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ENANTIOSPECIFIC SYNTHESIS OF A RIGID, C_2 SYMMETRIC, CHIRAL GUANIDINE BY A NEW AND DIRECT METHOD

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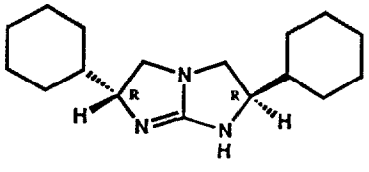
Summary: A broadly applicable method has been demonstrated for the efficient synthesis of chiral bicyclic guanidines such as **1** from chiral α-amino acids.

Compounds containing the guanidine unit are of considerable biological interest because of the hydrogen-bond mediated interaction of guanidinium ions with phosphate-containing biomolecules[1] and because of a range of biological activities, including hypotensive and adrenergic neuron blocking effects.[2] The cyclic marine-derived guanidines saxitoxin, ptilocaulin and tetrodotoxin are potent ion-channel blockers which have stimulated noteworthy research both in neuroscience and chemical synthesis.[3] A number of rigid, achiral, cyclic guanidines[4,5] and sterically hindered guanidines[6] have been synthesized and used as basic synthetic reagents.

This paper describes the first general synthetic route to chiral C_2 symmetric bicyclic guanidines as exemplified by 3*R*,7*R*-dicyclohexyl-1,4,6-triazabicyclo[3.3.0]oct-4-ene (**1**). The method provides access to chiral products without the need for resolution starting from readily available α-amino acids. It is also capable of producing unsymmetrically substituted guanidines starting from two different α-amino acids.

D-(-)-α-phenylglycine methyl ester (*R* enantiomer, **2**) was converted to the trityl-protected diamine **3** by the sequence: (1) amide formation with saturated ammonia in methanol at 0°C for 3 h and 22°C for 16 h (84%, mp 127-131°C, $[\alpha]^{22}_D$ -103° (c=1.2, EtOH)); (2) hydrogenation of phenyl to cyclohexyl using



1

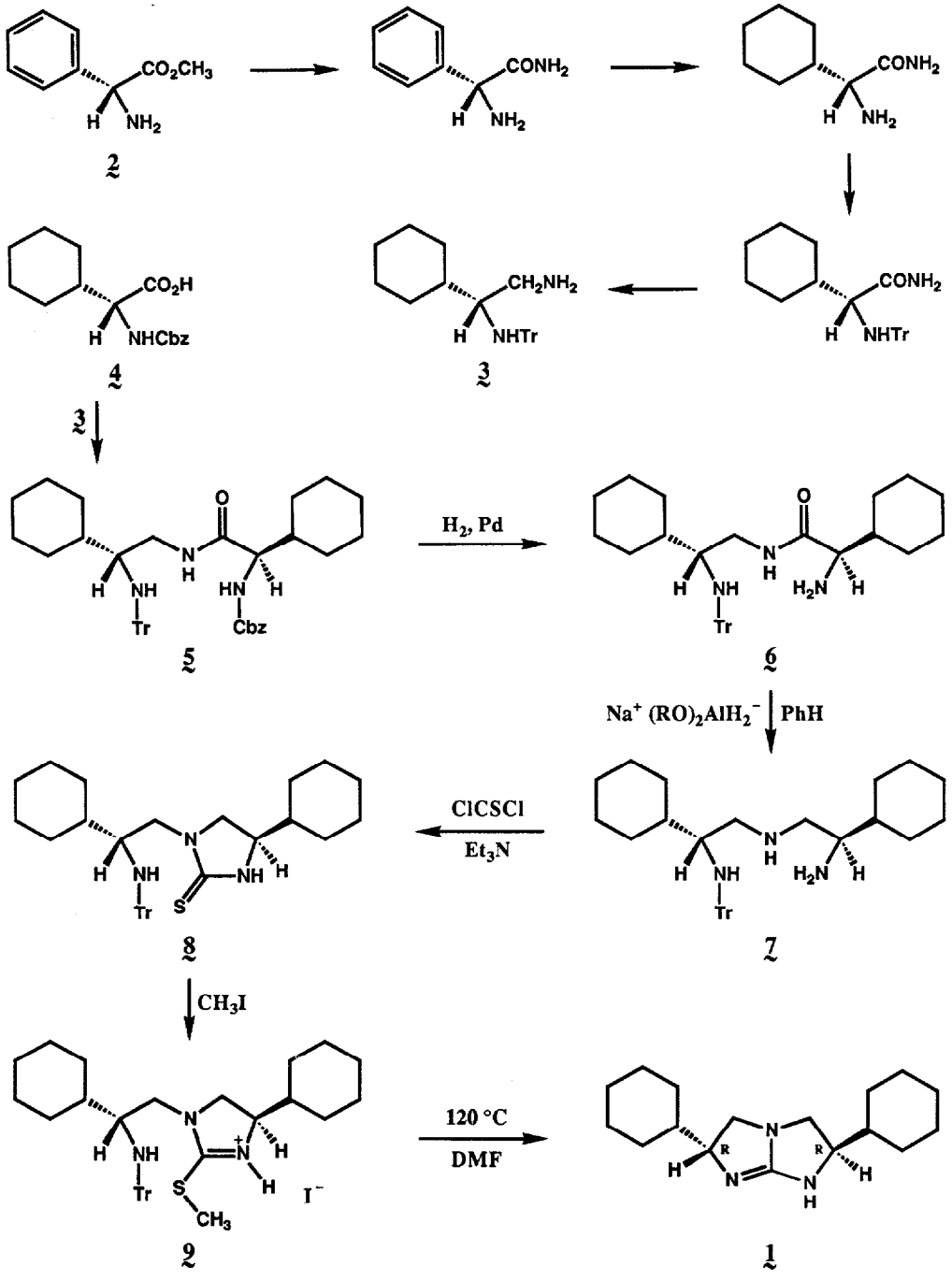
Adams' Pt catalyst in acetic acid with 1 atm of H_2 at 23°C for 40 h (87%, mp 123-125°C); (3) tritylation with 1 equiv of triphenylmethyl chloride (TrCl) in CH_2Cl_2 containing 1 equiv of triethylamine at 23°C for 2.5 h (94%, mp 223-225°C, $[\alpha]^{20}_D$ -35.5° (c=0.55, MeOH)); and (4) reduction with lithium aluminum hydride in ether at reflux for 40 h (97% of **3** as a colorless foam). Coupling of **3** with (*R*)-N-benzyloxycarbonylcyclohexylglycine (**4**) in THF using the dicyclohexylcarbodiimide-N-hydroxybenzotriazole method[7] afforded amide **5** selectively as colorless crystals (85%, mp 141-142°C).[8]

