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CYCLIC DERIVATIVES OF 3,3-DIPHENYLALANINE (DIP) (II), NOVEL α-AMINO ACIDS FOR PEPTIDES OF BIOLOGICAL INTEREST

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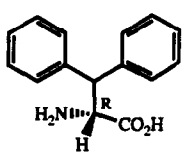
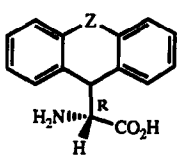
Abstract: The chiral and achiral syntheses of novel cyclic derivatives of 3,3-diphenylalanine (Dip) are described.

Recently, we reported the chiral synthesis of D- and L-3,3-diphenylalanines (Dip).[1] These hydrophobic amino acids incorporate a diphenylmethyl side chain which, in the case of D-Dip, has been shown to be a key substructural substitution in a potent peptidyl antagonist of the ET_A and ET_B endothelin receptors.[2] Progressing from this lead, we sought to constrain the two phenyl rings in Dip by a bridge Z, as in D- and L-α-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-acetic acid (Bhg) (Z = -CH_2-CH_2-) (**1a**, **1b**), D- and L-α-amino-5H-dibenzo[a,d]cycloheptene-5-acetic acid (unsaturated Bhg) (Z = -CH=CH-) (**2a**, **2b**), Z = -S- (**3**) and -O- (**4**), to advance such cyclic, hydrophobic α-amino acids for the synthesis of peptides of biological interest.[3]



D-Dip



D-(1-4a)

L-(1-4b)

Z:	Dip	-CH_2-CH_2- (1)	-CH=CH- (2)	-S- (3)	-O- (4)
Plane Angle:	100°	120°	120°	140°	150°

To explore the conformational effect of bridging, we measured the plane angles of the two phenyl rings by molecular modeling.[4,5,6] Relative to Dip, the angles increase significantly in the order from (**1**) to (**4**) as shown above. The hydrophobic tricyclic structure with Z = -CH=CH- (**2**) is rigid, but has the same biplane angle as the somewhat flexible saturated bridged analog (Z = -CH_2-CH_2-) (Bhg) (**1**). Cody and co-workers[3] recently reported that replacement of D-Dip in the peptidyl antagonist (PD 142893, N-Ac-D-Dip-Leu-Asp-Ile-Ile-Trp)[2] by the D-Bhg (**1a**) substantially enhanced its antagonist activity at the ET_A and ET_B receptors.

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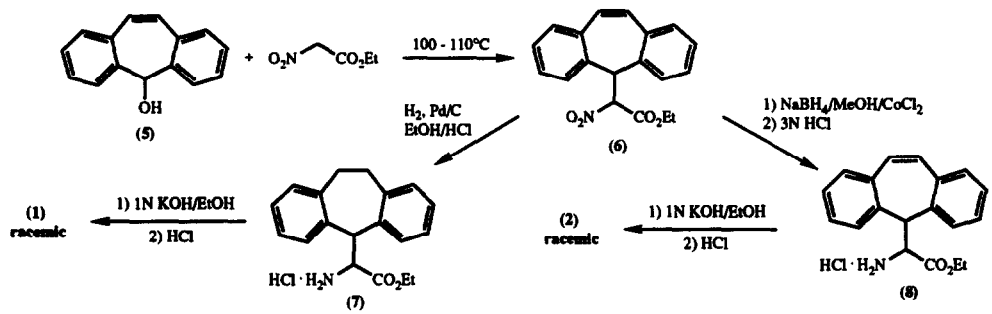
We envisioned that if the conformation of one of these tricyclic units closely corresponds to that required for an optimal receptor site interaction, the resulting favorable entropy effect should increase binding potency in the absence of other negative effects associated with introduction of the bridge. After this work was completed, Wiley and Rich,[7] in an incisive review "Peptidomimetics Derived from Natural Products", have pointed out that the diphenylmethyl group (or its cyclic variants) is a common structural feature of a number of medicinal agents, and they propose that the conformationally restricted diphenylmethyl group resists *hydrophobic collapse*, or simply is able to maintain its ligand conformational integrity in an aqueous environment. Bridging the diphenylmethyl group increases conformational restriction and should provide greater resistance to hydrophobic collapse, thus possibly further enhancing biological activity.

In this communication, we wish to report both the achiral and chiral synthesis of the bridged Dips (**1a,b and 2a,b**). Initially, these amino acids were synthesized in racemic form (Scheme I), and expeditiously separated as diastereomeric peptides. Later chiral syntheses were accomplished using Evans methodology[8] (Scheme II).

