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# The Anticonvulsant Activities of Functionalized *N*-Benzyl 2-Acetamidoacetamides. The Importance of the 2-Acetamido Substituent

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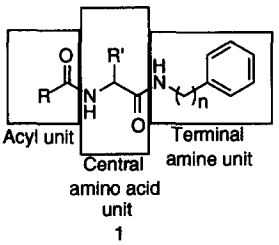
**Abstract**—Recent studies have demonstrated that substituted *N*-benzyl *2-acetamido*acetamides provide significant protection against maximal electroshock (MES)-induced seizures in mice and rats. In this study, we investigated whether the 2-acetamido moiety was necessary for anticonvulsant activity. Ten derivatives of the known anticonvulsant, *N*-benzyl 2-acetamido-2-phenylacetamide were prepared in which the 2-acetamido group was replaced by hydrogen, methyl, oxygen, and halogen substituents. Evaluation of these compounds in the MES-induced seizure test demonstrated that both the hydroxy and the methoxy compounds provided full protection against MES-induced seizures in mice given ip at 100 mg/kg. Moreover, evaluation of the individual stereoisomers for the hydroxy compound showed that the principal activity resided in the (*R*)-isomer. These findings demonstrated that the 2-acetamido substituent is important but not obligatory for the prevention of MES-induced seizures. Further supporting evidence was provided by comparing the pharmacological activities of *N*-benzyl 2,3-dimethoxypropionamide with *N*-benzyl 2-acetamido-3-methoxypropionamide. The $ED_{50}$ value for the former in the MES test was 30 mg/kg (ip), which compared favorably with phenobarbital ($ED_{50}$ = 22 mg/kg), but the $ED_{50}$ value for *N*-benzyl 2-acetamido-3-methoxypropionamide was 8.3 mg/kg. 

## Introduction

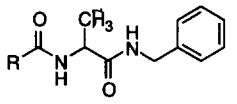
In recent years, we demonstrated that functionalized amino acids (**1**) are potent anticonvulsant agents that provide significant protection against maximal electroshock (MES)-induced seizures in mice and rats.[1-10] More than 150 analogues have been prepared and evaluated. In our structure–activity relationship (SAR) study, we divided **1** into three subunits: the acyl unit, the central amino acid, and the terminal amine (Fig. 1).




**1**

**Figure 1.**

Of the three subunits, little attention has been given to the acyl substituent in **1**. Progressive increase in the size of this moiety from acetyl (**2**) to trimethylacetyl (**4**) led to a reduction in anticonvulsant activity. The drop in activity, however, did not directly correlate with the size of the substituent.[3]

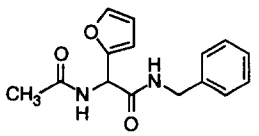


**2** R = $CH_3$ ($ED_{50}$ = 76 mg/kg)

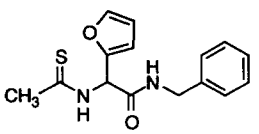
**3** R = $CH(CH_3)_2$ ($ED_{50}$ > 600 mg/kg)

**4** R = $C(CH_3)_3$ ($ED_{50}$ ~ 300 mg/kg)

When the acetyl oxygen in **5** was replaced with sulfur, compound **6** resulted and anticonvulsant activity decreased only modestly.[7]



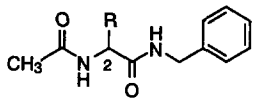
**5** ($ED_{50}$ = 10 mg/kg)



**6** ($ED_{50}$ = 18 mg/kg)

The central amino acid in **1** has been extensively evaluated. Sixteen compounds with varying R′ groups had

activity comparable to or better than phenobarbital in the MES-induced seizure tests in mice.[5–7,9,10] These included the phenyl analogue **7** ($ED_{50}=20$ mg/kg),[3] the electron-rich furan adduct **5** ($ED_{50}=10$ mg/kg),[5,7] the electron-deficient pyrimidine adduct **8** ($ED_{50}=8.1$ mg/kg),[9] and the aliphatic ether analogue **9** ($ED_{50}=8.3$ mg/kg).[10] We showed that the principal anticonvulsant activity for **2**, **5**, **7**, and **9** resided in the (*R*)-enantiomer.[1,4,7,10] The eudismic ratio[11] for the (*R*)- and (*S*)-stereoisomers for these four sets of compounds exceeded 10:1.



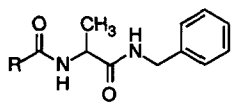
**5** R =  ($ED_{50}$ = 10 mg/kg)

**7** R =  ($ED_{50}$ = 20 mg/kg)

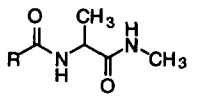
**8** R =  ($ED_{50}$ = 8.1 mg/kg)

**9** R = $-CH_2OCH_3$ ($ED_{50}$ = 8.3 mg/kg)

Investigation of the terminal amine group in **1** showed that maximal activity in the MES test was achieved when this unit was a *N*-benzyl moiety. Activity was lowered when the *N*-benzyl group in **2** was replaced with a *N*-methyl unit to give **10**.[3] Deletion of the methylene linkage between the terminal nitrogen and the benzene ring in **2** or progressive increase of the methylene linkage in **2** from one to four led to significant losses in anticonvulsant activity.[12]



**2** ($ED_{50}$ = 76 mg/kg)



**10** ($ED_{50}$ > 600 mg/kg)

We divided **1** into two subunits, the *N*-acyl substituent and the *N*-benzyl 2-substituted acetamide group, to determine if the *N*-acyl group was necessary for anticonvulsant activity (Fig. 2). We found that this moiety was an important structural unit but that other substituents could provide significant protection against MES-induced seizures.

## Results and Discussion

### Selection of test compounds

In our initial study, *N*-benzyl 2-acetamido-2-phenylacetamide (**7**) served as the reference compound.[3]

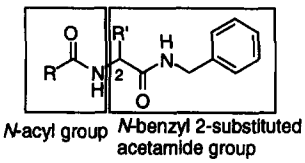
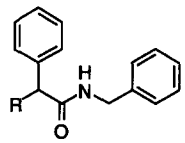


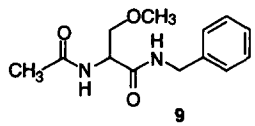

**Figure 2.**

Substitution of the *N*-acetyl group in **7** by hydrogen (**11**), methyl (**12**), hydroxy (**13**),[13] methoxy (**14**), acetoxy (**15**),[14] trifluoroacetoxy (**16**), methanesulfonato (**17**), chloro (**18**), bromo (**19**), and iodo (**20**) moieties provided the first series of compounds. Included in our list were the (*R*)- and (*S*)-stereoisomers of **13**[15] and **15**. These pairs of stereoisomers were prepared in light of our previous findings that the anticonvulsant activities for **2**, **5**, **7**, and **9** preferentially resided in the (*R*)-enantiomer.

