Title
P-Cresol methylhydroxylase

Permalink
https://escholarship.org/uc/item/2xv2201k

Author
Everhart, Edwin Thomas

Publication Date
1990

Peer reviewed|Thesis/dissertation

p-Cresol Methylhydroxylase: Mechanism and Stereochemistry

by

Edwin Thomas Everhart

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of
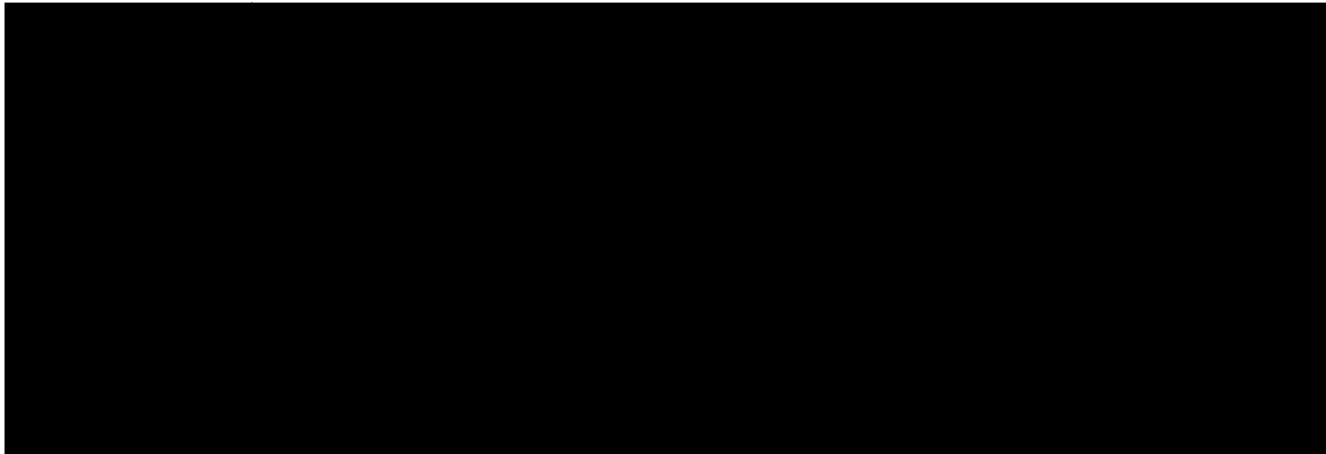
DOCTOR OF PHILOSOPHY

in

Pharmaceutical Chemistry

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

San Francisco

. . . .
Date   . University Librarian

MAR 25 1990

Degree Conferred: . . . .

"Tell me one more time so that I'll understand.

Are you sure Hank done it this way?

Did Hank really do it this way?"

Waylon Jennings

Dedication

To Harold and Anita, who gave me love, encouragement and refuge
from what sometimes seemed like an isolated and impersonal existence.

Acknowledgements

I would like to thank Dr. John Craig for providing me with the opportunity to work in his laboratory and complete this project. His enthusiasm and encouragement, without which this study could not have been brought to a successful conclusion, is deeply appreciated.

Particular thanks go to Dr. Steve Kahl for helpful and interesting discussions about boron chemistry and life, and Dr. Neal Castagnoli for helping to guide me through my orals. Dr. John Cashman took special interest in my progress, and his friendship has been especially valuable in helping me gain a sense of perspective. Dr. George Kenyon provided helpful advice and gentle prodding on thesis preparation.

I spent many a long evening in lab in the company of Drs. Vince Powers and Steve Torkelson. Vince was a valuable resource for information about enzymology and molecular biology, and provided critical appraisal of my ideas about mechanism. I think that I even managed to exorcise him of his demonic Dodger-Blue fanaticism in favor of the orange and black of the "Humm Babies".

Steve Torkelson's knowledge and expertise in synthetic chemistry was critical to my success, and we spent many pleasurable hours in the company of Perry Mason, Theodore Cleaver and Eliott Ness, not to mention Moe Howard, Larry Fine and Curly Howard.

Finally, I would like to thank Dr. Patsy Babbitt for her friendship and helpful attempts to increase my knowledge of molecular biology.

p-Cresol Methylhydroxylase: Mechanism and Stereochemistry

p-Cresol methylhydroxylase (PCMH), a flavocytochrome c from *Pseudomonas putida*, is an $\alpha_2\beta_2$ tetramer with flavoprotein subunits of $M_r \sim$ 49,000 and cytochrome subunits of $M_r \sim$ 8,500. PCMH catalyzes the hydroxylation of p-cresol to p-hydroxybenzyl alcohol and thence to p-hydroxy-benzaldehyde. The enzyme is not a monooxygenase and requires an electron acceptor rather than a donor. Incubation of p-cresol with PCMH in water enriched in ^{18}O results in p-hydroxybenzyl alcohol containing the theoretical amount of ^{18}O in the benzylic position, supporting a mechanism involving dehydrogenation of the substrate to a quinone methide followed by hydration to the alcohol. A second dehydrogenation followed by tautomerization would yield the aldehyde.

When the more loosely-bound substrate 4-ethylphenol is incubated with PCMH, 1-(4-hydroxyphenyl)ethanol is formed, as is 4-hydroxyacetophenone, although at a rate approximately two orders of magnitude slower than the alcohol. The 1-(4-hydroxyphenyl)ethanol has been shown to consist of $\geq$ 97% of the S-(–)-enantiomer.

To probe the stereochemistry of the dehydrogenation/hydration steps, RS-, R-(+)- and S-(–)-1-(4-hydroxyphenyl)ethane-1-d$_1$ were synthesized. The racemic and S-(–)-stereoisomers were obtained by treatment of RS- and R-(+)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$, respectively, with methanesulfonyl chloride, followed by displacement with lithium aluminum hydride and cleavage of the protecting group. The R-(+)- and S-(–)-enan-

tiomers were prepared by treatment of S-(–)- and R-(+)-ethyl-1-d$_1$ methanesulfonate, respectively, with the cuprate(I) derived from copper(I) t-butylacetylide and 4-methoxyphenyllithium in ether/THF, followed by cleavage of the methyl ether.

Incubation of RS-, R-(+)- and S-(–)-1-(4-hydroxyphenyl)ethane-1-d$_1$ with PCMH in steady-state kinetic assays revealed the kinetic isotope effects to be identical, showing the hydrogen-abstraction process to be non-stereoselective. The stereoselectivity observed in the hydroxylation is therefore due solely to the stereoselective hydration of the quinone methide intermediate.

R-(+)- and S-(–)-1-(4-hydroxyphenyl)ethanol and their deuterium-labeled analogs were obtained by either asymmetric reduction or classical resolution. The compounds were incubated with PCMH in stopped-flow and steady-state kinetic assays.

Table of Contents

xi

List of Figures

List of Tables

Introduction

Chapter I

p-Cresol methylhydroxylase

p-Cresol methylhydroxylase (PCMH) , a flavocytochrome c from *Pseudomonas putida*, catalyzes the hydroxylation of p-cresol to p-hydroxy-benzyl alcohol and the further oxidation of p-hydroxybenzyl alcohol to p-hydroxybenzaldehyde.[1-3] The enzyme is not a monooxygenase and requires an electron acceptor rather than a donor.[1] It was shown that cell extracts of *Pseudomonas putida* N.C.I.B. 9866, grown on 2,4-xylenol, catalyze the hydroxylation of p-cresol under anaerobic conditions when phenazine methosulfate (PMS) is employed as the electron acceptor, and that a similar activity converts p-hydroxybenzyl alcohol into p-hydroxybenzaldehyde.[1] Incubation of each substrate with the purified enzyme indicated that p-cresol methylhydroxylase is responsible for both activities, with acceptor reduced/substrate oxidized ratios of 2/1 for p-cresol and 1/1 for p-hydroxybenzyl alcohol.

Incubation of p-cresol with p-cresol methylhydroxylase from *Ps. putida* N.C.I.B. 9866 in water enriched with $H_2^{18}O$ resulted in the production of p-hydroxybenzyl alcohol, which was shown by mass spectrometry to contain the theoretical amount of ^{18}O incorporation in the benzylic position.[4] This result supported a mechanism for the hydroxylation of p-cresol involving dehydro-genation of the substrate to a quinone methide followed by hydration of the intermediate to the alcohol.[1] A second similar dehydrogenation followed by tautomerization would yield the aldehyde. The physiological importance of the latter reaction is not clear, since the cells also contain an NAD+-linked 4-hydroxybenzyl alcohol dehydrogenase.[2]

Subsequent studies[3,5] with two different p-cresol methylhydroxylases from *Pseudomonas putida* N.C.I.B. 9869: PCMH A from cells grown on 3,5-

xylenol and PCMH B from cells grown on p-cresol, showed that these enzymes only metabolize compounds with an alkyl or 1-hydroxyalkyl group para- to a phenolic hydroxyl group.

Treatment of *Ps. putida* N.C.I.B. 9869 cells grown on 3,5 xylenol and p-cresol, respectively, and Ps. putida N.C.I.B. 9866 cells grown on p-cresol, with EDTA and lysozyme indicated that the PCMH enzymes are located in the periplasmic space of the bacteria.[6] For strain N.C.I.B. 9869, this finding is in accord with the suggestion that the physiological acceptor for the enzyme is azurin,as this too was shown to be located mostly in the periplasm. It has been shown that azurin, a small, copper-containing protein, will accept electrons from the p-cresol methylhydroxylase and will also link electron flow to membranes resulting in O_2 uptake.[7]

The prosthetic group of the flavoprotein subunit of p-cresol methyl-hydroxylase is a covalently-linked 8α-(O-Tyrosyl)-FAD.[8,9] A pure flavin-decapeptide has been isolated from peptic digests of PCMH. The peptide shows the typical three-banded spectrum of flavins, with the second absorption peak shifted hypsochromically to 360 nm. Aminopeptidase digestion gave an aminoacylflavin, with a further shift of the second band to 352 nm at neutral pH.[8] This type of shift is usually taken as evidence that the covalent bond is on the 8α-carbon of the isoalloxazine ring system.[10] The dinucleotide nature of the flavin was indicated by a major change in mobility in thin-layer chroma-tography on treatment of the peptide with nucleotide pyrophosphatase and a further change on subsequent dephosphorylation with alkaline phosphatase.[8]

The flavin peptide, at the dinucleotide or mononucleotide level, showed negligible fluorescence (< 2% of that of riboflavin) in the pH range of 3 to 7. Oxidation with performic acid at 40°C increased the fluorescence to 40% of that of riboflavin.[8]

3

Dansylation of the flavin peptide followed by acid hydrolysis yielded N-dansyltyrosine, indicating that tyrosine in the peptide contains a blocked phenolic-hydroxyl group. Brief hydrolysis of the flavin peptide with amino-peptidase M gave an aminoacyl flavin which contained riboflavin and tyrosine in equal amounts. 8α-(O-Tyrosyl)-FAD is the NH_2-terminal residue of the peptide. Non-covalent interactions between the flavin and the tyrosine, as well as a tryptophan residue, seem to be responsible for the virtually complete quenching of the fluorescence.[8] Synthesis of 8α-(O-tyrosyl)riboflavin gave a product which comigrated with the (aminoacyl)riboflavin isolated from PCMH, and both showed identical absorption and fluorescence spectral properties.[9] The amino acid sequence of the flavin peptide from strain 9866 was shown to be

FAD-Tyr-Asn-Trp-Arg-Gly-Gly-Gly-(Gly, Ser, Met).

While the amino acid sequence has not been determined for the two peptides from strain 9869, the similarity of their amino acid compositions with that of the flavin peptide from strain 9866, and the presence of 8α-(O-tryosyl)-FAD, suggest that the flavin sites are identical in the three peptides.[9]

8α-(O-Tyrosyl)riboflavin, as well as the flavin-containing decapeptide from PCMH, undergoes reductive cleavage to form riboflavin and FAD, respectively, on anaerobic treatment with dithionite. In contrast, the native enzyme, on reduction with dithionite, yields a reduced flavin via a red, anionic-flavosemiquinone intermediate which remains covalently bound to the protein even under denaturing conditions.[9] Cleavage of the flavin peptide was rationalized by the following scheme:
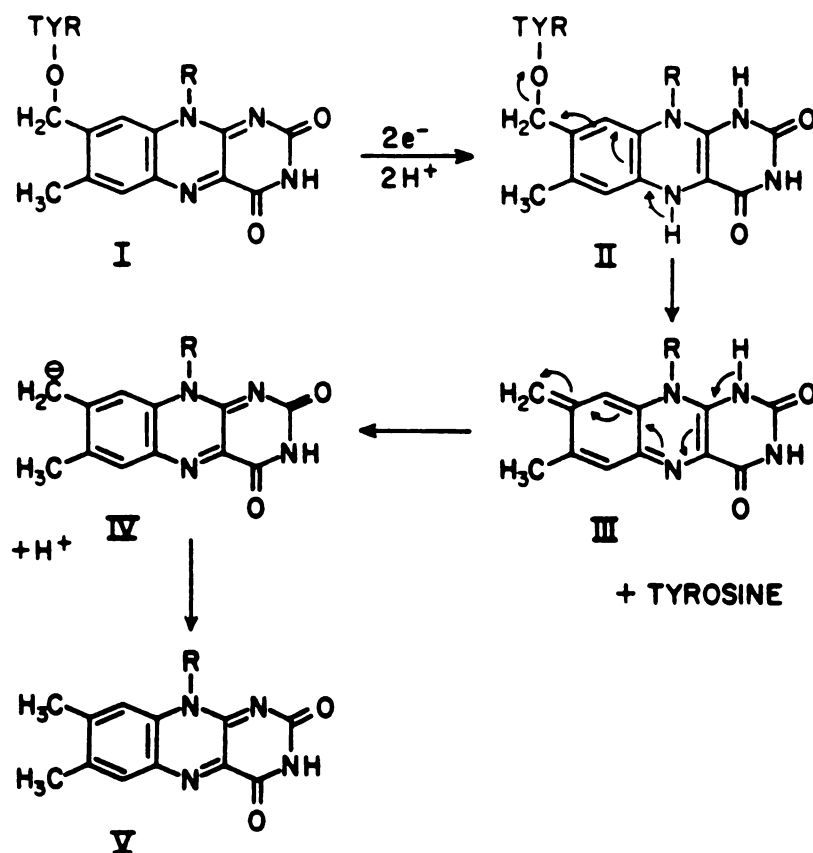
Flavin-peptide cleavage scheme.[9]

P-Cresol methylhydroxylase form A from *Ps. putida* strain 9869 has a molecular weight of 115,000.[3] It can be resolved by isoelectric focusing into two components.[11,12] One contains FAD covalently attached through the 8α-position to a tyrosine; the other contains a covalently-bound heme. The protein was originally thought to be a dimer with subunits of approximately equal size on the basis of ultracentrifugation and polacrylamide-gel electrophoresis experiments.[3] X-ray structural analysis at 6 Å resolution, however, revealed the enzyme to be an $\alpha_2\beta_2$ tetramer with flavoprotein subunits of $M_r \sim 49,000$ and cytochrome subunits of $M_r \sim 8,500$.[13] The flavoprotein subunits are tightly packed about the molecular 2-fold axis, whereas the cytochrome subunits are located on the outside of the molecule, each in a depression on the surface of a

5

flavoprotein subunit. Each cytochrome subunit is oriented with its heme group facing the flavoprotein subunit and located approximately at the center of the interface region. The area of the interface between the cytochome and flavoprotein subunits, estimated from a balsa wood model, is about half that of the interface between the flavoprotein subunits, explaining in part the tight association of the complex. The molecular weight of the native flavoprotein subunit was found to be about 100,000 on HPLC analysis, using an SK-3000 gel, showing that it exists in solution solely as a dimer.

Titration of the hydroxylase in solution with p-cresol results in the successive formation of three distinct products: reduced cytochrome-oxidized flavin, reduced cytochrome-flavin semiquinone and reduced cytochrome-flavin hydroquinone.[5] Each successive product differs by one electron, even though the substrate is an obligatory two-electron donor. This implies that single-electron transfer events between separate active sites occur during substrate oxidation. The $\alpha_2\beta_2$-tetrameric nature of the enzyme allows such intersubunit electron transfer to occur sufficiently fast that only transient intermediates between the three products can be detected.

Titration of the isolated flavoprotein subunit with p-cresol proceeds without formation of the anionic-flavin radical, i.e., only dihydroflavin is formed. This result implies that a mechanism whereby substrate can contribute one electron at a time to the flavin (a substrate-radical mechanism) cannot explain the appearance of the flavin radical in the flavocytochrome. Additionally, during stopped-flow experiments involving the flavoprotein reduction by p-cresol, no flavin radical was detected, again indicating the absence of a substrate-radical mechanism.[14]

Laser-flash photolysis studies of PCMH have been conducted, from which the rate of electron transfer from the initially-formed, neutral flavin-

semiquinone radical to the oxidized-heme moiety of the native enzyme has been calculated.[15] The anionic flavin-semiquinone radical formed during the steady-state titration of the enzyme appears to be formed by the slow deprotonation of the initially-formed, neutral radical.

The X-ray crystal structure of the flavocytochrome has been refined to a resolution of 3.5 Å.[16]

p-Cresol methylhydroxylase has been resolved into its component subunits and reconstituted with complete restoration of catalytic activity.[11,12] This is the first-reported instance of the reversible resolution of a flavo-cytochrome. The isolated flavoprotein subunit retains 2% of the catalytic activity of the holoenzyme in the p-cresol-PMS assays, while the K_m for p-cresol remains substantially unaltered during the cycle of dissociation and recombination.[5,14] In stopped-flow studies, reduction of the flavoprotein by p-cresol is at least an order of magnitude slower than the corresponding reaction in the flavocytochrome.[14] It is therefore likely that one of the functions of the cytochrome is to modulate the reactivity of the flavoprotein.

The redox potential of the isolated cytochrome subunit is +197 mV while the redox potential of the cytochrome in the intact flavocytochrome is + 248 mV.[17] Combination of the subunits to form PCMH entails a small but measurable change in the absorption spectra of the component proteins.[17]

PCMH enzymes from Ps. putida N.C.I.B. 9866 and 9869 (form A) and Ps. alcaligenes N.C.I.B. 9867 were resolved into their component subunits and then reconstituted to yield the nine possible hybrids.[17] The steady-state kinetic parameters and dissociation constants for the hybrids were determined, as well as the dissociation constant for PCMH form B from Ps. putida N.C.I.B. 9869, which cannot be resolved by isoelectric focusing.

The amino acid sequence of the cytochrome subunit of PCMH from *Ps. putida* N.C.I.B. 9869 (form A) has been determined and the sequence of the flavoprotein subunit partially determined.[18]

Bisubstrate-kinetic analysis of the unresolved enzyme from *Ps. putida* N.C.I.B. 9869 (form A) gives parallel-line kinetics in double-reciprocal plots, whereas the reaction of the separated flavoprotein subunit with substrates is described by converging lines[5], indicating a change in kinetic mechanism on removal of the cytochrome subunit.[11] The data were interpreted in terms of a ping-pong mechanism for the unresolved enzyme. Steady-state isotope effects for the flavoprotein subunit, incubated with p-cresol-α,α,α-d$_3$ and PMS at different concentrations of the nonvaried substrate, have been interpreted in terms of a random-binding mechanism.[19] The dependence of activity on pH and ionic strength was also investigated for both the unresolved enzyme and the separated flavoprotein subunit.[5]

Steady-state and stopped-flow kinetic studies for the reaction of the flavocytochrome from *Ps. putida* 9869 (form A) and the flavoprotein subunit with the reducing-substrates (S) p-cresol, 4-ethylphenol and their corresponding α-deuteriated analogs have been performed.[19] The results from the experiments with the flavocytochrome involving various reoxidizing substrates support the proposed apparent ping-pong mechanism. With phenazine methosulfate (PMS) as the reoxidant for studies at pH 7.6 and 6°C or 25°C, the isotope effects on k_{cat} are lower than the intrinsic isotope effect. The values for $^D(k_{cat}/K_s)$ are equal to the intrinsic effect for p-cresol at 25°C and for 4-ethylphenol at both 6 and 25°C. However, the value for this steady-state parameter at 6°C for p-cresol is lower than the intrinsic effect. The values for $^D(k_{cat}/K_{pms})$ are nearly equal to 1.0 under all conditions.

The stopped-flow kinetic studies indicate that at pH 7.6 the intrinsic isotope effect ($^Dk_2$) for the reduction of the enzyme by 4-ethylphenol is 4.8-5.0 at 25°C and 4.0 at 6°C. This technique yields a value for $^Dk_2$ of 7.05 at 6°C and pH 7.6 for p-cresol. The combined results from the stopped-flow and steady-state kinetic experiments at pH 7.6 and 6°C for p-cresol allow the calculation of several important kinetic parameters for this enzyme.

The average apparent steady-state isotope effect $^D(V/K_s)$ for the reduction of the flavoprotein subunit with p-cresol is 7.31.

The chemical and stereochemical course of the oxidation of 4-ethylphenol and other 4-alkylphenols by p-cresol methylhydroxylase have been studied.[20,21] Incubation of PCMH from *Ps. putida* N.C.I.B. 9869 (form A) with 4-ethylphenol results in the production of 1-(4-hydroxyphenyl)ethanol, 4-hydroxyacetophenone and 4-vinylphenol. The mechanism for the oxidation of 4-ethylphenol by PCMH is given by:

Mechanism 1

9
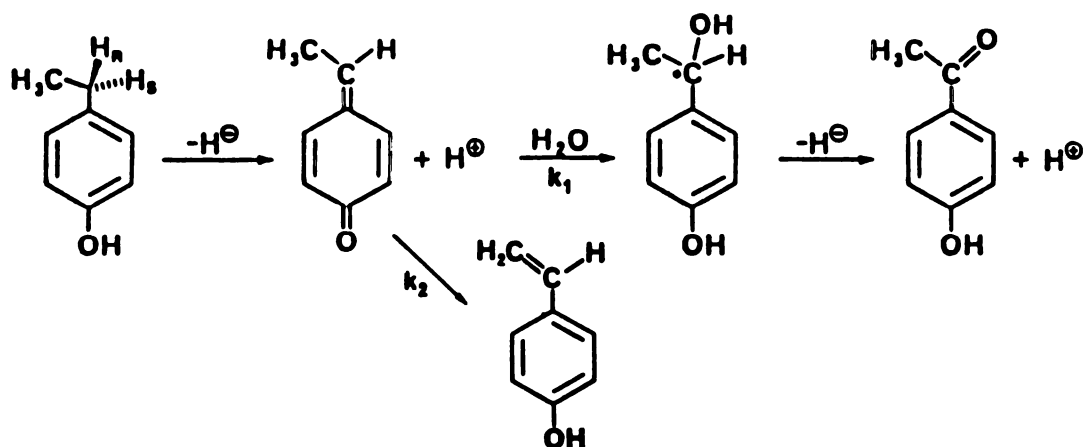
The time-course for the reaction of 4-ethylphenol with PCMH at room temperature and pH 7.6, employing horse-heart cytochrome c as the electron acceptor and cytochrome oxidase as the reoxidant for the cytochrome c, is given in Figure 1.[21] Notice that only 1/3 of the 4-ethylphenol is oxidized. Preliminary studies indicate that the accumulating 4-vinylphenol is a competitive inhibitor for this reaction.[21]
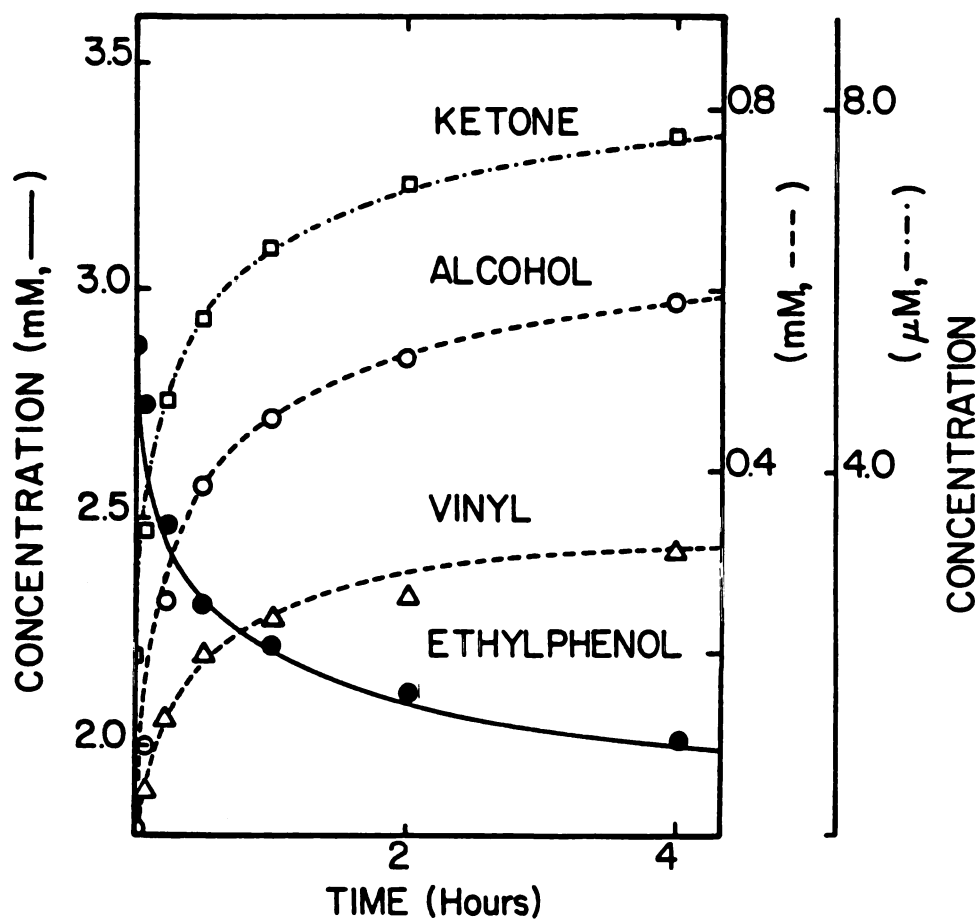
Time-course for the reaction of 4-ethylphenol with PCMH.[21]

Fig. 1

The enzymically-produced 1-(4-hydroxyphenyl)ethanol was quantitatively isolated, purified and shown to be > 97 % of the S-isomer.[21] This is in sharp contrast to the 70 % S-isomer found previously in a study employing phenazine methosulfate as the reoxidant and carried out at pH 9.5.[20]

The reaction of R,S-1-(4-hydroxyphenyl)ethanol with the enzyme was also monitored (Fig. 2).[21] The more rapid oxidation of the S-isomer progressively enriches the alcohol in the R-isomer; however, a large amount of ketone would need to be formed for this to significantly alter the enantiomeric purity of the alcohol. As seen in Fig. 1, the ketone is formed at about 1 % of the concentration of the alcohol when PCMH and 4-ethylphenol are incubated.
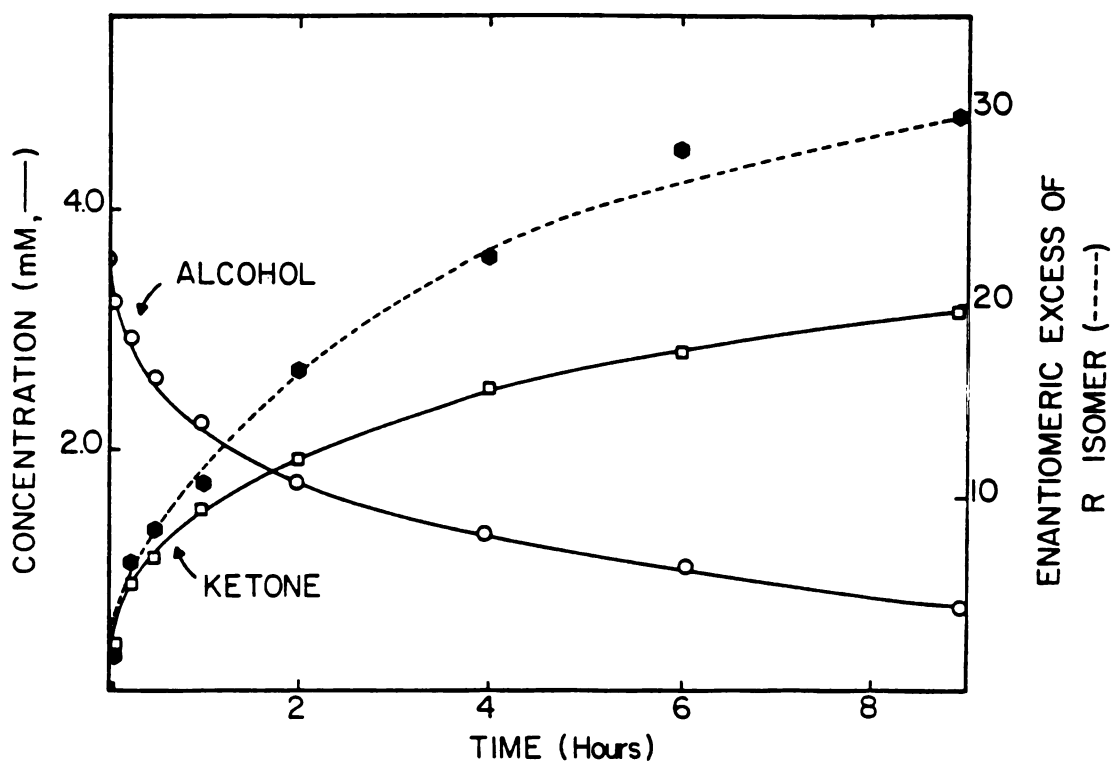
Time-course for the reaction of RS-1-(4-hydroxyphenyl)ethanol with PCMH.[21]

Fig. 2

In order to explain the formation of both 4-vinylphenol and 1-(4-hydroxy-phenyl)ethanol from 4-ethylphenol, two mechanisms were considered: the common-intermediate pathway given by Mechanism I and the parallel pathway given by Mechanism 2.[21]

enzyme + 4-ethylphenol $\longrightarrow$ $\nearrow \rightarrow \rightarrow$ alcohol [P_1]

$\searrow \rightarrow \rightarrow$ 4-vinylphenol [P_2]
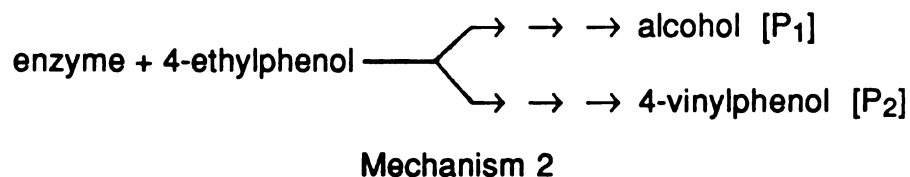
Mechanism 2

For I, the ratio [P_1]/[P_2] = k_1/k_2 and for II it is equal to v_1/v_2 = (V_1/K_1)[S_1]/(V_2/K_2)[S_2], where $S_1 = S_2$ = 4-ethylphenol.[22] The value for [P_1]/[P_2] was found to be invariant from 0.1 to 3.4 µM 4-ethylphenol, as predicted by either mechanism.[21] A value of 2.11 ± 0.08 was measured for this ratio. When 4-ethylphenol-α,α-d_2 and 4-ethylphenol-β,β,β-d_3 were substrates, the ratios were 2.53 ± 0.05 and 4.05 ± 0.13, respectively (Fig. 3).[21]
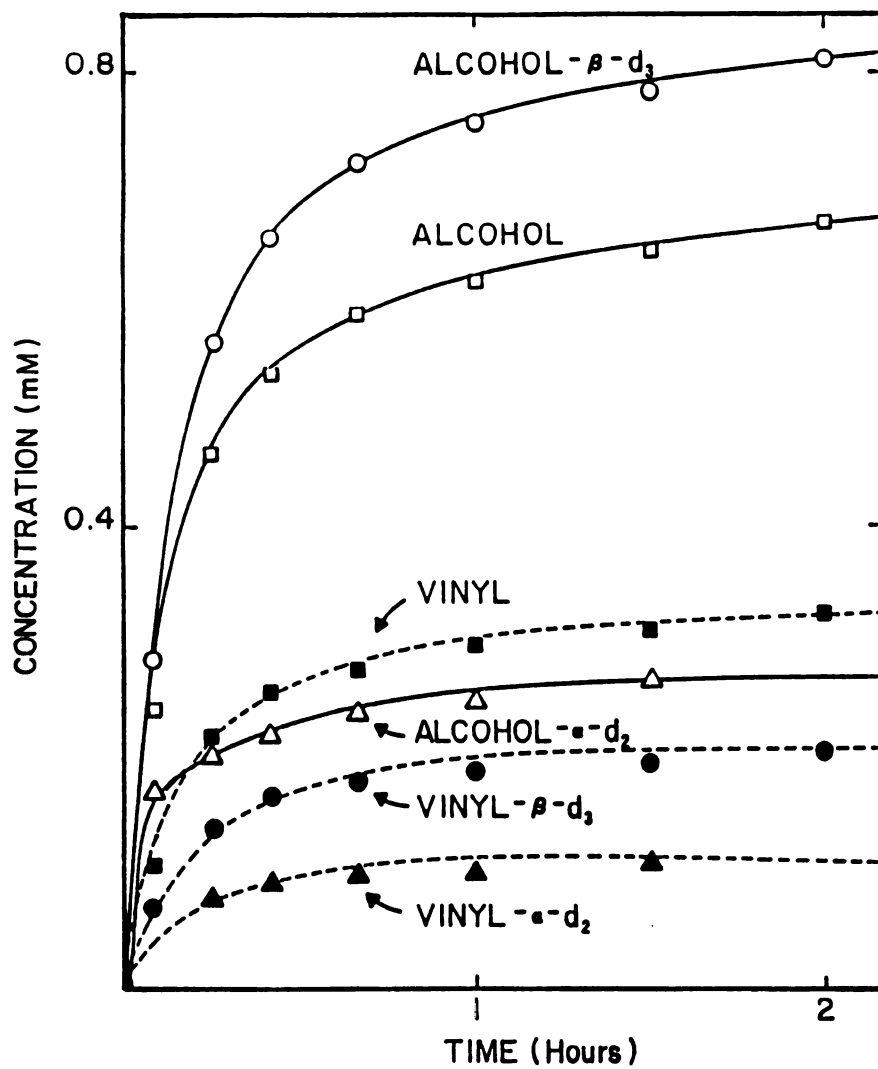
Products of the reaction of labeled and unlabeled 4-ethylphenol with PCMH as a function of time.[21]

Fig. 3

The alteration of the alcohol/vinyl ratio as a function of deuterium substitution is qualitatively in agreement with what would be expected if Mechanism I were operative.

13

In the case of 4-ethylphenol-α,α-d_2, an inverse secondary kinetic isotope effect would be expected in the hydration of the quinone methide since the carbon atom bearing the deuterium changes its hybridization from sp^2 to sp^3.[23] Tautomerization of the quinone methide to 4-(vinyl-1-d_1)phenol does not involve a change in hydridization, and consequently one would expect a slight increase in the ratio of alcohol/vinyl compounds produced, which is what is observed.

With 4-ethylphenol-β,β,β-d_3, a primary and a secondary kinetic isotope effect would be expected in the tautomerization of the quinone methide since both abstraction of a deuteron from the β-carbon atom and rehybridization of the atom from sp^3 to sp^2 are involved. However, hydration of the quinone methide should be little affected, and again one would expect an increase in the ratio of the alcohol/vinyl compounds, with the increase larger than that observed with the α,α-d_2 substrate. Again, this is exactly what is observed.

Steady-state and stopped-flow analysis indicated that the V/K ratio is not sensitive to any process following the removal of the α-hydrogen.[14] Therefore, if the chemistries of hydrogen-abstraction for the two branches of Mechanism 2 are similar, the $[P_1]/[P_2]$ ratio should be little affected by the deuterium-labeled substrates.[21] In contrast, k_1 and k_2 in Mechanism I should be differentially sensitive to isotopic substitution and the ratio should change. The results offer evidence in favor of Mechanism I.

The results of experiments investigating the interconversion of 1-(4-hydroxyphenyl)ethanol and 4-vinylphenol with reduced PCMH under argon are also compatible with Mechanism I and not Mechanism 2.[21]

The generality of the reaction was also investigated with 4-n-propyl-phenol, 4-isopropylphenol, 6-hydroxytetralin and 5-indanol as substrates.[21]

The electrochemical oxidation of p-cresol has been effected enzymatically, employing p-cresol methylhydroxylase with azurin or ferroceneboronic acid as the electron acceptor for the enzyme and mediator of the anodic reaction.[24] p-Hydroxybenzaldehyde was the only product isolated.

The experiments with azurin demonstrated that the ability to stimulate the direct electrochemical response of a redox protein can be exploited to couple an electrochemical device, through the redox protein, to the catalytic activity of an enzyme.

Ferroceneboronic acid was exploited to develop a bulk electrosynthetic system in which there is rapid conversion of p-cresol into p-hydroxybenzaldehyde by a catalytic quantity of the enzyme under mild conditions (pH 7.6, 30°C).

To date, seven forms of the enzyme have been isolated from six bacterial sources: *Pseudomonas putida* N.C.I.B. 9866 and 9869, the latter of which produces the so-called A and B forms under growth conditions of 3,5-xylenol or p-cresol as the carbon source, respectively; *Pseudomonas alcaligenes* N.C.I.B. 9867, *Pseudomonas testosteroni* N.C.I.B. 8955 and an *Alcaligenes* species. A preliminary comparison of the protein chemistry of these enzymes has been given.[14] The seventh form of the enzyme has been isolated from an anaerobic, p-cresol-utilizing, denitrifying bacterium, PC-07.[25] However, the enzyme activity is also present and stable in aerobically-prepared extracts of aerobically-grown PC-07 cells, and exhibits a similar elution profile during protein purification and an identical substrate range and affinity (e.g., K_m). Preliminary results with the azurin shown to be the natural electron acceptor for PCMH in aerobic *Pseudomonas* strains[6,7] indicate that the protein from aerobic strains is not the natural electron acceptor for the PC-07 PCMH.[25]

15

A PCMH-type of enzyme has been isolated from *Pseudomonas putida* JD1, a bacterium capable of growth on 4-ethylphenol.[26] The enzyme catalyzes the conversion of 4-ethylphenol to 1-(4-hydroxyphenyl)ethanol and thence to 4-hydroxyacetophenone, and is probably better adapted for substrates with larger side chains than those enzymes previously studied.

Another enzyme shown to function via the production of a quinone methide intermediate is cuticular polyphenol oxidase, a chitin-bound tyrosinase from *Sarcophaga bullata*.[27] Cuticular PPO plays a key role in the sclerotization of arthropod cuticle.[28] Sclerotization had been generally visualized as a process involving covalent-coupling of enzymatically-generated quinones with structural proteins.[29,30] Cuticular PPO was believed to catalyze the conversion of catechols to quinones for this process.[30,31] However, incubation of cuticular PPO with 4-alkyl-substituted catechols, with the exception of 4-methylcatechol, failed to produce the characteristic quinone UV spectra (λ_{max} 400 nm) generated by incubation of mushroom tyrosinase with the same substrates.[27] All 4-alkylcatechols yielded side-chain hydroxylated products, consistent with the initial formation of a quinone methide intermediate followed by hydration. *In vivo*,the quinone methides generated would be expected to react with the histidyl and lysyl residues that are abundant in cuticle.

Incubation of cuticular PPO with N-acetyldopamine resulted in the production of racemic N-acetylnorepinephrine.[27] So in this case, the enzymatic hydroxylation catalyzed by cuticular PPO is a non-stereoselective process. It was demonstrated that side-chain hydroxylation as a consequence of dopamine-ß-hydroxylase activity is very unlikely.

With the preceding background in mind, we planned the synthesis of a series of six compounds to probe the mechanism and stereochemistry of p-

cresol methyl-hydroxylase. The compounds were chosen to investigate both steps of the metabolism of 4-ethylphenol catalyzed by this enzyme.

