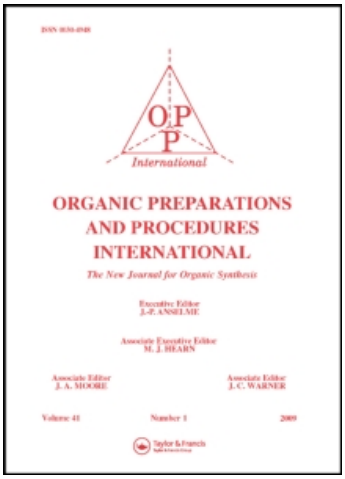

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RESOLUTION OF 5-VINYL-2-PYRROLIDINONE. A PRACTICAL SYNTHESIS OF (S)- AND (R)-VIGABATRIN

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RESOLUTION OF 5-VINYL-2-PYRROLIDINONE. A PRACTICAL SYNTHESIS OF (S)- AND (R)-VIGABATRIN

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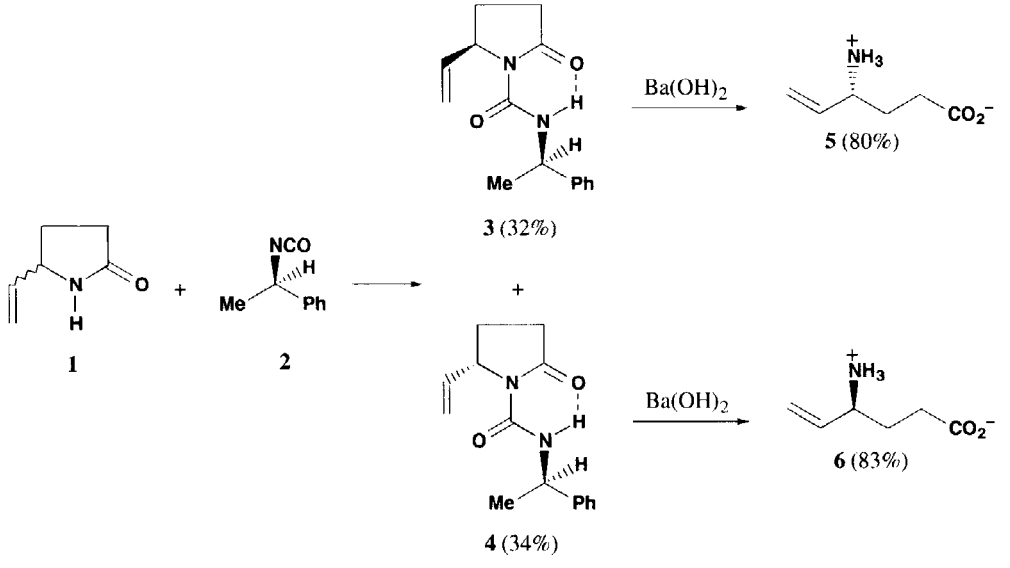
Vigabatrin (γ-vinyl GABA, 4-amino-5-hexenoic acid) is a highly selective enzyme-activated inhibitor of GABA-T in mammalian brain,[1] which crosses the blood-brain-barrier (BBB), and is used clinically primarily to control seizures refractory to other anticonvulsant drugs.[2] (S)-Vigabatrin is the pharmacological active enantiomer, whereas the (R)-antipode is inactive. The two enantiomers of vigabatrin have been prepared by asymmetric syntheses,[3-7] or by enzyme-catalyzed resolution[8] of

racemic vigabatrin. As part of a project involving the design and synthesis of a novel chemical delivery system, we required an efficient preparation of both enantiomers of vigabatrin, which was amenable to large scale synthesis and provided products having a high enantiomeric purity. We now describe a simple method for the preparation of (R)-vigabatrin (**5**) and (S)-vigabatrin (**6**) by resolution of racemic 5-vinyl-2-pyrrolidinone (**1**).

Pirkle *et al.*[9] have reported that diastereromeric ureido lactam derivatives, derived from a butyrolactam and a chiral isocyanate can be separated by high pressure liquid chromatography. This methodology has now been applied to the separation of a racemic 5-substituted-2-pyrrolidinone. Thus, reaction of 5-vinyl-2-pyrrolidinone (**1**), prepared from commercially available succinimide in two steps[10], with (R)-α-methylbenzyl isocyanate (**2**) in benzene at reflux temperature for 24 hrs afforded a diastereomeric mixture of the ureides **3** and **4**. Separation of the resulting ureides by silica gel column chromatography gave the pure ureides **3** (32%) and **4** (34%). Hydrolysis of the less polar diastereomer (**3**) using aqueous $Ba(OH)_2$ afforded (R)-vigabatrin (**5**, 80%), whereas a similar hydrolysis of the more polar diastereomer (**4**) yielded (S)-vigabatrin (**6**, 83%).



Scheme 1

In conclusion, the method described provides a facile method for the preparation of enantiomerically pure (R)- or (S)-vigabatrin on a practical scale in 26 and 28% overall yield from **1**, respectively. Since 5-substituted-2-pyrrolidinones can be readily prepared from succinimide[10], this procedure offers an attractive method to prepare other chiral γ-substituted-γ-amino acids, which may also act as GABA-T inhibitors.

