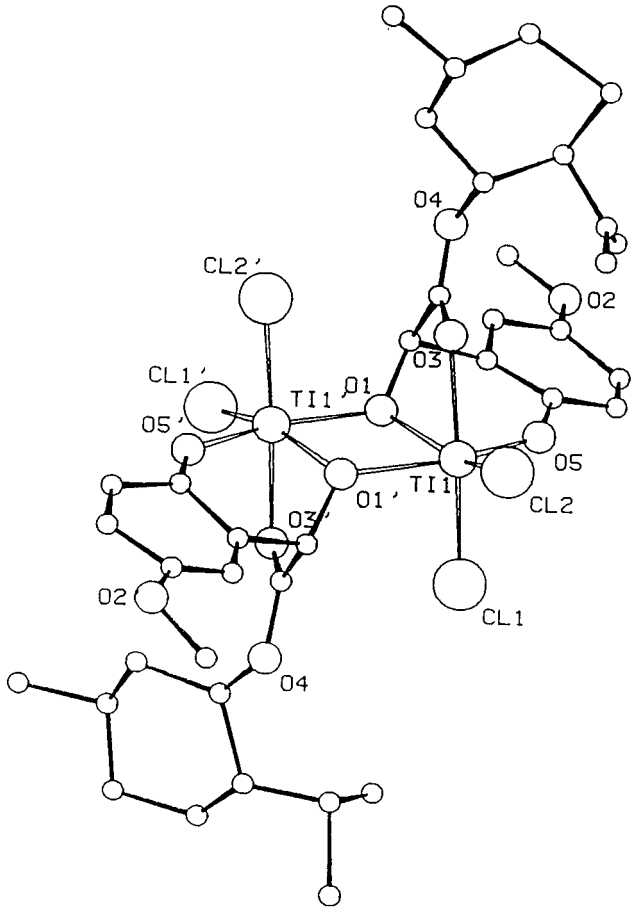


Figure 1. View of complex **8**.

oxygen and one chlorine atoms in the basal plane and with a second chlorine and a carbonyl oxygen in the apex positions. The chlorine atoms of each titanium adopt a *cis* orientation being Cl1 *trans* to the O2 carbonyl oxygen and Cl2 *trans* to the O1 benzylic atom.

On the basis of this crystal structure, we can state with confidence that the chiral glyoxylate can behave as a chelating ligand as drawn in Scheme 2, with both the oxygen atoms in the coordination sphere of titanium in the complex formed with the reaction product.

Complex **8** has some remarkable features. The alcohol functionality created in the reaction is present as a titanium alkoxide, giving a stable chelation complex that accounts for the absence of diphenylmethane[26] byproducts arising from further reaction of the benzylic alcohol. The distances between the metal and the benzylic oxygen atoms are in agreement with the calculated single covalent bond for Ti−O (2.01 Å), whereas the distances between the metal and the phenolic oxygen atoms are shorter, 1.785(2) and 1.834(2) Å, which indicates that there is some double-bond character between Ti and the phenolic oxygen atoms, as recently reported.[27] Moreover, the depicted structure of the titanium complex and the crystal structure of ester **4ic** confirm the preference for the (−)-menthyl esters to accommodate the axial methine hydrogen atom nearly coplanar and *syn* to the ester carbonyl.[1c,9a]

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Conclusions

We have presented the syntheses of optically active 2-hydroymandelic esters and acids via direct hydroxyalkylation of phenols with very high yields and diastereoselectivities (up to 96% de).

The reaction occurs with complete *ortho* regioselectivity with mono attack on the phenol ring, and no diphenylmethane derivatives are formed.

The hydrolysis and reduction of the products allow isolation of enantiomerically pure 2-hydroxymandelic acids **6** and 2-hydroxyphenyldiols **5**, respectively.

The crystal structure of the titanium complex represents strong support for the chelation mechanism presented for glyoxylate reactivity and supports our proposal for coordinated *ortho* alkylation of phenols.

Experimental Section

General Methods. Melting and boiling points are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz and at 400 MHz in the indicated solvents. ^{13}C NMR spectra were recorded at 25.18 MHz with proton decoupling. Mass spectra were obtained in EI mode. Microanalyses were carried out by Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica dell'Università degli Studi di Parma, Italy.

