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Synthesis and Anticonvulsant Activities of (*R*)-*N*-(4′-Substituted)benzyl 2-Acetamido-3-methoxypropionamides

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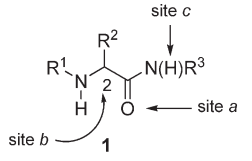
The structure−activity relationship (SAR) for the *N*-benzyl group in the clinical antiepileptic agent (*R*)-lacosamide [(*R*)-*N*-benzyl 2-acetamido-3-methoxypropionamide, (*R*)-**3**] has been explored. Forty-three compounds were prepared and then evaluated at the National Institute of Neurological Disorders and Stroke Anticonvulsant Screening Program for seizure protection in the maximal electroshock (MES) and subcutaneous Metrazol models. Comparing activities for two series of substituted aryl regioisomers (2′, 3′, 4′) showed that 4′-modified derivatives had the highest activity. Significantly, structural latitude existed at the 4′-site. The SAR indicated that nonbulky 4′-substituted (*R*)-**3** derivatives exhibited superb activity, independent of their electronic properties. Activities in the MES test of several compounds were comparable with or exceeded that of (*R*)-**3** and surpassed the activities observed for the traditional antiepileptic agents phenytoin, phenobarbital, and valproate.

Epilepsy, a major neurological disorder that affects all populations,[1] describes the types of recurrent seizures produced by paroxysmal, excessive, synchronous neuronal discharges in the brain.[2,3] In the United States alone, more than 2 million people suffer from epilepsy and its sequelae; 340000 are children.[4] For many of these individuals, the disabilities and associated neuropsychological and behavioral factors adversely affect their quality of life. The lifestyle restrictions and the large expense for treatment, lost productivity, and rehabilitation result in a huge cost to society.[4]

The treatment mainstay for patients with epileptic disorders has been the long-term and consistent administration of anticonvulsant drugs.[5,6] Unfortunately, current medications are ineffective for approximately one-third of these patients.[7] Many continue to have seizures, while others experience disturbing side effects (e.g., drowsiness, dizziness, nausea, and liver damage).[8] Thus, there is a need for more efficacious drugs that function by different pharmacological pathways.

In 1985, we discovered a novel class of anticonvulsant agents, termed functionalized amino acids (FAAs,[a] **1**).[9] We subsequently synthesized more than 250 FAAs.[10−18] Each of the newly synthesized molecules was evaluated for activity and toxicity in a series of in vivo animal models. Reports from our investigations have led other researchers to further pursue the pharmacological benefits of FAAs.[19] Most sites in **1** (e.g., R^1, R^2, and R^3) have been modified. We learned that acetyl [$CH_3C(O)$] exhibited the highest anticonvulsant activity in an induced rodent seizure model [maximal electroshock (MES)] for R^1. The MES test is a well-established, commonly used animal model for identifying new drug candidates having potential human efficacy to treat generalized and partial seizures that are secondarily generalized. We also determined that the optimal R^3 substituent was a benzyl ($PhCH_2$)-type moiety. Finally, isoelectronic substitution of the amide carbonyl (site *a*) with a thiocarbonyl group, insertion of an alkyl unit or deletion of the chiral center in **1** (site *b*), and replacement of the amide hydrogen with an alkyl group (site *c*) reduced anticonvulsant activity.[9−18]



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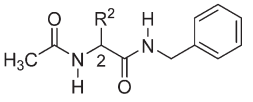

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The stringent structural requirements for **1** (R^1, R^3, sites *a*−*c*) led us to focus on molecular template **2**. We observed impressive anticonvulsant activities in both mice and rats for smaller R^2 groups (e.g., 2-furanyl, 2-pyrrolyl, 1-pyrazolyl, 2-oxazolyl, 2-thiazolyl, 2-pyridyl, 2-pyrimidyl, 2-pyrazinyl, *O*-methylhydroxylamino, and *N*,*O*-dimethylhydroxylamino) that contained a substituted heteroatom, that is, one atom removed from the C(2) chiral atom.[13−16,18] These compounds exhibited activity in the MES-induced seizure test (mice, ip) that were comparable with or exceeded that of the standard

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[a] Abbreviations: FAA, functionalized amino acid; MES, maximal electroshock seizure; SAR, structure−activity relationship; AB, affinity bait; CR, chemical reporter; IBCF, isobutyl chloroformate; NMM, *N*-methylmorpholine; DMTMM, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride; NINDS, National Institute of Neurological Disorders and Stroke; ASP, Anticonvulsant Screening Program; ip, intraperitoneally; po, orally; ED_{50}, effective dose (50%); TD_{50}, neurological impairment (toxicity, 50%); PI, protective index; scMet, subcutaneous Metrazol.

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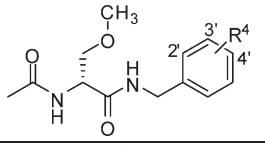
Table 1. Effect of Site of *N*-Benzyl Substitution on the Anticonvulsant Activities of (*R*)-*N*-(4-Substituted)benzyl 2-Acetamido-3-methoxypropionamide Derivatives[a]



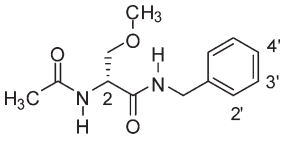
				mice (ip)[b]			rats (po)[c]		
no.	R^4	aryl site	mp (°C)	MES,[d] ED_{50}	Tox,[e] TD_{50}	PI[f]	MES,[d] ED_{50}	Tox,[g] TD_{50}	PI[f]
(*R*)-**3**[h]	H		143−144	4.5 [0.5] (3.7−5.5)	27 [0.25] (26−28)	6.0	3.9 [2] (2.6−6.2)	> 500 [0.5]	> 130
(*R*)-**4**	F	2′	173−175	> 10, < 30 [0.5]	> 100, < 300 [0.5]		11 [0.25] (9.5−13)	> 30 [0.5]	> 2.7
(*R*)-**5**[h]	F	3′	150−151	6.9 [0.25] (6.1−8.0)	46 [0.25] (40−55)	6.7	6.9 [0.5] (4.3−9.9)	> 400	> 58
(*R*)-**6**[h]	F	4′	144−145	4.2 [0.5] (3.5−5.1)	28 [0.25] (22−34)	6.7	2.6 [2] (1.9−3.6)	> 125, < 250	> 48
(*R*)-**7**	OCF_3	2′	130−131	> 30, < 100 [0.25]	> 100, < 300 [0.5]		23 [0.25] (16−35)	> 500	> 22
(*R*)-**8**	OCF_3	3′	147−148	> 10, < 30 [0.5]	> 30, < 100 [0.5]				
(*R*)-**9**	OCF_3	4′	134−135	3.6 [0.25] (3.0−4.3)	13 [0.25] (9.2−19)	3.6	1.7 [0.5] (1.4−2.2)	63 [0.5] (47−76)	37
phenytoin[i]				9.5 [2] (8.1−10)	66 [2] (53−72)	6.9	30 [4] (22−39)	*j*	> 100
phenobarbital[i]				22 [1] (15−23)	69 [0.5] (63−73)	3.2	9.1 [5] (7.6−12)	61 [0.5] (44−96)	6.7
valproate[i]				270 [0.25] (250−340)	430 [0.25] (370−450)	1.6	490 [0.5] (350−730)	280 [0.5] (190−350)	0.6

[a] The compounds were tested through the auspices of the NINDS ASP. [b] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. [c] The compounds were administered orally. ED_{50} and TD_{50} values are in milligrams per kilogram. [d] MES, maximal electroshock seizure test. [e] TD_{50} value determined from the rotorod test. [f] PI, protective index (TD_{50}/ED_{50}). [g] Tox, behavioral toxicity. [h] From ref 18. [i] From ref 34. [j] No ataxia observed up to 3000 mg/kg.

antiepileptic agent phenytoin (MES ED_{50} = 9.5 mg/kg) in the MES-induced seizure test.[20]

A single **1** structure−activity relationship (SAR) feature dominated all others. We demonstrated that the principal anticonvulsant activity of the test candidate resided in the D-amino acid configuration.[11−13,18] The potency ratio of the more active to the less active isomer[21] ranged from 10 to > 22. These differences are among the highest, if not the highest, reported for MES-selective anticonvulsants.

(*R*)-Lacosamide [(*R*)-**3**, (*R*)-*N*-benzyl 2-acetamido-3-methoxypropionamide[18]] emerged as the lead compound, **1**, and has been successfully marketed in the United States and Europe for the adjunctive treatment of partial-onset seizures in adults.[22] Whole animal pharmacology studies have revealed a distinctive profile for (*R*)-**3** and other **2**s.[11−18,23] Accordingly, we have used agents containing "affinity bait" (AB) and "chemical reporter" (CR) groups to initiate a chemical biology-based study to search the brain proteome for (*R*)-**3** binding targets.[24] The AB moiety is designed to irreversibly react with the target, and the CR group permits protein detection and capture. In an effort to facilitate these studies, we have determined the SAR for the C(2) side chain oxygen substituent in (*R*)-**3**[25] that identifes the structural parameters for the AB and CR moieties at this site. We report herein that substitution at the *N*-benzyl 4′-position in (*R*)-**3** provided compounds that exhibit superb anticonvulsant activities and safety profiles. This finding was surprising since preliminary studies with other **2**s suggested that substitutions made at this specific site were not very promising candidates.[15,26,27]



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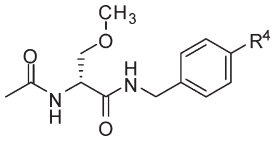
Results and Discussion

Choice of Compounds. Earlier studies of **2** indicated that substituting an *N*-benzyl group led to compounds with diminished anticonvulsant profiles.[15,26,27] When the 4′-substituted **2** compounds were compared with the 3′-substituted isomers, the 4′-substituted derivatives provided significantly greater seizure protection as defined in the rodent MES seizure model.[18,26] To confirm this finding, we prepared two different series of compounds in which we placed the *N*-benzyl amide substituent at either the 4′- or 3′-site (Table 1). In addition, we prepared the 2′-regioisomer. The fluoro [(*R*)-**4**−(*R*)-**6**] and the trifluoromethoxy [(*R*)-**7**−(*R*)-**9**] substituents were selected for this study. In both series, the order of favorable anticonvulsant activity in the MES test (mice, ip) was as follows: 4′ > 3′ > 2′ (see Pharmacological Activity). Accordingly, we focused our SAR study on the 4′-position in (*R*)-**3**.

Table 2 lists the prepared *N*-(4′-substituted)benzyl (*R*)-**3** derivatives [(*R*)-**6** and (*R*)-**9**−(*R*)-**39**]. The first set of compounds contained a hydrocarbon group attached at the 4′-benzyl site. We determined the effect of the structural size of the *N*-benzyl 4′-substituent on (*R*)-**3** anticonvulsant activity by preparing alkyl derivatives (*R*)-**10**−(*R*)-**14**. Next, the effect of a two-carbon hydrocarbon substituent at the 4′-site shape was evaluated by systematically changing it from tetrahedral (sp^3) [(*R*)-**11**] to planar (sp^2) [(*R*)-**21**] to linear (sp) [(*R*)-**23**[24]]. Then, to gauge the importance of size, electronic effects, hydrophobic interactions, and hydrogen bonding interactions on anticonvulsant activity, we synthesized 4′-substituted hydrocarbon derivatives (*R*)-**15**−(*R*)-**20**, (*R*)-**22**, and (*R*)-**24**−(*R*)-**27** in which additional groups were appended to the hydrocarbon moiety. A second set of compounds prepared were *N*-(4′-substituted)benzyl (*R*)-**3** analogues, (*R*)-**6**, (*R*)-**9**, and (*R*)-**28**−(*R*)-**39**, that contained a substituent directly attached to the *N*-benzyl moiety that either could withdraw or could donate electrons to the aromatic ring. Here, we synthesized the cyano [(*R*)-**28**], aldehyde [(*R*)-**29**], carboxylic acid [(*R*)-**30**], methyl ester [(*R*)-**31**], nitrogen-substituted [(*R*)-**32**−(*R*)-**34**], oxygen-containing [(*R*)-**9** and (*R*)-**35**], halogen-substituted [(*R*)-**6** and (*R*)-**36**−(*R*)-**38**], and sulfamide [(*R*)-**39**] (*R*)-**3** analogues.

Table 2. Selected Physical and Pharmacological Data for (*R*)-*N*-(4-Substituted)benzyl 2-Acetamido-3-methoxypropionamide Derivatives[a]



			mice (ip)[b]			rats (po)[c]		
no.	R^4	mp (°C)	MES,[d] ED_{50}	Tox,[e] TD_{50}	PI[f]	MES,[d] ED_{50}	Tox,[g] TD_{50}	PI[f]
(*R*)-**3**[h]	H	143−144	4.5 [0.5] (3.7−5.5)	27 [0.25] (26−28)	6.0	3.9 [2] (2.6−6.2)	> 500 [0.5]	> 130
(*R*)-**10**	CH_3	128−129	11 [0.25] (7.3−15)	31 [0.25] (22−38)	3	8.1 [0.25] (5.6−10)	> 500	> 62
(*R*)-**11**	CH_2CH_3	132−133	> 10, < 30 [0.5]	> 30, < 100 [0.5]		18 [0.25] (13−22)	> 250	> 14
(*R*)-**12**	$(CH_2)_2CH_3$	126−127	8.5 [0.25] (6.4−10)	13 [0.5] (12−15)	1.5	< 30 [0.25−0.5]	> 30 [0.25−4.0]	
(*R*)-**13**	$CH(CH_3)_2$	95−97	> 10, < 30 [0.5]	> 100, < 300 [0.5]		> 30 [0.25−4.0]	> 30 [0.25−4.0]	
(*R*)-**14**	$C(CH_3)_3$	125−126	> 100, < 300 [0.5]	> 100, < 300 [0.5]		> 30 [0.25−4.0]	> 30 [0.25−4.0]	
(*R*)-**15**	$CH_2NH_2 \cdot HCl$	> 210	> 300 [0.5]	> 300 [0.5]				
(*R*)-**16**	CH_2NH-t-Boc	153−154	> 300 [0.5]	> 300 [0.5]				
(*R*)-**17**	CH_2OCH_3	119−120	73 [0.25] (62−88)	180 [0.25] (160−210)	2.3	45 [0.5] (29−76)	> 500 [0.25−4.0]	> 11
(*R*)-**18**	CF_3	160−161	> 10, < 30 [0.5]	> 100, < 300 [0.5]		4.9 [1] (2.7−7.6)	> 280	> 57
(*R*)-**19**	$(CH_2)_3OH$	118	> 300 [0.5]	> 300 [0.5]				
(*R*)-**20**	$(CH_2)_3OCH_3$	105−107	20 [0.25] (18−23)	62 [0.25] (57−74)	3.1	16 [0.5] (8.8−25)	> 500 [0.5−4.0]	> 32
(*R*)-**21**	$CH{=}CH_2$	148−149	3.5 [0.25] (2.8−4.6)	16 [0.25] (11−19)	4.6	7.6 [0.5] (2.9−12)	> 150, < 225	> 20
(*R*)-**22**	C_6H_5	178−180	8.0 [0.5] (5.3−12)	11 [0.5]		2.0 [0.5] (0.8−3.4)	49 [0.5] (34−77)	> 25
(*R*)-**23**[i]	$C{\equiv}CH$	161−162	> 3, < 10 [0.5]	> 10, < 30 [0.5]		3.4 [0.5] (2.0−6.1)	> 250	> 74
(*R*)-**24**	$C{\equiv}C{-}CH_3$	178−180	> 10, < 30 [0.5]	> 30, < 100 [0.5]				
(*R*)-**25**	$C{\equiv}C{-}C(CH_3)_3$	120−121	> 300	> 30, < 100 [0.5]				
(*R*)-**26**	$C{\equiv}C{-}Si(CH_3)_3$	126−127	> 3 [0.5]	> 3, < 10 [0.5]				
(*R*)-**27**	$C{\equiv}CCH_2OCH_3$	141−142	10 [0.25] (7.7−12)	15 [0.25] (13−17)	1.5	18 [1] (8.6−33)	100 [0.5] (86−120)	5.5
(*R*)-**28**	CN	168−169	150 [1.0] (140−170)	> 500	> 3.3	> 30	> 30	
(*R*)-**29**	C(H)O	132−133	> 300	> 300				
(*R*)-**30**	CO_2H	197−198	> 300 [0.5]	> 300 [0.5]				
(*R*)-**31**	CO_2CH_3	167−168	> 100, < 300	> 300 [0.5]				
(*R*)-**32**	NH_2	151−152	> 300 [0.5]	> 300 [0.5]				
(*R*)-**33**	$N(H)C(O)CF_3$	202−204	> 300 [0.5]	> 100, < 300 [0.5]		> 30	> 30	
(*R*)-**34**	N_3	149−150	8.4 [0.25] (5.7−12)	46	5.5	3.9 [0.5] (2.5−6.2)	> 250	> 64
(*R*)-**35**	OCH_3	146−147	> 30, < 100 [0.5]	> 100, < 300 [0.5]		28 [0.5] (21−35)	> 500 [0.25−4.0]	> 18
(*R*)-**9**	OCF_3	134−135	3.6 [0.25] (3.0−4.3)	13 [0.25] (9.2−19)	3.6	1.7 [0.5] (1.4−2.2)	63 [0.5] (48−76)	37
(*R*)-**6**[h]	F	144−145	4.2 [0.25] (3.5−5.1)	28 [0.25] (22−34)	6.7	2.6 [2] (1.9−3.6)	> 125, < 250	> 48
(*R*)-**36**	Cl	155	5.0 [0.25] (4.4−5.6)	28 [0.25] (22−33)	5.6	1.0 [0.5] (0.4−1.8)	> 200	> 200
(*R*)-**37**	Br	159−161	8.7 [0.25] (7.2−10)	30 [0.25] (24−36)	3.5	4.9 [0.5] (3.0−7.2)	300 [0.25] (220−350)	61
(*R*)-**38**	I	159−160	16 [0.25] (14−18)	41 [0.25] (28−58)	2.6	12 [0.25] (7.0−19)	> 500 [0.25−4.0]	> 43
(*R*)-**39**	SO_2NH_2	177−179	> 300 [0.5]	> 300 [0.5]				
phenytoin[j]			9.5 [2] (8.1−10)	66 [2] (53−72)	6.9	30 [4] (22−39)	*k*	> 100
phenobarbital[j]			22 [1] (15−23)	69 [0.5] (63−73)	3.2	9.1 [5] (7.6−12)	61 [0.5] (44−96)	6.7
valproate[j]			270 [0.25] (250−340)	430 [0.25] (370−450)	1.6	490 [0.5] (350−730)	280 [0.5] (190−350)	0.6

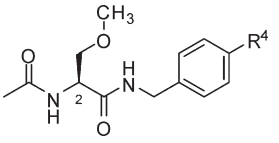
[a] The compounds were tested through the auspices of the NINDS ASP. [b] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. [c] The compounds were administered orally. ED_{50} and TD_{50} values are in milligrams per kilogram. [d] MES, maximal electroshock seizure test. [e] TD_{50} value determined from the rotorod test. [f] PI, protective index (TD_{50}/ED_{50}). [g] Tox, behavioral toxicity. [h] From ref 18. [i] From ref 24. [j] From ref 34. [k] No ataxia observed up to 3000 mg/kg.

