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A general synthesis of 2-alkoxy-2-phenylpropanoic acids

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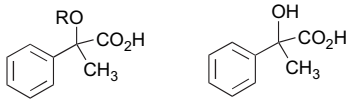
ABSTRACT

A preparation of a variety of 2-alkoxy-2-phenylpropanoic acids in two steps is described. Epoxidation of α-methylstyrene with *m*CPBA in methanol or primary alcohol solvents proceeded with an acid-catalyzed in situ ring opening reaction to give the corresponding 2-alkoxy-2-phenyl-1-propanols in 28–91% yield. Lower yields were realized with secondary (22–58%) and tertiary (14%) alcohols. These alcohols were cleanly oxidized to the corresponding carboxylic acids using a mild Heyns' oxidation (O_2, Pt/C) in generally good to excellent yields (25–92%). The derived (*S*)-α-methylbenzylamide diastereomers are nearly all well separated by capillary GC, and the use of this method to determine the enantiomeric purity of brucine-resolved 2-methoxy-2-phenylpropanoic acid was demonstrated.

1. Introduction

In the course of preparing new ligands for asymmetric catalysts, we desired to obtain a series of 2-alkoxy-2-arylpropanoic acids (**1**), i.e., ethers of atrolactic acid (**2**). These materials have no α-hydrogens and are not subject to the racemization that sometimes accompanies synthetic manipulations of mandelate derivatives.[1] In addition, the alkoxy group is a potential coordination site and may contribute to the effectiveness of any derived ligands.[2] However, a general preparation of atrolactic ethers is not available. For example, the preparation of the methyl ether generally requires either O-alkylation of atrolactic esters (or derivatives)[3] or C-alkylation of the mandelate ether.[2] Such alkylation approaches are at best limited to methyl and primary alkyl groups. A few asymmetric approaches to the methyl ether have been reported,[3a,b,4] but these are multistep routes that nearly always require alkylation of a tertiary alcohol, and thus do not serve as general syntheses of atrolactic ethers. Notably, even very recent workers[2] have chosen to resolve the racemic methyl ether rather than pursue any of the existing asymmetric routes. Atrolactic acid methyl ether has also been prepared in low yield (30%) directly from acetophenone and bromoform in methanol,[5] but this has not been accomplished for any other ether derivatives. Thus, none of these approaches are amenable to the preparation of a wide variety of atrolactic ethers, and consequently references to compounds of this type beyond the methyl ether are remarkably rare in the literature.



1 **2**

2. Results and discussion

Wishing to avoid the alkylation-approach restrictions, we studied the alcoholysis of α-methylstyrene oxide (**3**). The acid-catalyzed reaction of this epoxide with alcohols was expected to provide a variety of 2-alkoxy-2-phenyl-1-propanols that we hoped to oxidize to the corresponding atrolactic ethers (Scheme 1). Thus, our approach was based on the epoxidation of α-methylstyrene. The isolation of this epoxide has been reported many times, from *m*CPBA epoxidations,[6] especially in the presence of potassium fluoride,[7] from methyltrioxorhenium/H_2O_2,[8] and in optically active form from manganese-salen catalyzed epoxidations with hypochlorite.[9] The availability of asymmetric epoxidation raises the possibility of an asymmetric route to these compounds. Unfortunately, in our hands the ring opening of the isolated epoxide in the presence of alcohols produced little or none of the desired products even using a variety of both protic (H_2SO_4, $HClO_4$, and PTSA) and Lewis acid ($AlCl_3$, $MgBr_2$ etherate, and $EtAlCl_2$) catalysts. Instead, large amounts of 2-phenylpropanal were formed, resulting from the known[10] acid-catalyzed rearrangement of the epoxide.

The acid sensitivity of this epoxide suggested that carrying out the peracid epoxidation reaction in alcoholic solvents (Scheme 2) might result in an in situ ring opening to provide the desired alcohol by a one-flask procedure. We were pleased to find that the epoxidation of α-methylstyrene using *m*CPBA in methanol produced 2-methoxy-2-phenyl-1-propanol (**4a**) in greater than 90%

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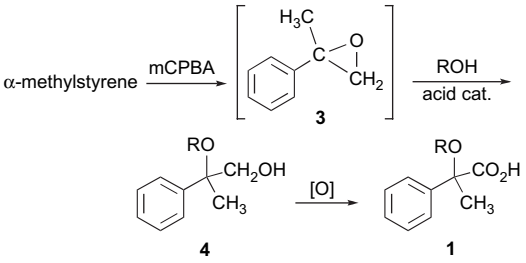
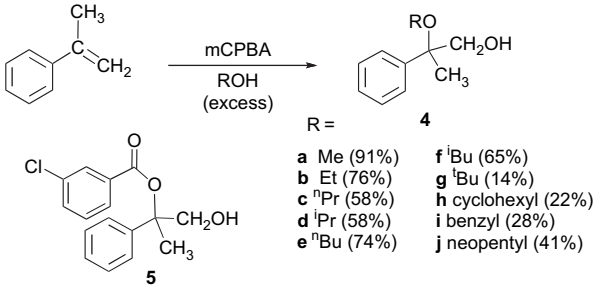