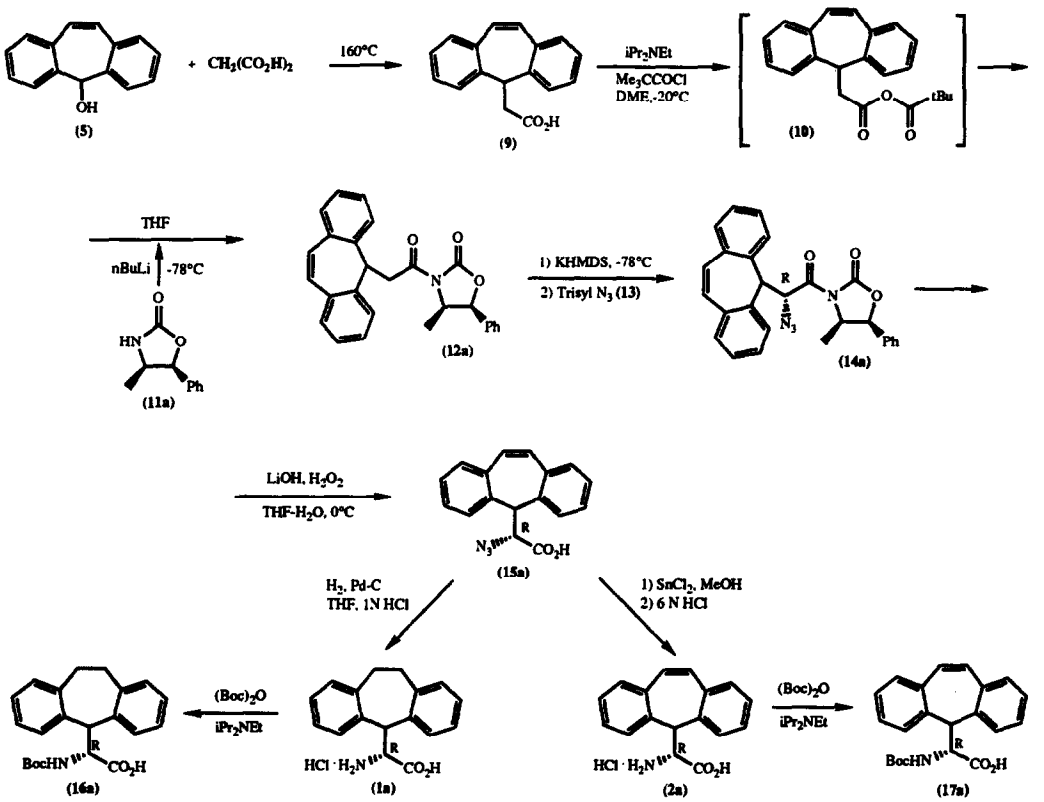
SCHEME I



The racemic (**1**) and (**2**) were synthesized using the method described by Ryaboi and Ginzburg[9] (Scheme I). Dibenzosuberenol (**5**) was heated with ethyl nitroacetate (15 equiv.) at 100 - 110°C for 1 h, and the resulting orange mixture, after distilling off the excess ethyl nitroacetate, was washed with ether to give the pure nitro ester (**6**), 79% yield, mp 101 - 103°C. Nitro ester (**6**) was then catalytically hydrogenated in EtOH/HCl (1 equiv.), on 20% Pd-C to give the bridged amino ester hydrochloride (**7**), which was then hydrolyzed in 1 N KOH in EtOH and acidified with HCl to give the racemic Bhg hydrochloride (**1**), mp 285°C, overall 56% yield from (**6**) to (**1**). The selective reduction of the nitro group of (**6**) with $NaBH_4$ (10 equiv.) and $CoCl_2 \cdot 6\ H_2O$ (2 equiv.) in MeOH,[10] followed by treatment with 3 N HCl gave the ester (**8**), 80% yield, mp 253 - 256°C. Base hydrolysis (1 N KOH in EtOH), followed by treatment of HCl gave the racemic unsaturated Bhg hydrochloride (**2**), 42% yield, mp 225°C. The oxygen bridged amino acid (**4**) was synthesized as reported in literature[9] (39% overall yield, mp 264 - 269°C). The corresponding novel sulfur bridged compound (**3**) was synthesized in 37% overall yield, mp, 269 - 273°C, starting with 9-hydroxythioxanthene and using the same methodology.

The chiral synthesis (Scheme II) started with the preparation of 5H-dibenzo[a,d]cycloheptene-5-acetic acid (**9**), which was accomplished by heating a mixture of dibenzosuberenol (**5**) and malonic acid at 160°C for 2 h, 85% yield, mp 167 - 168°C. Treatment of acid (**9**) with DIPEA (1.2 equiv.) and pivaloyl chloride (1.05 equiv.) in dry DME at -20°C gave mixed anhydride (**10**), which was then added to the lithiated oxazolidinone at -78°C, which was prepared by the addition of nBuLi (1.05 equiv.) to a solution of (4R, 5S)-