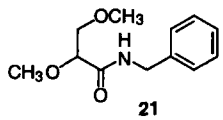


**7** R = $NHC(O)CH_3$ **16** R = $OC(O)CF_3$
**11** R = H **17** R = OMs
**12** R = $CH_3$ **18** R = Cl
**13** R = OH **19** R = Br
**14** R = $OCH_3$ **20** R = I
**15** R = $OC(O)CH_3$

The pharmacological results obtained for compounds **11**–**20** prompted us to prepare and evaluate dimethyl ether **21**. The corresponding reference compound for **21** was **9**.[10]



**9**

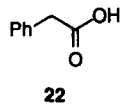


**21**

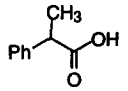
### Synthesis and structural characterization

Compounds **11** and **12** were prepared from commercially available phenylacetic acid (**22**) and 2-phenylpropionic acid (**23**), respectively, and benzylamine using the mixed anhydride coupling procedure[16] in 52–53% yields. Compounds **13**–**20** were synthesized from ethyl

(*R,S*)-mandelate (**24**) (Scheme 1). Reaction of **24** with benzylamide anion gave *N*-benzyl 2-hydroxy-2-phenylacetamide (**13**) in near quantitative yield.[13] Alcohol **13** was converted to the *O*-substituted derivatives **14–17** using standard procedures. The C(2) halogen derivatives **18–20** were synthesized from *O*-mesylate **17** and the appropriate tetrabutylammonium halide.[17] The low yield (10%) obtained for the 2-fluoro compound **25** did not permit us to readily synthesize the quantity (1 g) sufficient for pharmacological evaluation.




**22**

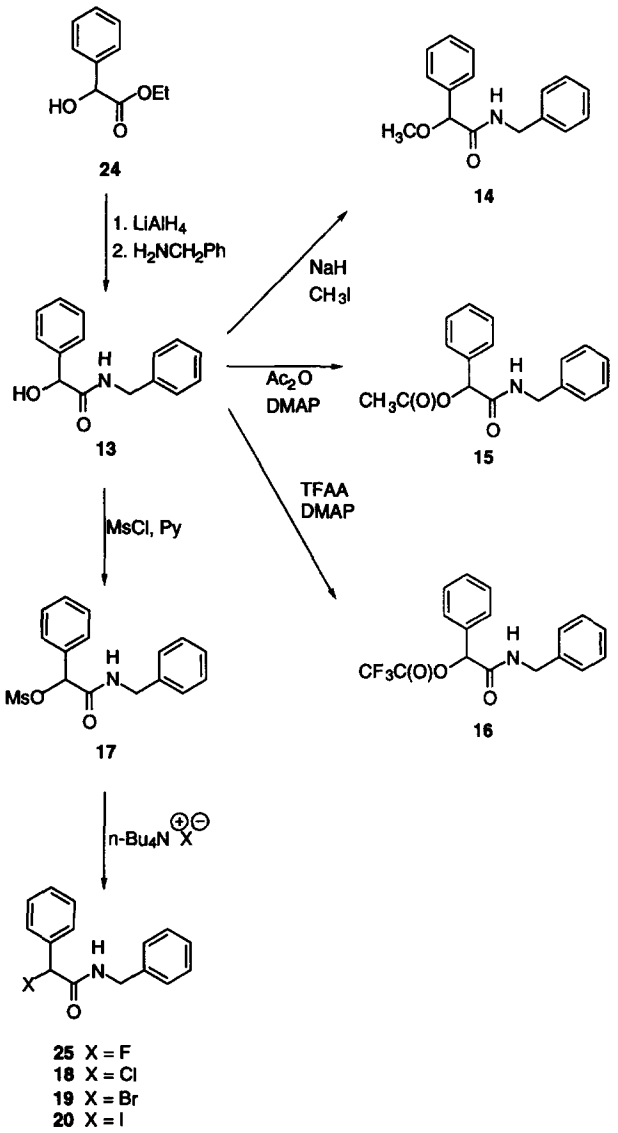



**23**

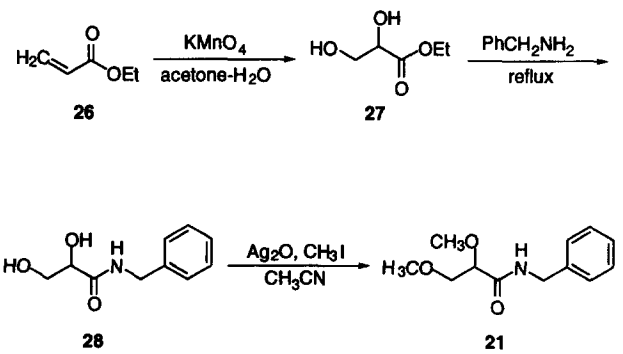
(*R*)-*N*-Benzyl 2-hydroxy-2-phenylacetamide ((*R*)-**13**) and (*S*)-*N*-benzyl 2-hydroxy-2-phenylacetamide ((*S*)-**13**) were prepared from commercially available ethyl (*R*)-(−)-mandelate ((*R*)-**24**), and ethyl (*S*)-(+)-mandelate ((*S*)-**24**), respectively, and *N*-benzylamide anion. Treatment of (*R*)-**13** and (*S*)-**13** with acetic anhydride and *N,N*-dimethylaminopyridine afforded (*R*)-**15** and (*S*)-**15**, respectively. Both sets of reactions proceeded without apparent racemization. The optical rotation observed for (*S*)-**13** corresponded to the reported value.[15] Addition of the chiral shift reagent,[7,10,18] tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) ($Eu(hfc)_3$), to deuteriochloroform solutions containing (*R*)-**15** and (*S*)-**15** gave only one signal for the acetyl protons while addition of $Eu(hfc)_3$ to (*R,S*)-**15** resulted in the appearance of two signals of equal height for the acetyl group ($\Delta$ ppm = 0.027).

Synthesis of **21** was accomplished from ethyl acrylate (**26**) in four steps in 19% overall yield (Scheme 2). Oxidation of **26** with $KMnO_4$ gave glycol **27** in 56% yield.[19] Treatment of **27** with *N*-benzylamine furnished **28**.[20] Conversion of **28** to dimethyl ether **21** was accomplished with methyl iodide and $Ag_2O$ in acetonitrile.

All compounds prepared in this study gave satisfactory IR, $^1H$, $^{13}C$ NMR, and mass spectral data and elemental analyses compatible with their proposed structures. In agreement with patterns reported in the literature,[21] we observed that the chemical shift value for the C(2) methine hydrogen in the $^1H$ NMR spectra for compounds **11–20** and **24** depended on the C(2) substituent. Significant downfield shifts ($\Delta$ ppm 0.91–1.24) were observed upon conversion of **13** to the acetyl derivatives **15** and **16**, and mesylate **17**. Correspondingly, the range for the C(2) proton chemical shift values for halogen adducts **18–20** and **25** was narrow (5.40–5.82 ppm). Characteristic patterns were also noted in the $^{13}C$ NMR spectra for the C(2) carbon signal in **11–20** and **25**. Conversion of the hydroxy group in **13** to **15**, **16**, and **17** led to only small changes in the chemical shift value. A progressive upfield shift (91.9–27.1 ppm) was detected for the halogen series




**Scheme 1.** Preparation of substituted *N*-benzyl 2-phenylacetamides.




**Scheme 2.** Preparation of compounds **21** and **28**.

**18–20** and **25** in proceeding from the C(2)-fluoro adduct **25** to the C(2)-iodo compound **20**. This trend is typical for halogen-substituted compounds.[22]

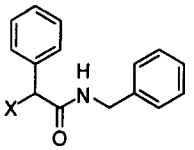
The observed spectral properties for compounds **21**, **27**, and **28** were compatible with the proposed structures. A key finding for **21** was the detection of two signals for the methoxy units at δ 3.40 and 3.48 in the $^1$H NMR spectrum and at 58.0 and 58.7 ppm in the $^{13}$C NMR spectrum.

