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Asymmetric Synthesis of Both Enantiomers of Vigabatrin®: An Approach Using Methionine as the Chiral Pool

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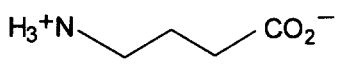
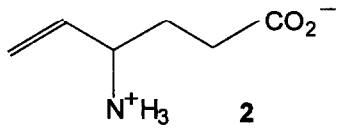
Abstract: Both enantiomers of the potent GABA-T inhibitor, 4-amino-5-hexenoic acid (**2**), were prepared in five steps from (R)- or (S)-methionine using a one-pot reduction-homologation of an α-amino ester as the key reaction step.

Epilepsy is a disease characterized by convulsive seizures, which result from repetitive and excessive electrical neuronal discharges, that is estimated to have a prevalence rate affecting one percent of the world population.[1] Although, the biochemical mechanisms causing epileptic seizures are not fully understood, it is known that γ-aminobutyric acid (GABA, **1**) is a major inhibitory neurotransmitter that prevents seizures. Indeed, convulsions occur when GABA levels diminish below a theshold level in brain,[2] and increasing the brain concentration of GABA prevents convulsions.[3] However, peripheral administration of GABA is ineffective since it does not cross the blood-brain-barrier (BBB), presumably due to its low lipophilicity.[4] Alternatively, a more lipophilic compound that is able to cross the BBB and selectively inhibit GABA-transaminase (GABA-T), the enzyme which degrades GABA,[5] would block the degradation of GABA. GABA levels would be expected to rise, provided inhibition of glutamic acid decarboxylase (GAD), the enzyme responsible for conversion of L-glutamate to GABA[5] does not occur, to provide an anticonvulsant effect. There is precedent for this approach since a number of *in vitro* GABA-T inhibitors elevate whole-brain GABA levels *in vivo* and exhibit anticonvulsant properties.[6]



1

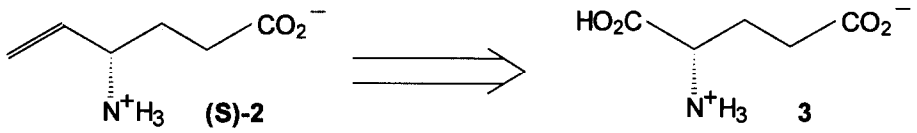


2

Vigabatrin® (γ-vinyl GABA, 4-amino-5-hexenoic acid, **2**), a synthetic analogue of GABA, is a highly selective enzyme-activated inhibitor of GABA-T in mammalian brain. Inhibition of GABA-T by γ-vinyl GABA, which replaces GABA as a substrate for GABA-T, increases the level of GABA in the central nervous system (CNS). Vigabatrin is therefore useful for treating disorders associated with depletion of GABA levels in the CNS such as tardive dyskinesia, schizophrenia and epilepsy.[7]

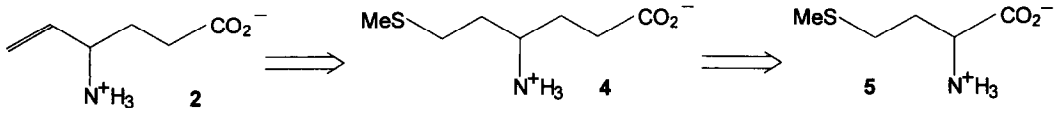
The biochemical and pharmacological effects of 4-amino-5-hexenoic acid have been studied extensively.[7,8] It was found that the biological activity of γ-vinyl GABA is highly dependent upon its absolute configuration. Although racemic vigabatrin is used in clinical practice, (S)-(+)-γ-vinyl GABA is the pharmacologically active enantiomer, whereas (R)-(-)-γ-vinyl GABA is inactive. To date, a number of

enantioselective syntheses of (S)-γ-vinyl GABA have been developed. These procedures all employ L-glutamic acid (**3**) as a starting material (Scheme 1). The vinyl moiety was introduced by pyrolysis of an N-oxide[9] or an ester moiety[10], or by a Wittig reaction[11], respectively.