SCHEME II



4-methyl-5-phenyl-2-oxazolidinone (**11a**) (1.0 equiv.) in THF. Standard work-up and recrystallization (hexane-AcOEt/2 : 1) gave the acyloxazolidinone (**12a**), 84% yield, mp 172 - 173°C, $[\alpha]_D$ = +10.1° (c = 1.0, $CHCl_3$). Deprotonation of (**12a**) with KHMDS (1.05 equiv.) in THF, at -78°C, followed by addition of trisyl azide (**13**) (1.25 equiv.), and quenching with AcOH (4.6 equiv.) yielded the azido oxazolidinone (**14a**), after flash chromatography (silica gel, hexane-AcOEt/ 1.5 : 1), 85% yield, mp 175°C, $[\alpha]_D$ = -119.4° (c = 1.0, $CHCl_3$). HPLC[11] showed a single diastereoisomer. The hydrolysis of the chiral auxiliary was performed by the treatment of (**14a**) in 4 : 1 THF-H_2O at 0°C with a solution of LiOH-H_2O (2.0 equiv.) in H_2O_2 (5.0 equiv., 30% aqueous). The azido acid (**15a**) was obtained in 89% yield, after flash chromatography (silica gel, hexane-AcOEt-AcOH/100 : 50 : 2), mp 119 - 120°C, $[\alpha]_D$ = -40.6° (c = 1.0, MeOH). The azide (**15a**) was reduced[12] by $SnCl_2$ (1.5 equiv.) in MeOH, then acidified with 6N HCl and purified with Dowex 50X8-100 ion exchange resin to give D-(R)-unsaturated Bhg hydrochloride (**2a**), 78% yield, mp 229 - 232°C (dec.), $[\alpha]_D$ = + 24.7° (c = 1.0, MeOH). Further treatment of (**2a**) with $(Boc)_2O$ (2.0 equiv.) and DIPEA (2.5 equiv.) in MeOH gave the corresponding N-t-Boc amino acid (**17a**), 92% yield, mp 150 - 151°C (dec.), $[\alpha]_D$ = +27.3° (c = 1.0, MeOH).

L-(S)-unsaturated Bhg hydrochloride (**2b**) (mp 230 - 232°C (dec.), $[\alpha]_D$ = -23.6° (c = 1.0, MeOH)), and the corresponding N-t-Boc-unsaturated Bhg (**17b**) (mp 148 - 150°C (dec.), $[\alpha]_D$ = - 26.8° (c = 1.0, MeOH)) were also prepared by the same method, using (4S, 5R)-4-methyl-5-phenyl-2-oxazolidinone (**11b**) as chiral auxiliary.

D-(R)-Bhg hydrochloride (**1a**) was synthesized by catalytic hydrogenation of the azido acid (**15a**) in THF-HCl (1N)/4 : 1, at 50 psi, on 20% Pd-C, quantitative yield, mp 313 - 314°C (dec.), $[\alpha]_D$ = - 47.6° (c = 1.0, MeOH). N-t-Boc-Bhg (**16a**) was prepared in 96% yield, mp 179 - 180°C (dec.), $[\alpha]_D$ = +29.8° (c = 1.0, MeOH). D-(R)-Bhg (**1a**) was also prepared from dibenzosuberol using the same method as in the synthesis of (**2a**) in 55% overall yield.

L-(S)-Bhg hydrochloride (**1b**) (mp 316 - 318°C (dec.), $[\alpha]_D$ = +45.6° (c = 1.0, MeOH)), and the corresponding N-t-Boc-Bhg (**16b**) (mp 178 - 179°C (dec.), $[\alpha]_D$ = - 30.2° (c = 1.0, MeOH)) were prepared by the same methods as described above, using (4S, 5R)-4-methyl-5-phenyl-2-oxazolidinone (**11b**) as chiral auxiliary.

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4. The molecules were constructed using SYBYL[5a] with the C_β hydrogen trans to the C_α hydrogen, and minimized using the Tripos force field[5a] with an RMS gradient of 0.001 as the convergence factor. The molecules were independently geometry optimized with MOPAC[5b] using the AMI method except in the sulfur bridged system where the MNDO method was used. The results between the SYBYL and AMI methods were consistent with the exception of the $-CH_2-CH_2-$ bridge compound. The plane angle in the molecular mechanics method was roughly 120°, and by AMI, approximately 105°. A search of the Cambridge Structure Database[6] provided a crystal structure of a very similar compound, 10,11-dihydro-5H-dibenzo[a,d]cycloheptane-5-aminoheptanoic acid hydrochloride, (BERWOK). The angle between the same planes for this molecule was 118°, agreeing with the molecular mechanics derived plane angle.

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11. Analytical HPLC was performed with a 0.46 x 3.3 cm silica cartridge column, Perkin Elmer, pentane:AcOEt/95 : 5, flow rate=1.5 ml/min, to give a single peak, t_R = 1.42 min.

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