## Pharmacological evaluation

The anticonvulsant activities for **13–20** (Table 1), and **21** and **28** (Table 2) were determined using the procedure described by Kupferberg[23] and the results compared with **7**,[5] and **9**,[10] and the clinically proven antiepileptic agents phenytoin,[24a] phenobarbital,[24b] and valproate.[24a] All compounds were administered intraperitoneally (ip) to mice. Tables 1 and 2 list the results obtained from the initial mouse identification and quantitation screening studies. They include the $ED_{50}$ value for **21**, which is protective in blocking hind limb extension induced in the MES test. Also contained in Tables 1 and 2 are the median doses for neurological impairment ($TD_{50}$) using the rotorod[25] test. The $TD_{50}$ levels were only determined for those compounds with good activity in the MES test. The protective indices ($PI = TD_{50}/ED_{50}$) for these adducts, where appropriate, are also shown in Tables 1 and 2.

The data for functionalized *N*-benzyl phenylacetamides (Table 1) showed that the racemic 2-hydroxy (**13**) and 2-methoxy (**14**) adducts provided full protection in mice against MES-induced seizures at doses below 100 mg/kg. Acylation (**15**, **16**) and mesylation (**17**) of the 2-hydroxy substituent in **13** or replacement of this moiety by a halogen (**18–20**) led to decreases in anticonvulsant activities ($ED_{50}$ >100, < 300 mg/kg). None of the compounds (**11–20**) evaluated in this study were as active as the reference compound, *N*-benzyl 2-acetamido-2-phenylacetamide (**7**). Examination of the individual stereoisomers for **13** indicated that the

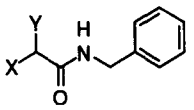
**Table 1.** Pharmacological data in mice for functionalized acetamide derivatives[a]




| Compound | X | mp[b] (°C) | MES[c] $ED_{50}$ | Tox[d] $TD_{50}$ | P.I.[e] |
|---|---|---|---|---|---|
| (*R,S*)-**7**[f] | $NHC(O)CH_3$ | 202–203 | 20 [0.5] (17–25) | 97 [0.5] (80–118) | 4.9 |
| **11** | H | 118–119 | >100, <300 [0.5] | >300 [0.5] | — |
| (*R,S*)-**12** | $CH_3$ | 76–77 | >100, <300 [0.5] | >100, <300 [0.5] | — |
| (*R,S*)-**13** | OH | 97–98 | >30, <100 [0.25] | >100 | — |
| (*R*)-**13** | OH | 133–134 | >30, <100 [0.25] | ~100 | — |
| (*S*)-**13** | OH | 133–134 | >100, <300 [0.5] | ~300 | — |
| (*R,S*)-**14** | $OCH_3$ | 80–81 | >30, <100 [0.5] | >100, <300 | — |
| (*R,S*)-**15** | $OC(O)CH_3$ | 89–90 | >100, <300 [0.5] | >100, <300 | — |
| (*R*)-**15** | $OC(O)CH_3$ | 63–64 | >100, <300 [0.5] | >100, <300 | — |
| (*S*)-**15** | $OC(O)CH_3$ | 64–66 | >100, <300 [0.5] | >100, <300 | — |
| (*R,S*)-**16** | $OC(O)CF_3$ | 123–125 | >100, <300 [0.5] | >300 | — |
| (*R,S*)-**17** | OMs | 90–92 | >100, <300 [0.5] | >100, <300 | — |
| (*R,S*)-**18** | Cl | 94–95 | >100, <300 [0.5] | >300 | — |
| (*R,S*)-**19** | Br | 97–98 | >100, <300 [0.5] | >300 | — |
| (*R,S*)-**20** | I | 119–120 | >300 [0.5] | >300 | — |
| | phenytoin[g] | | 6.5 [2] (5.7–7.2) | 43 [0.5] (36–48) | 6.6 |
| | phenobarbital[h] | | 22 [1] (15–23) | 69 [0.5] (63–73) | 3.1 |
| | valproate[g] | | 290 [0.25] (240–360) | 480 [0.25] (410–570) | 1.7 |

[a]The compounds were administered intraperitoneally. $ED_{50}$ and $TD_{50}$ values are in mg/kg. Numbers in parentheses are 95% confidence intervals. A dose–response curve was generated for all compounds that displayed sufficient activity. The dose effect data for these compounds was obtained at the 'time of peak effect' (indicated in hours in the brackets). The compounds were tested through the auspices of the National Institute of Neurological and Communicative Disorders and Stroke at the National Institutes of Health.
[b]Melting points are uncorrected.
[c]MES = maximal electroshock seizure test.
[d]Neurologic toxicity determined using the rotorod test.
[e]PI = protective index ($TD_{50}/ED_{50}$).
[f]Ref. 3.
[g]Ref. 24a.
[h]Ref. 24b.

**Table 2.** Pharmacological data in mice for compounds **21** and **28**[a]



| Compound | X | Y | mp[b] (°C) | MES[c] $ED_{50}$ | Tox[d] $TD_{50}$ | P.I.[e] |
|---|---|---|---|---|---|---|
| (*R,S*)-**9**[f] | $NHC(O)CH_3$ | $CH_2OCH_3$ | 121–122 | 8.3 | 43 | 5.2 |
| (*R,S*)-**21** | $OCH_3$ | $CH_2OCH_3$ | —[g] | 30 [0.25] (17–43) | 280 [0.25] (240–300) | 9.3 |
| (*R,S*)-**28** | OH | $CH_2OH$ | 83–84 | >100, <300 [0.5] | >300 | — |
| | phenytoin[h] | | | 6.5 [2] (5.7–7.2) | 43 [0.5] (36–48) | 6.6 |
| | phenobarbital[i] | | | 22 [1] (15–23) | 69 [0.5] (63–73) | 3.1 |
| | valproate[h] | | | 290 [0.25] (240–360) | 480 [0.25] (410–570) | 1.7 |

[a]The compounds were administered intraperitoneally. $ED_{50}$ and $TD_{50}$ values are in mg/kg. Numbers in parentheses are 95% confidence intervals. A dose–response curve was generated for all compounds that displayed sufficient activity. The dose effect data for these compounds was obtained at the 'time of peak effect' (indicated in hours in the brackets). The compounds were tested through the auspices of the National Institute of Neurological and Communicative Disorders and Stroke at the National Institutes of Health.
[b]Melting points are uncorrected.
[c]MES = maximal electroshock seizure test.
[d]Neurologic toxicity determined using the rotorod test.
[e]PI = protective index ($TD_{50}/ED_{50}$).
[f]Ref. 10.
[g]Oil.
[h]Ref. 24a.
[i]Ref. 24b.

anticonvulsant activity for this compound resided principally in the (*R*)-stereoisomer. The stereochemical specificity for **13** was reminiscent of the pronounced differences in activities previously observed for (*R*)- and (*S*)-**2**, **5**, **7**, and **9**.[1,4,7,10] No differences in activities were detected for the stereoisomers of the less active 2-acetoxy derivative **15**. These results lead us to conclude that the *N*-acetyl group in **1** is an important but not an obligatory structural unit for anticonvulsant activity.