Scheme 1

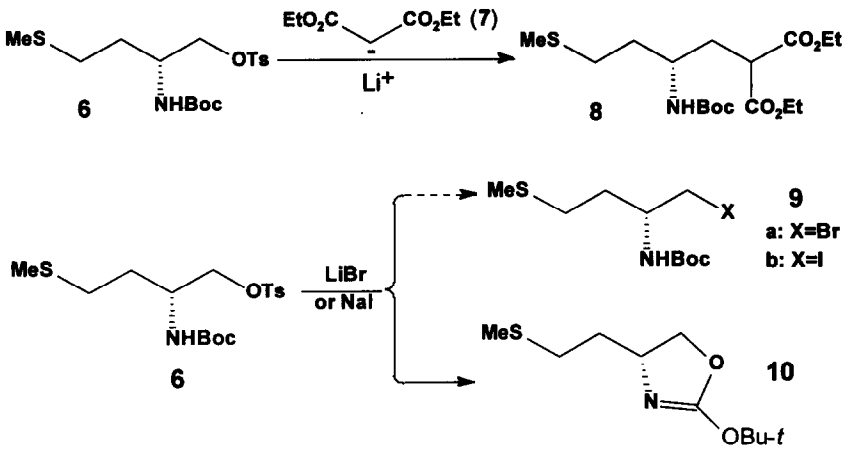
It was envisioned that γ-vinyl GABA (**2**) could be prepared from methionine (**5**, see Scheme 2).[12] Thus, a two carbon homologation of methionine (**5**) to give the sulfide (**4**), and pyrolysis of the sulfoxide of **4** to introduce the vinyl moiety, would afford γ-vinyl GABA (**2**). This strategy would provide γ-vinyl GABA with the opposite configuration to the chiral methionine employed. (S)- and (R)-γ-vinyl GABA would therefore be accessible from the commercially available (R)- and (S)-methionine, respectively.



Scheme 2

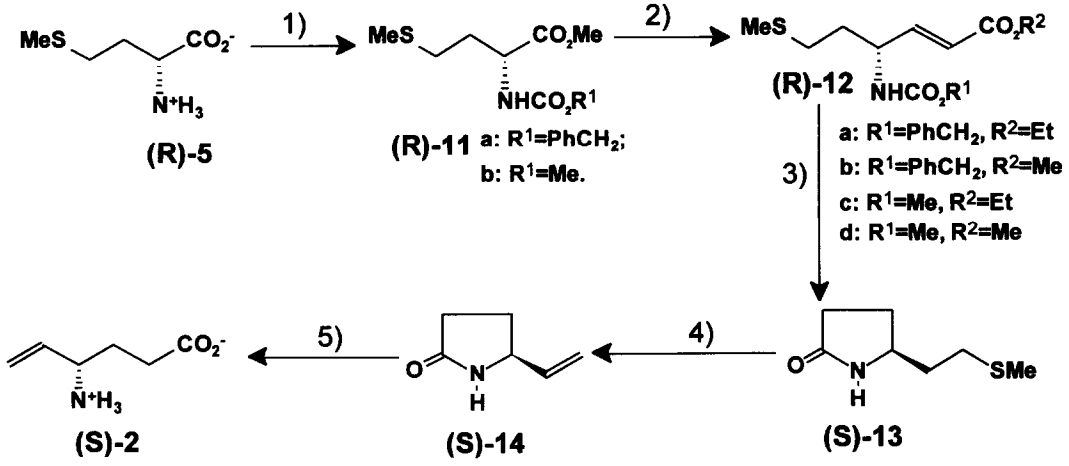
Pyrolysis of methionine derivatives, to introduce a vinyl group, is a well established reaction.[20,21] Therefore, the key step in the synthesis would require a method to achieve a two-carbon homologation of methionine. A survey of the literature suggested that this could be achieved using malonate chemistry.[13] Thus, initially the tosylate (**6**) was synthesized from (R)-methionine in three steps (protection of the amino group, reducing the acid group using BH_3, and tosylation of the alcohol). Unfortunately, treatment of tosylate (**6**) with malonate anion (**7**), prepared from diethyl malonate and *t*-butyl lithium, yielded the desired compound (**8**) in low yield (< 10% yield under the best conditions). Attempts to prepare more active halides such as **9a** or **9b** from the tosylate (**6**) were unsuccessful using standard reaction conditions since the oxazoline (**10**) was formed in near quantitative yield (Scheme 3).

In view of the failure of the malonate chemistry approach, an alternative method was sought which would give high product yields and involve a short reaction sequence. The Wittig-Horner reaction appeared to be a useful method to effect a two-carbon homologation of an aldehyde group. Thus, (R)-methionine (**5**) was first converted to its methyl ester hydrochloride using thionyl chloride in methanol. Reaction of this ester with benzyl chloroformate in aqueous alkaline medium gave the (R)-N-benzyloxycarbonyl α-amino carboxylate (**11a**) in 82% yield. The same procedure was employed to prepare the N-protected α-amino carboxylate [(R)-**11b**]. It was found that the methoxycarbonyl was a superior N-protective group, relative to a benzyloxycarbonyl moiety in this synthesis, since the isolation of **11b** was easier than **11a**.



