Pergamon

Bioorganic & Medicinal Chemistry 7 (1999) 2381–2389

BIOORGANIC & MEDICINAL CHEMISTRY

The Anticonvulsant Activities of *N*-Benzyl 3-Methoxypropionamides

Shridhar V. Andurkar,[a] James P. Stables[b] and Harold Kohn[a,*]

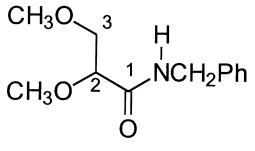
[a]*Department of Chemistry, University of Houston, Houston, TX 77204-5641, USA*
[b]*Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Federal Building, Room 114, Bethesda, MD 20892-9020, USA*

Received 3 December 1998; accepted 17 May 1999

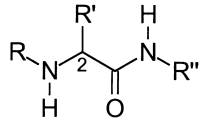
Abstract—We recently reported that the ED_{50} value for (*R,S*)-2,3-dimethoxypropionamide (**1**) in the maximal electroshock (MES)-induced seizure test in mice was 30 mg/kg (Choi, D.; Stables, J.P., Kohn, H. *Bioorg. Med. Chem.* **1996**, *4*, 2105). This value is comparable to that observed for phenobarbital (ED_{50} = 22 mg/kg). Compound **1** is structurally similar to a class of MES-selective anticonvulsant agents, termed functionalized amino acids (**2**), that were developed in our laboratory. The distinguishing feature of **2** is the differential activities observed for enantiomers. In this study, we asked whether comparable differences in activities were observed in the MES-induced seizure test for (*R*)- and (*S*)-**1**. We developed stereospecific syntheses for these enantiomers and showed that both compounds exhibit nearly equal anticonvulsant activity in mice (ip) (MES ED_{50} = 79–111 mg/kg). The surprisingly high ED_{50} values for (*R*)- and (*S*)-**1** required our redetermining the ED_{50} value for (*R,S*)-**1**. We revised this value to 79 mg/kg. A limited structure–activity relationship study for **1** was conducted. Special attention was given to the C(2) methoxy unit in **1**. We found that replacement of this moiety led to only modest differences in the MES activities upon ip administration to mice. Significantly, we observed an enhancement in the anticonvulsant activity for (*R,S*)-*N*-benzyl 2-hydroxy-3-methoxypropionamide ((*R,S*)-**6**) upon oral administration to rats ((*R,S*)-**6**: mice (ip) ED_{50} > 100, < 300 mg/kg; rat (oral) ED_{50} = 62 mg/kg). The activities of 3-methoxypropionamides, functionalized amino acids, and related compounds are discussed.

Introduction

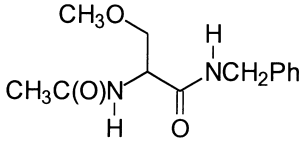
We reported that (*R,S*)-*N*-benzyl 2,3-dimethoxypropionamide (**1**) prevented maximal electroshock (MES)-induced seizures in mice (ED_{50} = 30 mg/kg) when administered intraperitoneally (ip)[1] at levels comparable to phenobarbital (ED_{50} = 22 mg/kg).[2] Compound **1** is structurally similar to a recently discovered class of anticonvulsant agents, termed functionalized amino acids (**2**),[3,4] which includes *N*-benzyl-2-acetamido-3-methoxypropionamide (**3**).[5] A detailed structure–activity relationship study for **2** revealed that placement of a substituted heteroatom one atom removed from the chiral C(2) atom led to enhanced anticonvulsant activity.[5,6] Moreover, we showed that the principal activity for **2** resided in the (*R*)-enantiomer. Comparison of the anticonvulsant activities in the MES test for four different pairs of enantiomers revealed that the potency of the (*R*)-stereoisomer exceeded the (*S*)-enantiomer by 10- to 22-fold.[4,5,7,8] This differential activity is among the highest ever reported for stereoisomers in the MES-induced seizure test.



1



2



3

The mode of action of **2** has not been determined. In the absence of a pharmacological basis for its activity, we asked whether the (*R*)- and (*S*)-enantiomers of **1** exhibited differential anticonvulsant activity in the MES-induced

Key words: Anticonvulsants; amino acids and derivatives; peptoids; substituents effects.

* Corresponding author. Tel.: +1-919-966-2680; fax: +1-919-966-6919; e-mail: harold_kohn@unc.edu

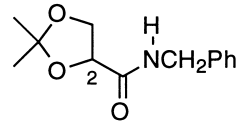
0968-0896/99/$ - see front matter
PII: S0968-0896(99)00186-8

seizure test. In this paper, we report stereospecific syntheses for (*R*)- and (*S*)-*N*-benzyl 2,3-dimethoxypropionamide (**1**), demonstrate that both stereoisomers have comparable activity in the MES-induced seizure test, revise the MES effective dose (ED_{50}) value for **1**, and delineate the structural components in **1** necessary for anticonvulsant activity. Our findings suggest that while **1** and **3** share common structural motifs their mode of anticonvulsant activity may be different.

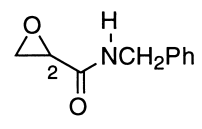
Results and Discussion

Selection of test compounds

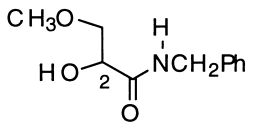
We wished to determine the anticonvulsant activities for the two stereoisomers of *N*-benzyl 2,3-dimethoxypropionamide (**1**) and learn the structural elements in **1** necessary for anticonvulsant activity. Accordingly, an abbreviated set of compounds was prepared and evaluated; they included (*R*)-**1** and (*S*)-**1**. Added to our list were **4** and **5**. These compounds, like **1,** contain *substituted* oxygen groups one atom removed from the



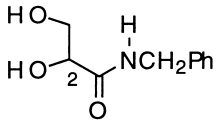
4



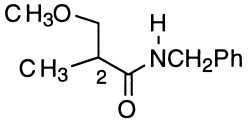
5



6



7

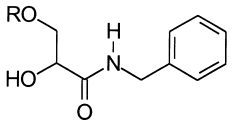


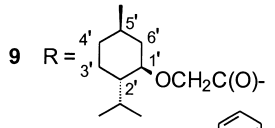
8

chiral C(2) atom. The pharmacological data for **1**, **4** and **5** were compared with the monohydroxy-**6** and dihydroxy-**7**[1] adducts. Finally, we added **8,** where we replaced the C(2)-methoxy group in **1** with a methyl substituent. Our synthesis of **8** permitted us to prepare both the (*R*)- and the (*S*)-enantiomers.

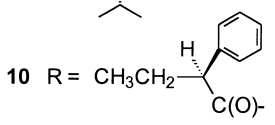
Synthesis

Our initial objective was to prepare the individual stereoisomers of (*R,S*)-*N*-benzyl 2,3-dimethoxypropionamide ((*R,S*)-**1**) and to determine their anticonvulsant activities. Accordingly, we attempted first to resolve (*R,S*)-**7** by chemical derivatization with a chiral acid. It served as the penultimate precursor of (*R,S*)-**1** in our original synthesis.[1] We expected that chromatographic separation of the diastereomeric mixture followed by ester hydrolysis and methylation would provide (*R*)- and (*S*)-**1**. Accordingly, we coupled (*R,S*)-**7** with (–)-menthoxyacetic acid and (*S*)-phenylbutyric acid using 1,1′-carbonyldiimidazole to give diastereomeric esters **9** and **10**, respectively. Attempted separations by PTLC using a variety of solvents and solvent mixtures were unsuccessful.