For the initial step of substrate oxidation, the conversion of 4-ethylphenol to 1-(4-hydroxyphenyl)ethanol, we planned to synthesize the R- and S-enantiomers of 1-(4-hydroxyphenyl)ethane-1-d_1. Incubation of the individual enantiomers with the enzyme, followed by harvesting of the product phenolic alcohols and mass-spectrometric measurement of deuterium incorporation, would yield information regarding the stereospecificity of the benzylic-hydrogen abstraction (i.e. whether the pro-R or pro-S hydrogen is transferred as hydride to the flavin). Stopped-flow kinetic analysis of the reduction of p-cresol methylhydroxylase with the stereoisomer containing deuterium in the position of the transferred hydrogen would yield the pure, intrinsic primary kinetic isotope effect ($^D k_2$) of the enzyme reduction.[19] Enzymatic reduction of the opposite stereoisomer would provide the secondary kinetic isotope effect.

Another question regarding the mechanism which can be addressed with the stereoisomeric, deuteriated 4-ethylphenols is the postulate of a common intermediate (the quinone methide) leading to the production of the phenolic benzylic alcohol and 4-vinylphenol.[21] Isolation of the 4-vinylphenol, as well as the 1-(4-hydroxyphenyl)ethanol formed in the enzymatic reduction of R- or S-1-(4-hydroxyphenyl)ethane-1-d_1, followed by a finding of comparable deuterium enrichment in both products, would lend powerful evidence in favor of this mechanism (Mechanism 1 in the introduction).

For use as substrates, both 4-vinylphenol and its labeled analog, 4-(vinyl-1-d_1)phenol, were required, and an improved synthesis of these compounds was needed.

For the second step of substrate oxidation, the conversion of 1-(4-hydroxy-phenyl)ethanol to 4-hydroxyacetophenone, we planned the syntheses of R- and

17

S-1-(4-hydroxyphenyl)ethanol and R- and S-1-(4-hydroxyphenyl)ethanol-1-d$_1$.
p-Cresol methylhydroxylase is known to metabolize both stereoisomers of the
substrate phenolic benzylic alcohol.[21] Steady-state and stopped-flow kinetic
analyses of the reduction of the enzyme with these substrates would provide
more detailed information relevant to this process.

The sequences employed in these syntheses are outlined in Schemes 1-
5. Scheme 6 outlines the proof of the absolute configuration of 1-(4-methoxy -
phenyl)ethanol by synthesis from 4-methoxymandelic acid, the absolute
configuration of which has been rigorously proven.[32]

CH₃OCH₂OCH₃ (MOM-OCH₃),
CH₂Cl₂, p-TsOH·H₂O, Δ

$CH_3OCH_2OCH_3$ (MOM-OCH₃),
CH_2Cl_2, p-TsOH·H_2O, Δ

→ or

$CH_3OCH_2CH_2OCH_2Cl$ (MEM-Cl),
EtN-i-pr₂, CH_2Cl_2

$(CH_3)_3SiCH_2CH_2OCH_2Cl$ (SEM-Cl),
EtN-i-pr₂, CH_2Cl_2

→ or →

NaBH₄, 95% EtOH   LAH(D), THF, N₂

→ or →

R = MOM- **3**,
      MEM- **10**,
      SEM- **27**

Phthalic anhydride,
pyridine, Δ or
Phthalic anhydride,
imidazole, DMF

→

RS-
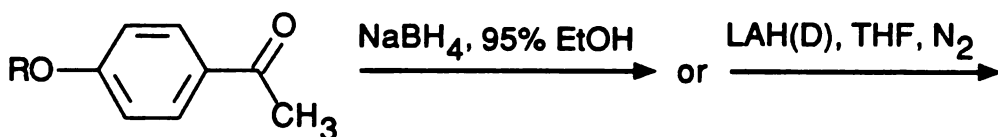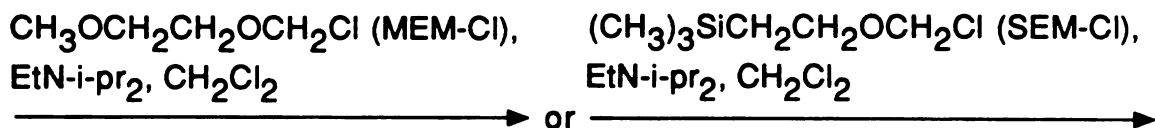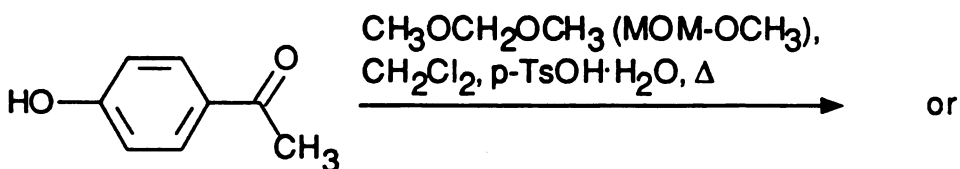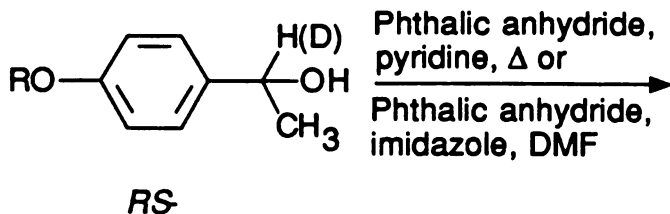
R = MOM- **4** (H),
      MEM- **11** (H), **12** (D),
      SEM- **28** (H), **29** (D)

RS-
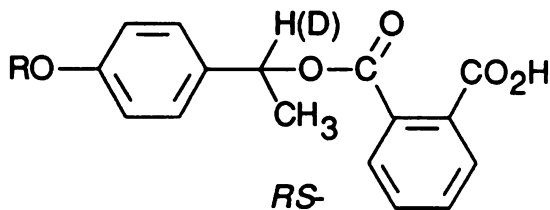
R = MOM- **5** (H),
      MEM- **17** (H), **22** (D),
      SEM- **30** (D)

Scheme 1

19

5, 17, 22, 30 $\xrightarrow{\begin{array}{c}\textit{R-}(+)\text{-1-Phenylethylamine,}\\ \text{Et}_2\text{O}\end{array}}$ *RR-* Precipitated salt +
SR- Soluble salt

RR- Precipitated salt $\xrightarrow{\begin{array}{l}\text{a)\ \ MeOAc crystallization,}\\ \text{b)\ \ H}_2\text{O, dil HCl, Et}_2\text{O, 0°C}\end{array}}$

RO—⟨aryl⟩—C(H(D))(CH₃)—O—C(=O)—⟨aryl⟩—CO₂H

R-(−)-
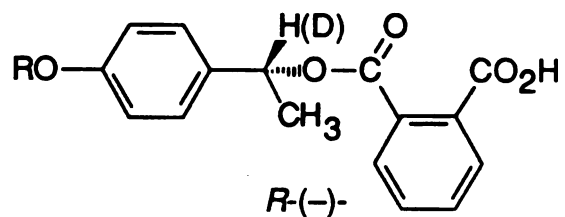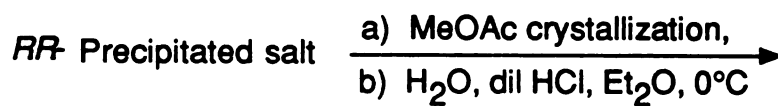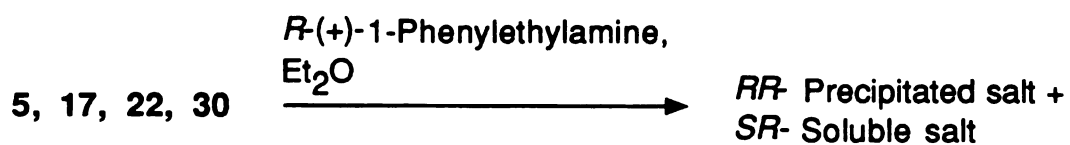
R = MOM- **6** (H),
     MEM- **19** (H), **24** (D),
     SEM- **32** (D)

6, 19, 24, 32 $\xrightarrow{\text{Na, 95\% EtOH, 10 min}}$ RO—⟨aryl⟩—C(H(D))(OH)(CH₃)

R-(+)-
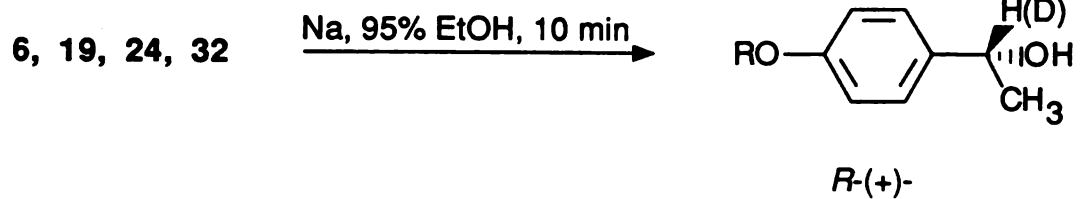
R = MOM- **9** (H),
     MEM- **21** (H), **26** (D),
     SEM- **34** (D)

Scheme 1 (contd.)

SR- Soluble salt $\xrightarrow[\text{b)} \ S\text{-}(-)\text{-}1\text{- Phenylethylamine}]{\text{a)} \ H_2O, \text{ dil HCl, } Et_2O, \ 0°C}$ *SS-* Precipitated salt

SS- Precipitated salt $\xrightarrow{\text{Same as for } RR\text{- precipitated salt}}$

RO—⟨benzene ring⟩—C(OH)(···H(D))—CH$_3$
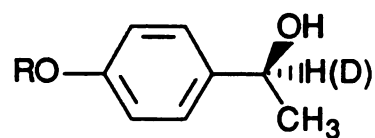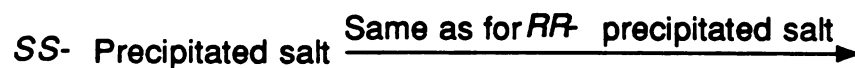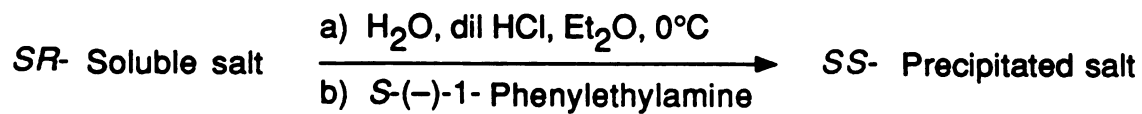
S-(−)-

R = MOM- **8** (H),
MEM- **20** (H), **25** (D),
SEM- **33** (D)

33 $\xrightarrow{\text{n-Bu}_4\text{NF, THF, 45°C, 24 h}}$ HO—⟨benzene ring⟩—C(OH)(···D)—CH$_3$

S-(−)- **38**
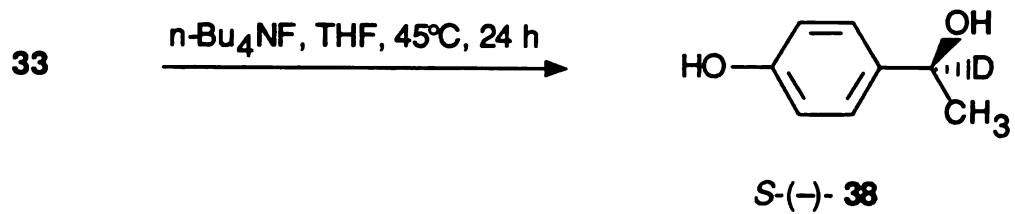
Same cleavage for *R-*(+)- **37** from *R-*(+)- **34**.

Scheme 1 (contd.)

21

$R = CH_3OCH_2CH_2$- **10** or
$(CH_3)_3SiCH_2CH_2$- **27**

R-(+)- **35** or S-(−)- **36**
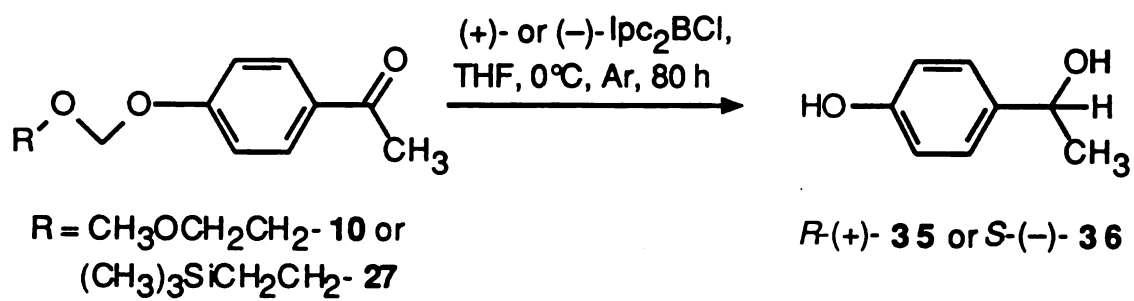
Ipc_2BCl = diisopinocampheylchloroborane

Scheme 2

a) MsCl, Et₃N, THF, –78°C, N₂, 15 h

b) LAH, THF, –78°C, N₂

R-(+)-**26** → *S*-(–)-**68**

2-Bromo-1,3,2-benzodioxaborole, EtN-i-pr₂, CH₂Cl₂, N₂, 1 h

68 → *S*-(–)-**73**

R = CH₃OCH₂CH₂OCH₂-
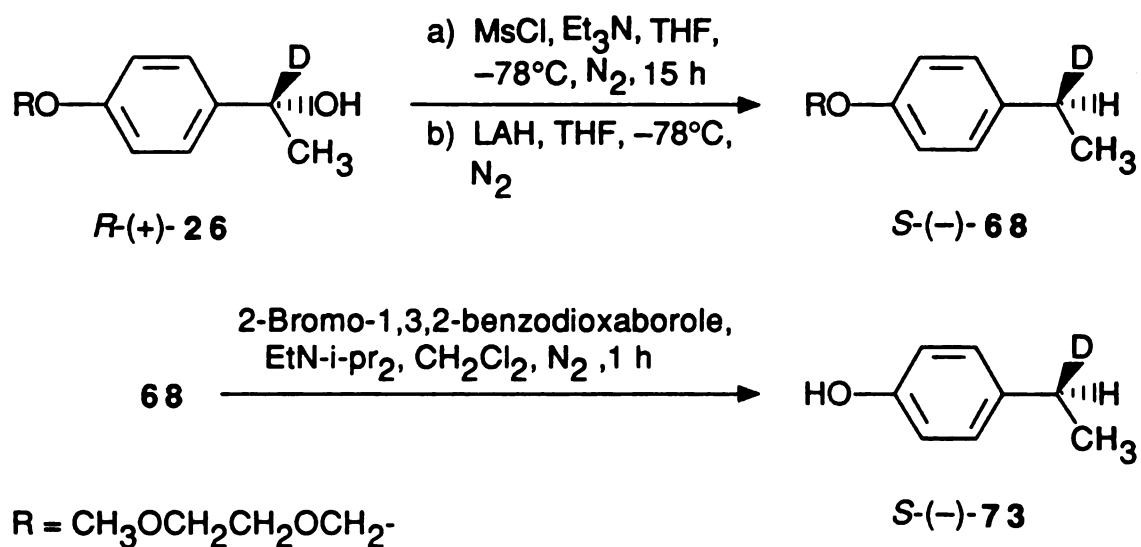
Same sequence for *RS*- **75** from *RS*- labeled alcohol **1 2** via*RS*- labeled, MEM-protected 4-ethylphenol **69**.

Scheme 3

RO—⟨benzene ring⟩—C(OH)(CH₃)—H(D) → 2-Chloro-1,3,2-benzodioxaborole, EtN-i-pr₂, CH₂Cl₂, N₂, 0°C → HO—⟨benzene ring⟩—CH(D)=CH₂

RS- **11** (H), **12** (D)

40 (H), **39** (D)

R = CH₃OCH₂CH₂OCH₂-

Scheme 4

EtOD $\xrightarrow{\text{Yeast alcohol dehydrogenase, ß-NAD}^+\text{, ß-NADD,}\\ \text{diaphorase, D}_2\text{O, pH 7.6, 28°C, 7 days}}$

D⟍ ͵ͥH
CH₃⟋ ⟍OD

R-(+)- **49**

49 $\xrightarrow{\text{MsCl, Et}_3\text{N, CH}_2\text{Cl}_2}$

D⟍ ͵ͥH
CH₃⟋ ⟍OMs

R-(+)- **60**

$(CH_3)_3C \equiv CH$ $\xrightarrow{\text{MeLi, Et}_2\text{O, Ar}}$ $(CH_3)_3C \equiv CLi$

A

CH₃O—⟨benzene⟩—I $\xrightarrow{\text{n-BuLi, hexanes-benzene, Ar}}$ CH₃O—⟨benzene⟩—Li

65

a) **A**, Et₂O, 5°C, Ar
b) **6 5**, Et₂O-THF, −78°C, Ar
c) **6 0**, Et₂O-THF, 0°C, Ar

CuI $\xrightarrow{\hspace{3cm}}$

D
CH₃O—⟨benzene⟩—C⟨ͥͥH / CH₃⟩

S-(−)-**7 1**

Scheme 5

2-Bromo-1,3,2-benzodioxaborole,
EtN-i-pr$_2$, CH$_2$Cl$_2$, N$_2$, 1 h

71 $\xrightarrow{\hspace{4cm}}$

S-(–)-**73**

Same sequence for R-(+)- **74**. Synthesize S-(–)-1-ethanol-1-d$_1$ **50** from ethanol-1,1-d$_2$ and the same enzyme preparation in H$_2$O.

Scheme 5 (contd.)

Scheme 6

45 $\xrightarrow{\text{LAH, THF, 0°C, Ar}}$

CH_3O—⟨benzene ring⟩—$\overset{OH}{\underset{H}{\text{C}}}$—$CH_2OH$

R-(−)- **46**

46 $\xrightarrow[\text{Ar, 15 h}]{\text{MsCl, Et}_3\text{N, CH}_2\text{Cl}_2, \text{0°C,}}$

CH_3O—⟨benzene ring⟩—$\overset{OH}{\underset{H}{\text{C}}}$—$CH_2OMs$

R-(−)- **47**

47 $\xrightarrow{\text{LAH, THF, 0°C, Ar}}$

CH_3O—⟨benzene ring⟩—$\overset{OH}{\underset{H}{\text{C}}}$—$CH_3$

S-(−)- **48**
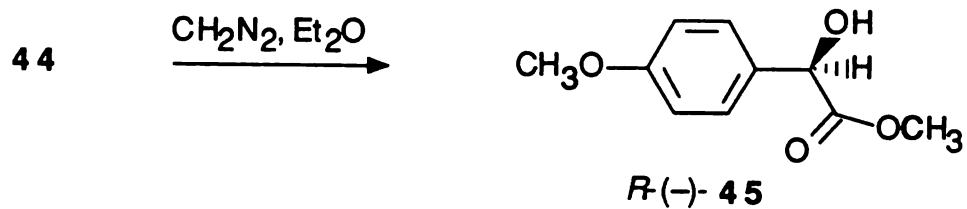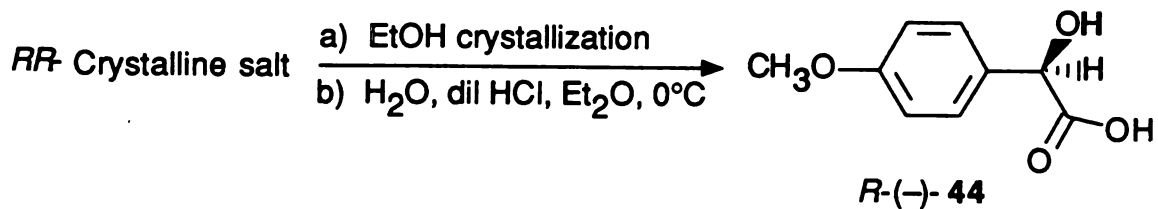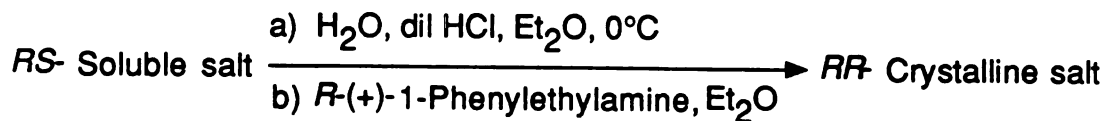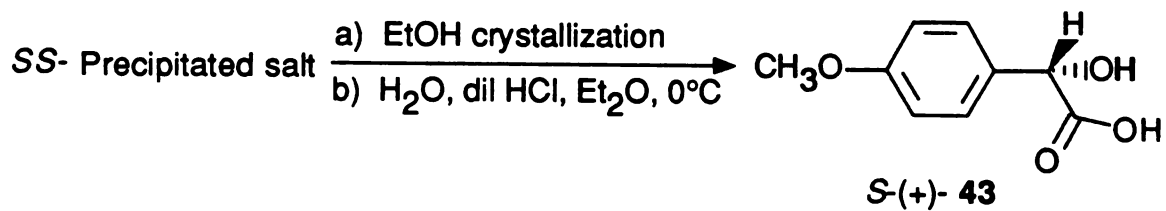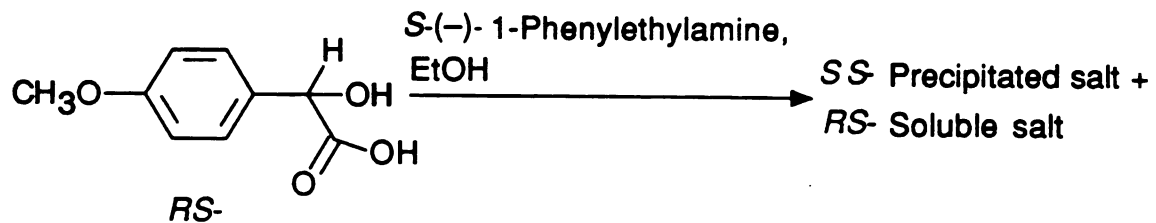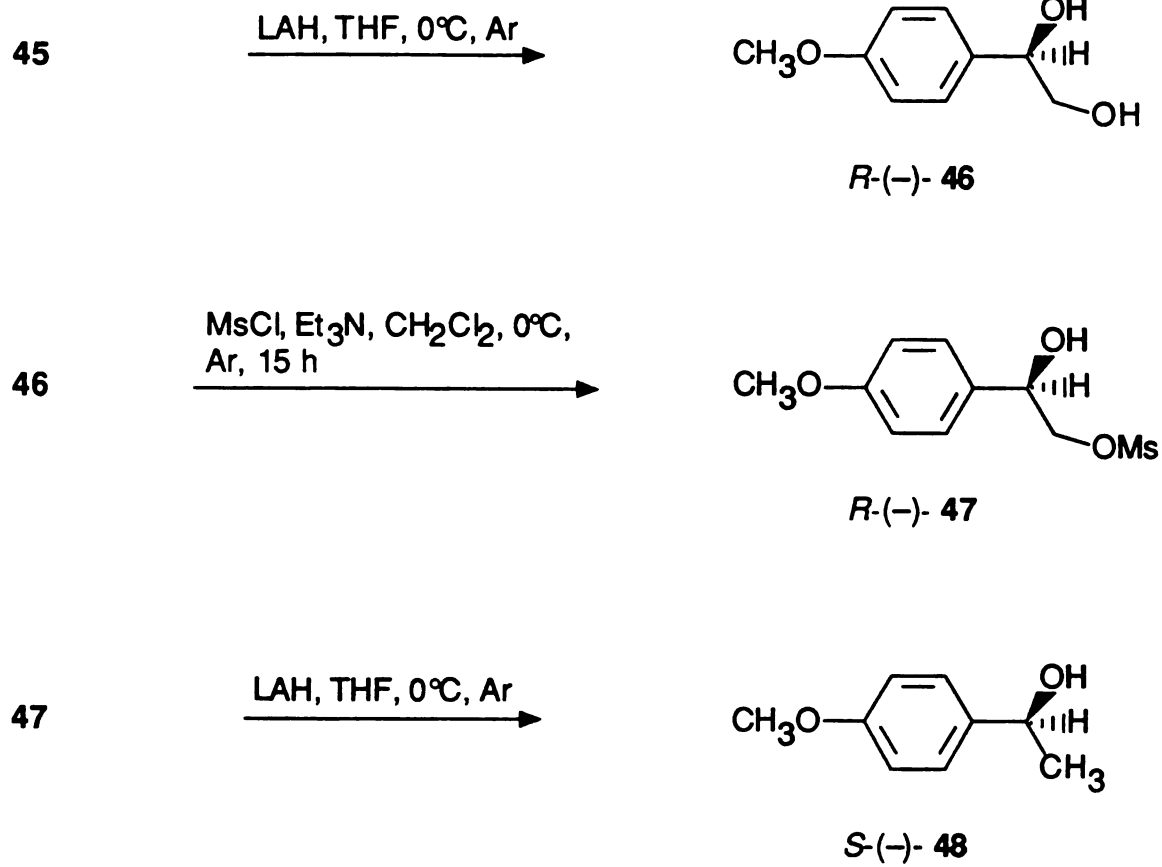
Scheme 6 (contd.)

References

1) Hopper, D.J. Biochem. Biophys. Res. Comm. **1976**, *69*, 462-468.

2) Hopper, D.J.; Taylor, D.G. Biochem. J. **1977**, *167*, 155-162.

3) Keat, M.J.; Hopper, D.J. Biochem. J. **1978**, *175*, 649-658.

4) Hopper, D.J. Biochem. J. **1978**, *175*, 345-347.

5) McIntire, W.; Hopper, D.J.; Singer, T.P. Biochem. J. **1985**, *228*, 325-335.

6) Hopper, D.J.; Jones, M.R.; Causer, M.J. FEBS Lett. **1985**, *182*, 485-488.

7) Causer, M.J.; Hopper, D.J.; McIntire, W.; Singer, T.P. Biochem. Soc. Trans. **1984**, *12*, 1131-1132.

8) McIntire, W.; Edmondson, D.E.; Singer, T.P.; Hopper. D.J. J. Biol. Chem. **1980**, *255*, 6553-6555.

9) McIntire, W.; Edmondson, D.E.; Hopper, D.J.; Singer, T.P. Biochemistry **1981**, *20*, 3068-3075.

10) Edmondson, D.E.; Kenney, W.C.; Singer, T.P. Methods Enzymol. **1978**, *53*, 449-465.

11) McIntire, W.; Singer, T.P. FEBS Lett. **1982**, *143*, 316-318.

12) Koerber, S.C.; McIntire, W.; Bohmont, C.; Singer, T.P. Biochemistry **1985**, *24*, 5276-5280.

13) Shamala, N.; Lim, L.W.; Mathews, F.S.; McIntire, W.; Singer, T.P.; Hopper, D.J. Proc. Natl. Acad. Sci. U.S.A. **1986**, *83*, 4626-4630.

14) McIntire, W. (1983), Ph.D. Thesis, University of California, Berkeley.

15) Bhattacharyya, A.; Tollin, G.; McIntire, W.; Singer, T.P. Biochem. J. **1985**, *228*, 337-345.

16) Bellamy, H.D.; Mathews, F.S.; McIntire, W.; Singer, T.P. Flavins and Flavoproteins 1987, Edmondson, D.E. and McCormick, D.B., eds., Walter de Gruyter and Co., 1987, pp. 673-676.

17) Koerber, S.C.; Hopper, D.J.; McIntire, W.; Singer, T.P. Biochem. J. **1985**, *231*, 383-387.

18) McIntire, W.; Singer, T.P.; Smith, A.J.; Mathews, F.S. Biochemistry **1986**, *25*, 5975-5981.

19) McIntire, W.S.; Hopper, D.J.; Singer, T.P. Biochemistry **1987**, *26*, 4107-4117.

20) McIntire, W.; Hopper, D.J.; Craig, J.C.; Everhart, E.T.; Webster, R.V.; Causer, M.J.; Singer, T.P. Biochem. J. **1984**, *224*, 617-621.

21) McIntire, W.S.; Bohmont, C. Flavins and Flavoproteins 1987, Edmondson, D.E. and McCormick, D.B., eds., Walter de Gruyter and Co., 1987, pp. 677-686.

22) Fersht, A. (1985) Enzyme Structure and Function. 2nd ed., W.H. Freeman and Co., New York, Chapter 3, pp. 98-120.

23) Lowry, T.H.; Richardson, K.S. (1981) Mechanism and Theory in Organic Chemistry. 2nd ed., Harper and Row, New York, Chapter 2, pp. 205-212.

24) Hill, H.A.O.; Oliver, B.N.; Page, D.J.; Hopper, D.J. J. Chem. Soc., Chem. Comm. **1985**, 1469-1471.

25) Bossert, I.D.; Whited, G.; Gibson, D.T.; Young, L.Y. J. Bacteriol. **1989**, *171*, 2956-2962.

26) Darby, J.M.; Taylor, D.G.; Hopper, D.J. J. Gen. Microbiol. **1987**, *133*, 2137-2146.

27) Sugumaran, M.; Lipke, H. FEBS Lett. **1983**, *155*, 65-68.

28) Andersen, S.O. Ann. Rev. Entomol. **1979**, *24*, 29-61.

29) Sugumaran, M.; Lipke, H. Proc. Natl. Acad. Sci. U.S.A. **1982**, *79*, 2480-2484.

30) Brunet, P.C.J. Insect Biochem. **1980**, *10*, 467-500.

31) Andersen, S.O. Insect Biochem. **1979**, *9*, 233-239.

32) Pratesi, P.; LaManna, A.; Campiglio, A.; Ghislandi, V. J. Chem. Soc. **1958**, 2069-2074.

The Synthesis and Absolute Configuration of the Enantiomers of 1-(4-Hydroxyphenyl)ethanol and 1-(4-Hydroxyphenyl)ethanol-1-d_1

Chapter II

Optically active 1-(4-hydroxyphenyl)ethanol has previously never been reported in the literature. The resolution of 1-phenylethanols is classically achieved by the use of brucine as a resolving agent on the hydrogen phthalate ester of the racemic alcohol.[15] This method is inefficient and gives only one enantiomer in high purity because of the availability of only one of the enantiomerically pure stereoisomers of the natural plant alkaloid, brucine. We have investigated two improved methods, one involving the use of R-(+)- and S-(−)-1-phenylethylamine as a resolving agent, and the other employing the asymmetric reducing agents (+)- and (−)- diisopinocampheylchloroborane.[10]

A number of acetal protecting groups were examined for the protection of the phenolic hydroxyl groups during this process, and the results are outlined below.

R-(+)- and S-(−)-1-(4-Methoxymethoxyphenyl)ethanol 9 & 8

4-Methoxymethoxyacetophenone **3** was obtained from 4-hydroxyacetophenone by heating at reflux with an excess of dimethoxymethane in dichloromethane containing a catalytic amount of 4-toluenesulfonic acid•H_2O, with removal of water by freshly activated 3A molecular sieve in a Soxhlet extractor.

The ketone was reduced with $NaBH_4$ in 95% ethanol to yield RS-1-(4-methoxymethoxyphenyl)ethanol **4**, which was then converted to the racemic monohydrogen phthalate by 2 different phthaloylation methods.

In the first method, the racemic alcohol was heated with 1 mole equivalent of phthalic anhydride, at 98°C for 75 min, in dry benzene containing 1 mole equivalent of pyridine. After the reaction mixture was cooled to room

temperature and diluted with water, the pH of the aqueous phase was adjusted to 2 with 1 N HCl and it was extracted with ether. The acids and neutrals were separated by washing the combined ether extracts with saturated NaHCO$_3$, washing the aqueous phase with ether and adjusting the pH of the aqueous phase to 2 with 1 N HCl. The acids were then extracted into ether, which was dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure to give a viscous oil that was dissolved in chloroform and filtered from a small amount of precipitated phthalic acid. Evaporation of the solvent under reduced pressure yielded *RS*-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate **5** as a viscous oil, which slowly crystallized in 63 % yield.

In the second method, the racemic alcohol was heated with 1 mole equivalent of phthalic anhydride, at 95°C for 1 h, in dry DMF containing 1.2 mole equivalents of imidazole. The reaction mixture was cooled to room temperature and worked up as described in the first method to afford *RS*-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate in 88 % yield. This material, after recrystallization from hexane/ethyl acetate, melted at 94-96°C.

The racemic acid phthalate was dissolved in ether and treated with 1 mole equivalent of *R*-(+)-1-phenylethylamine, which caused the precipitation, within 1 min, of the *RR*- salt, which was filtered and washed with ether. The dried salt was recrystallized from ethanol to give the pure *RR*-salt, melting at 145-146°C, in 70 % yield. The specific rotation was $[\alpha]_D^{25} = +6.55°$ (c = 2.61 in EtOH). The *SS*- salt was prepared in an analogous fashion from the racemic acid phthalate and *S*-(–)-1-phenylethylamine. The pure *SS*- salt melted at 144-145°C and exhibited an $[\alpha]_D^{25} = -6.62°$ (c = 2.52 in EtOH).

A slurry of the *RR*-1-phenylethylamine salt in water was cooled to 5°C, adjusted to pH 2 with 1 N HCl and extracted with ethyl acetate. The combined

extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield R-(–)-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate 6 as a viscous, orange-red oil with an $[\alpha]_D^{25}= -15.1°$ (c = 5.30 in EtOH). The sample, stored at 5°C, was found to have partially decomposed after 50 days, with an $[\alpha]_D^{25}= -13.2°$ (c = 5.07 in EtOH). The acid phthalate was liberated from the SS- 1-phenylethylamine salt in an analogous manner to afford S-(+)-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate 7 as a colorless, viscous oil with an $[\alpha]_D^{25}= +16.2°$ (c =5.04 in EtOH). After 16 days at 5°C, the specific rotation had decreased to $[\alpha]_D^{25}= +14.7°$ (c = 5.59 in EtOH).

After the observation of the decomposition of these compounds, all resolved, noncrystalline acid phthalates utilized in this study were either hydrolyzed immediately or stored at –78°C.

S-(+)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate was heated at reflux with an excess of $LiBH_4$ in THF, for 3 h. The reaction mixture was cooled to room temperature, quenched with water and worked up in the standard manner to yield an oil, which was distilled in vacuo to give S-(–)-1-(4-methoxymethoxyphenyl)ethanol 8 in 91 % yield. This material exhibited a specific rotation of $[\alpha]_D^{25}= -29.5°$ (c = 4.88 in EtOH).

The same monohydrogen phthalate was heated at reflux, for 1 h, in 1.15 N NaOH in 77 % ethanol. Standard workup gave an oil, which was distilled in vacuo to afford S-(–)-1-(4-methoxymethoxyphenyl)ethanol in 90 % yield. The specific rotation was recorded as $[\alpha]_D^{20}= -33.8°$ (c = 5.01 in EtOH). Reversed-phase gradient HPLC analysis (methanol/water) of the S-(–)-α-methoxy-α-trifluoromethylacetic acid (MTPA) ester indicated the product to be 96 %

enantiomerically pure (98 % S-(-)- and 2 % R-(+)-), corresponding to an $[\alpha]_D^{20}=$

$-$ 35.2° (c = 5.0 in EtOH) for the enantiomerically pure alcohol.

R-(-)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate was dissolved in a solution of sodium in 96 % ethanol and heated on the steam bath for a few min. The hydrolysis mixture was cooled to room temperature and worked up in standard fashion to yield an oil, which was distilled *in vacuo* to give R-(+)-1-(4-methoxymethoxyphenyl)ethanol **9** in 87 % yield. A specific rotation of $[\alpha]_D^{20}=$ + 31.1° (c = 5.44 in EtOH) was recorded for this material. LC analysis of the (-)-MTPA ester revealed the product to be 86.2 % enantiomerically pure, corresponding to an $[\alpha]_D^{20}=$ + 36.1° (c = 5.4 in EtOH) for the enantiomerically pure alcohol.

R-(+)- and S-(-)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol 21 & 20 and R-(+)- and S-(-)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$ 26 & 25

4-Hydroxyacetophenone and 2-methoxyethoxymethyl chloride (MEM-Cl) were coupled in dichloromethane containing N,N-diisopropylethylamine to form 4-[(2-methoxyethoxy)methoxy]-acetophenone **10**, and the ketone was reduced with LAD (99 atom %) in THF to yield RS-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$ **12**, and NaBH$_4$ in 95 % ethanol to give the racemic unlabeled alcohol **11**.

The labeled and unlabeled racemic alcohols were heated with 1 mole equivalent of phthalic anhydride, at 100°C for 2 h, in DMF containing 1 mole equivalent of imidazole. After the reaction mixture was cooled to 5°C and diluted with water, the pH was adjusted to 2 with dilute HCl and the mixture

extracted with ether. The combined extracts, after a water wash, were washed with saturated NaHCO$_3$, and the NaHCO$_3$ washings, after a wash with ether, were cooled to 5°C, adjusted to pH 2 with dilute HCl and extracted with ether. The combined extracts were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure to give a residue, which was redissolved in chloroform and filtered from precipitated phthalic acid. Evaporation of the solvent under reduced pressure afforded viscous RS-1-[4-(2-methoxyethoxy)-methoxyphenyl]-ethyl hydrogen phthalate **17** and its deuteriated analog **22**.

The racemic unlabeled monohydrogen phthalate was dissolved in ether and treated with 1 mole equivalent of S-(–)-1-phenylethylamine. The SS-salt precipitated within 1 min and was filtered from solution, washed with ether and recrystallized twice from methyl acetate to yield, after recycling the mother liquors, the pure SS-salt, melting at 141-143°C, in 66 % yield. The mother liquors were washed with ice-cold 0.2 N HCl and brine, dried over anhydrous Na$_2$SO$_4$, filtered and treated with R-(+)-1-phenylethylamine. The RR-salt precipitated from solution and was filtered and recrystallized from methyl acetate, like the SS-salt, to give the pure RR-salt, melting at 141-143°C, in 65 % yield. The pure salts required 30-33 ml of methyl acetate per gram for recrystallization. The SS-salt exhibited an $[\alpha]_D^{25} = -6.1°$ (c = 2.92 in EtOH) and the RR-salt an $[\alpha]_D^{25} = +6.1°$ (c = 2.82 in EtOH).

The (+)- and the (–)- salts of the labeled phthalates were obtained in exactly the same manner from the racemic deuteriated monohydrogen phthalate. Both the RR- and SS-salts melted at 142-143°C. The specific rotations were identical to those recorded for the unlabeled salts.

The SS-salt of the unlabeled monohydrogen phthalate was suspended in ice-cold water and the stirred suspension was slowly treated with one mole equivalent of aqueous oxalic acid. The free acid was extracted into ether, and

the solvent was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give a quantitative recovery of the viscous S-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate **18**. The R-acid **19** and the R- **24** and S-enantiomers **23** of the labeled monohydrogen phthalate were liberated in a like manner.

The method employed for the hydrolysis of the acid phthalates was the method of Dabby et al., which they used for the hydrolysis of S-1-(2-methoxy-phenyl)ethyl hydrogen phthalate.[1] S-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate, liberated from the levorotatory 1-phenylethylamine salt, was dissolved in a solution of sodium in 96 % ethanol. Solution was followed almost immediately by the precipitation of disodium phthalate, and the hydrolysis was completed by heating the mixture for a few min on the steam bath. Standard workup followed by distillation in vacuo afforded S-(−)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol **20** in 99.5 % yield overall from the SS-1-phenylethylamine salt. The R-(+)-alcohol **21** and the R-(+)- **26** and S-(−)-enantiomers **25** of the labeled alcohol were obtained in an analogous manner. The observed specific rotations are listed in Table 1.

compound	$[\alpha]_D^{20}$ (neat)
R-(+)-	+ 37.2°
R-(+)-, d	+ 37.9°
S-(−)-	− 37.4°
S-(−)-, d	− 38.0°

Recorded specific rotations of deuterium-labeled and unlabeled
1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanols.

Table 1.

RS-2-(Methoxyethoxy)methyl and 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether 13 and
RS-4-Methoxybenzyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether 14

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol **11** was condensed with MEM-Cl in dichloromethane containing N,N-diisopropylethylamine to afford *RS*-2-(methoxyethoxy)methyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether **13** as a colorless oil in 97 % yield.

The sodium salt of the racemic alcohol was condensed with 4-methoxybenzyl chloride in refluxing THF to give an oil, which was stirred with saturated NaHCO₃ to hydrolyze residual 4-methoxybenzyl chloride and separated from 4-methoxybenzyl alcohol by silica gel chromatography to give *RS*-4-methoxybenzyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether **14** as a colorless oil in 57 % yield.