Scheme 3

The next step required conversion of the N-protected α-amino carboxylates (**11**) to their corresponding N-protected γ-amino-α,β-unsaturated carboxylates (**12**). This transformation usually requires three reaction steps that involve reduction, oxidation and a Wittig-Horner reaction of the chiral α-amino aldehyde. A major limitation with this synthetic sequence is racemization[14] of the chiral α-amino aldehyde due to enolization. An efficient one-pot procedure was recently developed for this transformation.[15] Chiral N-protected α-amino carboxylates were elaborated to the corresponding N-protected γ-amino-α,β-unsaturated carboxylates in high chemical and optical yields. Using this one-pot reduction-homologation procedure, N-protected γ-amino-α,β-unsaturated carboxylates [(R)-**12a**, (R)-**12b**, (R)-**12c** and (R)-**11d**] were synthesized from N-protected α-amino carboxylates (**11**) in 62-78% yields.

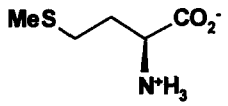


Reagents: 1): i, MeOH/$SOCl_2$; ii, $NaHCO_3$/$ClCO_2R^1$, 82-86%, 2): $(R_2O)_2P(O)CH_2CO_2R^2$/*t*-BuLi/DIBALH, 62-78%, 3): Mg/MeOH, 92-95%, 4): i, $NaIO_4$; ii, 190°C, 56%, 5): KOH/*i*-PrOH/H_2O, 96%.

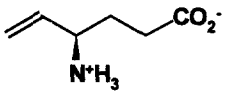
Scheme 4

Normally, reduction of the olefinic double bond of α,β-unsaturated carboxylates can be performed by catalytic hydrogenation or using hydride reagents. However, much difficulty was encountered in the reduction of the α,β-unsaturated carboxylates (**12**) using these reduction methods, due to the presence of the methylthio moiety[16] which is known to hinder catalytic hydrogenation reactions, or to poison hydride reagents. It was subsequently found that magnesium-methanol[17,18] was an efficient reducing reagent for this purpose. Thus, treatment of N-protected γ-amino α,β-unsaturated carboxylates (**12**) with magnesium in methanol afforded the γ-lactam (**13**) in near quantitative yield. This one-pot transformation[19] involved reduction of C=C double bond, cleavage of the carbamate and ester moieties, and intramolecular cyclization. Oxidation of γ-lactam (**13**) to the corresponding sulfoxide, followed by a thermal elimination reaction, afforded the (S)-5-vinyl γ-lactam (**14**) in 56% yield.[20,21] The (S)-5-vinyl γ-lactam (**14**) was hydrolyzed , under alkaline reaction conditions,[22] to γ-vinyl GABA in 96% yield.

A similar synthetic sequence starting from (S)-methionine [(S)-**5**] afforded (4R)-(-)-4-amino-5-hexenoic acid [(R)-**2**] in 29% overall yield.

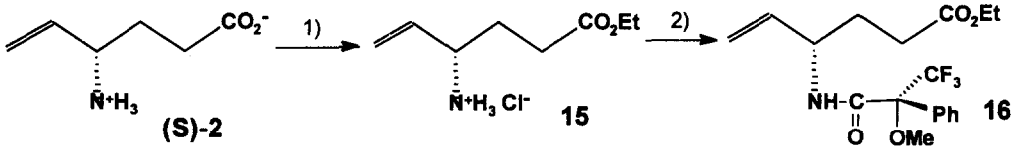


(S)-5

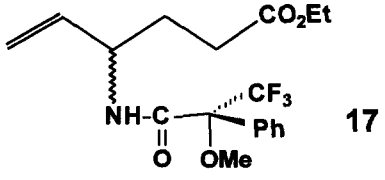


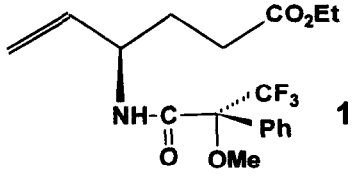
(R)-2

The optical purity of (S)-vigabatrin (**2**) was determined by the following method. Esterification of the amino acid with ethanol/HCl afforded the ethyl ester (**15**), which was then converted to the amide (**16**) by reaction with (S)-Mosher's acid chloride[23] (Scheme 5). The corresponding amide diastereomers (**17**) derived from racemic vigabatrin were also prepared using the method described for the amide diastereomer (**16**). The ^{19}F nmr spectrum of the amide diastereomers (**17**) exhibited two resonances of equal intensity at δ 92.35 and 92.44 (relative to C_6F_6), which indicated that the fluorine resonances for the two diastereomers were resolved. The corresponding ^{19}F NMR spectrum of the amide diastereomer (**16**) showed the two resonances in a ratio of > 99:1, respectively indicating that the enantiomeric excess of (S)-vigabatrin (**2**) was greater than 98%.