Scheme 1. Proposed route to 2-alkoxy-2-phenylpropanoic acids.

yield and greater than 95% purity by GC–MS after workup. In addition, we found that these reaction conditions could be applied to the preparation of a wide variety of 2-alkoxy-2-phenylpropanols (**4a–j**), shown in Scheme 2. With the exceptions of **4a**, **4d**,[11] and **4g**,[12] none of these alcohols had been reported previously[13] and characterization has been reported only for **4g**. The reactions are best accomplished through the slow addition of α-methylstyrene to an alcoholic solution containing *m*CPBA. Ring opening was very efficient in methanol, providing yields of greater than 90% even in large-scale preparations. Primary alcohols also generally responded well (58–76%), though in the case of benzyl alcohol, excess alcohol complicated the purification and the product was obtained in only a 28% isolated yield. However, with the increasing size of the nucleophile, lower yields of the desired product were obtained. Secondary alcohol solvents gave poor to fair yields (22–56%) and correspondingly more acetophenone, 2-phenylpropanal, and 3-chlorobenzoate ester **5**. Acetophenone probably results from rearrangement of the per-ester formed by ring opening of the epoxide by *m*CPBA itself. The one tertiary alcohol we studied, *tert*-butanol, produced only 14% yield of the desired product **4g**, again with significant amounts of the three major impurities. This outcome is not surprising, given that the nucleophilicity of these more hindered alcohols is relatively poor, and the rearrangement reactions compete to a greater degree. The reaction of neopentanol is a special case; because this alcohol is a solid, a solvent (CH_2Cl_2) was necessary, and the resulting dilution favored the rearrangement reactions, yet the desired product was obtained in 41% yield. The reaction with (−)-menthol was also studied, but very low yields (~8%) of a 1:1 mixture of diastereomers were obtained. In all cases, workup using diethyl ether was advantageous because the benzoate ester impurity **5** (from epoxide opening by 3-chlorobenzoic acid) was relatively insoluble, simplifying the chromatographic isolation of the desired products.

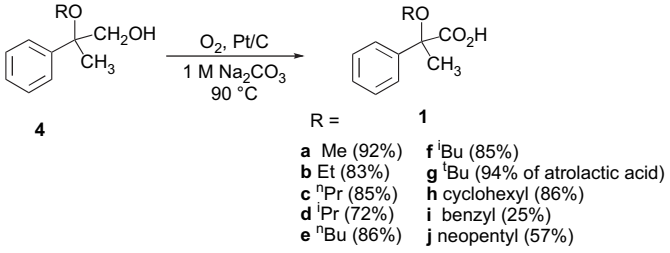


Scheme 2. Synthesis of 2-alkoxy-2-phenylpropanols **4a–j**.

The ^{1}H NMR spectra of these alcohols (in $CDCl_3$) are somewhat unique in that they typically (though not always) show coupling between the methylene protons and the proton of the hydroxyl group. This is probably due to intramolecular hydrogen bonding, which apparently slows the proton exchange rate and allows coupling to be observed. The hydroxy proton occurs invariably at 2.1–2.2 ppm, and couples differently (^3J~4.5 and 8–9 Hz) to each of the non-equivalent methylene protons, causing all three to usually appear as doublets-of-doublets. This coupling immediately disappears upon addition of a drop of D_2O to the NMR tube, providing the expected doublets (^2J=11 Hz) for the methylene protons.

The oxidation of these 2-alkoxy-2-phenyl-1-propanols to the corresponding carboxylic acids was somewhat problematic. The common oxidizing agents ($KMnO_4$, HNO_3, and H_2CrO_4) gave little or no desired product; rather, large amounts of acetophenone were formed. However, we found that the Heyns' oxidation[14] using platinum (Pt) on activated charcoal with oxygen in sodium bicarbonate solution worked well. This oxidation was used[15] by Sharpless and co-workers to convert related primary alcohols to carboxylic acids. This reaction allowed us to isolate the known[3c,16] methoxy acid **1a** in greater than 90% yield. The product was isolated in high purity, even on large scale (>50 g), after passage through a small amount of silica gel to remove very polar impurities.