RS--t-Butyldimethylsilyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether 15 and
RS--t-Butyldiphenylsilyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether 16

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol **11** was condensed with 1.2 mole equivalents of t-butyldimethylsilyl chloride in DMF containing 2.5 mole equivalents of imidazole to give RS-t-butyldimethylsilyl-1-[4-(2-methoxy-ethoxy)methoxyphenyl]-ethyl ether **15** in 98 % yield.

The racemic alcohol was condensed with t-butyldiphenylsilyl chloride in the same manner to yield, after silica gel chromatography, pure RS-t-butyldi-phenylsilyl-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether **16** in 95 % yield.

Cleavage of the 2-methoxyethoxymethyl (MEM) protecting group

With the enantiomerically pure R-(+)- **26, 21** and S-(–)-stereoisomers **25, 20** of the labeled and unlabeled 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanols, respectively, in hand, our efforts were directed to the cleavage of the MEM protecting group and the liberation of the free phenolic benzylic alcohols.

Corey et al., who introduced the MEM group for the protection of the hydroxyl function, reported that it could be cleaved with either $ZnBr_2$ or $TiCl_4$ in dichloromethane.[2] As an example they listed the cleavage of MEM-protected guaiacol (2-methoxyphenol) with 5 mole equivalents of $ZnBr_2$, in dichloro-methane at 25°C, in 5 h. Corey et al. also reported the cleavage of methoxymethyl (MOM) ethers under aprotic conditions, in the presence of the $ZnBr_2$ or $TiCl_4$, to be markedly slower than the reaction for the corresponding MEM ethers.[2] They rationalized the faster rates observed for the cleavage of

the MEM ethers on the basis of bidentate coordination of the MEM group to a Lewis acid, facilitating the cleavage reaction **A**, or cleavage via a cyclic oxonium ion intermediate **B** (Fig. 1.)
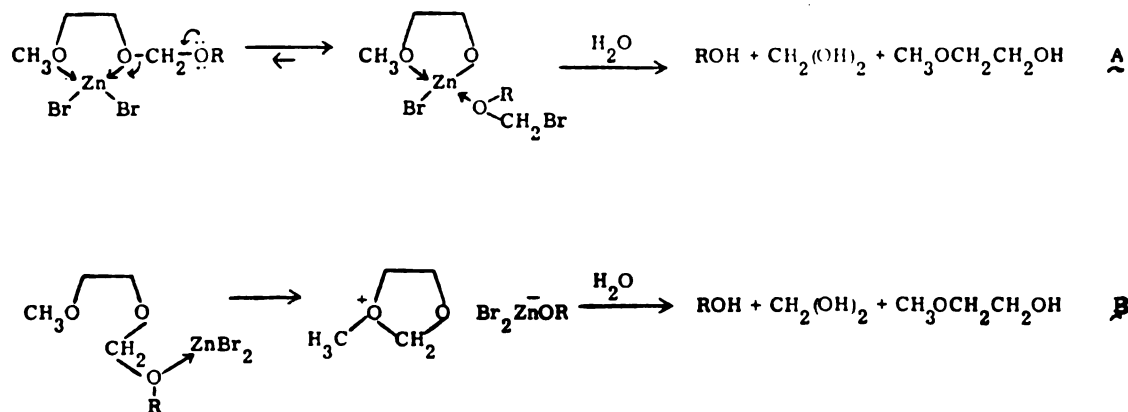
Postulated mechanisms for the $ZnBr_2$-mediated cleavage of MEM ethers, according to Corey et al.[2]

Fig. 1.

However, others have occasionally found MEM and MOM ethers particularly resistant to cleavage.[3,4,5,6] In this study, it was observed that MOM-protected 4-hydroxyacetophenone **3** was quantitatively cleaved with 5 mole equivalents of $ZnBr_2$ in dichloromethane, in 5 weeks. It has also been suggested that traces of HBr in some preparations of $ZnBr_2$, rather than $ZnBr_2$ itself, are responsible for the $ZnBr_2$-mediated cleavage of these formaldehyde acetals.[7] Indeed, Guindon et al. report wet $ZnBr_2$ to be more efficient than the dry reagent for the cleavage of menthol-MEM ether.[5]

The trouble experienced by other workers with the cleavage of MEM ethers by $ZnBr_2$, along with concern for possible racemization and/or elimination, catalyzed by traces of HBr or coordination of the $ZnBr_2$ with the secondary benzylic hydroxyl group, led us to abandon this method of cleavage.

Guindon et al. have promoted the use of dimethylboron bromide and diphenylboron bromide as reagents for the cleavage of MEM, MOM and methylthiomethyl (MTM) ethers.[5] They report the smooth cleavage of the MEM ether of 3-phenylpropanol with 3 mole equivalents of dimethyl- or diphenyl-boron bromide, in dichloromethane/1,2-dichloroethane at $-78°C$, in 1 h. However, in our hands this reagent was inert toward phenolic MEM ethers. When the MEM ether of 4-ethylphenol 67 was heated at reflux with 3 mole equivalents of diphenylboron bromide in 1,2-dichloroethane, for 32.5 h, no cleavage was observed! Guindon et al. do not provide an example of the cleavage of a phenolic MEM ether with either dimethylboron bromide or diphenylboron bromide. The mechanism which they suggest to rationalize the cleavage of MEM ethers by these reagents invokes a lone pair of electrons on the oxygen atom of the protected alcohol serving as a nucleophile, which attacks the coordinated chlorodialkyl(aryl)boron reagent (Fig. 2). Since the lone pairs on a phenolic oxygen, due to delocalization of the electrons into the ring, would not be as nucleophilic, the proposed mechanism would also rationalize the inertness of the reagents to phenolic MEM ethers.

41
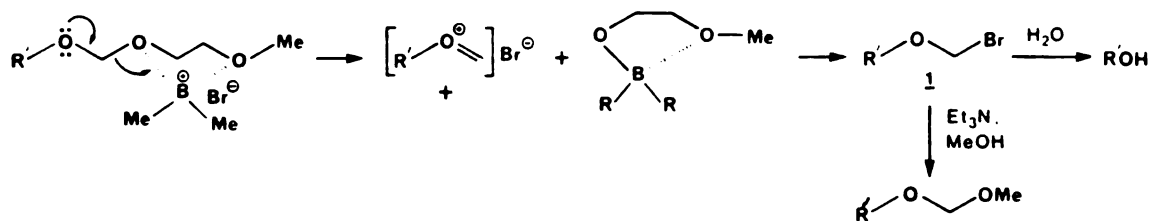
Proposed mechanism for the dimethyl(phenyl)boron bromide cleavage of
MEM ethers, according to Guindon et al.[5]

Fig. 2.

Boeckman, Jr., and Potenza recently introduced the catechol boron

halides (2-halo-1,3,2-benzodioxaboroles), bromo and chloro, as mild and

selective reagents for the cleavage of common protecting groups.[8] They report

the cleavage of unhindered aliphatic MEM ethers with 1 mole equivalent of

catechol boron bromide, in dichloromethane at room temperature, in 15 min.

Preliminary experiments with these reagents indicated that 1.1 mole equivalent

of catechol boron bromide would cleave the MEM ether of 4-ethylphenol in

dichloromethane, in 15 min. The same experiment, with 1.5 mole equivalents of

catechol boron chloride, resulted in quantitative cleavage in 3 h.

This reagent appeared attractive to us, because it was hoped that if the

cleavage of the MEM-protected phenolic benzylic alcohol 11 were carried out

in the presence of 2 mole equivalents of one of the catechol reagents and a

tertiary base, the boron ester of the secondary alcohol would be formed by one

of the mole equivalents of reagent.[9] Hydrolysis of the boron ester during

aqueous workup would then regenerate the hydroxyl function. However, the

possibility of halogenation of the benzylic position still existed, since the

cleavage of a tertiary alkyl methyl ether by 1 mole equivalent of catechol boron

bromide resulted in the production of the tertiary alkyl bromide.[8]

42

Having demonstrated the ability of both catechol boron bromide and catechol boron chloride to cleave phenolic MEM ethers, it was necessary to determine which tertiary amine bases could be employed as proton scavengers without seriously inhibiting the reactivity of the reagents. Both reagents are known, for example, to form stable 1:1 complexes with pyridine.[9]

N,N-Diisopropylethylamine was found to have no observable effect on the rate of cleavage of the MEM ether of 4-ethylphenol by catechol boron bromide. The addition of N,N-diisopropylethylamine to a dichloromethane solution of catechol boron bromide results in a white precipitate, which re-dissolves to give a gold-colored solution. The MEM ether of 4-ethylphenol is cleaved by 1.25 mole equivalents of catechol boron bromide in dichloro-methane, containing 25 mole equivalents of N,N-diisopropylethylamine, in 20 min. However, all attempts to cleave 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol with either catechol boron bromide or catechol boron chloride in dichloromethane, containing as much as 30 mole equivalents of N,N-diiso-propylethylamine, led to the production of either 4-vinylphenol or polymer. In fact, with careful control of the workup conditions, this became an efficient method of synthesis of 4-vinylphenol 40. Evidence that N,N-diisopropyl-ethylamine is just too sterically hindered to abstract the proton from the benzylic oxygen atom, as it attacks the electrophilic boron atom of the catechol reagent and acquires electropositive character, is the observation that N,N-diisopropyl-ethylamine and 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol form 2 phases when mixed. One would expect the two liquids to be miscible if the base were capable of hydrogen bonding with the alcohol. The para-alkoxybenzylic system is probably sufficiently labile to be eliminated as the oxygen atom acquires electropositive character upon coordination with the boron reagent, or the

43

benzylic position could be brominated or chlorinated and eliminate in the workup.

Triethylamine was found to inhibit the reactivity of the catechol reagents towards MEM ethers. The MEM ether of 4-ethylphenol was cleaved with 1.4 mole equivalents of catechol boron bromide in dichloromethane, containing 1.4 mole equivalents of triethylamine, in 30 min. When the reaction was repeated with 1.25 mole equivalents of reagent and 30 mole equivalents of triethylamine, only about 30 % cleavage was observed after 30 min. When the cleavage reaction was carried out with 2 mole equivalents of catechol boron chloride in dichloromethane, containing 20 mole equivalents of triethylamine, no cleavage was observed in 3 h. No cleavage was observed after 38 h when 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol was treated with 4 mole equivalents of catechol boron chloride in dichloromethane containing 14 mole equivalents of triethylamine.

With the inability of N,N-diisopropylethylamine or triethylamine to protect the sensitive secondary benzylic hydroxyl group of 1-[4-(2-methoxyethoxy)-methoxyphenyl]-ethanol, while allowing the efficient cleavage of the MEM ether, our attention turned to pyridine and the substituted pyridines.

When the MEM ether of 4-ethylphenol was treated with 2 mole equivalents of catechol boron chloride in dichloromethane, containing 20 mole equivalents of 2,6-lutidine, complete cleavage was obtained in 4 h. The MEM-protected phenolic benzylic alcohol was treated with 4 mole equivalents of catechol boron chloride, at 0°C, in dichloromethane containing 40 mole equivalents of 2,6-lutidine. Hydrolysis and workup, after 10 h, followed by reversed-phase HPLC analysis (methanol/water), indicated the presence of 4-vinylphenol and only a trace of the desired 1-(4-hydroxyphenyl)ethanol 1. So the 2,6-lutidine, less sterically hindered than N,N-diisopropylethylamine,

44

allowed the protection of the secondary benzylic hydroxyl group, but only to an insignificant extent.

Pyridine and 2-picoline were found to inhibit the catechol reagents to such an extent as to render them useless for our purposes.

Finally, a series of ethers of 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol were prepared and subjected to treatment with catechol boron bromide and catechol boron chloride. The first ether to be prepared was the bis-MEM derivative **13**. Treatment with either the bromo or chloro reagent in dichloromethane, containing 1 mole equivalent of N,N-diisopropylethylamine to absorb traces of HCl, led to the formation of 4-vinylphenol or polymer.

The second ether to be prepared was the 4-methoxybenzyl ether **14**. The rationale for the preparation of this compound was to incorporate 2 para-alkoxybenzylic centers in the molecule to approximate the same electronic environment at each benzylic center. When the benzylic ether oxygen atom coordinated with the electropositive boron atom of the catechol reagent (chloro or bromo), it was hoped that the halide would preferentially attack the primary para-methoxybenzylic center to form 4-methoxybenzyl halide and the catechol boron ester of the secondary benzylic alcohol, which would be regenerated in the hydrolytic quench of the reaction mixture. However, when the 4-methoxy-benzyl ether was treated with either catechol boron chloride or catechol boron bromide in dichloromethane, containing N,N-diisopropylethylamine, hydrolysis of the reaction mixture followed by workup and reversed-phase HPLC analysis (methanol/water) indicated the presence of only catechol, 4-methoxybenzyl alcohol and 4-vinylphenol. So it would appear that the thermodynamic driving force of elimination to the styrene controls the reactivity of this system.

The t-butyldimethylsilyl **15** and t-butyldiphenylsilyl ethers **16** were also prepared, but their reactions with catechol boron chloride or catechol boron bromide also led to 4-vinylphenol or polymers.

4-(Vinyl-1-d₁)phenol 39 and 4-Vinylphenol 40

4-(Vinyl-1-d$_1$)phenol was prepared from racemic 1-[4-(2-methoxy-ethoxy)methoxyphenyl]-ethanol-1-d$_1$ **12** by treatment with 2 mole equivalents of 2-bromo-1,3,2-benzodioxaborole in dichloromethane, at 0°C, containing N,N-diisopropylethylamine. Standard workup followed by silica gel chromatography and vacuum sublimation afforded 4-(vinyl-1-d$_1$)phenol **39** in 46 % yield.

The unlabeled material was obtained in an analogous manner from the unlabeled racemic alcohol **11** and 2-chloro-1,3,2-benzodioxaborole.

This method of preparation of the vinylphenol is a considerable improvement over the 4-step literature synthesis of this compound from 4-hydroxybenzaldehyde, in 34 % yield.[14]

R-(+)- and S-(−)-1-(4-Hydroxyphenyl)ethanol 35 & 36

The title compounds were prepared by the reduction of 4-[2-(methoxy-ethoxy)methoxy]-acetophenone with **10** (+)- and (−)-diisopinocampheyl-chloroborane, respectively. Diisopinocampheylchloroborane (Ipc$_2$BCl), prepared from α-pinene via hydroboration followed by treatment with dry

hydrogen chloride in ether, was introduced by Chandrasekharan et al. as an efficient chiral reducing agent for aromatic prochiral ketones.[10] The (−)-reagent, prepared from (+)-α-pinene, has been reported to reduce acetophenone in THF, at − 25°C in 7 h, to S-(−)-1-phenylethanol **42** in 97.4 % ee.

The dialkylborane is chlorinated to enhance the electropositive character of the boron atom, facilitating its ability to coordinate with the carbonyl oxygen atom of the substrate ketone. Reduction of the ketone is then accomplished by what is formally a ß-elimination of the hydrogen atom supplied by the borane monomer in the hydroboration of one of the α-pinene ligands. The reduction is accompanied by the elimination of that α-pinene ligand. (Fig. 3.)

Reduction of acetophenone with Ipc₂BCl.[10]
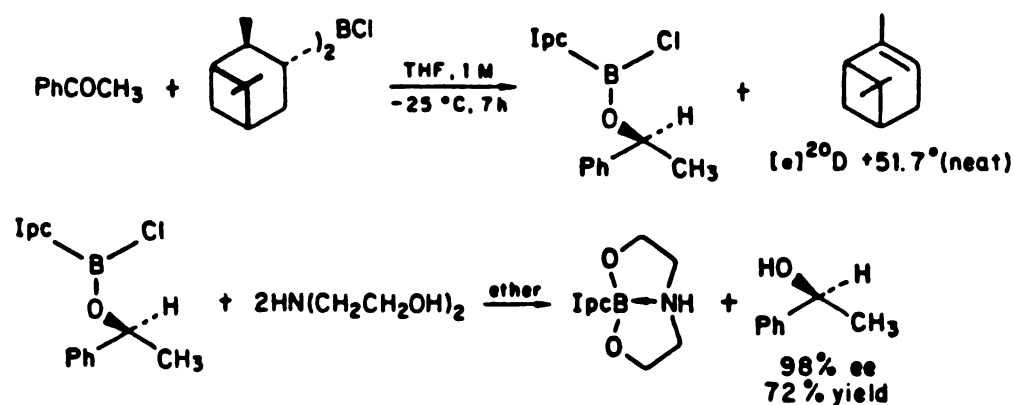
Fig. 3

Liberated α-pinene was removed in the workup under reduced pressure (0.1 mm Hg) and the residue was dissolved in ether. The boron complex of the product was decomposed and the second ß-pinene ligand was complexed by the addition of two molar equivalents of diethanolamine. The precipitate, consisting of diethanolamine hydrochloride and the diethanolamine-α-pinene complex, was filtered off and washed with pentane, and the combined ether and

pentane filtrates were concentrated under reduced pressure. The residue was distilled under reduced pressure to yield pure S-(–)-1-phenylethanol.

From inspection of their structures, it was anticipated that perhaps the dialkylchloroborane reagent, and certainly the alkylchloroborane complex of the product alcohol, would be capable of cleaving the MEM acetal protecting group to the free phenol.[5,8] Preliminary experiments showed that 1.2 mole equivalents of (+)- diisopinocampheylchloroborane would leave 4-(2-methoxyethoxy)methoxyphenylethane 67, in THF at 0°C, to 4-ethylphenol. The cleavage reaction went to 70 % completion in 43 h.

When the reduction of 4-[(2-trimethylsilylethoxy)methoxy]-acetophenone 27 was attempted with 1.2 mole equivalents of (+)-Ipc$_2$BCl in THF at – 25°C, an aliquot was taken after 7 h and quenched in aqueous methanol bascified with a few drops of triethylamine. TLC on silica gel (chloroform/methanol, 20:3) revealed a single spot at R$_f$ 0.83, corresponding to the starting material.

The reduction was repacked in ice and allowed to continue for 12 h before quench and workup. Since a free phenol was expected as the product, a modified workup procedure was adopted. One and a half mole equivalents of triethylamine, based on the Ipc$_2$BCl reagent, was added to the stirred reaction mixture at 0°C, followed by dilution with water. Saturation of the aqueous phase with NaCl was followed by ether extraction. Separation of the product phenol from (–)-α-pinene and other neutrals was effected by extraction of the organic phase with 1 N NaOH, washing the aqueous phase with ether, titrating to pH 7 with 1 N HCl at 0°C, saturation of the aqueous phase with NaCl, ether extraction, drying of the extract over anhydrous Na$_2$SO$_4$, filtering and evaporation of the solvent under reduced pressure. NMR (acetone-d$_6$) indicated the product to be the expected 1-(4-hydroxyphenyl)ethanol, contaminated with 5 mole % of 4-hydroxyacetophenone. The specific rotation

of the product was measured in ethanol and corrected for the presence of 4-hydroxyacetophenone: $[\alpha]_D^{20}= + 44.3°$ (c = 5.00 in EtOH). A sample of the

material was methylated with diazomethane in ether/methanol, and reversed-phase HPLC analysis (methanol/water) of the (–)-MTPA ester of the p-anisyl-methylcarbinol indicated the product to be 96 % enantiomerically pure. The p-anisylmethylcarbinol was also determined to be dextrorotatory, and Cervinka has correlated the absolute configuration of this compound with other arylmethylcarbinols of the R-(+)- absolute configuration .[11] So (+)-Ipc$_2$BCl reduces 4-[(2-trimethylsilylethoxy)methoxy]-acetophenone to R-(+)-1-(4-hydroxyphenyl)ethanol **35**, in agreement with the course of asymmetric induction observed by Chandrasekharan et al. for the reduction of aromatic prochiral ketones with diisopinocampheylchloroborane.

Ipc$_2$BCl was also found, as would be expected, to reduce 4-[(2-methoxy-ethoxy)methoxy]-acetophenone with a correspondingly-high degree of asymmetric induction. A time-course study of this reaction, employing 1.2 mole equivalents of (+)-Ipc$_2$BCl in THF at 0°C, was conducted, with 5 μl aliquots taken every hour initially and every several hours later on. The aliquots were quenched in 200 μl of water containing a few drops of triethylamine, diluted with methanol and analyzed by reversed-phase HPLC (methanol/water). The chromatograms showed a steady decrease in the concentration of the substrate ketone with a corresponding increase in the concentration of 1-[4-(2-methoxy-ethoxy)methoxyphenyl]-ethanol **11** and a slower increase in the concentration of 1-(4-hydroxyphenyl)ethanol. A small concentration of 4-hydroxyacetophe-none did not increase after the first hour. The concentrations of 1-(4-hydroxy-phenyl)ethanol and 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol became equal after about 25 h, and the concentration of 1-(4-hydroxyphenyl)ethanol

continued to increase, leveling off at about 65 h. Another charge of 0.25 mole

equivalents of (+)-Ipc$_2$BCl was added to the reaction mixture after 70 h. This

appeared to be followed by an initial increase in the concentration of 1-(4-

hydroxyphenyl)ethanol after 1 h, but after 2 h, the concentration appeared to

decrease slightly, accompanied by the appearance of an unknown polar

component in the chromatogram as well as an increase in the concentration of

4-vinylphenol **40**. The reaction mixture was quenched and worked up as

described to yield, after silica gel chromatography to remove 4-hydroxyaceto-

phenone and a trace of (–)-α-pinene, 65 % of R-(+)-1-(hydroxyphenyl)ethanol.

The specific rotation was measured in ethanol: $[\alpha]_D^{20}$= + 44.6° (c = 5.2 in EtOH).

Three reductions of 4-[(2-methoxyethoxy)methoxy]-acetophenone with

(+)-Ipc$_2$BCl and two with (–)-Ipc$_2$BCl followed by diazomethane methylation of

samples of the products and reversed-phase HPLC analysis (methanol/water)

of the (–)-MTPA esters of the p-anisylmethylcarbinols yielded average

asymmetric inductions of 95 % with (+)-Ipc$_2$BCl and 97 % with (–)-Ipc$_2$BCl. One

recrystallization of the enantiomerically impure product from ethyl acetate/

hexane increased the enantiomeric purity to > 99.5 %. The observed specific

rotations were $[\alpha]_D^{20}$= + 47.1° (c = 4.98 in EtOH) for the R-(+)-enantiomer and

$[\alpha]_D^{20}$= – 47.5° (c = 4.98 in EtOH) for the S-(–)- enantiomer **36**. The R-(+)-

stereoisomer melted at 157-158°C and the S-(–)- at 157-159°C. The mixed mp

was 137-138°C.

This is the first report of a one pot asymmetric reduction of a carbonyl

group and cleavage of an acetal protecting group with one mole equivalent of

diisopinocampheylchloroborane. A previously-described experiment in this

study demonstrated that Ipc$_2$BCl is capable of cleaving MEM acetals. If this

cleavage proceeds via the mechanism proposed by Guindon et al. for the

cleavage of acetals by dimethylboron bromide,[5] then the boron-containing product of the acetal cleavage ($Ipc_2BOCH_2CH_2OCH_3$) would be expected to be fully capable of coordinating with and reducing the carbonyl group. The intermediate boron complex of the product of the reduction of the substrate ketone with Ipc_2BCl (Fig. 3.), an alkoxydialkylborane, would also be expected to be capable of cleaving the MEM acetal.

The racemic phenolic benzylic alcohol **1** was obtained by reduction of 4-hydroxyacetophenone with $NaBH_4$ in 33 % ethanol.

R-(+)- and *S*-(–)-1-(4-Hydroxyphenyl)ethanol-1-d₁ 37 & 38

4-Hydroxyacetophenone and 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) were coupled in dichloromethane containing N,N-diisopropyl-ethylamine to form 4-[(2-trimethylsilylethoxy)methoxy]-acetophenone **27**, and the ketone was reduced with LAD (99 atom %) in THF to yield *RS*-1-[4(2-trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d₁ **29**, and $NaBH_4$ in 95 % ethanol to give the racemic unlabeled alcohol **28**.

The racemic labeled alcohol was stirred with 1 mole equivalent of phthalic anhydride in DMF, containing 2 mole equivalents of imidazole, for 24 h. Standard workup, as for the phthaloylation of the racemic MEM alcohols, with the elimination of the $NaHCO_3$ wash, provided viscous *RS*-1-[4-(2-trimethylsilyl-ethoxy)methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate **30** in quantitative yield. Interestingly, the sodium salt of this half phthalate could not be dissolved in dilute $NaHCO_3$. When an ether solution of the acid was washed with 4 % $NaHCO_3$, there did not appear to be an evolution of CO_2. The washing resulted in the appearance of 3 layers in the separatory funnel: a top organic layer, a bottom aqueous layer and an intermediate pale-blue emulsion with well-

defined boundaries. The aqueous phase was cooled to 5°C, acidified with 1 N HCl and extracted with ether. The extract was washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. There was no residue!

The racemic half phthalate was treated with one mole equivalent of S-(−)-1-phenylethylamine in ether. After several minutes, there appeared a gel with the same distinct, pale-blue color as the color observed when an ether solution of the half phthalate was shaken with dilute $NaHCO_3$. The ether was removed under reduced pressure and residual ether was stripped by co-distillation with methyl acetate. Attempted crystallization of the residue from methyl acetate yielded a thick, brown, molasses-like mass, which appeared to contain embedded white crystals . Careful trituration of this mass with ice-cold methyl acetate afforded an off-white powder. Concentration of the mother liquor and seeding the viscous solution with the crude salt gave a second crop of this powder. Two methyl acetate recrystallizations of the combined crops of powder, after recycling the mother liquors, afforded the pure SS-salt, melting at 137-138°C, in 48 % yield. The mother liquors were washed with ice-cold 0.2 N HCl and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. After treatment of the concentrate with R-(+)-1-phenylethyl-amine and methyl acetate recrystallization of the precipitated salt, the pure RR-salt, melting at 137-138°C, was obtained, after recycling the mother liquors, in 53 % yield.

Whereas the pure 1-phenylethylamine salts of the MEM half phthalates required approximately 30 ml of methyl acetate per gram of salt for recrystallization, the 1-phenylethylamine salts of the SEM half phthalates required only 3 ml of solvent per gram.

The specific rotation of this salt was highly concentration-dependent. The SS-salt exhibited an $[\alpha]_D^{25} = -10.1°$, when c = 5.2 in absolute ethanol, and and $[\alpha]_D^{25} = -7.09°$ when c = 2.86 in the same solvent. The comparable values for the RR-salt were $[\alpha]_D^{25} = +10.2°$ (c =5.1 in EtOH) and $[\alpha]_D^{25} = +6.95°$ (c = 2.8 in EtOH).

The SS- and RR-salts were decomposed with ice-cold aqueous oxalic acid, in a manner directly analogous to that employed for the decomposition of the 1-phenylethylamine salts of the MEM half phthalates, to afford S-31 and R-1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d_1 hydrogen phthalate 32, respectively, as viscous gums.

Hydrolysis of the resolved monohydrogen phthalates was carried out with alcoholic NaOH, according to the described procedure utilized in the hydrolysis of the resolved MEM monohydrogen phthalates, to yield S-(–)- 33 and R-(+)-1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d_1 34, respectively, from the S- and R--monohydrogen phthalates. The resolved alcohols exhibited specific rotations of $[\alpha]_D^{20} = -34.8°$ (neat) for the S-(–)-enantiomer and $[\alpha]_D^{20} = +35.0°$ (neat) for the R-(+)-enantiomer. Reversed-phase gradient HPLC analysis (methanol/water) of the S-(–)-MTPA ester indicated that the S-(–)-stereoisomer was > 99.3 % S-(–)- and the R-(+)-stereoisomer > 99.8 % R-(+)-. Whereas the reversed-phase HPLC system employed for the separation of the MTPA esters of the chiral alcohols investigated required < 40 min for the separation of the diastereomeric esters of the MEM alcohols (α = 1.03), the diastereomeric esters of the SEM alcohols required >180 min (α = 1.015).

Taken altogether, these observations indicate that the substitution of a trimethylsilyl group for the methoxy group in the acetal protecting group of these phenolic compounds results in a dramatic alteration of their physical properties.

The SEM group was removed by heating the resolved alcohols with 8 mole equivalents of n-Bu$_4$NF, in THF at 45°C, for 24 h. The deprotection, which requires the presence of "adventitious water",[12] is a kind of unraveling, with elimination of trimethylsilyl fluoride, ethylene and formaldehyde (Fig. 4.)

$$RO\!\frown\!O\!\frown\!SiMe_3 \xrightarrow{F^-} ROH + CH_2O + CH_2\!=\!CH_2 + Me_3SiF$$

The "unraveling" of the SEM protecting group.[12]

Fig. 4.

Lipshutz and Pegram described the product isolation as being accomplished by standard extractive workup followed by rough SiO$_2$ filtration.[12] However, in this case the product is a highly polar, water soluble benzylic phenolic alcohol and cannot be separated from the n-Bu$_4$NF by extractive workup. The desired separation was effected by stripping the THF under reduced pressure, dissolving the purple residue in ice-cold, pH 7.5, 0.2 M sodium phosphate buffer and precipitating the tetrabutylammonium cation as the perchlorate salt with 1 mole equivalent of aqueous NaClO$_4$. After the quantitative precipitate was filtered from solution, the filtrate was saturated with NaCl and extracted with ethyl acetate. The combined extracts were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure to give a viscous residue, which was subjected to column chromatography on silica gel to give the pure benzylic phenolic alcohol in 82 % yield. The R-(+)- and S-(−)-

SEM alcohols provided R-(+)- **37** and S-(–)-1-(4-hydroxyphenyl)ethanol-1-d$_1$ **38**, respectively.

The products were methylated with diazomethane in ether/methanol, and reversed-phase gradient HPLC analysis (methanol/water) of the (–)-MTPA esters of the p-anisylmethylcarbinols indicated that the R-(+)- stereoisomer was a mixture of 98.5 % R-(+)- isomer and 1.5% S-(–)-isomer. The S-(–)-stereoisomer was a mixture of 99.0 % S-(–)-isomer and 1.0 % R-(+)-isomer. Little racemization attendant to protecting group cleavage was observed. One recrystallization from ethyl acetate/hexane increased the enantiomeric purity of each stereoisomer to > 99.6 %. The observed specific rotations were $[\alpha]_D^{20}$= + 49.1° (c = 5.00 in EtOH) for the R-(+)- isomer and $[\alpha]_D^{20}$= – 48.8° (c = 5.02 in EtOH) for the S-(–)-isomer. Each enantiomer melted at 159-160°C and the mixed mp was 137-139°C.

The racemic 1-(4-hydroxyphenyl)ethanol-1-d$_1$ **2** was prepared by reduction of 4-hydroxyacetophenone with LAD (99 atom %) in THF.

S-(–)-1-(4-Methoxyphenyl)ethanol 48

A time-course study of the asymmetric reduction of 4-methoxy-acetophenone with (–)-Ipc$_2$BCl was carried out, employing 1.2 mole equivalents of reagent in THF at 0°C. Five μl aliquots were taken every hour and quenched with 0.5 ml of methanol containing a few drops of triethylamine. Reversed-phase HPLC analysis (methanol/water) indicated that 7 h was required for the reduction to proceed to 97 % completion (Table 2). The

chromatograms were very clean, exhibiting only product, substrate and less than 5 % of an unknown nonpolar component.

Chandrasekharan et al report 7 h for the completion of the reduction of acetophenone with (–)-Ipc$_2$BCl in THF at – 25°C.[10] It is not surprising that 4-methoxyacetophenone, with its deactivated carbonyl group (Fig. 5.), would require a 25°C increase in temperature to react with Ipc$_2$BCl at a rate comparable to that of acetophenone.

Time, h	Percent completion
1	77
2 $^1/_3$	89
3	91
5	95
7	97

Time-course of the reduction of 4-methoxyacetophenone with
1.2 molar equivalents of (–)-Ipc$_2$BCl in THF at 0°C.

Table 2.
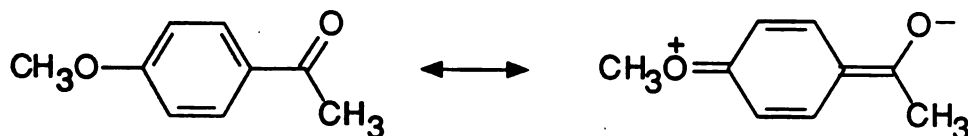
Mesomeric donation of electrons leading to deactivation of the
carbonyl group in 4-methoxyacetophenone.

Fig. 5.

Workup according to the method of Chandrasekharan et al. resulted in the yield of 27 % product which was only 55 % enantiomerically pure. This workup involves evaporating the THF under reduced pressure and pumping on the residue at 0.1 mm Hg for 8 h to remove the eliminated first mole of α-pinene. During this time, a trace of HCl resulting from partial hydrolysis of the alkylchloroboron complex of the product alcohol could have catalyzed racemization and elimination to the styrene polymer, or the complex may just be thermally labile. The same mesomeric electron donation by the methoxy group that deactivates the carbonyl group to nucleophilic attack promotes elimination at saturated benzylic carbon and stabilizes the incipient carbonium ion in the transition state leading to elimination.

A modified workup was adopted for this substrate to eliminate the decomposition accompanying the standard procedure. One and a half mole equivalents of triethylamine, based on the Ipc_2BCl reagent, was added to the stirred reaction mixture at 0°C, followed by dilution with water. Saturation of the aqueous phase with NaCl was followed by ether extraction, drying of the extract over anhydrous Na_2SO_4, filtering and evaporation of the solvent under reduced pressure. The residue was subjected to silica gel column chromatography to afford S-(−)-1-(4-methoxyphenyl)ethanol 48, in 84 % yield, which exhibited an $[\alpha]_D^{20}$= − 40.10° (neat). This corresponds to an enantiomeric purity of 80 %.[13]

This compound, as the R-(+)-stereoisomer, was first prepared in an enantiomerically pure form by Balfe et al., who obtained it by classical resolution of the cinchonidine salt of the hydrogen phthalate ester.[13] Currently, there is no rationalization for the observed difference in asymmetric induction of Ipc_2BCl toward 4-methoxyacetophenone and 4-[(2-methoxy-

ethoxy)methoxy]-acetophenone **10** and 4-[(2-trimethylsilylethoxy)methoxy]-

acetophenone **27**.

References

1) Dabby, R.E.; Davies, A.G.; Kenyon, J.; Lyons, B.J. J. Chem. Soc. **1953**, 3619-3623.

2) Corey, E.J.; Gras, J.L.; Ulrich, P. Tetrahedron Lett. **1976**, *11*, 809-812.

3) Corey, E.J.; Hua, D.H.; Seitz, S.P. Tetrahedron Lett. **1984**, *25*, 1-6.

4) Williams, D.R.; Sakdarat, S. Tetrahedron Lett. **1983**, *24*, 3965-3968.

5) Guindon, Y.; Yoakim, C.; Morton, M. Tetrahedron Lett. **1983**, *24*, 3969-3972.

6) Guindon, Y.; Yoakim, C.; Morton, M. Tetrahedron Lett. **1983**, *24*, 2969-2972.

7) Heathcock, C.H., Dept. of Chemistry, University of California, Berkeley, private communication.

8) Boeckman, Jr., R.K.; Potenza, J.C. Tetrahedron Lett. **1985**, *26*, 1411-1414.

9) Gerrard, W.; Lappert, M.F.; Mountfield, B.A. J. Chem. Soc. **1959**, 1529-1535.

10) Chandrasekharan, J.; Ramachandran, P.V.; Brown, H.C. J. Org. Chem. **1985**, *50*, 5448-5450.

11) Cervinka, O. Coll. Czechoslov. Chem. Comm. **1965**, *30*, 1684-1691.

12) Lipshutz, B.H.; Pegram, J.J. Tetrahedron Lett. **1980**, *21*, 3343-3346.

13) Balfe, M.P.; Evans, A.; Kenyon, J.; Nandi, K.N. J. Chem. Soc. **1946**, 803-807.

14) Dale, W.J.; Hennis, H.E. J. Am. Chem. Soc. **1958**, *80*, 3645-3649.

15) Optical Resolution, Procedures for Chemical Compounds, Vol. 3, Alcohols, Phenols, Thiols, Aldehydes and Ketones, Newman, P.; ed., Optical Resolution Information Center, Manhattan College, Riverdale, New York, 1984, Section 2, pp. 155-157.

The Synthesis and Absolute Configuration of the Enantiomers of 1-(4-Hydroxyphenyl)ethane and 1-(4-Hydroxyphenyl)ethane-1-d_1

Chapter III

The Synthesis of R-(+)- and S-(–)-1-(4-Hydroxyphenyl)ethane-1-d₁ 74 & 73

As outlined in the Summary of Planned Syntheses (Schemes 3 & 4), two basic strategies were employed for the synthesis of the title compounds. The first involved the *in situ* formation of the methanesulfonate ester of R-(+)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d₁ **26** at –78°C in THF, followed (without isolation) by the displacement of the mesylate *in situ* at –78°C with LAH. Cleavage of the MEM acetal protecting group with 2-bromo-1,3,2-benzodioxaborole in dichloromethane led to one of the enantiomers of the desired product.

The second strategy employed the synthetic utility of lithium diorganocuprate(I) reagents.[1] The heterocuprate(I) derived from copper(I) t-butylacetylide and 4-methoxyphenyllithium **65**, at –78°C in ether/THF, in a displacement reaction with the methanesulfonate esters of enzymatically generated, enantiomerically pure R-(+)- **49** and S-(–)-ethanol-1-d₁ **50** at 0°C in ether/THF, yielded S-(–)- **71** and R-(+)-1-(4-methoxyphenyl)ethane-1-d₁ **70**, respectively. Cleavage of the methyl ethers with 2-bromo-1,3,2-benzodioxaborole in dichloromethane containing N,N-diisopropylethylamine afforded S-(–)- **73** and R-(+)-1-(4-hydroxyphenyl)ethane-1-d₁ **74**.

S-(–)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethane-1-d₁ 68

S-(–)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethane-1-d₁ was formed from R-(+)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d₁ **26** by

treatment of the alcohol, in THF containing triethylamine, at $-78°C$ with methanesulfonyl chloride. After the reaction mixture was allowed to stand at $-78°C$ overnight, it was treated with an excess of LAH in THF and then quenched with water. Workup and silica gel chromatography afforded the pure product, which exhibited the following ORD curve (Table 1.).

λ(nm)	589	578	546	436	365
$[\alpha]_{\lambda}^{25}$	$-0.138°$	$-0.146°$	$-0.172°$	$-0.322°$	$-0.546°$

Specific rotations of S-(–)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethane-1-d_1.
(neat, l =1.000 dcm)

Table 1.

Preliminary experiments had indicated that the maximum conversion of substrate to product was obtained with 5 mole equivalents of methanesulfonyl chloride per mole of alcohol and with 2 mole equivalents of triethylamine per mole of mesyl chloride. Substitution of N,N-diisopropylethylamine for triethylamine resulted in a conversion to product of only a few %.

When the small amount of unreacted starting material (~2 %) was recovered from the silica gel column, reversed-phase LC analysis (methanol/water) of the (–)-MTPA ester revealed that the alcohol had completely racemized (Fig. 1.). This phenomenon was reproducible. Since there were 2.5 mole equivalents of triethylamine present for each mole of methanesulfonyl chloride to sequester any protons which could catalyze racemization, this observation was unexpected and remains unexplained.
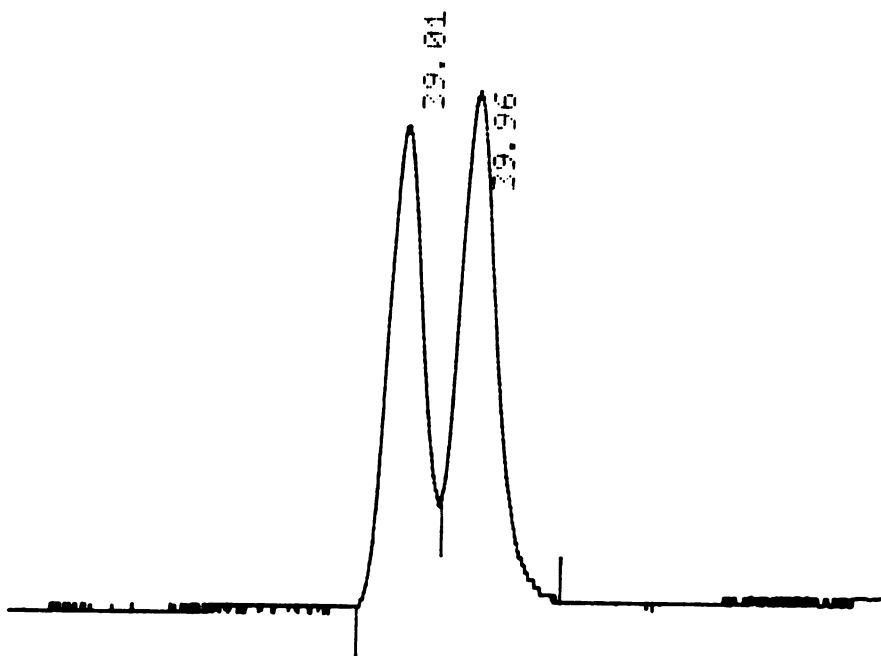
Reversed-phase HPLC chromatogram of the (–)-MTPA ester of unreacted R-(+)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d_1 recovered from the displacement reaction of the mesylate with LAH at –78°C.