1): EtOH, HCl; 2): (S)-Mosher's acid chloride, Et_3N.





Scheme 5

Similarly, (R)-vigabatrin (**2**) was converted to the amide diastereomer (**18**), whose ^{19}F NMR spectrum showed two resonances at δ 92.44 and 92.35 in a ratio of > 99:1, indicating that the enantiomeric excess of (R)-vigabatrin (**2**) was also greater than 98%.

Other asymmetric syntheses of (S)-γ-vinyl GABA have also been reported.[9-11] The Frieben and Gerhart[9] nine step synthesis involved the elaboration of L-glutamate → (S)-ethyl pyroglutamate → 5-(hydroxymethyl)-2-pyrrolidinone. Subsequent mesylation and reaction with cyanide afforded the cyanomethyl analog, which was transformed to the (dimethylamino)methyl derivative. Oxidation to the N-oxide, and then a Cope pyrolysis reaction under reduced pressure gave the target 5-vinyl-2-pyrrolidinone and the undesired deoxygenation product 5-(2-dimethylaminoethyl)-2-pyrrolidinone (≤ 40%). Acid hydrolysis yielded (S)-γ-vinyl GABA. This is a satisfactory synthesis, but a more efficient alternative to the Cope elimination reaction would be desirable. A related synthesis described by Mullins *et al.*[10] utilizes a drastic pyrolysis reaction performed at 530-545°C to introduce the 5-vinyl group following consecutive reduction, alkylation and acylation of methyl pyroglutamate. The procedure descibed by Smith *et al.*[11] provided a more efficient enantioselective synthesis of (S)-γ-vinyl GABA that was prepared from L-glutamic acid in 33% overall yield in six steps *via* 5-substituted 2-pyrrolidinone intermediate products. The alternate enantioselective synthesis developed in this study starting from (R)-methionine yielded (S)-γ-vinyl GABA in five steps in 32% overall yield. An attractive feature of the methodology developed is the one-pot reduction-homologation reaction which provides chiral γ-amino-α,β-unsaturated carboxylates which are also useful synthons for the synthesis of biologically important compounds, natural products, and as peptide isosteres or peptide mimics.

In summary, a new methodology has been developed for the synthesis of either (S)- or (R)-vigabatrin starting from methionine, which is commercially available in both the (R)- and (S)-configuration. The present methodology provides a synthetically expedient example whereby α-amino acids may be transformed into the corresponding γ-amino acids. We are currently employing this methodology to synthesize novel γ-amino acids for pharmacological evaluation as potential GABA-T inhibitors.

EXPERIMENTAL SECTION

All moisture-sensitive reactions were carried out under a positive pressure of nitrogen gas. Tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. Methanol and ethanol were distilled from the corresponding magnesium alkoxide. Most chemical reagents were purchased from the Aldrich Chemical Co. Column chromatography was performed using Mackery Nagel MN-Kieselgel 60 (70-230 mesh) silica gel. Nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR) were acquired on a Bruker AM-300 spectrometer. Infrared spectra were recorded using a Nicolet 5DX FT spectrometer, and only selected absorptions are reported. Mass spectra were recorded on an AEI MS-50 mass spectrometer. Optical rotations were obtained using a Optical Activity Ltd. polarimeter at 25°C. Melting points were determined using a capillary melting point apparatus and are uncorrected. All compounds were isolated as oils, except when a melting point is given.

General Procedure for the Preparation of N-Protected α-Amino Esters (11): To a stirred suspension of methionine [7.46 g, 50.0 mmol, (R)- or (S)-] in dry methanol (100 mL) was added thionyl chloride (5.95 g, 50.0 mmol) at 25°C. After heating at reflux for 2 hr, the reaction mixture was concentrated *in vacuo* to give a residue, which was dissolved in water (150 mL). The resulting aqueous solution was basified by addition of sodium bicarbonate (33.6 g, 0.4 mol). To this solution either benzyl or methyl chloroformate (75-100 mmol)

was added at 25°C, and the mixture was stirred for 12 hr at 25°C. After extraction with ethyl acetate (2 x 100 mL), the aqueous phase was cooled in an ice bath, the pH was adjusted to 5 using concentrated hydrochloric acid, and the resulting solution was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). The residue obtained upon removal of the solvent was purified by silica gel column chromatography using ethyl acetate:hexane (20-35%, v/v) as eluant.