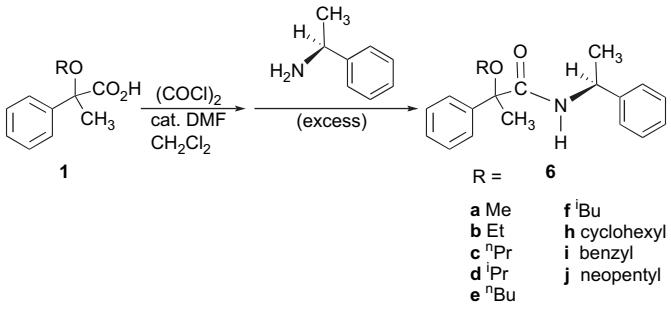
The oxidation of the various other alcohols **4b–j** was straightforward in most cases, and the corresponding acids **1b–j** were generally isolated in moderate to excellent yields (57–94%, Scheme 3). The benzyloxy acid (**1i**), which is the only such acid besides **1a** to have been previously reported[17] (and was only partially characterized), gives an exceptionally low yield (25%). We attribute this to partial cleavage of the benzyl group under what are essentially catalytic dehydrogenation conditions. In the case of the *tert*-butoxy alcohol **4g**, atrolactic acid (**2**) was obtained in high yield (94%); the ether cleavage in this case was probably a result of the acidic workup, *tert*-butyl ethers being especially susceptible to acid-catalyzed cleavage.[18] This oxidation is slow (3 days), but is simple and generally high-yielding. Despite requiring the use of platinum, the process is cost effective, since the catalyst can be recycled without loss of activity.



Scheme 3. Oxidation of 2-alkoxy-2-phenylpropanols to provide 2-alkoxy-2-phenylpropanoic acids **1a–j**.

The resolution of atrolactic acid methyl ether (**1a**) has been accomplished via the quinine[19] and brucine[20] salts. However, the quinine salt crystallizes very slowly (2 weeks) and so the brucine salt is preferred. We briefly examined a wide variety of chiral bases ((+)-cinchonine, (−)-cinchonidine, (−)-strychnine, (−)-nicotine, (+)-ephedrine, (+)-pseudoephedrine, (+)-dehydroabietylamine, (−)-α-methylbenzylamine, and (+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol) in hopes of identifying some that form crystalline salts with **1a** rather than the powders obtained from brucine, to no avail. The optical rotation of **1a** has historically not been a reliable means of determining enantiomeric purity. Reported values for enantiomerically pure material (corrected for % ee) range from[2] $[\alpha]_D$ 28.3 to[4d] 39 (all *c* 0.8–1.1, MeOH). To date, the only independent means of enantiomeric purity determination has been using a chiral shift reagent with ^{1}H NMR on the methyl ester.[2,3a,b] In our hands, chiral GC of both racemic **1a** and of the methyl ester gave only a slight separation (ChiraDex,[21] 30 m×0.25 mm) and was of no value. We found that the (*S*)-(−)-α-methylbenzylamide diastereomers **6a** (Scheme 4) were very well separated by capillary GC. This method allowed us to establish the enantiomeric purity of our brucine-resolved **1a**, which exhibited $[\alpha]_D$ −34.0 (c 1.08, MeOH), as 97.6±0.3% ee. Although no attempt was made to resolve the other acids **1b–i**, all of the (*S*)-(−)-α-methylbenzylamides **6a–j**

(except cyclohexyl derivative **6h**) were well separated by capillary GC (Table 1). A chromatographic resolution value of 1.5 is considered[22] to be suitable for very high purity analyses, and this derivatization approach represents a simple, accurate, and reliable method for the determination of enantiomeric purity in nearly all these cases.



Scheme 4. Conversion of 2-alkoxy acids to diastereomeric amides.

3. Experimental

3.1. General section

All reactions, which utilize air or moisture sensitive reagents were performed in oven-dried glassware under an argon atmosphere. Unless otherwise noted, alcohol reagents were used as received. Ethyl acetate, hexanes, and cyclohexanol were distilled prior to use. α-Methylstyrene was distilled prior to use and stored in a freezer. (*S*)-(−)-α-Methylbenzylamine was obtained from Aldrich and crystallized once as its (+)-tartaric acid salt, followed by re-isolation of the free amine, before use. Unless otherwise stated, all reactions were magnetically stirred and monitored by thin-layer chromatography on silica gel, gas chromatography, and/or gas chromatography–mass spectroscopy. Flash chromatography used 230–400 mesh silica gel obtained from EM Science. Isolated yields are reported. Gas chromatography was done on an HP-5 column (30 m×0.25 mm) using hydrogen carrier, split injection (~80:1) and FID detection. Elemental analysis was done by Atlantic Microlabs (Norcross, GA), and high resolution mass spectroscopy was done by the University of California, Riverside, mass spectroscopy facility using ESI/APCI ionization.

^{1}H and ^{13}C NMR spectra were obtained at 300 or 500 MHz for proton and 75 or 125 MHz for carbon. In all cases, $CDCl_3$ was used as the solvent with 0.03% TMS as the internal standard. Chemical shifts are expressed in parts per million (δ), and peaks are reported as singlets (s), doublets (d), triplets (t), quartets (q), pentets (pent), sextets (sext), septets (sept), multiplets (m), or combinations of each with coupling constants (J) expressed in hertz. All ^{13}C NMR spectra are proton-decoupled.