Fig. 1.

The racemic form of the title compound was prepared in an exactly analogous fashion, employing racemic substrate. It was also obtained from the racemic unlabeled alcohol, employing LAD as the reducing agent. When lithium triethylborodeuteride was employed as the reductant, a product was obtained which was determined by ^{1}H NMR spectroscopy to be a mixture of unlabeled and labeled material in a ratio of ca. 3.5 to 1. This reaction was not further investigated.

The unlabeled analog of the title compound was prepared by an analogous method, employing the racemic unlabeled alcohol and either LAH or lithium triethylborohydride as the reducing agent. It was also obtained by coupling 4-ethylphenol with 2-methoxyethoxymethyl chloride in methylene chloride containing N,N-diisopropylethylamine.

R-(+)- and *S*-(−)-Ethanol-1-d$_1$ 49 & 50

R-(+)- and *S*-(−)-Ethanol-1-d$_1$ were prepared by the enzymic equilibration method described by Simon and co-workers for the preparation of *R*-propanol-1-d$_1$.[2] Gorlach and Zagalak have reported, without details, that they used this method for the preparation of *R*-(+)-ethanol-1-d$_1$.[3] The adaptation employed in this study is that of Mosher.[4]

In this method ethanol-O-d was incubated with Bakers yeast alcohol dehydrogenase, bovine serum albumin, porcine-heart diaphorase, ß-NAD$^+$, ß-NADD and deuterium-exchanged potassium phosphate buffer, in D$_2$O adjusted to pD 7.9 and equilibrated at 28°C. During the equilibration, the pro-*R* hydrogen atom in the 1-position of ethanol-O-d is exchanged for deuterium.^{1}H NMR analysis indicated that the equilibration was complete in about 5 days. The *R*-(+)-ethanol-1-d$_1$ was distilled out of the reaction mixture through a Teflon spinning-band column as the ethanol/water azeotrope.

S-(−)-Ethanol-1-d$_1$ was prepared from ethanol-1,1-d$_2$ 52 (obtained from the reduction of phenyl acetate by LAD in diglyme) by the same procedure. The equilibration was carried out with unexchanged reagents in H$_2$O at pH 7.5.

The elegant experiments of Westheimer, Vennesland and collaborators have definitively established the stereospecificity of this hydrogen-transfer

reaction between 4-R-[^{2}H]-NADH and acetaldehyde.[5] However, it was decided to employ an enantiomerically pure chiral carboxylic acid as a derivatizing agent for the determination of the enantiomeric purity of the enzymatically-produced, labeled ethanols. These derivatives were also used for the determination of deuterium incorporation by mass spectrometry. The chiral acid chosen was R-(−)-O-acetylmandelic acid.[6]

The R-O-acetylmandelate esters of ethanol **53** and of RS- **55**, R-(+)- **56** and S-(−)-ethanol-1-d$_1$ **57** were prepared from R-(−)-O-acetylmandelic acid and the respective ethanols according to the method of Parker,[6] and the derivatives were subjected to analysis by^{1}H NMR at 500 MHz.

The diastereotopic methylene protons of the unlabeled derivative exhibited a pair of doublets of quartets, centered at 3.919 ppm and 3.790 ppm, corresponding to the pro-R and pro-S hydrogens, respectively (Fig. 2a.). This corresponds to a chemical shift difference ($\delta\Delta$) of 64 Hz.

The derivative of the racemic labeled ethanol provided a pair of quartets of triplets, centered at 3.911 ppm and 3.803 ppm, corresponding to the pro-R and pro-S hydrogens in the unlabeled ethanol, respectively (Fig. 2b.). This corresponds to a $\delta\Delta$ of 54 Hz. The pair of weak resonances slightly downfield of each quartet corresponds to the small amount of unlabeled ethyl ester (~ 3 % by mass spectrometry) present in the analytical sample, the remainder of each set of resonances being buried beneath the quartets of triplets corresponding to the labeled ester.

The R-O-acetylmandelate esters of R-(+)- and S-(−)-ethanol-1-d$_1$ exhibited quartets of triplets centered at 3.794 ppm and 3.904 ppm, corresponding to the pro-S and pro-R hydrogens in the unlabeled derivative, respectively (Figs. 2c. & 2d.). Neither spectrum exhibits a multiplet characteristic of the derivative of the other alcohol enantiomer. The weak

multiplets present downfield and upfield, respectively in each spectrum, again correspond to the small amount of unlabeled ester in each sample.

The 70 eV EI mass spectrum, monitoring m/z values $(M-1)^+$, M^+ and $(M+1)^+$ only, was recorded for each derivative. After correction for ^{13}C and ^{17}O content, the following deuterium enrichment was calculated for each labeled ethanol:

Isomer:	RS-	R-(+)-	S-(−)-
Deuterium enrichment:	97.1 %	98.3 %	97.6 %

Since the RS- isomer was synthesized by the reduction of acetaldehyde in diglyme with "99 atom %" LAD, the low enrichment (average: 97.7 %) was unexpected, and the necessity of employing fresh LAD to obtain high deuterium incorporation should be emphasized.

500 MHz ^1H NMR spectrum of the -OCH$_2$-region of ethyl R-O-acetyl mandelate.

Figure 2a.

500 MHz ^{1}H NMR spectrum of the -OCHD-region of *RS*-ethyl-1-d$_1$ *R*-O-acetylmandelate.

Figure 2b.

500 MHz ^{1}H NMR spectrum of the -OCHD-region of *R*-ethyl-1-d$_1$ *R*-O-acetylmandelate.

Figure 2c.

67

500 MHz ^{1}H NMR spectrum of the -OCHD-region of S-ethyl-1-d$_1$ R-O-acetylmandelate.

Figure 2d.

S-(+)-1-Phenylethane-1-d$_1$ 61

It was decided to investigate the synthetic utility of lithium diarylcuprate(I) reagents[1] for the transfer of isotopically-engendered chirality. The first substance to be synthesized was S-(+)-1-phenylethane-1-d$_1$, from lithium diphenylcuprate(I) and R-(+)-ethyl-1-d$_1$ methanesulfonate in ether.

R-(+)- 60 and S-(-)-ethyl-1-d$_1$ methanesulfonate 59 were prepared from R-(+)-ethanol-1-d$_1$-O-d and R-(+)-ethanol-1-d$_1$, respectively, and methane-sulfonyl chloride in methylene chloride containing triethylamine. The ORD curves for the purified materials, corrected for deuterium incorporation at the chiral center, were identical in amplitude at the five wavelengths monitored.

The R-(+)-mesylate was shown by mass spectrometry to be a mixture of approximately equal parts of mono- and di- deuteriated products, in accord with the well-known dual mechanism of formation of methanesulfonate esters from alcohols and methanesulfonyl chloride in the presence of triethylamine.[7] Briefly, the mesylates can be formed by the direct displacement of chloride ion from mesyl chloride, by attack of the alcohol on sulfur, leading to the mono-deuteriated product, or by the dipolar addition of the alcohol to the planar sulfene intermediate, formed by the reaction of mesyl chloride with triethylamine, leading to the dideuteriated product (Fig. 3.).
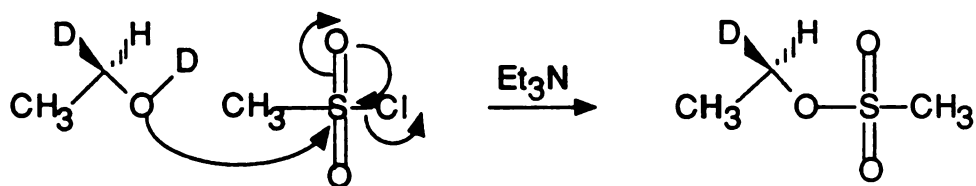
Route 1. Direct displacement
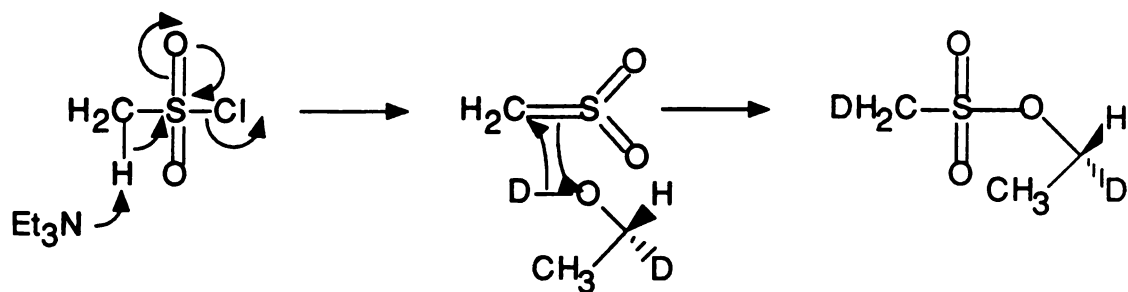
Route 2. Dipolar addition

Mechanisms of formation of R-(+)-ethyl-1-d$_1$ methanesulfonate from R-(+)-ethanol-1-d$_1$-O-d, methanesulfonyl chloride and triethylamine.

Figure 3.

However, since the displacement reactions of alkyl methanesulfonates result in the loss of the methanesulfonate anion, the incorporation of a deuterium atom in the methyl group of the methanesulfonate moiety is of no consequence in subsequent reactions of the alkylated product.

Preliminary experiments with lithium diphenylcuprate(I), formed *in situ* by the reaction of two mole equivalents of ice-cold ethereal phenyllithium with cuprous iodide, and unlabeled ethyl methanesulfonate showed that ethylbenzene could be obtained in high yield when freshly prepared phenyllithium[8] was employed. The use of commercial phenyllithium resulted in a lower yield of product (< 25 %).

When the reaction was applied to R-(+)-ethyl-1-d_1 methanesulfonate in ether at 0°C, normal workup and fractionation of the product through a Teflon spinning-band column, using bromobenzene as a "chaser", afforded S-(+)-1-phenylethane-1-d_1 in 62 % yield, shown by 240 MHz ^1H NMR spectroscopy to contain approximately 3 mole % benzene, formed in the hydrolysis of excess lithium diphenylcuprate(I) (Fig. 4.). The ORD curve of the neat-liquid product was recorded at five wavelengths and corrected for the trace of benzene present to yield the following data, compared with the literature values[9] for the enantiomerically pure S-(+)-1-phenylethane-1-d_1 (Table 2.) This comparison provides an average-minimum enantiomeric purity of 95.1 % for the synthetic product, indicating that the displacement proceeds with a minimum of 95 % inversion of configuration. This appears to be the first report in the literature employing lithium diarylcuprates(I) for the "transfer" of isotopically-engendered chirality.
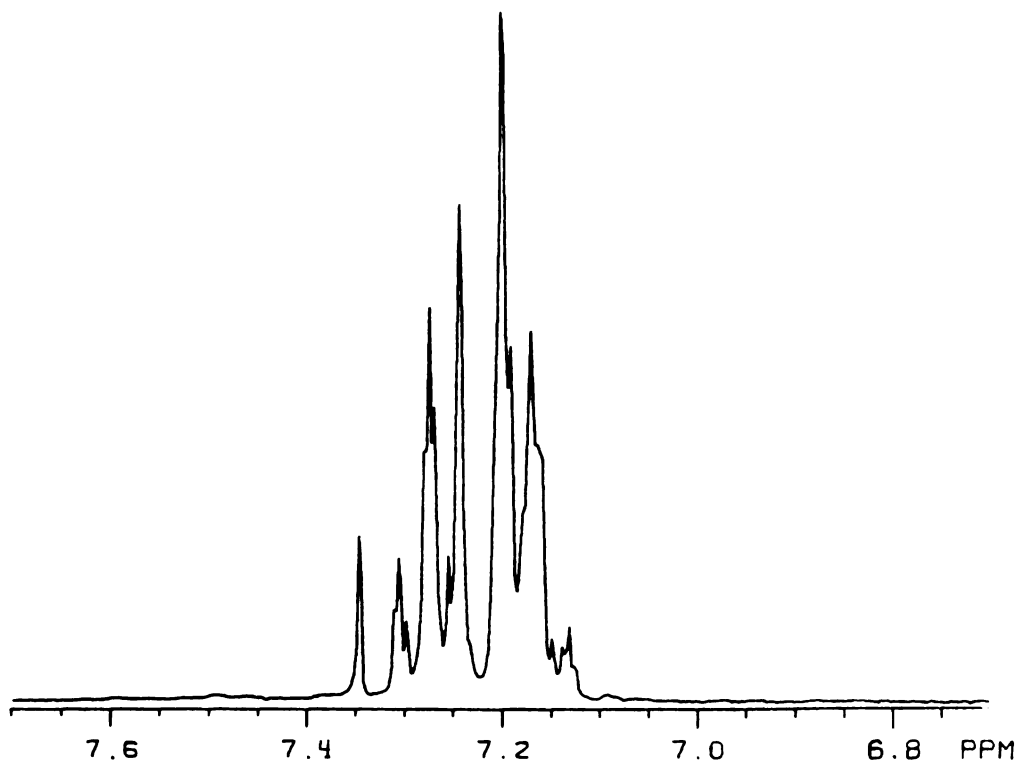
240 MHz ^{1}H NMR spectrum of the aromatic region of S-(+)-1-phenylethane-1-d$_1$.
The singlet at δ 7.35 ppm corresponds to benzene.

Figure 4.

a)
$$\alpha^{20}_D = + 0.676°, \quad \alpha^{20}_{578} = + 0.709, \quad \alpha^{20}_{546} = + 0.820, \quad \alpha^{20}_{436} = +1.527°, \quad \alpha^{20}_{365} = +2.686°$$

b)
$$\alpha^{20}_D = + 0.710°, \quad \alpha^{20}_{578} = + 0.743, \quad \alpha^{20}_{546} = + 0.861, \quad \alpha^{20}_{436} = +1.604°, \quad \alpha^{20}_{365} = +2.843°$$

(neat, l= 1.000 dcm)

Optical rotatory powers of S-(+)-1-phenylethane-1-d$_1$:
a) from lithium diphenylcuprate(I) and R-(+)-ethyl-1-d$_1$ methanesulfonate
b) from Elsenbaumer, et al.[9]

Table 2.

71

4-Methoxyphenyllithium 65

An attempt was made to prepare 4-(2-methoxyethoxy)methoxy-phenyllithium by the treatment of 4-(2-methoxyethoxy)methoxyphenyl iodide **64** (synthesized from the Grignard reagent of the bromo compound **63** and iodine) in dry benzene with n-butyllithium. However, the aryllithium produced was a viscous, orange-yellow oil, which could not be purified. Hydrolysis of a small amount of the reagent followed by reversed-phase LC analysis (methanol/water) of the hydrolysate, indicated a 4-1 ratio of 2-methoxyethoxymethoxy-benzene **62** to 4-(2-methoxyethoxy)methoxyphenyl iodide, corresponding to an 80 % conversion of 4-(2-methoxyethoxy)methoxyphenyl iodide to 4-(2-methoxy-ethoxy)methoxyphenyllithium. This approach was abandoned. Instead, 4-methoxyphenyllithium was prepared from 4-iodoanisole by the method of Schlosser and Ladenberger,[10] and the reagent was used in the preparation of the 4-methoxyphenyl-derived lithium diorganocuprate(I) reagents employed in this study. As noted in the experimental section, this material was found to be extremely unstable in a dry, finely divided state. In two instances, a three-necked flask containing approximately 20 g of the organolithium reagent, under high vacuum, became hot to the touch and blew out a glass stopper. The subsequent rush of air into the vessel resulted in the combustion of the pyrophoric reagent. In subsequent preparations of this material, the last pentane wash was decanted through a stainless steel cannula under dry nitrogen. The bulk of the residual pentane was removed in a stream of dry nitrogen and the solid aryllithium reagent was immediately dissolved in dry 80:20 ether/THF before standardization by the method of Vogel.[8]

R-(+)- and *S*-(−)-1-(4-Methoxyphenyl)ethane-1-d₁ 70 & 71

A series of preliminary experiments was carried out, employing unlabeled starting materials, to determine the best lithium diorganocuprate(I) reagent and the optimum experimental conditions for the synthesis of the title compounds from *S*-(−)- **59** and *R*-(+)-ethyl-1-d₁ methanesulfonate **60**.

Lithium di-(4-methoxyphenyl)cuprate(I) was prepared from 4-methoxyphenyllithium **65** and CuI, CuI•n-Bu₃P, CuBr•Me₂S or [CuCF₃SO₃]₂•C₆H₆. A solution of standardized 4-methoxyphenyllithium in ether/tetrahydrofuran was slowly added to a stirred solution/slurry of either complexed or uncomplexed cuprous salt in ether, cooled to −78°C, under nitrogen. An ethereal solution of ethyl methanesulfonate was then slowly added to the stirred solution of the lithium diarylcuprate(I). After the reaction mixture was allowed to warm to 0°C, it was quenched with saturated NH₄Cl. Workup, fractional distillation under reduced pressure in a Teflon spinning-band distillation apparatus and silica gel chromatography yielded pure 4-ethylanisole **66**.

Initial experiments employing commercial cuprous iodide failed due to decomposition of the lithium di-(4-methoxyphenyl)cuprate(I) reagent. Addition of the first equivalent of 4-methoxyphenyllithium appeared to proceed in a smooth manner, but near the end of the addition of the second equivalent the reagent would decompose and separate from solution as a amorphous, orange-brown mass. Purification of the cuprous iodide according to the method of Kauffman and Teter[11] did not prevent the decomposition from occurring. Similar problems with reagent decomposition were encountered with the other copper(I) reagents employed. Finally, the following quotation in a paper by House and Umen[12] led to the successful resolution of the problem:

"A number of pieces of circumstantial evidence have also led us to believe that the amount of iron impurities extracted from imperfectly sealed Teflon-coated magnetic stirring bars may also catalyze the decomposition of various cuprates; as a result, we believe it unwise to use any stirring device not completely encased in glass for organocuprate reactions."

This observation by House and Umen led us to abandon magnetic stirring bars in favor of overhead mechanical stirring. Also, all glassware employed in further preparations employing organocuprate(I) reagents was soaked overnight in concentrated nitric acid, washed with triple-distilled water and dried in a 110°C oven. Cuprous iodide continued to be purified by the method of Kauffman and Teter. When these additional precautions were taken, the premature decomposition of the lithium di-(4-methoxyphenyl)cuprate(I) reagents ceased.

Furthermore, after addition of the 4-methoxyphenyllithium reagent from the addition funnel, the residual reagent in the funnel was washed into the reaction vessel with fresh solvent. Whenever pure tetrahydrofuran was used for the wash of the organolithium reagent into an ether/tetrahydrofuran solution of uncomplexed lithium di-(4-methoxyphenyl)cuprate(I) at −78°C, the reagent precipitated and/or decomposed. The use of 2:1 ether/etrahydrofuran as the wash liquid eliminated the problem of precipitation/decomposition and this solvent mixture was employed as the wash liquid in the preparation of complexed and uncomplexed homo- and hetero- 4-methoxyphenyllithium-derived cuprates(I).

Commercial CuBr•Me$_2$S was also found to be unsuitable for the preparation of lithium di-(4-methoxyphenyl)cuprate(I)•Me$_2$S. Purification of the commercial salt complex according to the method of House et al.[13] failed to provide material of the required purity. However, preparation of CuBr•Me$_2$S from commercial CuBr and Me$_2$S according to the method of House et al.[13]

74

yielded pure CuBr•Me₂S, which was successfully employed in the preparation of the organocuprate complex.

All of the organocuprate(I) reactions utilizing complexed or uncomplexed lithium di-(4-methoxyphenyl)cuprate(I) led to the formation of 4,4'-dimethoxy-biphenyl as a byproduct. Whitesides et al.[1,14,15] have documented the formation of dimers from the oxidative decomposition of lithium diorgano-cuprate(I) reagents, promoted by either molecular oxygen or cupric ion. These dimers are also produced by thermal decomposition of the organocuprates(I).[1,16]

A second byproduct of the reaction of lithium diorganocuprates(I), derived from 4-methoxyphenyllithium, with ethyl methanesulfonate is 2-ethyl-anisole. Carbonation of an aliquot of 4-methoxyphenyllithium in ether/ THF, which had been stored in the refrigerator at 5°C for one month, was followed by acidification, ether extraction and diazomethane methylation of the product. Reversed-phase HPLC analysis (methanol/water) revealed a mixture of methyl 2-methoxyphenyl acetate and methyl 4-methoxyphenyl acetate, indicating a slow conversion of ether/tetrahydrofuran solutions of 4-methoxyphenyllithium to a mixture of the ortho- and para- isomers of the reagent. In order to minimize the contamination of 4-ethylanisole with its 2-substituted isomer, the 4-methoxyphenyllithium should be freshly prepared prior to use. In any event, it should not be stored for more than one week to minimize contamination with the 2-substituted isomer, and attendant loss of product, to less than 10 %. However, the more volatile and less polar 2-ethylanisole was easily removed from the product 4-ethylanisole by reduced-pressure fractional distillation in a Teflon spinning-band column followed by column chromatography on a silica gel. (Incidentally, it was observed in the reduced-

pressure evaporation of methanol solutions of samples of column fractions taken for HPLC analysis, that 4-ethylanisole will co-distill with methanol).

4-Bromoanisole has been well documented to undergo ortho-metallation as a side reaction in halogen-metal interconversion reactions.[17] According to Jones et al.:[18]

> "It is significant that side reactions of this type are favored when the metalating agent is an aromatic lithium compound like phenyllithium and when the reaction is allowed to proceed for a long period of time".

A heterocuprate(I) reagent was prepared from copper(I) t-butylacetylide, synthesized by the method of House and Umen,[12] and 4-methoxyphenyllithium. Tert-butylacetylene, as a ligand in heterocuprates(I), is known to stabilize thermally- and oxidatively-labile lithium diorganocuprate(I) reagents.[12] The aryl moiety is preferentially transferred in conjugate addition and displacement reactions.[12,19] Additionally, the heterocuprate(I) requires only one mole equivalent of the reactive, labile, pyrophoric 4-methoxyphenyllithium. This reagent was then employed in the displacement reaction with ethyl methanesulfonate. A trace of the dimer of t-butylacetylene, a byproduct of reagent oxidation,[12] was isolated from coupling reactions using this heterocuprate(I).

Solutions of complexed and uncomplexed lithium di-(4-methoxyphenyl)-cuprate(I) and the heterocuprate derived from 4-methoxyphenyllithium and copper(I) t-butylacetylide are light yellow-green in color. Shortly after the addition of the ethyl methanesulfonate substrate, lithium methanesulfonate precipitates from solution and, in the case of the heterocuprate, the color begins to change from yellow-green to the characteristic orange-red of copper(I) t-butylacetylide. In a couple of preparations of uncomplexed lithium

di-(4-methoxyphenyl)cuprate(I) and a preparation of the heterocuprate(I), the reagent solutions became dark purple. A clue to the origin of this anomalous color appeared in the workup of the coupling reactions. After the coupling reactions are quenched with saturated NH_4Cl, the aqueous phase is oxidized by atmospheric oxygen and the color changes from red to the characteristic deep blue of cupric ion. The organic and aqueous phases are then filtered from a precipitated yellow solid, presumably unhydrolyzed organocopper compounds. This yellow solid, when it contaminated ground glass joints, was found to be removed only by concentrated nitric acid, which dissolves it to afford a deep-purple solution. The appearance of the 4-methoxyphenyllithium-derived cuprate(I) solutions as dark purple in color may therefore be diagnostic of oxidation, either by atmospheric oxygen or metal ions. Interestingly, Gillmeister reported that 4,4'-dimethoxybiphenyl, the dimer formed in the thermal or oxidative decomposition of the cuprates(I) employed in this study, turns a dark blue color in the presence of an excess of nitric acid.[20]

After the addition of the 4-methoxyphenyllithium solution at $-78°C$, it was determined that a better yield of purer product could be obtained by allowing the reagent solution to rapidly warm to $0°C$ before substrate addition, rather than immediately adding the substrate at $-78°C$. This allows undissolved 4-methoxyphenyllithium to dissolve and cuprate(I) formation to go to completion, resulting in a clear solution.

A cuprate to ethyl methanesulfonate substrate ratio of 2 or 2.5 to 1 was used in the coupling reactions. Generally, ^{1}H NMR analysis indicated 0 to 10 % of unreacted ethyl methanesulfonate in the crude reaction products. This material could be removed either by reduction with LAH in ether or column chromatography on silica gel.

The ligand-complexed cuprous salts employed in the synthesis of the various cuprates(I) used in this study were reported to stabilize thermally or oxidatively labile lithium diorganocuprates(I).[13,15,19] CuI•n-Bu$_3$P was synthesized according to the method of Kauffman and Teter[11] and CuBr•Me$_2$S by the method of House and Umen[13]. [CuCF$_3$SO$_3$]$_2$•C$_6$H$_6$ was a commercial preparation and, like commercial CuBr•Me$_2$S, was found to be unsuitable for cuprate(I) preparation.

Tri-n-butylphosphine was removed from the product of the CuI•n-Bu$_3$P-derived cuprate(I) coupling reactions by reduced-pressure fractional distillation in a Teflon spinning-band column.

However, the best yield of product was found to be given by the heterocuprate(I) formed from copper(I) t-butylacetylide and 4-methoxyphenyl-lithium, and this reagent was employed for the synthesis of R-(+)- and S-(–)-1-(4-methoxyphenyl)ethane-1-d$_1$. The S-(–)-isomer was prepared from a cuprate(I) made from an aged preparation of 4-methoxyphenyllithium, and the product was contaminated with about 25 % of the 2-substituted positional isomer. The R-(+)-isomer exhibited optical rotatory powers which were, on average, 79 % of the comparable values exhibited by the S-(–)-enantiomer (Table 3.). It is interesting to note that the heterocuprate(I) solution which was used for the preparation of R-(+)-1-(4-methoxyphenyl)ethane-1-d$_1$ was the deep-purple color referred to above. It should also be noted that there is very strong evidence against the participation of a radical intermediate in conjugate addition and displacement reactions of lithium diorganocuprate(I) reagents.[21] However, there is no reported study in the literature of the use of a lithium diorganocuprate(I) with a 4-methoxyphenyl ligand in the synthesis of a chiral compound.

These compounds reveal that R- and S-1-(4-methoxyphenyl)ethane-1-d$_1$ are dextrorotatory and levorotatory, respectively, whereas R- and S-1-phenyl-ethane-1-d$_1$ are levorotatory and dextrorotatory, respectively.

λ	589 nm	578 nm	546 nm	436 nm	365nm
R-(+)-, $[\alpha]_\lambda^{25}$	+ 0.187° (neat)	+ 0.194°	+ 0.226°	+ 0.427°	+ 0.778°
S-(–)-, $[\alpha]_\lambda^{25}$ (neat)	– 0.236°	– 0.251°	– 0.282°	– 0.534°	–1.002°

Specific rotatory powers of R-(+)- and S-(–)-1-(4-methoxyphenyl)ethane-1-d$_1$.

Table 3.

S-(–)-1-(4-Hydroxyphenyl)ethane-1-d$_1$ 73

a) The S-(–)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethane-1-d$_1$ 68 produced from R-(+)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$ 26 was cleaved at 0°C with 2-bromo-1,3,2-benzodioxaborole in dichloromethane, containing a small amount of N,N-diisopropylethylamine, to S-(–)-1-(4-hydroxy-phenyl)ethane-1-d$_1$. The product was purified by column chromatography on silica gel and then sublimed *in vacuo* to yield S-(–)-1-(4-hydroxyphenyl)ethane-1-d$_1$ as white needles in 91% yield, 67 % overall yield from R-(+)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$. The racemic labeled phenol 75 was produced from the racemic acetal in an analogous fashion.

79

λ	589 nm	578 nm	546 nm	436 nm	365nm
$[\alpha]_{\lambda}^{25}$	− 0.25°	− 0.24°	− 0.30°	− 0.563°	− 1.04°

c = 25.3 in EtOH

Specific rotations of S-(−)-1-(4-hydroxyphenyl)ethane-1-d_1 from
S-(−)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethane-1-d_1.

Table 4.

R-(+)- and *S*-(−)-1-(4-Hydroxyphenyl)ethane-1-d_1 74 & 73

b) *R*-(+)- 70 and *S*-(−)-1-(4-Methoxyphenyl)ethane-1-d_1 71 were cleaved at room temperature with two mole equivalents of 2-bromo-1,3,2-benzodioxaborole in dichloromethane, containing a small amount of N,N-diisopropylethylamine, to *R*-(+)- and *S*-(−)-1-(4-hydroxyphenyl)ethane-1-d_1, respectively. The cleavage reactions were carried out in the dark, under argon, and required one week to go to completion. The products were purified by column chromatography on silica gel and sublimed *in vacuo* to give *R*-(+)- and *S*-(−)-1-(4-hydroxyphenyl)ethane-1-d_1 in 95% and 87% yield, respectively, which exhibited the following ORD (Table 5.) and CD (Table 6.) curves.

Dextrorotatory and levorotatory 1-(4-methoxyphenyl)ethane-1-d_1 are respectively cleaved to dextrorotory and levorotatory 1-(4-hydroxyphenyl)-ethane-1-d_1.

λ	589 nm	578 nm	546 nm	436 nm	365nm
R-(+)-, $[\alpha]_\lambda^{25}$	+ 0.16°	+ 0.17°	+ 0.20°	+ 0.37°	+ 0.690°
S-(−)-, $[\alpha]_\lambda^{25}$	− 0.24°	− 0.26°	− 0.29°	− 0.505°	− 0.927°

c = 25.6 in EtOH for R-(+)-
c = 25.3 in EtOH for S-(−)-

Specific rotatory powers of R-(+)- and S-(−)-1-(4-hydroxyphenyl)ethane-1-d_1.

Table 5.

λ	300 nm	281 nm	258 nm	246 nm
R-(+)-, $[\Theta]_\lambda$	0	211	0	− 22

c = 2.06 in EtOH

λ	300 nm	281 nm	255 nm	246 nm
S-(−)-, $[\Theta]_\lambda$	0	− 300	0	+ 44

c = 2.04 in EtOH

Molar ellipticies of R-(+)- and S-(−)-1-(4-hydroxyphenyl)ethane-1-d_1.

Table 6.

Displacement of Methanesulfonate Esters

The reaction of the methanesulfonate ester **60** of R-(+)-ethanol-1-d_1 **49** with the heterocuprate(I) derived from copper(I) t-butylacetylide and 4-methoxyphenyllithium **65** yielded S-(−)-1-(4-methoxyphenyl)ethane-1-d_1 **71**, which was cleaved with 2-bromo-1,3,2-benzodioxaborole to S-(−)-1-(4-hydroxy phenyl)ethane-1-d_1 **73**. However, when R-(+)-1-[4-(2-methoxyethoxy)methoxy-

phenyl]-ethanol-1-d$_1$ **26**, in THF at −78°C, was treated with triethylamine and methanesulfonyl chloride, and the product reduced *in situ* with LAH in THF, (−)-1-[4-(2-methoxyethoxy)methoxyphenyl]ethane-1-d$_1$ **68** was produced. This product, when cleaved with 2-bromo-1,3,2-benzodioxaborole, yielded (−)-1-(4-hydroxyethoxy)ethane-1-d$_1$. Assuming that the mesylate of the secondary benzylic alcohol is formed with retention of configuration and that the displacement of the mesylate occurs with inversion (an S$_n$^{2} process), the configuration of the product would be expected to be *R*- (Fig. 5.).
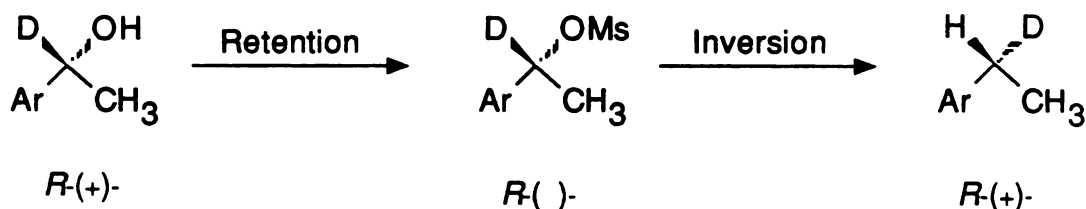
Predicted stereochemical course of the conversion of *R*-(+)-1-[4-(2-methoxyethoxy)methoxyphenyl)ethanol-1-d$_1$ to 1-[4-(2-methoxyethoxy)methoxyphenyl)-ethane-1-d$_1$.

Fig. 5.

Lithium diphenylcuprate(I) has been shown to react with *R*-(−)-2-bromobutane in refluxing ether/THF (51-52°C), in 72 h, to yield *S*-(+)-2-phenylbutane with 84-92 % inversion of configuration.[15] Johnson and Dutra, however, have demonstrated that lithium diphenylcuprate(I) will react with *S*-(+)-2-butyl tosylate in THF at −78°C, overnight, to give *R*-(−)-2-phenylbutane with 100 % inversion of configuration.[21] These authors suggested that halogen-metal exchange, which could take place under the conditions of time and temperature employed in the prior study, may be responsible for the lack of complete stereospecificity observed. In this study, when lithium diphenylcuprate(I) was

treated with R-(+)-ethyl-1-d$_1$ methanesulfonate in ether, S-(+)-1-phenylethane-1-d$_1$ **61** was formed. The absolute configuration of this material is well known,[9] so it would appear that the stereochemical course of the displacement reactions of lithium diphenylcuprate(I) has been well established. Although the specific heterocuprate(I) employed in this study does not appear in the literature, there is no reason to believe that this reagent does not also react via net inversion of configuration.

Assuming that the heterocuprate(I) displacement does occur via inversion, then it must be concluded that either the absolute configuration assigned to 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$ is incorrect, or that the reaction sequence of treatment with methanesulfonyl chloride followed by LAH reduction occurs with net retention (double inversion).

Cervinka, by asymmetric reduction of methylaryl ketones with complex hydrides prepared from LAH and optically active amino alcohols, has reported that the absolute configuration of 1-(4-methoxyphenyl)ethanol is R-(+)-.[22] However, whereas levorotatory 1-phenylethanol **42** exhibits a positive circular dichroism (CD) spectrum, levorotatory 1-(4-methoxyphenyl)ethanol **48** exhibits a negative CD curve in the 260-300 nm region. Reversed-phase LC analysis (methanol/water) of the MTPA esters of levorotatory 1-(4-methoxyphenyl)-, 1-(4-methoxymethoxyphenyl)- **8**, 1-[4-(2-methoxyethoxy)methoxyphenyl]- **20** and 1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethanols **33** indicates that these alcohols all have the same absolute configuration (i.e., the SR-(RS-) diastereomers of each alcohol elute before the SS-(RR-) diastereomers).

In addition, levorotatory 1-(4-methoxyphenyl)- and 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanols exhibited a negative CD curve for the 260-300 nm band, as did levorotatory 1-(4-hydroxyphenyl)ethanol **36** (Fig. 6.), showing these alcohols to be configurationally superimposable. The reversal of the sign

of the CD maximum of the ^1L_b band of benzene (260-300 nm region) on going from the unsubstituted levorotatory 1-phenylethanol (positive CD) to the configurationally superimposable levorotatory p-alkoxy- or p-hydroxyphenylethanols (negative CD) must therefore be due to an inversion in the direction of the major dipole, caused by the presence of charged species such as:
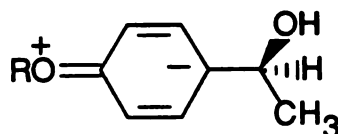
This dipole inversion is also responsible for the reversal of the sign of the CD maximum of the ^1L_b band of benzene in the same region on going from the unsubstituted levorotatory 1-phenylethane-1-d_1 (negative CD) to the configurationally superimposable dextrorotatory 1-(4-methoxyphenyl)ethane-1-d_1 **70** or 1-(4-hydroxyphenyl)ethane-1-d_1 **74** (positive CD).
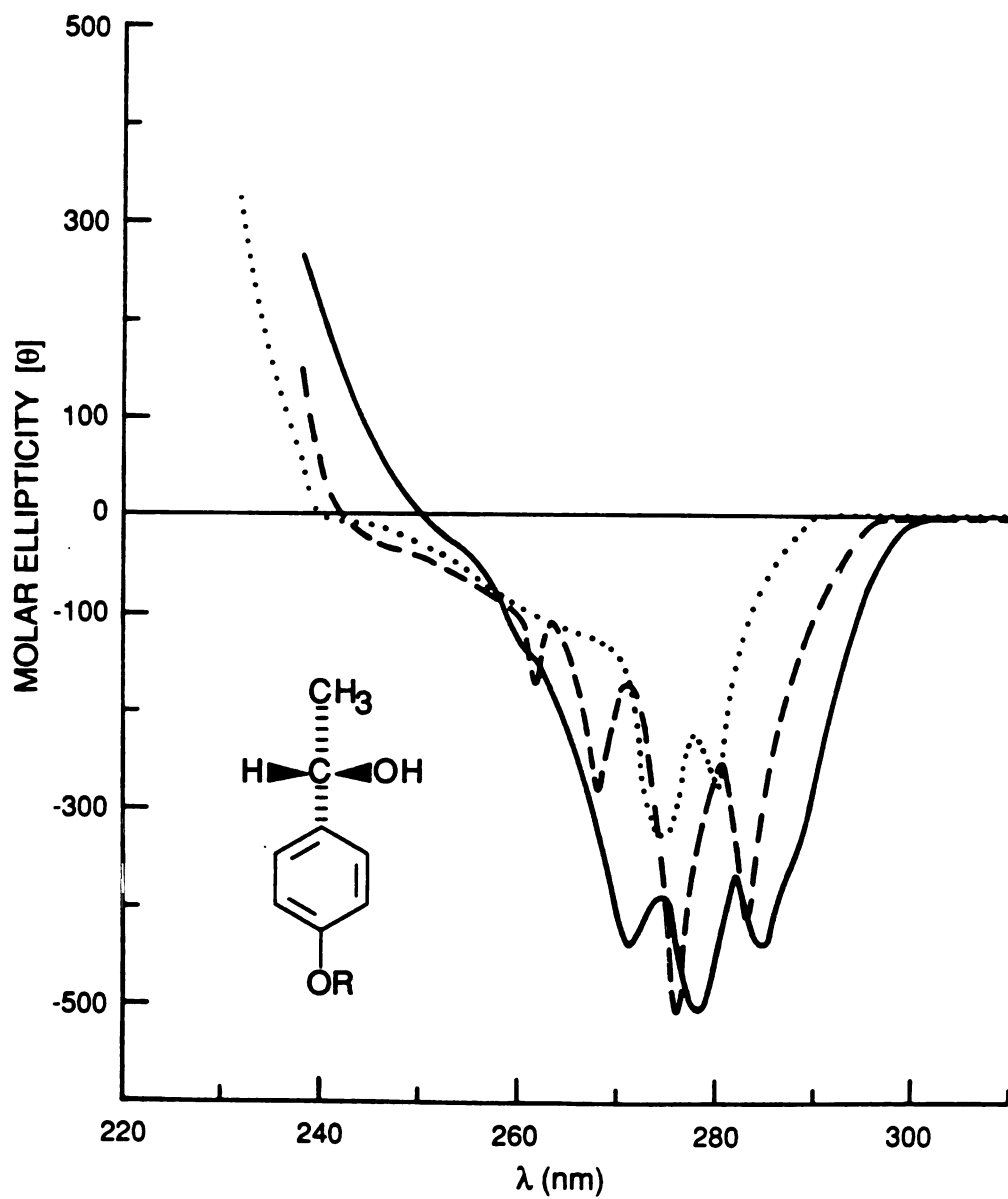
(————————————————) R= H
(- - - - - - - - - - - -) R= CH₃
(·································) R= CH₂OCH₂CH₂OCH₃

Circular dichroism of S-(−)-1-(4-alkoxyphenyl)ethanols.

