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Asymmetric Synthesis of *cis*-(-)-(2*R*4*S*)-4-(Phosphonomethyl)-2-Piperidinecarboxylic Acid, A Potent NMDA Receptor Antagonist

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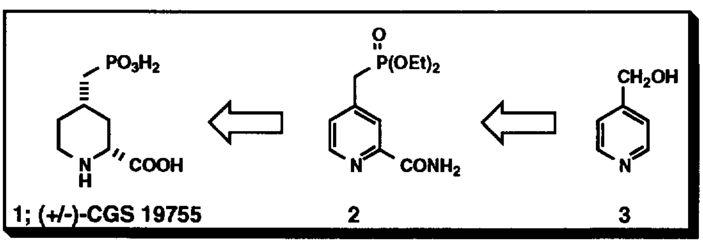
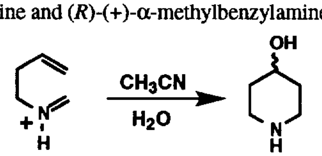
Abstract: The asymmetric synthesis of *cis*-(-)-(2*R*4*S*)-4-(phosphononomethyl)-2-piperidinecarboxylic acid (1), a potent and specific NMDA receptor antagonist, *via* an olefin-iminium cyclization is described. Copyright © 1996 Elsevier Science Ltd

The excitatory amino acids,[1] aspartate and glutamate, mediate their actions *via* at least three classes of receptors which are generally represented by the prototypical antagonist *N*-methyl-D-aspartic acid (NMDA), quisqualic acid (QUIS), and kainic acid (KA). Of these the NMDA receptor has been the most studied.[2] Excess activity at this receptor has deleterious effects on CNS function. Antagonists of the NMDA receptor could thus have potential utility in a number of CNS disorders, most notably in the treatment of epilepsy and the neuronal damage resulting from cerebral ischemia.

One of the most potent selective competitive NMDA receptor antagonists[3,4] is **1**; *cis*-(±)-CGS 19755 (Selfotel) which is presently undergoing extensive clinical evaluation as an antiischemic agent in serious traumatic brain injury (TBI)[5] and stroke.The previously described synthesis[3] of **1** initiates with 4-pyridinecarbinol (**3**) to afford ultimately racemic CGS 19755 *via* a catalytic ring reduction of the 2-pyridine carboxamide **2** as is shown in the schematic below. In this manner *cis*-(±)-CGS 19755 is obtained as a mixture of enantiomers. The preparation and biological activities of the individual enantiomers of *cis*-(±)-CGS 19755 has not been previously described. Herein we describe for the first time the preparation of both stereoisomers of *cis*-(±)-CGS 19755 and report their biological activities in the NMDA receptor binding assay.