Table 1
GC separability of (*S*)-(−)-α-methylbenzylamides **6a**–**j**

Compound	R=	Average retention time[a] (min)	Resolution[b]
6a	Me	6.35	3.02
6b	Et	6.50	2.19
6c	*n*-Pr	7.75	1.82
6d	*i*-Pr	7.10	1.78
6e	*n*-Bu	9.30	1.42
6f	*i*-Bu	8.35	1.46
6h	Cyclohexyl	15.8	0.41
6i	Benzyl	18.9	1.08
6j	Neopentyl	8.71	1.40

[a] Average of *RS* and *SS* diastereomers, initial temperature=200 °C, ramp=2 °C/min, HP-5, 30 m×0.25 mm, H_2 carrier.
[b] Calculated as (0.59)(difference in *RS* vs *SS* retention times)/sum of peak widths at half-height.

3.2. Large-scale synthesis of 2-methoxy-2-phenylpropanol (4a)

In a 1000 mL round bottom flask containing a large stir bar were added *m*CPBA (100.3 g, 406.8 mmol) and anhydrous methanol (350 mL). The flask was cooled to 0 °C in an ice-water bath. An addition funnel containing α-methylstyrene (46.5 mL, 358 mmol) was attached, and this was added dropwise over 45 min. The mixture was allowed to warm to room temperature over 5 h with continual stirring. The reaction mixture was transferred to a separatory funnel containing 100 mL of 3 M NaOH. The product was extracted with ether (3×50 mL). The organic extracts were combined, dried with magnesium sulfate, filtered, and concentrated to a colorless oil (53.96 g, 91%), >98% purity by GC. R_f (25% ethyl acetate/hexanes)=0.35. IR (neat): 3401, 1074 cm^{-1}. ^{1}H NMR: δ 1.61 (s, 3H, CH_3), 2.20 (br s, 1H, OH), 3.13 (s, 3H, OCH_3), 3.47 (d, 1H, J=11.1 Hz, CH_a), 3.65 (br d, 1H, J=11.1 Hz, CH_b), 7.31 (m, 5H, ArH). ^{13}C NMR: δ 19.2, 50.4, 71.3, 79.7, 126.5, 127.4, 128.3, 141.9. GC–MS: 166 (M^+), 135 (base peak). HRMS: calcd for $C_{10}H_{14}O_2 \cdot NH_4^+$=184.1337; found: 184.1331.

3.3. General procedure for the synthesis of 2-alkoxy-2-phenylpropanols using liquid alcohols as solvent

*m*CPBA (approximately 5.85 g, 23.7 mmol) was added to a 100 mL round bottom flask containing a stir bar and dissolved in 40 mL of the appropriate alcohol solvent. The flask was cooled to 0 °C in an ice-water bath with stirring, α-methylstyrene (2.75 mL, 21.2 mmol) was added slowly by syringe, and the reaction was allowed to warm to room temperature. The flask was then heated at 40 °C for approximately 5 h or until disappearance of alkene as determined by TLC. Following completion, the reaction mixture was transferred to a separatory funnel containing 50 mL of 1 M NaOH, and the product was extracted with methylene chloride or (preferably) diethyl ether (3×15 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated under reduced pressure. Kugelrohr distillation was used to remove alcohols that were not easily removed by rotary evaporation. The product was purified by flash chromatography eluting with 5–20% ethyl acetate in hexanes.

*3.3.1. 2-Ethoxy-2-phenylpropanol (**4b**)*

Isolated as a colorless oil (2.91 g, 76% yield); R_f (25% ethyl acetate/hexanes)=0.40. IR (neat): 3443, 1074 cm^{-1}. ^{1}H NMR: δ 1.19 (t, 3H, J=7.2 Hz, CH_3), 1.63 (s, 3H, CH_3), 2.15 (m, 1H, OH), 3.20 (dq, 1H, J=8.7, 7.2 Hz, CH_a), 3.39 (dq, 1H, J=8.7, 7.2 Hz, CH_b), 3.47 (dd, 1H, J=11.1, 8.7 Hz, $CH_{a'}$), 3.65 (dd, 1H, J=11.1, 4.5 Hz, $CH_{b'}$), 7.32 (m, 5H, ArH). ^{13}C NMR: δ 15.7, 19.9, 58.0, 71.7, 79.4, 126.3, 127.3, 128.3, 142.7. GC–MS: 180 (M^+), 149 (base peak). HRMS: calcd for $C_{11}H_{16}O_2 \cdot NH_4^+$=198.1494; found: 198.1487.

*3.3.2. 2-n-Propoxy-2-phenylpropanol (**4c**)*

Isolated as a colorless oil (2.389 g, 58% yield); R_f (15% ethyl acetate/hexanes)=0.24. IR (neat): 3404, 1075 cm^{-1}. ^{1}H NMR: δ 0.92 (t, 3H, J=7.5 Hz, CH_3), 1.60 (sext, 2H, J=7.5 Hz, CH), 1.63 (s, 3H, CH_3), 2.14 (dd, 1H, J=8.4, 4.5 Hz, OH), 3.11 (dt, 1H, J=8.4, 6.9 Hz, CH_a), 3.27 (dt, 1H, J=8.7, 6.9 Hz, CH_b), 3.48 (dd, 1H, J=11.1, 8.4 Hz, $CH_{a'}$), 3.66 (dd, 1H, J=11.1, 4.5 Hz, $CH_{b'}$), 7.23 (m, 5H, ArH). ^{13}C NMR: δ 10.7, 20.0, 23.5, 64.2, 71.7, 79.1, 126.5, 127.4, 128.3, 142.7. GC–MS: 163 (M−31), 121 (base peak). HRMS: calcd for $C_{12}H_{18}O_2 \cdot NH_4^+$=212.1650; found: 212.1656.

