3-methoxypropane was synthesized from 1-bromo-3-chloropropane by modifying the method of Henne and Haeckl.[23] Methyl 3-chloropropionate was prepared from 3-chloropropionic acid.[24] All other reagents were purchased from Tokyo Kasei Kogyo Co. and were used without further purification.

Solubility of AcOK. Solvent containing excess AcOK was placed in a 200-mL round-bottomed flask immersed in a thermostat. The mixture was stirred for 2 h at 70 °C and allowed to stand for 1 h. The supernatant liquid was pipetted off through a wool filter, and the AcOK content was determined by titration with 1 N ethylene glycol/isopropyl alcohol/HCl with thymol blue as an indicator.[25]

Analyses. GC analyses were performed on a Shimadzu GC-8A instrument using 10% PEG 6000 on Celite (60–80 mesh) packed in a stainless steel column (6 m × 4 mm diameter). GC yields were determined with an internal standard and authentic mixtures. For analytical determinations, correction factors for weight ratio/area ratio data were determined with the same standards. ^{1}H NMR spectra were measured on a JEOL JNM-MH-100 spectrometer with tetramethylsilane as internal standard.

Reaction of DCP and AcOK in Various Solvents. A mixture of 50 mL of solvent, 0.14 mol of AcOK, and 0.04 mol of DCP was placed in a 200-mL separable flask fitted with a mechanical stirrer, reflux condenser, and sampling nozzle. The flask was immersed in a thermostat at 80 °C. At regular intervals, 5 mL of samples were taken and poured into water. The aqueous layer was extracted with 5 mL of carbon tetrachloride, and the product was analyzed by GC.

Reaction of RCH_2CH_2Cl and AcOK in DMF. A mixture of 0.1 mol of RCH_2CH_2Cl, 0.3 mol of AcOK, 0.01 mol of toluene (GC standard), and 100 mL of DMF was placed in 500-mL three-necked flask. Unless otherwise stated, the reaction temperature was maintained at 60 °C. Sampling and analyses were carried out as described above.

Reaction of RCH_2CH_2Cl and AcOK in the Presence of TEAC in CH_3CN. The esterification of 0.1 mol of RCH_2CH_2Cl with 0.1 mol of AcOK in the presence of 0.03 mol of TEAC in 100 mL of CH_3CN was performed at 60 °C.

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Synthesis of *cis*-4-(Phosphonooxy)-2-piperidinecarboxylic Acid, an *N*-Methyl-D-aspartate Antagonist

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Excitatory amino acids, aspartate and glutamate, are major neurotransmitters within the mammalian central nervous system.[1-3] One subtype of the glutamate receptor selective for the agonist *N*-methyl-D-aspartate (NMDA) has received a great deal of attention due to its possible involvement in a variety of neuropathologies.[4-6] Therefore, the search for competitive NMDA antagonists has been the focus of considerable investigation and has led to the discovery of *cis*-4-(phosphonomethyl)-2-piperidinecarboxylic acid (CGS 19755) as a potent and selective antagonist at the NMDA site.[7,8] With the exception of *O*-phosphoserine, a phosphate derivative of serine that interacts at the AP4 preferring glutamate site,[9,10] phosphates have not been explored as excitatory amino acid receptor ligands. In order to further investigate the pharmacology of this receptor, we sought to prepare the phosphate analogue *cis*-4-(phosphonooxy)-2-piperidinecarboxylic acid (1). To achieve this allosteric replacement of the methylene group of CGS 19755 for an oxygen atom, we required *cis*-4-hydroxy-2-piperidinecarboxylic acid (2) as our primary synthetic intermediate (Figure 1).

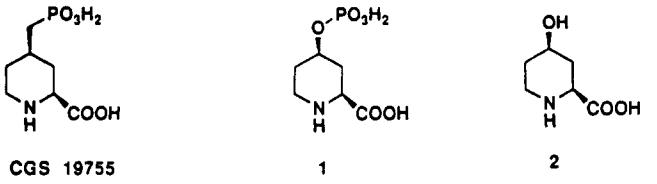
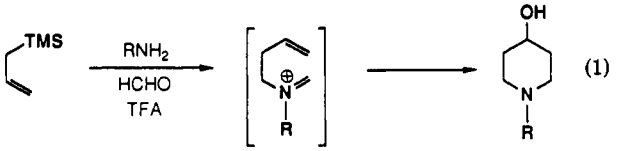


Figure 1.