Finally, for eight *N*-(4′-substituted)benzyl (*R*)-**3** derivatives, we prepared the corresponding (*S*)-stereoisomer (Table 3). Structural characterization of the (*S*)-derivatives [(*S*)-**11**, (*S*)-**21**, (*S*)-**23**, (*S*)-**26**, (*S*)-**28**, (*S*)-**29**, (*S*)-**34**, and (*S*)-**38**] confirmed that the syntheses routinely gave stereospecific products. Determining their pharmacological evaluation permitted us to verify that the principal activity for the *N*-(4′-substituted)benzyl 2-acetamido-3-methoxypropionamides resided in the (*R*)-stereoisomer (D-configuration).

Chemistry. Synthesis of (*R*)-**4**−(*R*)-**39** followed a standard protocol (Scheme 1). Beginning with either *N*-t-Boc (**40**)- or *N*-Cbz (**41**)-protected D-serine, the acid was coupled with the *N*-(4′-substituted)benzylamine **42**, using either the mixed anhydride [isobutyl chloroformate (IBCF) and *N*-methylmorpholine (NMM)][28a] or the 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[28b] procedure to give amide **43** or **44**, respectively. The 4′-substituted benzyl amine was either commercially available or synthesized using previously reported methods (see the Supporting Information). We observed that amide coupling proceeded with no racemization of the C(2) chiral center. After purification, methylation of the serine hydroxy group with CH_3I and Ag_2O provided the optically pure ethers **45** and **46**. Removing the N-protecting group (i.e., acid, H_2/Pd-C) followed by acetylation (acetyl chloride, Et_3N) gave the desired *N*-(4′-substituted)benzyl (*R*)-**3** derivative **47**, in most cases.

For the (*R*)-stereoisomers of **12**, **15**, **19**, **20**, **23**−**27**, **29**, **30**, and **32**−**34**, additional steps were required to generate the sought-after compound. 4′-Iodo derivative (*R*)-**38** served as a precursor to (*R*)-**12** and (*R*)-**23**−(*R*)-**27** (Scheme 2). Using Sonogashira coupling conditions [CuI, $PdCl_2(PPh_3)_2$, and

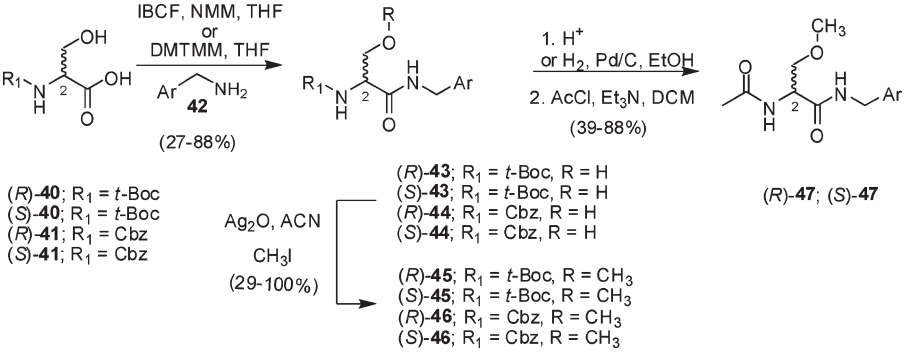
Table 3. Effect of C(2) (*S*)-Stereochemistry on the Anticonvulsant Activities of (4-Substituted)benzyl Analogues of *N*-Benzyl 2-Acetamido-3-methoxypropionamide Derivatives[a]



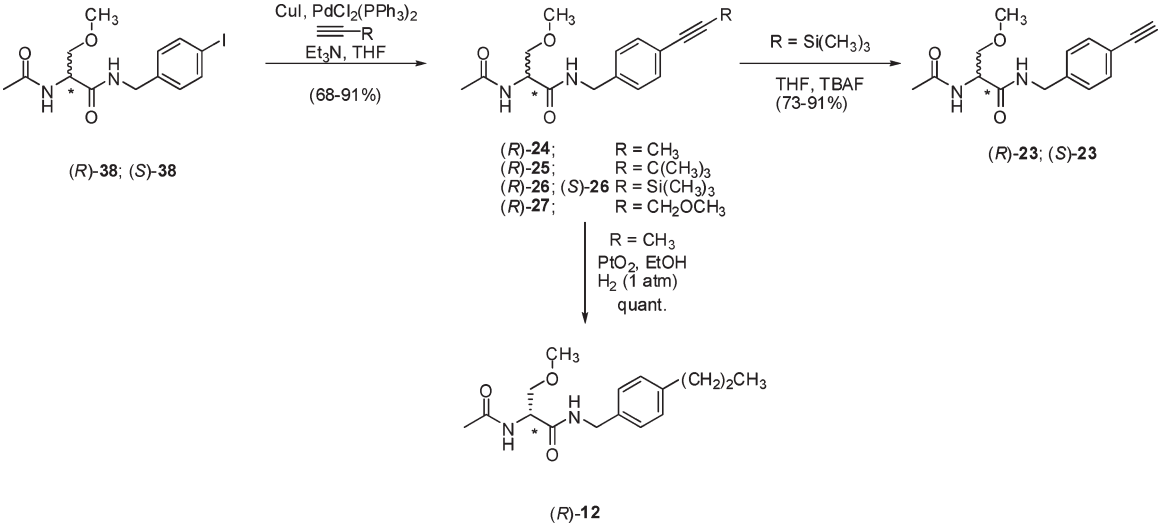
			mice (ip)[b]			rats (po)[c]		
no.	R^4	mp (°C)	MES,[d] ED_{50}	Tox,[e] TD_{50}	PI[f]	MES,[d] ED_{50}	Tox,[g] TD_{50}	PI[f]
(*S*)-**3**[h]	H	143−144	> 100, < 300	> 300		> 30	> 30	
(*S*)-**11**	CH_2CH_3	132−133	> 100, < 300 [0.5]	> 100, < 300 [0.5]		> 30 [0.25−4]	> 30 [0.25−4]	
(*S*)-**21**	$CH{=}CH_2$	140−142	> 100, < 300 [0.5]	> 300				
(*S*)-**23**[i]	C≡CH	159−160	> 300	> 300				
(*S*)-**26**	$C{\equiv}C{-}Si(CH_3)_3$	126−127	> 30, < 100 [0.5]	> 100, < 300 [0.5]		> 30	> 30	
(*S*)-**28**	CN	168−169	> 100, < 300 [0.5]	> 300 [0.5]		> 30	> 30	
(*S*)-**29**	C(H)O	132−133	> 300	> 300				
(*S*)-**34**	N_3	149−150	> 100, < 300	> 300		> 30	> 30	
(*S*)-**38**	I	159−160	> 100, < 300 [0.5]	> 300		> 30	> 30	
phenytoin[j]			9.5 [2] (8.1−10)	66 [2] (53−72)	6.9	30 [4] (22−39)	*k*	> 100
phenobarbital[j]			22 [1] (15−23)	69 [0.5] (63−73)	3.2	9.1 [5] (7.6−12)	61 [0.5] (44−96)	6.7
valproate[j]			270 [0.25] (250−340)	430 [0.25] (370−450)	1.6	490 [0.5] (350−730)	280 [0.5] (190−350)	0.6

[a] The compounds were tested through the auspices of the NINDS ASP. [b] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. [c] The compounds were administered orally. ED_{50} and TD_{50} values are in milligrams per kilogram. [d] MES, maximal electroshock seizure test. [e] TD_{50} value determined from the rotorod test. [f] PI, protective index (TD_{50}/ED_{50}). [g] Tox, behavioral toxicity. [h] From ref 18. [i] From ref 24. [j] From ref 34. [k] No ataxia observed up to 3000 mg/kg.

Scheme 1. General Procedure for the Preparation of (*R*)- and (*S*)-*N*-(4′-Substituted)benzyl 2-Acetamido-3-methoxypropionamide Derivatives

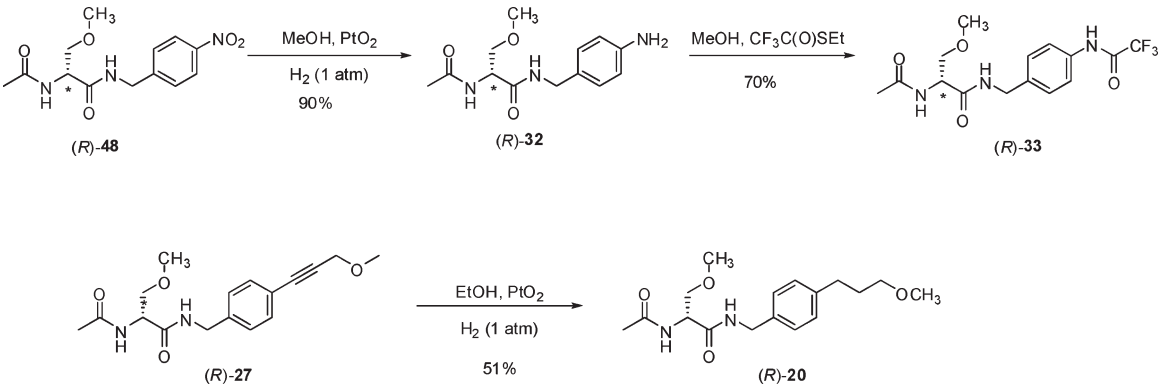


Scheme 2. Sonogashira Coupling of Compound **38** To Give Derivatives **12** and **23**−**27**

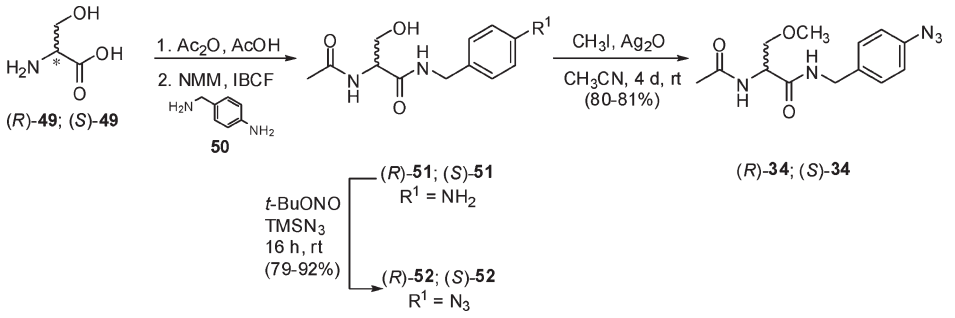


alkyne],[29] (*R*)-**38** was treated with 1-propyne, 3,3-dimethyl-but-1-yne, trimethylsilylacetylene, and 3-methoxyprop-1-yne to give alkynes (*R*)-**24**−(*R*)-**27**, respectively. In most cases, the Pd-based impurities were removed from the coupled

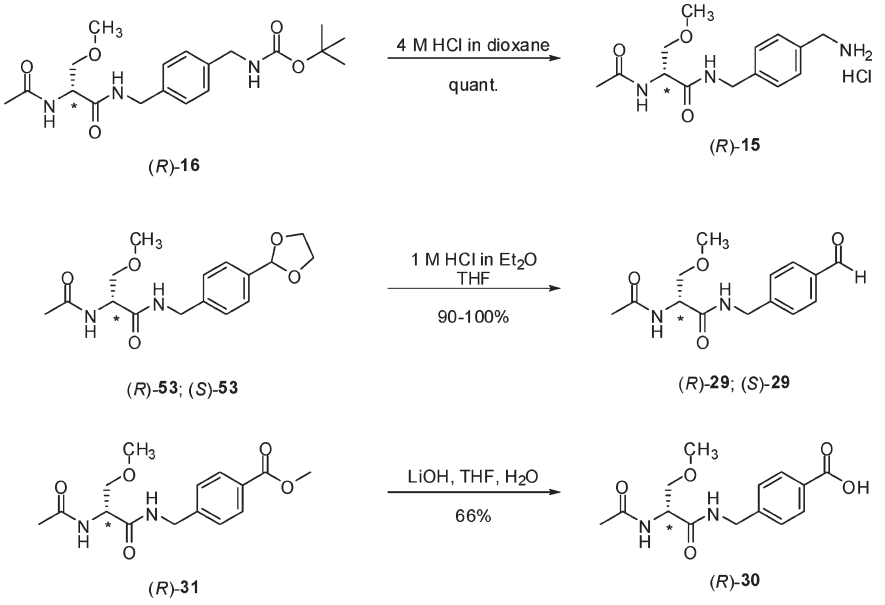
Scheme 3. Catalytic Reduction Procedures for Preparing Compounds **20**, **32**, and **33**



Scheme 4. Preparation of Compounds (*R*)-**34** and (*S*)-**34**

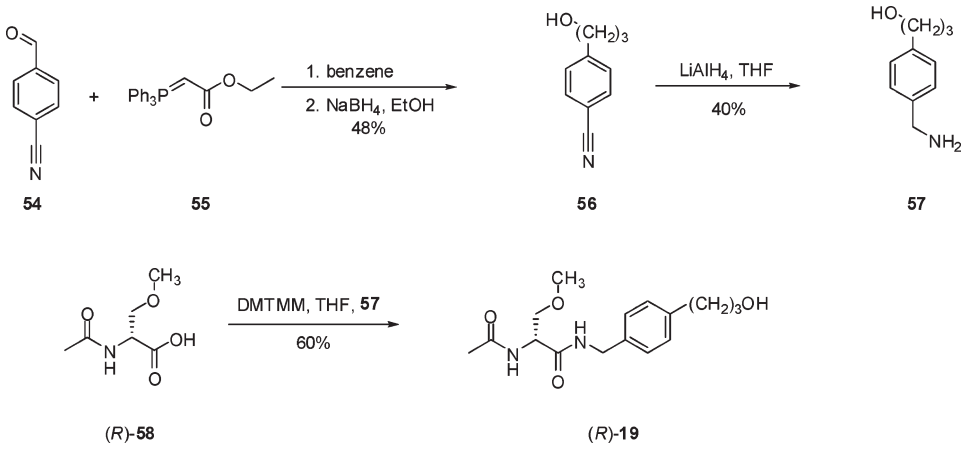


Scheme 5. Deprotection Procedures Used To Prepare Compounds **15**, **29**, and **30**



products with a scavenger resin (PhosPhonics, catalog no. SPM32). Treating (*R*)-**26** with TBAF gave the parent acetylene (*R*)-**23**, while hydrogenation (PtO_2) of (*R*)-**24** gave (*R*)-**12**. Catalytic reduction (PtO_2, H_2) of (*R*)-**27** provided (*R*)-**20** (Scheme 3). Similarly, the 4′-nitro derivative (*R*)-**48**[26] served as a precursor to the aniline derivative (*R*)-**32**, and trifluoroacetamide (*R*)-**33**. Catalytic reduction (PtO_2, H_2) of (*R*)-**48** gave (*R*)-**32**, which was then treated with ethyl trifluorothioacetate[30] to yield (*R*)-**33**. Synthesis of azide (*R*)-**34** began with (*R*)-serine [(*R*)-**49**] (Scheme 4). Acetylation followed by mixed anhydride coupling[28a] with 4-aminobenzylamine (**50**) gave (*R*)-**51**. The aniline derivative (*R*)-**51** was directly converted to the azide (*R*)-**52** by sequential addition of *tert*-butyl nitrite and trimethylsilyl azide,[31] which was then treated with CH_3I and Ag_2O to give (*R*)-**34**. We used different deprotection methods to prepare (*R*)-**15**, (*R*)-**29**, and (*R*)-**30** (Scheme 5). Compound (*R*)-**15** was prepared from (*R*)-**16** upon treatment with HCl in dioxane. Similarly, deprotection (HCl in a THF/H_2O mixture) of acetal (*R*)-**53** gave (*R*)-**29**. Finally, methyl ester (*R*)-**31** was converted to

Scheme 6. Preparation of Compound (*R*)-**19**



acid (*R*)-**30** with LiOH, followed by workup without racemization. We employed a different method to prepare (*R*)-**19** (Scheme 6). For this compound, we prepared optically pure (*R*)-**58**[25] and then coupled (DMTMM[28b]) it with benzylamine **57**.

The (*S*)-**3** analogues listed in Table 3 were prepared using the same methods employed for the corresponding (*R*)-stereoisomers.

Three criteria were used to assess the enantiopurity of (*R*)-**4**−(*R*)-**39** and (*S*)-**11**, (*S*)-**21**, (*S*)-**23**, (*S*)-**26**, (*S*)-**28**, (*S*)-**29**, (*S*)-**34**, and (*S*)-**38**. These were melting point, optical rotation, and the detection of only a single acetyl methyl and *O*-methyl signal in the ^{1}H NMR spectrum for each compound when a saturated solution of (*R*)-(−)-mandelic acid was added.[32]

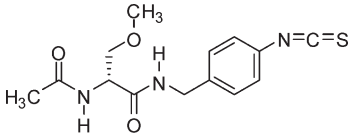
We report in the Experimental Section the details (synthetic procedure and characterization) for the final step for all compounds evaluated in the seizure models. In the Supporting Information, we provide a synthetic scheme for each compound tested, and for all the synthetic compounds prepared in this study the experimental procedures that were utilized and their physical and spectroscopic properties.

Pharmacological Activity. Compounds (*R*)-**4**−(*R*)-**39**, (*S*)-**11**, (*S*)-**21**, (*S*)-**23**, (*S*)-**26**, (*S*)-**28**, (*S*)-**29**, (*S*)-**34**, and (*S*)-**38** were tested for anticonvulsant activity at the National Institute of Neurological Disorders and Stroke's (NINDS) Anticonvulsant Screening Program (ASP) using the procedures described by Stables and Kupferberg.[33] The pharmacological data from the MES test are summarized in Tables 1−3, along with similar results obtained for (*R*)-**3** and the clinical antiepileptic agents phenytoin,[34] valproate,[34] and phenobarbital.[34] All compounds were administered intraperitoneally (ip) to mice and orally (po) to rats. The tables list the values that were determined to be protective in blocking hind limb extension induced in the MES seizure model from the rodent identification studies. For compounds that exhibited significant activity, we report the effective dose (50%) (ED_{50}) values obtained in quantitative screening evaluations. Also provided are the median doses for neurological impairment (50%) (TD_{50}) in mice, using the rotorod test,[35] and the behavioral toxicity effects observed in rats. TD_{50} values were determined for those compounds exhibiting significant activity in the MES test. The protective index (PI = TD_{50}/ED_{50}) values for these analogues are also listed. Although all of the compounds were evaluated in the subcutaneous Metrazol (scMet) seizure model, none provided any protection at the doses (typically 300 mg/kg) and times (0.5 and 4 h) tested (data not shown). The absence of seizure protection in this assay is a hallmark of FAA activity and this class of compounds.[9−18]

Table 1 provides the comparative anticonvulsant activities for *N*-benzyl 2-acetamido-3-methoxypropionamide derivatives in which we systematically placed either a fluoro or a trifluoromethoxy group at the 2′-, 3′-, and 4′-positions of the *N*-benzylamide moiety. We prepared only the (*R*)-stereoisomer for these studies since previous investigations showed that the principal anticonvulsant activity resided in this stereoisomer.[11−13,18] In Table 3, we present additional data consistent with this finding. In the two series of compounds listed in Table 1, the 4′-isomers [(*R*)-**6** and (*R*)-**9**] were more active than the corresponding 3′-regioisomers [(*R*)-**5** and (*R*)-**8**)], a result in agreement with earlier FAA studies.[18,26] Previously, our laboratory had not prepared any *N*-(2′-substituted)benzylamide **2**s. Thus, it was important for us to determine the effect on anticonvulsant activity of substitution at this site. Using the trifluoromethoxy series as an example, the ED_{50} values for the 2′-isomer [(*R*)-**7**], 3′-isomer [(*R*)-**8**], and 4′-isomer [(*R*)-**9**] in mice were 30−100, 10−30, and 3.6 mg/kg, respectively. A similar trend was observed for the 4′-fluoro regioisomers (*R*)-**4**−(*R*)-**6**. These findings led us to focus our SAR studies on *N*-(4′-substituted)benzyl (*R*)-**3** derivatives.