*3.3.3. 2-Isopropoxy-2-phenylpropanol (**4d**)*

Isolated as a colorless oil (2.38 g, 58% yield), which slowly crystallized (mp 34–35.2 °C); R_f (15% ethyl acetate/hexanes)=0.25. IR (KBr): 3340, 1105 cm^{-1}. ^1H NMR: δ 1.02 (d, 3H, J=6.0 Hz, CH_3), 1.16 (d, 3H, J=6.0 Hz, CH_3), 1.67 (s, 3H, CH_3), 2.15 (dd, 1H, J=8.7, 4.5 Hz, OH), 3.42 (dd, 1H, J=10.8, 8.7 Hz, CH_a), 3.61 (sept, 1H, J=6.0 Hz, CH), 3.68 (dd, 1H, J=10.8, 4.5 Hz, CH_b), 7.37 (m, 5H, ArH). ^{13}C NMR: δ 20.7, 24.5, 25.0, 65.7, 71.7, 79.5, 126.9, 127.5, 128.0, 143.4. GC–MS: 163 (M−31), 121 (base peak). Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; found: C, 73.96; H. 9.17.

*3.3.4. 2-n-Butoxy-2-phenylpropanol (**4e**)*

Isolated as a colorless oil (3.285 g, 74% yield); R_f (15% ethyl acetate/hexanes)=0.28. IR (neat): 3442, 1074 cm^{-1}. ^1H NMR: δ 0.90 (t, 3H, J=7.2 Hz, CH_3), 1.38 (dpent, 2H, J=7.2, 4.8 Hz, CH_2), 1.56 (dpent, 2H, J=8.7, 3.8 Hz, CH_2), 1.63 (s, 3H, CH_3), 2.11 (ddd, 1H, J=8.7, 4.5, 2.1 Hz, OH), 3.14 (dt, 1H, J=8.7, 6.6 Hz, CH_a), 3.30 (dt, 1H, J=8.7, 6.6 Hz, CH_b), 3.47 (dd, 1H, J=11.1, 8.7 Hz, $CH_{a'}$), 3.65 (dd, 1H, J=11.1, 4.8 Hz, $CH_{b'}$), 7.32 (m, 5H, ArH). ^{13}C NMR: δ 14.0, 19.5, 20.0, 32.4, 62.3, 71.7, 79.1, 126.4, 127.4, 128.3, 142.7. GC–MS: 177 (M−31), 121 (base peak). Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; found: C, 74.65; H. 9.71.

*3.3.5. 2-Isobutoxy-2-phenylpropanol (**4f**)*

Isolated as a colorless oil (2.851 g, 65% yield); R_f (25% ethyl acetate/hexanes)=0.50. IR (neat): 3442, 1073 cm^{-1}. ^1H NMR: δ 0.91 (d, 3H, J=6.3 Hz, CH_3), 0.92 (d, 3H, J=6.9 Hz, CH_3), 1.62 (s, 3H, CH_3), 1.85 (sept, 1H, J=6.6 Hz, CH), 2.14 (dd, 1H, J=9.0, 4.5 Hz, OH), 2.93 (dd, 1H, J=8.7, 6.6 Hz, CH_a), 3.06 (dd, 1H, J=8.7, 6.6 Hz, CH_b), 3.48 (dd, 1H, J=11.1, 9.0 Hz, $CH_{a'}$), 3.66 (dd, 1H, J=11.1, 4.2 Hz, $CH_{b'}$), 7.32 (m, 5H, ArH). ^{13}C NMR: δ 19.6, 19.6, 19.9, 29.0, 69.0, 71.7, 78.8, 126.5, 127.4, 128.3, 142.7. GC–MS: 177 (M−31), 121 (base peak). Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; found: C, 74.67; H, 9.70.

*3.3.6. 2-tert-Butoxy-2-phenylpropanol (**4g**)*

Isolated as a white solid (0.620 g, 14% yield), mp 37–39 °C, spectroscopically identical to that previously reported.[12]

*3.3.7. 2-Cyclohexyloxy-2-phenylpropanol (**4h**)*

Isolated as a white solid (1.392 g, 22% yield), can be recrystallized from hexanes, mp 63.8–64.5 °C; R_f (15% ethyl acetate/hexanes)=0.33. IR (KBr): 3300, 1083 cm^{-1}. ^1H NMR: δ 1.39 (m, 10H, CH_2), 1.66 (s, 3H, CH_3), 2.15 (br s, 1H, OH), 3.28 (m, 1H, CH), 3.42 (dd, 1H, J=11.1 Hz, 7.8 Hz, CH_a), 3.69 (br d, 1H, J=11.1 Hz, CH_b), 7.38 (m, 5H, ArH). ^{13}C NMR: δ 20.9, 24.6, 25.6, 34.7, 35.2, 71.6, 79.4, 126.8, 127.5, 128.0, 143.7. GC–MS: 203 (M−31), 121 (base peak). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.75; H, 9.42. HRMS: calcd for $C_{15}H_{22}O_2 \cdot Na^+$=257.1517; found: 257.1514.