Amino acid 2 or its derivatives have been synthesized previously by catalytic reduction of 2-carboxy-4-benzoxy- or 4-hydroxypyridines.[11,12] This route suffers from the drawback of erratic yields for the starting pyridine and from the high pressures (70 atm with Rh/Al_2O_3) required for final ring reduction. The preparation of 4-hydroxypipecolic acid has also been studied by Speckamp.[13] In this case, utilization of a Lewis acid catalyzed cyclization of a glycine cation equivalent at low temperature resulted in a moderate (45%) yield of protected 4-hydroxypipecolic acid and recovered starting material.

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 as shown in eq 1.[14] We



(1)

envisioned that 4-substituted pipecolic acids could be coveniently prepared under the aqueous conditions described by Grieco using an appropriately substituted homoallylamine and glyoxylic acid as precursors. We report here the facile synthesis of methyl *cis*-4-hydroxy-2-piperidinecarboxylate as an intermediate in route to the NMDA antagonist *cis*-4-(phosphonooxy)-2-piperidinecarboxylic acid (1).

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Scheme I

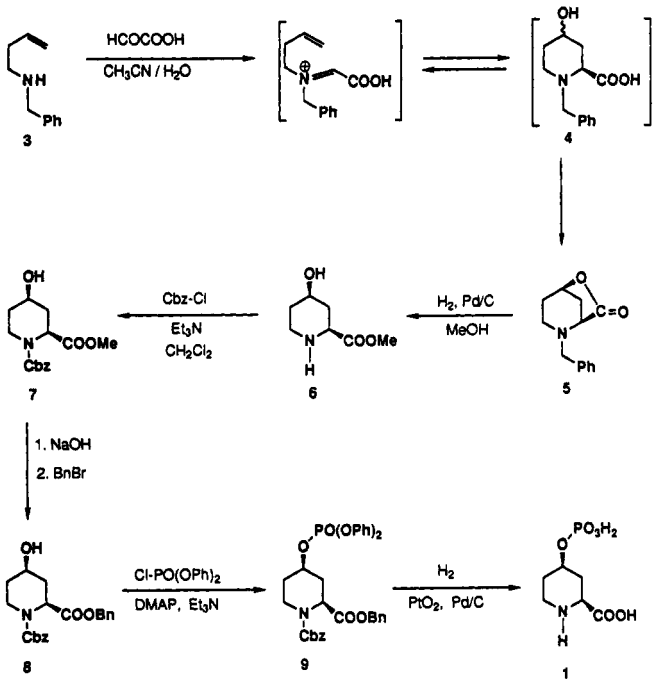

Table I. Selected Vicinal ^1H–^1H Coupling Constants and Chemical Shifts for 1[a]

proton	chemical shift	coupling constant (Hz)
2	3.75	
3 (eq)	2.62	$^3J_{2,3eq}$ 3.2
3 (ax)	1.80	$^3J_{2,3ax}$ 12.5
4	4.38	$^3J_{4,3eq} < 3$[b]
5 (eq)	2.29	$^3J_{4,5eq} < 3$[b]
5 (ax)	1.80	
6 (eq)	3.55	
6 (ax)	3.10	

[a] 250- or 300-MHz NMR data recorded on 25 mg dissolved in 0.6 mL of D_2O at 25 °C. [b] Estimated on the basis of a small decrease in the 3 and 5 proton line width when H-4 was irradiated.

Our improved methodology utilized *N*-3-butenylbenzenemethanamine (**3**) as the homoallylamine starting material[15] as shown in Scheme I. When **3** was treated with glyoxylic acid in aqueous acetonitrile, lactone **5** was isolated as the sole reaction product in 69% yield. We believe the reaction mechanism is consistent with the concerted olefin–iminium ion cyclization described by Grieco[14] followed by lactonization of the intermediate hydroxy acid **4**. Subsequent debenzylation and lactone cleavage occurs in one step when **5** is hydrogenated in methanol to produce the methyl ester **6**. The amino ester **6** was subsequently protected as the carbobenzoxy carbamate **7**. Transesterification of the methyl to the benzyl ester **8** occurs in high yield under phase-transfer conditions. Compound **8** is treated with diphenyl chlorophosphate to afford the protected phosphate **9**, which is conveniently deprotected in one step to produce the desired *cis*-4-(phosphonooxy)-2-piperidinecarboxylic acid (**1**). This stereoselective synthesis of phosphate **1** proceeded in an overall yield of 48% from the starting olefin **3**.