Table 2 reports the observed anticonvulsant activities for 32 *N*-(4′-substituted)benzyl (*R*)-**3** analogues. Listed first are the 4′-modified alkyl (*R*)-**3** analogues, (*R*)-**10**−(*R*)-**14**, in which the size of the 4′-alkyl group progressively increases. The MES seizure protection values in mice for the 4′-substituted methyl [(*R*)-**10**, 11 mg/kg], ethyl [(*R*)-**11**, 10−30 mg/kg], and propyl [(*R*)-**12**, 8.5 mg/kg] derivatives were only slightly lower than that of the parent compound (*R*)-**3** (4.5 mg/kg).[18] A similar finding was observed in the model but using the Sprague-Dawley rat. This finding was surprising since earlier results suggested that substituents placed at the 4′-position of the *N*-benzyl amide moiety in (*R*)-**3** resulted in a significant loss of MES seizure protection upon administration to mice.[15,26,27] For example, we reported previously that the MES ED_{50} values for the 4′-NO_2 [(*R*)-**48**] and 4′-NCS [(*R*)-**59**] analogues were 100−300 and 24 mg/kg, respectively.[26] However, when the *n*-propyl moiety in (*R*)-**12** was changed to the isopropyl group to give (*R*)-**13** (for mice, MES ED_{50} = 10−30 mg/kg; for rats, MES ED_{50} > 30 mg/kg) and then to a *tert*-butyl moiety to provide

(*R*)-**14** (for mice, MES ED_{50} = 100−300 mg/kg; for rats, MES ED_{50} > 30 mg/kg), we saw a progressive loss of anticonvulsant activity. These findings indicated that inclusion of bulky groups at the 4′-position interfered with drug function. Conversely, nonbulky hydrophobic groups retained excellent activity in both species.



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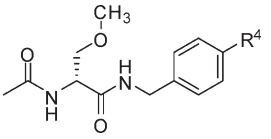
Next, we evaluated six modified 4′-alkyl (*R*)-**3** derivatives, (*R*)-**15**−(*R*)-**20**, that contained a functional group(s) attached to the 4′-substituted alkyl side chain. Incorporating an amino [(*R*)-**15**], a carbamate [(*R*)-**16**], or an alcohol [(*R*)-**19**] moiety into the alkyl side chain resulted in compounds with no anticonvulsant activity in mice at 300 mg/kg. Inclusion of a methoxy group to give (*R*)-**17** (for mice, MES ED_{50} = 73 mg/kg; for rats, MES ED_{50} = 45 mg/kg) and (*R*)-**20** (for mice, MES ED_{50} = 20 mg/kg; for rats, MES ED_{50} = 16 mg/kg) gave compounds that provided significant seizure protection. Nonetheless, the activity of (*R*)-**17** was noticeably lower than that of its isosteric propyl analogue (*R*)-**12** (for mice, MES ED_{50} = 8.5 mg/kg; for rats, MES ED_{50} = <30 mg/kg). Finally, the 4′-trifluoromethyl derivative (*R*)-**18** exhibited significant activity in mice (MES ED_{50} = 10−30 mg/kg) and exceptional anticonvulsant activity in rats (MES ED_{50} = 4.9 mg/kg). The activity of (*R*)-**18** in the rat closely matched that found for (*R*)-**3** (MES ED_{50} = 3.9 mg/kg), was slightly better than that of the 4′-methyl derivative (*R*)-**10** (MES ED_{50} = 8.1 mg/kg), and exceeded the values reported for the established anticonvulsants phenytoin,[20] phenobarbital,[34] and valproate.[20] Taken together, these findings show that additional attachment of specific functional groups (i.e., alcohol, amino, or carbamate) to the 4′-alkyl substituent led to compounds with reduced anticonvulsant activities.

The next set of compounds listed in Table 2 were the 4′-ethenyl [(*R*)-**21**], 4′-phenyl [(*R*)-**22**], and 4′-alkynyl [(*R*)-**23**−(*R*)-**27**] (*R*)-**3** derivatives. In this series, the spatial disposition of the 4′-group was changed from the tetrahedral (sp^3) arrangement found in (*R*)-**10**−(*R*)-**14** to either a trigonal (sp^2) or a linear (sp) arrangement. Superb activities in the primary models were observed for the nonbulky derivatives (*R*)-**21**−(*R*)-**24** and (*R*)-**27**. The MES ED_{50} values in mice ranged from 3 to 10 mg/kg. Similarly, (*R*)-**21** (MES ED_{50} = 7.6 mg/kg) and (*R*)-**23** (ED_{50} = 3.4 mg/kg) exhibited excellent seizure protection in the rat. Comparing the anticonvulsant activities for the 4′-substituted ethyl [(*R*)-**11**], ethenyl [(*R*)-**21**], and ethynyl [(*R*)-**23**] derivatives, we observed a modest improvement in anticonvulsant activities in both mice and rats as we progressively decreased the spatial size of the 4′-group. This finding is consistent with the pattern observed for the alkyl derivatives (*R*)-**10**−(*R*)-**14**. The effect of the steric size of the 4′-group on anticonvulsant activity was further reinforced by the activities of (*R*)-**25** and (*R*)-**27**. Attachment of a *tert*-butyl to the terminal end of the 4′-ethynyl group in (*R*)-**23** to give (*R*)-**25** led to a precipitous drop in anticonvulsant activity in mice (MES ED_{50} > 300 mg/kg), while adding the straight chain methoxymethylene unit to (*R*)-**23** to give (*R*)-**27** did not appreciably affect anticonvulsant activity [for (*R*)-**23** in mice MES ED_{50} = 3−10 mg/kg and in rats MES ED_{50} = 3.4 mg/kg; for (*R*)-**27** in mice MES ED_{50} = 10 mg/kg and in rats MES ED_{50} = 18 mg/kg]. When the trimethylsilylacetylenic derivative (*R*)-**26** was evaluated in the MES seizure model, significant toxicity was observed at a 3 mg/kg dose, thereby preventing us from assessing the trimethylsilyl group's impact on anticonvulsant activity. The pronounced anticonvulsant activity of the 4′-phenyl analogue (*R*)-**22** (for mice, MES ED_{50} = 3−10 mg/kg; for rats, MES ED_{50} = 2.0 mg/kg) was surprising given that the lowest-energy conformer for biphenyl in the gaseous state is twisted, and the dihedral angle between the two phenyl rings is close to 44°.[36] The progressive loss of activity observed as we proceeded from (*R*)-**12** to (*R*)-**14** suggested that increases in the three-dimensional steric size of the 4′-site would result in a loss in activity, and thus, the attachment of the 4′-phenyl group to give (*R*)-**22** would lead to a reduction in anticonvulsant activity. The excellent seizure protection of (*R*)-**22** can be rationalized by the low barrier for rotation around the central biphenyl bond (estimated to be 1.4 kcal/mol).[37] Accordingly, the energy penalty for a near-planar arrangement could be compensated by beneficial drug−receptor interactions (e.g., hydrophobic, aromatic interactions).

The final set of 4′-modified (*R*)-**3** analogues was the largest and comprised 14 derivatives, each of which contained a functional group directly attached to the *N*-benzyl moiety [(*R*)-**6**, (*R*)-**9**, and (*R*)-**28**−(*R*)-**39**]. This group of compounds together with the alkyl [(*R*)-**10**−(*R*)-**12**], trifluoromethyl [(*R*)-**18**], ethenyl [(*R*)-**21**], alkynyl [(*R*)-**23**, (*R*)-**24**, and (*R*)-**27**], and aryl [(*R*)-**22**] derivatives documented that attachment of functional groups at the 4′-site can provide strong seizure protection. Testing results demonstrated a highly significant anticonvulsant effect for the 4′-azido [(*R*)-**34**], 4′-trifluoromethoxy [(*R*)-**9**], 4′-F [(*R*)-**6**], and 4′-Cl [(*R*)-**36**] derivatives in mice (MES ED_{50} = 3.6−8.4 mg/kg) as well as in the rat (MES ED_{50} = 1.0−3.9 mg/kg). These values were either comparable with or exceeded that of (*R*)-**3** (for mice, MES ED_{50} = 4.5 mg/kg; for rats, MES ED_{50} = 3.9 mg/kg).[18] As a group, all the 4′-halogen-substituted (*R*)-**3** derivatives [(*R*)-**6** and (*R*)-**36**−(*R*)-**38**] exhibited pronounced activity. In addition, the smaller halogens (F and Cl) exhibited slightly better seizure protection than the larger halogen derivatives (Br and I). We noticed a significant loss of seizure protection in mice when proceeding from 4′-ethynyl derivative (*R*)-**23** (MES ED_{50} = 3−10 mg/kg) to the 4′-cyano analogue (*R*)-**28** (MES ED_{50} = 150 mg/kg). This finding was surprising given their similar size. Finally, attaching a 4′-substituent that could either ionize at physiological pH values or donate a hydrogen bond {i.e., 4′-CO_2H [(*R*)-**30**], 4′-NH_2 [(*R*)-**32**], 4′-$NHC(O)CF_3$ [(*R*)-**33**], and 4′-SO_2NH_2 [(*R*)-**39**]} provided compounds that were inactive in the MES test (mice) at the highest doses utilized (300 mg/kg).

The anticonvulsant activity observed for 4′-chloro derivative (*R*)-**36** in rats (MES ED_{50} = 1 mg/kg) made this compound the most potent **2** prepared to date; it was nearly 4 times more active than (*R*)-**3**. Using the methodology advanced by Topliss,[38] we explored whether the improved activity of (*R*)-**36** over (*R*)-**3** was due to an electronic effect provided by the 4′-chloro substituent. Accordingly, we prepared the 3′,4′-dichloro derivative (*R*)-**60**. When (*R*)-**60** was evaluated in mice, protection in the MES-induced seizure test was between 30 and 100 mg/kg, demonstrating that this derivative was considerably less active than (*R*)-**36**.

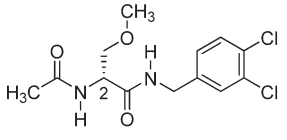
Table 4. Evaluation of Selected (*R*)-*N*-(4-Substituted)benzyl 2-Acetamido-3-methoxypropionamide Derivatives in the Rat Hippocampal Kindled Seizure Model Assay[a]



		preliminary hippocampal kindling test (rat)				
		seizure score		after-discharge duration (s)		hippocampal kindled rat (0.25 h) (ip)
no.	R^4	predrug	drug	predrug	drug	ED_{50} (mg/kg) (interval)
(*R*)-**17**	CH_2OCH_3	5	0	40−69	12	87 (58−130)
(*R*)-**20**	$(CH_2)_3OCH_3$	4−5	2	21−40	21	ND[d]
(*R*)-**21**	$CH{=}CH_2$	4−5	0	27−43	0−11	ND[d]
(*R*)-**34**	N_3	4	0	29−65	0	6 (3−9)
(*R*)-**36**	Cl	4−5	0	25−160	2	ND[d]
(*R*)-**38**	I	5	0	17−36	0−4	12 (7.5−18)
(*R*)-**3**[b,c]	H	5	0	33−53	0	14 (9.1−18)
phenytoin[c]		4−5	3	42−72	51	34 (21−45)
phenobarbital[c]						20 (14−28)
valproate[c]						210 (150−280)

[a] The compounds were tested through the auspices of the NINDS ASP. [b] From ref 23. [c] NINDS ASP internal control data. [d] Not determined.

Following the Topliss methodology, we compared the activity of (*R*)-**36** (MES ED_{50} = 5 mg/kg) with those of 4′-CF_3 [(*R*)-**18**; MES ED_{50} = 10−30 mg/kg], 4′-Br [(*R*)-**37**; MES ED_{50} = 8.7 mg/kg], 4′-I [(*R*)-**38**; MES ED_{50} = 16 mg/kg], 2′, 4′-dichloro [(*R*)-**61**; MES ED_{50} = 30−100 mg/kg], and 4′-NO_2 [(*R*)-**48**; MES ED_{50} = 100−300 mg/kg[26]] (*R*)-**3** derivatives in mice and found that (*R*)-**36** was the most potent. Collectively, these findings suggest that the improved activity observed for (*R*)-**36** over (*R*)-**3** is not due to electronic effects provided by the 4′-chloro substituent.[38]



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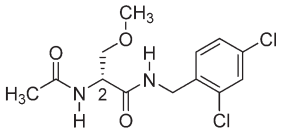

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Finally, we evaluated eight (*S*)-*N*-(4′-substituted)benzyl 2-acetamido-3-methoxypropionamide derivatives (Table 3). Included in this set were 4′-substituents [i.e., I, CH_2CH_3, C(H)CH_2, CCH, and N_3] that exhibited superb anticonvulsant activities when incorporated in the (*R*)-enantiomer. Most (*S*)-stereoisomers exhibited very little seizure protection in the MES test in mice with activities either between 100 and 300 mg/kg or greater than 300 mg/kg. Only (*S*)-**26** displayed protection, but it was modest (MES ED_{50} = 30−100 mg/kg). Our inability to determine the anticonvulsant activity for (*R*)-**26** prevented us from further exploring the pharmacological basis for this finding. The minimal anticonvulsant activities observed for these (*S*)-stereoisomers when compared with those of their *N*-(4′-substituted)benzyl (*R*)-**3** counterparts were in agreement with previous findings for chiral **2**s.[11−13,18]

Several of the more active *N*-(4′-substituted)benzyl (*R*)-**3** derivatives were also evaluated in the rapid hippocampal kindled rat model[39] (Table 4). This assay is considered a model of partial complex seizures, which are the most common type of seizures in humans. They also represent the subgroup of patients with the highest proportion of drug resistance.[40] Administration of (*R*)-**17**, (*R*)-**20**, (*R*)-**21**, (*R*)-**34**, (*R*)-**36**, and (*R*)-**38** led to a significant decrease in seizures (Racine score proceeding from 5 to 0−2) and a marked corresponding reduction in the after-discharge duration. The ED_{50} values for (*R*)-**34** and (*R*)-**38** in the hippocampal kindled test (rat, ip) were calculated to be 6 and 12 mg/kg, respectively, surpassing the ED_{50} value for (*R*)-**3** (14 mg/kg) and those of the standard antiepileptic drugs phenytoin, phenobarbital, and valproate.[23,41]

Conclusions

The SAR for the *N*-benzyl group in the clinically available antiepileptic agent (*R*)-**3** has been explored. We prepared and characterized 43 compounds, which were evaluated at the NINDS ASP for seizure protection in MES and scMet rodent models. Significant anticonvulsant protection against MES-induced seizures was observed for many of these compounds. Comparison of the protective actions for two series of substituted aryl regioisomers (2′, 3′, 4′) demonstrated that the 4′-modified derivatives exhibited the highest level of seizure protection. It was determined that some degree of structural latitude existed at this site. The SAR indicated that nonbulky 4′-substituted (*R*)-**3** derivatives exhibited superb activity independent of their electronic properties. The anticonvulsant activities of (*R*)-**6**, (*R*)-**9**, (*R*)-**21**−(*R*)-**23**, (*R*)-**34**, (*R*)-**36**, and (*R*)-**37** were either comparable with or exceeded that of (*R*)-**3**[18] in rodent MES tests, and they surpassed the activities observed for the traditional antiepileptic agents phenytoin,[34] phenobarbital,[34] and valproate.[34]

This study complements an earlier report that explored the effect of structural replacement of the C(2)-methoxy group in (*R*)-**3** on anticonvulsant activity.[25] In this investigation, we similarly observed that small, nonbulky 3-alkoxy groups provided the greatest seizure protection. Taken together, the SAR results provide clues concerning the topography and binding properties of the receptor binding site(s) that elicit (*R*)-**3** function. Furthermore, the finding that structural modifications can be made at the C(2) methoxy side chain and at the 4′-benzyl amide site in (*R*)-**3** without a loss of significant anticonvulsant activity sets the stage for the construction of AB&CR agents[24] designed to interrogate the brain proteome for drug binding sites.

Identification of the (*R*)-**3** receptor sites will advance future antiepileptic drug discovery efforts.

Experimental Section

General Methods. Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on an ATI Mattson Genesis FT-IR spectrometer. Absorption values are expressed in wavenumbers (cm^{-1}). Optical rotations were obtained on a Jasco P-1030 polarimeter at the sodium D line (589 nm) using a 1 dm path length cell. NMR spectra were recorded at 300 or 400 MHz (^1H) and 75 or 100 MHz (^{13}C) using TMS as an internal standard. Chemical shifts (δ) are reported in parts per million from tetramethylsilane. Low-resolution mass spectra were recorded with a BioToF-II-Bruker Daltonics spectrometer by M. Crowe and S. Habibi at the University of North Carolina Department of Chemistry. The high-resolution mass spectra were recorded on a Bruker Apex-Q 12 Telsa FTICR spectrometer by M. Crowe and S. Habibi. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Reactions were monitored by analytical thin-layer chromatography (TLC) plates (Aldrich, catalog no. Z12272-6, or Dynamic Adsorbents Inc., catalog no. 84111) and analyzed with 254 nm light. The reaction mixtures were purified by MPLC (CombiFlash Rf) with self-packed columns (silica gel from Dynamic Adsorbents Inc., catalog no. 02826-25) or by flash column chromatography using silica gel (Dynamic Adsorbents Inc., catalog no. 02826-25). All chemicals and solvents were reagent grade and used as obtained from commercial sources without further purification. THF was distilled from blue sodium benzophenone ketyl. Yields reported are for purified products and were not optimized. All compounds were checked by TLC, ^1H and ^{13}C NMR, MS, and elemental analyses. The analytical results are within 0.40% of the theoretical value. The TLC, NMR, and analytical data confirmed the purity of the products was ≥95%.

General Procedure for the Mixed Anhydride Coupling Reaction (Method A). To a cooled THF solution (−78 °C, dry ice/acetone bath) of acid (*R*)/(S)-**43** or **44** ([C] ∼ 0.1 M) were added NMM (1.0−1.2 equiv), followed by stirring for 2 min, IBCF (1.0−1.2 equiv), followed by stirring for 5 min, and then the desired benzylamine (1.0−1.2 equiv). Upon addition, the reaction mixture was allowed to warm to room temperature and further stirred (2−3 h). The salts were filtered and rinsed with THF, and the filtrate was concentrated in vacuo. The residue obtained was purified by flash chromatography and/or by recrystallization from EtOAc when necessary.

General Procedure for the Preparation of 3-Methoxy-2-amidopropionamide Derivatives (Method B). To a CH_3CN solution of alcohol ([C] ∼ 0.05−0.5 M) were successively added Ag_2O (5 equiv) and MeI (10 equiv) at room temperature. The reaction mixture was maintained at room temperature (2−4 days) and filtered through Celite, and the solvent was evaporated in vacuo. The residue was purified by column chromatography on SiO_2.

General Procedure for the Preparation of Cbz Deprotection (Method C). An EtOH or MeOH solution ([C] ∼ 0.01−0.2 M) of (*R*)- or (*S*)-**46** was treated with H_2 (1 atm) in the presence of 10% Pd/C [10−20% (w/w)] at room temperature (16 h). The mixture was carefully filtered through a bed of Celite. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo. The compounds were used without further purification.

General Procedure for N-Acetylation (Method D). The 2-aminopropionamide residue was dissolved in CH_2Cl_2 (0.05−0.3 M); triethylamine (1.2−6 equiv) and acetyl chloride (1.2−3 equiv) were carefully added at 0 °C, and the resulting solution was stirred at room temperature (2−4 h). An aqueous 10% citric acid solution was added, and the reaction mixture was extracted with CH_2Cl_2. The organic layers were combined, washed with a saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized with EtOAc and/or purified by column chromatography on SiO_2.