*3.3.8. 2-Benzyloxy-2-phenylpropanol (**4i**)*

The reaction and isolation was performed as above, but the difficulty of separating excess benzyl alcohol and the 3-chlorobenzoate impurity **5** from the desired product required additional manipulations. After excess benzyl alcohol was removed by Kugelrohr distillation (8 Torr, 150 °C), the residue was treated with 50 mL of 2 M NaOH at 40 °C for 2 h to hydrolyze the ester. The mixture was transferred to a separatory funnel and extracted with dichloromethane (3×15 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to steam distillation using three 50 mL portions of deionized water until benzyl alcohol was no longer present by GC–MS. Flash chromatography (20% EtOAc/hexanes) yielded a colorless oil (1.42 g, 28% yield); R_f (25% ethyl acetate/hexanes)=0.37. IR (neat): 3440, 1047 cm^{-1}. ^1H NMR: δ 1.73 (s, 3H, CH_3), 2.22 (br s, 1H, OH), 3.51 (1H, dd, J=10.5, 6.1 Hz, CH_a), 3.73 (d, 1H, J=11.3 Hz, CH_b), 4.22 (d, 1H, J=11.0 Hz, $CH_{a'}$), 4.36 (d, 1H, J=11.3 Hz, $CH_{b'}$), 7.25–7.53 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$): 19.2, 64.8, 71.7, 80.0, 126.5, 127.42, 127.43, 127.60, 128.3, 128.4, 138.7, 142.1. GC–MS: 91 (base), 134 (–BnOH), 165 (–C_6H_5), 211 (–CH_2OH). HRMS: calcd for $C_{15}H_{15}O$ (M−OH)=225.1274; found: 225.1278.

3.4. Procedure for the synthesis of 2-alkoxy-2-phenylpropanols using solid alcohols

*3.4.1. 2-Neopentyloxy-2-phenylpropanol (**4j**)*

To a 100 mL round bottom flask with a stir bar were added neopentyl alcohol (10.26 g, 116.4 mmol) and *m*CPBA (5.86 g, 23.8 mmol). The reactants were dissolved in 10 mL of methylene chloride, and α-methylstyrene (2.75 mL, 21.1 mmol) was added dropwise by syringe. A hot water bath was set up, and the flask was heated to 40 °C overnight. The product was isolated by transferring to a separatory funnel containing 50 mL of 1 M NaOH and extraction with methylene chloride (3×15 mL). The organic phases were combined, dried with magnesium sulfate, and concentrated under reduced pressure. The product was purified by flash chromatography, eluting with 5% ethyl acetate/hexanes. Compound **4j** was isolated as a white solid (1.95 g, 41% yield), mp 64–65 °C; R_f (15% ethyl acetate/hexanes)=0.51. IR (KBr): 3330, 1080 cm^{-1}. ^1H NMR: δ 0.93 (s, 9H, 3 CH_3), 1.61 (s, 3H, CH_3), 2.15 (dd, 1H, J=8.4, 3.6 Hz, OH), 2.82 (d, 1H, J=8.4 Hz, CH_a), 2.94 (d, 1H, J=8.1 Hz, CH_b), 3.47 (dd, 1H, J=10.8, 8.4 Hz, $CH_{a'}$), 3.68 (dd, 1H, J=10.8, 3.6 Hz, $CH_{b'}$), 7.34 (m, 5H, ArH). ^{13}C NMR: δ 19.9, 26.9, 31.8, 71.7, 72.0, 78.4, 126.6, 127.4, 128.2, 142.6. GC–MS: 193 (M−31), 121 (base peak). Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; found: C, 75.52; H. 9.87.

3.5. General procedure for the preparation of 2-alkoxy-2-phenylpropanoic acids 1a–j

To a round bottom flask containing a stir bar were added a 2-alkoxy-2-phenylpropanol **4a–j** and 5 mol equiv of 1 M aqueous sodium carbonate. The flask was purged with oxygen gas following the attachment of a reflux condenser. To the well-stirred solution was added 10% Pt on carbon (3–5 mol %), and the flask was heated to 90 °C in an oil bath for 3 days with a constant O_2 atmosphere. Following completion as determined by GC–MS, the reaction mixture was filtered through Celite to remove the catalyst, and the solution was acidified to pH 2 using 1 M sulfuric acid. The product was extracted with ethyl acetate (3×20 mL). The organic extracts were combined, dried with magnesium sulfate, and concentrated under reduced pressure. The product was purified by flash chromatography using ethyl acetate and hexanes.