To test this contention further we prepared *N*-benzyl 2,3-dimethoxypropionamide (**21**). This compound can be viewed as the *2-methoxy* analogue of *N*-benzyl *2-acetamido*-3-methoxypropionamide (**9**). Compound **9** displayed outstanding anticonvulsant activity in mice ($ED_{50}$ = 8.3 mg/kg, ip).[10] We observed that **21** provided full protection against MES-induced seizures in mice (ip) at doses below 100 mg/kg and possessed an $ED_{50}$ value of 30 mg/kg. The significant anticonvulsant activity observed for **21** coupled with its low neurological toxicity ($TD_{50}$ = 280 mg/kg) provided a PI value of 9.3. These values compared favorably with those previously reported for phenobarbital ($ED_{50}$ = 22 mg/kg; $TD_{50}$ = 69 mg/kg; PI = 3.1).[24b]

## Conclusions

We have determined that the *N*-acyl group in functionalized amino acids **1** is an important structural unit for maximal anticonvulsant activity but that other substituents can provide significant protection against MES-induced seizures. Pharmacological advantages that may accrue with the replacement of the *N*-acyl group in **1** by other entities may include tighter drug-receptor binding, enhanced metabolic stabilities, and improved biodistribution. The mechanism of action of **1** and structurally related compounds is currently being investigated.

## Experimental

### General methods

Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. IR spectra were run on a ATI Mattson Genesis Series FTIR™ spectrometer. Absorption values are expressed in wavenumbers ($cm^{-1}$). $^1H$ and $^{13}C$ NMR spectra were taken on a General Electric QE-300 NMR instrument. Chemical shifts (δ) are in parts per million (ppm) relative to tetramethylsilane and coupling constants (*J* values) are in Hertz. Low resolution mass spectra (+CI) were obtained with a Varian MAT CH-5 spectrometer by Dr M. Moini at the University of Texas–Austin. The high-resolution CI-MS was performed on a Finnigan MAT TSQ-70 by Dr M. Moini at the University of Texas–Austin. Microanalyses were provided by Atlantic Microlab, Inc (Norcross, GA). Thin-layer chromatography (TLC) was performed on precoated silica gel GHLF microscope slides (2.5 × 10 cm; Analtech No. 21521).

**Synthesis of *N*-benzyl 2-phenylacetamide (11).** To a tetrahydrofuran (THF) soln (150 mL) containing **22**

(2.72 g, 20 mmol) was successively added 4-methylmorpholine (2.42 mL, 22 mmol), isobutyl chloroformate (2.85 mL, 22 mmol), and benzylamine (2.40 mL, 22 mmol) at room temperature. The reaction was stirred at room temperature (0.5 h), and then the insoluble salts filtered, and the solvent removed in vacuo. The product was triturated (ether) to give 2.40 g (53%) of **11** as a white solid: mp 118–119 °C; $R_f$ 0.45 (50% EtOAc:hexanes); IR (KBr) 3288, 3083, 3063, 3030, 1637, 1553, 1453, 1028, 725, 693 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.46 (s, $CH_2$), 4.25 (d, $J=6.0$ Hz, $CH_2$), 7.20–7.32 (m, 10 PhH), 8.55 (t, $J=6.0$ Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 42.2 ($CH_2$), 42.4 ($CH_2$), 126.3, 126.8, 127.0, 128.2, 128.3, 129.0, 136.4, 139.5 (Ph), 170.1 (C(O)) ppm; MS, ($CI^+$) (rel. int.) 226 ($M^+ + 1$, 100), 154 (18); $M_r$ (+CI) 226.122 64 [$M^+ + 1$] (calcd for $C_{15}H_{16}NO$ 226.123 19). Anal. calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.85; H, 6.76; N, 6.19.

**Synthesis of (*R,S*)-*N*-benzyl 2-methyl-2-phenylacetamide (12).** The procedure for **11** was used utilizing **23** (2.73 mL, 20 mmol), 4-methylmorpholine (2.42 mL, 22 mmol), isobutyl chloroformate (2.85 mL, 22 mmol), and benzylamine (2.40 mL, 22 mmol) to give 2.50 g (52%) of **12** as a white solid: mp 76–77 °C; $R_f$ 0.37 (20% EtOAc:hexanes); IR (KBr) 3308, 3085, 3064, 3029, 1648, 1555, 1451, 731, 698 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.34 (d, $J=6.9$ Hz, $CH_3$), 3.65 (q, $J=6.9$ Hz, CH), 4.23 (d, $J=5.7$ Hz, $CH_2$), 7.13–7.33 (m, 10 PhH), 8.46 (t, $J=5.7$ Hz, NH); $^{13}C$ NMR (DMSO-$d_6$): 18.5 ($CH_3$), 42.0 ($CH_2$), 45.1 (CH), 126.4, 126.6, 127.0, 127.2, 128.1, 139.5, 142.2 (Ph), 173.2 (C(O)) ppm, one aromatic carbon signal was not detected and is believed to overlap with the observed peaks; MS, ($CI^+$) (rel. int.) 240 ($M^+ + 1$, 79), 153 (100); $M_r$ (+CI) 240.139 66 [$M^+ + 1$] (calcd for $C_{16}H_{18}NO$ 240.138 84). Anal. calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.22; H, 7.24; N, 5.77.

**Synthesis of (*R,S*)-*N*-benzyl 2-hydroxy-2-phenylacetamide ((*R,S*)-13).** A suspension of $LiAlH_4$ (1.20 g, 30 mmol) in anhydrous THF (40 mL) was heated at reflux (1.5 h), cooled to room temperature, and then benzylamine (16.4 mL, 150 mmol) was added dropwise with stirring. The reaction was maintained at room temperature until precipitation was complete (~30 min). A THF (15 mL) soln of (*R,S*)-**24** (5.57 g, 30.0 mmol) was added to the suspension and the mixture was stirred at room temperature (20 h) until the reaction became homogeneous. The reaction was carefully quenched by successive addition of $H_2O$ (1 mL), aq. 10% NaOH (1 mL), and $H_2O$ (3 mL) leading to the precipitation of a powdery white solid. The reaction was filtered, the precipitate washed with $CH_2Cl_2$ (200 mL), and the organic phase was dried ($MgSO_4$) and concd in vacuo to give a solid residue. The solid residue was successively washed with petroleum ether (200 mL), $Et_2O$ (50 mL), petroleum ether (100 mL), and $Et_2O$ (100 mL) to give 3.70 g (51%) of **13**: mp 97–98 °C (lit.[13b] mp 99–100 °C); $R_f$ 0.50 (50% EtOAc:hexanes); IR (KBr) 3406, 3184, 1649, 1536, 1452, 1288, 1238, 1059 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 4.27 (d, $J=6.0$ Hz, $CH_2$), 4.97 (d, $J=3.3$ Hz, CH), 6.20 (d, $J=3.3$ Hz, OH), 7.20–7.43 (m, 10 PhH), 8.52 (t, $J=6.0$ Hz, NH); $^{13}C$ NMR (DMSO-$d_6$): 41.8 ($CH_2$), 73.6 (CH), 126.5, 126.7, 127.1, 127.4, 127.9, 128.2, 139.6, 141.3 (Ph), 172.2 (C(O)) ppm; MS, ($CI^+$) (rel. int.) 242 ($M^+ + 1$, 87), 224 (57), 196 (100); $M_r$ (+CI) 242.117 43 [$M^+ + 1$] (calcd for $C_{15}H_{16}NO_2$ 242.118 10). Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.72; H, 6.26; N, 5.81. Found: C, 74.73; H, 6.29; N, 5.86.