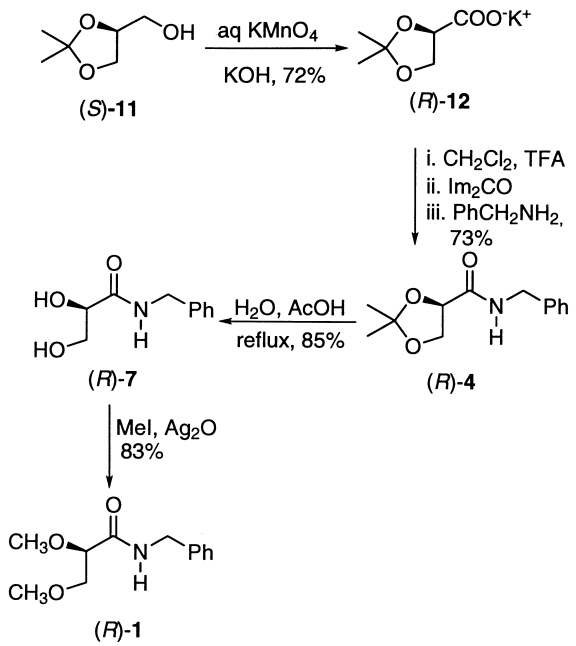


9



10

We then developed stereospecific syntheses of (*R*)- and (*S*)-**1** (Scheme 1). Commercially available (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol ((*S*)-**11**) was oxidized to (*R*)-**12**[9,10] with $KMnO_4$, and then coupled with benzylamine using 1,1′-carbonyldiimidazole to provide amide (*R*)-**4**. Deprotection of the acetonide group in (*R*)-**4** with aqueous acetic acid followed by methylation with MeI and Ag_2O gave (*R*)-**1**. An identical procedure was utilized to prepare (*S*)-**1** beginning with commercially available (*R*)-**11**. The enantiopurity of (*R*)- and (*S*)-**1** was verified by their optical rotation and the demonstration that adding the NMR chemical resolving agent[11–13] (*R*)-mandelic acid to a $CDCl_3$ solution containing either (*R*)- or (*S*)-**1** led to a single peak for the terminal methoxy group ((*R*)-**1**: δ 3.38; (*S*)-**1**: δ 3.39). In agreement with this finding, we observed that adding (*R*)-mandelic acid to (*R,S*)-**1** gave two distinct signals of

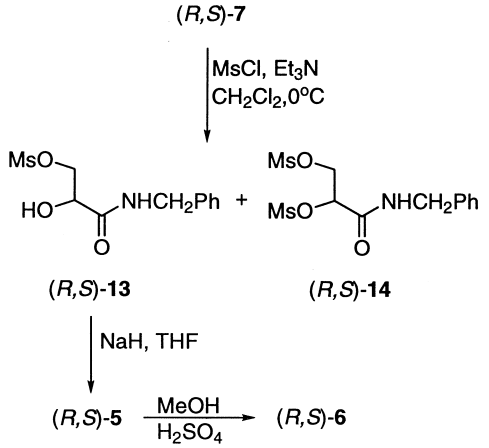


Scheme 1. Stereospecific synthesis of (*R*)-**1**.

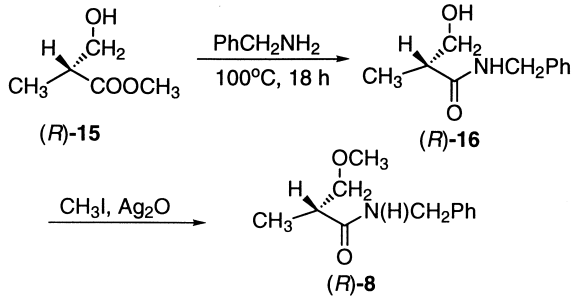
equal height for the terminal methoxy group. Compound (*R*,S)-**4** was prepared using the procedure outlined in Scheme 1, beginning with (*R,S*)-**11**. Syntheses of **5** and **6** were straight forward and proceeded from (*R,S*)-**7**. Addition of mesyl chloride (1 equiv) to a dichloromethane solution of (*R,S*)-**7** and triethylamine produced the C(3)-monomesylate **13** and the C(2), C(3)-dimesylate **14**, respectively, in a ~6:1 ratio (Scheme 2). The mesylates were separated by chromatography, and **13** was converted to epoxide (*R,S*)-**5** with NaH. Methanolysis of **5** in acid led to a regiospecific opening of the epoxide ring to give (*R,S*)-**6**. Preparation of (*R*)-**8** proceeded from commercially available (*R*)-**15** (Scheme 3). Treatment of (*R*)-**15** with benzylamine gave amide (*R*)-**16** without racemization, and conversion of (*R*)-**16** to ether (*R*)-**8** was accomplished with methyl iodide and Ag_2O in acetonitrile. The same methodology was used to prepare (*S*)-**8**, starting with (*S*)-**15**.

Pharmacological evaluation

Table 1 lists the anticonvulsant activities in the MES (ip) and the subcutaneous (sc) Metrazol seizures tests conducted in mice for compounds (*R,S*)-**1**, (*R*)-**1**, (*S*)-**1**, (*R,S*)-**4**, (*R,S*)-**5**, (*R,S*)-**6**, (*R*)-**8**, and (*S*)-**8** using the procedure described by Stables and Kupferberg.[14] The corresponding values for (*R*)-**3**, (*S*)-**3**, (*R,S*)-**3**,[5] (*R,S*)-**7**[1] and the clinically proven antiepileptic agents phenytoin,[15] phenobarbital.[2] and valproate[15] are also provided. Table 1 includes information concerning neurological impairment (TD_{50}) for these compounds in the rotorod test[16] and, where appropriate, the protective index ($PI = TD_{50}/ED_{50}$) for these adducts.



Scheme 2. Synthesis of (*R,S*)-**5** and (*R,S*)-**6**.



Scheme 3. Stereospecific synthesis of (*R*)-**8**.

We first determined the anticonvulsant activity for the two enantiomers of (*R,S*)-**1** in the MES-induced seizure test. The compounds displayed comparable activity. The ED_{50} value for (*R*)-**1** was 79 mg/kg while (*S*)-**1** exhibited slightly less activity, $ED_{50} = 111$ mg/kg. The unexpectedly high ED_{50} values obtained for the stereoisomers of **1** were inconsistent with the original measurement reported for the racemate (MES $ED_{50} = 30$ mg/kg).[1] In subsequent experiments, we attempted to reproduce the original finding for (*R,S*–**1**) utilizing newly synthesized compound at the previously determined ED_{50} value of 30 mg/kg. Eight animals were predosed with (*R,S*)-**1** at the previously determined time of peak effect of 0.25 h as well as at 0.5 h. All other parameters were consistent with the original experiment. No protection was afforded against MES induced seizures at either time point. Accordingly, we quantitatively re-evaluated (*R,S*)-**1** determining a new MES ED_{50} value of 79 mg/kg. The diminished protection against MES-induced seizures confirmed that the original measurement could not be reproduced. The factors that contributed to the inaccurate ED_{50} value for (*R,S*)-**1**[1] could not fully be determined. The testing parameters[17] for the pharmacological studies (e.g. time of test, animal species, weight, sex) were kept constant so it is unlikely that these contributed to the experimental error. All the test animals had free access to food and water except when used for experiments. Therefore, pharmacokinetic interactions resulting from the animal feed should have had little effect on the absorption rates of (*R,S*)-**1**. Likewise, structural confirmation of the test compounds ((*R*)-**1**, (*S*)-**1**, (*R,S*)-**1**) were verified by TLC and optical measurements**.** We suspect the most likely explanation for the variance in data is due to physical characteristics of (*R,S*)-**1** itself. This compound is an oil. Oils are often difficult to get into either uniform suspension or solution. This factor can lead to appreciable differences in the actual concentration of compound dilutions being prepared for administration. In the later experiments special care was taken in preparation of all suspensions. It is likely, administration of a more concentrated suspension was responsible for the *originally* reported MES ED_{50} for (*R,S*)-**1**.[1] Finally, we note that the experimental slopes in the calculation of the ED_{50} value for (*R,S*)-**1**, (*R*)-**1**, and (*S*)-**1** and the confidence limits are large, leading us to view the ED_{50} values in Table 1 with additional caution. We concluded that (*R*)- and (*S*)-**1** are only moderate anticonvulsants with comparable activity. These experimental concerns do not exist for functionalized amino acid **3** or for other compounds similar to **1** in structure (e.g. **7, 17**). Compounds **3** and **7** are solids, while **17** although an oil is a primary amine. All these compounds readily dissolved in the testing vehicle.

