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The synthesis of potential Neramexane metabolites: *cis*- and *trans*-3-amino-1,3,5,5-tetramethylcyclohexanecarboxylic acids

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Abstract—A seven step synthetic route toward potential Neramexane metabolites *cis*- and *trans*-3-amino-1,3,5,5-tetramethylcyclohexanecarboxylic acids, *cis*-**1** and *trans*-**1**, has been developed from isophorone. The synthetic procedure represents a useful method for the preparation of γ-amino acids with both amino and carboxyl groups situated at tertiary carbon atoms.

Neramexane is among NMDA receptor antagonists undergoing phase II clinical trials for the treatment of alcohol abuse.[1] As part of a clinical investigation, we have undertaken studies of Neramexane metabolism in living organisms. Among other metabolic pathways, the complete oxidation of the C3-methyl group of Neramexane by enzymes involved in drug metabolism can be expected, leading to the formation of *cis*- and/or *trans*-3-amino-1,3,5,5-tetramethylcyclohexanecarboxylic acids *cis*-**1** and *trans*-**1** (Fig. 1).[2] To prove the proposed metabolic pathway using analytical methods like GC/MS or HPLC/MS, it was necessary to prepare potential metabolites *cis*-**1** and *trans*-**1** as reference standards.

γ-Amino acids *cis*-**1** and *trans*-**1** are intriguing synthetic targets since both amino and carboxyl groups are situated at a tertiary carbon atom. Commonly used methods for the synthesis of γ-amino acids with the amino group at a tertiary carbon atom involve conjugate addition of α,α-disubstituted nitro compounds to acrylates and subsequent reduction of the nitro group in the addition product,[3] or selective degradation of one carboxyl to an amino group in pentanedicarboxylic acids and masked dicarboxylic acids.[4] These approaches, however,

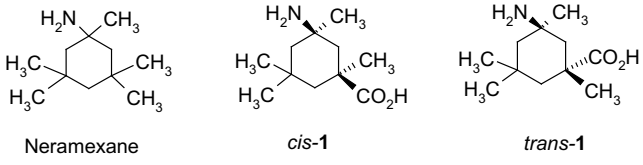

Figure 1.

could not be applied to prepare amino acids *cis*-**1** and *trans*-**1** due to difficulties in accessing starting materials.

The Ritter reaction[5] (reaction of an in situ generated carbenium ion with nitriles) has been used to prepare 3-aminoadamantane-1-carboxylic acid derivatives from 3-hydroxyadamantane-1-carboxylic acid.[6] Since 3-substituted-1-alkylcyclohexanols are readily available,[7] this seemed to be an attractive synthetic strategy for the synthesis of aminocyclohexanecarboxylic acids *cis*-**1** and *trans*-**1**. We preferred to use a latent carboxyl group at the desired position in cyclohexane because a carboxyl group is known to retard the Ritter reaction considerably.[6] Moreover, 1-alkylcyclohexanecarboxylic acids can eliminate CO_2 in strong acidic media.[5b] A phenyl group[8] was chosen as an appropriate latent carboxyl group primarily due to its high chemical resistance, and secondly, that it could facilitate the separation of diastereomers at a later stage.

A diastereomeric mixture of 3-phenylcyclohexanols **3** was prepared from isophorone **1** according to the

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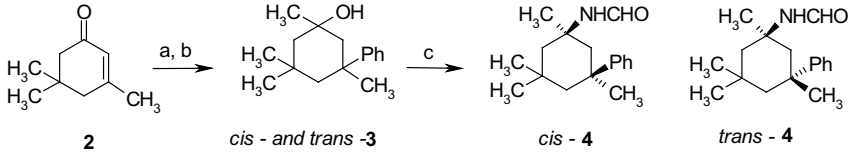
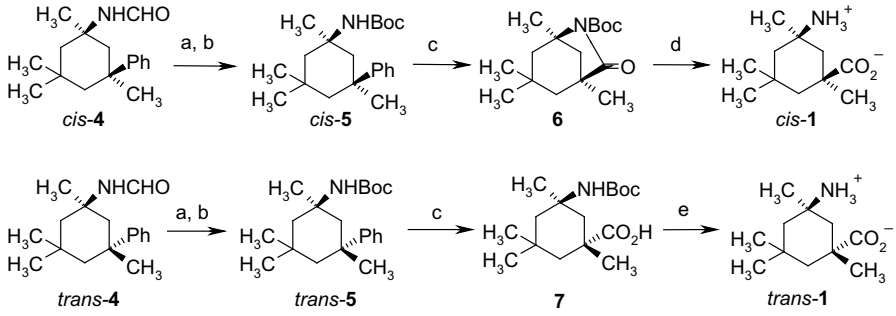


Scheme 1. Reagents and conditions: (a) PhMgBr, CuCl, Et_2O, −20 °C, 2 h, 76%; (b) MeLi, Et_2O, 0 °C to rt, 1 h, 82%; (c) TMSCN, H_2SO_4, AcOH, 0 °C to rt, 20 h, separation of isomers (light petroleum ether–ethyl acetate, 10:1, *cis*-**4** eluted first followed by *trans*-**4**), *cis*-**4** 47%, *trans*-**4** 29%.