**Synthesis of (*R*)-*N*-benzyl 2-hydroxy-2-phenylacetamide ((*R*)-13).** The procedure utilized for the preparation of (*R,S*)-**13** was repeated using $LiAlH_4$ (1.00 g, 25 mmol), benzylamine (13.7 mL, 125 mmol), and (*R*)-**24** (4.04 mL, 25 mmol) to give 5.60 g (93%) of (*R*)-**13**: mp 133–134 °C; $[\alpha]^{23}_D$ (*c* 1.09, $CHCl_3$) −78.7°; $R_f$ 0.50 (50% EtOAc:hexanes); IR (KBr) 3406, 3186, 1649, 1536, 1452, 1282, 1095 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 4.26 (d, $J=6.0$ Hz, $CH_2$), 4.95 (d, $J=4.5$ Hz, CH), 6.19 (d, $J=4.5$ Hz, OH), 7.18–7.43 (m, 10 PhH), 8.53 (t, $J=6.0$ Hz, NH); $^{13}C$ NMR (DMSO-$d_6$): 41.8 ($CH_2$), 73.6 (CH), 126.5, 126.6, 127.1, 127.3, 127.9, 128.1, 139.5, 141.3 (Ph), 172.2 (C(O)) ppm; MS, ($CI^+$) (rel. int.) 242 ($M^+ + 1$, 100), 224 (15), 196 (11); $M_r$ (+CI) 242.117 62 [$M^+ + 1$] (calcd for $C_{15}H_{16}NO_2$ 242.118 10). Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.46; H, 6.31; N, 5.88.

**Synthesis of (*S*)-*N*-benzyl 2-hydroxy-2-phenylacetamide[15] ((*S*)-13).** The procedure utilized for the preparation of (*R,S*)-**13** was repeated using $LiAlH_4$ (1.00 g, 25 mmol), benzylamine (13.7 mL, 125 mmol), and (*S*)-**24** (4.04 mL, 25 mmol) to give 5.40 g (90%) of (*S*)-**13**: mp 133–134 °C; $[\alpha]^{23}_D$ (*c* 1.09, $CHCl_3$) +78.6° (lit.[15] $[\alpha]^{23}_D$ +79.9 (*c* 1.09, $CHCl_3$)); $R_f$ 0.50 (50% EtOAc:hexanes); IR (KBr) 3406, 3181, 1649, 1536, 1443, 1287, 1065, 757, 705 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 4.26 (d, $J=6.0$ Hz, $CH_2$), 4.95 (d, $J=3.6$ Hz, CH), 6.19 (d, $J=3.6$ Hz, OH), 7.18–7.43 (m, 10 PhH), 8.52 (t, $J=6.0$ Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 41.8 ($CH_2$), 73.6 (CH), 126.5, 126.6, 127.1, 127.4, 127.9, 128.1, 139.6, 141.3 (Ph), 172.2 (C(O)) ppm; MS, ($CI^+$) (rel. int.) 242 ($M^+ + 1$, 100), 224 (23), 196 (7); $M_r$ (+CI) 242.118 16 [$M^+ + 1$] (calcd for $C_{15}H_{16}NO_2$ 242.118 10). Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.58; H, 6.31; N, 5.85.

**Synthesis of (*R,S*)-*N*-benzyl 2-methoxy-2-phenylacetamide (14).** Compound (*R,S*)-**13** (2.41 g, 10.0 mmol) was dissolved in THF (50 mL) and then NaH (0.48 g, 12.0 mmol) was added at room temperature. After the $H_2$ evolution ceased (20 min), MeI was slowly added, and the reaction mixture was stirred at room temperature (1 h). The reaction mixture was concd under reduced pressure and the resulting residue purified by flash column chromatography (50% ethyl acetate:hexanes) to give 1.45 g (57%) of **14**: mp 80–81 °C; $R_f$ 0.28 (25% EtOAc:hexanes); IR (KBr) 3386, 3300, 3032, 2929, 1698, 1659, 1526, 1453, 1090, 746, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 3.35 (s, $OCH_3$), 4.40–4.53 (m, $CH_2$),

4.68 (s, CH), 7.06 (br s, NH), 7.26–7.42 (m, 10 PhH); $^{13}$C NMR ($CDCl_3$): δ 43.0 ($CH_2$), 57.2 ($OCH_3$), 83.8 (CH), 127.0, 127.5, 127.8, 128.5, 128.6, 128.7, 137.0, 138.1 (Ph), 170.5 (C(O)) ppm; MS, ($CI^+$) (rel. int.) 256 ($M^+ + 1$, 100), 224 (17), 196 (5); $M_r$ (+CI) 256.133 17 [$M^+ + 1$] (calcd for $C_{16}H_{18}NO_2$ 256.133 75). Anal. calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48. Found: C, 75.16; H, 6.72; N, 5.53.

**Synthesis of (*R,S*)-*N*-benzyl 2-acetoxy-2-phenylacetamide[14] ((*R,S*)-15).** Compound (*R,S*)-**13** (1.93 g, 8.0 mmol) was dissolved in $CH_2Cl_2$ (25 mL) and then 4-*N,N*-dimethylaminopyridine (1.63 g, 13.4 mmol), and acetic anhydride (1.06 mL, 11.2 mmol) were added at room temperature, and the reaction mixture was stirred at room temperature (0.5 h). The mixture was concd in vacuo and then $H_2O$ (20 mL) and $Et_2O$ (50 mL) were added to the resulting residue. The $Et_2O$ layer was separated and successively washed with aq. 5% citric acid (100 mL) and aq satd $NaHCO_3$ (100 mL) solns. The $Et_2O$ layer was dried ($MgSO_4$) and concd in vacuo to give **15** (2.20 g, 97%): mp 89–90 °C (lit.[14] mp 90–91 °C); $R_f$ 0.50 (50% EtOAc:hexanes); IR (KBr) 3327, 3063, 2944, 1742, 1657, 1530, 1224, 1046, 748 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 2.12 (s, C(O)$CH_3$), 4.25 (dd, $J$=5.7, 15.3 Hz, C*H*H′), 4.32 (dd, $J$=5.7, 15.3 Hz, CHH′), 5.88 (s, CH), 7.13–7.49 (m, 10 PhH), 8.81 (t, $J$=5.7 Hz, NH), addition of Eu(hfc)$_3$ to a $CDCl_3$ soln containing (*R,S*)-**15** gave two signals of equal height for the acetyl groups at δ 2.60 and 2.58; $^{13}$C NMR (DMSO-$d_6$): δ 20.7 (C(O)$CH_3$), 41.8 ($CH_2$), 75.1 (CH), 126.7, 126.9, 127.3, 128.2, 128.4, 128.6, 135.8, 139.0 (Ph), 168.1 (C(O)NH or C(O)$CH_3$), 169.7 (C(O)NH or C(O)$CH_3$) ppm; MS, ($CI^+$) (rel. int.) 284 ($M^+ + 1$, 16), 224 (82), 196 (100); $M_r$ (+CI) 284.127 97 [$M^+ + 1$] (calcd for $C_{17}H_{18}NO_3$ 284.128 67). Anal. calcd for $C_{17}H_{17}NO_3$: C, 72.12; H, 6.05; N, 4.95. Found: C, 71.95; H, 6.07; N, 4.86.