Preparation of (*R*)-*N*-(2′-Fluoro)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-4]. TFA (10 mL) was added to a CH_2Cl_2 solution (200 mL) of (*R*)-*N*-(2′-fluoro)benzyl 2-*N*-(*tert*-butoxycarbonyl)-amino-3-methoxypropionamide (2.90 g, 8.9 mmol), and the solution was stirred at room temperature (1 h). A saturated aqueous $NaHCO_3$ solution was added until the pH reached ∼9. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo.

Using method D, triethylamine (3.7 mL, 26.7 mmol) and acetyl chloride (1.3 mL, 17.8 mmol) gave 1.12 g (88%) of (*R*)-**4** as a white solid after purification by flash column chromatography on silica gel with an EtOAc/MeOH mixture (10/0 to 9/1) as the eluant: R_f = 0.52 (EtOAc); mp 173−175 °C; $[\alpha]^{25.2}_D$ −23.0° (*c* 1.0, $CHCl_3$); IR (nujol) 3289, 2925, 2858, 1638, 1550, 1457, 1376, 1237, 1135, 977, 842, 754, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 [s, C**H**$_3$C(O)], 3.35 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.2, 9.0 Hz, C**H**H′O), 3.76 (dd, *J* = 4.5, 9.0 Hz, CH**H**′O), 4.46−4.63 (m, C**H**$_2$NH, C**H**), 4.84−4.91 (br s, N**H**CH$_2$), 6.64 [d, *J* = 7.2 Hz, N**H**C(O)CH$_3$], 7.00−7.13 (m, 2 Ar**H**), 7.23−7.32 (m, 2 Ar**H**); addition of an excess of (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**4** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.0 [**C**H$_3$C(O)], 37.4 (d, *J* = 4.0 Hz, NH**C**H$_2$), 52.4 (**C**HCH$_2$), 58.9 (O**C**H$_3$), 71.8 (**C**H$_2$OCH$_3$), 115.1 (d, *J* = 21.0 Hz, **C**$_3$), 124.2 (d, *J* = 3.4 Hz, **C**$_5$), 124.8 (d, *J* = 14.5 Hz, **C**$_4$ or **C**$_6$), 129.1 (d, *J* = 8.2 Hz, **C**$_6$ or **C**$_4$), 129.6−129.7 (br d, **C**$_1$), 160.8 (d, *J* = 244.7 Hz, **C**F), 170.1, 170.4 [2 **C**(O)]; HRMS (M + Cs^+) (ESI^+) 401.0278 [M + Cs^+] (calcd for $C_{13}H_{17}FN_2O_3Cs^+$ 401.0274). Anal. ($C_{13}H_{17}FN_2O_3$): C, H, F, N.

Preparation of (*R*)-*N*-(2′-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-7]. An EtOH solution (200 mL) of (*R*)-*N*-(2′-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)-amino-3-methoxypropionamide (3.40 g, 8.0 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (340 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo.

Using method D, triethylamine (3.3 mL, 24.0 mmol) and acetyl chloride (1.2 mL, 16.0 mmol) gave 3.50 g (88%) of (*R*)-**7** as a white solid after purification by flash column chromatography on silica gel with an EtOAc/MeOH mixture (10/0 to 9/1) as the eluant: R_f = 0.36 (EtOAc); mp 130−131 °C; $[\alpha]^{24.8}_D$ −15.1° (*c* 1.0, $CHCl_3$); IR (nujol) 2919, 2858, 1640, 1547, 1458, 1272, 1203, 1164, 767, 712, 606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 [s, C**H**$_3$C(O)], 3.35 (s, OC**H**$_3$), 3.45 (br dd, *J* = 7.2, 9.3 Hz, C**H**H′O), 3.76 (dd, *J* = 4.2, 9.3 Hz, CH**H**′O), 4.46−4.63 (m, C**H**$_2$NH, C**H**), 6.71 [br d, *J* = 6.3 Hz, N**H**C(O)CH$_3$], 7.22−7.40 (m, CH$_2$N**H**, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**7** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 22.9 [**C**H$_3$C(O)], 38.1 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 58.9 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 120.4 (1 Ar**C**), 120.5 (q, *J*=256.1 Hz, O**C**F$_3$), 127.0, 128.8, 129.7, 130.3, 147.1 (5 Ar**C**), 170.2, 170.4 [2 C(O)]; HRMS (M + Na^+) (ESI^+) 357.1038 [M + Na^+] (calcd for $C_{14}H_{17}F_3N_2O_4Na^+$ 357.1038). Anal. ($C_{14}H_{17}F_3N_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-(3′-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-8]. An EtOH solution (200 mL) of (*R*)-*N*-(3′-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)-amino-3-methoxypropionamide (1.80 g, 4.2 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (180 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a yellow oil.

Using method D, triethylamine (0.7 mL, 5.0 mmol) and acetyl chloride (0.35 mL, 5.0 mmol) gave 750 mg (54%) of (*R*)-**8** as a white solid after recrystallization with EtOAc: R_f = 0.33

(EtOAc); mp 147−148 °C; $[\alpha]^{25.0}_D$ −12.1° (*c* 1.0, $CHCl_3$); IR (nujol) 3287, 3041, 2859, 2355, 1637, 1552, 1456, 1377, 1272, 1214, 1150, 715, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 [s, C**H**$_3$C(O)], 3.39 (s, OC**H**$_3$), 3.44 (dd, *J* = 7.6, 9.0 Hz, C**H**H′O), 3.83 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 4.43−4.60 (m, C**H**$_2$NH, C**H**), 6.38−6.46 [br d, N**H**C(O)CH$_3$], 6.82−6.91 (br t, CH$_2$N**H**), 7.11−7.15 (m, 2 Ar**H**), 7.19 (d, *J* = 7.8 Hz, 1 Ar**H**), 7.36 (dt, *J* = 1.9, 7.8 Hz, 1 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**8** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 42.8 (**C**H$_2$NH), 52.5 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.6 (**C**H$_2$OCH$_3$), 120.4 (q, *J* = 255.6 Hz, O**C**F$_3$), 119.7, 119.8, 125.6, 130.0, 140.4 (5 Ar**C**), 149.5 (**C**OCF$_3$), 170.2, 170.4 [2 **C**(O)]; LRMS (M + Na$^+$) (ESI$^+$) 357.1 [M + Na$^+$] (calcd for $C_{14}H_{17}F_3N_2O_4$ Na$^+$ 357.1). Anal. ($C_{14}H_{17}F_3N_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-(4′-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-9]. An EtOH solution (400 mL) of (*R*)-*N*-(4′-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)-amino-3-methoxypropionamide (3.90 g, 9.2 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (390 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a brown oil: ^1H NMR ($CDCl_3$) δ 1.44−1.95 (br s, N**H**$_2$), 3.38 (s, OC**H**$_3$), 3.50−3.67 (br m, C**H**$_2$, C**H**), 4.46 (d, *J* = 5.7 Hz, NC**H**$_2$), 7.17 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.31 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.80−8.00 [br s, N**H**C(O)].

Using method D, triethylamine (1.5 mL, 11.0 mmol) and acetyl chloride (0.78 mL, 11.0 mmol) gave 2.50 g (83%) of (*R*)-**9** as a white solid after recrystallization with EtOAc: R_f = 0.49 (EtOAc); mp 134−135 °C; $[\alpha]^{24.9}_D$ −17.6° (*c* 0.5, $CHCl_3$); IR (nujol) 3279, 3088, 2958, 2858, 1638, 1553, 1456, 1377, 1285, 1221, 1148, 988, 918, 841, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 [s, C**H**$_3$C(O)], 3.39 (s, OC**H**$_3$), 3.44 (dd, *J*=7.5, 9.0 Hz, C**H**H′O), 3.82 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 4.44−4.52 (m, C**H**$_2$NH), 4.52−4.59 (m, C**H**), 6.41 [br d, *J* = 6.6 Hz, N**H**C(O)CH$_3$], 6.78−6.89 (br t, CH$_2$N**H**), 7.18 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.29 (d, *J* = 8.1 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**9** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 42.7 (**C**H$_2$NH), 52.5 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 120.4 (q, *J* = 255.5 Hz, **C**F$_3$), 121.2, 128.7, 136.7 (3 Ar**C**), 148.4 (d, *J* = 1.7 Hz, **C**OCF$_3$), 170.1, 170.4 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 335.1219 [M + H$^+$] (calcd for $C_{14}H_{17}F_3N_2O_4H^+$ 335.1218). Anal. ($C_{14}H_{17}F_3N_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-(4′-Methyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-10]. An EtOH solution (250 mL) of (*R*)-*N*-(4′-methyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (3.20 g, 9.0 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (320 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a colorless oil: ^1H NMR ($CDCl_3$) δ 1.60−1.65 (br s, N**H**$_2$), 2.33 (s, PhC**H**$_3$), 3.37 (s, OC**H**$_3$), 3.56−3.67 (m, C**H**$_2$, C**H**), 4.34−4.43 (m, HNC**H**$_2$), 7.10−7.79 (m, 4 Ar**H**), 7.70−7.77 [br s, N**H**C(O)]; ^{13}C NMR ($CDCl_3$) δ 21.0 (Ph**C**H$_3$), 42.9 (**C**H$_2$NH), 54.8 (**C**H), 58.8 (O**C**H$_3$), 74.5 (**C**H$_2$), 127.6, 129.3, 135.3, 137.0 (4 Ar**C**), 172.5 [**C**(O)].

Using method D, triethylamine (1.5 mL, 10.8 mmol) and acetyl chloride (766 μL, 10.8 mmol) gave 1.70 g (72%) of (*R*)-**10** as a white solid after two recrystallizations with EtOAc: R_f = 0.50 (EtOAc); mp 128−129 °C; $[\alpha]^{25}_D$ −22.4° (*c* 1.0, $CHCl_3$); IR (nujol) 3285, 3062, 1637, 1548, 1458, 1375, 1311, 1105, 915, 808, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 [s, C**H**$_3$C(O)], 2.32 (PhC**H**$_3$), 3.35 (s, OC**H**$_3$), 3.45 (dd, *J* = 6.9, 9.3 Hz, C**H**H′O), 3.75 (dd, *J* = 4.2, 9.3 Hz, CH**H**′O), 4.36−4.43 (m, C**H**$_2$NH), 4.57−4.62 (m, C**H**), 6.71 [br d, *J* = 6.9 Hz, N**H**C(O)CH$_3$], 6.98−7.04 (br t, CH$_2$N**H**), 7.09−7.16 (m, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**10** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 21.0 (Ph**C**H$_3$), 23.1 [**C**H$_3$C(O)], 43.3 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 127.4, 129.3, 134.8, 137.1 (4 Ar**C**), 169.9, 170.3 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 265.1552 [M + H$^+$] (calcd for $C_{14}H_{20}N_2O_3H^+$ 265.1552). Anal. ($C_{14}H_{20}N_2O_3$): C, H, N.

Preparation of (*R*)-*N*-(4′-Ethyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-11]. A MeOH solution (250 mL) of (*R*)-*N*-(4′-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.20 g, 3.0 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (120 mg) at room temperature (3 days). The mixture was carefully filtered through a bed of Celite. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo to yield a yellow solid.

Using method D, triethylamine (0.5 mL, 3.5 mmol) and acetyl chloride (250 μL, 3.5 mmol) gave (*R*)-**11** as a white solid after recrystallization with EtOAc: mp 132−133 °C; IR (nujol) 3413, 3305, 3057, 2968, 2932, 1693, 1528, 1266, 1116 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7.5 Hz, C**H**$_3$CH$_2$), 2.02 [s, C**H**$_3$C(O)], 2.63 (q, *J* = 7.5 Hz, CH$_3$C**H**$_2$), 3.37 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.2, 9.0 Hz, C**H**H′O), 3.79 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 4.43 (d, *J* = 6.0 Hz, C**H**$_2$NH), 4.50−4.58 (m C**H**), 6.47 [br d, *J* = 6.9 Hz, N**H**C(O)CH$_3$], 6.71−6.82 (br t, CH$_2$N**H**), 7.15−7.18 (m, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**11** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 15.5 (CH$_2$**C**H$_3$), 23.1 [**C**H$_3$C(O)], 28.5 (**C**H$_2$CH$_3$), 43.3 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 127.5, 128.1, 135.0, 143.5 (4 Ar**C**), 169.8, 170.3 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 279.1708 [M + H$^+$] (calcd for $C_{15}H_{22}N_2O_3H^+$ 279.1705). Anal. ($C_{15}H_{22}N_2O_3$): C, H, N.

Preparation of (*S*)-*N*-(4′-Ethyl)benzyl 2-Acetamido-3-methoxypropionamide [(*S*)-11]. A MeOH solution (250 mL) of (*S*)-*N*-(4′-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.20 g, 3.0 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (120 mg) at room temperature (3 days). The mixture was carefully filtered through a bed of Celite. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo to yield a yellow solid.

Using method D, triethylamine (0.5 mL, 3.5 mmol) and acetyl chloride (250 μL, 3.5 mmol) gave (*S*)-**11** as a white solid after recrystallization with EtOAc: mp 132−133 °C; IR (nujol) 3286, 2932, 2928, 1637, 1554, 1458, 1375, 1311, 1197, 1102, 1051, 909, 821, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7.5 Hz, C**H**$_3$-CH$_2$), 2.02 [s, C**H**$_3$C(O)], 2.62 (q, *J* = 7.5 Hz, CH$_3$C**H**$_2$), 3.37 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.2, 9.0 Hz, C**H**H′O), 3.79 (dd, *J* = 4.5, 9.0 Hz, CH**H**′O), 4.43 (d, *J* = 5.7 Hz, C**H**$_2$NH), 4.43−4.58 (m, C**H**), 6.48 [br d, *J* = 6.3 Hz, N**H**C(O)CH$_3$], 6.71−6.82 (br t, CH$_2$N**H**), 7.15−7.18 (m, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**11** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 15.8 (CH$_2$**C**H$_3$), 23.4 [**C**H$_3$C(O)], 28.7 (**C**H$_2$CH$_3$), 43.5 (**C**H$_2$NH), 52.6 (**C**HCH$_2$), 59.3 (O**C**H$_3$), 72.0 (**C**H$_2$OCH$_3$), 127.7, 128.4, 135.2, 143.8 (4 Ar**C**), 170.1, 170.5 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 279.1708 [M + H$^+$] (calcd for $C_{15}H_{22}N_2O_3H^+$ 279.1705). Anal. ($C_{15}H_{22}N_2O_3$): C, H, N.

Preparation of (*R*)-*N*-(4′-Propyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-12]. PtO_2 (100 mg) was added to an EtOH solution of (*R*)-**24** (700 mg, 2.25 mmol), and the mixture was stirred at room temprerature under H_2 (1 atm) for 24 h. The reaction mixture was filtered through a pad of Celite, and the pad was washed successively with EtOH and CH_2Cl_2. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel with an EtOAc/hexane mixture (8/2 to 10/0) as the eluant to yield (*R*)-**12** (560 mg, 79%) as a white solid: R_f = 0.37 (EtOAc); mp 126−127 °C; $[\alpha]^{25.4}_D$ −27.2° (*c* 0.5, $CHCl_3$); IR (nujol) 3439, 3374, 3140, 2949, 2859, 1637, 1548, 1457, 1374, 1305, 1137, 1098, 972, 832, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.5 Hz, C**H**$_3$CH$_2$), 1.57−1.64 (m, CH$_2$C**H**$_2$CH$_3$), 2.04 [s, C**H**$_3$C(O)], 2.57 (t, *J* = 7.8 Hz, C**H**$_2$CH$_2$CH$_3$), 3.34−3.45 (m,

CHH′O, OC**H**$_3$), 3.81 (dd, J = 4.2, 9.0 Hz, CH**H**′O), 4.44 (d, J = 5.7 Hz, C**H**$_2$NH), 4.50−4.57 (m, C**H**), 6.38−6.46 (br m, CHN**H**), 6.63−6.73 (br m, CH$_2$N**H**), 7.12−7.19 (m, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**12** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 13.8 (CH$_2$**C**H$_3$), 23.1 [**C**H$_3$-C(O)], 24.5 (**C**H$_2$CH$_3$), 37.6 (**C**H$_2$CH$_2$CH$_3$), 43.3 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.8 (**C**H$_2$OCH$_3$), 123.4, 128.7, 135.0, 142.0 (4 Ar**C**), 169.9, 170.3 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 293.1865 [M + H$^+$] (calcd for $C_{16}H_{24}N_2O_3H^+$ 293.1865). Anal. ($C_{16}H_{24}N_2O_3$): C, H, N.

Preparation of (*R*)-*N*-(4′-Isopropyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-13]. An EtOH solution (250 mL) of (*R*)-*N*-(4′-isopropyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.80 g, 4.7 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (180 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.24 [d, J = 6.9 Hz, CH(C**H**$_3$)$_2$], 2.89 [sept, J = 6.9 Hz, C**H**(CH$_3$)$_2$], 3.38 (s, OC**H**$_3$), 3.59−3.66 (m, C**H**$_2$, C**H**), 4.35−4.49 (m, HNC**H**$_2$), 7.16 (m, 4 Ar**H**), 7.69−7.82 [br s, N**H**C(O)]; ^{13}C NMR ($CDCl_3$) δ 23.9 [CH(**C**H$_3$)$_2$], 33.8 [**C**H(CH$_3$)$_2$], 42.9 (**C**H$_2$NH), 54.8 (**C**HCH$_2$), 58.8 (O**C**H$_3$), 74.5 (**C**H$_2$), 126.7, 127.7, 135.6, 148.1 (4 Ar**C**), 172.5 [**C**(O)].

Using method D, triethylamine (0.79 mL, 5.6 mmol) and acetyl chloride (0.40 mL, 5.6 mmol) gave 2.40 g (62%) of (*R*)-**13** as a white solid after purification by flash column chromatography on silica gel with an EtOAc/hexane mixture (80/20 to 100/0) as the eluant: R_f = 0.39 (80/20 EtOAc/hexanes); mp 95−97 °C; $[\alpha]^{27.0}_D$ −10.5° (c 0.5, $CHCl_3$); IR (nujol) 3289, 2921, 2858, 1635, 1550, 1457, 1376, 1312, 1193, 1101, 1048, 913, 811, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 [d, J = 6.9 Hz, CH(C**H**$_3$)$_2$], 2.03 [s, C**H**$_3$C(O)], 2.90 [sept, J = 6.9 Hz, C**H**-(CH$_3$)$_2$], 3.38 (s, OC**H**$_3$), 3.43 (dd, J = 7.8, 9.0 Hz, CH**H**′O), 3.81 (dd, J = 4.2, 9.0 Hz, CH**H**′O), 4.44 (d, J = 5.7 Hz, C**H**$_2$NH), 4.50−4.56 (m, C**H**), 6.44 [br d, J = 6.3 Hz, N**H**C(O)CH$_3$], 6.65−6.74 (br t, CH$_2$N**H**), 7.19 (s, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**13** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 [**C**H$_3$C(O)], 24.0 [CH(**C**H$_3$)$_2$], 33.8 [**C**H(CH$_3$)$_2$], 43.3 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 126.7, 127.5, 135.1, 148.2 (4 Ar**C**), 169.9, 170.3 [2 **C**(O)]; LRMS (M + Na$^+$) (ESI$^+$) 315.2 [M + H$^+$] (calcd for $C_{16}H_{22}N_2O_3Na^+$ 315.2). Anal. ($C_{16}H_{22}N_2O_3$): C, H, N.