Diastereomeric excesses were determinated by reversed-phase HPLC using an octadecylsilyl column (ODS 5 μm) with methanol/water solvent system with UV detector at 280 nm. TLC analyses were carried out on Merck 60PF_{254} silica gel plates using mixtures of hexanes−ethyl acetates.

All reagents were commercial materials from freshly opened containers. Dichloromethane was stored over 4 Å molecular sieves. Glyoxylates esters were prepared by the reported methods.[6,9c,28]

(−)-Menthol was purchased from Carlo Erba. (−)-8-Phenylmenthol was synthesized from (+)-pulegone (from EGA-Chemie) following the reported procedure.[8]

Satisfactory microanalyses and spectroscopic data were obtained for all new compounds described.

Single-Crystal X-ray Diffraction Analysis of Complex 8. A prismatic crystal of approximately 0.09 × 0.11 × 0.14 mm was mounted in a glass capillary, sealed under nitrogen, and diffracted on a Siemens AED diffractometer using Cu Kα radiation with wavelength 1.5418 Å. The space group of this $C_{38}H_{52}O_{10}Cl_4Ti_2$ crystal was $P2_1$ with a = 10.928(3) Å, b = 27.371(4) Å, c = 8.374(3) Å, β = 98.92(4)°. Other crystal parameters were as follows: cell volume = 2474.46 Å^3, Z = 4, d_{calc} = 1.22 g cm^{-3}, and μ = 5.11 cm^{-1}. A total of 1750 reflections were collected in the 3−50° θ range, and 1695 were unique (R_{int} = 0.075). A decay of a check reflection, monitored periodically every 100 reflections, of about 54% was found during the data collection time. The effects of this decomposition were corrected, together with those for Lorentz and polarization effects, during the data reduction procedure,[29] and an empirical absorption correction was applied. This significant decomposition, the limited θ range, and the small dimensions of the available crystal affect the quality and quantity of experimental data. Use of the SIR97[30] package permits the structure solution and the definition of the molecular skeleton. The structure was refined by full-matrix least-squares methods using SHELX93[31] with the anisotropic thermal parameters only for titanium, chlorine, and oxygen atoms. Hydrogens were not located. Most of the atoms were found to have a considerable freedom of thermal motion, but any attempts to sharply elucidate the ordering of these atoms over two or more positions was limited by the quality of data. The final R factors for 309 refined parameters were 0.078 for 1036 reflections with $F_o > 4\sigma(F_o)$ and 0.105 for all 1695 data.

(2*S*)- and (2*R*)-2-Hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)ethanoic Acid (−)-Menthyl Esters (3ia and 4ia). Typical Procedure. To a solution of 3-*tert*-butylphenol (1.5 g, 10 mmol) in anhydrous CH_2Cl_2 (34 mL) was added at −30 °C 5.0 mL of a 1 M solution of $TiCl_4$ freshly prepared in anhydrous CH_2Cl_2, under a stream of dry nitrogen. After the mixture was stirred for 30 min, anhydrous (−)-menthyl glyoxylate (**2i**) (10 mmol) was added. Anhydrous (−)-menthyl glyoxylate (**2i**) was obtained as a viscous oil by heating the hydrate form (white solid) at 90 °C under high vacuum before use, and a CH_2Cl_2 solution, about 1 M, was prepared. The reaction mixture was stirred for 16 h at −30 °C, quenched with saturated aqueous ammonium chloride solution, and extracted with CH_2Cl_2 (3 × 70 mL). After the solution was dried (Na_2SO_4), the solvent was removed under reduced pressure, and **3ia** and **4ia** were separated from the residue by chromatography on silica gel using CH_2Cl_2 or hexane/ethyl acetate (80:20) to give 2.97 g (82% yield). HPLC analysis of the major isomer **3ia** showed the lower t_R.