Fig. 6.

^{1}H NMR experiments with a series of 4-substituted 1-phenylethanols, as the esters of S-(–)-α-methoxy-α-trifluoromethylphenyl acetic acid,[23] or employing the chiral lanthanide shift reagent Eu(hfbc)$_3$[24] appear to support Cervinka's assignment.

To determine the absolute configuration of 1-(4-methoxyphenyl)ethanol (and by correlation, the configuration of 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol and its deuteriated analog) the compound was synthesized from 4-methoxymandelic acid, the absolute configuration of which has been rigorously proven,[25] by the scheme outlined in the Summary of Planned Syntheses section (Scheme 5). Resolution of 4-methoxymandelic acid with 1-phenylethylamine was followed by diazomethane methylation of the R-(–)-acid **44** to the R-(–)-methyl ester **45**. The ester was reduced with LAH to the R-(–)-diol **46**, which was treated with methanesulfonyl chloride/triethylamine to form the R-(–)- mesylate ester **47** of the primary alcohol. Reduction of the mesylate with LAH provided S-(–)-1-(4-methoxyphenyl)ethanol. The configuration descriptor changes from R- to S- because the carbon atom bearing the -OSO$_2$CH$_3$ group in the mesylate, and assuming second priority in the Cahn-Ingold-Prelog system,[26] is converted to a methyl group in the reduction and drops to third priority, second priority now assumed by the 4-methoxyphenyl group. Thus, R-(–)-mandelic acid provides S-(–)-1-(4-methoxy-phenyl)ethanol, which exhibits a negative rotation at the sodium D line, and Cervinka's assignment is therefore correct. The conclusion must therefore be that the treatment of the secondary benzylic alcohol with methanesulfonyl chloride/triethylamine, followed by reduction with LAH, must have proceeded by a double inversion. Kenyon et al. have shown that the tosylate of 1-phenylethyl alcohol, produced by oxidation of the p-toluenesulfinate with hydrogen peroxide in acetic anhydride, undergoes displacement with lithium chloride at room

temperature with inversion of configuration.[27] The thermodynamic driving force for the analogous reaction of the mesylate of 1-[4-(2-methoxyethoxy)-methoxyphenyl]-ethanol-1-d_1 with triethylammonium chloride in THF at −78°C could be the precipitation of insoluble triethylammonium methanesulfonate. Another analogous reaction is found in the well-known backside displacement by chloride ion on the intermediate sulfite ester derivatives formed in the chlorination of chiral alcohols with thionyl chloride in polar solvents in the presence of pyridine.[28]

p-Methoxybenzyl tosylate has been described as a compound which decomposes rapidly, even at −60°C.[29] The authors report the material to be so reactive it could not be isolated in pure form at room temperature. 1-Phenylethyl methanesulfonate was described as a highly reactive liquid, which decomposes violently at room temperature.[30] In a recent publication, 1-phenylethyl and 1-(p-methoxyphenyl)ethyl tosylates were reported for the first time and described as crystalline solids.[31] However, the ^{1}HNMR spectral data recorded for the compounds do not correspond to the assigned structures and this report must be regarded as suspect.

Determination of The Enantiomeric Purity of 1-(4-Hydroxy-phenyl)ethane-1-d_1

RS--4-(Ethyl-1-d_1)phenyl R-O-acetylmandelate **58** was synthesized from *RS*-1-(4-hydroxyphenyl)ethane-1-d_1 **75** and *R*-(−)-O-acetylmandelic acid by the same method employed for the synthesis of the *R*-(−)-O-acetylmandelate esters of the deuterium-labeled ethanols. The ^{1}H NMR spectrum of the ester in benzene-d_6 was recorded at 240 MHz; however, inspection of the spectrum in the benzylic region revealed only a single quartet of triplets centered at 2.240

ppm (Fig. 7.). So in this case, it appears that the chiral center in the acetyl-mandelic acid moiety is too far removed from the chiral center in the ethylphenol moiety to result in the perturbation of the proton resonances. There is no observable chemical shift difference in the benzylic proton resonances for the two diastereomeric ester derivatives, and the method is not effective for the determination of the enantiomeric purity of optically active 1-(4-hydroxyphenyl)-ethane-1-d_1.
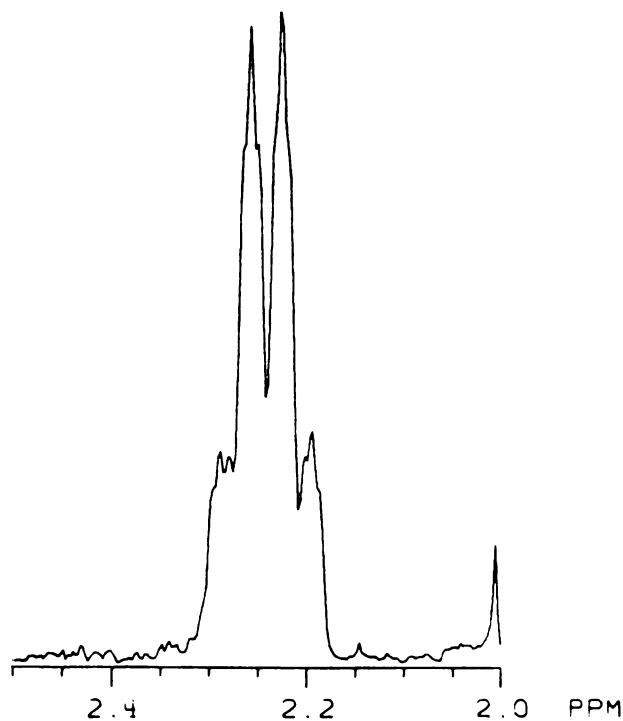
240 MHz ^{1}H NMR spectrum of the benzylic region of RS-4-(Ethyl-1-d_1)phenyl R-O-acetylmandelate.

Fig. 7.

In a second attempt to determine the enantiomeric purity of the labeled 4-ethylphenol, an equimolar mixture of RS-1-(4-hydroxyphenyl)ethane-1-d_1 and 100% e.e. S-(+)-1-phenyl-2,2,2-trifluoroethanol was prepared in chloroform-d. The ^{1}H NMR spectrum of this mixture, recorded at 80 MHz, again exhibited a single quartet of triplets centered at 2.54 ppm.

With the failure of ^{1}H NMR methods for deducing the enantiomeric purity of the product enantiomers, a literature search was conducted of methods which could be employed for the conversion of a phenolic hydroxyl group to a hydrogen atom. The rationale for such a conversion would be the transformation of 1-(4-hydroxyphenyl)ethane-1-d_1, a previously unreported compound, to 1-phenylethane-1-d_1 **61**, a compound which has been well characterized and for which the absolute configuration has been well established, as have the ORD and CD curves for the enantiomerically pure stereoisomers.[9,32] Such a transformation of an optically active 1-(4-hydroxy-phenyl)ethane-1-d_1 and measurement of the ORD curve of the product hydrocarbon would give a measurement of the enantiomeric purity of the starting material as well as a confirmation of the assignment of the absolute configuration.

The two procedures recorded in the literature, which appear to be the most applicable, both involve conversion of the phenol to a phosphate ester followed by dissolving-metal reduction of the aryl phosphate to the corresponding arene.

In the first method, the phenol is dissolved in toluene at 0-5°C and treated with aqueous sodium hydroxide and diethyl phosphorochloridate to form the diethyl phosphate ester.[33] The aryl diethyl phosphate is then dissolved in liquid ammonia with diethyl ether as a cosolvent, and the solution is cooled to −78°C and then treated with small chunks of lithium, sodium or

potassium (Fig. 8.). After acidification of the reaction mixture with solid ammonium chloride, the products are isolated by standard techniques. Phenol was converted to benzene by this method in an overall yield of 67%.

$$RC_6H_4OH + (C_2H_5O)_2POCl \xrightarrow{\text{NaOH}} RC_6H_4OPO(OC_2H_5) + 2 M \xrightarrow{\text{NH}_3}$$

$$RC_6H_5 + (C_2H_5O)_2PO_2^- \; M^+ + \; M^+ NH_2^-$$

$$M = \text{Li, Na or K.}$$
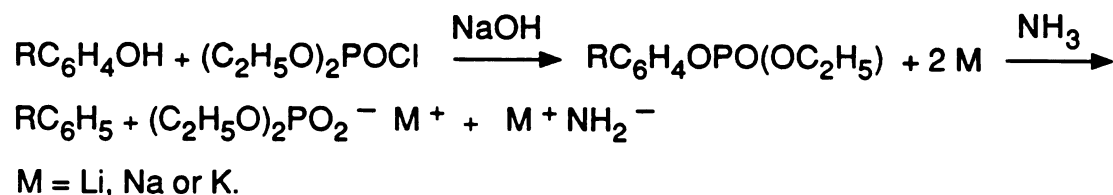
Liquid ammonia hydrogenolysis of phenyl diethyl phosphate esters.[33]

Fig. 8

Since the cleavage reaction is known to proceed via a radical-anion intermediate (Fig. 9), the method would have to be used for the conversion of racemic 1-(4-hydroxyphenyl)ethane-1-d_1 to 1-phenylethane-1-d_1 to determine if the deuterium label will survive the reaction conditions.

$$[RC_6H_4OPO(OC_2H_5)_2]^{\overline{\cdot}} \longrightarrow RC_6H_4\cdot + (C_2H_5O)_2PO_2^-$$
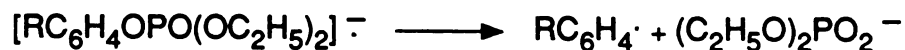
Radical-anion mechanism of hydrogenolysis of phenyl diethyl phosphate esters.[33]

Fig. 9

The second method also utilizes the aryl diethyl phosphate derivatives, which are then reduced with freshly prepared, highly activated titanium metal in refluxing tetrahydrofuran (Fig. 10). Reduction of the diethylphosphate ester derived from carvacrol, with titanium metal in refluxing tetrahydrofuran for 8 to 16 h, followed by quenching with deuterium oxide, does not incorporate

90

deuterium. 4-Nonylphenol was converted to nonylbenzene by this method in an overall yield of 92 %.[34]

Again, it would have to be shown that benzylic deuterium will survive the reaction conditions.

$$3 \text{ ArOH} \xrightarrow[\text{2) } 3 \times \text{ClPO}(\text{OC}_2\text{H}_5)_2]{\text{1) } 3.3 \times \text{NaH, THF}} 3 \text{ ArOPO}(\text{OC}_2\text{H}_5)_2$$
$$\text{A}$$

$$6 \text{ K} + 2 \text{ Ti Cl}_3 \xrightarrow[\text{THF}]{\Delta} 2 \text{ Ti}$$
$$\text{B}$$

$$3 \text{ A} + 2 \text{ B} \xrightarrow{\text{1) } \Delta, \text{ 6-16 h/THF}} 3 \text{ Ar} - \text{H}$$
2) MeOH, 5°C
3) filter silica gel:celite (1:4)
4) –THF
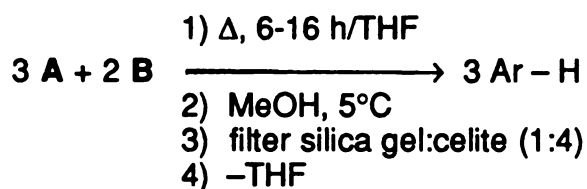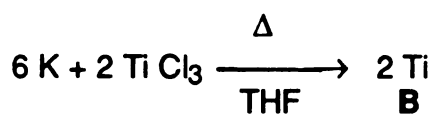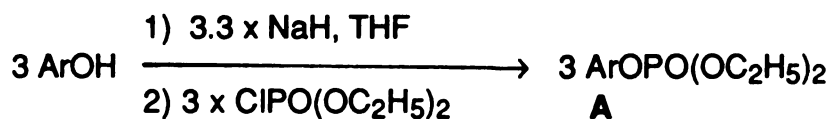
Titanium-metal reduction of phenyl diethyl phosphate esters.[34]

Fig. 10

References

1) Posner, G.H. Org. Reactions **1975**, *22*, 253-400.

2) Günther, H.; Biller, F.; Kellner, M.; Simon, S. Angew. Chem. Int. Ed. **1973**, *12*, 146-147.

3) Gorlach, H.; Zagalak, B. J. Chem. Soc. Chem. Comm. **1973**, 274-275.

4) Mosher, H.S. Stanford University, Dept. of Chemistry, private communication.

5) Levy, R.H.; Loewus, F.A.; Vennesland, B. J. Am. Chem. Soc. **1957**, *79*, 2949-2953.

6) Parker, D. J. Chem. Soc. Perkin Trans. II **1983**, 83-88.

7) Truce, W.E.; Campbell, R.W. J. Am. Chem. Soc. **1966**, *88*, 3599-3604.

8) Vogel's Textbook of Practical Organic Chemistry, 4th ed., Furniss, B.S.; Hannaford, A.J.; Rogers, V.; Smith, P.W.G.; Tatchell, A.R., eds., Longman Inc., New York, 1978. Chapter VI, pp. 901-902.

9) Elsenbaumer, R.L.; Mosher, H.S. J. Org. Chem. **1979**, *44*, 600-604.

10) Schlosser, M.; Ladenberger, V. J. Organometal. Chem. **1967**, *8*, 193-197.

11) Kauffman, G.B.; Teter, L.A. Inorg. Syntheses **1963**, *7*, 9-12.

12) House, H.O.; Umen, M.J. J. Org. Chem. **1973**, *38*, 3893-3901.

13) House, H.O.; Chu, C.Y.; Wilkins, J.M.; Umen, M.J. J. Org. Chem. **1975**, *40*, 1460-1469.

14) Whitesides, G.M.; San Filippo, Jr., J.; Casey, C.P.; Panek, E.J. J. Am. Chem. Soc. **1967**, *89*, 5302-5303.

15) Whitesides, G.M.; Fischer, Jr., W.F.; San Filippo, Jr., J.; Bashe, R.W.; House, H.O. J. Am. Chem. Soc. **1969**, *91*, 4871-4882.

16) Whitesides, G.M; Casey, C.P. J. Am. Chem. Soc. **1966**, *88*, 4541-4543.

17) Gilman, H.; Langham, W.; Willis, H.B. J. Am. Chem. Soc. **1940**, *62*, 346-348.

18) Jones, R.G.; Gilman, H. Org. Reactions, **1951**, *6*, 348-349.

19) Mandeville, W.H.; Whitesides, G.M.; J. Org. Chem. **1974**, *39*, 400-405.

20) Gillmeister, A. Chem. Berichte **1897**, *30*, 2849-2851.

21) Johnson, C.R.; Dutra, G.A. J. Am. Chem. Soc. **1973**, *95*, 7783-7788.

22) Cervinka, O. Coll. Czech. Chem. Comm. **1965**, *30*, 1684-1691.

23) Eichberger, G.; Faber, K.; Griengl, H. Monatshefte für Chemie **1985**, *116*, 1233-1236.

24) Mandal, A.K.; Kasar, T.G.; Mahajan, S.W.; Jawalkar, D.G. Synthetic Comm. **1987**, *17*, 563-574.

25) Pratesi, P.; LaManna, A.; Campiglio, A.; Ghislandi, V. J. Chem. Soc. **1958**, 2069-2074.

26) Cahn, R.S. J. Chem. Ed. **1964**, *41*, 116-125.

27) Kenyon, J.; Phillips, H.; Taylor, F.M.H. J. Chem. Soc. **1933**, 173-178.

28) Advanced Organic Chemistry, 3rd ed., March, J., John Wiley and Sons, New York, 1985, Chapter 10, pp. 286-287.

29) Kochi, J.K,; Hammond, G.S. J. Am. Chem. Soc. **1953**, *75*, 3443-3444.

30) Crossland, R.K.; Servis, K.L. J. Org. Chem. **1970**, *9*, 3195-3196.

31) Lee, I.; Kim, Y.H.; Kang, K.H.; Lee, H.W. J. Org. Chem. **1988**, *53*, 2678-2683.

32) Ringdahl, B; Craig, J.C.; Mosher, H.S. Tetrahedron **1981**, *37*, 859-862.

33) Rossi, R.O.; Bunnett, J.F. J. Org. Chem. **1973**, *38*, 2314-2318.

34) Welch, S.C.; Walters, M.E. J. Org. Chem. **1978**, *43*, 4797-4799.

Enzymology

Chapter IV

The labeled and unlabeled 4-ethylphenols were incubated with PCMH in the steady-state assays described by McIntire et al.[1] to yield the data contained in Table 1. These results reveal the process of benzylic-hydrogen abstraction to be an entirely non-stereoselective process. The kinetic isotope effects measured for the R-(+)-, S-(–)- and RS-1-(4-hydroxyphenyl)ethanes-1-d_1 (1.56 ± 0.10, 1.49 ± 0.06 and 1.59 ± 0.06, respectively) are identical within the calculated error limits. This can be interpreted in terms of a mechanism which places the 8α-(O-Tyrosyl)riboflavin in the active site, approximately equidistant from the two prochiral benzylic hydrogen atoms, such that there is no preference expressed for either. In the case of 1-(4-hydroxyphenyl)ethane-1, 1-d_2, the enzyme has no choice and must abstract a deuterium atom. The observed k.i.e. of 5.09 ± 0.18 is the product of both primary and secondary k.i.e.'s. The position of the 8α-(O-Tyrosyl)riboflavin relative to the substrate will have to await a high-resolution X-ray crystal structure of PCMH bound to a competitive inhibitor like 4-bromophenol.

The possibility of two binding sites, one directing the pro-R hydrogen toward the flavin and the other the pro-S, would seem to be ruled out by the clean parallel-line kinetics exhibited by PCMH in double-reciprocal plots.[2]

The results also indicate that the overall stereoselectivity observed in the hydroxylation catalyzed by PCMH[3] is due solely to the stereoselective hydration of the putative quinone methide intermediate.

Substrate (S)	V/K_S $(min^{-1}M^{-1})$	V/K_{pms} $(min^{-1}M^{-1})$
4-ethylphenol	6.97 ($\pm$ 0.24) x 10^6	4.01 ($\pm$ 0.08) x 10^6
*1-(4-hydroxyphenyl)ethane-1,1-d_2	1.37 ($\pm$ 0.01) x 10^6	4.02 ($\pm$ 0.06) x 10^6
R-(+)-1-(4-hydroxyphenyl)ethane-1-d_1	4.46 ($\pm$ 0.23) x 10^6	4.01 ($\pm$ 0.14) x 10^6
S-(−)-1-(4-hydroxyphenyl)ethane-1-d_1	4.68 ($\pm$ 0.08) x 10^6	3.99 ($\pm$ 0.05) x 10^6
RS-1-(4-hydroxyphenyl)ethane-1-d_1	4.39 ($\pm$ 0.07) x 10^6	4.13 ($\pm$ 0.08) x 10^6

Substrate (S)	$^H(V/K_S)/^D(V/K_S)$ Isotope effects
1-(4-hydroxyphenyl)ethane-1,1-d_2	5.09 $\pm$ 0.18
R-(+)-1-(4-hydroxyphenyl)ethane-1-d_1 74	1.56 $\pm$ 0.10
S-(−)-1-(4-hydroxyphenyl)ethane-1-d_1 73	1.49 $\pm$ 0.06
RS-1-(4-hydroxyphenyl)ethane-1-d_1 75	1.59 $\pm$ 0.06

*Obtained from 4-hydroxyacetophenone by Clemmensen reduction (Zn(Hg)) in DCl/EtOD.

The experiments were carried out in 0.05 M Tris-HCl buffer (I = 0.05) at 25°C and pH 7.6. Phenazine methosulfate (PMS) and 2,6-dichlorophenolindophenol (DCIP) were employed as reoxidants in the coupled assay.(1)

Steady-state kinetic isotope effects for deuterium-labeled 4-ethylphenols and p-cresol methylhydroxylase at 25°C.

Table 1.

The labeled and unlabeled 1-(4-hydroxyphenyl)ethanols were incubated with PCMH in the stopped-flow and steady-state assays described by McIntire et al.(1) The stopped-flow experiments were done at 25°C, in 50 mM Tris-HCl buffer at pH 7.6. The k_{obs} values from the stopped-flow experiments were derived by computer-fitting each absorbance (at 418 nm) vs. time trace to the equation:

$$A = A_0 + A_1 (1-e^{-k_1 t}) + A_2 (1-e^{-k_2 t})$$

A_0 is the absorbance at $t = 0$, $k_1 = k_{obs}$ is the rate constant for reduction of p-cresol methylhydroxylase and is dependent on the concentration of the substrate, and k_2 (0.03 sec^{-1}) is the rate constant for a second, slower process seen for all the alcohols and is independent of the substrate concentration[1]. The absorbance change for this slow process accounted for ~ 1/3 of the change at 418 nm. The enzyme concentration was 1.4 μM, and [S] was varied from 0.625 to 10 mM. A plot of k_{obs} vs. [S] is given in Fig. 1, and a plot of 1/k_{obs} vs. 1/[S] in Fig. 2, for the S-(−)-H and S-(−)-D alcohols.
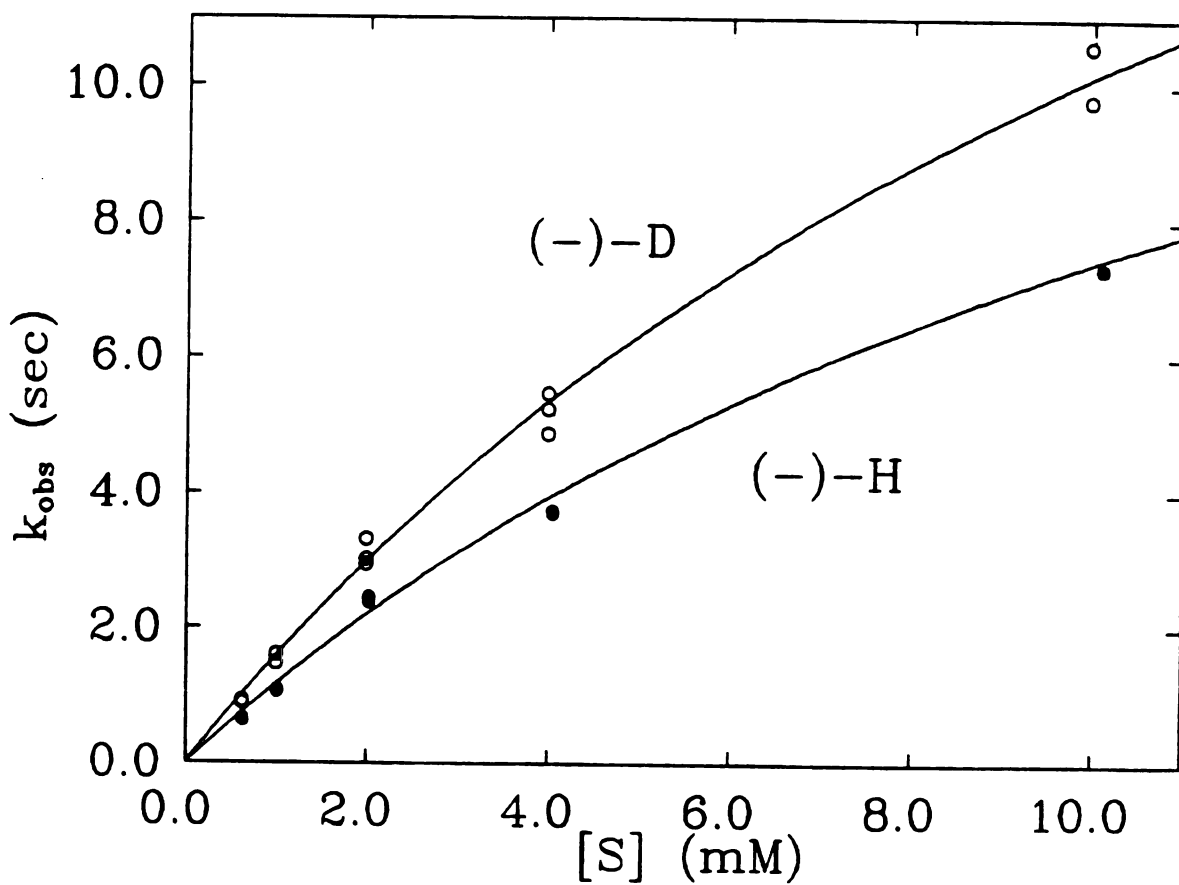
Plot of k_{obs} vs [S] for the S-(−)-H and S-(−)-D 1-(4-hydroxyphenyl)ethanols.

Fig. 1
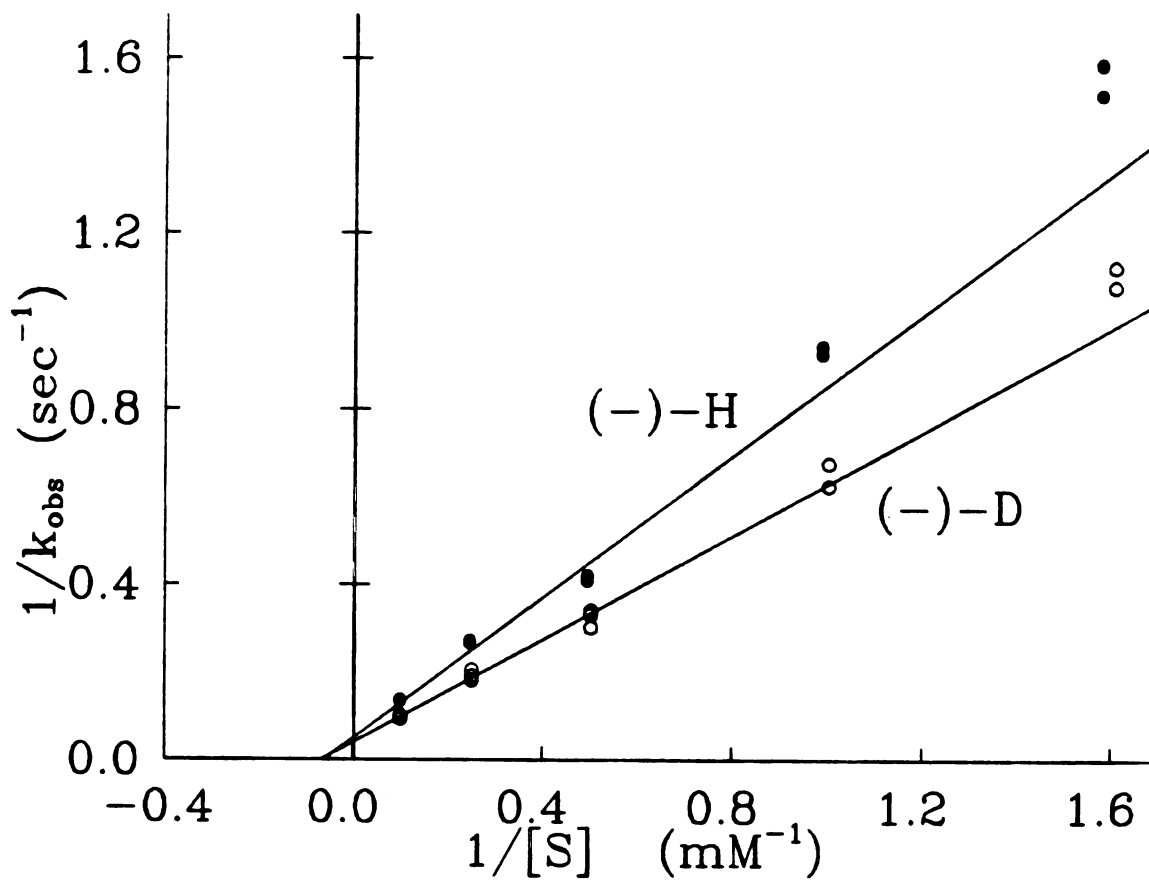
Plot of $1/k_{obs}$ vs $1/[S]$ for the S-(−)-H and S-(−)-D 1-(4-hydroxyphenyl)ethanols.

Fig. 2

The mechanism for this reaction is:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E \cdot S \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E + P$$
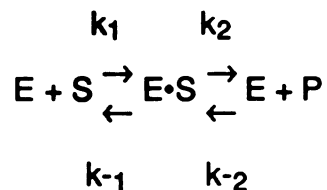
for which the following equation is derived, assuming that a steady-state condition exists:[4]

$$k_{obs} = \frac{k_1[S](k_2 + k_{-2}) + k_{-1}k_2}{k_1 + k_{-1} + k_2}$$

The second step is assumed to be irreversible (i.e., $k_{-2} \approx 0$) and the first step is in rapid equilibrium (i.e., $k_{-1} \gg k_2$). With these assumptions the equation becomes:

$$k_{obs} = \frac{k_2[S]}{[S] + k_{-1}/k_{-1}} = \frac{k_2[S]}{[S] + K_d} = \frac{k_2/K_d[S]}{[S]/K_d + 1}$$

The isotope effect for the reaction is $^Hk_2/^Dk_2$; however, the value of k_2 (and K_d for that matter) for each substrate could not be determined accurately from the data. For accurate estimates of the parameters, runs needed to be performed at substrate concentrations at and above the K_d value (i.e., ~ 20-30 mM; see Table 2), which was impossible because of the limited amount of material available. The equation on the far right, above was used to determine k_2/K_d and K_d by computer analysis. The isotope effects were determined from the ratio $^H(k_2/K_d)/^D(k_2/K_d)$, which assumes that $^HK_d = {}^DK_d$, i.e., there is no isotope effect on binding.

Substrate	k_2/K_d (sec^{-1}M^{-1})	K_d (mM)	$^H(k_2/K_d)/^D(k_2/K_d)$ isotope effects
(±) -H **1**	8.60 (± 0.13) x 10^{-4}	30.0 ± 3.7	1.59 ± 0.03
(±) -D **2**	5.40 (± 0.08) x 10^{-4}	11.9 ± 0.9	
(+) -H **35**	7.17 (± 0.11) x 10^{-4}	18.6 ± 1.6	0.608 ± 0.018
(+) -D **37**	1.18 (± 0.03) x 10^{-3}	28.5 ± 6.2	
(−) -H **36**	1.25 (± 0.08) x 10^{-3}	14.5 ± 5.5	0.740 ± 0.054
(−) -D **38**	1.69 (± 0.06) x 10^{-3}	15.0 ± 2.4	

Stopped-flow kinetic data for labeled and unlabeled 1-(4-hydroxyphenyl)ethanols

Table 2.

The steady-state kinetic experiments were done at 25°C in 50 mM Tris-HCl buffer, pH 7.6, using phenazine ethosulfate (PES) and dichlorophenol-indophenol (DCPIP), and monitoring DCPIP reduction at 600 nm. The 1/v vs. 1/[S] plots at high and low [PES] were parallel, as were the 1/v vs. 1/[PES] plots at high and low [S], indicating that the ping-pong mechanism is operating for these alcohols. For the isotope effect data, the range of [S] was 2 to 10 mM at 0.58 mM PES. The data were fit by computer to the Michealis-Menten equation and its rearranged form:

$$v = \frac{V_{max}[S]}{Km + [S]} = \frac{V_{max}/K_m[S]}{1 + [S]/K_m}$$

The ratio $^H(V_{max}/K_m)/^D(V_{max}/K_m)$ is the measure of the intrinsic isotope effect.

Substrate	V_{max}/K_m (μmol min^{-1}mg^{-1})	K_m (mM)	$^H(V_{max}/K_m)/^D(V_{max}/K_m)$ isotope effects
(±) -H	0.404 (± 0.007) x 10^{-4}	10.8 ± 0.4	1.65 ± 0.04
(±) -D	0.246 (± 0.004) x 10^{-4}	7.18 ± 0.27	
(+) -H	0.352 (± 0.004) x 10^{-4}	12.8 ± 0.6	0.832 ± 0.018
(+) -D	0.423 (± 0.008) x 10^{-4}	8.96 ± 0.25	
(−) -H	0.629 (± 0.016) x 10^{-4}	12.9 ± 0.5	1.10 ± 0.03
(−) -D	0.573 (± 0.009) x 10^{-4}	6.06 ± 0.33	

Steady-state kinetic data for labeled and unlabeled 1-(4-hydroxyphenyl)ethanols

Table 3.

The isotope effects measured for the racemic 1-protio- and 1-deuterio- 1-(4-hydroxyphenyl)ethanols, by stopped-flow and steady-state methods, were identical within the calculated error limits. The same cannot be said, however, for the resolved alcohols. As discussed previously, accurate values for k_2 and K_D could not be determined for the enantiomerically pure alcohols and, as a result, the k.i.e.'s. derived from the stopped-flow data for these substances should be viewed with caution. However, even the steady-state data provide an inverse isotope effect in the case of the *R*-(+)- alcohols. Since no physical model can rationalize this result, perhaps some trace level impurity, undetected by HPLC and NMR spectroscopy, is responsible for inhibition of enzyme activity.

References

1) McIntire, W.S.; Hopper, D.J.; Singer, T.P. Biochemistry **1987**, *26*, 4107-4117.

2) McIntire, W.S.; Hopper, D.J.; Singer, T.P. Biochem. J. **1985**, *228*, 325-335.

3) McIntire, W.S.; Hopper, D.J.; Craig, J.C.; Everhart, E.T.; Webster, R.V.; Causer, M.J.; Singer, T.P. Biochem. J. **1984**, *224*, 617-621.

4) Strickland, S.; Palmer, G.; Massey, V. J. Biol. Chem. **1975**, *250*, 4048-4052.

Experimental

Chapter V

General

Tetrahydrofuran (THF) and diethylether were distilled from lithium aluminum hydride (LAH), under nitrogen, prior to use. Benzene, dichloromethane, N,N-diisopropylethylamine (Aldrich) and triethylamine were distilled from calcium hydride. Anhydrous 2-methoxyethyl ether (diglyme) and N,N-dimethylformamide (DMF) were purchased from Aldrich in Sure/Seal™ bottles and used without further purification. Lithium aluminum deuteride (LAD), 99 atom % D, was purchased from Merck. Methanesulfonyl chloride was distilled under reduced pressure prior to use. Diazomethane was prepared by the method of DeBoer and Backer.[1] R-(+)- and S-(−)-α-Methoxy-α-trifluoro-methylphenylacetic acids (MTPA) were purchased from Aldrich and the acid chlorides were prepared by the method of Dale et al.[2] MTPA esters of chiral alcohols were also prepared by the method of Dale et al., with the elimination of the acid wash. All lithium diorganocuprate(I) displacement reactions were carried out in glassware that had been bathed overnight in concentrated nitric acid, rinsed with triple-distilled H_2O and oven dried. The enzymatic syntheses of R -(+)- and S -(−)-ethanol -1-d$_1$ were performed with Dr. William McIntire of the Veterans Administration Medical Center, San Francisco, CA 94121.

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points associated with Kugelrohr distillations refer to oven temperatures. Fractional distillations were carried out in a Nester-Faust NF-51 Teflon spinning-band column. Liquid-chromatographic (LC) analyses were performed on a Beckman Instruments Model 344 Gradient Liquid Chromatograph. Analyses of reaction-product mixtures were carried out, unless otherwise stated, on a Beckman 4.6 mm x 250 mm Ultrasphere™-ODS

reversed-phase column. An (80:20) methanol/H_2O isocratic mobile phase was employed at a flow rate of 1 mL/min. The detector was set to monitor a wavelength of 275 nm. Separation of the MTPA diastereomeric esters of 1-(4-methoxyphenyl)-, 1-(4-methoxymethoxyphenyl)- and 1-[4-(2-methoxyethoxy)-methoxyphenyl]-ethanols were performed on a Phenomenex 4.6 mm x 250 mm Ultracarb™ 5 ODS 30 reversed-phase column. A methanol/H_2O gradient was employed, with the mobile phase composition programmed from (60:40) methanol/H_2O to pure methanol in 90 min. The flow rate was 1.1 mL/min and the detector was set to monitor a wavelength of 267 nm. The MTPA esters of 1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethanol required the same column, but the mobile phase composition was programmed from (60:40) methanol/H_2O to pure methanol in 270 min. The flow rate and the wavelength monitored were the same.

Routine ^1H NMR spectra were recorded on either a Varian Associates FT-80 spectrometer or a home-built 240 MHz NMR spectrometer with a Nicolet 1180 computer and a 293B pulse programmer. The spectra were run in deuteriochloroform unless otherwise stated. Chemical shifts are reported in parts per million (ppm) with TMS as an internal reference, with the exception of the spectra of trimethylsilyl or t-butyldimethylsilyl derivatives, where chemical shifts are referenced to the highest-field methylsilyl resonance. Coupling constants (J) are reported in hertz (Hz). ^1H NMR spectra of the R-O-acetyl-mandelate esters of unlabeled, RS, R- and S-deuterium-labeled ethanols were recorded on a General Electric GN-500 spectrometer. Infrared spectra were acquired on a Nicolet Instrument Corp. 5 DX FTIR spectrometer. Mass spectra were obtained on a Kratos MS-50 mass spectrometer. Elemental analyses were performed by the microanalytical laboratory at the University of California at Berkeley. ORD data was recorded on a Perkin-Elmer Model 141 Polarimeter.

CD spectra were determined on a Jasco J-500A Spectropolarimeter and recorded in terms of molecular ellipticity units [Θ]. Ellipticities are given only for (a) the highest and lowest wavelength measured and (b) for peaks and troughs.

RS-1-(4-Hydroxyphenyl)ethanol 1

4-Hydroxyacetophenone (Aldrich) (5.19 g, 38.1 mmol) in 33 % ethanol (75 mL) was slowly treated with $NaBH_4$ (2.88 g, 76.2 mmol) in H_2O (29 mL). The mixture was stirred for 3 h and quenched by the slow addition of 25 % HOAc until gas evolution ceased. The aqueous phase was saturated with NaCl and extracted with ether (150 mL x 3). The combined extracts were washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield RS-1-(4-hydroxyphenyl)ethanol (4.89 g, 35.4 mmol, 93 %), which was recrystallized from benzene/ethanol to give 3.75 g of pure product: mp 132-135°C; lit.[3] mp 132-133°C.

RS-1-(4-Hydroxyphenyl)ethanol-1-d₁ 2

4-Hydroxyacetophenone (5.05 g, 37.1 mmol) in dry THF (50mL) was slowly added, under nitrogen, to a stirred suspension of LAD (99 atom % D, 2.16 g, 51.4 mmol) in dry THF (200 mL). The addition of substrate caused an immediate precipitation of a white solid, and the mixture was heated at reflux for 10 h, cooled to 5°C and quenched by the slow addition of H_2O (2.2 mL), 15 % NaOH (2.2 mL) and H_2O (7 mL). The supernatant was filtered from the suspended solids and evaporated under reduced pressure to give 2.80 g of

crude product. The aluminum salts were washed with methanol and the washings were evaporated under reduced pressure to give an additional 2.45 g of material. Recrystallization of 3.37 g of this material from benzene/ethanol gave RS-1-(4-hydroxyphenyl)ethanol-1-d_1 (1.43 g, 10.3 mmol): mp 131-135°C; ^{1}H NMR (DMSO-d_6) δ 7.17, 7.07, 6.72, 6.62 (q, 4H, para-substituted aromatic), 1.26 (s, 3H, CH$_3$); IR (KBr) 3396 (OH), 3104, 3017, 2964, 2931, 2891, 2811, 2685, 2606, 2506, 2147 (CD), 1895, 1616, 1596, 1457, 1390, 1364, 1224, 1171, 1131, 1111, 1098, 1065, 932, 832 cm^{-1}; mass spectrum (EI, 70 eV), m/z (relative intensity) 139 (M$^+$, 23) 124 (100), 121 (11), 96 (14), 78 (35), 77 (14), 65 (13); exact mass calcd for C$_8$H$_9$DO$_2$ m/z 139.0744, found m/z 139.0737 (−5 ppm).