The stereochemical assignment for compound **1** was made by examination of the ^1H NMR data (Table I). The proton assignments were made via a COSY spectrum. The coupling constants relative to the stereochemistry were determined by direct measurement from the ^1H NMR spectrum or by observation of line width changes upon decoupling of specific protons. The C-2 proton showed a large coupling of 12.5 Hz and a small coupling of 3.2 Hz to the protons on the C-3 methylene. Assuming that the C-4 phosphate group occupies an equatorial position and that the piperidine assumes a chairlike conformation, the cis (equatorial–equatorial) conformation for **1** is the only geometry consistent with the observed coupling patterns.

The phosphate **1** had an IC_{50} of 14.9 μM in a tritiated CPP binding assay[16] compared to 0.065 μM for CSG 19755. Clearly, the replacement of an oxygen atom for the methylene carbon of CGS 19755 has a detrimental effect on NMDA antagonist activity.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. IR spectra were obtained on a Nicolet MX-1 FT spectrometer. ^1H NMR spectra were recorded on a Bruker AM250 NMR spectrometer, a Varian XL200 NMR spectrometer, a Varian XL300 spectrometer, or an IBM WP-SC 100 MHz NMR spectrometer. ^1H NMR chemical shifts are reported as δ values in parts per million relative to internal tetramethylsilane. ^1H NMR coupling constants (J) are reported in hertz; abbreviations used are s, singlet, d, doublet, t, triplet, and m, complex multiplet. Mass spectra were obtained on a Finnigan 4500 mass spectrometer or a VG Analytical 7070E/HF mass spectrometer. Microanalyses were performed by the Parke-Davis Analytical Department. TLC and column chromatography utilized E. Merck silica gel.

(1α,5α)-2-(Phenylmethyl)-6-oxa-2-azabicyclo[3.2.1]octan-7-one (5). A solution of amine **3** (10.9 g, 67 mmol) in 500 mL of 1:1 CH_3CN/H_2O (v/v) was treated with glyoxylic acid monohydrate (5.5 g, 60 mmol). The resulting solution was allowed to stir at room temperature for 24 h. Additional glyoxylic acid monohydrate (5.5 g) was added, and the reaction mixture was stirred for an additional 6 h. The reaction mixture was concentrated to remove the acetonitrile. The aqueous residue was made basic using 1 N NaOH, and the product was extracted into CH_2Cl_2, dried (Na_2SO_4), and concentrated. The residue was filtered through a plug of silica gel, eluting with ethyl acetate to remove the product. A colorless oil was obtained (13.9 g, 69%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.25 (m, 5 H, Ar*H*), 4.83 (t, 1 H, J = 5.1 Hz, OC*H*), 3.67 (ABq, 2 H, J_{AB} = 13.1 Hz, $\Delta\nu_{AB}$ = 18.1 Hz), 3.30 (d, 1 H, J = 5.1 Hz), 3.02 (dd, 1 H, J = 11.9, 6.4 Hz), 2.46 (dt, 1 H, J = 11.9, 5.4 Hz), 2.28–2.22 (m, 1 H), 2.20–1.84 (m, 3 H); IR (neat) 1774 (C=O) cm^{-1}; MS (EI) 217 (M^+, 6) 173 (100). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.92; H, 7.03; N, 6.27.

Methyl *cis*-4-Hydroxy-2-piperidinecarboxylate (6). A solution of the lactone **5** (4.03 g, 18.5 mmol) and 20% palladium on carbon (0.4 g) in 100 mL of methanol was hydrogenated at 50.4 psi for 2.2 h. The reaction mixture was filtered through Celite and the filtrate concentrated. The title compound was isolated as a colorless oil (3.0 g, quantitative): ^1H NMR (250 MHz, $CDCl_3$) δ 5.31 (m, 4 H, C*H*OC*H*$_3$), 3.39 (dd, 1 H, J = 10.8, 3.1 Hz, NC*H*CO$_2$Me), 3.22 (dt, 1 H, J = 12.8, 3.9 Hz), 2.72–2.58 (m, 1 H), 2.30 (m, 1 H), 1.95–1.80 (m, 3 H), 1.52–1.35 (m, 2 H); IR (neat) 3400 (b s), 1741 (C=O) cm^{-1}; MS (CI) 160 (MH^+, 100), 142 (23).