Several of the remaining compounds evaluated also displayed similar anticonvulsant activity in the MES-induced seizure test. Although actual ED_{50} values were

Table 1. Pharmacological data in mice[a]

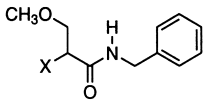
Compound	mp[b] (°C)	MES[c] ED_{50}	scMet[d] ED_{50}	Tox[e] TD_{50}	P.I.[f] TD_{50}/MES ED_{50}
(*R*)-**1**	—[g]	79 [0.5] (73–88)	180 [0.5] (125–241)	279 [0.25] (257–293)	3.5
(*S*)-**1**	—[g]	111 [1] (86–129)	150 [0.25] (114–189)	308 [0.25] (279–348)	2.8
(*R,S*)-**1**	—[g]	79 [0.25] (67–114)	145 [0.25] (113–187)	280 [0.25] (253–308)	3.5
(*R*)-**3**[h]	143–144	4.5 [0.5] (3.7–5.5)	> 25 [0.25]	27 [0.25] (26–28)	6.0
(*S*)-**3**[h]	143–144	> 100, < 300 [0.5]	> 300 [0.5]	> 300 [0.5]	—
(*R,S*)-**3**[h]	121–122	8.3 [0.5] (7.9–9.8)	> 300 [0.5]	43 [0.25] (38–47)	5.2
(*R,S*)-**4**	98–100	> 30, < 100 [0.25]	> 300 [0.25]	> 100, < 300 [0.5]	—
(*R,S*)-**5**	61–63	> 100, < 300 [0.5]	> 300 [0.5]	> 100, < 300 [0.5]	—
(*R,S*)-**6**	—[g]	> 100, < 300 [0.5]	> 300 [0.5]	> 100, < 300 [0.5]	—
(*R,S*)-**7**[i]	83–84	> 100, < 300 [0.5]	> 100, < 300 [0.5]	> 300 [0.5]	—
(*R*)-**8**	—[g]	> 30, < 100 [0.25]	> 300 [0.5]	> 300 [0.5]	—
(*S*)-**8**	—[g]	81 [0.25] (60–96)	> 300 [0.5]	221 [0.25] (183–259)	2.7
Phenytoin[j]		9.5 [2] (8.1–10.4)	≥NP[k]	66 [2] (53–72)	6.9
Phenobarbital[l]		22 [1] (15–23)	13 (5.9–16)	69 [0.5] (63–73)	3.1
Valproate[j]		272 [0.25] (247–338)	149 [0.25] (123–177)	426 [0.25] (369–450)	1.6

[a] The compounds were administered intraperitoneally unless otherwise indicated. 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 Institute of Health unless otherwise indicated.
[b] Melting points (°C) are uncorrected.
[c] MES = maximal electroshock seizure text.
[d] scMet = subcutaneous pentylenetetrazole (metrazole) seizure test.
[e] Neurologic toxicity determined using the rotorod test.
[f] PI = protective index (TD_{50}/MES ED_{50}).
[g] Oil.
[h] Ref 5.
[i] Ref 1.
[j] Ref 15.
[k] NP = no protection.
[l] Data from *Antiepileptic Drugs*, 2nd ed.; Woodbury, D. M.; Penry, J. K.; Pippenger, C. E.; Eds.; Raven Press: New York, 1982; p 120.

not calculated for (*R,S*)-**4-7**, (*R*)-**8** and (*S*)-**8**, qualitative evaluations using two time points and three different doses (30, 100 and 300 mg/kg) provide us with some estimates for the protective ranges of observed anticonvulsant activity. Recognizing this limitation we observed that acetonide (*R,S*)-**4** exhibited a range of activity comparable to (*R,S*)-**1** and that substituting the 2-methoxy group in **1** with a methyl unit to provide **8** gave no appreciable losses in MES-seizure protection. Significantly, (*R*)- and (*S*)-**8** possessed comparable activities that paralleled our finding for (*R*)- and (*S*)-**1**. Finally, epoxide (*R,S*)-**5** and alcohol (*R,S*)-**6** exhibited decreased activity compared with (*R,S*)-**1**. The effect of the C(2) substituent on the MES anticonvulsant activity for *N*-benzyl 3-methoxypropionamides is highlighted in Table 2. We have included values previously determined for C(2) acetamido ((*R,S*)-**3**) and C(2) amino ((*R*)-**17**[18]) 3-methoxypropionamides. Also listed in Table 2 are the MES ED_{50} values for select compounds after oral administration to rats. In the mice (ip) test data we observed that most of the C(2) substituted *N*-benzyl 3-methoxypropionamides displayed fairly uniform activity with only the 2-acetamido derivative (*R,S*)-**3**[5] affording excellent protection against MES-induced seizures. Comparable levels of activity were observed regardless of the electronic nature of the C(2) substituent and the ability of this moiety to undergo hydrogen bond donor/acceptor interactions. Enhancement in the MES anticonvulsant activity was observed for (*R,S*)-**6** upon oral administration to rats (ED_{50} > 100, < 300 mg/kg, mice, ip; ED_{50} = 62 mg/kg, rat, po). Furthermore, (*R,S*)-**6** provided increased levels of protection against MES-induced seizures with time over the 4 h test period. These findings parallel those observed for (*R*)-**17**[18] and indicate that (*R,S*)-**6** is a moderately potent anticonvulsant with an extended duration of action.

Table 1 includes the ED_{50} values obtained for the test compounds in the Metrazol (sc) seizure assay. We observed that both (*R*)- and (*S*)-**1** exhibited

Table 2. Comparative pharmacological data for 2-substituted 3-methoxypropionamides in mice (ip) and rats (po)



		mice (ip)[a]		rat (po)[d]	
Compound	X	MES[b] ED_{50}	Tox[c] TD_{50}	MES ED_{50}	Tox[c] TD_{50}
(*R*,*S*)-**1**	OCH_3	79 [0.25] (67–114)	280 [0.25] (253–308)	> 30 [1]	> 30 [1]
(*R*,*S*)-**7**	OH	> 100, < 300 [0.5]	> 100, < 300 [0.5]	62 [4] (43–88)	> 200 [4]
(*R*)-**17**	NH_2	> 30, < 100 [0.5]	> 100, < 300 [0.5]	18 [4]	500 [4]
(*R*)-**8**	CH_3	> 30, < 100 [0.25]	> 300 [0.5]	> 30 [4]	—[e]
(*S*)-**8**	CH_3	81 [0.25] (60–96)	221 [0.25] (183–259)	> 30 [4]	—[e]
(*R*,*S*)-**3**[f]	$N(H)C(O)CH_3$	8.3 [0.5] (7.4–9.8)	43 [0.25] (38–47)	3.8 [2] (2.9–5.5)	390 [1] (320–510)

[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 Institute of Health unless otherwise indicated.
[b] MES = maximal electroshock seizure test.
[c] Tox = neurologic toxicity determined from rotorod test.
[d] The compounds were administered orally.
[e] Not determined.
[f] Ref 5.

anticonvulsant activity (ED_{50} = 150–180 mg/kg) comparable to valproate (ED_{50} = 149 mg/kg). By comparison, the structurally similar amino acid derivative (*R*,*S*)-**3** was devoid of activity in this assay at concentrations below 300 mg/kg.[5] None of the remaining compounds ((*R*,*S*)-**4**, (*R*,*S*)-**5**, (*R*,*S*)-**6**, (*R*)-**8**, (*S*)-**8**) in the current study showed detectable anticonvulsant activity in the Metrazol (sc) seizure assay at the highest concentration employed (300 mg/kg).

Conclusions

The overall pharmacological profile for **1** differs significantly from functionalized amino acid **3** in two important ways. First, no appreciable differences in anticonvulsant activities were found for the (*R*)- and (*S*)- enantiomers of **1**. The ED_{50} values for (*R*)- and (*S*)-**1** were within a factor of two and were noticeably less than the 22-fold difference in activity observed for the enantiomers of **3**.[5] Second, both (*R*)- and (*S*)-**1** exhibited moderate levels of anticonvulsant activity in the Metrazol (sc) seizure test in mice (ED_{50} = 150–180 mg/kg) while neither (*R*,*S*)- nor (*S*)-**3** (ED_{50} > 300 mg/kg) did.[5] The anticonvulsant activity for (*R*)-**3** in the Metrazol (sc) seizure test was not tested above 25 mg/kg;[5] however, in corresponding tests conducted in rats the ED_{50} values in the Metrazol (sc) test for (*R*)-**3** and (*R*,*S*)-**3** exceeded 250 mg/kg (data not shown). These results taken together suggest that **1** and **3** may express their anticonvulsant activities by different mechanisms and that 3-methoxypropionamides may represent a pharmacologically distinct class of anticonvulsants. Future research will focus on understanding the oral activity of (*R*,*S*)-**6** and its amino counterpart (*R*)-**17**.

Experimental

General methods

Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on an ATI Mattson Genesis Series FTIR™ spectrometer. Absorption values are expressed in wave-numbers (cm^{-1}). Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance 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 chemical ionization mass spectrum was performed on a Finnigan MAT TSQ-70 by Dr. M. Moini at the University of Texas–Austin. Optical rotations were recorded on Perkin–Elmer 241 MC and Jasco P-1030 polarimeters. Microanalyses were provided by Atlantic Microlab, Inc. (Norcross, GA). Thin-layer chromatography was performed on precoated silica gel GHLF microscope slides (2.5×10 cm; Analtech No. 21521).