Methyl (2R)-2-(benzyloxycarbonylamino)-4-methylthiobutyrate [(2R)-11a]: This compound was prepared from (R)-methionine in 82% yield according to the general procedure. $[\alpha]_D^{25}$ = -17.9° (c 5.0, $CHCl_3$); IR 3339 (w), 2959 (w), 2917 (w), 1722 (s), 1511 (m), 1441 (m), 1216 (m), 1054 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.98 (m, 1H), 2.07 (s, 3H), 2.14 (m, 1H), 2.52 (t, J=7.5 Hz, 2H), 3.74 (s, 3H), 4.49 (m, 1H), 5.10 (s, 2H), 5.53 (br s, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 15.3, 29.8, 31.9, 52.4, 53.1, 67.0, 128.0, 128.1, 128.4, 136.2, 155.8, 172.3; Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.65; H, 6.50; N, 4.68.

Methyl (2S)-2-(benzyloxycarbonylamino)-4-methylthiobutyrate [(2S)-11a]: This compound was prepared from (S)-methionine in 89% yield according to the general procedure, and it was identical to (2R)-**11a** in all respects (^1H NMR, ^{13}C NMR, IR) except for the optical rotation: $[\alpha]_D^{25}$ = +17.7° (c 4.3, $CHCl_3$).

Methyl (2R)-2-(methoxycarbonylamino)-4-methylthiobutyrate [(2R)-11b]: This compound was prepared from (R)-methionine in 86% yield according to the general procedure. $[\alpha]_D^{25}$ = -21.5° (c 2.1, $CHCl_3$); IR 3361 (m), 2951 (m), 2918 (m), 1721 (s), 1516 (s), 1442 (s), 1360 (m), 1220 (s), 1065 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.94 (m, 1H), 2.08 (s, 3H), 2.12 (m, 1H), 2.52 (t, J=7.5 Hz, 2H), 3.67 (s, 3H), 3.74 (s, 3H), 4.46 (m, 1H), 5.45 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 15.1, 29.6, 31.5, 52.1, 52.2, 52.8, 156.4, 172.4; Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.43; H, 6.83; N, 6.33. Found: C, 43.54; H, 6.83; N, 6.30.

Methyl (2S)-2-(methoxycarbonylamino)-4-methylthiobutyrate [(2S)-11b]: This compound was prepared from (S)-methionine in 94% yield according to the general procedure, and it was identical to (2R)-**11b** in all respects (^1H NMR, ^{13}C NMR, IR) except for its optical rotation: $[\alpha]_D^{25}$ = +22.8° (c 21.0, $CHCl_3$).

General Procedure for the Preparation of N-Protected γ-Amino-α,β-unsaturated Esters (12): To a solution of the trialkylphosphonoacetate (11 mmol) in THF (50 mL) at -78°C was added dropwise with stirring a solution of *t*-butyl lithium in hexane (6.5 mL of a 1.7 M solution, 11.0 mmol). After stirring for 30 min, a solution of the α-amino acid ester (**11**, 10.0 mmol) in THF (10 mL) and then a solution of DIBALH in toluene (13 mL of a 1.5 M solution, 19.5 mmol) was added. The resulting mixture was stirred for 5 hr at -78°C prior to warming to 25°C. Water (10 mL) and then 2N hydrochloric acid (20 mL) was added, the organic layer was separated, and the aqueous mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic fractions were washed with saturated brine, the organic fraction was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The products were purified by silica gel flash chromatography to yield the γ-amino-α,β-unsaturated carboxylate (**12**).

Ethyl (4R)-4-(benzyloxycarbonylamino)-6-methylthio-2-hexenoate [4R)-12a]: This compound was prepared by reaction of (2R)-**11a** with triethylphosphonoacetate according to the general procedure (78% yield). $[\alpha]_D^{25}$ = +15.7° (c 26.0, $CHCl_3$); IR 3431 (m), 2977 (m), 2922 (m), 1717 (s), 1657 (m), 1506 (s), 1281 (m), 1221 (m), 1045 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.24 (t, J=7.2 Hz, 3H), 1.80 (m, 2H), 2.04 (s, 3H), 2.48 (m, 2H), 4.15 (q, J=7.2 Hz, 2H), 4.45 (m, 1H), 5.07 (s, 2H), 5.24 (br s, 1H), 5.92 (d, J=15.6 Hz, 1H), 6.80 (dd, J=15.6, 5.5 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 13.6, 14.8, 29.7, 33.1, 50.9, 59.9, 66.2, 120.7, 127.4, 127.5, 127.9, 136.0, 147.0, 155.4, 165.6; HRMS *m/z* 337.1350 (M^+ 337.1348 calcd for $C_{17}H_{23}NO_4S$), 297, 246, 223, 181, 162, 154, 145, 108, 91; Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15. Found: C, 59.98; H, 6.86; N, 4.22.