**Synthesis of (*R*)-*N*-benzyl 2-acetoxy-2-phenylacetamide ((*R*)-15).** Utilizing the procedure for (*R,S*)-**15** and using (*R*)-**13** (1.69 g, 7 mmol), 4-*N,N*-dimethylaminopyridine (1.43 g, 11.69 mmol), and acetic anhydride (0.93 mL, 9.8 mmol) gave a product that was further purified by recrystallization ($Et_2O$) to give 1.55 g (78%) of (*R*)-**15**: mp 63–64 °C; $[\alpha]_D^{23}$ (*c* 1.09, $CHCl_3$) −111.2 °; $R_f$ 0.50 (50% EtOAc:hexanes); IR (KBr) 3296, 3063, 3011, 1736, 1655, 1541, 1235, 757, 695 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 2.13 (s, C(O)$CH_3$), 4.22 (dd, $J$=5.4, 15.3 Hz, C*H*H′), 4.32 (dd, $J$=6.0, 15.3 Hz, CH*H*′), 5.87 (s, CH), 7.13–7.49 (m, 10 PhH), 8.82 (dd, $J$=5.4, 6.0 Hz, NH), addition of Eu(hfc)$_3$ to a $CDCl_3$ soln containing (*R*)-**15** gave only one signal for the acetyl proton at δ 2.60; $^{13}$C NMR (DMSO-$d_6$): δ 20.6 (C(O)C$H_3$), 41.8 ($CH_2$), 75.1 (CH), 126.7, 126.9, 127.3, 128.1, 128.3, 128.5, 135.8, 139.0 (Ph), 168.0 (C(O)NH or C(O)$CH_3$), 169.7 (C(O)NH or C(O)$CH_3$) ppm; MS, ($CI^+$) (rel. int.) 284 ($M^+ + 1$, 100), 224 (20); $M_r$ (+CI) 284.127 72 [$M^+ + 1$] (calcd for $C_{17}H_{18}NO_3$ 284.128 67). Anal. calcd for $C_{17}H_{17}NO_3$: C, 72.12; H, 6.05; N, 4.95. Found: C, 72.12; H, 6.10; N, 4.96.

**Synthesis of (*S*)-*N*-benzyl 2-acetoxy-2-phenylacetamide ((*S*)-15).** Utilizing the procedure for the preparation of (*R,S*)-**15** and using (*S*)-**13** (1.69 g, 7 mmol), 4-*N,N*-dimethylaminopyridine (1.43 g, 11.69 mmol), and acetic anhydride (0.93 mL, 9.8 mmol) gave a product that was further purified by recrystallization ($Et_2O$) to give 1.50 g (76%) of (*S*)-**15**: mp 64–66 °C; $[\alpha]_D^{23}$ (*c* 1.09, $CHCl_3$) +107.4 °; $R_f$ 0.50 (50% EtOAc-hexanes); IR (KBr) 3296, 3063, 2930, 1736, 1655, 1541, 1235, 757, 699 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 2.13 (s, C(O)$CH_3$), 4.21 (dd, $J$=5.4, 15.3 Hz, C*H*H′), 4.32 (dd, $J$=6.0, 15.3 Hz, CH*H*′), 5.86 (s, CH), 7.13–7.49 (m, 10 PhH), 8.83 (dd, $J$=5.4, 6.0 Hz, NH), addition of Eu(hfc)$_3$ to a $CDCl_3$ soln containing (*S*)-**15** gave only one signal for the acetyl proton at δ 2.58; $^{13}$C NMR (DMSO-$d_6$): δ 20.6 (C(O)$CH_3$), 41.9 ($CH_2$), 75.1 (CH), 126.7, 126.9, 127.3, 128.2, 128.3, 128.5, 135.8, 139.0 (Ph), 168.1 (C(O)NH or C(O)$CH_3$), 169.7 (C(O)NH or C(O)$CH_3$) ppm; MS, ($CI^+$) (rel. intensity) 284 ($M^+ + 1$, 100), 224 (27); $M_r$ (+CI) 284.127 63 [$M^+ + 1$] (calcd for $C_{17}H_{18}NO_3$ 284.128 67). Anal. calcd for $C_{17}H_{17}NO_3$: C, 72.12; H, 6.05; N, 4.95. Found: C, 72.12; H, 6.07; N, 4.97.

**Synthesis of (*R,S*)-*N*-benzyl 2-trifluoroacetoxy-2-phenylacetamide (16).** Utilizing the procedure for (*R,S*)-**15** and using (*R,S*)-**13** (2.02 g, 8.4 mmol), 4-*N,N*-dimethylaminopyridine (1.03 g, 8.4 mmol), and trifluoroacetic anhydride (1.19 mL, 8.4 mmol) gave 2.50 g of **16** after recrystallization with $Et_2O$:hexanes; mp 123–125 °C; $R_f$ 0.50 (50% EtOAc:hexanes); IR (KBr) 3186, 3030, 2940, 2896, 1649, 1537, 1453, 1288, 1239, 1066, 758, 706 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 4.46 (dd, $J$=5.7, 15.0 Hz, C*H*H′), 4.54 (dd, $J$=5.7, 15.0 Hz, CH*H*′), 6.21 (s, CH), 6.26 (br s, NH), 7.20–7.56 (m, 10 PhH); $^{13}$C NMR ($CDCl_3$): δ 43.6 ($CH_2$), 78.4 (CH), 114.4 (q, $J_{CF}$=284.7 Hz, OC(O)$CF_3$), 127.6, 127.8, 128.9, 129.2, 130.0, 133.1, 137.2 (Ph), 156.0 (q, $J_{CF}$=42.2 Hz, OC(O)$CF_3$), 166.1 (C(O)) ppm, one aromatic carbon signal was not detected and is believed to overlap with one of the observed peaks; MS, ($CI^+$) (rel. int.) 338 ($M^+ + 1$, 8), 224 (100), 196 (88); $M_r$ (+CI) 338.099 28 [$M^+ + 1$] (calcd for $C_{17}H_{15}F_3NO_3$ 338.100 40). Anal. calcd for $C_{17}H_{14}F_3NO_3 \cdot 0.2H_2O$: C, 59.90; H, 4.25; N, 4.11. Found: C, 59.86; H, 4.29; N, 4.10.

**Synthesis of (*R,S*)-*N*-benzyl 2-methanesulfonato-2-phenylacetamide (17).** Compound (*R,S*)-**13** (2.41 g, 10.0 mmol) was dissolved in pyridine (5 mL) and then methanesulfonyl chloride (1.94 mL, 25.0 mmol) was added at room temperature, and the reaction soln was stirred at room temperature (0.5 h). The mixture was concd in vacuo and then $H_2O$ (150 mL) and EtOAc (200 mL) were added to the residue. The organic layer was sepd and washed with $H_2O$ (150 mL). The organic layer was dried ($MgSO_4$) and concd in vacuo. The residue was triturated with $Et_2O$ (200 mL) and hexanes (100 mL) to give 2.64 g (83%) of **17**: mp 90–92 °C; $R_f$ 0.65 (50% EtOAc:hexanes); IR (KBr) 3358, 3302, 3026, 2934, 1666, 1525, 1354, 1177, 961, 849, 740, 698 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.76 (s, OS($O_2$)$CH_3$), 4.45

(dd, $J$=5.7, 15.0 Hz, C*H*H'), 4.55 (dd, $J$=6.0, 15.0 Hz CH*H'*), 5.92 (s, CH), 6.84 (br s, NH), 7.25–7.46 (m, 10 PhH); $^{13}$C NMR ($CDCl_3$): δ 39.4 ($OS(O_2)CH_3$), 43.6 ($CH_2$), 81.5 (CH), 127.8, 127.9, 128.8, 129.2, 130.0, 134.0, 137.3 (Ph), 166.7 (C(O)) ppm, one aromatic carbon signal was not detected and is believed to overlap with one of the observed peaks; MS, ($CI^+$) (rel. int.) 320 ($M^+$+1, 31), 224 (100), 196 (38); $M_r$ (+CI) 320.095 62 [$M^+$+1] (calcd for $C_{16}H_{18}NO_4S$ 320.095 66). Anal. calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36; N, 4.39. Found: C, 60.31; H, 5.43; N, 4.34.