Synthesis of *N*-benzyl 2-hydroxy-3-(2-menthoxyacetyloxy)propionamide (9). A THF solution (1 mL) of (–)-menthoxyacetic acid (0.06 g, 0.3 mmol) and 1,1′-carbonyldiimidazole (0.04 g, 0.3 mmol) was heated at reflux (45 min), allowed to cool to room temperature and then a THF solution (0.5 mL) of (*R*,*S*)-**7** (0.05 g, 0.3 mmol) was added and the solution was heated at reflux (4 h). The solvent was evaporated in vacuo and the residue purified by preparative TLC (SiO_2, 10% MeOH–$CHCl_3$) to afford the oily ester (0.06 g, 54%) as an ~1:1 mixture of diaster-

eomers: R_f 0.75 (10% MeOH–$CHCl_3$);[19] IR (liquid film) 3365, 2954, 2869, 1760, 1651, 1532, 1455, 1122, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (d, $J=7.2$ Hz, C(5′)CH_3, diastereomer *a* or *b*), 0.78 (d, $J=6.9$ Hz, C(5′)CH_3 diastereomer *a* or *b*), 0.80–1.05 (m, 9 H), 1.20–1.40 (m, 2 H), 1.60–1.67 (m, 2 H), 1.95–2.05 (m, 1 H), 2.15–2.30 (m, 1 H), 3.05–3.20 (m, 1 H), 4.10 (ABq, $J=16.2$ Hz, OCH_2C(O)O diastereomer *a* or *b*), 4.11 (ABq, $J=16.2$ Hz, OCH_2C(O)O diastereomer *a* or *b*), 4.35–4.65 (m, 6 H), 7.15–7.25 (m, 5 Ph*H* and N*H*); ^{13}C NMR ($CDCl_3$) 16.2, 20.9, 22.2, 23.2, 25.5, 31.4, 34.3, 39.8 (2-menthoxyacetyloxy, diastereomer *a* and *b*), 43.1 ($\underline{C}H_2$Ph), 47.9 (2-menthoxyacetyloxy, diastereomer *a* and *b*), 65.7 ($\underline{C}HOCH_2$ diastereomer *a* or *b*), 65.8 ($\underline{C}H$-OCH_2 diastereomer *a* or *b*), 66.9 (C(O)O$\underline{C}H_2$), 71.0 (O$\underline{C}H_2$-C(O)), 80.4 ($\underline{C}$HOH diastereomer *a* or *b*), 80.5 ($\underline{C}$HOH diastereomer *a* or *b*), 127.5, 127.6, 128.7, 137.7 (Ph), 170.2 ($\underline{C}$(O)O or $\underline{C}$(O)NH), 171.7 ($\underline{C}$(O)O or $\underline{C}$(O)NH) ppm; MS, (CI+) (rel. int.) 392 ($M^+ + 1$, 92), 374 (13), 255 (13), 254 (100), 236 (12), 196 (41); M_r (+ CI) 392.242 91 [$M^+ + 1$] (calcd for $C_{22}H_{34}NO_5$ 392.243 69).

Synthesis of *N*-benzyl 2-hydroxy-3-(2-(*S*)-phenylbutyryloxy)propionamide (10). A THF solution (2 mL) of (*S*)-phenylbutyric acid (0.05 g, 0.3 mmol) and 1,1′-carbonyldiimidazole (0.05 g, 0.3 mmol) was heated at reflux (1 h), allowed to cool to room temperature and then a THF solution (1.0 mL) of (*R,S*)-**7** (0.05 g, 0.3 mmol) was added and the solution heated at reflux (3 h). The solvent was evaporated in vacuo and the residue purified by preparative TLC (SiO_2, 10% MeOH–$CHCl_3$) to afford an oily ester (0.05 g, 54%) as an ~1:1 mixture of diastereomers: R_f 0.62 (10% MeOH–$CHCl_3$);[19] IR (liquid film) 3386, 2966, 2876, 1738, 1652, 1538, 1455, 1124, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, $J=7.2$ Hz, CH_2CH_3 diastereomer *a* or *b*), 0.88 (t, $J=7.2$ Hz, CH_2CH_3 diastereomer *a* or *b*), 1.70–1.86 (m, CH_3CHH'), 2.00–2.20 (m, CH_3 CHH'), 3.47 (t, $J=7.5$ Hz, CH_2CHPh diastereomer *a* or *b*), 3.48 (t, $J=7.5$ Hz, CH_2CHPh diastereomer *a* or *b*), 4.25–4.60 (m, $CH_2CH(OH)$, CH_2Ph), 6.85–7.10 (m, N*H*), 7.15–7.40 (m, 10 Ph*H*); ^{13}C NMR ($CDCl_3$) 12.0 ($\underline{C}H_3$ CH_2), 26.3 ($CH_3\underline{C}H_2$ diastereomer *a* or *b*), 26.4 ($CH_3\underline{C}H_2$ diastereomer *a* or *b*), 43.0 ($\underline{C}H_2$Ph diastereomer *a* or *b*), 43.1 ($\underline{C}H_2$Ph diastereomer *a* or *b*), 53.2 ($CH_2\underline{C}$HPh), 66.5 (C(O)O$\underline{C}H_2$ diastereomer *a* or *b*), 66.7 (C(O)O$\underline{C}H_2$ diastereomer *a* or *b*), 71.2 ($\underline{C}$HOH diastereomer *a* or *b*), 71.3 ($\underline{C}$HOH diastereomer *a* or *b*), 127.4, 127.5, 127.6, 127.7, 127.8, 128.6, 137.6, 138.4, 138.6 (Ph diastereomer *a* and *b*), 170.2 ($\underline{C}$(O)NH), 175.1 ($\underline{C}$(O)O) ppm; MS, (CI+) (rel. int.) 342 ($M^+ + 1$, 100), 196 (18), 178 (15), 165 (11), 162 (13); M_r (+ CI) 342.170 10 [$M^+ + 1$] (calcd for $C_{20}H_{24}NO_4$ 342.170 53).

Synthesis of (*R*)-*N*-benzyl 2,2-dimethyl-1,3-dioxolane-4-carboxamide ((*R*)-4). To an N_2-blanketed suspension of (*R*)-**12**[9] (1.31 g, 7.1 mmol) in dry CH_2Cl_2 (50 mL) was added trifluoroacetic acid (0.81 g, 7.1 mmol). The mixture was stirred at room temperature (30 min) and then 1,1′-carbonyldiimidazole (1.15 g, 7.1 mmol) was added and the mixture was heated at reflux until CO_2 evolution ceased (~45 min). The mixture was cooled to room temperature, treated with benzylamine (0.78 mL, 7.1 mmol) and then stirred (18 h). The mixture was washed with water (2×25 mL), and the organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, 5% MeOH–$CHCl_3$) followed by recrystallization from ethyl ether-petroleum ether to afford pure (*R*)-**4** (1.22 g, 73%): mp 81–84°C; $[\alpha]_D^{23}$ +17.1° (*c* 0.1, MeOH); R_f 0.70 (5% MeOH–$CHCl_3$); IR (KBr) 3336, 1649, 1540, 1221, 1090, 735, 500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, CCH_3), 1.45 (s, CCH_3), 4.16 (dd, $J=5.4$, 9.0 Hz, OC*H*H′), 4.32 (dd, $J=7.4$, 9.0 Hz, OCH*H*′), 4.49 (d, $J=6.0$ Hz, CH_2Ph), 4.55 (dd, $J=5.4$, 7.4 Hz, OC*H*), 6.80–6.95 (m, N*H*), 7.23–7.41 (m, 5 Ph*H*); ^{13}C NMR ($CDCl_3$) 25.1 ($\underline{C}CH_3$), 26.3 ($\underline{C}CH_3$), 43.0 ($\underline{C}H_2$Ph), 67.9 ($\underline{C}H_2$), 75.2 ($\underline{C}$H), 111.0 ($\underline{C}(CH_3)_2$), 127.7, 128.9, 137.9 (Ph), 171.3 ($\underline{C}$(O)) ppm, the remaining aromatic signal was not detected and is believed to overlap with nearby peaks; MS (CI+) (rel. int.) 236 ($M^+ + 1$, 100), 208 (72), 178 (43); M_r (+ CI) 236.128 99 [$M^+ + 1$] (calcd for $C_{13}H_{18}NO_3$ 236.128 67); Anal. calcd for $C_{13}H_{17}NO_3 \cdot 0.5\ H_2O$: C, 63.93; H, 7.38; N, 5.74. Found: C, 64.23; H, 7.14; N, 5.69.