Ethyl (4S)-4-(benzyloxycarbonylamino)-6-methylthio-2-hexenoate [(4S)-12a]: This compound was prepared from (2S)-**11a** and triethylphosphonoacetate in 64% yield according to the general procedure, and it was identical to (4R)-**12a** in all respects (^{1}H NMR, ^{13}C NMR, IR) except for its optical rotation: $[\alpha]_D^{25}$ = -16.2° (c 25.0, $CHCl_3$).

Methyl (4R)-4-(benzyloxycarbonylamino)-6-methylthio-2-hexenoate [(4R)-12b]: This compound was obtained from reaction of (2R)-**11a** with trimethylphosphonoacetate in 68% yield according to the general procedure (*trans:cis* = 65:35). $[\alpha]_D^{25}$ = +15.8° (c 14.6, $CHCl_3$); IR 3339 (m), 3030 (w), 2952 (m), 2917 (m), 1722 (s), 1701 (s), 1659 (m), 1511 (m), 1441 (m), 1223 (m), 1047 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.80 (m, 2H), 2.04 (*trans*) and 2.06 (*cis*) (two s, 3H total), 2.45 (m, 2H), 3.69 (s, 3H), 4.44 (m, 0.65H, *trans*), 5.05 (*trans*) and 5.07 (*cis*) (two s, 2H total), 5.20 (m, 0.35H, *cis*), 5.3-5.7(m, 1H), 5.79 (d, J=10.8 Hz, 0.35H, *cis*), 5.94 (d, J=15.6 Hz, 0.65H, *trans*), 6.10 (m, 0.35H, *cis*), 6.82 (dd, J=15.6, 5.3 Hz, 0.65H, *trans*), 7.30 (m, 5H); Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.59; H, 6.60; N, 4.36.

Ethyl (4R)-4-(methoxycarbonylamino)-6-methylthio-2-hexenoate [(4R)-12c]: This compound was obtained by reaction of (2R)-**11b** with triethylphosphonoacetate in 62% yield according to the general procedure (*trans:cis* = 93:7). $[\alpha]_D^{25}$= +19.6° (c 1.4, $CHCl_3$); IR 3339 (m), 2959 (m), 2917 (m), 1715 (s), 1659 (m), 1511 (m), 1448 (m), 1370 (m), 1279 (m), 1195 (m), 1047 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, J=7.2 Hz, 3H), 1.88 (m, 2H), 2.11 (s, 3H), 2.55 (m, 2H), 3.68 (s, 3H), 4.19 (q, J=7.2 Hz, 2H), 4.46 (m, 1H), 5.35 (d, J=8.5 Hz, 1H), 5.96 (dd, J=15.6, 1.6 Hz, 1H), 6.85 (dd, J=15.6, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 15.3, 30.1, 33.6, 49.1, 51.3, 60.3, 121.3, 147.0, 156.2, 165.9; Anal. Calcd for $C_{11}H_{19}NO_4S$: C, 50.56; H, 7.33; N, 5.36. Found: C, 50.21; H, 7.38; N, 5.33.

Ethyl (4S)-4-(methoxycarbonylamino)-6-methylthio-2-hexenoate [(4S)-12c]: This compound was prepared by reaction of (2S)-**11b** with triethylphosphonoacetate in 63% yield according to the general procedure, and it was identical (^{1}H NMR, ^{13}C NMR) to (4R)-**12c** in all respects except for its optical rotation: $[\alpha]_D^{25}$ = -20.4° (c 19, $CHCl_3$).

Methyl (4R)-4-(methoxycarbonylamino)-6-methylthio-2-hexenoate [(4R)-12d]: This compound was prepared by reaction of (2R)-**11b** with trimethylphosphonoacetate in 66% yield according to the general procedure (*trans:cis* > 95:5). $[\alpha]_D^{25}$ = +17.6° (c 8.8, $CHCl_3$); IR 3346 (s), 2952 (m), 2917 (m), 1722 (s), 1518 (s), 1441 (s), 1279 (s), 1195 (m), 1054 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.86 (m, 2H), 2.08 (s, 3H), 2.52 (m, 2H), 3.64 (s, 3H), 3.71 (s, 3H), 4.45 (m, 1H), 5.75 (m, 1H), 5.94 (dd, J=15.6, 1.6 Hz, 1H), 6.84 (dd, J=15.6, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 15.0, 29.9, 33.3, 51.0, 51.2, 51.8, 120.5, 147.5, 156.2, 166.2; Anal. Calcd for $C_{10}H_{17}NO_4S$: C, 48.57; H, 6.93; N, 5.66. Found: C, 48.76; H, 7.19; N, 5.59.