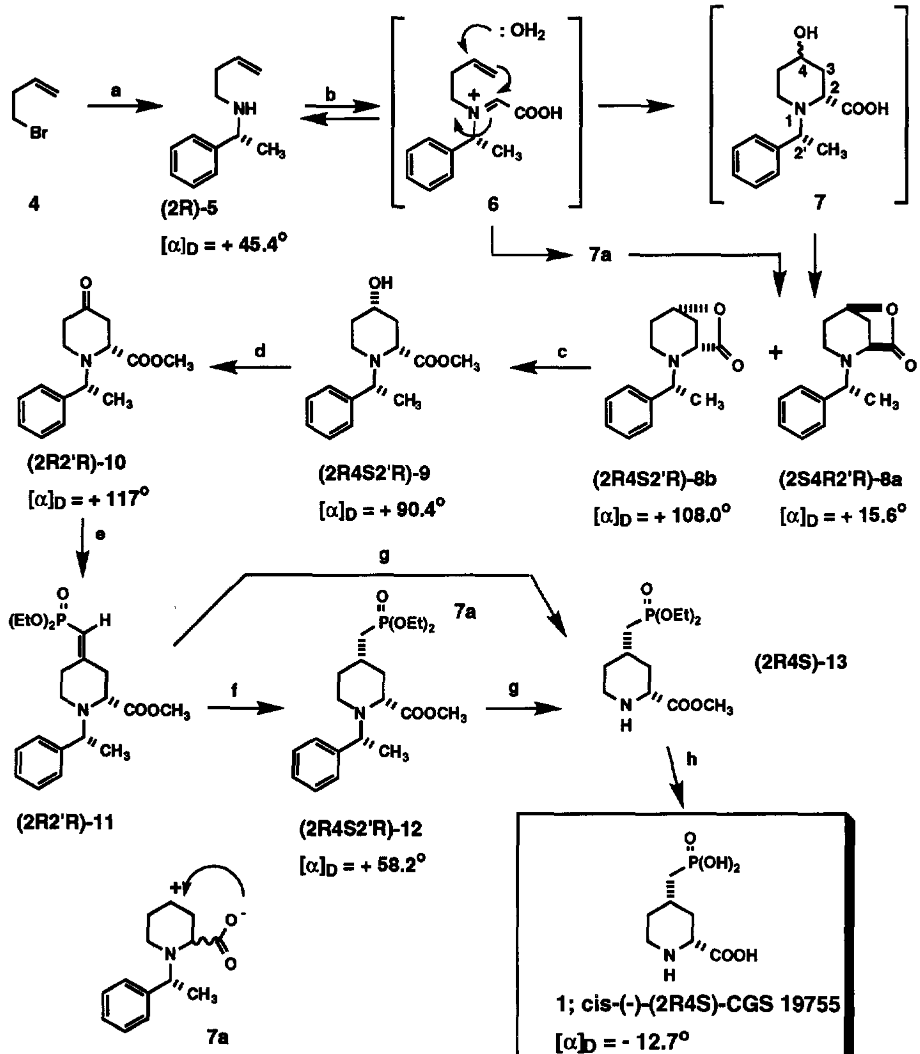
In 1986, Grieco and co-workers demonstrated that a variety of 4-hydroxypiperidines may be formed under aqueous conditions by an iminium ion cyclization of a homoallylic amine intermediate.[6,7] We envisioned that 4-substituted pipecolinic acids could be formed under aqueous conditions described by Grieco using an appropriately substituted homoallylic amine and gloxylic acid as precursors.[8,9] In order to induce the formation of diastereomers, the homoallylic amines used for the cyclization were prepared from (*S*)-(-)-α–methylbenzylamine and (*R*)-(+)-α-methylbenzylamine.



According to the scheme given below the homoallylic amine **5** was prepared by refluxing a mixture of (*R*)-(+)-α–methylbenzylamine, 4-bromo-1-butene (**4**), and Et_3N in CH_3CN. The chiral homoallyl amine **5**, $[a]_D = +45.4°$ (c = 1 $CHCl_3$), was dissolved in a mixture of CH_3CN and H_2O (1:1) and treated with glyoxylic acid at room temperature for several days to provide the diasteromeric lactams *cis*-(2*S*4*R*2'*R*)-**8a** and *cis*-(2*R*4*S*2'*R*)-**8b** in a diastereomeric ratio of 1:2 respectively. It was later found the reaction could be pushed to completion within 4 hours at room temperature if the reaction was conducted in CH_3CN in the absence of H_2O and in the presence of 4 Å molecular sieves. Of the several potential mechanisms for this conversion it is most likely that the incipient carbocation **7a** is trapped internally by the carboxylate and rarely, if ever, by H_2O solvent to afford the lactones **8a** and **8b** directly. Supporting evidence for this mechanism, although not proven, is the fact that we obseved no *trans*-