Synthesis of (*S*)-*N*-benzyl 2,2-dimethyl-1,3-dioxolane-4-carboxamide ((*S*)-4). Compound (*S*)-**4** was prepared using the preceding procedure and beginning with (*S*)-**12**[9] (2.86 g, 15.5 mmol), trifluoroacetic acid (1.77 g, 15.5 mmol), 1,1′-carbonyldiimidazole (2.60 g, 16 mmol) and benzylamine (1.81 mL, 16.5 mmol): yield, 3.00 g (82%); mp 84–87°C; $[\alpha]_D^{23}$ −17.2° (*c* 0.1, MeOH); R_f 0.70 (5% MeOH–$CHCl_3$); IR (KBr) 3336, 1649, 1540, 1220, 1090, 735, 502 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, CCH_3), 1.45 (s, CCH_3), 4.16 (dd, $J=5.4$, 9.0 Hz, OC*H*H′), 4.32 (dd, $J=7.6$, 9.0 Hz, OCH*H*′), 4.49 (d, $J=6.0$ Hz, CH_2Ph), 4.55 (dd, $J=5.4$, 7.6 Hz, OC*H*), 6.80–6.95 (m, N*H*), 7.20–7.41 (m, 5 Ph*H*); ^{13}C NMR ($CDCl_3$) 25.0 ($\underline{C}CH_3$), 26.2 ($\underline{C}CH_3$), 42.9 ($\underline{C}H_2$Ph), 67.8 ($\underline{C}H_2$), 75.1 ($\underline{C}$H), 110.9 ($\underline{C}(CH_3)_2$), 127.6, 128.8, 137.9 (Ph), 171.2 ($\underline{C}$(O)) ppm, the remaining aromatic signal was not detected and is believed to overlap with nearby peaks; MS (CI+) (rel. int.) 236 ($M^+ + 1$, 100), 208 (7), 178 (20); M_r (+ CI) [$M^+ + 1$] 236.128 44 (calcd for $C_{13}H_{18}NO_3$ 236.128 67); Anal. calcd for $C_{13}H_{17}NO_3 \cdot 0.25\ H_2O$: C, 65.14; H, 7.31; N, 5.85. Found: C, 65.33; H, 7.32; N, 5.81.

Synthesis of (*R*)-*N*-benzyl 2,3-dihydroxypropionamide ((*R*)-7). A 50% aqueous acetic acid solution (30 mL) containing (*R*)-**4** (1.22 g, 5.19 mmol) was heated at reflux (30 min) and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 10% MeOH–$CHCl_3$) to obtain (*R*)-**7** as a white solid (0.86 g, 85%); mp 83–84°C; $[\alpha]_D^{23}$ +35.4° (*c* 0.2, MeOH); R_f 0.35 (10% MeOH–$CHCl_3$); IR (KBr) 3336, 1649, 1623, 1542, 1110, 1049, 972, 739, 697 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.42–3.56 (m, C*H*H′OH), 3.58–3.64 (m, CH*H*′OH), 3.89–3.95 (m, C*H*OH), 4.28 (d, $J=6.0$ Hz, CH_2Ph), 4.74 (t, $J=5.7$ Hz, CH_2OH), 5.57 (d, $J=5.4$ Hz, CHO*H*), 7.19–7.35 (m, 5 Ph*H*), 8.24 (t, $J=6.0$ Hz, N*H*); ^{13}C NMR (DMSO-d_6) 41.7 ($\underline{C}H_2$Ph), 64.0 ($\underline{C}H_2$OH), 73.1 ($\underline{C}$HOH), 126.6, 127.2, 128.2, 139.6 (Ph), 172.2 ($\underline{C}$(O)NH) ppm; MS (CI+) (rel. int.) 196 ($M^+ + 1$, 100); M_r (+ CI) 196.098 03 [$M^+ + 1$] (calcd for $C_{10}H_{14}NO_3$ 196.097 37); Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.54; H, 6.67; N, 7.13. Found: C, 61.45; H, 6.69; N, 7.13.

Synthesis of (*S*)-*N*-benzyl 2,3-dihydroxypropionamide ((*S*)-7). The preceding procedure was employed to prepare (*S*)-**7** using (*S*)-**4** (3.49 g, 14.8 mmol) and 50% aqueous acetic acid (86 mL): yield, 2.26 g (78%); mp 83–84°C; $[\alpha]_D^{23}$ −35.1° (*c* 0.1, MeOH); R_f 0.35 (10% MeOH–$CHCl_3$); IR (KBr) 3337, 1649, 1623, 1546, 1109, 1049, 971, 739, 697 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.45–3.59 (m, C*H*H′OH), 3.60–3.66 (m, CH*H*′OH), 3.90–3.98 (m, C*H*OH), 4.29 (d, *J* = 6.2 Hz, CH_2Ph), 4.65–4.85 (m, O*H*), 5.40–5.65 (m, O*H*), 7.15–7.40 (m, 5 Ph*H*), 8.25 (t, *J* = 6.2 Hz, N*H*); ^{13}C NMR (DMSO-d_6) 41.8 ($\underline{C}H_2Ph$), 64.1 ($\underline{C}H_2OH$), 73.2 ($\underline{C}HOH$), 126.7, 127.2, 128.3, 139.7 (Ph), 172.4 ($\underline{C}(O)NH$) ppm; MS (CI+) 196 ($M^+ + 1$); M_r (+ CI) 196.097 09 [$M^+ + 1$] (calcd for $C_{10}H_{14}NO_3$ 196.097 37). Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.54; H, 6.67; N, 7.13. Found: C, 61.25; H, 6.59; N, 7.01.

Synthesis of (*R*)-*N*-benzyl 2,3-dimethoxypropionamide ((*R*)-1). An acetonitrile solution (44 mL) of (*R*)-**7** (1.35 g, 6.9 mmol) was stirred at room temperature in the presence of Ag_2O (8.05 g, 35 mmol) and MeI (4.4 mL, 70 mmol) (2 days). The salts were filtered, and the filtrate was evaporated in vacuo to obtain an oily residue that was purified by column chromatography (SiO_2, EtOAc) to furnish (*R*)-**1** (1.29 g, 83%) as a clear oil: $[\alpha]_D^{23}$ +33.6° (*c* 0.1, MeOH); R_f 0.43 (EtOAc); IR (liquid film) 3320, 2930, 1662, 1528, 1455, 1107, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.41 (s, CH_2OCH_3), 3.49 (s, $CHOCH_3$), 3.71 (dd, *J* = 4.5, 10.5 Hz, C*H*H′OCH_3), 3.80 (dd, *J* = 2.7, 10.5 Hz, CH*H*′OCH_3), 3.88 (dd, *J* = 2.7, 4.5 Hz, C*H*OCH_3), 4.51 (d, *J* = 6.0 Hz, CH_2Ph), 6.95–7.05 (m, N*H*), 7.28–7.40 (m, 5 Ph*H*), addition of excess (*R*)-mandelic acid gave only one signal (δ 3.38) for the CH_2OCH_3 protons; ^{13}C NMR ($CDCl_3$) 43.0 ($\underline{C}H_2Ph$), 58.6 ($CH_2\underline{O}CH_3$), 59.4 ($CHO\underline{C}H_3$), 72.3 ($\underline{C}H_2OCH_3$), 81.8 ($\underline{C}HOCH_3$), 127.5, 127.6, 128.7, 138.0 (Ph), 170.0 ($\underline{C}(O)$) ppm; MS (CI+) (rel. int.) 224 ($M^+ + 1$, 100), 119 (3); M_r (+ CI) 224.127 99 [$M^+ + 1$] (calcd for $C_{12}H_{18}NO_3$ 224.128 67); Anal. calcd for $C_{12}H_{17}NO_3 \cdot 0.15\ H_2O$: C, 63.80; H, 7.67; N, 6.20. Found: C, 63.85; H, 7.53; N, 6.17.