Preparation of (*R*)-*N*-(4′-*tert*-Butyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-14]. An EtOH solution (250 mL) of (*R*)-*N*-(4′-*tert*-butyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (4.00 g, 10.0 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (400 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.31 [s, C(C**H**$_3$)$_3$], 1.58−1.62 (br s, N**H**$_2$), 3.38 (s, OC**H**$_3$), 3.59−3.66 (m, C**H**$_2$, C**H**), 4.36−4.49 (m, HNC**H**$_2$), 7.21 (d, J = 8.4 Hz, 2 Ar**H**), 7.36 (d, J = 8.4 Hz, 2 Ar**H**), 7.69−7.81 [br s, N**H**C(O)]; ^{13}C NMR ($CDCl_3$) δ 31.3 [C(**C**H$_3$)$_3$], 34.5 [**C**(CH$_3$)$_3$], 42.8 (**C**H$_2$NH), 54.9 (**C**H), 58.8 (O**C**H$_3$), 74.5 (**C**H$_2$), 125.5, 127.4, 135.2, 150.3 (4 Ar**C**), 172.5 [**C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 265.1916 [M + H$^+$] (calcd for $C_{15}H_{24}N_2O_2H^+$ 265.1916).

Using method D, triethylamine (1.7 mL, 12.0 mmol) and acetyl chloride (856 μL, 12.0 mmol) gave 1.70 g (55%) of (*R*)-**14** as a white solid after recrystallization with EtOAc: R_f = 0.73 (EtOAc); mp 125−126 °C; $[\alpha]^{26.8}_D$ −26.0° (c 1.0, $CHCl_3$); IR (nujol) 3280, 2920, 2860, 1636, 1544, 1456, 1374, 1301, 1247, 1197, 1119, 966, 815, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 [s, C(C**H**$_3$)$_3$], 1.99 [s, C**H**$_3$C(O)], 3.37 (s, OC**H**$_3$), 3.46 (dd, J = 7.2, 9.0 Hz, CH**H**′O), 3.77 (dd, J = 4.2, 9.0 Hz, CH**H**′O), 4.36−4.44 (m, C**H**$_2$NH), 4.56−4.62 (m, C**H**), 6.63 [br d, J = 6.6 Hz, N**H**C(O)CH$_3$], 6.89−6.98 (br t, CH$_2$N**H**), 7.18 (d, J = 8.1 Hz, 2 Ar**H**), 7.35 (d, J = 8.1 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**14** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 31.3 [C(**C**H$_3$)$_3$], 34.4 [**C**(CH$_3$)$_3$], 43.2 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.8 (**C**H$_2$OCH$_3$), 125.5, 127.2, 134.7, 150.4 (4 Ar**C**), 169.9, 170.3 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 307.2022 [M + H$^+$] (calcd for $C_{17}H_{26}N_2O_3H^+$ 307.2021). Anal. ($C_{17}H_{26}N_2O_3$): C, H, N.

Preparation of (*R*)-*N*-(4′-Aminomethyl)benzyl 2-Acetamido-3-methoxypropionamide Hydrochloride [(*R*)-15]. A saturated HCl solution in dioxane (11.25 mL, 45.0 mL) was added to (*R*)-**16** (1.70 g, 4.5 mmol) at 0 °C, and the solution was stirred at room temperature (4 h). The reaction solution was concentrated in vacuo and dried (30 min). The residue was triturated with Et_2O, and the white solid was filtered to yield (*R*)-**15** (1.20 g, quantitative): R_f = 0.00 (EtOAc); mp >210 °C; $[\alpha]^{26.2}_D$ −1.6° (c 1.0, DMSO); IR (nujol) 3124, 2919, 2860, 1635, 1639, 1457, 1374, 1281, 1195, 1121, 974, 728 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.87 [s, C**H**$_3$C(O)], 3.25 (s, OC**H**$_3$), 3.44−3.56 (m, C**H**$_2$OCH$_3$), 3.97 (q, J = 5.7 Hz, C**H**$_2$NH$_3$Cl), 4.28 (d, J = 6.0 Hz, C**H**$_2$NH), 4.36−4.50 (m, C**H**), 7.26 (d, J = 7.9 Hz, 2 Ar**H**), 7.43 (d, J = 7.9 Hz, 2 Ar**H**), 8.15 [br d, J = 7.8 Hz, N**H**C(O)CH$_3$], 8.38−8.55 (br m, N**H**$_3$Cl), 8.58 (br t, J = 6.0 Hz, CH$_2$N**H**); ^{13}C NMR (DMSO-d_6) δ 22.5 [**C**H$_3$C(O)], 41.6, 41.8 (2 **C**H$_2$NH), 52.6 (**C**HCH$_2$), 58.1 (O**C**H$_3$), 72.0 (**C**H$_2$OCH$_3$), 127.0, 128.7, 132.2, 139.6 (4 Ar**C**), 169.3, 169.7 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 280.1661 [M + H$^+$] (calcd for $C_{14}H_{21}N_3O_3H^+$ 280.1661). Anal. ($C_{14}H_{22}ClN_3O_3\cdot 0.49HCl$): C, H, N.

Preparation of (*R*)-*N*-[4′-(*tert*-Butoxycarbonyl)aminomethyl]-benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-16]. An EtOH solution (400 mL) of (*R*)-*N*-[4′-(*tert*-butoxycarbonyl)aminomethyl]-benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (5.30 g, 11.2 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (530 mg) at room temperature (24 h); then an additional 470 mg of Pd/C was added, and the mixture was allowed to stir at room temperature (12 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a brown oil.

Using method D, triethylamine (1.9 mL, 13.5 mmol) and acetyl chloride (0.96 mL, 13.5 mmol) gave 2.50 g (60%) of (*R*)-**16** as a white solid after recrystallization with EtOAc: R_f = 0.47 (EtOAc); mp 153−154 °C; $[\alpha]^{24.9}_D$ −15.9° (c 1.0, $CHCl_3$); IR (nujol) 3318, 2919, 2861, 1675, 1639, 1530, 1458, 1374, 1260, 1167, 1127, 1057, 835, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 [s, C(C**H**$_3$)$_3$], 2.01 [s, C**H**$_3$C(O)], 3.37 (s, OC**H**$_3$), 3.44 (dd, J = 7.2, 9.0 Hz, CH**H**′O), 3.79 (dd, J = 4.2, 9.0 Hz, CH**H**′O), 4.28 (d, J = 5.7 Hz, C**H**$_2$NH), 4.43 (d, J = 5.7 Hz, C**H**$_2$NH), 4.51−4.57 (m, C**H**), 4.86−4.95 (br s, t-BocN**H**), 6.49−6.57 [br d, N**H**C-(O)CH$_3$], 6.83−6.93 (br m, CH$_2$N**H**), 7.17−7.26 (m, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**16** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$-C(O)], 28.4 [C(**C**H$_3$)$_3$], 43.2, 44.3 (2 **C**H$_2$NH), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 79.5 [**C**(CH$_3$)$_3$], 127.7, 136.9, 138.3 (3 Ar**C**), 155.9 [N**C**(O)O], 170.0, 170.4 [2 **C**(O)]; one signal was not detected and is believed to overlap with nearby peaks; HRMS (M + H$^+$) (ESI$^+$) 380.2186 [M + H$^+$] (calcd for $C_{19}H_{29}N_3O_5H^+$ 380.2185). Anal. ($C_{19}H_{29}N_3O_5$): C, H, N.

Preparation of (*R*)-*N*-(4′-Methoxymethyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-17]. A MeOH solution (400 mL) of (*R*)-*N*-(4′-methoxymethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (3.50 g, 9.1 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (350 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a colorless oil.

Using method D, triethylamine (1.5 mL, 10.9 mmol) and acetyl chloride (772 μL, 10.9 mmol) gave 1.50 g (56%) of (*R*)-**17** as a white solid after trituration with EtOAc: R_f = 0.35 (EtOAc); mp 119−120 °C; $[\alpha]^{25}_D$ −25.4° (c 0.5, $CHCl_3$); IR (nujol) 3266, 3069, 2935, 2863, 1635, 1550, 1458, 1457, 1382, 1282, 1226, 1194, 1125, 948, 836, 792, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03 [s, C**H**$_3$C(O)], 3.37, 3.38 (2 s, 2 OC**H**$_3$), 3.43 (dd, J = 7.5, 9.1, CH**H**′O), 3.80 (dd,

J = 4.2, 9.1 Hz, CH**H′**O), 4.41−4.49 (m, C**H$_2$**OCH$_3$, C**H$_2$**NH), 4.51−4.58 (m, C**H**), 6.42−6.52 [br d, N**H**C(O)CH$_3$], 6.75−6.84 (br t, CH$_2$N**H**), 7.24 (d, J = 7.9 Hz, 2 Ar**H**), 7.30 (d, J = 7.9 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**17** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 [**C**H$_3$C(O)], 43.3 (**C**H$_2$NH), 52.5 (**C**HCH$_2$), 58.1 (O**C**H$_3$), 59.1 (O**C**H$_3$), 71.8 (**C**H$_2$OCH$_3$), 74.3 (**C**H$_2$OMe), 127.5, 128.1, 137.3, 137.5 (4 Ar**C**), 170.0, 170.3 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 295.1658 [M + H$^+$] (calcd for $C_{15}H_{22}N_2O_4H^+$ 295.1658). Anal. ($C_{15}H_{22}N_2O_4$): C, H, N.

Preparation of (*R*)-*N*-(4′-Trifluoromethyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-18]. An EtOH solution (250 mL) of (*R*)-*N*-(4′-trifluoromethyl)benzyl 2-*N*-(benzyloxycarbonyl)-amino-3-methoxypropionamide (1.20 g, 3.0 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (120 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo to yield a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.62−1.67 (br d, N**H$_2$**), 3.39 (s, O**CH$_3$**), 3.58−3.72 (m, **CH$_2$**, **CH**), 4.52 (d, J = 6.0 Hz, HNC**H$_2$**), 7.39 (d, J = 8.2 Hz, 2 Ar**H**), 7.58 (d, J = 8.2 Hz, 2 Ar**H**), 7.88−7.89 [br s, N**H**C(O)].

Using method D, triethylamine (0.5 mL, 3.5 mmol) and acetyl chloride (250 μL, 3.5 mmol) gave 495 mg (55%) of (*R*)-**18** as a white solid after recrystallization with EtOAc: R_f = 0.45 (EtOAc); mp 160−161 °C; $[\alpha]^{26.7}_D$ 2.6° (c 0.5, DMSO); IR (nujol) 3393, 3278, 3145, 2923, 2834, 2723, 2673, 1638, 1552, 1456, 1374, 1157, 1111, 965, 840, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 [s, C**H$_3$**C(O)], 3.40 (s, O**CH$_3$**), 3.45 (dd, J = 7.8, 9.3 Hz, C**H**H′O), 3.83 (dd, J = 4.2, 9.3 Hz, CH**H′**O), 4.50−4.61 (m, C**H$_2$**NH, C**H**), 6.37−6.44 [br d, N**H**C(O)CH$_3$], 6.85−6.94 (br t, CH$_2$N**H**), 7.38 (d, J = 8.2 Hz, 2 Ar**H**), 7.58 (d, J = 8.2 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**18** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 42.9 (**C**H$_2$NH), 52.5 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.6 (**C**H$_2$OCH$_3$), 124.0 (q, J = 270.4 Hz, **C**F$_3$), 125.6 (q, J = 3.4 Hz, **C$_3$**), 127.5 (**C$_2$**), 129.7 (q, J = 31.9 Hz, **C$_4$**), 142.0 (**C$_1$**), 170.3, 170.5 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 319.1270 [M + H$^+$] (calcd for $C_{14}H_{17}F_3N_2O_3H^+$ 307.1269). Anal. ($C_{14}H_{17}F_3N_2O_3$): C, H, F, N.

Preparation of (*R*)-*N*-[4′-(3-Hydroxypropyl)]benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-19]. 4-(3-Hydroxypropyl)benzylamine (600 mg, 3.6 mmol) was added to a THF (33 mL) solution of the (*R*)-2-acetamido-3-methoxypropionoic acid [(*R*)-**58**][25] (532 mg, 3.3 mmol), and the mixture was stirred at room temperature (5 min). DMTMM[28b] (1.10 g, 4.0 mmol) was added, and the reaction mixture was stirred at room temperature (16 h). The white precipitate was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc to an EtOAc/acetone mixture (5/5) as the eluant to yield after recrystallization with EtOAc a white solid (560 mg, 55%): R_f = 0.26 (8/2 EtOAc/acetone); mp 118 °C; $[\alpha]^{26.9}_D$ −25.0° (c 0.5, $CHCl_3$); IR (nujol mull) 3339, 3279, 2951, 2862, 1630, 1552, 1456, 1376, 1304, 1195, 1140, 1097, 1038, 909, 820, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34−1.45 (br m, O**H**), 1.83−1.93 (br m, CH$_2$-C**H$_2$**CH$_2$), 2.03 [s, C**H$_3$**C(O)], 2.70 (t, J = 7.8 Hz, C**H$_2$**Ar), 3.38 (s, O**CH$_3$**), 3.43 (dd, J = 7.5, 9.0 Hz, C**H**H′O), 3.63−3.72 (br m, C**H$_2$**OH), 3.80 (dd, J = 3.9, 9.0 Hz, CH**H′**O), 4.44 (d, J = 6.0 Hz, C**H$_2$**NH), 6.41−6.50 [br d, CH$_3$C(O)N**H**], 6.69−6.79 (m, N**H**), 7.12−7.23 (m, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**19** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.0 [**C**H$_3$C(O)], 31.7, 34.2 (2 **C**H$_2$), 43.2 (N**C**H$_2$), 52.6 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 61.9 (**C**H$_2$OH), 72.1 (**C**H$_2$O), 127.5, 128.7, 135.3, 141.2 (4 Ar**C**), 170.1, 170.6 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 309.1815 [M + H$^+$] (calcd for $C_{16}H_{24}N_2O_4H^+$ 319.1814). Anal. ($C_{16}H_{24}N_2O_4$): C, H, N.

Preparation of (*R*)-*N*-[4′-(3-Methoxypropyl)]benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-20]. An EtOH solution (30 mL) of (*R*)-**27** (1.00 g, 3.1 mmol) was treated with H_2 (1 atm) in the presence of 10% PtO_2 (50 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with EtOAc as the eluant to yield (*R*)-**20** (510 mg, 51%) as a white solid: R_f = 0.27 (EtOAc); mp 105−107 °C; $[\alpha]^{25}_D$ 3.0° (c 0.5, DMSO); IR (nujol) 3283, 3085, 1638, 1550, 1457, 1379, 1299, 1122, 979, 725, 605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81−1.92 (m, C**H$_2$**), 2.03 [s, C**H$_3$**C(O)], 2.67 (t, J = 7.8 Hz, C**H$_2$**Ph), 3.33−3.46 (m, C**H**H′O, C**H$_2$**O, 2 O**CH$_3$**), 3.80 (dd, J = 4.0, 9.1 Hz, CH**H′**O), 4.44 (d, J = 5.7 Hz, C**H$_2$**NH), 4.50−4.57 (m, C**H**), 6.45 [br d, J = 6.6 Hz, N**H**C(O)CH$_3$], 6.70−6.75 (br t, CH$_2$N**H**), 7.15−7.20 (m, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**20** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 [**C**H$_3$C(O)], 31.2, 31.9 (2 **C**H$_2$), 43.3 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 58.6, 59.1 (2 O**C**H$_3$), 71.7, 71.9 (2 **C**H$_2$OMe), 127.5, 128.8, 135.3, 141.4 (4 Ar**C**), 169.9, 170.2 [2 **C**(O)]; HRMS (M + Na$^+$) (ESI$^+$) 345.1784 [M + Na$^+$] (calcd for $C_{17}H_{26}N_2O_4Na^+$ 345.1790). Anal. ($C_{17}H_{26}N_2O_4$): C, H, N.

Preparation of (*R*)-*N*-(4′-Vinyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-21]. *p*TSA (769 mg, 4.04 mmol) was added to a CH_2Cl_2 (6 mL) solution of (*R*)-*N*-(4′-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (900 mg, 2.7 mmol). The reaction mixture was stirred at room temperature (24 h), and then triethylamine (2.3 mL, 16.2 mmol) followed by acetyl chloride (574 μL, 8.1 mmol) was added at 0 °C. The solution was stirred at room temperature (30 min). Aqueous 10% citric acid was added, and then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, washed with aqueous saturated $NaHCO_3$ and H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2; EtOAc) to yield 700 mg (77%) of white solid: R_f = 0.49 (5/5 EtOAc/acetone); mp 148−149 °C; $[\alpha]^{26}_D$ 3.5° (c 1.0, DMSO); IR (nujol) 3281, 3093, 1638, 1552, 1456, 1381, 1298, 1246, 1125, 1043, 986, 917, 825, 722, 604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03 [s, C**H$_3$**C(O)], 3.38 (s, O**CH$_3$**), 3.43 (dd, J = 7.2, 9.0 Hz, C**H**H′O), 3.80 (dd, J = 4.2, 9.0 Hz, CH**H′**O), 4.43−4.52 (m, C**H$_2$**NH), 4.53−4.58 (m, C**H**), 5.24 (d, J_{cis} = 10.8 Hz, CH=C**H**H′), 5.75 (d, J_{trans} = 17.7 Hz, CH=CH**H′**), 6.46 [br d, J = 6.6 Hz, N**H**C(O)-CH$_3$], 6.70 (dd, J_{cis} = 10.8 Hz, J_{trans} = 17.7 Hz, C**H**=CH$_2$), 6.75−6.82 (br m, CH$_2$N**H**), 7.24 (d, J = 8.1 Hz, 2 Ar**H**), 7.35 (d, J = 8.1 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**21** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.3 [**C**H$_3$C(O)], 43.4 (**C**H$_2$NH), 52.6 (**C**HCH$_2$), 59.2 (O**C**H$_3$), 72.0 (**C**H$_2$OCH$_3$), 114.1 (CH=**C**H$_2$), 126.7, 127.8, 136.6, 137.0, 137.6 (4 Ar**C**, **C**H=CH$_2$), 170.2, 170.6 [2 **C**(O)]; HRMS (M + K$^+$) (ESI$^+$) 315.1115 [M + K$^+$] (calcd for $C_{15}H_{20}N_2O_3K^+$ 315.1111). Anal. ($C_{15}H_{20}N_2O_3$): C, H, N.

Preparation of (*S*)-*N*-(4′-Vinyl)benzyl 2-Acetamido-3-methoxypropionamide [(*S*)-21]. Employing the same procedure utilized for (*R*)-*N*-(4′-vinyl)benzyl 2-acetamido-3-methoxypropionamide and using (*S*)-*N*-(4′-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (900 mg, 2.7 mmol), triethylamine (2.3 mL, 16.2 mmol), and acetyl chloride (574 μL, 8.1 mmol) gave 690 mg (76%) of (*S*)-**21** after silica gel column chromatography: R_f = 0.45 (1/9 MeOH/EtOAc); mp 140−142 °C; $[\alpha]^{26}_D$ −3.1° (c 1.0, DMSO); IR (nujol) 3284, 3087, 1640, 1548, 1457, 1378, 1298, 1244, 1198, 1127, 1046, 985, 912, 826, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 [s, C**H$_3$**C(O)], 3.38 (s, O**CH$_3$**), 3.44 (dd, J = 7.5, 9.0, Hz, C**H**H′O), 3.80 (dd, J = 4.2, 9.0 Hz, CH**H′**O), 4.39−4.48 (m, C**H$_2$**NH), 4.53−4.59 (m, C**H**), 5.24 (d, J_{cis} = 11.1 Hz, CH=C**H**H′), 5.75 (d, J_{trans} = 17.4 Hz, CH=CH**H′**), 6.48 [br d, J = 6.6 Hz, N**H**C(O)CH$_3$], 6.70 (dd, J_{cis} = 11.1 Hz, J_{trans} = 17.4 Hz, C**H**=CH$_2$), 6.82−6.85 (br m, CH$_2$N**H**), 7.22 (d, J = 8.1 Hz, 2 Ar**H**), 7.34 (d, J = 8.1 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**21** gave only one signal

for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.4 [**C**H_3C(O)], 43.5 (**C**H_2NH), 52.6 (**C**HCH$_2$), 59.3 (O**C**H_3), 71.9 (**C**H_2OCH$_3$), 114.2 (CH=**C**H$_2$), 126.7, 127.8, 136.5, 137.1, 137.6 (4 Ar**C**, **C**H=CH$_2$), 170.2, 170.5 [2 **C**(O)]; HRMS (M + K$^+$) (ESI$^+$) [M + K$^+$] 315.1114 (calcd for $C_{15}H_{20}N_2O_3K^+$ 315.1111). Anal. ($C_{15}H_{20}N_2O_3 \cdot 0.10H_2O$): C, H, N.