2-Methyl 1-(Phenylmethyl) *cis*-4-Hydroxy-1,2-piperidinedicarboxylate (7). A solution of amino ester **6** (3.0 g, 18 mmol) and triethylamine (2.4 g, 24 mmol) in 75 mL of CH_2Cl_2 was cooled to 5 °C and treated dropwise with benzyl chloroformate (4.09 g, 24 mmol) over a 5-min period. The resulting solution was stirred at 5 °C for 1 h and warmed to room temperature. The reaction mixture was concentrated, and the crude product was partitioned between CH_2Cl_2 and water. The organic layer was collected, dried over Na_2SO_4, and concentrated. The residue (5.2 g) was purified by chromatography (silica gel, petroleum ether/ethyl acetate, gradient elution) to afford a white solid that was crystallized from 1:1 petroleum ether/ethyl acetate to give the product as a white solid (4.47 g, 84%), mp 99–100 °C: ^1H NMR

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(100 MHz, $CDCl_3$) δ 7.33 (s, 5 H, ArH), 5.17 (s, 2 H, $ArCH_2$), 5.00–4.67 (m, 1 H), 4.23–3.80 (m, 2 H), 3.73 (s, 3 H, OCH_3), 3.60–3.23 (m, 1 H), 2.46 (d, 1 H, J = 16.6 Hz), 2.02–1.60 (m, 4 H); IR (KBr) 1749, 1666 cm^{-1}; MS (CI) 294 (MH^+, 100). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.35, 6.53; N, 4.61.

Bis(phenylmethyl) *cis*-4-Hydroxy-1,2-piperidinedicarboxylate (8). A solution of the methyl ester 7 (2.6 g, 9.0 mmol) in 25 mL of dioxane and 2 mL of aqueous 1 N NaOH was stirred at room temperature for 18 h. The reaction mixture was treated with a saturated sodium bicarbonate solution until the pH = 8. The solvent was removed under reduced pressure, and the residue was dissolved in 2 mL of saturated aqueous sodium bicarbonate solution. The resulting solution was treated sequentially with Adogen-464 (3.64 g) in 20 mL of CH_2Cl_2 and benzyl bromide (1.85 g, 10.8 mmol). The resulting solution was stirred at room temperature for 4 days. The reaction mixture was partitioned between water and CH_2Cl_2, and the organic phase was collected. The aqueous phase was extracted with additional CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatograpphy (silica gel, 9:1 CH_2Cl_2/MeOH) to give the product as an oil that was crystallized from ethyl acetate (3.32 g, 86%), mp 123–125 °C: ^1H NMR (200 MHz, $CDCl_3$) δ 7.34 (s, 10 H, ArH), 5.16–5.10 (m, 4 H), 4.90 (dd, 1 H, J = 27.6, 6.6 Hz), 4.16 (s, 1 H), 4.07–3.86 (m, 1 H), 3.66–3.36 (m, 1 H), 2.61–2.40 (d, 1 H, J = 16.7 Hz), 2.00–1.85 (m, 1 H), 1.84–1.50 (m, 3 H); IR (neat) 1774, 1698 cm^{-1}; MS (CI) 370 (MH^+). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.31; H, 6.32; N, 3.63.

Bis(phenylmethyl) *cis*-4-(Diphenylphosphonooxy)-1,2-piperidinedicarboxylate (9). A solution of the alcohol 8 (0.92 g, 2.7 mmol), triethylamine (0.41 g, 4.1 mmol), and (dimethylamino)pyridine (0.49 g, 4.0 mmol) in 30 mL of CH_2Cl_2 was treated with diphenylphosphoryl chloride (1.07 g, 4.0 mmol) over a 1–2-min period. The resulting solution was allowed to stir at room temperature for 24 h. The reaction mixture was transferred to a separatory funnel and washed sequentially with water (20 mL), 0.5 N HCl (20 mL), and water (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue (2.08 g) was purified by chromatography (silica gel, 2% MeOH in CH_2Cl_2) to give the product as a colorless oil (1.62 g, 73%): ^1H NMR (200 MHz, $CDCl_3$) δ 7.53–7.00 (m, 20 H, Ar*H*), 5.32–4.77 (m, 6 H), 4.15–3.90 (m, 1 H), 3.61–3.27 (m, 1 H), 2.85–2.65 (m, 2 H), 2.12–1.55 (m, 3 H). Anal. Calcd for $C_{33}H_{32}NO_8P$: C, 65.88; H, 5.36; N, 2.33. Found: C, 66.12; H, 5.38; N, 2.38.