*3.5.1. 2-Methoxy-2-phenylpropanoic acid (**1a**)*

Isolated as a low-melting white solid at room temperature (53.45 g, 92% yield), mp 35.5–37.5 °C and spectroscopically identical to that reported previously.[3c,16]

*3.5.2. 2-Ethoxy-2-phenylpropanoic acid (**1b**)*

Isolated as a colorless oil (1.657 g, 83% yield), which slowly crystallized (mp 53–55 °C). IR (neat): 3165, 1749, 1137 cm^{-1}. ^1H NMR: δ 1.27 (t, 3H, J=6.9 Hz, CH_3), 1.86 (s, 3H, CH_3), 3.39 (dq, 1H, J=8.7, 6.9 Hz, CH_a), 3.47 (dq, 1H, J=8.7, 6.9 Hz, CH_b), 7.38 (m, 5H, ArH). ^{13}C NMR: δ 15.6, 21.3, 59.8, 81.1, 126.1, 128.4, 128.6, 139.3, 175.3. GC–MS: 177 (M−17), 149 (base peak). Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; found: C, 67.78; H. 7.12.

*3.5.3. 2-n-Propoxy-2-phenylpropanoic acid (**1c**)*

Isolated as a colorless oil (2.050 g, 85% yield). IR (neat): 3150 (br), 1719, 1228 cm^{-1}. ^1H NMR: δ 0.95 (t, 3H, J=7.5 Hz, CH_3), 1.66 (sext, 2H, J=7.5 Hz, CH_2), 1.85 (s, 3H, CH_3), 3.28 (dt, 1H, J=8.7, 6.6 Hz, CH_a), 3.37 (dt, 1H, J=8.7, 6.6 Hz, CH_b), 7.38 (m, 5H, ArH). ^{13}C NMR: δ 10.6, 21.3, 23.2, 65.8, 81.0, 126.1, 128.4, 128.5, 139.5, 175.9. GC–MS: 207 (M−1), 163 (M−45), 121 (base peak). HRMS: calcd for $C_{12}H_{16}O_3 \cdot NH_4^+$=226.1443; found: 226.1445.

*3.5.4. 2-Isopropoxy-2-phenylpropanoic acid (**1d**)*

Isolated as a colorless oil (0.836 g, 72% yield), which slowly crystallized (mp 57–61 °C). IR (KBr): 2990, 1695, 1282 cm^{-1}. ^1H NMR: δ 1.07 (d, 3H, J=6.3 Hz, CH_3), 1.22 (d, 3H, J=6.3 Hz, CH_3), 1.86 (s, 3H, CH_3), 3.75 (sept, 1H, J=6.3 Hz, CH), 7.38 (m, 5H, ArH). ^{13}C NMR: δ 22.1, 24.2, 24.3, 67.9, 81.3, 126.3, 128.4, 128.4, 140.1, 175.9. GC–MS: 207 (M−1), 121 (base peak). Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; found: C, 69.09; H. 7.66.

*3.5.5. 2-n-Butoxy-2-phenylpropanoic acid (**1e**)*

Isolated as a colorless oil (1.985 g, 86% yield). IR (neat): 2959, 1713, 1226 cm^{-1}. ^1H NMR: δ 0.91 (t, 3H, J=7.2 Hz, CH_3), 1.41 (dpent, 2H, J=9.3, 6.6 Hz, CH_2), 1.63 (dpent, 2H, J=9.3, 6.6 Hz, CH_2), 1.85 (s, 3H, CH_3), 3.31 (dt, 1H, J=8.7, 6.6 Hz, CH_a), 3.41 (dt, 1H, J=8.7, 6.6 Hz, CH_b), 7.37 (m, 5H, ArH). ^{13}C NMR: δ 13.8, 19.3, 21.2, 32.0, 63.9, 81.0, 126.1, 128.4, 128.6, 139.4, 175.3. GC–MS: 177 (M−45), 121 (base peak). HRMS: calcd for $C_{13}H_{18}O_3 \cdot NH_4^+$=240.1599; found: 240.1605.

*3.5.6. 2-Isobutoxy-2-phenylpropanoic acid (**1f**)*

Isolated as a colorless oil (2.57 g, 85% yield), which slowly crystallized (mp 48–50 °C). IR (KBr): 2964, 1703, 1281 cm^{-1}. ^1H NMR: δ 0.93 (d, 3H, J=6.9 Hz, CH_3), 0.95 (d, 3H, J=7.2 Hz, CH_3), 1.83 (s, 3H, CH_3), 1.92 (nonet, 1H, J=6.6 Hz, CH), 3.10 (dd, 1H, J=8.4, 6.6H, CH_a), 3.17 (dd, 1H, J=8.4, 6.6 Hz, CH_b), 7.37 (m, 5H, ArH). ^{13}C NMR: δ 19.4, 21.3, 28.7, 70.6, 80.9, 126.1, 128.3, 128.5, 139.6, 175.7. GC–MS: 177 (M−45), 121 (base peak). Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; found: C, 70.39; H. 8.30.