The carbobenzyloxy protective group was removed from bis amide **5** by hydrogenation at 1 atm using Pd-C in methanol at 23°C to afford the corresponding amide diamine (**6**) (100% as a colorless foam, ^{1}H NMR ($CDCl_3$): δ 0.6 - 2.10 (22H, m, cyclohexyl), 2.30 (1H, m, CH_2-C***H***-NHTr), 3.10 (2H, m, NH-C***H***$_2$-CH<), 3.35 (1H, m, C-C***H***(NH_2)CO), 6.95-7.65 (15H, m, arom.). Reduction of **6** with sodium bis(2-methoxyethoxy)aluminum dihydride in benzene at reflux for 40 min produced triamine **7** (100%) as a colorless oil which upon reaction with 1.1 equiv of thiophosgene and 2.2 equiv of triethylamine at -50°C to -30°C for 2 h and then at 23°C for 1 h gave after extractive workup and silica gel chromatography the thiourea **8** (69%) as colorless prisms, mp 97-99°C, R_f 0.40 (hexane-EtOAc, 4 : 1).

Thiourea **8** was transformed by reaction with 2 equiv of methyl iodide in methanol at 60°C for 45 min into the isothiouronium iodide **9**, obtained in 100% yield as pale yellow prisms, mp 114-115°C. For the final step, a solution of **9** in DMF (10 ml/g) was heated at 120°C for 1 h, cooled, and partitioned between ethyl acetate and 4 N sodium hydroxide. The organic layer was washed with water, dried (Na_2SO_4) and concentrated in vacuo, and the residue was chromatographed on basic alumina to give guanidine **1** (60%) as colorless prisms, mp 94-95°C, R_f 0.20 on Merck Type T Al_2O_3 plate using 1 : 1 methanol-ethyl acetate, $[\alpha]^{25}_D$ -51.1° (c=1.0, C_6H_6). The following physical data were obtained for **1**: IR ($CHCl_3$, cm^{-1}): 1660 (guanidine C-N stretch); ^{1}H NMR: δ 0.65 - 2.2 (22H, m, cyclohexyl), 2.83 (2H, dd, J=6.4, 7.7 Hz, N-CH-C***H***$_a$H$_b$-N), 3.11 (2H, t, J=7.7 Hz, N-CH-CH$_a$***H***$_b$-N), 3.77 (2H, m, N-C***H***-CH_2-N), 4.08 (1H, br s, N-H, disappears upon addition of D_2O); Mass: m/e 275 (M^+), 192 (M^+ - C_6H_{11}); $[\alpha]^{22}_D$ -11.0° (c=0.9, C_6H_6).

One especially noteworthy feature of the above synthesis of **1** is the outstanding utility of the trityl protective group which not only simplifies the isolation and purification of intermediates but also ensures a high degree of selectivity in the conversions **5** → **6**, **6** → **7**, **7** → **8**, and **8** → **9**. Finally, having served so well in these steps, it obligingly leaves the scene in the last step, the cyclization of **9** to guanidine **1**.

We expect that guanidines such as **1** will be of synthetic utility. In addition they are prime candidates for biological studies. Further work will be reported in due course.[9]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2
CONH2
H NH2
CONH2
H NH2
CONH2
H NHTr
CH2NH2
H NHTr
3
CO2H
H NHCbz
4
3
H2, Pd
Tr
Cbz
5
6
Na+ (RO)2AlH2− PhH
ClCSCl
Et3N
7
8
CH3I
I−
120 °C
DMF
9
1

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8. *R*-N-carbobenzyloxycyclohexylglycine (**4**) was prepared in three steps from the methyl ester of *R*-(-)-α-phenylglycine: (1) hydrogenation of the aromatic ring (Adams' Pt catalyst, 1 atm H_2 in HOAc at 23°C); (2) N-acylation (1 equiv each of benzyloxycarboxylchloride and pyridine in CH_2Cl_2 at 0°C for 1 h) to give a colorless oil, $[\alpha]^{22}_D$ -5.6° (c=1.0, MeOH); and (3) ester saponification in aqueous methanol at 23°C. Acid **4** was obtained as a crystalline solid, mp 103°C, $[\alpha]^{22}_D$ -5.6° (c=1.3 in MeOH).

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