Preparation of (*R*)-*N*-(Biphenyl-4-yl)methyl 2-Acetamido-3-methoxypropionamide [(*R*)-22]. Using method D, triethylamine (0.79 mL, 5.7 mmol), acetyl chloride (561 μL, 2.8 mmol), and (*R*)-*N*-(biphenyl-4-yl)methyl 2-amino-3-methoxypropionamide hydrochloride (600 mg, 1.9 mmol) gave 380 mg (55%) of (*R*)-*N*-(biphenyl-4-yl)methyl 2-acetamido-3-methoxypropionamide as a white solid after purification by flash column chromatography on silica gel with an EtOAc/MeOH mixture (100/0 to 80/20) as the eluant and recrystallization with EtOAc: R_f = 0.20 (EtOAc); mp 178−180 °C; $[\alpha]^{26.9}_D$ −8.8° (*c* 0.5, $CHCl_3$); IR (nujol) 3293, 3087, 2870, 1642, 1547, 1457, 1376, 1298, 1127, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 [s, C**H**$_3$C(O)], 3.40 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.5, 9.2 Hz, CH**H**′O), 3.83 (dd, *J* = 3.9, 9.2 Hz, CH**H**′O), 4.50−4.61 (m, C**H**$_2$NH, C**H**), 6.45 [br d, *J* = 5.7 Hz, N**H**C(O)CH$_3$], 6.76−6.84 (br t, CH$_2$N**H**), 7.31−7.38 (m, 3 Ar**H**), 7.41−7.48 (m, 2 Ar**H**), 7.55−7.60 (m, 4 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**22** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 [**C**H$_3$C(O)], 43.2 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.6 (**C**H$_2$OCH$_3$), 127.0, 127.3, 127.4, 127.8, 128.8, 136.9, 140.5 (7 Ar**C**), 170.0, 170.3 [2 **C**(O)]; one signal was not detected and is believed to overlap with nearby peaks; HRMS (M + H$^+$) (ESI$^+$) 327.1709 [M + H$^+$] (calcd for $C_{19}H_{22}N_2O_3H^+$ 327.1708). Anal. ($C_{19}H_{22}N_2O_3 \cdot 0.1H_2O$): C, H, N.

Preparation of (*R*)-*N*-(4′-Ethynyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-23]. A 1 M THF solution of TBAF (8.7 mL, 8.66 mmol) was added to a THF (60 mL) solution of (*R*)-**26** (1.50 g, 4.33 mmol), and then the solution was stirred at room temperature (4 h). CH_2Cl_2 and an aqueous 10% citric acid solution were added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc as the eluant to yield (*R*)-**23** (0.81 g, 68%) as a white solid: R_f = 0.41 (EtOAc); mp 161−162 °C; $[\alpha]^{24}_D$ 4.2° (*c* 0.5, DMSO); IR (nujol) 3290, 1634, 1544, 1458, 1375, 1311, 1240, 1197, 1104, 1041, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 [s, C**H**$_3$C(O)], 3.07 (s, C≡C**H**), 3.37 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.2, 9.3 Hz, CH**H**′O), 3.77 (dd, *J* = 4.5, 9.3 Hz, CH**H**′O), 4.36−4.49 (m, C**H**$_2$NH), 4.56−4.63 (m, C**H**), 6.60 [br d, *J* = 6.9 Hz, N**H**C(O)CH$_3$], 7.01−7.10 (br t, CH$_2$N**H**), 7.20 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.44 (d, *J* = 8.2 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**23** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 43.1 (**C**H$_2$NH), 52.5 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 77.3 (**C**≡C), 82.2 (C≡**C**), 121.2, 127.3, 132.4, 138.7 (4 Ar**C**), 170.1, 170.4 [2 **C**(O)]; HRMS (M + Na$^+$) (ESI$^+$) 297.1210 [M + Na$^+$] (calcd for $C_{15}H_{18}N_2O_3Na^+$ 297.1215). Anal. ($C_{15}H_{18}N_2O_3$): C, H, N.

Preparation of (*S*)-*N*-(4′-Ethynyl)benzyl 2-Acetamido-3-methoxypropionamide [(*S*)-23]. Employing the preceding procedure and using (*S*)-**26** (50 mg, 0.145 mmol) and TBAF (290 μL, 0.290 mmol) gave 753 mg (91%) of (*S*)-**23** as a white solid: R_f = 0.41 (EtOAc); mp 159−160 °C; $[\alpha]^{24}_D$ −4.4° (*c* 0.5, DMSO); IR (nujol) 3289, 2728, 1635, 1544, 1458, 1375, 1304, 1234, 975, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03 [s, C**H**$_3$C(O)], 3.07 (s, C≡C**H**), 3.38 (s, OC**H**$_3$), 3.44 (dd, *J* = 7.5, 9.0 Hz, CH**H**′O), 3.80 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 4.41−4.51 (m, C**H**$_2$NH), 4.52−4.57 (m, C**H**), 6.46 [br d, *J* = 5.4 Hz, N**H**C(O)CH$_3$], 6.80−6.92 (br t, CH$_2$N**H**), 7.21 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.45 (d, *J* = 8.4 Hz, 2 Ar**H**); ^{1}H NMR (DMSO-d_6) δ 1.87 [s, C**H**$_3$C(O)], 3.25 (s, OC**H**$_3$), 3.44−3.55 (m, CH**H**′, CH**H**′), 4.14 (s, C≡C**H**), 4.29 (d, *J* = 6.0 Hz, C**H**$_2$NH), 4.43−4.48 (m, C**H**), 7.25 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.42 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.11 [br d, *J* = 7.8 Hz, N**H**C(O)CH$_3$], 8.52 (br t, *J* = 6.0 Hz, CH$_2$N**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**23** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 [**C**H$_3$C(O)], 43.2 (**C**H$_2$NH), 52.5 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 77.3 (**C**≡C), 83.3 (C≡**C**), 121.2, 127.3, 132.4, 138.8 (4 Ar**C**), 170.1, 170.4 [2 **C**(O)]; the HMQC experiment showed a correlation between the δ 3.07 signal in the ^{1}H NMR spectrum and the δ 77.3 peak in the ^{13}C NMR spectrum; ^{13}C NMR (DMSO-d_6) δ 22.3 [**C**H$_3$C(O)], 41.6 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 58.0 (O**C**H$_3$), 71.8 (**C**H$_2$OCH$_3$), 80.2 (**C**≡C), 83.2 (C≡**C**), 119.8, 126.9, 131.3, 140.2 (4 Ar**C**), 169.2, 169.6 [2 **C**(O)]; the HMQC experiment showed a correlation between the δ 4.14 signal in the ^{1}H NMR spectrum and the δ 80.2 peak in the ^{13}C NMR spectrum; HRMS (M + Na$^+$) (ESI$^+$) 297.1212 [M + Na$^+$] (calcd for $C_{15}H_{18}N_2O_3Na^+$ 297.1215). Anal. ($C_{15}H_{18}N_2O_3 \cdot 0.25H_2O$): C, H, N.

Preparation of (*R*)-*N*-[4′-(Prop-1-ynyl)]benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-24]. To an anhydrous triethylamine solution (0.1 M, 2.66 mL) of (*R*)-**38** (100 mg, 0.266 mmol) were sequentially added dichlorobis(triphenylphosphine)palladium(II) (19 mg, 0.026 mmol) and CuI (2.5 mg, 0.013 mmol) in a flame-dried Schlenk tube under Ar. The mixture was cooled to −78 °C, and then the reaction vessel was evacuated and propyne bubbled into the triethylamine solution until the solution reached ∼1 atm. The mixture was stirred at room temperature (16 h). The mixture was cooled to −78 °C and re-evacuated. A balloon of propyne was bubbled into the mixture, and the reaction mixture was stirred at room temperature (24 h). The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with an EtOAc/hexane mixture (5/5 to 10/0) as the eluant to yield (*R*)-**24** (70 mg, 92%) as a white solid. The desired product (60 mg) was purified with 340 mg of resin scavenger (PhosPhonics, catalog no. SPM32) to remove the traces of palladium to yield 50 mg (66%) of (*R*)-*N*-[4′-(prop-1-ynyl)]benzyl 2-acetamido-3-methoxypropionamide: R_f = 0.37 (EtOAc); mp 178−180 °C; $[\alpha]^{24.3}_D$ −18.0° (*c* 0.5, $CHCl_3$); IR (nujol) 3474, 3273, 2960, 2856, 1683, 1550, 1457, 1375, 1299, 1125, 978, 811, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 [s, C**H**$_3$C(O)], 2.05 (s, C**H**$_3$), 3.38−3.45 (m, CH**H**′O, OC**H**$_3$), 3.81 (dd, *J* = 4.2, 9.3 Hz, CH**H**′O), 4.39−4.50 (m, C**H**$_2$NH), 4.51−4.57 (m, C**H**), 6.39−6.45 [br d, N**H**C(O)CH$_3$], 6.71−6.79 (br t, CH$_2$N**H**), 7.17 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.35 (d, *J* = 8.1 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**24** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 4.33 (**C**H$_3$), 23.2 [**C**H$_3$C(O)], 43.3 (**C**H$_2$NH), 52.4 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 79.4 (**C**≡C), 86.1 (C≡**C**), 123.2, 127.3, 131.8, 137.3 (4 Ar**C**), 170.0, 170.3 [2 **C**(O)]; HRMS (M + H$^+$) (ESI$^+$) 311.1372 [M + H$^+$] (calcd for $C_{16}H_{20}N_2O_3H^+$ 311.1372). Anal. ($C_{16}H_{20}N_2O_3 \cdot 0.2H_2O$): C, H, N.

Preparation of (*R*)-*N*-[4′-(3,3-Dimethylbut-1-ynyl)]benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-25]. To an anhydrous THF (10 mL) solution of (*R*)-**38** (376 mg, 1.0 mmol) were sequentially added triethylamine (280 μL, 2.0 mmol), 3,3-dimethylbut-1-yne (182 μL, 1.5 mmol), dichlorobis(triphenylphosphine)palladium(II) (35 mg, 0.05 mmol), and CuI (19 mg, 0.1 mmol) under Ar. The mixture was stirred at room temperature (4 h), and then Et_2O (10 mL) was added and the precipitate filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with an EtOAc/MeOH mixture (9/1) as the eluant to yield (*R*)-**25** (220 mg, 66%) as a brown solid: R_f = 0.22 (EtOAc); mp 120−121 °C; $[\alpha]^{25}_D$ 4.8° (*c* 1.0, DMSO); IR (nujol) 3287, 2727, 2364, 1641, 1547, 1458, 1375, 1297, 1132, 972, 816, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 [s, (C**H**$_3$)$_3$C], 2.00 [s, C**H**$_3$C(O)], 3.35 (s, OC**H**$_3$), 3.42 (dd, *J* = 7.5, 9.0 Hz, CH**H**′O), 3.76 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 4.33−4.50 (m, C**H**$_2$NH), 4.50−4.61 (m, C**H**), 6.60 [d, *J* = 6.3 Hz, N**H**C(O)CH$_3$], 6.91−6.99 (br t, CH$_2$N**H**), 7.14 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.33 (d, *J* = 8.1 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**25** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2

[$CH_3C(O)$], 27.9 [$C(CH_3)_3$], 31.0 [$C(CH_3)_3$], 43.3 (CH_2NH), 52.5 ($CHCH_2$), 59.1 (OCH_3), 71.8 (CH_2OCH_3), 78.6 (C≡C), 98.8 (C≡C), 123.3, 127.2, 131.8, 137.1 (4 ArC), 170.2, 170.6 [2 C(O)]; HRMS (M + H^+) (ESI^+) 331.2019 [M + H^+] (calcd for $C_{19}H_{26}N_2O_3H^+$ 331.2029). Anal. ($C_{19}H_{26}N_2O_3 \cdot 0.2H_2O$): C, H, N.

Preparation of (*R*)-*N*-[4′-(Trimethylsilyl)ethynyl]benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-26]. To an anhydrous THF (70 mL) solution of (*R*)-**38** (2.40 g, 6.38 mmol) were sequentially added triethylamine (1.8 mL, 12.76 mmol), trimethylsilylacetylene (1.35 mL, 9.57 mmol), dichlorobis(triphenylphosphine)palladium(II) (224 mg, 0.319 mmol), and CuI (121 mg, 0.638 mmol) under Ar. The mixture was stirred at room temperature (4 h), and then Et_2O was added and the precipitate filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with an EtOAc/MeOH mixture (9/1) as the eluant to yield (*R*)-**26** (1.50 g, 68%). The desired product (1.50 g) was purified with 7.50 g of resin scavenger (PhosPhonics, catalog no. SPM32) to remove the traces of palladium to yield 1.20 g (55%) of (*R*)-**26** as a brown solid: R_f = 0.41 (EtOAc); mp 126−127 °C; $[\alpha]^{24}_D$ 6.1° (*c* 1.0, DMSO); IR (nujol) 3285, 2157, 1641, 1546, 1457, 1375, 1302, 1248, 1130, 975, 862, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.24 [s, (CH_3)$_3$Si], 1.99 [s, CH_3C(O)], 3.35 (s, OCH_3), 3.45 (dd, *J* = 7.2, 9.0 Hz, CHH′O), 3.75 (dd, *J* = 4.2, 9.0 Hz, CHH′O), 4.33−4.47 (m, CH_2NH), 4.57−4.62 (m, CH), 6.66 [br d, *J* = 6.9 Hz, NHC(O)CH_3], 7.07−7.13 (br t, CH_2NH), 7.17 (d, *J* = 7.9 Hz, 2 ArH), 7.40 (d, *J* = 7.9 Hz, 2 ArH); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**26** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ −0.1 [(CH_3)$_3$Si], 23.2 [CH_3C(O)], 43.2 (CH_2NH), 52.4 ($CHCH_2$), 59.1 (OCH_3), 71.6 (CH_2OCH_3), 94.4 (C≡C), 104.7 (C≡C), 122.4, 127.2, 132.3, 138.3 (4 ArC), 170.0, 170.3 [2 C(O)]; HRMS (M + Na^+) (ESI^+) 369.1605 [M + Na^+] (calcd for $C_{18}H_{26}N_2O_3SiNa^+$ 369.1610). Anal. ($C_{18}H_{26}N_2O_3Si$): C, H, N.

Preparation of (*S*)-*N*-[4′-(Trimethylsilyl)ethynyl]benzyl 2-Acetamido-3-methoxypropionamide [(*S*)-26]. Employing the preceding procedure and using (*S*)-**38** (2.40 g, 6.38 mmol), triethylamine (1.8 mL, 12.76 mmol), CuI (121 mg, 0.638 mmol), dichlorobis(triphenylphosphine)palladium(II) (224 mg, 0.319 mmol), and trimethylsilylacetylene (1.35 mL, 9.57 mmol) gave 1.97 g (91%) of (*S*)-**26** as a brown solid: R_f = 0.41 (EtOAc); mp 126−127 °C; $[\alpha]^{24}_D$ −6.2° (*c* 1.0, DMSO); IR (nujol) 3285, 2727, 2157, 1641, 1546, 1457, 1374, 1304, 1250, 1137, 862, 725 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.22 [s, (CH_3)$_3$Si], 1.87 [s, CH_3C(O)], 3.25 (s, OCH_3), 3.44−3.55 (m, CHH′O, CHH′O), 4.29 (d, *J* = 5.7 Hz, CH_2NH), 4.43−4.51 (m, CH), 7.24 (d, *J* = 8.2 Hz, 2 ArH), 7.40 (d, *J* = 8.2 Hz, 2 ArH), 8.10 [br d, *J* = 8.1 Hz, NHC(O)CH_3], 8.53 (br t, *J* = 6.0 Hz, CH_2NH); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**26** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ −0.2 [(CH_3)$_3$Si], 22.4 [CH_3C(O)], 41.7 (CH_2NH), 52.6 ($CHCH_2$), 58.1 (OCH_3), 71.9 (CH_2OCH_3), 93.6 (C≡C), 105.1 (C≡C), 120.0, 127.1, 131.4, 140.4 (4 ArC), 169.3, 169.8 [2 C(O)]; HRMS (M + Na^+) (ESI^+) 369.1603 [M + Na^+] (calcd for $C_{18}H_{26}N_2O_3SiNa^+$ 369.0161). Anal. ($C_{18}H_{26}N_2O_3Si$): C, H, N.

Preparation of (*R*)-*N*-[4′-(3-Methoxyprop-1-ynyl)]benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-27]. To an anhydrous THF (10 mL) solution of (*R*)-**38** (376 mg, 1.0 mmol) were sequentially added triethylamine (280 μL, 2.0 mmol), 3-methoxyprop-1-yne (125 μL, 1.5 mmol), dichlorobis(triphenylphosphine)palladium(II) (70 mg, 0.1 mmol), and CuI (38 mg, 0.2 mmol) under Ar. The mixture was stirred at room temperature (4 h), and then Et_2O (10 mL) was added and the precipitate filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with an EtOAc/MeOH mixture (9/1) as the eluant to yield (*R*)-**27** (260 mg, 82%) as a beige solid: R_f = 0.27 (EtOAc); mp 141−142 °C; $[\alpha]^{27}_D$ 4.4° (*c* 1.0, DMSO); IR (nujol) 3278, 3096, 1640, 1554, 1458, 1370, 1304, 1257, 1192, 1099, 966, 903, 810, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 [s, CH_3C(O)], 3.37 (s, OCH_3), 3.45−3.47 (m, CHH′O, OCH_3), 3.78 (dd, *J* = 4.2, 9.0 Hz, CHH′O), 4.32 (s, C≡CCH_2OCH_3), 4.38−4.52 (m, CH_2NH), 4.54−4.61 (m, CH), 6.52 [d, *J* = 6.6 Hz, NHC(O)CH_3], 6.91−6.99 (br t, CH_2NH), 7.19 (d, *J* = 7.9 Hz, 2 ArH), 7.41 (d, *J* = 7.9 Hz, 2 ArH); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**27** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 [CH_3C(O)], 43.2 (CH_2NH), 52.5 ($CHCH_2$), 57.7 (C≡CCH_2OCH_3), 59.1 (OCH_3), 60.4 (C≡CCH_2OCH_3), 71.7 (CH_2OCH_3), 85.2 (C≡C), 86.0 (C≡C), 121.8, 127.3, 132.1, 138.4 (4 ArC), 170.4 [br, 2 C(O)]; HRMS (M + H^+) (ESI^+) 319.1652 [M + H^+] (calcd for $C_{17}H_{22}N_2O_4H^+$ 319.1658). Anal. ($C_{17}H_{22}N_2O_4 \cdot 0.33H_2O$): C, H, N.