Scheme 2. Reagents and conditions: (a) 20% aq H_2SO_4 reflux 10 h then NaOH until pH ~ 10; (b) Boc_2O, Et_2O, rt, 19 h, *cis*-**5** 77%, *trans*-**5** 70% over two steps; (c) RuO_2, $NaIO_4$, H_2O, CCl_4, CH_3CN, rt, 3 d, **6** 40%, **7** 68%; (d) 20% aq HCl, reflux, 31 h, then aq NH_4OH, 68%; (e) CF_3CO_2H, CH_2Cl_2, rt, 15 min then aq NH_4OH, 78%.

literature procedure (Scheme 1).[9] The Ritter reaction of cyclohexanol **3** with hydrogen cyanide[10] (generated in situ from TMSCN) gave a mixture of diastereomeric formamides *cis*-**4** and *trans*-**4**. Gratifyingly, at this point diastereomers *cis*-**4** and *trans*-**4** were readily separable by flash chromatography on silica gel. An initial attempt to convert the phenyl to a carboxyl group in *N*-formyl aminocyclohexanes **4** using the RuO_2–$NaIO_4$ oxidizing system[8a] failed probably due to concomitant oxidation of the formyl group. The formyl group was changed to a *tert*-butoxycarbonyl (Boc) group that was expected to be resistant to the oxidation conditions (Scheme 2). Treatment of *N*-Boc protected 3-phenylcyclohexylamine isomer *cis*-**5** with RuO_2–$NaIO_4$ gave *N*-Boc protected bicyclic lactam **6**[11] as the major product obviously formed via cyclization of an intermediate *N*-Boc protected aminocyclohexanecarboxaldehyde. Acidic hydrolysis of lactam **6** gave amino acid *cis*-**1**.[11] The *cis*-configuration of amino and carboxyl groups in amino acid *cis*-**1** was defined by lactam **6** since no change of configuration at C-1 and C-3 was possible during hydrolysis. The oxidative degradation of the phenyl group in *N*-Boc protected 3-phenylcyclohexylamine isomer *trans*-**5** gave, as expected, *N*-Boc protected amino acid **7**. The Boc group in compound **7** was removed using standard conditions to yield amino acid isomer *trans*-**1**.[11]

In summary, we have developed a seven step synthetic route toward potential Neramexane metabolites *cis*-**1** and *trans*-**1** from isophorone in 6% and 7% overall yields, respectively. The synthetic procedure represents a useful method for the preparation of γ-amino acids with amino and carboxyl groups situated at tertiary carbon atoms.

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11. *N-tert*-Butoxycarbonyl-1,3,3,5-tetramethyl-6-azabicyclo [3.2.1] octan-7-one **6**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (3H, s, 3-CH_3); 0.97 (3H, s, 3-CH_3); 1.10 (3H, s, 1-CH_3); 1.24 and 1.26 (total 2H, both d, J = 14 Hz, ring protons); 1.40–1.60 (2H, m, ring protons); 1.45 (3H, s, 5-CH_3); 1.52 (9H, s, *t*-Bu); 1.69 (1H, dt, J = 12 Hz and 2 Hz, ring proton), and 2.10 ppm (1H, d, J = 14 Hz, ring proton); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.28, 25.69, 28.05, 30.36. 30.48, 35.87, 43.07, 44.37, 47.37, 49.04, 60.66, 82.38, 150.35, 178.41. *c*-3-Amino-1,3,5,5-tetramethylcyclohexane-*r*-1-carboxylic acid (*cis*-**1**): ^{1}H NMR (200 MHz, D_2O): δ 0.76 and 0.78 (total 6H, both s, 5,5-CH_3); 0.98 (3H, s, 1-CH_3); 1.21 (3H, s, 3-CH_3); 0.99 (1H, d, J = 14 Hz, ring proton); 1.12 (1H, d, J = 15 Hz, ring proton); 1.26 (1H, d, J = 15 Hz, ring proton); 1.60 (1H, d, J = 15 Hz, ring proton); 1.84 (1H, d, J = 14 Hz, ring proton), and 2.18 ppm (1H, d, J = 15 Hz, ring proton); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.15, 32.74, 32.98, 36.44, 45.29, 45.71, 49.90, 50.21, 55.76, 190.16. *t*-3-Amino-1,3,5,5-tetramethylcyclohexane-*r*-1-carboxylic acid (*trans*-**1**): ^{1}H NMR (200 MHz, D_2O): δ 0.80 (6H, s, 5,5-CH_3); 0.85 (1H, d, J = 14 Hz, ring proton); 0.97 (3H, s, 1-CH_3); 1.06 (1H, d, J = 13 Hz, ring proton); 1.28 (3H, s, 3-CH_3); 1.13 (1H, d, J = 13 Hz, ring proton); 1.51 (1H, d, J = 13 Hz, ring proton); 2.00 (1H, d, J = 14 Hz, ring proton), and 2.37 ppm (1H, d, J = 13 Hz, ring proton);^{13}CNMR (50 MHz, $CDCl_3$): δ 27.70, 29.13, 33.34, 34.32, 37.05, 45.72, 48.75, 50.24, 58.18, 187.34.