Crystallization from hexane/CH_2Cl_2 afforded pure (2*S*)-**3ia**: colorless needles; mp 187−188 °C; $[\alpha]^{25}_D$ = −24.9 (*c* 0.4, CH_2Cl_2); IR (KBr) 1722 cm^{-1}; UV λ_{max} 278 nm (ϵ 2003); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.77 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H), 1.29 (s, 9H), 0.8−2.1 (m, 9H), 3.5 (br s, 1H), 4.80 (td, J = 10.8, 4.4 Hz, 1H), 5.28 (s, 1H), 6.91 (dd, J = 8.6, 1.9 Hz, 1H), 6.92 (d, J = 1.9 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 7.15 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.35, 20.69, 21.91, 23.42, 26.35, 31.20, 31.37, 34.05, 34.58, 40.23, 46.85, 72.26, 77.09, 114.67, 117.46, 119.58, 127.94, 153.54, 154.74, 172.81; MS *m*/*z* (rel intensity) 362 (9, M$^+$), 224 (20), 180 (100), 179 (38). Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.21; H, 9.30.

(2*R*)-4ia: mp 110−113 °C; $[\alpha]^{25}_D$ = −118 (*c* 0.7, EtOH); IR (KBr) 1723 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.45 (d, J = 6.9 Hz, 3H), 0.59 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 1.27 (s, 9H), 0.7−2.2 (m, 9H), 3.1 (br s, 1H), 4.67 (td, J = 10.8, 4.3 Hz, 1H), 5.23 (s, 1H), 6.88−6.92 (m, 2H), 7.0 (br s, 1H), 7.09 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.72, 20.53, 21.98, 23.09, 25.50, 31.25, 31.41, 34.12, 34.58, 40.66, 47.08, 72.67, 77.01, 114.32, 117.24, 119.99, 128.68, 153.54, 154.85, 172.96. MS *m*/*z* (rel intensity) 362 (40, M$^+$), 224 (29), 180 (100), 179 (73). Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.26; H, 9.20.

The following diastereomeric pairs of esters listed in Table 1 were prepared in a similar way:

2-Hydroxy-2-(2-hydroxy-5-methoxyphenyl)ethanoic acid (−)-menthyl ester ((2*S*)-3ib): white needles (hexane/CH_2Cl_2); mp 123 °C; $[\alpha]^{25}_D$ = −10.7 (*c* 0.4, EtOH); IR (KBr) 1725 cm^{-1}; UV λ_{max} 297 nm (ϵ 4818); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.76 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.2 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.7−2.1 (m, 9H), 3.68 (d, J = 3.6 Hz, 1H), 3.75 (s, 3H), 4.80 (td, J = 10.8, 4.3 Hz, 1H), 5.26 (d, J = 3.6 Hz, 1H), 6.7 (s, 1H), 6.7−7.0 (m, 3H); MS *m*/*z* (rel intensity) 336 (44, M$^+$), 198 (100), 152 (73). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.50; H, 8.19.

2-Hydroxy-2-(2-hydroxyphenyl)ethanoic acid (−)-menthyl ester ((2*S*)-3ic): colorless needles (hexane/CH_2Cl_2); mp 119−120 °C; $[\alpha]^{25}_D$ = +4.5 (*c* 0.8, EtOH); IR (KBr) 1719 cm^{-1}; UV λ_{max}277 nm (ϵ 3364); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.7−2.0 (m, 9H), 3.55 (d, J = 4.0 Hz, 1H), 4.80 (td, J = 10.9, 4.4 Hz, 1H), 5.30 (d, J = 4.0 Hz, 1H), 6.8−7.0 (m, 2H), 7.14 (s,1H), 7.20 (d, J = 8.5 Hz, 1H), 7.24 (d, J = 7.7, 1H); MS

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m/z (rel intensity) 306 (6, M^+), 168 (15), 123 (89). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.67; H, 8.90.

(2*R*)-4ic: colorless prismatic crystals from an enriched diastereomeric mixture in hexane/CH_2Cl_2; mp 122−123 °C; $[\alpha]^{25}_D = -144.7$ (*c* 0.6, EtOH); IR (KBr) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.48 (d, $J = 6.9$ Hz, 3H), 0.61 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.7−2.2 (m, 9H), 3.62 (d, $J = 3.0$ Hz, 1H), 4.69 (td, $J = 10.8$, 4.4 Hz, 1H), 5.26 (d, $J = 3.0$ Hz, 1H), 6.8−7.3 (m, 4H), 7.06 (s, 1H); MS *m/z* (rel intensity) 306 (5, M^+), 168 (24), 123 (100). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.76; H, 8.42.