Synthesis of (*S*)-*N*-benzyl 2,3-dimethoxypropionamide ((*S*)-1). Using the preceding procedure, (*S*)-**1** was prepared in 70% yield (1.89 g) beginning with (*S*)-**7** (2.26 g, 11.6 mmol), Ag_2O (13.4 g, 58 mmol), MeI (7.4 mL, 116 mmol) and acetonitrile (74 mL): $[\alpha]_D^{23}$ −33.2° (*c* 0.1, MeOH); R_f 0.43 (EtOAc); IR (liquid film) 3324, 2931, 1667, 1528, 1455, 1108, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.41 (s, CH_2OCH_3), 3.49 (s, $CHOCH_3$), 3.72 (dd, *J* = 4.5, 10.5 Hz, C*H*H′OCH_3), 3.80 (dd, *J* = 2.7, 10.5 Hz, CH*H*′OCH_3), 3.88 (dd, *J* = 2.7, 4.5 Hz, C*H*OCH_3), 4.51 (d, *J* = 6.0 Hz, CH_2Ph), 6.85–7.03 (m, N*H*), 7.25–7.38 (m, 5 Ph*H*), addition of excess (*R*)-mandelic acid gave only one signal (δ 3.39) for the CH_2OCH_3 protons; ^{13}C NMR ($CDCl_3$) 42.8 ($\underline{C}H_2Ph$), 58.5 ($CH_2\underline{O}CH_3$), 59.2 ($CHO\underline{C}H_3$), 72.2 ($\underline{C}H_2OCH_3$), 81.7 ($\underline{C}HOCH_3$), 127.3, 127.5, 128.5, 138.0 (Ph), 169.9 ($\underline{C}(O)NH$) ppm; MS (CI+) (rel. int.) 224 ($M^+ + 1$, 100), 222 (11), 191 (2); M_r (+ CI) 224.129 29 [$M^+ + 1$] (calcd for $C_{12}H_{18}NO_3$ 224.128 67); Anal. calcd for $C_{12}H_{17}NO_3 \cdot 0.25\ H_2O$: C, 63.30; H, 7.69; N, 6.15. Found: C, 63.32; H, 7.76; N, 6.19.

Synthesis of (*R*,*S*)-*N*-benzyl 2,2-dimethyl-1,3-dioxolane-4-carboxamide ((*R*,*S*)-4). Employing the procedure for (*R*)-**4** and using (*R,S*)-**12**[9,10] (2.63 g, 19 mmol), trifluoroacetic acid (1.1 mL, 19 mmol), 1,1′-carbonyldiimidazole (2.4 g, 21 mmol), and benzylamine (1.6 mL, 19 mmol), compound (*R*,*S*)-**4** was produced in 78% yield (2.83 g): mp 83–85°C; R_f 0.70 (5% MeOH–$CHCl_3$); IR (KBr) 3336, 1649, 1540, 1220, 1090, 735, 502 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, CCH_3), 1.45 (s, CCH_3), 4.16 (dd, *J* = 5.4, 9.0 Hz, OC*H*H′), 4.32 (dd, *J* = 7.6, 9.0 Hz, OCH*H*′), 4.49 (d, *J* = 6.0 Hz, CH_2Ph), 4.55 (dd, *J* = 5.4, 7.6 Hz, OC*H*), 6.80–6.95 (m, N*H*), 7.20–7.41 (m, 5 Ph*H*); ^{13}C NMR ($CDCl_3$) 25.0 ($\underline{C}CH_3$), 26.2 ($\underline{C}CH_3$), 42.9 ($\underline{C}H_2Ph$), 67.8 ($\underline{C}H_2$), 75.1 ($\underline{C}H$), 110.9 ($\underline{C}(CH_3)_2$), 127.6, 128.8, 137.9 (Ph), 171.2 ($\underline{C}(O)$) ppm, the remaining aromatic signal was not detected and is believed to overlap with nearby peaks; MS (CI+) (rel. int.) 236 ($M^+ + 1$, 100), 178 (28); M_r (+CI) 236.129 30 [$M^+ + 1$] (calcd for $C_{13}H_{18}NO_3$ 236.128 67); Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.97. Found: C, 66.33; H, 7.34; N, 5.97.

Synthesis of (*R*,*S*)-*N*-benzyl 2-hydroxy-3-methanesulfonatopropionamide ((*R*,*S*)-13). To a cold (0°C), N_2-blanketed solution of (*R,S*)-**7** (4.52 g, 23.2 mmol) and triethylamine (3.3 mL, 23 mmol) in dry tetrahydrofuran (100 mL) was added dropwise methanesulfonyl chloride (2.7 g, 23 mmol). The mixture was allowed to warm to room temperature and then stirred (1 h). The solvent was evaporated in vacuo, and the residue was purified by column chromatography (SiO_2, ethyl ether) to obtain pure (*R,S*)-**13** (2.5 g, 40%) and (*R,S*)-*N*-benzyl-2,3-dimethanesulfonatopropionamide (*R*,*S*)-**14** (0.41 g, 5%).

(*R*,*S*)-**13**: mp 139–141°C; R_f 0.68 (EtOAc); IR (KBr) 3392, 3243, 1653, 1558, 1404, 1347, 1172, 1127, 989, 966, 721, 529 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.12 (s, CH_3), 4.22–4.40 (m, CH_2Ph, CH_2OMs, C*H*OH), 6.28 (d, *J* = 5.4 Hz, CHO*H*), 7.17–7.35 (m, Ph*H*), 8.54 (t, *J* = 6.2 Hz, N*H*); ^{13}C NMR (DMSO-d_6) 36.7 ($\underline{C}H_3$), 41.9 ($\underline{C}H_2Ph$), 69.7 ($\underline{C}H_2OMs$), 72.4 ($\underline{C}HOH$), 126.7, 127.1, 128.2, 139.4 (Ph), 170.1 ($\underline{C}(O)$) ppm; MS (CI^+) (rel. int.) 274 ($M^+ + 1$, 100), 178 (27); M_r (+CI) 274.074 90 [$M^+ + 1$] (calcd for $C_{11}H_{16}NO_5S$ 274.074 92); Anal. calcd for $C_{11}H_{15}NO_5S \cdot 0.25\ H_2O$: C, 47.58; H, 5.59; N, 5.05. Found: C, 47.80; H, 5.62; N, 5.02.

(*R*,*S*)-**14**: mp 104–105°C; R_f 0.83 (EtOAc); IR (KBr) 3341, 3034, 2939, 1658, 1540, 1356, 1182, 1069, 959, 903, 787, 703, 529 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (s, CH_3), 3.20 (s, CH_3), 4.43 (dd, *J* = 5.7, 15.3 Hz, C*H*H′Ph), 4.57 (dd, *J* = 6.6, 15.3 Hz, CH*H*′Ph), 4.64 (dd, *J* = 5.1, 11.7 Hz, C*H*H′OMs), 4.70 (dd, *J* = 3.0, 11.7 Hz, CH*H*′OMs), 5.32 (dd, *J* = 3.0, 5.1 Hz, C*H*OMs), 6.94–7.00 (m, N*H*), 7.25–7.40 (m, Ph*H*); ^{13}C NMR ($CDCl_3$) 37.8 ($\underline{C}H_3$), 39.3 ($\underline{C}H_3$), 43.9 ($\underline{C}H_2Ph$), 68.6 ($\underline{C}H_2OMs$), 76.5 ($\underline{C}HOMs$), 127.8, 128.1, 129.1, 137.1 (Ph), 164.7 ($\underline{C}(O)$) ppm; MS (CI^+) (rel. int.) 352 ($M^+ + 1$, 100), 257 (12), 256 (97), 178 (22); M_r (+CI) 352.052 00 [$M^+ + 1$] (calcd for $C_{12}H_{18}NO_7S_2$ 352.052 47); Anal. calcd for $C_{12}H_{17}NO_7S_2$: C, 41.02; H, 4.84; N, 3.99. Found: C, 41.60; H, 4.80; N, 3.94.