**Synthesis of (*R,S*)-*N*-benzyl 2-chloro-2-phenylacetamide (18).** To a benzene soln (100 mL) containing (*R,S*)-**17** (1.92 g, 7 mmol) was added tetrabutylammonium chloride (4.58 g, 14 mmol), and the reaction mixture was heated at reflux (2 h). The mixture was concd in vacuo and then $H_2O$ (250 mL) and $Et_2O$ (100 mL) were added to the resulting residue. The organic layer was sepd and washed with $H_2O$ (100 mL). The organic layer was dried ($MgSO_4$) and concd in vacuo. The resulting white solid was triturated with hexanes (100 mL) to give 1.50 g (83%) of **18**: mp 94–95 °C; $R_f$ 0.36 (25% EtOAc:hexanes); IR (KBr) 3333, 3031, 2930, 1649, 1536, 1452, 730 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 4.48 (d, $J$=5.7 Hz, $CH_2$), 5.40 (s, CH), 7.08 (br s, NH), 7.25–7.43 (m, 10 PhH); $^{13}$C NMR (DMSO-$d_6$): 44.0 ($CH_2$), 61.7 (CH), 127.7, 128.8, 128.9, 129.1, 137.0, 137.4 (Ph), 167.3 (C(O)) ppm, two aromatic carbon signals were not detected and are believed to overlap with the observed peaks; MS, ($CI^+$) (rel. int.) 262 ($M^+$+1, 40), 260 ($M^+$+1, 100), 224 (53), 196 (8); $M_r$ (+CI) 260.084 07 [$M^+$+1] (calcd for $C_{15}H_{15}ClNO$ 260.084 22). Anal. calcd for $C_{15}H_{14}ClNO$: C, 69.37; H, 5.43; N, 5.39. Found: C, 69.11; H, 5.47; N, 5.34.

**Synthesis of (*R,S*)-*N*-benzyl 2-bromo-2-phenylacetamide (19).** Using the procedure for **18** and utilizing (*R,S*)-**17** (1.92 g, 7 mmol) and tetrabutylammonium bromide (4.51 g, 14 mmol) gave 1.75 g (82%) of **19**: mp 97–98 °C; $R_f$ 0.36 (25% EtOAc:hexanes); IR (KBr) 3287, 3064, 3028, 2929, 1659, 1543, 1453, 1234, 693 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 4.51 (d, $J$=5.4 Hz, $CH_2$), 5.48 (s, CH), 6.94 (br s, NH), 7.21–7.43 (m, 10 PhH); $^{13}$C NMR ($CDCl_3$): δ 44.2 ($CH_2$), 51.0 (CH), 127.6, 128.3, 128.7, 128.9, 129.0, 137.2, 137.3 (Ph), 167.1 (C(O)) ppm, one aromatic carbon signal was not detected and is believed to overlap with one of the observed peaks; MS, ($CI^+$) (rel. int.) 306 ($M^+$+1, 67), 304 ($M^+$+1, 70), 224 (100), 196 (6); $M_r$ (+CI) 304.034 83 [$M^+$+1] (calcd for $C_{15}H_{15}{}^{79}BrNO$ 304.033 70). Anal. calcd for $C_{15}H_{14}BrNO$: C, 59.23; H, 4.64; N, 4.60. Found: C, 59.31; H, 4.62; N, 4.57.

**Synthesis of (*R,S*)-*N*-benzyl 2-iodo-2-phenylacetamide (20).** Using the procedure for **18** and utilizing (*R,S*)-**17** (1.92 g, 7 mmol) and tetrabutylammonium iodide (5.17 g, 14 mmol) gave 1.20 g (49%) of **20** after purification by flash column chromatography (20% EtOAc:hexanes): mp 119–120 °C dec; $R_f$ 0.36 (25% EtOAc:hexanes); IR (KBr) 3295, 3263, 3064, 3027, 1651, 1548, 1525, 1452, 1220, 1122, 749, 694 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 4.47 (d, $J$=5.7 Hz, $CH_2$), 5.63 (s, CH), 6.36 (br s, NH), 7.24–7.55 (m, 10 PhH); $^{13}$C NMR ($CDCl_3$) 27.1 (CH), 44.6 ($CH_2$), 127.7, 128.8, 129.0, 137.5, 138.4 (Ph), 168.2 (C(O)) ppm, three aromatic carbon signals were not detected and are believed to overlap with the observed peaks; MS, ($CI^+$) (rel. int.) 352 ($M^+$+1, 100), 224 (66); $M_r$ (+CI) 352.019 75 [$M^+$+1] (calcd for $C_{15}H_{15}INO$ 352.019 84). Anal. calcd for $C_{15}H_{14}INO \cdot 0.6H_2O$: C, 49.77; H, 4.23; N, 3.87. Found: C, 49.45; H, 3.83; N, 3.78.

**Synthesis of (*R,S*)-*N*-benzyl 2-fluoro-2-phenylacetamide (25).** Compound (*R,S*)-**17** (0.32 g, 1 mmol) was dissolved in benzene (10 mL) and then tetrabutylammonium fluoride (0.63 g, 2 mmol) was added at room temperature. The reaction mixture was stirred at room temperature (0.5 h), and then concd in vacuo. The resulting residue was purified by preparative TLC (2×) (25% EtOAc:hexanes) to give 26 mg (10%) of **25**: mp 93–95 °C; $R_f$ 0.46 (25% EtOAc:hexanes); IR (KBr) 3312, 3063, 3032, 2926, 1659, 1545, 1455, 1034, 729, 694 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 4.52 (d, $J$=4.8 Hz, $CH_2$), 5.82 (d, $J_{CF}$=48.3 Hz, CH), 6.78 (br s, NH), 7.23–7.38 (m, 10 PhH); $^{13}$C NMR ($CDCl_3$): δ 43.2 ($CH_2$), 91.9 (d, $J_{CF}$=186.4 Hz, CH), 126.5, 126.6, 127.8, 128.7, 128.8, 129.4, 134.8 (d, $J_{CF}$=40.1 Hz), 137.4 (Ph), 168.4 (d, $J_{CF}$=21.5 Hz, C(O)) ppm; MS, ($CI^+$) (rel. intensity) 244 ($M^+$+1, 100), 224 (15), 196 (5); $M_r$ (+CI) 244.114 13 [$M^+$+1] (calcd for $C_{15}H_{15}FNO$ 244.113 77).