hydroxy acid in the NMR of the crude reaction mixture when run in the mixture of CH_3CN and H_2O (1:1). The diastereomeric lactones **8** were easily separated by a simple recrystallization from *n*-hexane. The lactone *cis*-(2*R*4*S*2'*R*)-**8b**, *vide infra,* was subjected to CH_3OH and anhydrous NH_3 to afford the alcoholic methyl ester (2*R*4*S*2'*R*)-**9** which *via* a Swern oxidation provided the ketone (2*R*2'*R*)-**10**. The ketone (2*R*2'*R*)-**10** was easily transformed into a 2:1 mixture of *E* and *Z*- phosphonates (2*R*2'*R*)-**11** by treatment with $[(EtO)_2P(O)]_2CH_2$, DBU, and LiCl in CH_3CN or THF.[10] Catalytic reduction and hydrogenolysis (10 % Pd/C, H_2) of *cis*-(2*R*2'*R*)-**11** gave cleanly the triester *cis*-(2*R*4*S*)-**13** which was hydrolyzed with aqueous 6 N HCL to afford *cis*-(-)-(2*R*4*S*)-**1**, the minus isomer of (±)-CGS 19755. Alternatively, according to the scheme below, **11** could be converted in a stepwise manner to **13** by a reduction - hydrogenolysis procedure (10 % Pt/C followed by 10 % Pd/C). In a manner similar to that described above but using the lactone *cis*-(2*S*4*R*2'*R*)-**8a** the *cis*-(+)-(2*S*4*R*)-**1** triacid was obtained which corresponds to the (+)-isomer of (±)-CGS 19755.[11]

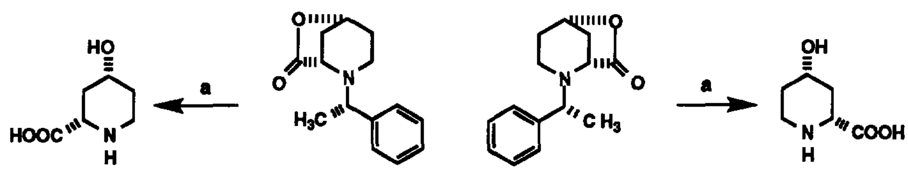
Scheme I: Synthesis of *cis*-(-)-(2*R*4*S*)-CGS 19755



Reagents: All rotations taken in $CHCl_3$ (c = 1) with the exception of **1** (1 N NaOH); a) (*R*)-(+)-α-methylbenzylamine, Et_3N, CH_3CN; b) OHCCOOH, 4 Å molecular sieves, CH_3CN; c) NH_3, CH_3OH; d) $(ClCO)_2$, Et_3N, DMSO, CH_2Cl_2; e) $(EtO)_2P(O)]_2CH_2$, DBU, LiCl, THF; f) 5 % Pt/C, H_2 (45 psi), EtOH; g) 10 % Pd/C, H_2 (45 psi), EtOH; h) 6 N HClΔ; i) $KHCO_3$, H_2O, EtOH.

Assignment of the absolute stereochemistry of the diastereomeric lactones **8** was done by correlation to the known natural product *cis*-(-)-(2*S*4*R*)-4-hydroxypipecolinic acid (**14b**) which was isolated from *Acacia oswaldii* leaves.[12] Using (*S*)-(-)-(α)-methylbenzylamine and (*R*)-(+)-(α)-methylbenzylamine all four possible isomers of **8** were prepared in an analogous manner to that described above and isolated *via* crystallization (*n*-hexane) and/or chromatography (silica gel; EtOAc/*n*-hexane, 1:3). Thus (2*R*4*S*2'*S*)-**8a**, *vide infra*, was subjected to hydrogenolysis conditions to afford *cis*-(+)-(2*R*4*S*)-4-hydroxypipecolinc acid (**14a**), $[a]_D$ = + 20.4° (c = 1.0 CH_3OH). In a likewise manner (2*S*4*R*2'*R*)-**8b** was subjected to hydrogenolysis conditions to give *cis*-(-)-(2*S*4*R*)-4-hydroxypipecolinic acid (**14b**). The reported optical rotation for the (2*S*4*R*)-**14b** natural product is $[a]_D$ = - 17° (c = 1.0 CH_3OH).[12] Thus in effect the conversion of the enantiomeric (2*R*4*S*2'*S*) and (2*S*4*R*2'*R*) lactones **8a** and **8b** to the known *cis*-4-hydoxypipecolinic acids **14a** and **14b** and comparison of optical rotations with those given in the literature has allowed assignment of the absolute configurations of all four lactones **8** and as well as the *cis*-acids **1**.[13]

Scheme 2. Cofimation of absolute steeochemistry of **8a** and **8b** lactones.



