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Enantioselective Synthesis of (+) and (-)-cis-3-Aminocyclopentanecarboxylic acids by Enzymatic Asymmetrization

Robert Chênevert* and Richard Martin

Département de Chimie, Faculté des Sciences et de Génie
Université Laval, Québec , Canada, G1K 7P4

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Abstract: *Both enantiomers of cis-3-aminocyclopentanecarboxylic acid (GABA analogs, inhibitory neurotransmitter) have been prepared via enzymatic asymmetrization of cis -1,3-cyclopentanedicarboxylic acid.*

All four stereoisomers of 3-aminocyclopentanecarboxylic acid have a potent action on mammalian central nervous system. These compounds are conformationally restricted analogues of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and they are useful stereomeric probes of the GABA binding sites topography[1]. This potent activity of 3-aminocyclopentanecarboxylic acids contrasts with the much weaker effects of the corresponding 3-aminocyclohexanecarboxylic acids. We report here a chemoenzymatic synthesis of both enantiomers of cis-3-aminocyclopentanecarboxylic acid.

The previously reported routes to the 3-aminocyclopentanecarboxylic acids involved separation of cis/trans mixtures and resolution of enantiomers[2]. The key feature of the present approach is an enzymic discrimination of enantiotopic ester groups of the meso cis-1,3-cyclopentanedicarboxylic acid **2**. Ozonolysis of norbornylene **1**, followed by treatment with hydrogen peroxide gave diacid **2** (scheme 1). Esterification of diacid **2** with methanol in the presence of an acidic resin as a catalyst gave diester **3**. Pig liver esterase (PLE) catalyzed hydrolysis of diester **3** has been reported[3] but the enantiomeric purity of the product (mono-ester **4**) was low (ee = 34%). We did some preliminary screening to find suitable enzymes for the enantiotopic hydrolysis of meso-**3**. Among various proteases, lipases and esterases tested, it was found that both cholesterol esterase (CE) and subtilisin Carlsberg (SC) give the (1S, 3R) mono-ester **4** in high chemical and optical yield (SC : 85% yield, ee = 88%; CE : 95% yield, 90% ee). Racemic **4** obtained by dehydration of **2** with acetic anhydride followed by reaction of anhydride **5** with methanol was employed as a reference compound in NMR experiments.

The absolute configuration of **4** was determined by comparison of the specific rotation with reported values[3]. The enantiomeric purity of **4** was measured by reaction with (S)-(+)-1-(1-napthyl) ethyl amine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) followed by ^{1}H-NMR (200 MHz) analysis of the resulting diastereoisomeric amides. The carboxyl group of (1S, 3R)-**4** was converted to an amino group with retention of configuration through a Curtius rearrangement; thus, the mono-ester was first treated with ethyl chloroformate at 0°C in acetone and with sodium azide. Acetone was replaced by toluene and the solution was heated to 100°C and the resulting isocyanate **6** was hydrolysed with aqueous HCl to give (1R,3S)-**7**: $[\alpha]_D^{20}$ -6.4 (C 1, H_2O); lit.[2b] $[\alpha]_D^{20}$ -7 (C 1, H_2O). On the other hand, ammonolysis of **4** in a pressure tube produced the corresponding amide **8** which was submitted to an Hofmann rearrangement with bis(trifluoroacetoxy)iodobenzene to give (1S, 3R)-**7**: $[\alpha]_D^{20}$ +6.4 (C 1, H_2O); lit.[2b] $[\alpha]_D^{20}$ +6 (C 1, H_2O).

The enantiomeric purity of (-)-**7** and (+)-**7** was checked by NMR analysis of diastereoisomeric N-trifluoroacetyl amides obtained by reaction with (R)-1-(1-napthyl) ethyl amine.

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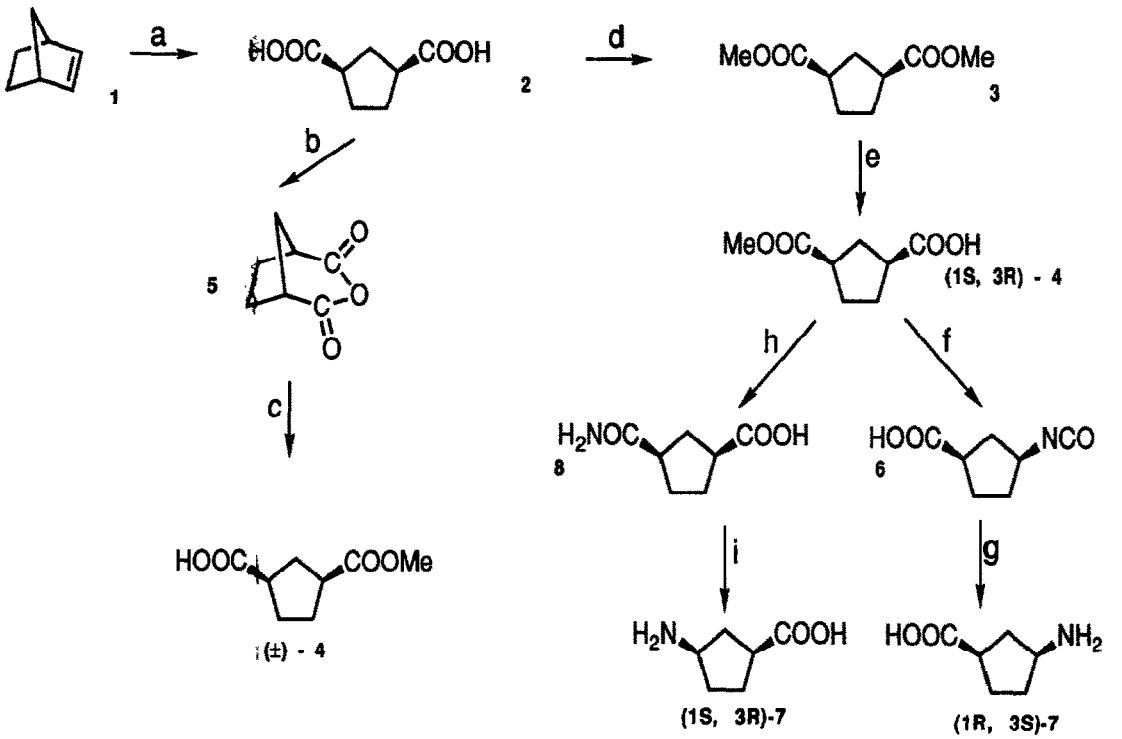
Scheme1



Reagents and Conditions: (a) *i*) O_3, MeOH, -78°C, *ii*) H_2O_2 30%, HCOOH, 50°C, (93%); (b) Acetic anhydride, 120°C, (83%); (c) MeOH, reflux, (94%); (d) MeOH, Dowex® H^+ resin, reflux (91%); (e) cholesterol esterase, phosphate buffer pH 7.0, 37°C, MeCN 1%, (95%); (f) *i*) Ethyl chloroformate, Et_3N, acetone, -5°C, *ii*) NaN_3, H_2O, -5°C, *iii*) toluene, reflux, (74%) (g) HCl 8N, MeOH 10%, (80%); (h) NH_3, MeOH, pressure, (82%) (i) Bis(trifluoroacetoxy)iodobenzene, MeCN, H_2O, (92%)

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