**Synthesis of ethyl (*R,S*)-glycerate[19] (27).** $KMnO_4$ (15.65 g, 99 mmol) was dissolved in $H_2O$ (150 mL) and acetone (300 mL) and then cooled to −78 °C. Ethyl acrylate (**26**) (9.75 mL, 90 mmol) was slowly added with stirring at −78 °C, and then the reaction mixture was allowed to warm up to 0 °C. The inorganic salts were removed by filtration and washed with acetone (150 mL). The combined filtrates were concd under red pressure at temperatures below 40 °C. The product was extracted using EtOAc (3×200 mL), dried ($Na_2SO_4$), and then the solvent was removed under reduced pressure to afford **27** as a white oil (6.70 g, 56%): $R_f$ 0.60 (30% MeOH:$CHCl_3$); $^1$H NMR ($CDCl_3$): δ 1.32 (t, $J$=7.2 Hz, $OCH_2CH_3$), 2.31 (br s, OH), 3.27 (br s, OH), 3.85 (dd, $J$=3.0, 11.7 Hz, CHH'OH), 3.91 (dd, $J$=3.3, 11.7 Hz, CH*H'*OH), 4.25–4.27 (m, CH), 4.29 (q, $J$=7.2 Hz, $OCH_2CH_3$); $^{13}$C NMR ($CDCl_3$): δ 13.6 ($OCH_2CH_3$), 61.1 ($OCH_2CH_3$), 63.7 ($CH_2OH$), 71.6 (CHOH), 172.5 (C(O)) ppm.

**Synthesis of (*R,S*)-*N*-benzyl 2,3-dihydroxypropionamide[20] (28).** To **27** (6.71 g, 50 mmol) was added benzylamine (5.74 mL, 100 mmol), and then the reaction soln was stirred at 100 °C (18 h). The excess benzylamine was removed in vacuo and the residue triturated with $CHCl_3$ (100 mL) to solidify the product. The mixture was filtered to give **28** as a white solid (6.30 g, 65%): mp 83–84 °C; $R_f$ 0.37 (10% MeOH:$CHCl_3$); IR (KBr) 3408, 3294, 3033, 2926, 1627, 1531, 1426, 1103, 1067, 730 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 3.40–3.51 (m, C*H*H'OH), 3.57–3.63 (m,

CH*H'*OH), 3.89–3.94 (m, CHOH), 4.28 (d, $J=6.3$ Hz, C*H*$_2$NH), 4.72 (t, $J=5.7$ Hz, CH$_2$O*H*), 5.55 (d, $J=5.4$ Hz, CHO*H*), 7.12–7.32 (m, 5 PhH), 8.22 (t, $J=6.3$ Hz, CH$_2$N*H*); $^{13}$C NMR (DMSO-$d_6$): δ 41.7 ($CH_2NH$), 63.9 ($CH_2OH$), 73.1 (CHOH), 126.6 ($C_4'$), 127.1 ($2C_2'$ or $2C_3'$), 128.1 ($2C_2'$ or $2C_3'$), 139.6 ($C_1'$), 172.2 (C(O)) ppm; MS, ($CI^+$) (rel. int.) 196 ($M^+ + 1$, 100); $M_r$ (+CI) 196.097 51 [$M^+ + 1$] (calcd for $C_{10}H_{14}NO_3$ 196.097 37). Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.57; H, 6.71; N, 7.18. Found: C, 61.68; H, 6.76; N, 7.18.

**Synthesis of (*R,S*)-*N*-benzyl 2,3-dimethoxypropionamide (21).** $Ag_2O$ (9.27 g, 40 mmol) and MeI (4.98 mL, 80 mmol) were added at room temperature to a stirred acetonitrile soln (50 mL) of **28** (1.56 g, 8 mmol), and then the reaction mixture was stirred at room temperature (2 d). The insoluble salts were filtered, and the solvent was removed in vacuo. The product was purified by flash column chromatography (EtOAc), and then further purified by distillation under red pressure (147 °C/0.8 Torr) to give **21** as a white oil (1.20 g, 67%): $R_f$ 0.67 (5% MeOH:$CHCl_3$); IR (KBr) 3419, 3319, 2931, 1661, 1529, 1454, 1131, 1108, 735, 701 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 3.40 (br s, $CH_2OCH_3$), 3.48 (br s, $CHOCH_3$), 3.70 (dd, $J=4.5$, 10.5 Hz, C*H*H'OCH$_3$), 3.79 (dd, $J=2.4$, 10.5 Hz, CH*H'*OCH$_3$), 3.87 (dd, $J=2.4$, 4.5 Hz, CH), 4.50 (d, $J=6.0$ Hz, C*H*$_2$NH), 6.98 (br s, $CH_2NH$), 7.25–7.36 (m, 5 PhH); $^{13}$C NMR ($CDCl_3$) 42.3 ($CH_2NH$), 58.0 ($CH_2OCH_3$ or $CHOCH_3$), 58.7 ($CH_2OCH_3$ or $CHOCH_3$), 71.8 ($CH_2OCH_3$), 81.3 ($CHOCH_3$), 126.8 ($C_4'$), 126.9 ($2C_2'$ or $2C_3'$), 128.0 ($2C_2'$ or $2C_3'$), 137.7 ($C_1'$), 169.4 (C(O)) ppm; MS, ($CI^+$) (rel. int.) 224 ($M^+ + 1$, 100); $M_r$ (+CI) 224.128 47 [$M^+ + 1$] (calcd for $C_{12}H_{18}NO_3$ 224.128 67). Anal. calcd for $C_{12}H_{17}NO_3 \cdot 0.33H_2O$: C, 62.91; H, 7.77; N, 6.11. Found: C, 63.12; H, 7.65; N, 6.09.

**Pharmacology.** Compounds were screened under the auspices of the National Institutes of Health for anticonvulsant activity in male albino Carthworth Farms No. 1 mice (ip route). Activity was established using the electrical (maximal electroshock or MES) test.[26] In the MES test, a drop of electrolyte solution with anesthetic (0.5% butacaine hemisulfate in 0.9% sodium chloride) was used in the eyes of the animals prior to positioning the corneal electrodes and delivery of current. A 60 cycle alternating current was administered for 0.2 s at 50 mA.[27] Protection endpoints were defined as the abolition of the hind limb tonic extensor component of the induced seizure. The effects of compounds on forced spontaneous motor activity were determined using the rotorod test. The inability of animals to maintain their balance for 1 min on a 1 inch diameter knurled rod rotating at 6 rpms in three successive trials demonstrated motor impairment. Normally under these conditions, a mouse can maintain its balance almost indefinitely. In the mouse identification screening study all compounds were given at three dose levels (30, 100, and 300 mg/kg) and two time periods (0.5 and 4 h). Typically, in the MES seizures test one animal was used at 30 and 300 mg/kg, and three animals at 100 mg/kg. In the rotorod toxicity test four animals were used at 30 and 300 mg/kg, and eight animals at 100 mg/kg (Tables 1 and 2).

The quantitative determination of the median effective ($ED_{50}$) and toxic doses ($TD_{50}$) were conducted at previously calculated times of peak effect. Groups of at least eight animals were tested using different doses of test compound until at least two points were determined between 100 and 0% protection and minimal motor impairment. The dose of candidate substance required to produce the defined endpoint in 50% of the animals in each test, and the 95% confidence interval were calculated by a computer program based on methods described by Finney.[28]

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