(2*S*)-2-Hydroxy-2-(2-hydroxy-5-*tert*-butylphenyl)ethanoic acid (−)-menthyl ester (3id): white wooly needles from hexane/CH_2Cl_2; mp 159−160 °C; $[\alpha]^{25}_D = -8.8$ (*c* 0.7, EtOH); IR (KBr) 3520, 3300, 1703, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, $J = 7.0$ Hz, 3H), 0.85 (d, $J = 6.5$ Hz, 3H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.8−2.0 (m, 9H), 1.28 (s, 9H), 3.53 (d, $J = 4.5$ Hz, 1H), 4.79 (td, $J = 10.9$, 4.4 Hz, 1H), 5.33 (d, $J = 4.5$ Hz, 1H), 6.82 (d, $J = 8.5$ Hz, 1H), 7.04 (s, 1H), 7.17 (d, $J = 2.4$ Hz, 1H), 7.23 (dd, $J = 8.5$, 2.4 Hz, 1H); MS (CI) *m/z* (rel intensity) 362 (14, M^+), 224 (100), 207 (47), 179 (62). Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.10; H, 9.20.

(2*S*)- and (2*R*)-2-Hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)ethanoic Acid (−)-8-Phenylmenthyl Esters (3ja and 4ja). Typical Procedure. To a solution of 3-*tert*-butylphenol (**1a**) (0.75 g, 5 mmol) in anhydrous CH_2Cl_2 (17 mL) was added 5.0 mL of a freshly prepared 1 M solution of $TiCl_4$ in anhydrous CH_2Cl_2 at room temperature under nitrogen. After the mixture was stirred for 30 min, (−)-8-phenylmenthyl glyoxylate (**2j**) (obtained as a mixture of anhydrous and hydrate form) (1.53 g, 5 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 6 h at room temperature. Workup as above furnished a residue from which pure diastereomeric esters **3ja** and **4ja** were separated and purified by chromatography on silica gel using CH_2Cl_2 as eluent, 2.08 g (95% yield). HPLC analysis of the major isomer **3ja** showed the higher t_R.

(2*S*)-3ja: white solid; mp 60−62 °C; $[\alpha]^{25}_D = +19.2$ (*c* 0.8, EtOH); IR (KBr) 1730 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.80 (d, $J = 6.5$ Hz, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.25 (s, 9H, $(CH_3)_3$ C), 1.32 (s, 3H, CH_3), 0.7−2.2 (m, 8H), 3.22 (d, $J = 3.1$ Hz, 1H, OH), 4.14 (d, $J = 3.1$ Hz, 1H, *CH*OH), 4.91 (td, $J = 10.6$, 4.4 Hz, 1H, CHO), 6.67 (d, $J = 8.8$ Hz, 1H, H-6), 6.75−6.90 (m, 2H, H-3 and H-5), 6.94 (br s, 1H, OH), 7.1−7.4 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 21.59 (CH_3), 22.91 (CH_3), 26.20 (CH_2), 29.60 (CH_3), 31.15 ((CH_3)$_3$ and CH), 34.32(CH_2), 34.40 (C), 39.37 (C), 40.75 (CH_2), 50.19 (CH), 71.58 (CHOH), 76.23(CHO), 114.17 and 116.96 (C3 and C5), 119.34 (C), 125.32 (Ph), 128.10 (C6 and Ph), 151.80 (C), 153.07 (C), 154.50 (C), 172.34 (C); the assignment of signals between 21 and 50 ppm was established on the basis of DEPT experiments, and the peaks between 71 and 128 ppm were assigned on the basis of ^1H, ^{13}C 2D correlation in the ^1H decoupled version; MS *m/z* (rel intensity) 438 (7, M^+), 224 (33), 214 (11), 199 (12), 179 (71), 163 (13), 119 (80), 105 (100), 91 (44). Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.30; H, 8.41.

The following diastereomeric pairs of esters listed in Table 1 were prepared in a similar way:

(2*S*)-2-Hydroxy-2-(2-hydroxy-5-methoxyphenyl)ethanoic acid (−)-8-phenylmenthyl esters (3jb): $[\alpha]^{25}_D = +16.5$ (*c* 0.3, EtOH); ^1H NMR (200 MHz, $CDCl_3$) δ 0.78 (d, $J = 6.5$ Hz, 3H), 1.19 (s, 3H), 1.32 (s, 3H), 0.6−2.2 (m, 8H), 3.49 (d, $J = 4.0$ Hz, 1H), 3.71 (s, 3H), 4.09 (d, $J = 4.0$ Hz, 1H), 4.92 (td, $J = 10.6$, 4.4 Hz, 1H), 6.3−6.9 (m, 3H), 6.50 (s, 1H), 7.1−7.5 (m, 5H); MS *m/z* (rel intensity) 412 (2, M^+), 198 (75), 119 (82), 105 (100). Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 73.07; H, 8.03.