Preparation of (*R*)-*N*-(4′-Cyano)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-28]. A MeOH solution (150 mL) of (*R*)-*N*-(4′-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.80 g, 4.8 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (250 mg) at room temperature (36 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a colorless oil.

Using method D, triethylamine (810 μL, 5.8 mmol) and acetyl chloride (410 μL, 5.8 mmol) gave 320 mg (42%) of (*R*)-**28** as a white solid after trituration with EtOAc: R_f = 0.54 (9/1 EtOAc/MeOH); mp 168−169 °C; $[\alpha]^{24}_D$ 4.9° (*c* 1.0, DMSO); IR (nujol) 3273, 2725, 2226, 1635, 1547, 1458, 1374, 1309, 1191, 1093, 907, 727 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 [s, CH_3C(O)], 3.26 (s, OCH_3), 3.45−3.57 (m, CH_2OCH_3), 4.36 (d, *J* = 6.0 Hz, CH_2NH), 4.43−4.49 (m, CH), 7.34 (d, *J* = 8.6 Hz, 2 ArH), 7.42 (d, *J* = 8.6 Hz, 2 ArH), 8.14 [d, *J* = 7.8 Hz, NHC(O)CH_3], 8.61 (t, *J* = 6.0 Hz, CH_2NH); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**28** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ 22.4 [CH_3C(O)], 41.7 (CH_2NH), 52.6 ($CHCH_2$), 58.1 (OCH_3), 71.9 (CH_2OMe), 109.3 (CCN), 118.8 (CN), 127.6, 132.1, 145.3 (3 ArC), 169.4, 170.0 [2 C(O)]; HRMS (M + Na^+) (ESI^+) 298.1163 [M + Na^+] (calcd for $C_{14}H_{17}N_3O_3Na^+$ 298.1168). Anal. ($C_{14}H_{17}N_3O_3 \cdot 0.25H_2O$): C, H, N.

Preparation of (*S*)-*N*-(4′-Cyano)benzyl 2-Acetamido-3-methoxypropionamide [(*S*)-28]. Employing the preceding procedure and using (*S*)-*N*-(4′-cyano)benzyl 2-*N*-(benzyloxycarbonyl)-amino-3-methoxypropionamide (1.20 g, 3.2 mmol), 10% Pd/C (250 mg), triethylamine (540 μL, 3.8 mmol), and acetyl chloride (273 μL, 3.8 mmol) gave 620 mg (70%) of (*S*)-**28** as a white solid after trituration with EtOAc: R_f = 0.54 (9/1 EtOAc/MeOH); mp 168−169 °C; $[\alpha]^{25}_D$ −4.9° (*c* 1.0, DMSO); IR (nujol) 3271, 2726, 2228, 1630, 1552, 1458, 1374, 1312, 1194, 1095, 908, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 [s, CH_3C(O)], 3.40 (s, OCH_3), 3.45 (dd, *J* = 7.2, 9.6 Hz, CHH′O), 3.81 (dd, *J* = 3.9, 9.6 Hz, CHH′O), 4.49−4.61 (m, CH_2NH, CH), 6.48 [br d, *J* = 5.7 Hz, NHC(O)CH_3], 7.06−7.08 (br m, CH_2NH), 7.34 (d, *J* = 8.4 Hz, 2 ArH), 7.36 (d, *J* = 8.4 Hz, 2 ArH); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**28** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [CH_3C(O)], 43.0 (CH_2NH), 52.5 ($CHCH_2$), 59.1 (OCH_3), 71.5 (CH_2OCH_3), 111.2 (CCN), 118.6 (CN), 127.8, 132.4, 143.5 (3 ArC), 170.3, 170.4 [2 C(O)]; HRMS (M + Na^+) (ESI^+) 298.1163 [M + Na^+] (calcd for $C_{14}H_{17}N_3O_3Na^+$ 298.1168). Anal. ($C_{14}H_{17}N_3O_3$): C, H, N.

Preparation of (*R*)-*N*-(4′-Formyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-29]. (*R*)-*N*-[4′-(1,3-Dioxolan-2-yl)]benzyl 2-acetamido-3-methoxypropionamide (1.62 g, 5.0 mmol) was dissolved in a 2:1 THF/H_2O mixture (30 mL), and 2 M HCl (10 drops) was added. The reaction mixture was stirred at room temperature overnight and diluted with H_2O (20 mL). The solution was neutralized with the dropwise addition of a saturated aqueous $NaHCO_3$ solution at 0 °C. The THF was removed in vacuo, and the remaining aqueous layer was extracted with $CHCl_3$ (5 × 25 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo, and the residue was recrystallized from EtOAc to give 930 mg (66%) of (*R*)-**29** as a white solid. The mother liquor was concentrated and purified

by flash chromatography (5/95 MeOH/$CHCl_3$) to yield 336 mg of product (24%) [total yield, 1.27 g (90%)]: R_f = 0.40 (5/95 MeOH/$CHCl_3$); mp 132−133 °C; $[\alpha]^{25}_D$ 10.4° (*c* 1.0, $CHCl_3$); IR (nujol) 3288, 1687, 1642, 1549, 1458, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 [s, C**H**$_3$C(O)], 3.36 (s, OC**H**$_3$), 3.53 (dd, *J* = 6.0, 9.3 Hz, C**H**H′O), 3.75 (dd *J* = 4.8, 9.3 Hz, CH**H**′O), 4.38−4.58 (m, NHC**H**$_2$), 4.71 (app dt, *J* = 5.4, 6.0 Hz, C**H**), 7.03 (d, *J* = 7.8 Hz, N**H**CH$_2$), 7.38 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.68 [t, *J* = 5.4 Hz, N**H**C(O)CH$_3$], 7.77 (d, *J* = 8.4 Hz, 2 Ar**H**), 9.93 [s, C(O)**H**]; addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**29** gave only one signal for the methoxy protons and the acetyl peak protons, and addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**29** and (*R*)-**29** (1/2 ratio) gave two signals for the acetyl methyl protons [δ 2.037 (*S*) and 2.023 (*R*) (Δppm = 0.014)] and two signals for the methoxy protons [δ 3.346 (*S*) and 3.377 (*R*) (Δppm = 0.031)]; ^{13}C NMR ($CDCl_3$) δ 23.0 [**C**H$_3$C(O)], 43.1 (NH**C**H$_2$), 52.8 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 72.0 (**C**H$_2$OCH$_3$), 127.7, 130.0, 135.5, 145.3 (4 Ar**C**), 170.5, 170.7 [2 **C**(O)], 192.0 [**C**(O)H]; HRMS [M + Na^+] (ESI^+) 301.1158 [M + Na^+] (calcd for $C_{14}H_{18}N_2O_4Na^+$ 301.1164). Anal. ($C_{14}H_{18}N_2O_4$): C, H, N.

Preparation of (*S*)-*N*-(4′-Formyl)benzyl 2-Acetamido-3-methoxypropionamide [(*S*)-29]. Using the preceding procedure, (*S*)-*N*-[4′-(1,3-dioxolan-2-yl)]benzyl 2-acetamido-3-methoxypropionamide (1.65 g, 5.1 mmol) gave 900 mg (63%) of (*S*)-**29** after recrystallization from EtOAc and another 268 mg (19%) after flash chromatography [total yield, 1.17 g (82%)]: R_f = 0.40 (5/95 MeOH/$CHCl_3$); mp 132−133 °C; $[\alpha]^{25}_D$ −10.4° (*c* 1.0, $CHCl_3$); IR (nujol) 3288, 3073, 1687, 1637, 1551, 1458, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 [s, C**H**$_3$C(O)], 3.40 (s, OC**H**$_3$), 3.46 (dd, *J* = 7.5, 9.6 Hz, C**H**H′O), 3.83 (dd *J* = 4.2, 9.6 Hz, CH**H**′O), 4.48−4.64 (m, NHC**H**$_2$, C**H**), 6.45 [d, *J* = 6.6 Hz, N**H**C(O)CH$_3$], 6.99−7.15 (m, N**H**CH$_2$), 7.42 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.85 (d, *J* = 8.1 Hz, 2 Ar**H**), 9.99 [s, C(O)**H**]; addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**29** gave only one signal for the acetyl peak protons and the methoxy protons, and addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**29** and (*R*)-**29** (1/2 ratio) gave two signals for the acetyl methyl protons [δ 2.037 (*S*) and 2.023 (*R*) (Δppm = 0.014)] and two signals for the methoxy protons [δ 3.317 (*S*) and 3.351 (*R*) (Δppm = 0.034)]; ^{13}C NMR ($CDCl_3$) δ 23.4 [**C**H$_3$C(O)], 43.4 (NH**C**H$_2$), 52.7 (**C**H), 59.4 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 128.0, 130.3, 135.9, 145.2 (4 Ar**C**), 170.5, 170.6 [2 C(O)], 192.0 [**C**(O)H]; HRMS [M + Na^+] (ESI^+) 301.1161 [M + Na^+] (calcd for $C_{14}H_{18}N_2O_4Na^+$ 301.1164). Anal. ($C_{14}H_{18}N_2O_4$): C, H, N.

Preparation of (*R*)-*N*-(4′-Carboxy)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-30]. To a solution of (*R*)-**31** (0.75 g, 2.6 mmol) in a THF/H_2O mixture (1/1, 50 mL) at 0 °C was added $LiOH \cdot H_2O$ (66 mg, 2.8 mmol). The resulting solution was stirred (36 h). The solvent was removed in vacuo, washed with Et_2O (4 × 100 mL), acidified to a pH of ∼2 (1 N HCl), extracted with EtOAc (8 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield 472 mg of a white powder (66%): R_f = 0.51 (9/1 $CHCl_3$/MeOH); mp 197−198 °C; $[\alpha]^{25}_D$ 6.0° (*c* 0.8, MeOH); IR (nujol) 3163, 2923, 2856, 1692, 1637, 1533, 1457, 1376, 1291, 1122, 939 cm^{-1}; ^1H NMR (CD_3OD) δ 2.03 [s, C**H**$_3$-C(O)], 3.37 (s, OC**H**$_3$), 3.60 (dd, *J* = 5.1, 9.7 Hz, C**H**H′O), 3.72 (dd, *J* = 5.1, 9.7 Hz, CH**H**′O), 4.48 (d, *J* = 6.0 Hz, C**H**$_2$NH), 4.53 (t, *J* = 9.7 Hz, C**H**), 7.39 (d, *J* = 8.3 Hz, 2 Ar**H**), 7.97 (d, *J* = 8.3 Hz, 2 Ar**H**), 8.57−8.66 (br t, N**H**CH$_2$); one amide proton and the carboxylic acid proton were not observed; ^{13}C NMR (75 MHz, CD_3OD) δ 21.4 [**C**H$_3$C(O)], 42.7 (**C**H$_2$NH), 54.2 (**C**H), 58.2 (**C**H$_3$O), 72.0 (**C**H$_2$OCH$_3$), 127.1, 129.6, 129.8, 144.3 (4 Ar**C**), 168.8 [HO**C**(O)], 171.6, 172.6 [2 **C**(O)]; LRMS (ESI) 295.1 [M + H^+] (calcd for $C_{14}H_{18}N_2O_5H^+$ 295.1). Anal. ($C_{14}H_{18}N_2O_5$): C, H, N.

Preparation of (*R*)-*N*-[4′-(Methyloxycarbonyl)]benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-31]. Pd/C (10%, 400 mg) was added to a solution of (*R*)-*N*-[4′-(methyloxycarbonyl)]benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.28 g, 3.2 mmol) in anhydrous MeOH (35 mL). The mixture was hydrogenated (45 psi, 24 h) and then filtered through Celite. The filtrate was evaporated in vacuo, leaving a mixture (0.80 g) of a white solid and an oil of the desired amine (TLC analysis using ninhydrin indicated the presence of a primary amine).

Using method D, triethylamine (1.25 mL, 9 mmol) and acetyl chloride (0.32 mL, 4.5 mmol) gave 0.43 g of a white solid (47%) after recrystallization with EtOAc: R_f = 0.62 (9/1 $CHCl_3$/MeOH); mp 167−168 °C; $[\alpha]^{25}_D$ −11.4° (*c* 2.2, $CHCl_3$); IR (nujol) 3279, 2927, 1712, 1639, 1550, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 [s, C**H**$_3$C(O)], 3.39 (s, C**H**$_3$O), 3.45 (dd, *J* = 7.5, 9.0 Hz, C**H**H′O), 3.82 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 3.91 [s, C**H**$_3$OC(O)], 4.51−4.55 (m, C**H**, C**H**$_2$NH), 6.45 [d, *J* = 6.6 Hz, N**H**C(O)CH$_3$], 6.85−6.95 (br m, N**H**CH$_2$), 7.32 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.00 (d, *J* = 8.4 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**31** gave only one signal for the acetyl methyl protons and one signal for the ether methyl protons; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3 [**C**H$_3$C(O)], 43.3 (**C**H$_2$NH), 52.3 [**C**H$_3$OC(O)], 52.7 (**C**H), 59.2 (**C**H$_3$OCH$_2$), 72.0 (**C**H$_2$OCH$_3$), 127.3, 129.4, 130.1, 143.4 (4 Ar**C**), 167.0 [O**C**(O)], 170.4, 170.6 [2 **C**(O)]; HRMS (ESI) 309.1451 [M + H^+] (calcd for $C_{15}H_{20}N_2O_5H^+$ 309.1450). Anal. ($C_{15}H_{20}N_2O_5$): C, H, N.

Preparation of (*R*)-*N*-(4′-Amino)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-32].[7] A MeOH solution (150 mL) of (*R*)-*N*-(4′-nitro)benzyl 2-acetamido-3-methoxypropionamide (2.00 g, 6.8 mmol) was treated with H_2 (1 atm) in the presence of PtO_2 (160 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a colorless oil that was triturated with EtOAc to give 1.67 g of (*R*)-**32** as a white solid (90%): R_f = 0.39 (9/1 $CHCl_3$/MeOH); mp 151−152 °C (lit.[7] mp 183−184 °C); ^1H NMR ($CDCl_3$) δ 2.02 [s, C**H**$_3$C(O)], 3.36 (s, OC**H**$_3$), 3.42 (dd, *J* = 7.8, 9.3 Hz, C**H**H′O), 3.78 (dd, *J* = 4.5, 9.3 Hz, CH**H**′O), 4.34 (d, *J* = 5.4 Hz, C**H**$_2$NH), 4.48−4.55 (m, C**H**), 6.48 [br d, *J* = 6.0 Hz, N**H**C(O)CH$_3$], 6.60−6.67 (m, CH$_2$N**H**, 2 Ar**H**), 7.05 (d, *J* = 8.1 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**32** gave only one signal for the acetyl methyl and one signal for the ether methyl protons.

Preparation of (*R*)-*N*-[4′-(2,2,2-Trifluoroacetamido)]benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-33]. (*S*)-Ethyl trifluoroacetate (2.99 g, 18.9 mmol) was added to a MeOH (10 mL) solution of (*R*)-**32** (1.00 g, 3.8 mmol) at room temperature, and then the reaction mixture was maintained at this temperature (3 h). Addition of EtOAc (10 mL) led to the precipitation of (*R*)-**33** as a white solid (600 mg) after filtration. The filtrate was concentrated in vacuum and the residue purified by flash chromatography on silica gel with EtOAc as the eluant to yield an additional 350 mg of (*R*)-**33** as a white solid. The solids were combined to produce 950 mg (70%) of (*R*)-**33**: R_f = 0.24 (EtOAc); mp 202−204 °C; $[\alpha]^{26}_D$ −1.2° (*c* 0.5, DMSO); IR (nujol) 3389, 3282, 1721, 1653, 1536, 1459, 1375, 1294, 1249, 1206, 1150, 1066, 974, 896, 838, 727, 653 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 [s, C**H**$_3$C(O)], 3.25 (s, OC**H**$_3$), 3.45−3.55 (m, C**H**H′O), 4.27 (d, *J* = 5.8 Hz, C**H**$_2$NH), 4.44−4.50 (m, C**H**), 7.27 (d, *J* = 8.7 Hz, 2 Ar**H**), 7.58 (d, *J* = 8.7 Hz, 2 Ar**H**), 8.11 [d, *J* = 7.8 Hz, CH$_3$C-(O)N**H**], 8.51 (t, *J* = 5.8 Hz, CH$_2$N**H**), 11.23 [s, CF$_3$C(O)N**H**]; ^{13}C NMR (DMSO-d_6) δ 22.4 [**C**H$_3$C(O)], 41.5 (**C**H$_2$NH), 52.6 (**C**H), 58.1 (O**C**H$_3$), 71.9 (**C**H$_2$OCH$_3$), 115.7 (q, *J* = 284.6 Hz, **C**F$_3$), 120.1, 127.4, 134.7, 136.7 (4 Ar**C**), 154.3 [q, *J* = 37.5 Hz, HN**C**(O)CF$_3$], 169.3, 169.7 [2 **C**(O)]; HRMS (M + H^+) (ESI^+) 362.1321 [M + H^+] (calcd for $C_{15}H_{18}F_3N_3O_4H^+$ 362.1328). Anal. ($C_{15}H_{18}F_3N_3O_4$): C, H, F, N.

Preparation of (*R*)-*N*-(4′-Azido)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-34]. Ag_2O (4.85 g, 20.9 mmol) was added to a CH_3CN solution (100 mL) of (*R*)-*N*-(4′-azido)benzyl 2-acetamido-3-hydroxypropionamide (1.16 g, 4.2 mmol) and CH_3I (2.61 mL, 41.9 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (5 days) and filtered, and the filtrate was concentrated in vacuo. The solid was purified by flash column chromatography

on silica gel (1/9 MeOH/$CHCl_3$) to yield 0.98 g (80%) of (*R*)-**34** as a white solid: R_f = 0.50 (1/9 MeOH/$CHCl_3$); mp 149−150 °C; $[\alpha]^{26}_D$ −15.2° (*c* 1.0, MeOH); IR (nujol) 3285, 2931, 2113, 1635, 1560, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 [s, C**H**$_3$C(O)], 3.38 (s, OC**H**$_3$), 3.44 (dd, *J* = 7.5, 9.3 Hz, C**H**H′O), 3.80 (dd, *J* = 4.2, 9.3 Hz, CH**H**′O), 4.40 (1/2AB$_q$, *J* = 6.2, 15.0 Hz, C**H**H′Ar), 4.46 (1/2AB$_q$, *J* = 6.2, 15.0 Hz, CH**H**′Ar), 4.52−4.58 (m, C**H**), 6.48 [br d, *J* = 6.3 Hz, N**H**C(O)CH$_3$], 6.82−6.85 (br m, CH_2N**H**), 6.96−7.01 (m, 2 Ar**H**), 7.23−7.28 (m, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**34** gave only a single signal for the acetyl methyl protons and the ether methyl protons, and addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**34** and (*S*)-**34** (1/2 ratio) gave two signals for the acetyl methyl protons [δ 1.995 (*R*) and 2.010 (*S*) (Δppm = 0.015)] and two signals for the ether methyl protons [δ 3.302 (*S*) and 3.342 (*R*) (Δppm = 0.040)]; ^{13}C NMR ($CDCl_3$) δ 23.4 [**C**H$_3$C(O)], 43.1 (**C**H$_2$NH), 52.7 (**C**H), 59.3 (O**C**H$_3$), 71.8 (**C**H$_2$OCH$_3$), 119.5, 129.1, 134.9, 139.5 (4 Ar**C**), 170.2, 170.5 [2 **C**(O)]; HRMS (M + H^+) (ESI^+) 292.1406 [M + H^+] (calcd for $C_{13}H_{17}N_5O_3H^+$ 292.1410). Anal. ($C_{13}H_{17}N_5O_3$): C, H, N.