Methyl (4S)-4-(methoxycarbonylamino)-6-methylthio-2-hexenoate [(4S)-12d]: This compound was prepared from (2S)-**11b** and trimethylphosphonoacetate in 66% yield according to the general procedure, and it was identical to (4R)-**12d** in all respects (^{1}H NMR, ^{13}C NMR)) except for its optical rotation: $[\alpha]_D^{25}$ = -17.2° (c 11.6, $CHCl_3$).

General Procedure for the Conversion of N-Protected γ-Amino-α,β-unsaturated Carboxylates (12) to γ-Lactams (13): A mixture of the N-protected γ-amino-α,β-unsaturated carboxylate (**12**, 20 mmol) and magnesium turnings (4.86 g, 0.2 mol) in methanol (100 mL) was stirred for 4 hr at 0°C and for 8 hr at 25°C. After neutralization with hydrochloric acid (2N), the mixture was extracted with chloroform (3 x 200 mL). The

combined chloroform phase was washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a residue which was purified by silica gel column chromatography (methanol:ethyl acetate = 4:96, v/v) to afford the γ-lactam (**13**).

(5S)-5-(2-Methylthioethyl)-2-pyrrolidinone [(5S)-13]: This compound was obtained by reaction of the (4R)-N-protected γ-amino-α,β-unsaturated carboxylates (**12a**, 94%; **12b**, 92%; **12c**, 95%; and **12d**, 92%) with magnesium in methanol according to the general procedure. mp 56-57°C; $[\alpha]_D^{25}$ = +10.3° (c 2.5, $CHCl_3$); IR 3213 (m), 2980 (m), 2917 (m), 1687 (s), 1427 (m), 1265 (m), 1089 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.60-1.85 (m, 3H), 2.08 (s, 3H), 2.16-2.34 (m, 3H), 2.52 (t, J=7.2 Hz, 2H), 3.74 (m, 1H), 7 07 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 15.1, 26.6, 29.9, 30.1, 35.6, 53.4, 178.3. Anal. Calcd for $C_7H_{13}NOS$: C, 52.80; H, 8.23; N, 8.80. Found: C, 52.76; H, 8.33; N, 8.67.

(5R)-5-(2-Methylthioethyl)-2-pyrrolidinone [(5R)-13]: This compound was obtained by reaction of the (4S)-N-protected γ-amino-α,β-unsaturated carboxylates (**12a**, 89%; and **12d**, 84%) according to the general procedure. The product was identical to (5S)-**13** in all respects (^1H NMR, ^{13}C NMR, IR) except for its optical rotation and melting point: mp 59-60°C; $[\alpha]_D^{25}$ = -9.8° (c 14, $CHCl_3$).

General Procedure for the Preparation of 5-Vinyl-2-pyrrolidinones (14): A solution of sodium periodate (2.57 g, 12.0 mmol) in water (20 mL) was added dropwise to a vigorously stirred ice-cold solution of the γ-lactam (**13**, 1.59 g, 10.0 mmol) in methanol (50 mL). The reaction mixture was stirred for 4 hr, the precipitated iodate was filtered off and washed with methanol, the combined filtrates were concentrated *in vacuo* and the organic material was dissolved in chloroform. Evaporation of the chloroform solution afforded the corresponding sulfoxide product, which was immediately dissolved in *o*-dichlorobenzene (30 mL). This solution was heated at reflux temperature for 4 hr, and then applied to a silica gel column, which was eluted with methanol-ethyl acetate (1:99, v/v) to give the 5-vinyl-2-pyrrolidinone (**14**).

(5S)-5-Vinyl-2-pyrrolidinone [(5S)-14]: This compound was obtained from (5S)-**13** in 56% yield according to the general procedure. $[\alpha]_D^{25}$ = +50.4° (c 2.2, EtOH); IR 3220 (m), 3086 (w), 2945 (w), 1694 (s), 1420 (w), 1251 (w), 1061 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.74 (m, 1H), 2.25 (m, 3H), 4.08 (m, 1H), 5.04 (dd, J=10.2, 0.9 Hz, 1H), 5.14 (dd, J=17.0, 0.9 Hz, 1H), 5.72 (ddd, J=17.0, 10.2, 6.6 Hz, 1H), 7.43 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 27.1, 29.4, 56.0, 114.4, 138.2, 178.2. Anal. Calcd for C_6H_9NO . 0.2 H_2O: C, 62.81; H, 8.25. Found: C, 62.80; H, 8.15.

(5R)-5-Vinyl-2-pyrrolidinone [(5R)-14]: This compound was obtained from (5R)-**13** in 62% yield according to the general procedure. It was identical to (5S)-**14** in all respects (^1H NMR, ^{13}C NMR, IR) except for its optical rotation: $[\alpha]_D^{25}$ = -50.6° (c 5.2, EtOH).