EXPERIMENTAL SECTION

Mps were determined using a capillary melting point apparatus and are uncorrected. 5-Vinyl-2-pyrrolidinone (**1**) was prepared from succinimide,[10] and (R)-(+)-α-methylbenzyl isocyanate (**2**) was 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 (^{1}H NMR, ^{13}C NMR) were acquired using a Bruker AM-300 spectrometer. Chemial shifts are given in parts per million, and are referenced to the deuterium lock signal from the sample solvent. Infrared spectra were obtained on a Nicolet 5DX-FT spectrometer, and only selected absorptions are reported. Optical rotations were obtained using an Optical Activity Ltd. polarimeter at 25°.

Procedure for the Preparation of the Ureide Diastereomers (3 and 4).- A mixture of racemic 5-vinyl-2-pyrrolidinone (**1**, 1.11 g, 10.0 mmol) and (R)-α-methylbenzyl isocyanate (**2**, 1.62 g, 11.0 mmol) in dry benzene (20 mL) was refluxed for 24 hrs prior to cooling to 25°. The solvent was removed *in vacuo*, and the residue obtained was separated by silica gel column chromatography using a gradient of EtOAc-hexane (5:95 to 15:85, v/v) to afford the diastereomeric uriedes **3** (0.83 g, 32%, less polar diastereomer) and **4** (0.88 g, 34%, more polar diastereomer), respectively.

N-[(R)-1-Phenylethyl]-(5R)-5-vinyl-2-pyrrolidinone-1-carboxamide (3).- Diastereomer **3** was isolated as a yellow oil; $[\alpha]_D$ = +17.2° (c 10.8, $CHCl_3$); IR (film): 3297 (s), 3036 (m), 2988 (s), 1715 (s), 1687 (s), 1532 (s), 1377 (s), 1230 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.52 (d, J = 7.0 Hz, 3H), 1.86 (m, 1H), 2.21 (m, 1H), 2.49 (ddd, J = 17.5, 8.9, 2.2 Hz, 1H), 2.68 (ddd, J = 17.5, 11.3, 8.8 Hz, 1H), 4.85 (m, 1H), 5.04 (m, 1H), 5.20 (m, 2H), 5.92 (m, 1H), 7.26 (m, 1H), 7.33 (m, 4H), 8.84 (d, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 22.3, 23.3, 31.0, 49.1, 57.9, 114.6, 125.4, 126.6, 128.1, 136.0, 143.2, 150.9, 176.5.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.81; H, 6.98; N, 10.69

N-[(R)-1-Phenylethyl]-(5S)-5-vinyl-2-pyrrolidinone-1-carboxamide (4).- Diastereomer **4** was isolated as a yellow oil; $[\alpha]_D$ = -16.3° (c 11.7, $CHCl_3$); IR (film): 3016 (s), 1715 (s), 1687 (s), 1532 (s), 1377 (s), 1216 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.52 (d, J = 7.0 Hz, 3H), 1.86 (m, 1H), 2.24 (m, 1H), 2.49 (ddd, J = 17.4, 9.0, 2.0 Hz, 1H), 2.68 (ddd, J = 17.4, 11.5, 8.7 Hz, 1H), 4.91 (m, 1H), 5.07 (m, 1H), 5.13 (m, 2H), 5.87 (m, 1H), 7.26 (m, 1H), 7.33 (m, 4H), 8.85 (d, J = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 22.4, 23.5, 31.2, 49.1, 58.0, 114.4, 125.5, 126.8, 128.2, 136.0, 143.1, 151.1, 176.7.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.49; H, 7.11; N, 10.60

(4S)-4-Amino-5-hexenoic Acid (6).- A mixture of **4** (0.78 g, 3.0 mmol), $Ba(OH)_2.H_2O$ (0.95 g, 5.0 mmol), water (2 mL) and isopropanol (8 mL) was heated at reflux temperature for 12 hrs. After cooling to 0°, water (10 mL) was added to the mixture, which was then washed with chloroform (3 x 10 mL). The aqueous solution was acidified using hydrochloric acid (6 mL of 2N), the solution was concentrated *in vacuo* to a volume of 5 mL, and this solution was applied to the top of a Dowex 50X2-200 column (H^+ form, 100-200 mesh). The column was eluted with water until the eluant was neutral. Further elution with 2N aqueous ammonium hydroxide, and removal of the solvent from the eluant *in vauco*, afforded (4S)-4-amino-5-hexenoic acid (**6**, 0.32 g, 83%); mp 163-165°, $[\alpha]_D$ = +12.5°

(c 3.0, H_2O), {lit.[5] $[\alpha]_D$ = +12.2 (c 9.5, H_2O at pH 6.6}; IR (KBr): 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.

(4R)-4-Amino-5-hexenoic Acid (5).- Compound **5** was prepared from the ureide diastereomer **3** in 80% yield using the same procedure described for the preparation of compound **6**. Compound **5** was identical to the (4S)-enantiomer **6** in all respects (^1H NMR, ^{13}C NMR), except for its optical rotation and melting point: mp 164-165°; $[\alpha]_D$ = -12.2° (c 4.5, H_2O).

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