4-Methoxymethoxyacetophenone 3

A mixture of 4-hydroxyacetophenone (50.6 g, 373 mmol), dimethoxymethane (Aldrich) (138 g, 1.81 mol), 4-toluenesulfonic acid•H$_2$O (407 mg, 2.14 mmol) and dichloromethane (800 mL) was heated at reflux, with removal of H$_2$O by 3A molecular sieve (224 g) in a Soxhlet thimble, for 7 h. The pot was recharged with dichloromethane (200 mL) and the mixture was heated at reflux for 12 h, when the pot was again recharged with dimethoxymethane (85.9 g, 1.13 mol) and dichloromethane (400 mL). The mixture was heated at reflux for an additional 24 h, cooled to room temperature, treated with triethylamine (3 mL), washed with 1N NaOH (200 mL x 3) and H$_2$O (200 mL x 5), dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure to yield 4-methoxymethoxyacetophenone (56.0 g, 310 mmol, 84 %): mp 32-34°C; bp 87-89°C (0.350 mm Hg); ^{1}H NMR δ 7.97, 7.86, 7.11, 7.00 (q, 4H, para-substituted

aromatic), 5.22 (s, 2H, OCH$_2$O), 3.47 (s, 3H, CH$_3$O), 2.54 (s, 3H, CH$_3$CO); IR (neat) 2959, 2910, 2828, 1672 (C=O), 1598, 1507, 1417, 1360, 1270, 1237, 1155, 1081, 982, 925, 843 cm^{-1}; Anal calcd for C$_{10}$H$_{12}$O$_3$: C, 66.65; H, 6.72. Found: C, 66.46; H, 6.84.

RS-1-(4-Methoxymethoxyphenyl)ethanol 4

4-Methoxymethoxyacetophenone (43.7 g, 242 mmol) in 95 % ethanol (380 mL) was slowly treated with NaBH$_4$ (9.67 g, 256 mmol). The mixture was stirred overnight and quenched with H$_2$O (100 mL). After the aqueous phase was saturated with NaCl and the layers were separated, the aqueous phase was extracted with ether. The ethanol was evaporated under reduced pressure and the residue was dissolved in the ether extract, which was dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure to yield *RS*-1-(4-methoxymethoxyphenyl)ethanol (43.8 g, 240 mmol, 99 %): bp 79-81°C (0.005 mm Hg); ^{1}H NMR δ 7.29, 7.18, 7.00, 6.89 (q, 4H, para-subsituted aromatic), 5.09 (s, 2H, OCH$_2$O), 4.75 (q, 1H, ArCH, J = 6.5 Hz), 3.41 (s, 3H, CH$_3$O), 2.86 (bs, 1H, D$_2$O exch, OH), 1.40 (d, 3H, CH$_3$, J = 6.5 Hz); IR (neat) 3394 (OH), 2968, 2927, 2894, 1614, 1507, 1228, 1196, 1155, 1081, 999, 925, 835 cm^{-1}; Anal calcd for C$_{10}$H$_{14}$O$_3$: C, 65.91; H, 7.74. Found: C, 65.81; H, 7.73.

RS-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate 5

a) *RS*-1-(4-Methoxymethoxyphenyl)ethanol (6.18 g, 33.9 mmol) in dry benzene (3 mL) was slowly added to a solution of phthalic anhydride (5.02 g, 33.9 mmol) in dry pyridine (2.69 g, 34.0 mmol) protected from atmospheric moisture, at 98°C. The mixture was stirred for 75 min, cooled to room temperature and partitioned between ether (50 mL) and H_2O (50 mL). The aqueous phase was adjusted to pH 2 with 1N HCl, the layers were separated and the aqueous phase was extracted with ether (75 mL x 2). The combined extracts were washed with saturated $NaHCO_3$ (40 mL x 2) and the washings were adjusted to pH 2 with 1N HCl and extracted with ether (100 mL x 4). The combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give a viscous oil that was dissolved in chloroform and filtered from a small amount of phthalic acid (1.38 g, 8.85 mmol). Evaporation of the filtrate under reduced pressure yielded *RS*-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate (6.98 g, 21.2 mmol, 63 %) as a viscous oil which slowly crystallized: mp 94-96°C (hexane/ethyl acetate); ^{1}H NMR δ 11.16 (bs, 1H, D_2O exch, CO_2H), 7.94-7.47 (m, 4H, ortho-substituted aromatic), 7.41, 7.30, 7.05, 6.94 (q, 4H, para-substituted aromatic), 6.11 (q, 1H, ArCH, J = 6.5 Hz), 5.11 (s, 2H, OCH_2O), 3.42 (s, 3H, CH_3O), 1.64 (d, 3H, CH_3, J = 6.6 Hz); IR (neat) 3400, 3130, 3070, 2992, 2896, 2828, 2664, 2549, 1737 (C=O), 1516, 1286, 1212, 1154, 1081, 998, 835, 774 cm^{-1}; Anal calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.66; H, 5.46.

b) *RS*-1-(4-Methoxymethoxyphenyl)ethanol (5.40 g, 24.6 mmol) in dry DMF (5 mL) was slowly added to a solution of phthalic anhydride (4.38 g, 24.6 mmol) in dry DMF (8 mL) protected from atmospheric moisture and containing

imidazole (2.03 g, 29.9 mmol). The reaction mixture was stirred at 95°C for 1 h, cooled to room temperature and worked up as described for the previous phthaloylation to yield RS-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate (8.61 g, 26.1 mmol, 88 %).

R-(–)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate 6

A vigorously-stirred solution of RS-1-(4-methoxymethoxyphenyl)ethyl hydrogen phthalate (5.04 g, 15.3 mmol) in ether (80 mL) was treated with R-(+)-1-phenylethylamine (Aldrich) (1.88 g, 15.5 mmol), and the salt, which precipitated within 1 min, was filtered from solution by suction and washed with ether. The air-dried salt (3.44 g, 7.63 mmol, 100 %) was recrystallized from ethanol to yield 2.42 g (5.35 mmol) of pure salt as rosettes of needles: mp 145-146°C; $[\alpha]_D^{25}$= + 6.55° (c = 2.61 in EtOH); Anal calcd for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 68.91; H, 6.47; N, 3.09.

A slurry of the dextrorotatory salt (2.93 g, 6.45 mmol) in H_2O (75 mL) was cooled to 5°C, adjusted to pH 2 with 1N HCl and extracted with ethyl acetate (75 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield R-(–)-1-(4-methoxy-methoxyphenyl)ethyl hydrogen phthalate (2.29 g) as a viscous, orange-red oil that contained a small amount of solvent (Th. yield = 2.14 g): $[\alpha]_D^{25}$= –15.1° (c = 5.30 in EtOH). The sample was stored at 5°C, but it was determined that the phthalate was unstable at this temperature, since 50 days later the specific rotation had decreased: $[\alpha]_D^{25}$= –13.2° (c = 5.07 in EtOH).

S-(+)-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate 7

RS-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate in ether was treated with *S*-(–)-1-phenylethylamine (Aldrich), in a manner analogous to that reported for the *R*-(+)-amine, to yield the levorotatory salt as rosettes of needles: mp 144-145°C; $[\alpha]_D^{25}$ = – 6.62° (c = 2.52 in EtOH); Anal calcd for $C_{26}H_{29}NO_6$:

C, 69.16; H, 6.47; N, 3.10. Found: C, 69.06; H, 6.47; N, 3.09.

The free acid was liberated from the levorotatory salt in a manner analogous to that reported for the dextrorotatory salt. *S*-(+)-1-(4-methoxy-methoxyphenyl)ethyl hydrogen phthalate was a colorless,s viscous oil: $[\alpha]_D^{25}$= +16.2° (c = 5.04 in EtOH). The sample was stored at 5°C, and in 16 days the specific rotation had decreased to $[\alpha]_D^{25}$= +14.7° (c = 5.59 in EtOH).

S-(–)-1-(4-Methoxymethoxyphenyl)ethanol 8

a) *S*-(+)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate (1.13 g, 3.43 mmol) in dry THF (50 mL), at 0°C under nitrogen, was treated with 2 M LiBH₄ in dry THF (Aldrich) (6 mL, 6 mmol). The mixture was heated at reflux for 3 h, cooled to 0°C and quenched by the slow addition of H_2O (45 mL). The aqueous phase was saturated with NaCl, separated from the organic phase and extracted with ether (50 mL x 2). The combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield an oil, which was distilled to yield *S*-(–)-1-(methoxymethoxyphenyl)ethanol (568 mg, 3.12 mmol, 91 %: bp 81°C (0.005 mm Hg, Kugelrohr); $[a]_D^{20}$= – 29.5°,

$[a]_D^{25}$= –28.8° (c = 4.88 in EtOH); The ¹H NMR and IR (neat) spectra were

identical to those recorded for the racemic alcohol. Anal calcd for $C_{10}H_{14}O_3$:

C, 65.91; H, 7.74. Found: C, 65.48; H, 7.89.

b) *S*-(+)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate (1.17 g,

3.53 mmol) was dissolved in 1.15 N NaOH in 77 % ethanol (25 mL, 29 mmol)

and the mixture was heated at reflux for 1 h. The hydrolysate was cooled to

room temperature, diluted with H_2O (25 mL) and saturated with NaCl. The

layers were separated and the aqueous phase was extracted with ether (50 mL

x 2). The ethanol was evaporated under reduced pressure and the residue was

dissolved in the combined ether extracts, which were dried over anhydrous

Na_2SO_4, filtered and evaporated under reduced pressure to yield *S*-(–)-1-(4-

methoxymethoxyphenyl)ethanol (579 mg, 3.18 mmol, 90 %): bp 81°C (0.005

mm Hg Kugelrohr); $[\alpha]_D^{20}= -33.8°$, $[\alpha]_D^{25}= -33.2°$ (c = 5.01 in EtOH); LC

analysis of the *S*-(–)-MTPA ester indicated the product to be a mixture of 98 %

S-(–)-isomer and 2 % *R*-(+)-isomer.

R-(+)-1-(4-Methoxymethoxyphenyl)ethanol 9

R-(-)-1-(4-Methoxymethoxyphenyl)ethyl hydrogen phthalate (1.04 g, 3.14

mmol), in a solution of sodium (348 mg, 15.1 mmol) in 96 % ethanol (7 mL), was

heated on the steam bath for several min until a thick precipitate was produced.

The mixture was diluted with H_2O (50 mL) and extracted with ether (50 mL x 3),

and the combined extracts were dried over anhydrous Na_2SO_4, filtered and

evaporated under reduced pressure to yield *R*-(+)-1-(4-methoxymethoxy-

phenyl)ethanol (498 mg, 2.74 mmol, 87 %): bp 81°C (0.005 mm Hg, Kugelrohr); $[\alpha]_D^{20} = + 31.7°$, $[\alpha]_D^{25} = + 31.1°$ (c = 5.44 in EtOH); LC analysis of the S-(–)-MTPA ester indicated the product to be a mixture of 93.1 % R-(+)-isomer and 6.9 % S-(–)-isomer; the ^{1}H NMR and IR (neat) spectra were identical to those recorded for the racemic alcohol. Anal calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.58; H, 7.90.

4-[(2-Methoxyethoxy)methoxy]-acetophenone 10

A stirred solution of 4-hydroxyacetophenone (39.0 g, 287 mmol) in dry dichloromethane (410 mL), protected from atmospheric moisture and containing N,N-diisopropylethylamine (55.5 g, 429 mmol), was slowly treated with 2-methoxyethoxymethyl chloride (Aldrich) (53.5 g, 429 mmol). After 4 h, the mixture was washed with H_2O (300 mL x 2), 1 N NaOH (200 mL x 2) and H_2O (300 mL x 2), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 4-[(2-methoxyethoxy)methoxy]-acetophenone (64.2 g, 287 mmol, 100 %): bp 100-109°C (0.005 mm Hg); ^{1}H NMR δ 7.97, 7.86, 7.11, 7.02 (q, 4H, para-substituted aromatic), 5.31 (s, 2H, OCH_2O), 3.87-3.47 (m, 4H, OCH_2CH_2O), 3.35 (s, 3H, CH_3O), 2.53 (s, 3H, CH_3CO); IR (neat) 2921, 2888, 2814, 1677 (C=O), 1603, 1509, 1416, 1362, 1275, 1235, 1175, 1108, 987, 840 cm^{-1}; Anal calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.96; H, 7.07.

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol 11

4-[(2-Methoxyethoxy)methoxy]-acetophenone (123 g, 548 mmol) in 95 % ethanol (900 mL) was slowly treated with $NaBH_4$ (10.4 g, 274 mmol). The

mixture was stirred overnight and quenched with H_2O (300 mL). After the aqueous phase was saturated with NaCl and the layers were separated, the aqueous phase was extracted with ether. The ethanol was evaporated under reduced pressure and the residue was dissolved in the ether extract, which was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield *RS*-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol (122 g, 533 mmol, 97 %): bp 120-125°C (0.005 mm Hg); ^{1}H NMR δ 7.34, 7.23, 7.06, 6.95 (q, 4H, para-substituted aromatic), 5.24 (s, 2H, OCH_2O), 4.82 (q, 1H, ArCH, J = 6.5 Hz), 3.87 - 3.47 (m, 4H, OCH_2CH_2O), 3.35 (s, 3H, CH_3O), 2.13 (bs, 1H, D_2O exch, OH), 1.45 (d, 3H, CH_3, J = 6.4 Hz); IR (neat) 3418 (OH), 2973, 2926, 2842, 1611, 1509, 1219, 1091, 1004, 846, 835 cm^{-1}; Anal calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.58; H, 8.05.

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol-1-d₁ 12

RS-1-[4-(2-Methoxyethoxy)methoxy]-acetophenone (49.5 g, 221 mmol) in dry THF (50 mL) was slowly added, under nitrogen, to a stirred suspension of LAD (99 atom % D, 9.28 g, 221 mmol) in dry THF (400 mL). The reaction mixture was allowed to stir overnight, cooled to 5°C and hydrolyzed by the slow addition of H_2O (10 mL), 15% NaOH (10 mL) and H_2O (30 mL). The supernatant was filtered from the suspended solids and evaporated under reduced pressure to yield *RS*-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d₁ (47.5 g, 209 mmol, 95 %): bp 120-125°C (0.005 mmHg); ^{1}H NMR δ 7.33, 7.22, 7.05, 6.94 (q, 4H, para-substituted aromatic), 5.22 (s, 2H, OCH_2O), 3.86-3.46 (m, 4H, OCH_2CH_2O), 3.34 (s, 3H, CH_3O), 2.23 (s, 1H, D_2O exch, OH), 1.43 (s, 3H, CH_3); IR (neat) 3426 (OH), 2968, 2928, 2887, 2127 (CD), 1609, 1514, 1225, 1097,

1003, 841 cm^{-1}; Anal calcd for C$_{12}$H$_{17}$DO$_4$: C, 63.41; H, 7.98. Found: C, 63.07; H, 8.02.

RS-2-(Methoxyethoxy)methyl 1-[4-(2-methoxyethoxy)-methoxyphenyl]-ethyl ether 13

A stirred solution of RS-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol (2.52 g, 11.1 mmol) in dry dichloromethane (25 mL), protected from atmospheric moisture and containing N,N-diisopropylethylamine (2.16 g, 16.7 mmol), was slowly treated with 2-methoxyethoxymethyl chloride (2.08 g, 16.7 mmol) in dichloromethane (2 mL). After 24 h, the reaction mixture was washed with H$_2$O (50 mL x 3), 1N NaOH (50 mL x 3) and H$_2$O (50 mL x 3), dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure to give RS-2-(methoxyethoxy)methyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether (3.34 g, 10.8 mmol, 97 %): bp: 130-132°C (0.020 mm Hg). The product was shown by LC to contain 2 % of the starting material. Purification by column chromatography on silica gel (hexane/ethyl acetate) was attempted, but the product appeared to be unstable and began to decompose. It was stored at – 20°C. ^{1}H NMR δ 7.31, 7.20, 7.05, 6.95 (q, 4H, para-subsituted aromatic), 5.25 (s, 2H, OCH$_2$OPh), 4.86-4.53 (m, 3H, ArCH+OCH$_2$O-CHAr), 3.88-3.44 (m, 8H, OCH$_2$CH$_2$O), 3.37 (s, 6H, CH$_3$O), 1.44 (d, 3H, CH$_3$, J = 6.3 Hz); IR (neat) 2931, 2884, 1609, 1510, 1224, 1098, 1038, 1012, 839 cm^{-1}; mass spectrum (EI, 70 eV), m/z (relative intensity) 314 (M+, 0.3), 269 (5), 225 (12), 209 (9), 131 (9), 121 (11), 120 (9), 84 (100); exact mass calculated for C$_{16}$H$_{26}$O$_6$ m/z 314.1729, found m/z 314.1720 (–3 ppm).

RS-4-Methoxybenzyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether 14

RS-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol (3.89 g, 17.2 mmol) in dry THF (5 mL) was added, under nitrogen, to a stirred suspension of NaH (1.28 g, 53.2 mmol) in dry THF (50 mL). The mixture was heated at reflux for 2 h, cooled to room temperature and treated with 4-methoxybenzyl chloride (Aldrich) (4.16 g, 26.6 mmol) in dry THF (5 mL). After the mixture was heated at reflux for 24 h, it was cooled to room temperature and quenched by the slow addition of H_2O (25 mL). The aqueous phase was saturated with NaCl and separated from the organic phase, which was washed with brine (50 mL x3), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give 7.42 g of an oil, shown by LC to contain product, starting material, 4-methoxybenzyl alcohol and 4-methoxybenzyl chloride. The trace of 4-methoxy-benzyl chloride was hydrolyzed by treatment of the crude product with a stirred solution of saturated $NaHCO_3$ (50 mL), for 3.5 h. The residue was dissolved in ether (50 mL) and the layers were separated. The extract was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 7.18 g of material, which was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford *RS*-4-methoxybenzyl 1-[4-(2-methoxyethoxy)-methoxyphenyl]-ethyl ether (3.42 g, 9.88 mmol, 57 %): bp 190°C (0.005 mm Hg, Kugelrohr). This material appeared to be unstable and was stored at − 20°C. ^{1}H NMR (240 MHz) δ 7.28-6.84 (m, 8H, ArH), 5.27 (s, 2H, OCH_2O), 4.43 (q, 1H, ArCH, J = 6.4 Hz), 4.35 (d, 1H, ArCH$_A$H$_B$, J = 11.4 Hz), 4.20 (d, 1H, ArCH$_A$H$_B$, J = 11.4 Hz), 3.86-3.55 (m, 4H, OCH_2CH_2O), 3.79 (s, 3H, CH_3O), 3.38 (s, 3H, CH_3O), 1.43 (d, 3H, CH_3, J = 6.4 Hz); IR (neat) 2973, 2931, 2882,

1609, 1511, 1244, 1223, 1089, 1005, 836 cm^{-1}; Anal calcd for C$_{20}$H$_{26}$O$_5$: C, 69.34; H, 7.57. Found: C, 69.29; H, 7.62.

RS-t-Butyldimethylsilyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether 15

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol (3.70 g, 16.4 mmol) in dry DMF (5 mL) was slowly added, under nitrogen, to a solution of t-butyldimethylsilyl chloride (Aldrich) (2.89 g, 19.2 mmol) in dry DMF (6 mL) containing imidazole (2.87 g, 42.1 mmol). The reaction mixture was stirred overnight, diluted with H$_2$O (50 mL) and extracted with ether (100 mL x 4). The combined extracts were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure to give a residue containing DMF, which was removed by co-distillation with benzene under reduced pressure to give RS-t-butyldimethylsilyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether (5.48 g, 16.1 mmol, 98 %): bp 115°C (0.003 mm Hg); ^{1}H NMR δ 7.33, 7.22, 7.06, 6.95 (q, 4H, para-substituted aromatic), 5.28 (s, 2H, OCH$_2$O), 4.86 (q, 1H, ArCH, J = 6.3 Hz), 3.92-3.53 (m, 4H, OCH$_2$CH$_2$O), 3.40 (s, 3H, CH$_3$O), 1.41 (d, 3H, CH$_3$, J = 6.5 Hz), 0.93 (s, 9H, (CH$_3$)$_3$), 0.08 (s, 3H, CH$_3$-Si-), 0.00 (s, 3H, CH$_3$ -Si-); IR (neat) 2957, 2931, 2891, 2858, 1609, 1510, 1251, 1224, 1091, 1005, 959, 839, 779 cm^{-1}; Anal calcd for C$_{18}$H$_{32}$SiO$_4$: C, 63.48; H, 9.47. Found: C, 63.62; H, 9.48.

RS-t-Butyldiphenylsilyl 1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl ether 16

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol (3.94 g, 17.4 mmol) in dry DMF (4 mL) was slowly added, under nitrogen, to a solution of t-butyldiphenylsilyl chloride (Aldrich) (5.75 g, 21.0 mmol) in dry DMF (10 mL) containing imidazole (3.15 g, 48.2 mmol). The reaction mixture was stirred overnight, diluted with H_2O (75 mL) and extracted with ether (100 mL x 4). The combined extracts were washed with H_2O (200 mL x 2), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 8.88 g of crude product. Purification by column chromatography on silica gel (hexane/benzene) afforded *RS*-t-butyldiphenylsilyl 1-[4-(2-methoxyethoxy)-methoxyphenyl]-ethyl ether (7.68 g, 16.5 mmol, 95 %): bp 180-200°C (0.005 mm Hg, Kugelrohr); ^{1}H NMR δ 7.73-6.68 (m, 14H, ArH), 5.24 (s, 2H, OCH_2O), 4.80 (q, 1H, ArCH, J = 6.3 Hz), 3.36 (s, 3H, CH_3O), 1.30 (d, 3H, CH_3, J = 6.3 Hz), 1.05 (s, 9H, $(CH_3)_3$); IR (neat) 3070, 3050, 2964, 2431, 2898, 2858, 1609, 1510, 1430, 1224, 111, 1005, 959, 832, 706 cm^{-1}; Anal calcd for $C_{28}H_{36}SiO_4$: C, 72.37; H, 7.81. Found: C, 72.60; H, 7.90.

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate 17

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethyl alcohol (24.8 g, 110 mmol) in dry DMF (25 mL) was slowly added to a solution of phthalic anhydride (16.3 g, 110 mmol) in dry DMF (75 mL) protected from atmospheric moisture and containing imidazdole (7.47 g, 110 mmol). The mixture was stirred for 2 h at 100°C, cooled to room temperature and partitioned between H_2O (100 mL)

and ether (100 mL). The aqueous phase was cooled to 5°C, adjusted to pH 2 with 6 N HCl, saturated with NaCl, separated from the organic phase and extracted with ether (150 mL x 3). The combined organic phases were concentrated under reduced pressure to 200 mL and washed with saturated NaHCO$_3$ (150 mL). The NaHCO$_3$ wash was washed with ether (150 mL), cooled to 5°C, adjusted to pH 2 with 6 N HCl, saturated with NaCl and extracted with ether (150 mL x 3). The combined extracts were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure to give a residue, which was dissolved in chloroform (100 mL) and filtered from the precipitated phthalic acid. Evaporation of the solvent under reduced pressure yielded RS-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate (29.8 g, 79.5 mmol, 72 %) as a viscous oil: ^{1}H NMR δ 10.21 (bs, 1H, D$_2$O exch, CO$_2$H), 7.93-7.44 (m, 4H, ortho-substituted aromatic), 7.40, 7.29, 7.07, 6.96 (q, 4H, para-substituted aromatic), 6.10 (q, 1H, ArCH, J = 6.6 Hz), 5.21 (s, 2H, OCH$_2$O), 3.85-3.44 (m, 4H, OCH$_2$CH$_2$O), 3.35 (s, 3H, CH$_3$O), 1.64 (d, 3H, CH$_3$, J = 6.6 Hz); IR (neat) 3543, 3353, 3128, 3072, 2981, 2931, 2896, 2826, 2636, 2538, 1729 (C=O), 1511, 1286, 1223, 1124, 1103, 1075, 1005, 836, 752 cm^{-1}; anal calcd for C$_{20}$H$_{22}$O$_7$: C, 64.16; H, 5.92. Found: C, 63.96; H, 6.01. The methyl ester was prepared from the free acid with diazomethane; mass spectrum (EI, 70 eV), m/z (relative intensity) 388 (M+, 58), 225 (56), 209 (41), 208 (30), 163 (100), 149 (27), 120 (66); exact mass calcd for C$_{21}$H$_{24}$O$_7$ m/z 388.1520, found 388.1517 (–0.8 ppm).

S-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate 18

A vigorously-stirred solution of RS-1-[4-(2-methoxyethoxy)methoxy-phenyl]-ethyl hydrogen phthalate (18.6 g, 49.6 mmol) in ether (300 mL) was treated with S-(–)-1-phenylethylamine (6.02 g, 49.7 mmol), and the salt, which precipitated within 1 min, was filtered from solution by suction and washed with ether. The air-dried salt (12.5 g, 25.3 mmol) was recrystallized twice from methyl acetate (Aldrich) to yield the pure salt as rosettes of needles (8.12 g, 16.4 mmol, 66 %): mp 141-143°C; $[\alpha]_D^{25} = -6.1°$ (c = 2.92 in EtOH); Anal calcd

for $C_{28}H_{33}NO_7$: C, 67.86; H, 6.71; N, 2.83. Found: C, 67.67; H, 6.63; N, 2.83.

The levorotatory salt (32.5 g, 65.7 mmol) was suspended in H_2O (700 mL) at 5°C and the rapidly-stirred mixture was slowly treated with oxalic acid·$2H_2O$ (8.29 g, 65.8 mmol) in H_2O (160 mL). The aqueous phase was saturated with NaCl and extracted with ether (700 mL x 3), and the combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield S-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate (27.2 g) as a viscous oil that contained a small amount of residual solvent (Th. = 24.6 g). The acid phthalate was either hydrolyzed immediately or stored at –78°C. It was not characterized.

R-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate 19

The ether-soluble fraction (150 mL) from the treatment of RS-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate in ether with S-(–)-

1-phenylethylamine was washed with ice-cold 0.2 N HCl (125 mL) and brine

(125 mL x 2), and dried over anhydrous $MgSO_4$. The stirred filtrate was treated

with R-(+)-1-phenylethylamine (6.02 g, 49.7 mmol) and the precipitated salt was

filtered from solution by suction and washed with ether. The air-dried salt (10.1

g, 20.4 mmol) was recrystallized twice with methyl acetate to yield the pure salt

as rosettes of needles (7.92 g, 16.0 mmol, 65 %): mp 141-143°C; $[\alpha]_D^{25}= + 6.1°$

(c = 2.82 in EtOH); Anal calcd for $C_{28}H_{33}NO_7$: C, 67.86; H, 6.71; N, 2.83.

Found: C, 67.63; H, 6.62; N, 2.85. The free acid was liberated from the salt in

a manner analogous to that employed for the levorotatory salt and was either

hydrolyzed immediately or stored at -78°C. It was not characterized.

S-(–)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol   20

The S-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate

liberated from the levorotatory salt (65.7 mmol) was dissolved in a solution of

sodium (7.45 g, 324 mmol) in 96% ethanol (130 mL), and the mixture was

heated on the steam bath for several min until a thick precipitate was produced.

The hydrolysate was diluted with H_2O (750 mL), saturated with NaCl and

extracted with ether (600 mL x 4). The combined extracts were dried over

anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield S-

(–)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol (14.8 g, 65.4 mmol, 100 %)

as a pale-yellow liquid which was distilled: bp 120-125°C (0.005 mm Hg);

d_4^{20} 1.108; $[\alpha]_D^{20}= - 37.44°$ (neat); CD $[\Theta]_{290} = 0$, $[\Theta]_{280} = - 275$, $[\Theta]_{275} =   -$

143 (sh), $[\Theta]_{240} = 0$, $[\Theta]_{232} = + 326$ (c = 2.20 in EtOH); LC analysis of the S-(–)-

MTPA ester of the alcohol (t_R 35.1 min) showed no trace of the R-(+)-isomer;

the ¹H NMR and IR (neat) spectra were identical to those recorded for the racemic alcohol; Anal calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.44; H, 8.07.

R-(+)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol 21

The R-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl hydrogen phthalate liberated from the dextrorotatory salt was hydrolyzed, in a manner analogous to that employed for the S-hydrogen phthalate, to yield R-(+)-1-[4-(2-methoxy-ethoxy)methoxyphenyl]-ethanol: bp 120-125°C (0.005 mm Hg); d_4^{20} 1.108; $[\alpha]_D^{20}$ = + 37.2° (neat); LC analysis of the S-(–)-MTPA ester of the alcohol (t_R 34.0 min) showed no trace of the S-(–)-isomer. The ¹H NMR and IR (neat) spectra were identical to those recorded for the racemic alcohol; Anal calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.62; H, 8.13.

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate 22

The title compound was synthesized from RS-1-[4-(2-methoxyethoxy) methoxyphenyl]-ethanol-1-d₁ employing the same method used for the synthesis of the unlabeled analog: ¹H NMR δ 10.77 (bs, 1H, D_2O exch, CO_2H), 7.95-7.46 (m, 4H, ortho-substituted aromatic), 7.41, 7.29, 7.07, 6.96 (q, 4H, para-substituted aromatic), 5.22 (s, 2H, OCH_2O), 3.86-3.46 (m, 4H, OCH_2CH_2O), 3.35 (s, 3H, CH_3O), 1.63 (s, 3H, CH_3); IR (neat) 3418, 3147, 3067, 3041, 2982, 2928, 2896, 2816, 2638, 2545, 1725 (C=O), 1514, 1302, 1263, 1223, 1091, 1071, 998, 840 cm⁻¹; mass spectra of the methyl ester (EI,

70 eV), m/z (relative intensity) 389 (M$\ddagger$, 100), 226 (23), 210 (18), 163 (91), 149 (20), 122 (21), 121 (44); exact mass calcd for $C_{21}H_{23}DO_7$ m/z 389.1582, found m/z 389.1583 (+0.3 ppm).

S-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethyl-1-d$_1$ hydrogen phthalate 23

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethyl-1-d$_1$ hydrogen phthalate in ether was treated with S-(–)-1-phenylethylamine, in a manner analogous to that employed for the unlabeled hydrogen phthalate, to yield the levorotatory salt as rosettes of needles: mp 142-143°C; $[\alpha]_D^{25}$= – 6.1° (c = 2.94 in EtOH); Anal calcd for $C_{28}H_{32}DNO_7$: C, 67.72; H, 6.70; N, 2.82. Found: C, 67.96; H, 6.76; N, 2.92.

The free acid was liberated from the salt in a manner analogous to that employed for the unlabeled material and was either hydrolyzed immediately or stored at –78°C. It was not characterized.

R-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethyl-1-d$_1$ hydrogen phthalate 24

The ether-soluble fraction from the treatment of RS-1-[4-(2-methoxy-ethoxy)methoxyphenyl]-ethyl-1-d$_1$ hydrogen phthalate in ether with S-(–)-1-phenylethylamine was converted to the dextrorotatory salt in a manner analogous to that employed for the unlabeled hydrogen phthalate: mp 142-143°C: $[\alpha]_D^{25}$= + 6.1° (c = 2.90 in EtOH); Anal calcd for $C_{28}H_{32}DNO_7$: C, 67.72; H, 6.70; N, 2.82. Found: C, 67.86; H, 6.71; N, 2.85.

The free acid was liberated from the salt, in a manner analogous to that employed for the unlabeled material, and was either hydrolyzed immediately or stored at −78°C. It was not characterized.

S-(−)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$ 25

The S-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl-1-d$_1$ hydrogen phthalate liberated from the levorotatory salt was hydrolyzed, in a manner analogous to that employed for the protio analog, to yield S-(−)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$: bp 120-125°C (0.005 mm Hg); d_4^{20} 1.112; $[\alpha]_D^{20}$= − 38.0° (neat); LC analysis of the S-(−)-MTPA ester of the alcohol (t$_R$ 35.1 min) showed no trace of the R-(+)-isomer. The ^{1}H NMR and IR (neat) spectra were identical to those recorded for the racemic alcohol; mass spectrum (EI, 70 eV), m/z (relative intensity) 227 (M$\dot+$, 27), 209 (43), 152 (17), 134 (17), 124 (23), 122 (18), 121 (100); exact mass calcd for C$_{12}$H$_{17}$DO$_4$ m/z 227.1268, found m/z 227.1272 (+2 ppm).

R-(+)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$ 26

The R-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethyl-1-d$_1$ hydrogen phthalate liberated from the dextrorotatory salt was hydrolyzed, in a manner analogous to that employed for the protio analog, to yield R-(+)-1-[4-(2-methoxy-ethoxy) methoxyphenyl]-ethanol-1-d$_1$: bp 120-125°C (0.005 mm Hg); d_4^{20} 1.112; $[\alpha]_D^{20}$= + 37.9° (neat); LC analysis of the S-(−)-MTPA ester of the alcohol (t$_R$ 34.0 min) showed no trace of the S-(−)-isomer. The ^{1}H NMR and IR

(neat) spectra were identical to those recorded for the racemic alcohol. The mass spectrum was identical to the spectrum of the S-(−)-alcohol; exact mass calcd for $C_{12}H_{17}DO_4$ m/z 227.1268, found m/z 227.1266 (−0.9 ppm).

4-[(2-Trimethylsilylethoxy)methoxy]-acetophenone 27

A stirred solution of 4-hydroxyacetophenone (13.6 g, 100 mmol) in dry dichloromethane (140 mL), protected from atmospheric moisture and containing N, N-diisopropylethylamine (20.0 g, 155 mmol), was slowly treated with 2-(trimethylsilyl)ethoxymethyl chloride (Aldrich) (25.6 g, 153 mmol). After 2 h, the mixture was washed with H_2O (200 ml x 3), 1 N NaOH (100 mL x 2) and H_2O (200 mL x 2), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 4-[(2-trimethylsilylethoxy)methoxy]-acetophenone (25.7 g, 96 mmol, 96 %): mp 22-23°C; bp 108-109°C (0.010 mm Hg); ^{1}H NMR δ 7.98, 7.87, 7.12, 7.01 (q, 4H, para-substituted aromatic), 5.27 (s, 2H, OCH_2O), 3.76 (t, 2H, CH_2O, J = 8.2 Hz), 2.56 (s, 3H, CH_3CO), 0.95 (t, 2H, $C\underline{H}_2Si(CH_3)_3$, J = 8.2 Hz), 0.00 (s, 9H, $(CH_3)_3Si$); IR (neat) 2957, 2898, 1682 (C=O), 1603, 1510, 1417, 1357, 1271, 1244, 1231, 1171, 1091, 992, 859, 839, 759 cm^{-1}; Anal calcd for $C_{14}H_{22}SiO_3$: C, 63.12; H, 8.33. Found: C, 62.93; H, 8.22.

The (2-trimethylsilylethoxy)methyl (SEM) protecting group was quantitatively removed (TLC, silica gel, $CHCl_3$/MeOH) by nBu_4NF (8.5 mol) in THF, at room temperature, in 3 h.[4]

RS-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethanol 28

4-[(2-Trimethylsilylethoxy)methoxy]-acetophenone (2.08 g, 7.79 mmol) in
95 % ethanol (60 mL) was slowly treated with $NaBH_4$ (313 mg, 8.28 mmol). The
mixture was stirred overnight and quenched with H_2O (150 mL). After the
aqueous phase was saturated with NaCl and the layers were separated, the
aqueous phase was extracted with ether. The ethanol was evaporated under
reduced pressure and the residue was dissolved in the ether extract, dried over
anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield
RS-1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethanol (1.99 g, 7.42 mmol, 95
%): bp 107-111°C (0.010 mm Hg); ^{1}H NMR δ 7.34, 7.23, 7.05, 6.94 (q, 4H,
para-substituted aromatic), 5.19 (s, 2H, OCH_2O), 4.83 (q, 1H, ArCH, J = 6.25
Hz), 3.74 (dd, 2H, RCH_2O, J = 7.3 Hz, 8.1 Hz), 1.94 (s, 1H, D_2O exch, OH), 1.46
(d, 3H, CH_3, J = 6.4 Hz), 0.96 (dd, 2H, $C\underline{H}_2Si(CH_3)_3$, J = 7.4 Hz, 8.1 Hz), 0.00
(s, 9H, $(CH_3)_3Si$); IR (neat) 3396 (OH), 2957, 2924, 2891, 1609, 1510, 1251,
1224, 1091, 998, 832 cm^{-1}; Anal calcd for $C_{14}H_{24}SiO_3$: C, 62.64; H, 9.01.
Found: C, 62.33; H, 9.03. This material decomposed over a period of several
months, even at $-20°C$.

RS-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d$_1$ 29

4-[(2-Trimethylsilylethoxy)methoxy]-acetophenone (26.8 g, 101 mmol) in
dry THF (26 mL) was slowly added, under nitrogen, to a stirred suspension of
LAD (99 atom % D, 2.15 g, 51.2 mmol) in dry THF (52 mL). The reaction mixture

was stirred for 1 h at room temperature, heated at reflux for 90 min, cooled to 5°C and hydrolyzed by the slow addition of H_2O (2.2 mL, 15% NaOH (2.2 mL) and H_2O (6.6 mL). The supernatant was filtered from the suspended solids and evaporated under reduced pressure to yield RS-1-[4-(2-trimethylsilylethoxy)-methoxyphenyl]-ethanol-1-d_1 (27.1 g, 101 mmol, 100 %): bp 113-115°C (0.010 mm Hg); ^{1}H NMR δ 7.34, 7.23, 7.05, 6.94 (q, 4H, para-substituted aromatic), 5.19 (s, 2H, OCH_2O), 3.74 (dd, 2H, RCH_2O, J = 7.3 Hz, 8.1 Hz), 1.96 (s, 1H, D_2O exch, OH), 1.45 (s, 3H, CH_3), 0.96 (dd, 2H, $\underline{C}H_2Si(CH_3)_3$, J = 7.4 Hz, 8.0 Hz), 0.00 (s, 9H, $(CH_3)_3Si$); IR (neat) 3409 (OH), 2951, 2924, 2898, 2121 (CD), 1609, 1510, 1251, 1224, 1144, 1091, 1005, 939, 832 cm^{-1}; mass spectrum (EI, 70 eV), m/z (relative intensity) 269 (M‡, 4), 211 (32), 196 (100), 181 (16), 168 (11), 151 (21), 103 (11); exact mass calcd for $C_{14}H_{23}DSiO_3$ m/z 269.1558, found 269.1557 (−0.4 ppm).

RS-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d_1 hydrogen phthalate 30

4-[(2-Trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d_1 (24.9 g, 92.5 mmol) in dry DMF (30 mL) was added to a solution of phthalic anhydride (14.1 g, 95.5 mmol) in dry DMF (60 mL), protected from atmospheric moisture and containing imidazole (13.0 g, 191 mmol), and the mixture was stirred for 24 h. The mixture was cooled to 5°C and titrated with 1N HCl (190 mL) to pH 3.5, the layers were separated and the aqueous phase was extracted with ether (200 mL x 4). The combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 40.7 g of a viscous oil, which ^{1}H NMR analysis showed to contain about 2 g of DMF. The theoretical yield of

RS-1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate was 38.6 g. LC (100 % MeOH) showed the product (excluding DMF) to be > 99.6 % pure. ^{1}H NMR δ 10.06 (bs, 1H, D_2O exch, CO_2H), 7.95-7.49 (m, 4H, ortho-substituted aromatic), 7.42, 7.31, 7.07, 6.96 (q, 4H, para-substituted aromatic), 5.18 (s, 2H, OCH_2O), 3.73 (dd, 2H, RCH_2O, J = 7.1, 8.2 Hz), 1.65 (s, 3H, CH_3), 0.96 (dd, 2H, $C\underline{H}_2Si(CH_3)_3$, J = 7.1, 8.2 Hz), 0.00 (s, 9H, $(CH_3)_3Si$); IR (neat) 3442, 3157, 3070, 3044, 2951, 2891, 2905, 2639, 2532, 1722 (C=O), 1643, 1516, 1304, 1251, 1231, 1091, 1072, 998, 859, 839 cm^{-1}. The methyl ester was prepared from the free acid and diazomethane; mass spectrum (EI, 70 eV), m/z (relative intensity) 431 (M⁺, 0.4), 373 (11), 253 (10), 237 (17), 221 (11), 210 (96), 208 (20), 194 (68), 193 (18), 192 (26), 178 (18), 177 (12), 163 (100), 121 (34) 103 (18); exact mass calcd for $C_{23}H_{29}DSiO_6$ m/z 431.1874, found m/z 431.1866 (−1.9 ppm).