***cis*-4-(Phosphonooxy)-2-piperidinecarboxylic Acid (1).** A solution of ester 9 (1.10 g, 1.8 mmol) was dissolved in 35 mL of trifluoroacetic acid and 40 mL of acetic acid. The resulting solution was hydrogenated over PtO_2 for 2.5 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was partitioned between water and CH_2Cl_2. The aqueous layer was collected and concentrated to give a white solid. The solid material was treated with a 1:1 EtOH/H_2O solution and heated to 50 °C. The resulting suspension was cooled to room temperature and the solid collected by filtration. The collected material was dried under vacuum (100 °C) to give the product as a white solid (0.28 g, 69%), mp 282–284 °C dec: ^1H NMR (250 MHz, D_2O) δ 4.40–4.27 (m, 1 H, C*H*OP), 3.75 (dd, 1 H, J = 12.5, 3.0 Hz NC*H*COOH), 3.54–3.49 (m, 1 H), 3.07 (dt, 1 H, J = 13.0, 3.0 Hz), 2.64–2.53 (m, 1 H), 2.31–2.22 (m, 1 H), 1.82–1.68 (m, 2 H); IR (KBr) 1718 cm^{-1}; MS (FAB) 209 (M – 16). Anal. Calcd for $C_6H_{12}NO_6P$: C, 32.01; H, 5.37; N, 6.22. Found: C, 32.10; H, 5.47; N, 5.83.

Acknowledgment. We thank Dr. Michael Reily for assistance and discussions concerning ^1H NMR spectra and Linda Coughenour and Laura Brahce for receptor binding data.

Registry No. 1, 133192-42-4; 3, 17150-62-8; 5, 133192-43-5; 6, 133192-44-6; 7, 133192-45-7; 8, 133192-46-8; 9, 133192-47-9; NMDA, 6384-92-5; HCOCOOH, 298-12-4.

Additions and Corrections

Vol. 55, 1990

Edward E. Schweizer,* Cao Zhisong, Arnold Rheingold, and Martha Bruch. Reactions of Azines. 15. Preparation of Pyrazolo[1,5-*c*][1,3]oxazepin-6-ones.

Page 6363, column 2, lines 9–13, should read as follows: Therefore, the major isomer has a *Z* configuration, that is, the hydrogen atom on C6 is on the same side as the C4-methyl group. The ylidenes **6** have a characteristic absorption around 5.86 ± 0.17 ppm for C6-H (see Table III), thus suggesting that they should all be in the *Z* form.

Page 6364, column 1, lines 7–10, should read as follows: However, when R was phenyl of methyl and $R^1 = R^2$ = Ph (**6g** and **6f**) or R = Ph and $R^1 = R^2$ = Me (**6e**), the rearrangement reaction did not take place under refluxing xylene.

Vol. 56, 1991

Jeffrey Aubé,* Marlys Hammond, Elyse Gherardini, and Fusao Takusagawa. Syntheses and Rearrangements of Spirocyclic Oxaziridines Derived from Unsymmetrical Ketones.

Page 502, footnote *a* to Table I should read "Ketones were racemic and reacted with (*R*)-α-MBA unless otherwise noted."

In addition, some errors in absolute configuration and locant descriptors occur in the compound names given in the Experimental Section. The structures drawn in the text are correct and do correspond to those identified by numbers in the Experimental Section. None of the conclusions of the paper are altered. The correct prefixes follow: **2**, [2*S*-[2*R**(*S**),3*R**,5*S**)]]; **3**, [2*R*-[2*R**(*S**),3*S**,5*R*)]]; **11**, [2*S*-[2*R**(*S**),3*R**,4*R**)]]; **12**, [2*S*-[2*R**-(*S**),3*R**,4*S**)]]; **15**, [2*S*-(2*R**(*S**),3*S**,4*S**)]]; **14**, [2*S*-(2*R**-(*S**),3*R**,4*R**)]; **17**, [2*S*-(2*R**(*S**),3*R**,4*S**)]; **18**, [2*S*-(2*R**-(*S**),3*R**,4*R**)]; **5a**, [*R*-(*R**,*S**)]; **26**, [*S*-(*R**,*S**)]; **28**, [*S*-(*R**,*S**)]; **29**, [*S*-(*R**,*R**)].