(2*S*4*R*)-**14b** $[\alpha]_D$ = - 20.3° $[\alpha]_D$ = -17° (lit.)[11]

(2*S*4*R*2'*R*)-**8b** $[\alpha]_D$ = - 102.4°

(2*R*4*S*2'*S*)-**8a** $[\alpha]_D$ = + 99.4°

(2*R*4*S*)-**14a** $[\alpha]_D$ = + 20.4° $[\alpha]_D$ = +17° (lit.)[11]

Reagents and conditions: Optical rotations of **8** taken in CH_2Cl_2; **14** taken in CH_3OH; a) 10 % Pd/C (45 psi), EtOAc, H_2O.

The *cis*-(-)-(2*R*4*S*)-4-(phosphonomethyl)piperidine-2-carboxylic acid (**1**) has an IC_{50} of 29 ηM in a tritiated CPP receptor binding assay compared to 10,000 ηM for *cis*-(+)-(2*S*4*R*)-**1**.[14] This activity is in agreement with *N*-methyl-D-aspartate having an (*R*)-configuration at what corresponds to the 2-position of *cis*-(-)-(2*R*4*S*)-**1**.

Table 1. NMDA receptor binding results for enantiomers of *cis*-(±)-CGS 19755.

Compound	CGS Number	IC_{50} (ηM)
cis - (±) - 1	CGS 19755	69
cis - (-) - (2*R*4*S*) - 1	CGS 20281	29
cis - (+) - (2*S*4*R*) - 1	CGS 20282	10,000

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10. Conditions other than these (e.g., NaH, *n*-BuLi, LDA, etc.) failed or gave low yields of inferior quality product. The conditions described by Masamune and Roush (DBU and LiCl in THF or CH_3CN) consistently afforded **11** in good yield (82 - 90 %) as a mixture of *E* and *Z*-isomers: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

11. All compounds exhibited satisfactory C, H, and N microanalysis and were within 0.4 % of theoretical values. All new compounds exhibited ^1H and ^{13}C NMR which are consistent with the assigned structures.

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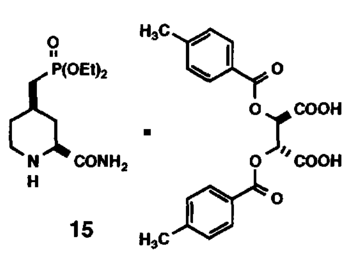
13. As an additional proof of the absolute stereochemical assignments, the carboxamide diethyl ester of *cis*-(±)-**1** could also be resolved into the respective enantiomers *via* its di-*p*-toluoyl-L-tartarate salts (see **15** below). Hydrolysis of each enantiomer with 6 N HCl afforded both *cis*-(+)-**1** and *cis*-(-)-**1**. Optical rotaions as well as NMR, MS, and IR of these resolved materials were identical to those prepared by synthetic means. In addition to correlation with the known natural product (2*S*4*R*)-**14b** the single crystal X-ray structure of the *cis*-(+)-carboxamide diethyl ester di-*p*-toluoyl-L-tartaric acid salt of **1**, i.e. **15** below, confirmed our absolute stereochemical assignments. Complete listings of atomic coordinates, bond lengths, bond angles, thermal parameters and structure factors for compound **15** have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW England.



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14. For details of the NMDA receptor binding assay see references 3 and 4.

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