S-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate 31

A vigorously-stirred solution of *RS*-1-[4-(2-trimethylsilylethoxy)-methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate (38.6 g, 92.5 mmol) in ether (600 mL) was treated with *S*-(−)-1-phenylethylamine (11.3 g, 93.1 mmol). The solvent was removed under reduced pressure and the gelatinous residue was dissolved in hot methyl acetate (60 mL), which was slowly cooled to room temperature. The separated crystalline salt was filtered by suction from the thick, molasses-like supernatant, washed with ice-cold methyl acetate and air-dried to give 12.7 g of crude salt. Concentration of the mother liquor afforded another 8.0 g of material. Two recrystallizations of the combined solids from

methyl acetate yielded 11.9 g (22.1 mmol, 48 %) of pure salt as white needles: mp 137-138°C; $[\alpha]_D^{25} = -10.2°$ * (c = 5.30 in EtOH); Anal calcd for

$C_{30}H_{38}DNSiO_6$: C, 66.88; H, 7.30; N, 2.60. Found: C, 66.99; H, 7.36; N, 2.54.

The salt (11.9 g, 22.1 mmol) in H_2O (150 mL) was cooled to 5°C, slowly treated with a solution of oxalic acid • $2H_2O$ (2.79 g, 22.1 mmol) in H_2O (50 mL) and extracted with ethyl acetate (150 mL x 3). The combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 9.92 g of viscous S-1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate that contained about 0.7 g of ethyl acetate (Th. yield = 9.24 g). The product was not characterized and was either hydrolyzed immediately or stored at −78°C.

* This rotation was concentration-dependent.

R-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate 32

The methyl acetate-soluble fraction (300 mL) from the treatment of RS-1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate in ether with S-(−)-1-phenylethylamine was washed with ice-cold 0.2 N HCl (150 mL x 3) and brine (150 mL x 3), and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to about 50 mL. The stirred solution was treated with R-(+)-1-phenylethylamine (7.05 g, 58.3 mmol) and concentrated under reduced pressure to about 40 ml. The hot solution was slowly cooled to room temperature and the resultant hardened mass was broken up, washed

with ice-cold methyl acetate and air-dried to give 13.5 g of crude salt.

Concentration of the mother liquor afforded another 1.71 g of material. Two

recrystallizations of the combined solids from methyl acetate yielded 13.3 g

(24.7 mmol, 53%) of pure salt as white needles: mp 137-138°C; $[\alpha]_D^{25}$= +10.4° *

(c = 5.26 in EtOH); Anal calcd for $C_{30}H_{38}DNSiO_6$: C, 66.88; H, 7.30; N, 2.60.

Found: C, 66.89; H, 7.31; N, 2.57.

The free acid was liberated, in a manner analogous to that employed for

the S- acid, to give 11.5 g of viscous R-1-[4-(2-trimethylsilylethoxy)methoxy-

phenyl]-ethyl-1-d_1 hydrogen phthalate that contained about 1.1 g of ethyl

acetate (Th. yield = 10.4 g). This product was not characterized and was either

hydrolyzed immediately or stored at −78°C.

* This rotation was concentration-dependent.

S-(−)-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d_1 33

S-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d_1 hydrogen

phthalate (9.24 g, 22.1 mmol), in a solution of sodium (2.65 g, 116 mmol) in 96

% ethanol (40 mL), was heated on the steam bath for several min until a thick

precipitate was produced. The mixture was diluted with H_2O and extracted with

ether, and the combined extracts were dried over Na_2SO_4, filtered and

evaporated under reduced pressure to yield S-(−)-1-[4-(2-trimethylsilylethoxy)-

methoxyphenyl]-ethanol-1-d_1 (5.73 g, 21.3 mmol, 96 %): bp 102-104°C (0.007

mm Hg); d_4^{20} 1.011; $[\alpha]_D^{20}$= − 34.8° (neat); > 99.3% S-(−)-isomer by LC

analysis of the S-(−)-MTPA ester (t_R 186.2 min). The ^1H NMR, IR (neat) and

mass spectra (EI, 70 eV) were identical to those recorded for the racemic and R-(+)-alcohols. Exact mass calcd for $C_{14}H_{23}DSiO_3$ m/z 269.1558, found m/z 269.1557 (–0.4 ppm). This material, like the racemic and R-(+)-alcohols, decomposed over a period of several months at – 20°C.

R-(+)-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d₁ 34

R-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethyl-1-d₁ hydrogen phthalate (10.4 g, 24.7 mmol) was hydrolyzed, in a manner analogous to that for the S-(–)-isomer, to yield R-(+)-1-[4-(2-trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d₁ (6.52 g, 24.2 mmol, 98 %): bp 102-104°C (0.005 mm Hg): d_4^{20} 1.011; $[\alpha]_D^{20}$= + 35.0° (neat); > 99.9% R-(+)-isomer by LC analysis of the S-(–)-MTPA ester (t_R 183.6 min). The ^{1}H NMR, IR (neat) and mass spectra (EI, 70 eV) were identical to those recorded for the racemic and S-(–)-alcohols. Exact mass calcd for $C_{14}H_{23}DSiO_3$ m/z 269.1558, found m/z 269.1556 (–0.7 ppm). This material, like the racemic and S-(–)-alcohols, decomposed over a period of several months at – 20°C.

R-(+)-1-(4-Hydroxyphenyl)ethanol 35

4-[2-(Methoxyethoxy)methoxy]-acetophenone (8.88 g, 39.6 mmol) in dry THF (18 mL) was slowly added, under nitrogen, to a solution of (+)-diisopino -campheylchloroborane (Aldrich) (15.2 g, 47.4 mmol) in dry THF (26 mL), at 0°C. The reaction mixture was stirred for 72 h and quenched by the slow addition of triethylamine (7.20 g, 71.3 mmol) and H_2O (40 mL). The aqueous phase was saturated with NaCl, separated from the organic phase and extracted with ether

(50 mL x 3), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give a mixture of product and (–)-α-pinene. The mixture was dissolved in ether (120 mL) and extracted with 1 N NaOH (40 mL x 6), and the combined extracts were washed with ether (150 mL x 3), cooled to 5°C and titrated to pH 7* with 1 N HCl (240 mL). The aqueous phase was saturated with NaCl and extracted with ethyl acetate (400 mL x 3), and the combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 4.04 g of crude product. Purification by column chromatography on silica gel (hexane/ethyl acetate) afforded pure R-(+)-1-(4-hydroxyphenyl)ethanol {3.58 g, 25.9 mmol, 65 %, mp 147-150°C, $[\alpha]_D^{20}$= + 44.7° (c = 5.17 in EtOH)}, which was recrystallized from hexane/ethyl acetate: mp 157-158°C (colorless, rhombic-prismatic plates); mixed melt with the S-(–)-isomer: 136-138°C; $[\alpha]_D^{20}$= + 47.5°, $[\alpha]_{578}^{20}$= + 49.7°, $[\alpha]_{546}^{20}$= + 56.9°, $[\alpha]_{436}^{20}$= + 101.0°, $[\alpha]_{365}^{20}$= + 168.5°, (c = 5.06 in EtOH); a sample of the recrystallized product was methylated with diazomethane, and LC analysis of the S-(–)-MTPA ester of the p-anisyl-methylcarbinol indicated the product to be > 99.8% R-(+)-isomer; ^{1}H NMR (acetone -d_6) δ 8.16 (bs, 1H, D_2O exch, ArOH), 7.26, 7.15, 6.82, 6.71 (q, 4H, para-substituted aromatic), 4.75 (q, 1H, ArCH, J = 6.2 Hz), 4.08 (bs, 1H, D_2O exch, OH), 1.36 (d, 3H, CH_3, J = 6.4 Hz); IR (KBr) 3396 (OH), 3310, 2971, 2924, 2825, 2692, 2612, 2499, 1895, 1616, 1596, 1516, 1463, 1238, 1078, 1072, 1012, 899, 832 cm^{-1}; Anal calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.78; H, 7.43.

* It was determined that titration to pH < 4 could result in a product of reduced enantiomeric purity.

S-(−)-1-(4-Hydroxyphenyl)ethanol 36

4-[2-(Methoxyethoxy)methoxy]-acetophenone was reduced with (−)-diisopinocampheylchloroborane in dry THF, in a manner analogous to that employed for the reduction with the dextrorotatory reagent, to yield S-(−)-1-(4-hydroxyphenyl)ethanol: mp 157-159°C (colorless, rhombic-prismatic plates); mixed melt with the R-(+)-isomer: 136-138°C; $[\alpha]_{D}^{20}$ = − 47.5° $[\alpha]_{578}^{20}$ = − 49.5°,

$[\alpha]_{546}^{20}$ = − 56.9°, $[\alpha]_{436}^{20}$ = − 101.0°, $[\alpha]_{365}^{20}$ = − 168.4°, (c = 4.98 in EtOH); CD

$[\Theta]_{300}$ = 0°, $[\Theta]_{285}$ = − 433°, $[\Theta]_{278}$ = − 506°, $[\Theta]_{271}$ = − 433°, $[\Theta]_{250}$ = 0°,

$[\Theta]_{238}$ = + 263°; LC analysis of the S-(−)-MTPA ester of the p-anisylmethyl - carbinol indicated the product to be > 99.7 % S-(−)-isomer; ^{1}H NMR (acetone-d_6) δ 8.15 (s, 1H, D_2O exch, ArOH), 7.25, 7.15, 6.82, 6.71 (q, 4H, para-substituted aromatic), 4.90-4.61 (m, 1H, ArCH), 4.04 (d, 1H, D_2O exch, OH, J = 4.0 Hz), 1.36 (d, 3H, CH_3, J = 6.4 Hz); the IR (KBr) spectrum was identical to that recorded for the R-(+)-isomer. Anal calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.68; H, 7.41.

A dimorphic crystalline form of this material crystallized from hexane/ ethyl acetate as jagged needles: mp 115-118°C; $[\alpha]_{D}^{20}$ = − 47.8°, $[\alpha]_{578}^{20}$ = − 49.9°, $[\alpha]_{546}^{20}$ = − 57.2°, $[\alpha]_{436}^{20}$ = − 101.5°, $[\alpha]_{365}^{20}$ = − 169.3°, (c = 5.12 in EtOH); LC analysis of the S-(−)-MTPA ester of the p-anisylmethylcarbinol indicated the product to be > 99.7 % S-(−)-isomer; the ^{1}H NMR and IR (KBr) spectra were identical to those recorded for the other crystal form. Anal calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.58; H, 7.34.

R-(+)-1-(4-Hydroxyphenyl)ethanol-1-d₁ 37

R-(+)-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d$_1$ (5.40 g,

20.0 mmol) was dissolved in 1M n-Bu$_4$NF in THF (Aldrich) (160 mL, 160 mmol)

and the mixture was stirred at 45°C for 24 h. Evaporation of the solvent under

reduced pressure gave a viscous residue, which was dissolved in ice-cold

0.2 M pH 7.5 sodium phosphate buffer containing NaClO$_4$ (19.8 g, 162 mmol).

The precipitated n-Bu$_4$NClO$_4$ (53.3 g, 97 %) was filtered from solution by

suction and washed with ice-cold buffer. The combined filtrate and washings

were saturated with NaCl and extracted with ethyl acetate. The combined

extracts were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under

reduced pressure to give 7.0 g of a viscous residue, which was subjected to

column chromatography on silica gel (hexane/ethyl acetate) to yield 2.29 g

(16.5 mmol, 82 %) of a white powder, shown by ^{1}H NMR spectroscopy to be

pure product. A sample of the product was methylated with diazomethane, and

LC analysis of the S-(–)-MTPA ester of the p-anisylmethylcarbinol indicated the

product to be a mixture of 98.5 % R-(+)-isomer (t$_R$ 49.9 min) and 1.5 % S-(–)-

isomer (t$_R$ 51.0 min). Recrystallization of the product from hexane/ethyl acetate

afforded pure R-(+)-1-(4-hydroxyphenyl)ethanol-1-d$_1$ as colorless, rhombic-

prismatic plates.: m.p. 159-160°C; mixed mp with the S-(–)-isomer: 137-

139°C; $[\alpha]_D^{20}$= + 49.1°, $[\alpha]_{578}^{20}$= + 51.4°, $[\alpha]_{540}^{20}$= + 58.5°, $[\alpha]_{436}^{20}$= + 103.7°,

$[\alpha]_{365}^{20}$= + 173.4°, (c = 5.00 in EtOH); LC analysis of the S-(–)-MTPA ester of

the p-anisylmethylcarbinol indicated the recrystallized material to be > 99.8%

R-(+)-isomer. ^{1}H NMR (acetone-d$_6$) δ 8.16 (bs, 1H, D$_2$O exch, ArOH), 7.26,

7.15, 6.82, 6.71 (q, 4H, para-substituted aromatic), 4.05 (bs, 1H, D$_2$O exch, 2°

OH), 1.36 (s, 3H, CH$_3$). The IR (KBr) and mass spectra (EI, 70 eV) were

identical to those recorded for the racemic and S-(-)-isomers. Exact mass calcd for $C_8H_9DO_2$ m/z 139.0744, found m/z 139.0741 (-2 ppm).

S-(-)-1-(4-Hydroxyphenyl)ethanol-1-d$_1$ 38

S-(-)-1-[4-(2-Trimethylsilylethoxy)methoxyphenyl]-ethanol-1-d$_1$ (4.04 g, 15.0 mmol) was cleaved with 1M n-Bu$_4$NF in THF, in a manner analogous to that employed for the R-(+)-isomer, to yield 1.08 g (7.74 mmol, 52 %) of product. LC analysis of the S-(-)-MTPA ester of the p-anisylmethylcarbinol indicated the product to be a mixture of 99.2 % S-(-)-isomer and 0.8 % R-(+)-isomer. Recrystallization (hexane/ethyl acetate) afforded pure S-(-)-1-(4-hydroxy-phenyl)ethanol-1-d$_1$ as colorless, rhombic-prismatic plates: mp 159-160°C; mixed mp with the R-(+)-isomer: 137-139°C; $[\alpha]_D^{20} = - 48.8°$,

$[\alpha]_{578}^{20} = - 50.9°$, $[\alpha]_{546}^{20} = - 58.3°$, $[\alpha]_{436}^{20} = - 103.6°$, $[\alpha]_{365}^{20} = - 173.4°$, (c = 5.02 in EtOH); LC analysis of the S-(-)-MTPA ester of the p-anisylmethyl-carbinol indicated the recrystallized material to be > 99.8% S-(-)-isomer. The ^{1}H NMR (acetone-d$_6$) was identical to that recorded for the R-(+)-isomer. The IR (KBr) and mass spectra (EI, 70 eV) were identical to those recorded for the racemic and R-(+)-isomers. Exact mass calcd for $C_8H_9DO_2$ m/z 139.0744, found m/z 139.0755 (+7.9 ppm).

4-(Vinyl-1-d$_1$)phenol 39

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol-1-d$_1$ (236 mg, 1.04 mmol), in dry dichloromethane (2 mL) containing N,N-diisopropylethylamine

(4.08 g, 31.6 mmol), was cooled to 0°C and slowly treated, under nitrogen, with a 0.2 M solution of 2-bromo-1,3,2-benzodioxaborole (Fluka) (15 mL, 3.0 mmol) in dry dichloromethane. The reaction mixture was stirred for 3 h, quenched with H_2O (25 mL) and stirred for an additional 15 min. The aqueous phase was adjusted to pH 7 with 1 M H_3PO_4, saturated with NaCl, separated from the organic phase and extracted with ether (40 mL x 2). The combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 570 mg of a purple, viscous oil, which was chromatographed on silica gel (dichloromethane) to yield 94 mg of product, which was sublimed (50°C, 0.35 mm Hg) to afford pure 4-(vinyl-1-d_1)phenol (58 mg, 0.48 mmol, 46 %) as white needles: mp 70-71°C; ^1H NMR (DMSO-d_6) δ 9.50 (s, 1H, D_2O exch, ArOH), 7.33, 7.23, 6.78, 6.67 (q, 4H, para-substituted aromatic), 5.56 (bs, 1H, vinyl H trans to D), 5.03 (s, 1H, vinyl H cis to D); IR (KBr) 3369 (OH), 2227 (C-D), 1609, 1510, 1257, 905, 839 cm^{-1}; mass spectrum (EI, 70 eV), m/z (relative intensity) 121 (M+, 100), 92 (63); exact mass calcd for C_8H_7DO m/z 121.0638, found m/z 121.0639.

This conversion was also accomplished employing the chloro analog of the catechol reagent, 2-chloro-1,3,2-benzodioxaborole.[5] The crude yield was 51 %.

4-Vinylphenol 40

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethanol, in dry dichloromethane containing N,N-diisopropylethylamine, was treated with 2-chloro-1,3,2-benzodioxaborole, for 12 h, in a manner analogous to that employed for the reaction of the labeled analog of the substrate with the bromo

analog of the reagent. The same workup conditions provided 59 % of the crude product. Sublimation (60°C, 0.350 mm Hg) yielded pure 4-vinylphenol as white needles: mp 66-68°C; lit.[6] mp 71-72°C.

R-(−)-1-Phenyl-1,2-ethanediol-2-methanesulfonate 41

Methanesulfonyl chloride (1.15 g, 10.0 mmol) in dry dichloromethane (15 mL) was slowly added, under argon, to a − 5°C solution of *R*-(−)-1-phenyl-1,2-ethanediol* (1.38 g, 10.0 mmol) in dry dichloromethane (40 mL) containing triethylamine (1.52 g, 15.1 mmol). The reaction mixture was stirred at 0°C for 3 h and quenched with ice-cold H_2O (30 mL). After 15 min, the layers were separated and the organic phase was washed with H_2O (40 mL), dried over anhydrous K_2CO_3, filtered and evaporated under reduced pressure to yield 2.31 g of a viscous oil, which was reduced immediately: IR (neat) 3522 (OH), 3031, 2938, 1497, 1457, 1350 (SO_2OR), 1171 (SO_2OR), 959, 919, 872, 806, 759, 700 cm^{-1}.

* $[\alpha]_D^{13} = -39.98°$ (c = 3.10 in EtOH); lit.[7] $[\alpha]_D^{24} = -39.9°$ (c = 6.6 in EtOH).

S-(−)-1-Phenylethanol 42

R-(−)-1-Phenyl-1,2-ethanediol-2-methanesulfonate (2.13 g, 9.86 mmol) in dry THF (20 mL) was slowly added, under argon, to an ice-cold solution of 1 M LAH in dry THF (Aldrich) (10 mL, 10 mmol), diluted with THF to 30 mL. The reaction mixture was stirred at 0°C overnight and quenched by the slow

addition of H_2O (0.4 mL), 15% NaOH (0.4 mL) and H_2O (1.2 mL). The supernatant was filtered from the suspended solids and evaporated under reduced pressure to yield 1.12 g of crude product, shown by LC to contain a significant amount of the diol. Purification by column chromatography on silica gel (hexane/dichloromethane) gave S-(–)-1-phenylethanol (765 mg, 6.27 mmol, 64 %) which was > 99% pure by LC: $[\alpha]_D^{25} = -39.4°$ (neat); lit.[8] $[\alpha]_D^{25} = -43.7°$ (neat).

S-(+)-Methoxymandelic acid 43

A vigorously-stirred solution of RS-4-methoxymandelic acid (Aldrich) (9.01 g, 49.5 mmol) in absolute ethanol (102 mL) was treated with S-(–)-1-phenylethylamine (6.02 g, 49.8 mmol). The instantly-precipitated salt was filtered, washed with ice-cold absolute ethanol and air-dried (7.84 g). Two recrystallizations from absolute ethanol gave the pure salt (5.62 g, 18.5 mmol): mp 192-193°C; $[\alpha]_D^{25} = +50.3°$ (c = 2.51 in MeOH). Anal calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.39; H, 7.09; N, 4.58.

The pure salt (5.62 g, 18.5 mmol) in H_2O (475 mL) was cooled to 5°C and slowly treated with 0.200 N HCl (93 mL). The aqueous phase was saturated with NaCl and extracted with ether, and the combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure to yield the pure acid (3.34 g, 18.4 mmol): mp 102-103°C; $[\alpha]_D^{18} = +146.6°$ (c = 2.476 in H_2O); lit.[9] mp 105-106°C; $[\alpha]_D^{18} = +141.5°$ (c = 2.45% w/v in H_2O).

R-(–)-Methoxymandelic acid 44

The ethanol-soluble fraction from the treatment of RS-methoxymandelic acid in ethanol with S-(–)-1-phenylethylamine was evaporated under reduced pressure to yield 6.39 g of salt, which was dissolved in H_2O (250 mL). The stirred solution was cooled to 5°C, treated with 0.200 N HCl (65 mL), saturated with NaCl and extracted with ether. The combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure to yield 3.93 g (21.6 mmol) of crude R-(–)-acid. This acid in ether (100 mL) was treated with R-(+)-1-phenylethylamine (2.63 g, 21.7 mmol), and the precipitated salt was collected, washed with ether and air-dried (6.80 g). Two recrystallizations from absolute ethanol gave the pure salt (4.93 g, 16.3 mmol): mp 192-193°C; $[\alpha]_D^{25} = -49.8°$

(c = 2.45 in MeOH). Anal calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.20; H, 6.94; N, 4.56.

The free acid was liberated from the salt (4.92 g, 16.2 mmol), in a manner analogous to that for the S-(+)-acid, to give R-(–)-4-methoxymandelic acid (2.92 g, 16.0 mmol): mp 102-103°C; $[\alpha]_D^{18} = -147.0°$ (c = 2.53 in H_2O); lit.[10] mp 104.5°C; $[\alpha]_D = -146.6°$ (c = 2.375 in H_2O).

R-(–)-Methyl 4-methoxymandelate 45

R-(–)-4-Methoxymandelic acid (2.90 g, 15.9 mmol) in ether (80 mL) was treated with diazomethane in ether until a yellow color persisted. The solvent was evaporated under reduced pressure to yield R-(–)-methyl 4-methoxy-mandelate (3.12 g, 15.9 mmol, 100 %): mp 61-62.5°C; $[\alpha]_D^{20} = -134.9°$ (c =

3.40 in EtOH); lit.[10] mp 63-64°C; lit. [10][α]$_D^{20.6}$ = +140.3° (c = 3.357 in EtOH)

for the S-(+)-isomer.

R-(−)-1-(4-Methoxyphenyl)-1,2-ethanediol   46

R-(−)-Methyl-4-methoxymandelate (3.12 g, 15.9 mmol) in dry THF (25 mL) was slowly added, under argon, to an ice-cold solution of 1 M LAH in dry THF (17 mL, 17 mmol), diluted with THF to 37 mL. The mixture was stirred overnight at room temperature and heated at reflux for 1 h. After the reaction was cooled to 5°C, it was quenched by the slow addition of H_2O (0.7 mL), 15% NaOH (0.7 mL) and H_2O (2.1 mL). The supernatant was filtered from the suspended solids and evaporated under reduced pressure to yield R-(−)-1-(4-methoxyphenyl)-1,2-ethanediol (2.40 g, 14.3 mmol, 90 %): mp 91-93°C; [α]$_D^{20}$ = − 35.27°, [α]$_{546}^{20}$ = − 42.26° (c = 2.52 in EtOH); lit.[11] mp 94-95°C; [α]$_{546}^{18-23}$ = − 41.2° (EtOH).

R-(−)-1-(4-Methoxyphenyl)-1,2-ethanediol-2-methanesulfonate   47

Methanesulfonyl chloride (673 mg, 5.90 mmol) in dry dichloromethane (15 mL) was slowly added, under argon, to a − 5°C solution of R-(−)-1-(4-methoxyphenyl)-1,2-ethanediol (986 mg, 5.86 mmol) in dry dichloromethane (35 mL) containing triethylamine (1.23 g, 12.2 mmol). The reaction mixture was stirred overnight at 0°C and quenched with ice-cold H_2O (35 mL). After fifteen min, the layers were separated and the organic phase was washed with ice cold H_2O (40 mL), dried over anhydrous K_2CO_3, filtered and evaporated under

reduced pressure to yield 1.24 g (5.04 mmol, 86 %) of product, which was recrystallized from benzene to give R-(–)-1-(4-methoxyphenyl)-1,2-ethanediol-2-methanesulfonate as white plates (704 mg, 2.86 mmol): mp 90-91 °C; $[\alpha]_D^{20}=$

– 41.9° (c = 2.45 in dioxane); ^{1}H NMR δ 7.35, 7.25, 6.95, 6.84 (q, 4H, para-substituted aromatic), 4.98 (dd, 1H, ArCH, J ~ 5.3 Hz), 4.30, 4.24, 4.22 (m, 2H, CH_2), 3.80 (s, 3H, CH_3O), 3.02 (s, 3H, CH_3SO_2OR), 2.45 (bs, 1H, D_2O exch, OH); IR (KBr) 3515 (OH), 3024, 2944, 2898, 2844, 1616, 1516, 1357 (SO_2OR), 1251, 1171 (SO_2OR), 1085, 1032, 985, 959, 879, 773 cm^{-1}; Anal calcd for $C_{10}H_{14}SO_5$: C, 48.76; H, 5.73. Found: C, 49.02; H, 5.73.

S-(–)-1-(4-Methoxyphenyl)ethanol 48

a) R-(–)-1-(4-Methoxyphenyl)-1,2-ethanediol-2-methanesulfonate (1.26 g, 5.13 mmol) in dry THF (20 mL) was slowly added, under argon, to an ice-cold solution of 1M LAH in dry THF (6 mL, 6 mmol), diluted with THF to 26 mL. The mixture was stirred at room temperature for 4 h, cooled to 5°C and quenched by the slow addition of H_2O (0.23 mL), 15% NaOH (0.23 mL) and H_2O (0.70 mL). The supernatant was filtered from the suspended solids and evaporated under reduced pressure to yield 803 mg of crude product, shown by LC to contain 6 % of the diol. Purification by column chromatography on silica gel (hexane/dichloromethane/ethyl acetate) gave S-(–)-1-(4-methoxyphenyl)ethanol (526 mg, 3.46 mmol, 67 %): bp 78-80°C (0.05 mm Hg, Kugelrohr); > 99.8% pure by LC; $[\alpha]_D^{20}=$ – 49.94°, $[\alpha]_{578}^{20}=$ – 52.20°, $[\alpha]_{546}^{20}=$ – 59.85°, $[\alpha]_{436}^{20}=$ – 107.1°, $[\alpha]_{365}^{20}=$ – 180.9° (neat); lit.[12] $[\alpha]_D^{20}=$ + 50.38°, $[\alpha]_{578}^{20}=$ + 52.79°, $[\alpha]_{546}^{20}=$ + 61.74°, $[\alpha]_{436}^{20}=$ + 109.0° (neat).

b) 4-Methoxyacetophenone (4.79 g, 31.9 mmol) in dry THF (15 mL) was slowly added, under nitrogen, to a solution of (–)-diisopinocampheylchloroborane (Aldrich) (12.3 g, 38.3 mmol) in dry THF (22 mL), at 0°C. The reaction mixture was stirred for 15 h and quenched by the slow addition of triethylamine (5.81 g, 57.4 mmol) and H_2O (25 mL).[13] The aqueous phase was saturated with NaCl, separated from the organic phase and extracted with ether (50 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 15.1 g of a mixture of product and (+)-α-pinene, which was separated by column chromatography on silica gel (hexane/benzene/ethyl acetate) to give pure S-(–)-1-(4-methoxyphenyl)ethanol (4.09 g, 26.9 mmol, 84 %): bp 62-62.5°C (0.010-0.015 mm Hg); $[\alpha]_D^{20}$= –40.10°, $[\alpha]_{578}^{20}$= – 42.59°, $[\alpha]_{546}^{20}$= – 48.92° (neat), corresponding to an

enantiomeric purity of 80 %; CD $[\Theta]_{300}$ = 0, $[\Theta]_{283}$ = – 330, $[\Theta]_{276}$ = – 402, $[\Theta]_{268}$ = – 222, $[\Theta]_{262}$ = – 132, $[\Theta]_{242}$ = 0, $[\Theta]_{238}$ = + 120 (c = 2.60 in EtOH).

R-(+)-Ethanol-1-d₁-O-d 49

The procedure used was the method employed by Mosher[14]:

The enzymic equilibration method described by Simon[15] and co-workers for (R)-propanol-1-d was used. Gorlach and Zagalak[16] have reported, without details, that they used this method for the preparation of (R)-ethanol-1-d. A buffer solution of 0.88 g of NaOH, 6.1 g of KH_2PO_4 and 48 mL of D_2O (99.7 %) was lyophilized and the residue dissolved in 50 mL of D_2O (99.7 %) to which was added 100 mg of EDTA (disodium salt), 200 mg of crystalline bovine

albumin (Sigma A 4378), 60 mg of ß-NAD⁺ (Sigma 98 %, N 7004) and 60 mg of ß-NADH disodium salt (Sigma 98 %, N 8129). A suspension of 40 units porcine-heart diaphorase* in 3.2 M $(NH_4)_2SO_4$ (Sigma D 3752) was centrifuged and the residue washed twice with an equal volume of 3.2 M solution of $(ND_4)_2SO_4$ in D_2O. The previously deuterium-exchanged reagents, 100 mg of crystalline Bakers yeast alcohol dehydrogenase (Sigma A 7011, 30,000 units) and the diaphorase were added to 300 mL of 99.7 % D_2O and the pH adjusted with 0.1 M NaOD to 7.5. EtOD, (10.4 mL, 95 %) was added to the enzyme-coenzyme-buffer mixture and kept at 28°C until NMR analysis indicated that conversion to CH_3CHDOD was complete (148 h). The reaction mixture was fractionated through a 3/32" glass helices-packed column (1 x 25 cm, 28 theoretical plates); the distillate up to 100°C was collected and refractionated to give 8.8 g, bp 78-80°C; $\alpha_D^{20}= 0.19 \pm 0.00°$ (neat, l =1).

* The reaction was unsuccessful when dried powdered diaphorase preparations were used.

R-(+)-Ethanol-1-d₁-O-d was prepared by an analogous method and fractionated through a Teflon spinning-band column to give a product which exhibited the following optical rotatory powers: $\alpha_D^{20}= + 0.218°$, $\alpha_{578}^{20}= + 0.229°$, $\alpha_{546}^{20}= + 0.266$, $\alpha_{436}^{20}= + 0.490°$, $\alpha_{365}^{20}= + 0.848°$; $\alpha_D^{25}= + 0.212°$, $\alpha_{578}^{25}= + 0.223°$, $\alpha_{546}^{25}= + 0.255°$, $\alpha_{436}^{25}= + 0.475°$, $\alpha_{365}^{25}= + 0.818°$ (neat, l = 1.000); ¹H NMR (500 MHz) spectroscopy of the R-O-acetylmandelate[17] indicated the product to be 100% ee. EI mass spectrometry (70 eV) of the R-O-acetylmandelate indicated ~ 98.3 % deuterium incorporation at the chiral center (after correction for ¹³C and ¹⁷O content).

S-(–)-Ethanol-1-d$_1$ 50

The title compound was prepared from ethanol-1,1-d$_2$ employing the same procedure used for the production of R-(+)-ethanol-1-d$_1$-O-d from ethanol-d; the exchange was carried out in H_2O with the enzyme-coenzyme-buffer mixture in the protio form. Fractionation of the product mixture through a Teflon spinning-band column gave a product which exhibited the following optical rotatory powers: $\alpha^{20}_D = -0.191°$, $\alpha^{20}_{578} = -0.200°$, $\alpha^{20}_{546} = -0.232°$, $\alpha^{20}_{436} = -0.433°$, $\alpha^{20}_{365} = -0.754°$; $\alpha^{25}_D = -0.185°$, $\alpha^{25}_{578} = -0.193°$, $\alpha^{25}_{546} = -0.224°$, $\alpha^{25}_{436} = -0.421°$, $\alpha^{25}_{365} = -0.731°$ (neat, l = 1.000); ^{1}H NMR (500 MHz) spectroscopy of the R-O-acetylmandelate indicated the product to be 100 % ee. EI mass spectrometry, at 70 eV, of the R-O-acetylmandelate indicated ~ 97.7 % deuterium incorporation at the chiral center.

RS-Ethanol-1-d$_1$ 51

To a stirred suspension of 3.64 g (86.6 mmol) of 99 atom % LAD in 80 mL of dry diglyme, at 0°C under nitrogen, was slowly added a solution of 8.62 g (196 mmol) of acetaldehyde in 12 mL of dry diglyme. The mixture was stirred at 0°C for 70 min and quenched by the slow addition of 12 mL of H_2O. Distillation of the hydrolysate through a vacuum-jacketed Vigreux column and collection of the distillate up to 98°C gave 15.0 g of liquid, which was refractionated to give 6.3 g of RS-ethanol-1-d$_1$ (bp 77-79°C), shown by ^{1}H NMR spectroscopy in

acetone-d_6 to contain about 15 % H_2O. The H_2O content was reduced to about 1 % by drying over successive 1.5 g portions of freshly-activated 3A molecular sieve: ^{1}H NMR δ 3.84 (dt, 1H, D_2O exch, OH, J_H = 5.1 Hz, J_D = 1.7 Hz), 3.74-3.37 (m, 1H, CHD), 1.12 (dt, 3H, CH_3, J_H = 6.9 Hz, J_D = 1.0 Hz).

Ethanol-1,1-d_2 52

To a stirred suspension of 16.7 g (398 mmol) of 99 atom % LAD in 350 mL of dry diglyme, under nitrogen, was slowly added a solution of 45.1 g (331 mmol) of phenyl acetate in 60 mL of dry diglyme. The mixture was stirred at room temperature for 6.5 h and at 100°C for 3 h, cooled to 0°C and hydrolyzed by the slow addition of 17 ml of H_2O, 17 mL of 15% NaOH and 25 mL of H_2O. After dilution of hydrolysate with 350 mL of diglyme, the mixture was distilled through a vacuum-jacketed Vigreux column. Collection of the distillate up to 99°C gave 50 g of liquid, which was refractionated to yield 6.4 g of ethanol-1,1-d_2 (bp 78-80°C), shown by ^{1}H NMR spectroscopy in acetone-d_6 to contain about 10% H_2O: ^{1}H NMR (acetone-d_6) δ 3.99 (bs, 1H, D_2O exch, OH), 1.11 (bs, 3H, CH_3).

Ethyl R-O-acetylmandelate 53

To a stirred solution of 267 mg (1.38 mmol) of R-(–)-O-acetylmandelic acid (Aldrich) and 8.0 mg (0.066 mmol) of 4-N,N-dimethylaminopyridine in 7 mL of dry dichloromethane, protected from atmospheric moisture at 0°C, was added a solution of 96 mg (2.1 mmol) of absolute ethanol and 319 mg (1.55 mmol) of

dicyclohexylcarbodiimide in 7 mL of dry dichloromethane. The mixture was stirred for 7 h, filtered from the precipitated dicyclohexylurea, and the solvent was evaporated under reduced pressure to give a residue which was purified by column chromatography on silica gel (hexane/ethyl acetate) to yield 297 mg (1.34 mmol, 97 %) of ethyl R-O-acetylmandelate as a viscous oil: ^{1}H NMR (benzene-d_6, 500 MHz) δ 7.493-7.051 (m, 5H, ArH), 6.044 (s, 1H, ArCH), 3.951-3.887 (dq, 1H, CH$_S$H$_R$, J$_{HSHR}$ = 11.5 Hz, J$_{CH2CH3}$ = 7.2 Hz), 3.809-3.772 (dq, 1H, CH$_R$H$_S$, J$_{HRHS}$ = 11.5 Hz, J$_{CH2CH3}$ = 7.2 Hz), 1.757 (s, 3H, CH$_3$CO), 0.801 (t, 3H, CH$_3$, J= 7.2 Hz); with irradiation of the methyl group adjacent to the methylene group: 3.933 and 3.912 (d, 1H, CH$_S$H$_R$, J$_{HSHR}$ = 10.5 Hz), 3.820 and 3.798 (d, 1H, CH$_R$H$_S$, J$_{HRHS}$ = 11 Hz).

Ethyl-1,1-d$_2$ R-O-acetylmandelate 54

Ethanol-1,1-d$_2$ was treated with R-(−)-O-acetylmandelic acid in dichloromethane containing 4-N,N-dimethylaminopyridine and dicyclohexyl-carbodiimide, in a manner analogous to that employed for unlabeled ethanol, to yield ethyl-1,1-d$_2$ R-O-acetylmandelate as a viscous oil: ^{1}H NMR (benzene-d_6) δ 7.53-7.04 (m, 5H, ArH), 6.04 (s, 1H, ArCH), 1.76 (s, 3H, CH$_3$CO), 0.79 (bs, 3H, CH$_3$); mass spectrum (EI, 70 eV), m/z (relative intensity) 224 (M$^+$, 4), 182 (21), 176 (24), 149 (43), 107 (100), 105 (20), 90 (5), 89 (5); exact mass calcd for C$_{12}$H$_{12}$D$_2$O$_4$ m/z 224.1018, found m/z 224.1012 (−3 ppm).

RS-Ethyl-1-d$_1$ *R*-O-acetylmandelate 55

RS-Ethanol-1-d$_1$ was treated with *R*-(−)-O-acetylmandelic acid in dichloromethane containing 4-N,N-dimethylaminopyridine and dicyclohexyl-carbodiimide, in a manner analogous to that employed for unlabeled ethanol, to yield *RS*-ethyl-1-d$_1$ *R*-O-acetylmandelate as a viscous oil: ^{1}H NMR (benzene - d$_6$, 500 MHz) δ 7.493-7.051 (m, 5H, ArH), 6.041 (s, 1H, ArCH), 3.911 (qt, 1H, CH$_R$D, J$_H$ = 7.0 Hz, J$_D$ = 1.5 Hz), 3.803 (qt, 1H, CH$_S$D, J$_H$ = 7.0 Hz, J$_D$ = 1.5 Hz), 1.776 (s, 3H, CH$_3$CO), 0.808 (d, 3H, CH$_3$, J = 7.5 Hz); with irradiation of the methyl group adjacent to the methylene group: 3.916 (t, 1H, CH$_R$D, J$_D$ = 1.5 Hz), 3.809 (t, 1H, CH$_S$D, J$_D$ = 1.5 Hz); mass spectrum (EI, 70eV), m/z (relative intensity) 223 (M†, 2), 181 (14), 176 (16), 149 (43), 107 (100), 105 (27), 90 (9), 89 (7); exact mass calcd for C$_{12}$H$_{13}$DO$_4$ m/z 223.0955, found m/z 223.0953. (−0.9 ppm).

R-Ethyl-1-d$_1$ *R*-O-acetylmandelate 56

R-(+)-Ethanol-1-d$_1$-O-d was treated with *R*-(−)-O-acetylmandelic acid in dichloromethane containing 4-N,N-dimethylaminopyridine and dicyclohexyl-carbodiimide, in a manner analogous to that employed for unlabeled ethanol, to yield *R*-ethyl-1-d$_1$ *R*-O-acetylmandelate as a viscous oil: ^{1}H NMR (benzene-d$_6$, 500 MHz) δ 7.493-7.051 (m, 5H, ArH), 6.045 (s, 1H, ArCH), 3.791 (qt, 1H, CH$_S$D, J$_H$ = 7.0 Hz, J$_D$ = 1.5 Hz), 1.760 (s, 3H, CH$_3$CO), 0.795 (d, 3H, CH$_3$, J = 7.0 Hz); with irradiation of the methyl group adjacent to the methylene group: 3.795 (t, 1H, CH$_S$D, J$_D$ = 1.5 Hz); the mass spectrum was identical to the spectrum

recorded for the derivative of the racemic labeled ethanol; exact mass calcd for $C_{12}H_{13}DO_4$ m/z 223.0955, found m/z 223.0943 (−5.5 ppm).