Synthesis of (*R,S*)-*N*-benzyl 2,3-epoxypropionamide ((*R,S*)-5). To a dry tetrahydrofuran solution (100 mL) of mesylate (*R,S*)-**13** (2.02 g, 7.4 mmol) was added NaH (60% suspension in mineral oil, 0.30 g, 7.5 mmol) and stirred at room temperature (1 h). The mixture was poured into H_2O (150 mL) and the "pH" adjusted to 7 (5% aq H_2SO_4) and then extracted with EtOAc (3×75 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and evaporated in vacuo. The oily residue obtained was purified by column chromatography (SiO_2, EtOAc) to give epoxide (*R,S*)-**5** as a white crystalline solid (1.25 g, 95%): mp 61–63°C; R_f 0.80 (EtOAc); IR (KBr) 3262, 3085, 2989, 2358, 1654, 1559, 1493, 1426, 1364, 1268, 1238, 1041, 888, 735, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (dd, $J=2.6$, 5.8 Hz, C*H*H′O), 3.00 (dd, $J=4.8$, 5.8 Hz, CH*H*′O), 3.50 (dd, $J=2.6$, 4.8 Hz, C*H*), 4.35–4.50 (m, CH_2Ph), 6.35–6.45 (m, N*H*), 7.21–7.39 (m, Ph*H*); ^{13}C NMR ($CDCl_3$) 43.0 (CH_2Ph), 47.8 (CH_2O), 49.8 (CH), 127.9, 128.9, 137.7 (Ph), 168.6 (C(O)) ppm, the remaining aromatic signal was not detected and is believed to overlap with nearby peaks. MS (CI^+) (rel. int.) 178 ($M^+ + 1$, 100); M_r (+CI) 178.086 42 [$M^+ + 1$] (calcd for $C_{10}H_{12}NO_2$ 178.086 80); Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.21; N, 7.91. Found: C, 67.64; H, 6.22; N, 7.98.

Synthesis of (*R,S*)-*N*-benzyl 2-hydroxy-3-methoxypropionamide ((*R,S*)-6). An anhydrous MeOH (150 mL) solution containing epoxide (*R,S*)-**5** (1.52 g, 8.6 mmol) and concentrated H_2SO_4 (1 mL) was stirred at reflux (2 h) under N_2. The solution was allowed to cool to room temperature and the "pH" was adjusted to 7.0 (saturated aq $NaHCO_3$). The mixture was concentrated in vacuo without the use of heat and the resulting aqueous concentrate was extracted with EtOAc (3×100 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and evaporated in vacuo to obtain a clear viscous oil. Further purification was achieved by column chromatography (SiO_2, EtOAc) to afford (*R,S*)-**6** as a clear viscous oil (1.27 g, 71%): R_f 0.64 (EtOAc); IR (liquid film) 3337, 2929, 1653, 1540, 1455, 1260, 1194, 1129, 1029, 699 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.26 (s, OCH_3), 3.46 (dd, $J=6.0$, 9.9 Hz, C*H*H′OCH$_3$), 3.53 (dd, $J=3.3$, 9.9 Hz, CH*H*′OCH$_3$), 4.02–4.09 (m, C*H*OH), 4.28 (d, $J=6.0$ Hz, CH_2Ph), 5.69 (d, $J=5.4$ Hz, CHO*H*), 7.19–7.40 (m, Ph*H*), 8.27 (t, $J=6.0$ Hz, N*H*), the ^1H NMR assignments were consistent with the COSY spectrum; ^{13}C NMR (DMSO-d_6) 41.7 (CH_2Ph), 58.4 (OCH_3), 71.1 (CH), 74.6 (CH_2OCH$_3$), 126.6, 127.0, 128.1, 139.6 (Ph), 171.6 (C(O)) ppm; MS (CI^+) (rel. int.) 210 ($M^+ + 1$, 100), 121 (16), 120 (51); M_r (+CI) 210.113 86 [$M^+ + 1$] (calcd for $C_{11}H_{16}NO_3$ 210.113 01); Anal. calcd for $C_{11}H_{15}NO_3 \cdot 0.45\ H_2O$: C, 60.80; H, 7.12; N, 6.45. Found: C, 60.95; H, 7.11; N, 6.47.

Synthesis of (*R*)-*N*-benzyl 3-hydroxy-2-methylpropionamide ((*R*)-16). A solution containing (*R*)-**15** (2 g, 17 mmol) and benzylamine (10 mL) was stirred neat at 100°C (18 h). The solution was allowed to cool to room temperature and then triturated with ethyl ether (150 mL) to give a white solid, which was isolated by filtration and washed with additional amounts (50 mL) of ethyl ether to afford (*R*)-**16** as a white crystalline solid (1.75 g, 54%): mp 120–121°C; $[\alpha]_D^{24}$ −24.9° (*c* 1.5, MeOH); R_f 0.53 (EtOAc); IR (KBr) 3369, 3266, 3088, 1649, 1559, 1453, 1332, 1265, 1073, 1026, 739, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, $J=7.2$ Hz, CH_3), 2.10–2.40 (m, O*H*), 2.45–2.58 (m, C*H*), 3.74 (d, $J=6.0$ Hz, CH_2OH), 4.46 (d, $J=5.4$ Hz, CH_2Ph), 6.10–6.30 (m, N*H*), 7.20–7.40 (m, Ph*H*); ^{13}C NMR (DMSO-d_6) 14.4 (CH$_3$), 41.8 (CH$_2$Ph), 42.8 (CH), 63.8 (CH$_2$OH), 126.6, 127.0, 128.2, 139.7 (Ph), 174.4 (C(O)) ppm, the ^{13}C NMR assignments were consistent with the APT spectrum; MS (CI^+) (rel. int.) 194 ($M^+ + 1$, 100); M_r (+CI) 194.118 13 [$M^+ + 1$] (calcd for $C_{11}H_{16}NO_2$ 194.118 10); Anal. calcd for $C_{11}H_{15}NO_2$: C, 68.40; H, 7.80; N, 7.25. Found: C, 68.27; H, 7.82; N, 7.15.

Synthesis of (*S*)-*N*-benzyl 3-hydroxy-2-methylpropionamide ((*S*)-16). Following the preceding procedure and using (*S*)-**15** (2.00 g, 17 mmol) and benzylamine (10 mL), (*S*)-**16** was obtained as a white crystalline solid (1.82 g, 56%): mp 120–122°C; $[\alpha]_D^{24}$ +25.6° (*c* 1.3, MeOH); R_f 0.53 (EtOAc); IR (KBr) 3372, 3269, 3054, 1650, 1562, 1445, 1340, 1268, 1070, 1025, 742, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (d, $J=6.9$ Hz, CH_3), 2.40–2.60 (m, O*H*, C*H*), 3.73 (d, $J=5.7$ Hz, CH_2OH), 4.45 (d, $J=5.7$ Hz CH_2Ph), 6.20–6.35 (m, N*H*), 7.20–7.40 (m, Ph*H*); ^{13}C NMR (DMSO-d_6) 14.3 (CH$_3$), 41.8 (CH$_2$Ph), 42.8 (CH), 63.8 (CH$_2$OH), 126.6, 127.0, 128.2, 139.7 (Ph), 174.4 (C(O)) ppm, the ^{13}C NMR assignments were consistent with the APT spectrum; MS (CI^+) (rel. int.) 194 ($M^+ + 1$, 100); M_r (+CI) 194.118 32 [$M^+ + 1$] (calcd for $C_{11}H_{16}NO_2$ 194.118 10). Anal. calcd for $C_{11}H_{15}NO_2$: C, 68.40; H, 7.80; N, 7.25. Found: C, 68.17; H, 7.79; N, 7.14.

Synthesis of (*R*)-*N*-benzyl 3-methoxy-2-methylpropionamide ((*R*)-8). To an acetonitrile solution (50 mL) of (*R*)-**16** (1.15 g, 6.0 mmol) was successively added Ag_2O (2.10 g, 9.0 mmol) and MeI (0.6 mL, 9.0 mmol) and the mixture was stirred at room temperature (18 h). The insoluble salts were removed by filtration, and the filtrate was evaporated in vacuo. The oily residue was purified by column chromatography (SiO_2, ethyl ether: pet. ether, 1:1) to afford pure (*R*)-**8** as a clear oil (1.23 g, 60%): $[\delta]_D^{24}$ −5.7° (*c* 3.2, MeOH); R_f 0.40 (ethyl ether: pet. ether, 1:1); IR (liquid film) 3311, 2932, 2830, 1653, 1553, 1455, 1388, 1258, 1205, 1109, 1029, 955, 732, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, $J=6.9$ Hz, CH_3), 2.49–2.61 (m, C*H*), 3.34 (s, OCH_3), 3.38–3.55 (m, CH_2OCH$_3$), 4.46 (d, $J=5.7$ Hz, CH_2Ph), 6.42–6.55 (m, N*H*), 7.20–7.39 (m, Ph*H*); ^{13}C, NMR ($CDCl_3$) 14.1 (CH$_3$), 41.2 (CH), 43.4 (CH$_2$Ph), 59.0 (OCH$_3$), 75.0 (CH$_2$OCH$_3$), 127.3, 127.6, 128.7, 138.7 (Ph), 174.8 (C(O)) ppm, the ^{13}C NMR assignments were consistent with the APT spectrum; MS (CI^+) (rel. int.) 208 ($M^+ + 1$, 100); M_r (+CI) 208.134 37 [$M^+ + 1$] (calcd for $C_{12}H_{18}NO_2$ 208.133 75); Anal. calcd for $C_{12}H_{17}NO_2 \cdot 0.25\ H_2O$: C, 68.09; H, 8.27; N, 6.62. Found: C, 68.28 H, 8.20; N, 6.52.