Preparation of (*S*)-*N*-(4′-Azido)benzyl 2-Acetamido-3-methoxypropionamide [(*S*)-34]. Utilizing the preceding procedure, (*S*)-*N*-(4′-azido)benzyl 2-acetamido-3-hydroxypropionamide (2.40 g, 8.7 mmol), Ag_2O (10.04 g, 43.3 mmol), and MeI (5.40 mL, 86.6 mmol) gave crude (*S*)-*N*-(4′-azido)benzyl 2-acetamido-3-methoxypropionamide after 4 days. The product was purified by column chromatography (SiO_2; 1/9 MeOH/$CHCl_3$) to yield 2.05 g (81%) of (*S*)-**34** as a white solid: R_f = 0.50 (1/9 MeOH/$CHCl_3$); mp 149−150 °C; $[\alpha]^{26}_D$ 15.4° (*c* 1.0, MeOH); IR (nujol) 3285, 2927, 2112, 1635, 1565, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 [s, C**H**$_3$C(O)], 3.38 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.5, 9.0 Hz, C**H**H′O), 3.81 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 4.40 (1/2AB$_q$, *J* = 6.0, 15.0 Hz, C**H**H′Ar), 4.46 (1/2AB$_q$, *J* = 6.0, 15.0 Hz, CH**H**′Ar), 4.51−4.57 (m, C**H**), 6.43 [br d, *J* = 6.3 Hz, N**H**C(O)CH$_3$], 6.78−6.83 (br m, N**H**CH$_2$), 6.96−7.01 (m, 2 Ar**H**), 7.23−7.27 (m, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**34** gave only a single signal for the acetyl methyl protons and the ether methyl protons, and addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**34** and (*S*)-**34** (1/2 ratio) gave two signals for the acetyl methyl protons [δ 1.995 (*R*) and 2.010 (*S*) (Δppm = 0.015)] and the ether methyl protons [δ 3.302 (*S*) and 3.342 (*R*) (Δppm = 0.040)]; ^{13}C NMR ($CDCl_3$) δ 23.3 [**C**H$_3$C(O)], 43.1 (**C**H$_2$NH), 52.7 (**C**H), 59.2 (O**C**H$_3$), 72.0 (**C**H$_2$OCH$_3$), 119.4, 129.1, 135.0, 139.4 (4 Ar**C**), 170.3, 170.6 [2 **C**(O)]; HRMS (M + H^+) (ESI^+) 292.1405 [M + H^+] (calcd for $C_{13}H_{17}N_5O_3H^+$ 292.1410). Anal. ($C_{13}H_{17}N_5O_3$): C, H, N.

Preparation of (*R*)-*N*-(4′-Methoxy)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-35]. A MeOH solution (300 mL) of (*R*)-*N*-(4′-methoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (2.40 g, 6.4 mmol) was treated with H_2 (1 atm) in the presence of 10% Pd/C (480 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite, and the filtrate was evaporated in vacuo to yield a colorless oil.

Using method D, triethylamine (1.1 mL, 7.74 mmol) and acetyl chloride (550 μL, 7.74 mmol) gave 900 mg (70%) of (*R*)-**35** as a white solid after trituration in EtOAc: R_f = 0.82 (EtOAc); mp 146−147 °C; $[\alpha]^{25}_D$ −26.0° (*c* 0.5, $CHCl_3$); IR (nujol) 3283, 2861, 1642, 1520, 1458, 1377, 1299, 1255, 1176, 1127, 1031, 978, 719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 [s, C**H**$_3$C(O)], 3.37 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.8, 9.3 Hz, C**H**H′O), 3.76−3.81 (m, C**H**$_3$OC$_6$H$_4$, CH**H**′O), 4.39 (d, *J* = 6.0 Hz, C**H**$_2$NH), 4.50−4.57 (m, C**H**), 6.49 [br d, *J* = 6.0 Hz, N**H**C(O)CH$_3$], 6.71−6.82 (br t, CH_2N**H**), 6.86 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.18 (d, *J* = 8.4 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**35** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 [**C**H$_3$C(O)], 43.0 (**C**H$_2$NH), 52.4 (**C**H), 55.3 (C$_6$H$_4$-O**C**H$_3$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 114.1, 128.8, 129.9, 159.0 (4 Ar**C**), 169.8, 170.3 [2 **C**(O)]; HRMS (M + Na^+) (ESI^+) 303.1320 [M + Na^+] (calcd for $C_{14}H_{20}N_2O_4Na^+$ 303.1321). Anal. ($C_{14}H_{20}N_2O_4$): C, H, N.

Preparation of (*R*)-*N*-(4′-Chloro)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-36]. A saturated HCl solution in dioxane (1 mmol/2 mL, 24.0 mL) was added to (*R*)-*N*-(4′-chloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (4.10 g, 12.0 mmol) at 0 °C, and the solution was stirred at room temperature (2 h). The reaction solution was concentrated in vacuo and dried (30 min).

Using method D, triethylamine (5.0 mL, 36.0 mmol) and acetyl chloride (1.3 mL, 18.0 mmol) gave 3.10 g (80%) of (*R*)-**36** as a white solid after recrystallization with EtOAc: R_f = 0.42 (EtOAc); mp 155 °C; $[\alpha]^{27.0}_D$ −20.5° (*c* 1.0, $CHCl_3$); IR (nujol) 3288, 3277, 3162, 2900, 1634, 1556, 1457, 1375, 1306, 1259, 1193, 1137, 1098, 1045, 964, 909, 801, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 [s, C**H**$_3$C(O)], 3.37 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.8, 9.2 Hz, C**H**H′O), 3.78 (dd, *J* = 4.2, 9.2 Hz, CH**H**′O), 4.34−4.49 (m, C**H**$_2$NH), 4.54−4.61 (m, C**H**), 6.54 [br d, *J* = 6.6 Hz, N**H**C-(O)CH$_3$], 6.94−7.03 (br t, CH_2N**H**), 7.19 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.29 (d, *J* = 8.8 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**36** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 42.8 (**C**H$_2$NH), 52.5 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 128.7, 133.2, 136.4 (3 Ar**C**), 170.1, 170.4 [2 **C**(O)]; one signal was not detected and is believed to overlap with nearby peaks; HRMS (M + H^+) (ESI^+) 285.1006 [M + H^+] (calcd for $C_{13}H_{17}ClN_2O_3H^+$ 285.1006). Anal. ($C_{13}H_{17}ClN_2O_3$): C, H, Cl, N.

Preparation of (*R*)-*N*-(4′-Bromo)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-37]. Using method D, (*R*)-*N*-(4′-bromo)benzyl 2-amino-3-methoxypropionamide hydrochloride (1.00 g, 3.1 mmol), triethylamine (1.3 mL, 9.3 mmol), and acetyl chloride (0.3 mL, 3.7 mmol) gave 690 mg (68%) of (*R*)-**37** as a white solid after recrystallization with EtOAc: R_f = 0.08 (7/3 EtOAc/hexanes); mp 159−161 °C; $[\alpha]^{25}_D$ −15.9° (*c* 1.0, $CHCl_3$); IR (nujol mull) 3272, 3093, 2919, 2860, 1634, 1555, 1457, 1375, 1306, 1254, 1197, 1135, 1046, 964, 907, 795, 740, 606, 550, 468 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 [C**H**$_3$C(O)], 3.39 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.5, 9.0 Hz, C**H**H′O), 3.81 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 4.37−4.48 (m, C**H**$_2$NH), 4.51−4.57 (m, C**H**), 6.40−6.42 [br d, N**H**C(O)CH$_3$], 6.76−6.84 (br t, CH_2N**H**), 7.14 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.45 (d, *J* = 8.6 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**37** gave only one signal for the acetyl methyl protons and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 42.8 (**C**H$_2$NH), 52.4 (**C**H), 59.1 (O**C**H$_3$), 71.6 (**C**H$_2$OCH$_3$), 121.3, 129.1, 131.7, 137.0 (4 Ar**C**), 170.1, 170.4 [2 **C**(O)]; LRMS (ESI^+) 351.0 [M + Na]$^+$ (100%), 353.0 [M + 2 + Na]$^+$ (100%) (calcd for $C_{13}H_{17}BrN_2O_3Na^+$ 351.0 [M + Na]$^+$). Anal. ($C_{13}H_{17}BrN_2O_3$): C, H, Br, N.

Preparation of (*R*)-*N*-(4′-Iodo)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-38]. A saturated HCl solution in dioxane (1 mmol/2 mL, 25.0 mL) was added to (*R*)-*N*-(4′-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (5.50 g, 12.7 mmol) at 0 °C, and the solution was stirred at room temperature (2 h). The reaction solution was concentrated in vacuo and dried (30 min).

Using method D, triethylamine (10.7 mL, 76.0 mmol) and acetyl chloride (2.7 mL, 38.0 mmol) gave 3.40 g (71%) of (*R*)-**38** as a white solid after recrystallization with EtOAc: R_f = 0.76 (5/5 acetone/EtOAc); mp 159−160 °C; $[\alpha]^{25}_D$ 3.3° (*c* 1.0, DMSO); IR (nujol) 3279, 1636, 1552, 1457, 1375, 1305, 1139, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 [s, C**H**$_3$C(O)], 3.38 (s, OC**H**$_3$), 3.44 (dd, *J* = 7.2, 9.0 Hz, C**H**H′O), 3.79 (dd, *J* = 4.2, 9.0 Hz, CH**H**′O), 4.38−4.41 (m, C**H**$_2$NH), 4.52−4.59 (m, C**H**), 6.46 [br d, *J* = 6.6 Hz, N**H**C(O)CH$_3$], 6.85−6.93 (br t, CH_2N**H**), 7.00 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.64 (d, *J* = 8.4 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**38** gave only one signal for the acetyl methyl and one signal for the ether methyl

protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H_3C(O)], 42.9 (**C**H_2NH), 52.4 (**C**H), 59.1 (O**C**H_3), 71.6 (**C**H_2OCH$_3$), 92.7 (**C**I), 129.3, 137.7, 139.1 (3 Ar**C**), 170.1, 170.3 [2 **C**(O)]; HRMS (M + Na^+) (ESI^+) 399.0177 [M + Na^+] (calcd for $C_{13}H_{17}IN_2O_3Na^+$ 399.0182). Anal. ($C_{13}H_{17}IN_2O_3$): C, H, I, N.

Preparation of (*S*)-*N*-(4′-Iodo)benzyl 2-Acetamido-3-methoxypropionamide [(*S*)-38]. Employing the preceding procedure and using (*S*)-2-*N*-(4′-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (3.70 g, 8.5 mmol), a saturated dioxane solution of HCl (1 mmol/2 mL, 17.0 mL), triethylamine (3.6 mL, 25.6 mmol), and acetyl chloride (906 μL, 12.3 mmol) gave 2.43 g (76%) of (*S*)-**38** as a white solid after recrystallization with EtOAc: R_f = 0.76 (5/5 acetone/EtOAc); mp 159−160 °C; $[\alpha]^{24}_D$ −3.2° (*c* 1.0, DMSO); IR (nujol) 3278, 1636, 1552, 1458, 1375, 1305, 1138, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 [s, C**H**$_3$C(O)], 3.38 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.2, 9.0 Hz, CHH′O), 3.79 (dd, *J* = 4.2, 9.0 Hz, CHH′O), 4.38−4.42 (m, C**H**$_2$NH), 4.53−4.59 (m, C**H**), 6.47 [br d, *J* = 6.0 Hz, NHC(O)CH$_3$], 6.85−6.93 (br t, CH$_2$N**H**), 7.00 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.64 (d, *J* = 8.4 Hz, 2 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**38** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ 22.4 [**C**H$_3$C(O)], 41.4 (**C**H$_2$NH), 52.5 (**C**H), 58.1 (O**C**H$_3$), 71.9 (**C**H$_2$OCH$_3$), 92.2 (**C**I), 129.3, 136.8, 139.1 (3 Ar**C**), 169.3, 169.7 [2 **C**(O)]; HRMS (M + Na^+) (ESI^+) 399.0177 [M + Na^+] (calcd for $C_{13}H_{17}IN_2O_3Na^+$ 399.0182). Anal. ($C_{13}H_{17}IN_2O_3$): C, H, I, N.

Preparation of (*R*)-*N*-(4′-Sulfamoyl)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-39]. Using method A, (*R*)-2-acetamido-3-methoxypropionoic acid[25] (1.00 g, 6.2 mmol), NMM (1.5 mL, 13.7 mmol), IBCF (1.0 mL, 7.9 mmol), and methyl 4-(aminomethyl) benzenesulfonamide hydrochloride (2.07 g, 9.3 mmol) gave 1.25 g (61%) of (*R*)-**39** as a white solid after purification by column chromatography (1/7 MeOH/$CHCl_3$) and recrystallization (MeOH/$CHCl_3$): R_f = 0.35 (1/7 MeOH/$CHCl_3$); mp 177−179 °C; $[\alpha]^{25}_D$ 10.7° (*c* 1.0, MeOH); IR (nujol) 3293, 2935, 1623, 1557, 1459 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.87 [s, C**H**$_3$(O)], 3.26 (s, O**C**H$_3$), 3.46−3.56 (m, C**H**$_2$OCH$_3$), 4.34 (d, *J* = 6.1 Hz, C**H**$_2$NH), 4.43−4.50 (m, C**H**), 7.31 (s, N**H**$_2$), 7.41 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.75 (d, *J* = 8.6 Hz, 2 Ar**H**), 8.13 [d, *J* = 7.8 Hz, NHC(O)CH$_3$], 8.59 (t, *J* = 6.1 Hz, NHCH$_2$); ^{13}C NMR (DMSO-d_6) δ 22.5 [**C**H$_3$(O)], 41.7 (**C**H$_2$NH), 52.7 (**C**H), 58.2 (O**C**H$_3$), 72.0 (**C**H$_2$OCH$_3$), 125.5, 127.2, 142.5, 143.5 (4 Ar**C**), 169.5, 169.9 [2 **C**(O)]; HRMS (M + H^+) (ESI^+) 330.1117 [M + H^+] (calcd for $C_{13}H_{19}N_3O_5SH^+$ 330.1124). Anal. ($C_{13}H_{19}N_3O_5S$): C, H, N, S.

Preparation of (*R*)-*N*-(3′,4′-Dichloro)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-60]. Using method D, (*R*)-*N*-(3′,4′-dichloro)benzyl 2-amino-3-methoxypropionamide hydrochloride (3.50 g, 11.2 mmol), triethylamine (4.6 mL, 33.5 mmol), and acetyl chloride (0.95 mL, 13.4 mmol) gave 1.60 g (45%) of (*R*)-**60** as a white solid after recrystallization with EtOAc: R_f = 0.16 (7/3 EtOAc/hexanes); mp 165 °C; $[\alpha]^{24.9}_D$ −10.5° (*c* 1.0, $CHCl_3$); IR (nujol) 3292, 3096, 2927, 2859, 1636, 1555, 1459, 1379, 1256, 1135, 1034, 815, 724, 604, 491 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 [C**H**$_3$C(O)], 3.41 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.5, 9.3 Hz, CHH′O), 3.82 (dd, *J* = 4.1, 9.3 Hz, CHH′O), 4.39−4.49 (m, C**H**$_2$NH), 4.52−4.59 (m, C**H**), 6.39−6.41 [br d, NHC(O)CH$_3$], 6.80−6.90 (br t, CH$_2$N**H**), 7.10 (dd, *J* = 2.1, 8.1 Hz, 1 Ar**H**), 7.36 (d, *J* = 2.1 Hz, 1 Ar**H**), 7.40 (d, *J* = 8.1 Hz, 1 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**60** gave only one signal for the acetyl methyl protons and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 42.2 (**C**H$_2$NH), 52.6 (**C**H), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 126.6, 129.1, 130.5, 131.3, 132.6, 138.3 (6 Ar**C**), 170.2, 170.4 [2 **C**(O)]; LRMS (ESI^+) 341.05 [M + Na^+] (100%), 343.05 [M + 2 + Na^+] (64%), 345.05 [M + 4 + Na^+] (11%) (calcd for $C_{13}H_{16}Cl_2N_2O_3Na^+$ 341.04). Anal. ($C_{13}H_{16}Cl_2N_2O_3$): C, H, Cl, N.

Preparation of (*R*)-*N*-(2′,4′-Dichloro)benzyl 2-Acetamido-3-methoxypropionamide [(*R*)-61]. Using method D, (*R*)-*N*-(2′,4′-dichloro)benzyl 2-amino-3-methoxypropionamide hydrochloride (2.70 g, 7.2 mmol), triethylamine (3.0 mL, 21.5 mmol), and acetyl chloride (0.6 mL, 8.6 mmol) gave 1.45 g (63%) of (*R*)-**61** as a white solid after recrystallization with EtOAc: R_f = 0.26 (EtOAc); mp 149 °C; $[\alpha]^{23.7}_D$ −11.0° (*c* 1.0, $CHCl_3$); IR (nujol) 3477, 3399, 3276, 2919, 2854, 2725, 2363, 1637, 1552, 1458, 1376, 1304, 1251, 1135, 1102, 1050, 974, 821, 724, 606, 505 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 [C**H**$_3$C(O)], 3.37−3.43 (m, OC**H**$_3$, CHH′O), 3.80 (dd, *J* = 4.1, 9.2 Hz, CHH′O), 4.43−4.57 (m, C**H**$_2$NH, C**H**), 6.36−6.40 [br d, NHC(O)CH$_3$], 6.90−7.02 (br t, CH$_2$N**H**), 7.22 (dd, *J* = 2.1, 8.3 Hz, 1 Ar**H**), 7.30 (d, *J* = 8.3 Hz, 1 Ar**H**), 7.39 (d, *J* = 2.1 Hz, 1 Ar**H**); addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**61** gave only one signal for the acetyl methyl protons and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 [**C**H$_3$C(O)], 40.9 (**C**H$_2$NH), 52.4 (**C**H), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 127.2, 129.2, 130.3, 133.8, 133.9 (5 Ar**C**), 170.2, 170.4 [2 **C**(O)]; one signal was not detected and is believed to overlap with nearby peaks; LRMS (ESI^+) 341.08 [M + Na^+] (100%), 343.08 [M + 2 + Na^+] (66%), 345.07 [M + 4 + Na^+] (13%) (calcd for $C_{13}H_{16}Cl_2N_2O_3Na^+$ 341.04). Anal. ($C_{13}H_{16}Cl_2N_2O_3$): C, H, Cl, N.

Pharmacology. Compounds were screened under the auspices of the National Institutes of Health's Anticonvulsant Screening Program (ASP). Experiments were performed in male rodents [albino Carworth Farms No. 1 mice (intraperitoneal route, ip) or albino Sprague-Dawley rats (oral route, po)]. Housing, handling, and feeding were in full accordance with recommendations contained in the Guide for the Care and Use of Laboratory Animals. Anticonvulsant activity was established using the MES test,[33,42] the scMet test,[33] and the rapid hippocampal kindled rat model[39] using previously reported methods.[26]

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Supporting Information Available: Synthetic procedures for the intermediates leading to the preparation of (*R*)-**4**, (*R*)-**7**−**31**, (*R*)-**33**−**39**, (*R*)-**60**, and (*R*)-**61** and (*S*)-**11**, (*S*)-**21**, (*S*)-**23**, (*S*)-**26**, (*S*)-**28**, (*S*)-**29**, (*S*)-**34**, and (*S*)-**38**, elemental analyses, and ^{1}H and ^{13}C NMR spectra of compounds evaluated in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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