(2*S*)-2-Hydroxy-2-(2-hydroxy-5-chlorophenyl)ethanoic acid (−)-8-phenylmenthyl esters (3je): mp 63−66 °C; $[\alpha]^{25}_D = +26.5$ (*c* 0.4, EtOH); IR (KBr) 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.81 (d, $J = 6.4$ Hz, 3H), 1.18 (s, 3H), 1.31 (s, 3H), 0.6−2.3 (m, 8H), 3.4 (br s, 1H), 4.01 (s, 1H), 4.90 (td, $J = 10.7$, 4.3 Hz, 1H), 6.65 (d, $J = 2.6$ Hz, 1H), 6.70 (d, $J = 8.6$ Hz, 1H), 7.07 (dd, $J = 8.6$, 2.6 Hz, 1H), 7.15−7.5 (m, 6H); MS *m/z* (rel intensity) 416 (1, M^+), 119 (100), 105 (88). Anal. Calcd for $C_{24}H_{29}O_4Cl$: C, 69.13; H, 7.01; Cl, 8.50. Found: C, 69.00; H, 7.23; Cl, 8.25.

Reduction Procedure.[14] **(−)-1-(2-Hydroxy-4-*tert*-butylphenyl)-1,2-dihydroxyethane (5a).** To a solution of (2*S*)-**3ia** (0.36 g, 1 mmol) in anhydrous THF (8 mL) and absolute EtOH (12 mL) were added $NaBH_4$ (0.37 g, 10 mmol) and LiCl (0.42 g, 10 mmol), and the mixture was refluxed for 2 h with stirring, providing complete reduction. After being cooled to room temperature, the reaction was quenched with water and extracted with hexane (3 × 15 mL) in order to recover (−)-menthol. The aqueous phase was acidified with HCl 1 N to pH ∼3 and extracted with diethyl ether (3 × 30 mL). After the aqueous phase was dried (Na_2SO_4), the solvent was removed under reduced pressure and **5a** was purified by chromatography on silica gel using hexane/ethyl acetate (70:30) to give a white solid (0.16 g, 76%). Attempts to perform the reduction using $LiAlH_4$ in diethyl ether resulted in unselective reaction. The enantiomeric excess of compound (2*S*)-**5a** was determined by using MPTA (α-methoxy-α-trifluoromethylphenylacetic acid) derivatives.[18] ^1H NMR (400 MHz, $CDCl_3$) spectra of the corresponding Mosher monoester, formed by esterification of the primary alcoholic function, revealed that **5a** is enantiomerically pure. On the other hand, the (−)-MPTA derivative of enriched **5a** (de 50%) showed distinguishible signals for the two diastereoisomers: three dd at δ 4.49 and 4.56 for methylene hydrogens and δ 5.12 for methine proton of the major isomer and the corresponding three dd at δ 4.47, 4.58, and 5.13 of the minor isomer.

5a: white solid; mp 88−89 °C; $[\alpha]^{25}_D = +36$ (*c* 0.3, EtOH); IR (KBr) 3275, 1078, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 2.05 (br s, 1H), 3.15 (s, 1H), 3.8−3.9 (m, 2H), 4.94 (dd, $J = 7.5$, 4.9 Hz, 1H), 6.87 (dd, $J = 7.9$, 1.9 Hz, 1H), 6.92 (d, $J = 1.9$ Hz, 1H), 6.94 (d, $J = 7.9$ Hz, 1H), 7.92 (br s, 1H); MS *m/z* (rel intensity) 210 (20, M^+), 192 (27), 180 (100), 163 (50). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.20; H, 8.30.

Hydrolysis Procedure:[17] (+)-Hydroxy-2-(2-hydroxyphenyl)ethanoic Acid (6c). To a solution of **3ic** (0.61 g, 2.0 mmol) in THF/H_2O (2:1) (33 mL) was added $LiOH \cdot H_2O$ (0.25 g, 6.0 mmol) under nitrogen.