Synthesis of (*S*)-*N*-benzyl 3-methoxy-2-methylpropionamide ((*S*)-8). The procedure utilized for the preparation of (*R*)-**8** was repeated using (*S*)-**16** (1.47 g, 7.62 mmol), acetonitrile (50 mL), Ag_2O (3.20 g, 13.7 mmol) and MeI (0.91 mL, 13.7 mmol) to afford pure (*S*)-**8** as a clear oil (1.32 g, 84%): $[\alpha]_D^{24}$ +5.3° (*c* 4.7, MeOH); R_f 0.40 (ethyl ether: pet. ether, 1:1); IR (liquid film) 3315, 2927, 2835, 1650, 1550, 1457, 1390, 1255, 1198, 1097, 1030, 950, 740, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, $J=7.2$ Hz, CH_3),

2.50–2.61 (m, C*H*), 3.34 (s, OCH_3), 3.40–3.55 (m, CH_2OCH_3), 4.46 (d, $J = 5.7$ Hz, CH_2Ph), 6.40–6.52 (m, N*H*), 7.20–7.40 (m, Ph*H*); ^{13}C NMR ($CDCl_3$) 14.2 (CH$_3$), 41.33 (CH), 43.5 (CH$_2$Ph), 59.2 (OCH$_3$), 75.1 (CH$_2$OCH$_3$), 127.5, 127.7, 128.9, 138.8 (Ph), 174.8 (C(O)), the ^{13}C NMR assignments were consistent with the APT spectrum; MS (CI^+) (rel. int.) 208 ($M^+ + 1$, 100); M_r (+CI) 208.134 36 [$M^+ + 1$] (calcd for $C_{12}H_{18}NO_2$ 208.133 75); Anal. calcd for $C_{12}H_{17}NO_2 \cdot 0.25\ H_2O$: C, 68.09; H, 8.27; N, 6.62. Found: C, 68.11; H, 8.19; N, 6.47.

Pharmacology. Compounds were screened under the auspices of the National Institutes of Health's Anticonvulsant Screening Project. Experiments were performed in male rodents, specifically, albino Carthworth Farms No. 1 mice (intraperitoneal route), and albino Sprague–Dawley rats (oral route). The mice weighed between 18 and 25 g while rats were between 100 and 150 g. All animals had free access to feed and water except during the actual testing period. Housing, handling and feeding were all in accordance with recommendations contained in the "Guide for the Care and Use of Laboratory Animals". All of our compounds were administered in suspensions of 0.5% (w/v) of methylcellulose in water. The volumes administered were 0.01 mL/g of body weight for mice and 0.2 mL/10 g for rats. Anticonvulsant activity was established using the electrical (maximal electroshock of MES) test.[20] For the MES test, a drop of electrolyte solution with an anesthetic (0.5% butacaine hemisulfate in 0.9% sodium chloride) was placed in the eyes of the animals prior to positioning the corneal electrodes and delivery of a nonlethal current. A 60-cycle alternating current was administered for 0.2 s in both species, utilizing 50 mA in mice and 150 mA in rats.[21] Protection endpoints were defined as the abolition of the hind limb tonic extensor component of the induced seizure.[22] In mice, effects of compounds on forced spontaneous motor activity were determined using the rotorod test. The inability of experimental mice to maintain their balance for 1 min on a 1 in diameter knurled rod rotating at 6 rpm in three successive trials was interpreted as a demonstration of motor impairment. Under these conditions, mice can normally maintain their balance indefinitely. Motor impairment in rats was assessed by observing the overt evidence of ataxia, abnormal gait and stance, and/or loss of placing response and muscle tone. In the mouse identification screens all compounds were administered at three dose levels (30, 100, 300 mg/kg) and two time periods (0.5 and 4 h). Typically, in the MES seizure 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 (Table 1). Oral rat identification screening was performed using four animals at a fixed dose of 30 mg/kg for both the MES and the rotorod toxicity tests over five time periods ranging from one-quarter to four hours post drug administration. The quantitative determination of the median effective (ED_{50}) and toxic doses (TD_{50}) were conducted at previously calculated times of peak effect using the ip route in mice and oral route for rats. 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 desired endpoint (abolition of hindlimb tonic extensor component) 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.[23]

References and Notes

1. Choi, D.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **1996**, *4*, 2105.
2. Porter, R. J.; Cereghino, J. J.; Gladding, G. D.; Hessie, B. J.; Kupferberg, H. J.; Scoville, B.; White, B. G. *Cleveland Clin. Q.* **1984**, *51*, 293.
3. Conley, J. D.; Kohn, H. *J. Med. Chem.* **1987**, *30*, 567.
4. Kohn, H.; Conley, J. D. *Chem. Brit.* **1988**, *24*, 231.
5. Choi, D.; Stables, J. P.; Kohn, H. *J. Med. Chem.* **1996**, *39*, 1907.
6. Kohn, H.; Sawhney, K. N.; LeGall, P.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1991**, *34*, 2444.
7. Kohn, H.; Conley, J. D.; Leander, J. D. *Brain Res.* **1988**, *457*, 371.
8. Kohn, H.; Sawhney, K. N.; Bardel, P.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1993**, *36*, 3350.
9. Gluchowski, C.; Bischoff, T. E.; Garst, M. E.; Kaplan, L. J.; Dietrich, S. W.; Aswad, A. S.; Gaffney, M. A.; Aoki, K. R.; Garcia, C.; Wheeler, L. A. *J. Med. Chem.* **1991**, *34*, 392.
10. Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1980**, *44*, 199.
11. For comparable procedures for resolving stereoisomers, see: Weisman, G. R. In *Asymmetric Synthesis—Analytical Methods*, Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, pp 153–171.
12. For comparable procedures resolving stereoisomers, see: Dyllick-Brenzinger, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 1166.
13. For comparable procedures resolving stereoisomers, see: Parker, D.; Taylor, R. J. *Tetrahedron* **1987**, *43*, 5431.
14. Stables, J. P.; Kupferberg, H. J. In *Molecular and Cellular Targets for Antiepileptic Drugs*, Avanzini, G.; Tanganelli, P.; Avoli, M., Eds.; John Libbey: London, 1997, pp 191–198.
15. Swinyard, E. A.; Woodhead, J. H.; White, M. S.; Franklin, M. R. In *Antiepileptic Drugs*, 3rd ed., Levy, R. H.; Dreifuss, F. E.; Mattson, R. H.; Meldrum, B. S.; Penry, J. K., Eds.; Raven Press: New York, 1989, p 97.
16. Dunham, N. W.; Miwa, T. S. *J. Am. Pharm. Assoc.* **1957**, *46*, 208.
17. White, H. S.; Woodhead, J. H.; Franklin, M. R. In *Antiepileptic Drugs*, 4th ed., Levy, R. H.; Mattson, R. H.; Meldrum, B. S., Eds.; Raven Press: New York, 1995, pp 99–110.
18. Andurkar, S. V.; Stables, J. P.; Kohn, H. *Tetrahedron: Asymmetry* **1998**, *9*, 3841.
19. Attempted separation of the diastereomers using other blends of TLC solvents (e.g. ethyl acetate–petroleum ether, ethyl acetate–hexanes, ethyl acetate–acetone, chloroform–methanol) were unsuccessful.
20. Swinyard, E. A.; Woodhead, J. H.; White, H. S.; Franklin, M. R. General Principles: Experimental Selection, Quantification, and Evaluation of Anticonvulsants. In *Antiepileptic Drugs,* 3rd edn; Levy, R. H.; Driefuss, F. E.; Mattson, R. H.; Meldrum, B. S.; Penry, J. K., Eds.; Raven Press: New York, 1989; pp 85–102.
21. Woodbury, L. A.; Davenport, V. D. *Arch. Int. Pharamacodyn. Ther.* **1952**, *92*, 97–104.
22. White, H. S.; Woodhead, J. H.; Franklin, M. R. In *Antiepileptic Drugs*, Levy, R. H.; Mattson, R. H.; Meldrum, B. S. Eds.; Raven: New York, 1998, pp 99–100.
23. Finney, D. J. *Probit Analysis*, 3rd ed. Cambridge University Press: London, 1971.