General Procedure for Hydrolysis of 5-Vinyl-2-pyrrolidinones (14): A mixture of 5-vinyl-2-pyrrolidinone (**14**, 0.56 g, 5.0 mmol), potassium hydroxide (0.50 g), water (0.6 mL), and isopropanol (6 mL) was refluxed for 24 hr. After cooling to 0°C, the reaction mixture was neutralized with glacial acetic acid (0.45 g), and the solvent was removed *in vacuo* to give a residue, which was dissolved in water (2 mL) and this solution was applied to the top of a Dowex 50X 2-200 column (H^+ form, 100-200 mesh). The column was eluted with water until the eluant was neutral. Further elution with 1N aqueous ammonium hydroxide, and removal of the solvent from the eluant *in vacuo,* afforded the 4-amino-5-hexenoic acid (**2**).

(4S)-4-Amino-5-hexenoic acid [(4S)-2]: This compound was obtained from (5S)-5-vinyl-2-pyrrolidinone (**14**) in 96% yield according to the general procedure. mp 161-162°C; $[\alpha]_D^{25}$ = +11.6° (c 4.5, H_2O), {lit.[11] $[\alpha]_D^{25}$ = +12.2° (c 9.5, H_2O at pH 6.6}; IR 3427 (m), 2935 (s), 1639 (s), 1573 (s), 1524 (s), 1393 (s), 1122 (s), 991

(m), 933 (s) cm^{-1}; ^1H NMR (D_2O) δ: 1.58-1.74 (m, 1H), 1.74-1.92 (m, 1H), 1.98-2.14 (m,2H), 3.68 (ddd, J=8.2, 8.2, 5.4 Hz, 1H), 5.19-5.25 (m, 2H), 5.61 (ddd, J=16.9, 10.6, 8.2 Hz, 1H); ^{13}C NMR (D_2O) δ: 29.4, 33.9, 54.5, 121.6, 133.4, 181.9. Anal. Calcd for $C_6H_{11}NO_2$. 0.1 H_2O: C, 55.03; H, 8.62; N, 10.70. Found: C, 55.15; H, 8.80; N, 10.99.

(4R)-4-Amino-5-hexenoic acid [(4R)-2]: This compound was obtained from (5R)-5-vinyl-2-pyrrolidinone (**14**) in 91% yield according to the general procedure, and it was identical to (4S)-**2** in all respects (^1H NMR, ^{13}C NMR) except for its optical rotation and melting point: mp 164-165°C; $[\alpha]_D^{25}$ = -12.0° (c 2.5, H_2O).

Ethyl (4S)-4-amino-5-hexenoate hydrochloride [(4S)-15]: (4S)-4-Amino-5-hexenoic acid (**2**, 40 mg) was dissolved in ethanol saturated with hydrogen chloride gas (6 mL), and the resulting solution was stirred for 12 hr at 25°C. The solvent was evaporated *in vacuo* to afford **15** as a pale yellow solid, which was used immediately in the subsequent reaction.

Ethyl N-[(2R)-2-methoxy-2-phenyl-3,3,3-trifluoropropionoyl]-(4S)-4-amino-5-hexenoate (16): To a stirred suspension of (4S)-**15** in dry methylene chloride (10 mL) was added triethylamine (0.2 mL) and (S)-Mosher's acid chloride, prepared from (R)-Mosher's acid (50 mg) and excess thionyl chloride. The mixture was stirred for 4 hr at 25°C, and then cooled in an ice bath prior to addition of hydrochloric acid solution (0.1N, 5 mL). After extraction with ethyl acetate (2 x 20 mL), the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The residue obtained upon removal of the solvent was then analysed by ^{19}F NMR spectroscopy, which showed two fluorine resonances at δ 92.35 and 92.44 (ratio: 99 > 1) relative to C_6F_6.

Ethyl N-[(2R)-2-methoxy-2-phenyl-3,3,3-trifluoropropionoyl]-(4S,4R)-4-amino-5-hexenoate diastereomers (17): This diastereomeric mixture, prepared according to the method described above for the preparation of **16**, using racemic 4-amino-5-hexenoic acid (**2**), showed two fluorine resonances of equal intensity at δ 92.35 and 92.44 relative to C_6F_6.

Ethyl N-[(2R)-2-methoxy-2-phenyl-3,3,3-trifluoropropionoyl]-(4R)-4-amino-5-hexenoate (18): This diastereomer, prepared according to the method described above for the synthesis of **16** using (4R)-4-amino-5-hexenoic acid (**2**), exhibited two fluorine resonances at δ 92.44 and 92.35 (ratio: 99 > 1) relative to C_6F_6.

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