S-Ethyl-1-d₁ R-O-acetylmandelate 57

S-(−)-Ethanol-1-d$_1$ was treated with R-(−)-O-acetylmandelic acid in dichloromethane containing 4-N,N-dimethylaminopyridine and dicychlohexyl-carbodiimide, in a manner analogous to that employed for unlabeled ethanol, to yield S-ethyl-1-d$_1$ R-O-acetylmandelate as a viscous oil: ^{1}H NMR (benzene-d$_6$, 500 MHz) δ 7.493-7.051 (m, 5H, ArH), 6.044 (s, 1H, ArCH), 3.904 (qt, 1H, CH$_R$D, J_H = 7.5 Hz, J_D = 1.5 Hz), 1.763 (s, 3H, CH$_3$CO), 0.798 (d, 3H, CH$_3$, J = 7.0 Hz); with irradiation of the methyl group adjacent to the methylene group: 3.906 (t, 1H, CH$_R$D, J_D = 1.5 Hz); the mass spectrum was identical to the spectrum recorded for the derivative of the racemic labeled ethanol; exact mass calcd for $C_{12}H_{13}DO_4$ m/z 223.0955, found m/z 223.0957 (+0.9 ppm).

RS-4-(Ethyl-1-d₁)phenyl R-O-acetylmandelate 58

To a stirred solution of 198 mg (1.02 mmol) of R-(−)-O-acetylmandelic acid and 6.9 mg (0.057 mmol) of 4-N,N-dimethylaminopyridine in 10 mL of dry dichloromethane at 0°C, under argon, was added a solution of 188 mg (1.52 mmol) of RS-4-(ethyl-1-d$_1$)phenol and 329 mg (1.59 mmol) of dicychlohexyl-carbodiimide in 5 mL of dry dichloromethane. The mixture was stirred overnight at room temperature, filtered from the precipitated dicyclohexylurea, and the solvent was evaporated under reduced pressure. The residue was purified by

column chromatography on silica gel (hexane/ethyl acetate) to yield 134 mg (0.45 mmol, 44 %) of RS-4-(ethyl-1-d_1)phenyl R-O-acetylmandelate as a viscous oil: ^{1}H NMR (benzene-d_6, 240 MHz) δ 7.546-7.065 (m, 5H, ArH), 6.947, 6.911, 6.802, 6.767 (q, 4H, para-substituted aromatic), 6.220 (s, 1H, ArCH), 2.240 (qt, 1H, ArCHD, J_H = 7.6 Hz, J_D = 1.6 Hz), 1.737 (s, 3H, CH$_3$CO), 0.920 (d, 3H, CH$_3$, J = 7.5 Hz); mass spectrum (EI, 70 eV), m/z (relative intensity) 299 (M$\ddagger$, 1), 177 (33), 165 (5), 149 (34), 123 (100), 108 (65), 107 (47); exact mass calcd for $C_{18}H_{17}DO_4$ m/z 299.1268, found m/z 299.1276 (+3 ppm).

S-(−)-Ethyl-1-d_1 methanesulfonate 59

To a stirred solution of 3.28 g (~ 66 mmol) of 95% S-(−)-ethanol-1-d_1 and 11.8 g (116 mmol) of triethylamine in 300 mL of dichloromethane at 0°C, under nitrogen, was slowly added 9.77 g (85.3 mmol) of methanesulfonyl chloride in 10 mL of dichloromethane. The mixture was allowed to stir at 0°C for 1 h and at room temperature overnight ,and was then washed with 250 mL of ice-cold H$_2$O, 250 mL of ice-cold 12% HCl, 250 mL of 5% of NaHCO$_3$ and 250 mL of brine. The solvent was dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure to yield 7.53 g (60.2 mmol, ~ 90 %) of S-(−)-ethyl-1-d_1 methanesulfonate: bp 85-86°C (10 mm Hg); d_4^{22} 1.154, calcd from lit. value[18] of d_4^{22} 1.145 for the unlabeled material, corrected for deuterium content[19]; $[\alpha]_D^{22}$= − 0.481°, $[\alpha]_{578}^{22}$= − 0.505°, $[\alpha]_{546}^{22}$= − 0.572°, $[\alpha]_{436}^{22}$= − 1.000°, $[\alpha]_{365}^{22}$= − 1.605°* (neat); ^{1}H NMR δ 4.28 (qt, 1H, OCHD, J_H = 7.1 Hz, J_D = 1.5 Hz), 3.01 (s, 3H, CH$_3$SO$_3$), 1.41 (dt, 3H, CH$_3$, J_H = 7.1 Hz, J_D = 1.0 Hz); mass spectrum (EI, 70 eV), m/z (relative intensity) 125 (M$\ddagger$, 5) 110 (74), 98 (10), 97

(19), 79 (100); exact mass calcd for $C_3H_7DSO_3$ m/z 125.0257, found m/z 125.0257 ($\pm$0 ppm).

* These $[\alpha]_\lambda^{22}$ values are corrected for a deuterium incorporation of 97.7% at the chiral center.

R-(+)-Ethyl-1-d$_1$ methanesulfonate 60

R-(+)-Ethanol-1-d$_1$-O-d was treated with methanesulfonyl chloride in dichloromethane containing triethylamine, in a manner analogous to that employed for *S*-(−)-ethanol-1-d$_1$, to yield a product shown by mass spectrometry to be a mixture[20] of ~ 52% *R*-(+)-ethyl-1-d$_1$ methanesulfonate and ~ 48 % *R*-(+)-ethyl-1-d$_1$ methanesulfonate-d$_1$: bp 85-86°C (10 mm Hg); d_4^{22} 1.159, calcd from lit. value[18] of d_4^{22} 1.145 for the unlabeled material, corrected for weighted-average deuterium content[19] of the mixture; $[\alpha]_D^{22}$ = + 0.480°, $[\alpha]_{578}^{22}$ = + 0.501°, $[\alpha]_{546}^{22}$ = + 0.573°, $[\alpha]_{436}^{22}$ = + 0.998°, $[\alpha]_{365}^{22}$ = + 1.608°* (neat); The ^{1}H NMR spectrum was identical to the spectrum recorded for the *S*-(−)-isomer, with the exception of an additional resonance at δ 2.97 ppm, corresponding to DCH$_2$SO$_3$- for the dideuterio analog: mass spectrum (EI, 70 eV), m/z (relative intensity) 126 (M+, 6), 125 (M+, 6), 111 (68), 110 (75), 99 (11), 98 (25), 97 (18), 80 (93), 79 (100); exact mass calcd for $C_3H_6D_2SO_3$ m/z 126.0320, found m/z 126.0316 (−3 ppm); exact mass calcd for $C_3H_7DSO_3$ m/z 125.0257, found m/z 125.0252 (−4 ppm).

* These $[\alpha]_\lambda^{22}$ values are corrected for a deuterium incorporation of 98.3 % at the chiral center.

S-(+)-1-Phenylethane-1-d₁ 61

To a stirred ice-cold suspension of 8.84 g (46.4 mmol) of CuI in 35 mL of dry ether, under nitrogen, was slowly added 76 mL of 1.22 M phenyllithium[21] (92.7 mmol) in ether. The mixture was stirred for 1 h and slowly treated, at 0°C, with a solution of 2.92 g (23.2 mmol) of *R*-(+)-ethyl-1-d₁ methanesulfonate in 30 mL of dry ether. After 12 h, the reaction mixture was quenched with 50 mL of saturated NH₄Cl and filtered from the suspended solids. The layers were separated and the aqueous phase was extracted with 50 mL of ether. The combined extracts were washed twice with 50 mL of brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residual liquid was distilled in a Teflon spinning-band column to afford 1.56 g (14.6 mmol, 62 %) of *S*-(+)-1-phenylethane-1-d₁: bp 136°C; ¹H NMR δ 7.20 (s, 5H, ArH), 2.62 (qt, 1H, ArCH, J_H = 7.6 Hz, J_D = 2.1 Hz), 1.22 (dt, 3H, CH₃, J_H = 7.6 Hz, J_D = 1.1 Hz). A small signal at δ 7.34, corresponding to benzene, was integrated at 240 MHz. The integration revealed a 2.92 mol % relative concentration of benzene; α_D^{20}=+ 0.676°, α_{578}^{20}= + 0.709°, α_{546}^{20}= + 0.820°, α_{436}^{20}= + 1.527°, α_{365}^{20}= + 2.686° (neat, l = 1.000 dcm), corrected for volume % of benzene present; lit.[22] α_D^{20}=+ 0.710°, α_{578}^{20}= + 0.743°, α_{546}^{20}= + 0.861°, α_{436}^{20}= + 1.604°, α_{365}^{20}= + 2.843°.

2-Methoxyethoxymethoxybenzene 62

To a stirred solution of 2.67 g (28.4 mmol) of phenol and 5.49 g (42.6 mmol) of N,N-diisopropylethylamine in 40 mL of dry dichloromethane, under nitrogen, was slowly added 5.28 g (42.4 mmol) of 2-methoxyethoxymethyl

chloride. The mixture was stirred at room temperature for 1.5 h and then heated at reflux for 6 h, cooled to room temperature and washed three times with 50 mL of H_2O, three times with 50 mL of 1 N NaOH and three times with 50 mL of H_2O. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 4.43 g (24.3 mmol, 86 %) of 2-methoxyethoxy - methoxybenzene: bp 60-61°C (0.010 mm Hg); ^1H NMR δ 7.40-6.87 (m, 5H, ArH), 5.26 (s, 2H, OCH_2O), 3.89-3.47 (m, 4H, OCH_2CH_2O), 3.36 (s, 3H, CH_3O); IR (neat) 3064, 3037, 2931, 2884, 2818, 1995, 1955, 1596, 1496, 1224, 1105, 1032, 1012, 985, 852, 759, 693 cm^{-1}; mass spectrum (EI, 70 eV), m/z (relative intensity) 182 (M$^+$, 13), 107 (17), 94 (12), 89 (100); exact mass calcd for $C_{10}H_{14}O_3$ m/z 182.0943, found m/z 182.0935 (−4 ppm).

4-(2-Methoxyethoxy)methoxyphenyl bromide 63

To a stirred solution of 24.4 g (141 mmol) of 4-bromophenol (Aldrich) and 45.3 g (350 mmol) of N,N-diisopropylethylamine in 200 mL of dry dichloro - methane, under nitrogen, was slowly added 43.6 g (350 mmol) of 2-methoxy- ethoxymethyl chloride. The mixture was stirred at room temperature for 4.5 h and then heated at reflux for 2 h, cooled to room temperature and washed twice with 250 mL of H_2O, twice with 200 mL of 1 N NaOH and twice with 250 mL of H_2O. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 36.4 g (140 mmol, 99 %) of 4-(2- methoxyethoxy)methoxyphenyl bromide: bp 105-106°C (0.020 mm Hg); ^1H NMR δ 7.43, 7.31, 6.99, 6.87 (q, 4H, para-substituted aromatic), 5.23 (s, 2H, OCH_2O), 3.87-3.48 (m, 4H, OCH_2CH_2O), 3.36 (s, 3H, CH_3O); IR (neat) 2924, 2884, 2818, 1589, 1576, 1490, 1224, 1105, 998, 826 cm^{-1}; Anal calcd for

$C_{10}H_{13}BrO_3$: C, 45.99; H, 5.02; Br, 30.60. Found: C, 45.70; H, 5.00; Br, 30.40.

4-(2-Methoxyethoxy)methoxyphenyl Iodide 64

To a stirred mixture of 14.0 g (576 mmol) of magnesium turnings in 25 mL of dry THF, under nitrogen, was slowly added 140 g (535 mmol) of 4-(2-methoxy ethoxy)methoxyphenyl bromide in 500 mL of dry THF, and the mixture was allowed to stir overnight. To the stirred Grignard reagent was slowly added a solution of 136 g (537 mmol) of iodine in 500 mL of dry ether, and the mixture was stirred overnight. The reaction mixture was poured onto 500 mL of crushed ice and 500 mL of 0.2 N HCl. The layers were separated and the organic phase was washed three times with 250 mL of 0.15 M $Na_2S_2O_3$ and three times with 250 mL of H_2O, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give 152 g of dark brown liquid, shown by LC to contain 4-bromophenol. The residue was dissolved in 300 mL of ether and washed five times with 200 mL of 1N NaOH and twice with 200 mL of H_2O. The solvent was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield 140 g (456 mmol, 85 %) of 4-(2-methoxyethoxy)methoxyphenyl iodide: bp 103-105°C (0.005 mm Hg); ^1H NMR δ 7.61, 7.49, 6.88, 6.76 (q, 4H, para-substituted aromatic), 5.22 (s, 2H, OCH_2O), 3.85-3.46 (m, 4H, OCH_2CH_2O), 3.36 (s, 3H, CH_3O); IR (neat) 2924, 2878, 2818, 1583, 1570, 1483, 1224, 1105, 998, 826 cm^{-1}; mass spectrum (EI, 70 eV), m/z (relative intensity) 308 (M+, 16), 89 (100); exact mass calcd for $C_{10}H_{13}IO_3$ m/z 307.9909, found m/z 307.9910 (+0.3 ppm). Anal calcd for $C_{10}H_{13}IO_3$: C, 38.98; H, 4.25. Found: C, 39.00; H, 4.30.

An attempt to prepare the aryllithium by reaction of the product with n-Bu-Li in hexanes/benzene resulted in a viscous oil which could not be purified.

4-Methoxyphenyllithium 65

The title compound was prepared according to the method of Schlosser and Ladenberger.[23] However, it was observed that very finely divided 4-methoxyphenyllithium was not only pyrophoric, but exhibited a tendency to detonate when stirred in vacuum. A 1.1 M solution of the reagent in 80:20 ether/THF, stored at 5°C, was observed to slowly convert to a mixture of the ortho- and para- substituted reagents.

4-Ethylanisole 66

a) To a mechanically-stirred solution of 19.0 g (48.4 mmol) of $CuI \cdot n\text{-}Bu_3P$[24] in 250 mL of dry ether at −78°C, under nitrogen, was slowly added 86 mL of 1.13 M 4-methoxyphenyllithium (97.2 mmol) in 14 vol % THF in ether. The residue in the addition funnel was washed into reaction vessel with 60 mL of 2:1 ether/THF and the mixture was allowed to rapidly warm to 0°C. A solution of 3.02 g (24.3 mmol) of ethyl methanesulfonate in 30 mL of dry ether was added dropwise to the light-green diaryl cuprate(I) solution and the mixture was packed in ice and stirred overnight. After the reaction mixture was cooled to 0°C, it was quenched by the addition of 100 mL of saturated NH_4Cl and stirred for 20 min as a stream of compressed air was passed over the surface of the hydrolysate. The aqueous and organic phases were filtered from the

precipitated solids and separated. The organic layer was washed twice with 100 mL of brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give 26.8 g of liquid residue, which was dissolved in 100 mL of pentane and cooled to $-10°C$. The solution was filtered from the precipitated solid and evaporated under reduced pressure. The solid was washed with pentane and air dried to give 1.23 g (5.7 mmol) of 4,4'-dimethoxy-biphenyl: mp 176-177°C; lit.[25] mp 176.5-177°C; ^{1}H NMR δ 7.53, 7.41, 7.00, 6.91 (q, 8H, para-substituted aromatic), 3.83 (s, 6H, CH_3O). The liquid residue was fractionated in a Teflon spinning-band column at 20 mm Hg to yield 1.26 g (9.26 mmol, 38 %) of 4-ethylanisole: bp 88-91°C (20 mm Hg); lit. [26] bp 88.5-91°C (21 mm Hg).

b) To a mechanically stirred slurry of 11.3 g (59.3 mmol) of CuI* in 70 mL of dry ether at 0°C, under nitrogen, was slowly added a solution of 5.21 g (59.1 mmol) of lithium t-butylacetylide[27] in 100 mL of dry ether. The orange-red copper(I) t-butylacetylide solution was diluted with 60 mL of 2:1 ether/THF, cooled to $-78°C$ and slowly treated with 53.5 mL of 1.11 M 4-methoxyphenyllithium (59.4 mmol) in 14 vol % THF in ether. The residue in the addition funnel was washed into the reaction vessel with 60 mL of 2:1 ether/THF and the mixture was allowed to rapidly warm to 0°C. The yellow-green heterocuprate solution was then treated with 3.68 g (29.7 mmol) of ethyl methanesulfonate in 40 mL of dry ether. The reaction mixture was stirred at 0°C for 2 h and overnight at room temperature. After the mixture was cooled to 5°C, it was quenched by the addition of 75 mL of saturated NH_4Cl and stirred for 20 min as a stream of compressed air was passed over the surface of the hydrolysate. The aqueous and organic phases were filtered from the precipitated solids and separated. The precipitate was washed with ether and the washings were added to the

organic phase. The combined organic phases were washed three times with 75 mL of brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give 7.14 g of dark red oil, which was dissolved in 25 mL of pentane and cooled to −10°C. Filtration of the suspended solid from solution and air-drying yielded 335 mg (1.55 mmol) of 4,4'-dimethoxybiphenyl: mp 173-177°C. The filtrate was evaporated under reduced pressure and the liquid residue was fractionated in a Teflon spinning-band column at 20 mm Hg, employing 1.5 mL of 1-methoxynaphthalene (Aldrich) as a "chaser", to yield 2.68 g (19.7 mmol, 66 %) of 4-ethylanisole: bp 88-91°C (20 mm Hg).

* Purified by the method of ref. 24.

4-(2-Methoxyethoxy)methoxyphenylethane 67

To a stirred solution of 3.14 g (25.7 mmol) of 4-ethylphenol and 10.0 g (77.5 mmol) of N,N-diisopropylethylamine in 35 mL of dry dichloromethane, under nitrogen, was slowly added 9.76 g (78.3 mmol) of 2-methoxyethoxy-methyl chloride. The mixture was stirred at room temperature for 3 h, heated at reflux for 6 h, cooled to room temperature and washed three times with 100 mL of H_2O, three times with 100 mL of 1N NaOH and three times with 100 mL of H_2O. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to yield 5.41 g (25.7 mmol, 100 %) of 4-(2-methoxy-ethoxy)methoxyphenylethane: bp 73-75°C (0.003 mm Hg); ^{1}H NMR δ 7.17-6.89 (m, 4H, ArH), 5.23 (s, 2H, OCH_2O), 3.87-3.48 (m, 4H, OCH_2CH_2O), 3.36 (s, 3H, CH_3O), 2.58 (q, 2H, CH_2, J = 7.6 Hz), 1.20 (t, 3H, CH_3, J = 7.6 Hz), IR (neat) 2962, 2929, 2876, 1607, 1508, 1222, 1103, 1003, 830 cm^{-1}; mass spectrum

(EI, 70 eV), m/z (relative intensity) 210 (M$\ddagger$, 27), 135 (9), 122 (8), 121 (6), 107 (23), 89 (100); exact mass calcd for $C_{12}H_{18}O_3$ m/z 210.1256, found m/z 210.1254 (−1 ppm). Anal calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.47; H, 8.70.

S-(−)-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethane-1-d$_1$ 68

To a stirred solution of 2.52 g (11.1 mmol) of R-(+)-1-[4-(2-methoxy-ethoxy)methoxyphenyl]-ethanol-1-d$_1$ and 14.0 g (139 mmol) of dry triethylamine in 110 mL of dry THF at −78°C, under nitrogen, was slowly added 6.36 g (55.5 mmol) of methanesulfonyl chloride in 10 mL of dry THF. The mixture was packed in dry ice, placed in the −70°C freezer overnight and then back in the dry ice-iprOH −78°C bath. To the stirred mixture was slowly added 110 ml of 1M LAH in THF. After 1 h, the mixture was allowed to slowly rise to 0°C and then hydrolyzed by the careful addition of 4.5 mL of H_2O, 4.5 mL of 15% NaOH and 13 mL of H_2O. The supernatant was filtered from the suspended solids and evaporated under reduced pressure to give 2.52 g of crude residue. Purification by column chromatography on silica gel (hexane/benzene) yielded 1.71 g (8.10 mmol, 73 %) of pure S-(−)-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethane-1-d$_1$: bp 73-75°C (0.003 mm Hg); d_4^{25} 1.029*; $[\alpha]_D^{25}$= − 0.138°,

$[\alpha]_{578}^{25}$= − 0.146°, $[\alpha]_{546}^{25}$= − 0.172°, $[\alpha]_{436}^{25}$= − 0.322°, $[\alpha]_{365}^{25}$= − 0.546°

(neat); ^{1}H NMR δ 7.17-6.89 (m, 4H, ArH), 5.23 (s, 2H, OCH$_2$O), 3.87-3.48 (m, 4H, OCH$_2$CH$_2$O), 3.36 (s, 3H, CH$_3$O), 2.56 (qt, 1H, ArCH, J_H = 7.5 Hz, J_D = 2.0 Hz), 1.18 (dt, 3H, CH$_3$, J_H = 7.5 Hz, J_D =1.0 Hz); the IR (neat) spectrum was identical to the spectrum recorded for the unlabeled material in all respects, with

the exception of an additional broad absorption from 2174 to 2134 cm^{-1}, corresponding to the C-D stretching mode; mass spectrum (EI, 70 eV) m/z (relative intensity) 211 (M$\dagger$, 100), 137 (9), 136 (48), 123 (30), 122 (18), 108 (90), 106 (23); exact mass calcd for $C_{12}H_{17}DO_3$ m/z 211.1319, found m/z 211.1314 (–2 ppm).

The same reaction, carried out in dry ether and employing N,N-diisopropylethylamine as a base, resulted in a conversion (based on LC) to the hydrocarbon of only about 2 %.

* Based on the density, $d_4^{25} 1.024$, of the unsubstituted compound, corrected for isotopic substitution by the method of ref. 19.

RS-1-[4-(2-Methoxyethoxy)methoxyphenyl]-ethane-1-d$_1$ 69

The title compound was prepared by treating RS-1-[4-(2-methoxyethoxy)-methoxyphenyl]-ethanol-1-d$_1$, in THF containing triethylamine, with LAH in a manner analogous to that employed for the reduction of the "mesylate" of the R-(+)-alcohol. It was also prepared by the reduction of the "mesylate" of the racemic unlabeled alcohol with LAD in THF: bp 73-75°C (0.003 mm Hg); the ^{1}H NMR, IR (neat) and mass spectra (EI, 70 eV) were identical to those recorded for the S-(–)-isomer; exact mass calcd for $C_{12}H_{17}DO_3$ m/z 211.1319, found m/z 211.1330 (+5.2 ppm).

R-(+)-1-(4-Methoxyphenyl)ethane-1-d₁ 70

The heterocuprate(I) derived from copper(I) t-butylacetylide and 4-methoxyphenyllithium was treated with S-(–)-ethyl-1-d₁ methanesulfonate, in a manner analogous to that employed for the unlabeled substrate, to give R-(+)-1-(4-methoxyphenyl)ethane-1-d₁: bp 88-91°C (20 mm Hg); $[\alpha]\backslash S(15, D) = +0.187°$, $[\alpha]_{578}^{15} = +0.194°$, $[\alpha]_{546}^{15} = +0.226°$, $[\alpha]_{436}^{15} = +0.422°$, $[\alpha]_{365}^{15} = +0.778°$

(neat); the ¹H NMR, IR (neat) and mass spectra (EI, 70 eV) were identical to those recorded for the S-(–)-isomer; exact mass calcd for $C_9H_{11}DO$ m/z 137.0951, found m/z 137.0961 (+7.1 ppm).

S-(–)-1-(4-Methoxyphenyl)ethane-1-d₁ 71

The heterocuprate(I) derived from copper(I) t-butylacetylide and 4-methoxyphenyllithium was treated with R-(+)-ethyl-1-d₁ methanesulfonate, in a manner analogous to that employed for the unlabeled substrate, to give S-(–)-1-(4-methoxyphenyl)ethane-1-d₁: bp 88-91°C (20 mm Hg); $d_4^{15}\,0.9695$, calcd from lit. value[28] of $d_4^{15}\,0.9624$ for the unlabeled material, corrected for deuterium content;[19] $[\alpha]_D^{15} = -0.236°$, $[\alpha]_{578}^{15} = -0.251°$, $[\alpha]_{546}^{15} = -0.282°$,

$[\alpha]_{436}^{15} = -0.534°$, $[\alpha]_{365}^{15} = -1.002°$ (neat); ¹H NMR δ 7.16, 7.05, 6.86, 6.75 (q, 4H, para-substituted aromatic), 3.76 (s, 3H, CH₃O), 2.56 (qt, 1H, ArCH, $J_H = 7.5$ Hz, $J_D = 2.0$ Hz), 1.19 (dt, 3H, CH₃, $J_H = 7.5$ Hz, $J_D = 1.0$ Hz); IR (neat) 3104, 3064, 3031, 3004, 2964, 2931, 2904, 2871, 2838, 2174-2134 (C-D), 2061, 1876, 1609, 1583, 1510, 1463, 1304, 1284, 1244, 1178, 1111, 1039, 826, 806 cm⁻¹; mass spectrum (EI, 70 eV), m/z (relative intensity) 137 (M⁺, 34), 122

(100), 92 (4); exact mass calcd for $C_9H_{11}DO$ m/z 137.0951, found m/z 137.0962 (+7.9 ppm).

S-1-(2-Methoxyphenyl)ethane-1-d₁ 72

The preparation of *S*-(−)-1-(4-methoxyphenyl)ethane-1-d₁ from the heterocuprate(I) derived from copper(I) t-butylacetylide and a 1.11 M solution of 4-methoxyphenyllithium, which had set in the refrigerator at 5°C for 30 days, resulted in a product which was about 25 % ortho-substituted. Purification by column chromatography on silica gel (hexane/ethyl acetate) yielded *S*-1-(2-methoxyphenyl)ethane-1-d₁: ¹H NMR δ 7.27-6.75 (m, 4H, ortho-substituted aromatic), 3.80 (s, 3H, CH₃O), 2.61 (qt, 1H, ArCH, J_H = 7.5 Hz, J_D = 2.0 Hz), 1.18 (dt, 3H, CH₃, J_H = 7.5 Hz, J_D = 1.0 Hz); IR (neat) 3110, 3064, 3024, 2997, 2964, 2938, 2871, 2838, 2167 (C-D), 2048, 1928, 1888, 1769, 1716, 1682, 1603, 1589, 1497, 1463, 1457, 1370, 1331, 1291, 1244, 1178, 1125, 1098, 1052, 1032, 925, 806, 753 cm⁻¹; mass spectrum (EI, 70 eV), m/z (relative intensity) 137 (M⁺, 54), 122 (100), 92 (64); exact mass calcd for $C_9H_{11}DO$ m/z 137.0951, found m/z 137.0948 (2 ppm).

S-(−)-1-(4-Hydroxyphenyl)ethane-1-d₁ 73

a) A mixture of 1.40 g (10.2 mmol) of *S*-(−)-1-(4-methoxyphenyl)ethane -1-d₁, 4.44 g (22.3 mmol) of 2-bromo-1,3,2-benzodioxaborole and 263 mg (2.04 mmol) of N,N-diisopropylethylamine in 140 mL of dry dichloromethane, under argon, was stirred in the dark for 168 h. The reaction mixture was hydrolyzed by

the addition of 3.2 g (32 mmol) of triethylamine and 100 mL of H_2O, and after

the two-phase system was stirred for 20 min, the layers were separated. The

aqueous phase was saturated with NaCl and extracted with 100 mL of

dichloromethane, and the combined organic phases were dried over anhydrous

Na_2SO_4, filtered and evaporated under reduced pressure to give 6 g of a purple

residue. Purification by column chromatography on silica gel (hexane/ethyl

acetate) yielded 1.19 g of yellow solid, which was sublimed (45°C, 0.350 mm

Hg) to afford 1.09 g (8.87 mmol, 87 %) of pure S-(–)-1-(4-hydroxyphenyl)-

ethane-1-d_1 as long, white needles: mp 44.5-46°C; $[\alpha]_D^{25} = -0.24°$, $[\alpha]_{578}^{25} = -$

0.26°, $[\alpha]_{546}^{25} = -0.29°$, $[\alpha]_{436}^{25} = -0.505°$, $[\alpha]_{365}^{25} = -0.927°$ (c = 25.3 in EtOH);

CD $[\Theta]_{300} = 0$, $[\Theta]_{280} = -300$, $[\Theta]_{255} = 0$, $[\Theta]_{230} = +44$ (c = 2.04 in EtOH); ^1H

NMR δ 7.11, 7.00, 6.79, 6.68 (q, 4H, para-substituted aromatic), 4.83 (s, 1H, D_2O

exch, ArOH), 2.55 (qt, 1H, ArCH, J_H = 7.6 Hz, J_D = 2.0 Hz), 1.18 (dt, 3H, CH_3, J_H

= 7.5 Hz, J_D = 1.0 Hz); IR (KBr) 3250 (OH), 3024, 2964, 2904, 2871, 2180-2134

(C-D), 1882, 1616, 1596, 1516, 1450, 1370, 1238, 819 cm^{-1}; mass spectrum

(EI, 70 eV), m/z (relative intensity) 123 (M+, 37), 108 (100); exact mass calcd for

C_8H_9DO m/z 123.0794, found m/z 123.0798 (+3 ppm).

b) To a stirred solution of 1.12 g (5.30 mmol) of S-(–)-1-[4-(2-methoxyethoxy) -

methoxyphenyl]-ethane-1-d_1 and 145 mg (1.12 mmol) of N,N-diisopropyl -

ethylamine in 25 mL of dry dichloromethane at 0°C, under nitrogen and in the

dark, was added 43 mL of 0.20 M 2-bromo-1,3,2-benzodioxaborole (8.6 mmol)

in dry dichloromethane. The mixture was stirred for 2 h and cannulated into 50

mL of rapidly-stirred, saturated $NaHCO_3$. After 20 min, the layers were

separated and the aqueous phase was saturated with NaCl. The aqueous

phase was extracted three times with 50 mL of dichloromethane and the

162

combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (benzene) to yield 642 mg of material, which was sublimed (45°C, 0.350 mm Hg) to afford 591 mg (4.80 mmol, 91 %) of pure S-(–)-1-(4-hydroxyphenyl)ethane-1-d$_1$ as white needles: mp 44-46°C; $[\alpha]_D^{25} = -0.25°$, $[\alpha]_{578}^{25} = -0.24°$, $[\alpha]_{546}^{25} = -0.30°$, $[\alpha]_{436}^{25} = -0.563°$, $[\alpha]_{365}^{25} = -1.04°$ (c = 25.3 in EtOH). The ^1H NMR, IR (KBr) and mass spectra were identical to those recorded for the previous preparation.

R-(+)-1-(4-Hydroxyphenyl)ethane-1-d$_1$ 74

R-(+)-1-(4-Methoxyphenyl)ethane-1-d$_1$ was cleaved with 2-bromo -1,3,2-benzodioxaborole in dichloromethane containing N,N-diisopropylethylamine, in a manner analogous to that employed for the S-(–)-isomer, to yield R-(+)-1-(4-hydroxyphenyl)ethane-1-d$_1$ as long, white needles: mp 44.5-46°C; $[\alpha]_D^{25} = +0.16°$, $[\alpha]_{578}^{25} = +0.17°$, $[\alpha]_{546}^{25} = +0.20°$, $[\alpha]_{436}^{25} = +0.37°$, $[\alpha]_{365}^{25} = +0.690°$(c = 25.6 in EtOH); CD $[\Theta]_{300} = 0°$, $[\Theta]_{281} = +211°$, $[\Theta]_{258} = 0°$, $[\Theta]_{246} = -22°$ (c = 2.06 in EtOH); The ^1H NMR, IR (neat) and mass spectra were identical to those recorded for the S-(–)-isomer. Exact mass calcd for C_8H_9DO m/z 123.0794, found m/z 123.0800 (+5 ppm).

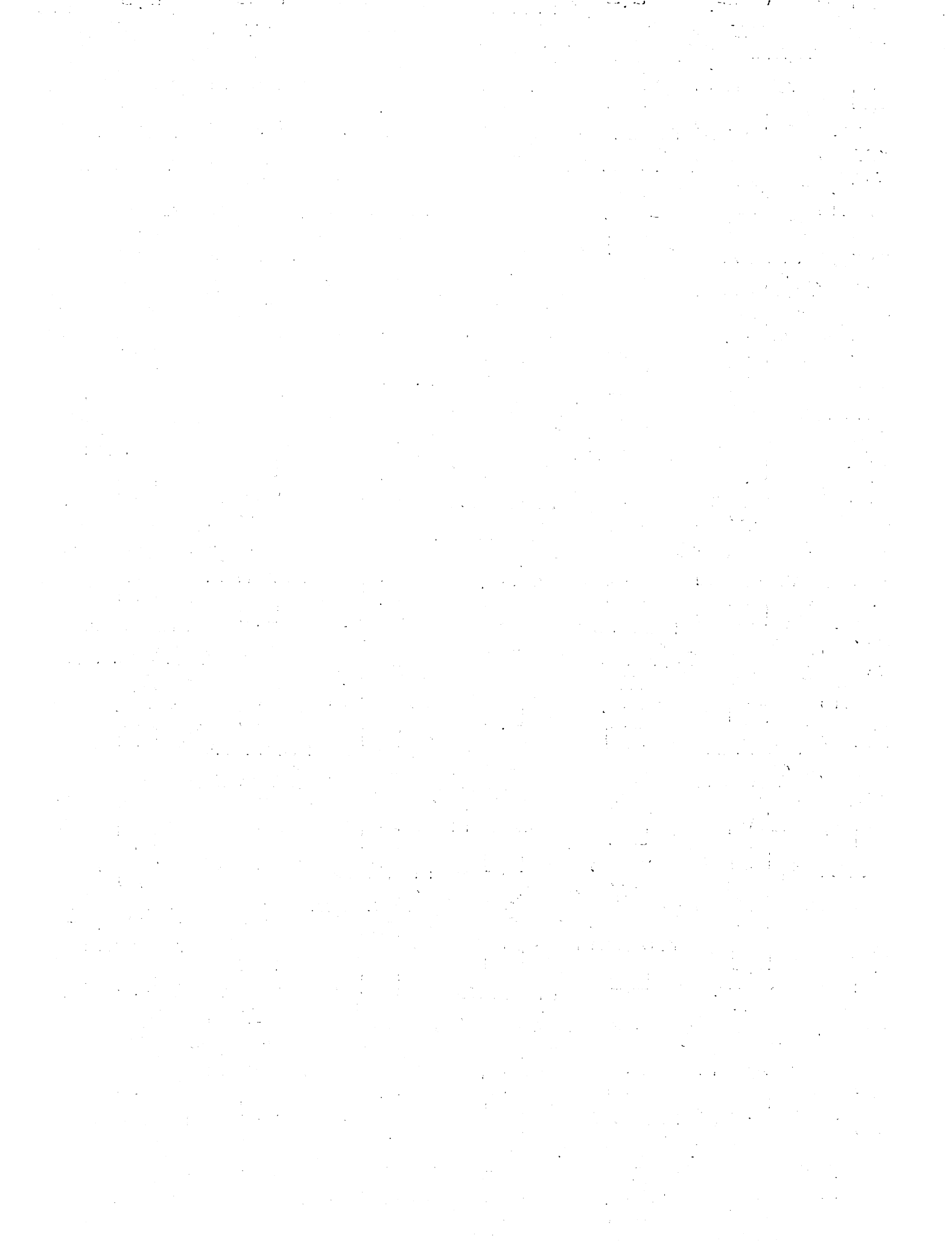### RS-1-(4-Hydroxyphenyl)ethane-1-d$_1$ 75

RS-1-[4-(2-methoxyethoxy)methoxyphenyl]-ethane-1-d$_1$ was treated with 2-bromo-1,3-2-benzodioxaborole in dichloromethane containing N,N-diiso-

propylethylamine, in a manner of analogous to that employed for the S-(–)-isomer, to yield RS-1-(4-hydroxyphenyl)ethane-1-d$_1$. Sublimation (45°C, 0.350 mm Hg) afforded the pure product as white needles: mp 41.5-43°C, ^{1}H NMR δ 7.10, 7.00, 6.78, 6.68 (q, 4H, para-substituted aromatic), 4.38 (bs, 1H, D$_2$O exch, ArOH), 2.54 (qt, 1H, ArCH, J$_H$ = 7.7 Hz, J$_D$ = 1.5 Hz), 1.18 (d, 3H, CH$_3$, J$_H$ = 7.5 Hz, J$_D$ = 1.0 Hz); IR (KBr) 3350 (OH), 3222 (OH), 3022, 2962, 2935, 2875, 2165, 2138 (C-D), 1884, 1616, 1596, 1516, 1440, 1375, 1235, 820 cm^{-1}; mass spectrum (EI, 70 eV), m/z (relative intensity) 123 (M⁺, 33), 108 (100); exact mass calcd for C$_8$H$_9$DO m/z 123.0794, found m/z 123.0794 (±0 ppm).

References

1) DeBoer, Th.J.; Backer, H.J. Org. Syntheses, Coll. Vol. IV, **1963**, 250-253.

2) Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. **1969**, *34*, 2543-2549.

3) Mitsui, S.; Imaizumi, S., Nippon Kagaku Zasshi **1954**, *75*, 974-976.

4) Lipshutz, B.H.; Pegram, J.J.; Tetrahedron Lett. **1980**, *21*, 3343-3346.

5) Gerrard, W.; Lappert, M.F.; Mountfield, B.A. J. Chem. Soc. **1959**, 1529-1534.

6) Dale, W.J.; Hennis, H.E. J. Am. Chem. Soc. **1958**,*80*, 3645-3649.

7) Bakshi, S.P.; Turner, E.E. J. Chem. Soc. **1961**, 168-170.

8) White, E.H.; Aufdermarsh, C.A. J. Am. Chem. Soc. **1961**, *83*, 1179-1190.

9) Pratesi, P.; La Manna, A.; Campiglio, A.; Ghislandi, V. J. Chem. Soc. **1958**, 2069-2074.

10) McKenzie, A.; Pirie, D.J.C. Chem. Berichte **1936**, *69B*, 861-875.

11) Neilson, D.G.; Zakir, U.; Scrimgeour, C.M. J. Chem. Soc. (C). **1971**, 898-904.

12) Calculated from data given for the *R*-(+)-isomer by Balfe, M.P.; Evans, A.; Kenyon, J.; Nandi, K.N. J. Chem. Soc. **1946**, 803-807.

13) Workup by the method of Chandrasekharan, J.; Ramachandran, P.V.; Brown, H.C. J. Org. Chem. **1985**, *50*, 5446-5448, resulted in the yield of 27 % product which was only 55 % enantiomerically pure.

14) Mosher, H.S., Dept. of Chemistry, Stanford Univ., Stanford, CA , private communication.

15) Günther, H.; Biller, F.; Kellner, M.; Simon, H. Angew. Chem. Int. Ed. **1973**, *12*, 146-147.

16) Gorlach, H.; Zagalak, B. J. Chem. Soc. Chem. Comm. **1973**, 274-275.

17) Parker, P. J. Chem. Soc. Perkin Trans. II. **1983**, 83-88.

18) The Merck Index, 10th Ed., Windholz, M.; Budavari, S.; Blumetti, R.F.; Otterbein, E.S., Eds., Merck and Co., Inc., Rahway, N.J., 1983. p 553.

19) McLean, A.; Adams, R. J. Am. Chem. Soc. **1936**, *58*, 804-810.

20) Truce, W.E.; Campbell, R.W. J. Am. Chem. Soc. **1966**, *88*, 3599-3604.

21) Vogel's Textbook of Practical Organic Chemistry, 4th ed., Furniss, B.S.; Hannaford, A.J.; Rogers, V.; Smith, P.W.G.; Tatchell, A.R., eds., Longman Inc., New York, 1978, Chapter VI, pp 901-902.

22) Elsenbaumer, R.L.; Mosher, H.S. J. Org. Chem. **1979**, *44*, 600-604.

23) Schlosser, M.; Ladenberger, V. J. Organometal. Chem. **1967**, *8*, 193-197.

24) Kauffman, G.B.; Teter, L.A. Inorg. Syntheses **1963**, *7*, 9-12.

25) Williamson, B.; Rodebush, W.H. J. Am. Chem. Soc. **1941**, *63*, 3018-3025.

26) Straus, F.; Grindel, H. Annalen der Chemie **1924**, *439*, 276-312.

27) House, H.O.; Umen, M.J. J. Org. Chem. **1973**, *38*, 3893-3901. Tert-butylacetylene was purchased from Farchan Laboratories, Inc. Gainsville, Fl.

28) Klages, A.; Eppelsheim, A. Chem. Berichte **1903**, *36*, 3584-3597.