The solution was stirred at room temperature overnight, giving a complete hydrolysis. After addition of water, the reaction was extracted with hexane (3 × 30 mL). From the organic phase, after drying (Na_2SO_4) and solvent removal, (−)-menthol (0.30 g, 1.9 mmol, 97% yield) was recovered. The aqueous layer was acidified with 0.5 N HCl. After extraction with ethyl acetate (4 × 20 mL), drying (Na_2SO_4), and removal of the solvent under reduced pressure, crude **6c** was obtained as a viscous oil that became a sticky solid after warming in vacuo at 70 °C for 3 h (0.31 g, 92% yield): ^1H NMR (400 MHz, DMSO-d_6) 5.22 (s, 1H), 5.52 (br s, 1H), 6.75 (t, $J = 7.5$ Hz, 1H), 6.77 (d, $J = 8.1$ Hz, 1H), 7.07 (pseudo td, $J = 8.1$, 7.5, 1.5 Hz, 1H), 7.22 (dd, $J = 7.5$, 1.5 Hz, 1H), 10.9 (br s, 1H); MS *m/z* (rel intensity) 168 (12, M^+), 150 (21), 123 (46), 121 (100).

It was not possible to exactly measure the $[\alpha]_D$ value because the purification on silica gel (using CH_2Cl_2/MeOH 80:20) resulted in product transformation (probably polymerization[3c]) giving a white solid, insoluble in ether and $CDCl_3$,that shows a methine signal in ^1H NMR (DMSO) at lower δ (4.7 ppm); this material decomposed without melting. However, polarimetric measurement revealed that **5c** is dextrorotatory ($[\alpha]^{25}_D = +118.8$ (*c* 0.5, EtOH)), as expected for the 2*S* configuration.[15]

The enantiomeric excess of compound **6c** was determined directly by HPLC chiral separation or, after esterification with diazomethane, by Mosher ester analysis. Reaction of crude **6c** (84 mg, 0.5 mmol) in anhydrous Et_2O (8 mL) with diazomethane at 0 °C for 4 min gave quantitatively the methyl ester **9c**. The enantiomeric excess of compound **9c** was determined using MPTA derivatives.[18] Reversed-phase HPLC analysis of the (−)- and (+)-MPTA diester **10** revealed that the ee of **9c** is > 99%. ^1H NMR (300 MHz, $CDCl_3$) spectra confirmed this result; indeed, the benzylic methine peaks for the (−)- and (+)-MPTA derivative are easily distinguishible at δ 6.27 and 6.17 ppm, respectively. **9c**: viscous oil that solidified on standing overnight; mp 65−67 °C;[3c] $[\alpha]^{25}_D =$

+127.2 (*c* 0.2, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.6 (br s, 1H), 3.79 (s, 3H), 5.33 (s,1H), 6.88 (d, J = 8.0 Hz, 1H), 6.91 (td, J = 7.5, 1.1 Hz, 1H), 7.1 (br s, 1H), 7.15−7.3 (m, 2H); MS *m*/*z* (rel intensity) 182 (82, M^+), 123 (100).

(+)-Hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)ethanoic Acid (6a). The acid **6a** was prepared by hydrolysis of the ester **3ia** (0.72 g, 2.0 mmol). The acidified aqueous layer was extracted with diethyl ether (4 × 20 mL), giving pure hydroxy acid **6a** (0.40 g, 90% yield) as a white solid: mp 89−92 °C, 97−98 °C when dehydrated by warming in vacuo at 70 °C; $[\alpha]^{25}_D$ = +113.1 (*c* 0.5, EtOH); IR (KBr) 3350, 1729, 1248, 1062 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (s, 9H), 5.19 (s, 1H), 5.42 (br s, 1H), 6.77−6.84 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 9.27 (br s, 1H), 12.22 (br s, 1H); MS *m*/*z* (rel intensity) 224 (26, M^+), 179 (100), 163 (18). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 63.9; H, 7.5.

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Supporting Information Available: X-ray crystallographic data for complex **8** and a crystal structure with the labeling scheme. ^{1}H NMR spectral data for all compounds reported (**3**−**6**, **9**). This material is available free of charge via the Internet at http://pubs.acs.org.

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