*3.5.7. 2-Cyclohexyloxy-2-phenylpropanoic acid (**1h**)*

Isolated as a crystalline solid (0.859 g, 86% yield), mp 104.5–105.2 °C. IR (KBr): 2943, 1704, 1073 cm^{-1}. ^1H NMR: δ 1.41 (m, 10H, CH_2), 1.86 (s, 3H, CH_3), 3.42 (dpent, 1H, J=7.5, 3.9 Hz, CH), 7.38 (m, 5H, ArH), 9.95 (br s, 1H, COOH). ^{13}C NMR: δ 22.2, 24.3, 25.3, 34.2, 34.3, 73.7, 81.2, 126.3, 128.4, 140.2, 176.2. GC–MS: 231 (M−17), 203 (M−45), 121 (base peak). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.10.

*3.5.8. 2-Benzyloxy-2-phenylpropanoic acid (**1i**)*

Isolated as an off-white solid (0.206 g, 25% yield), mp 86–88 °C. IR (KBr): 2982, 1698, 1128 cm^{-1}. ^1H NMR: δ 1.97 (s, 3H, CH_3), 4.42 (d, 1H, J=10.8 Hz, CH_a), 4.46 (d, 1H, J=10.8 Hz, CH_b), 7.22–7.44 (m, 8H, ArH), 7.56 (d, 2H, J=6.8 Hz, ArH), 9.2 (v br s, 1H, CO_2H). ^{13}C NMR: δ 21.8, 66.6, 81.6, 126.2, 127.7, 127.9, 128.4, 128.55, 128.6, 137.5, 139.2, 176.1. GC–MS: 211(M−45), 177 (M−79), 150, 105. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.86; H, 6.36.

*3.5.9. 2-Neopentoxy-2-phenylpropanoic acid (**1j**)*

Isolated as a white solid (0.581 g, 57% yield), mp 61–63 °C. IR (KBr): 2958 (v br), 1710, 1152 cm^{-1}. ^1H NMR: δ 0.97 (s, 9H, $3CH_3$), 1.84 (s, 3H, CH_3), 3.01 (d, 1H, J=8.2 Hz, CH_a), 3.08 (d, 1H, J=8.2 Hz, CH_b), 7.38 (m, 5H, ArH). ^{13}C NMR: δ 21.1, 26.8, 31.8, 73.8, 80.9, 126.1, 128.5, 128.6, 139.4, 175.0. GC–MS: 191 (M−45), 121 (base peak). Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; found: C, 71.09; H. 8.34.

3.6. Resolution of 2-methoxy-2-phenylpropanoic acid (1a)

Racemic acid **1a** (5.05 g, 28 mmol) was dissolved in 75 mL of acetone and treated with (−)-brucine (11.95 g, 30.3 mmol). A white precipitate formed within 10 min. After stirring at room temperature for 1 h, the suspension was heated to 60 °C and the solid was isolated by filtration. This material was suspended in additional acetone (50 mL) at 60 °C and again isolated by filtration. After drying under vacuum, this gave the (−)-brucine salt as a white powder (6.43 g, 40%), $[\alpha]_D$ −18 (*c* 1.05, MeOH) (lit.[20] $[\alpha]_D$ −11 (*c* 1.00, MeOH)). Treatment of this with 1 M HCl and extraction into ether gave the free acid (*R*)-(−)-**1a** in ~99% purity, $[\alpha]_D$ −34.0 (*c* 1.08, MeOH) (lit.[4a] $[\alpha]_D$ −31.5 (*c* 0.8, MeOH)).[4a]

3.7. Preparation of (*S*)-(−)-α-methylbenzylamides 6a–i

Racemic acid **1a** (22 mg, 0.12 mmol) was dissolved in 1 mL of anhydrous dichloromethane and treated with a catalytic amount of DMF (2 μL) and oxalyl chloride (31 μL, 0.36 mmol, 3 equiv). Gas evolution was evident and the mixture was stirred at room temperature for 20 min. Vacuum (20 mmHg) was applied to remove all volatiles and 1 mL of fresh anhydrous dichloromethane was added, followed by (*S*)-(−)-α-methylbenzylamine (60 μL, 0.47 mmol, 3.9 equiv). After 10 min, the mixture was transferred to a separatory funnel using dichloromethane. After extraction with 1 M HCl, the organic phase was dried with anhydrous Na_2SO_4 and analyzed by capillary GC (200–240 °C at 2 °C per min). The *RS* diastereomer eluted at 6.13 min, and the *SS* diastereomer at 6.54 min. This procedure was repeated with brucine-resolved (*R*)-(−)-**1a** and gave an *RS*/*SS* ratio of 98.8±0.15:1.2±0.15 (97.5±0.3% ee). This procedure was repeated with each of the other racemic acids **1b–i**; average retention times and chromatographic resolution values are given in Table 1.

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