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Synthesis of a Novel Constrained α-Amino Acid with Quinoxaline Side Chain : 7-Amino-6,7-dihydro-8H-cyclopenta[g]quinoxaline-7-carboxylic Acid

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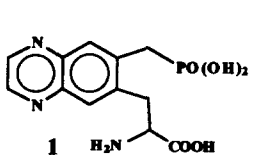
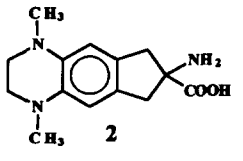
Abstract: A novel constrained 7-amino-6,7-dihydro-8H-cyclopenta[g]quinoxaline-7-carboxylic acid derivative was prepared starting from 4,5-dimethyl-*o*-phenylenediamine.

Synthetic amino acids which bear unnatural side chains [1] have proven useful for probing structural aspects of proteins and peptides. These also show interesting biological properties. Recently quinoxaline-spaced phosphono α-amino acids of the AP-6 type have been synthesized as competitive NMDA antagonists (e.g. **1**).[2] In connection with our project related to photoinduced electron transfer between two custom-designed redox α-amino acids (donor **2** and acceptor **4**), we needed access to amino acid derivative **2**, with tetrahydroquinoxaline (ThQx) side chain as donor component.[3] We chose to incorporate this powerful donor as a cyclic α-amino acid in order to ensure maximum 3_{10}-helical stability and to maintain a well-defined geometrical relationship with no (χ_1, χ_2) torsional degrees of freedom.[4]

Direct synthetic transformation of such donor side chains to the corresponding amino acid is not a trivial procedure as such molecules are highly electron rich, and usually not compatible with the reaction conditions employed during the development of amino acid functionality.[5] The side chain of tetrahydroquinoxaline belongs to the *o*-phenylenediamine class of molecules, therefore a natural starting point for the synthesis of 1,2,3,4-tetrahydro-1,4,6,7-tetramethylquinoxaline **3** is 4,5-dimethyl-*o*-phenylenediamine **3a**. Assembly of the target N,N–dimethyltetrahydroquinoxaline carbon frame **3** from **3a** involves two basic steps;



1



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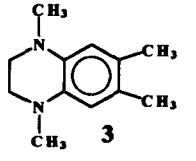

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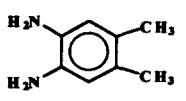
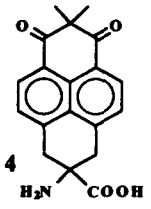


3a



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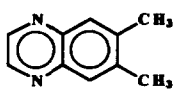


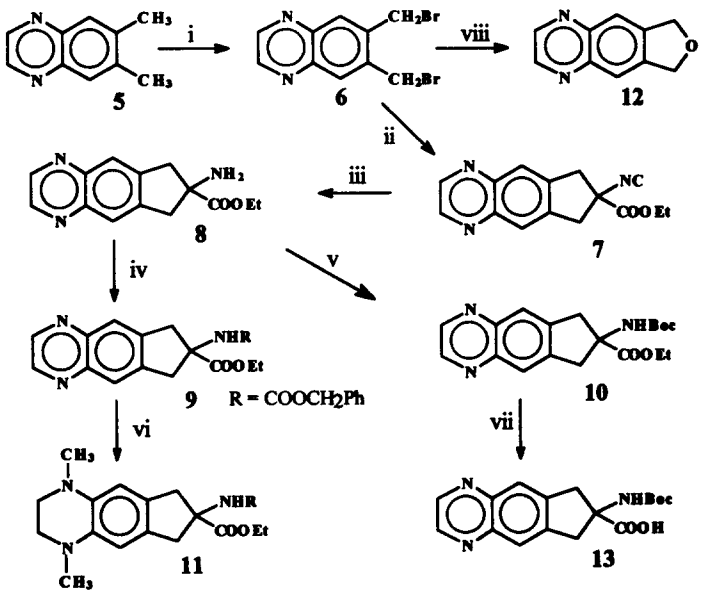
5

formation of the six-membered heterocyclic ring and methylation of the two nitrogen atoms. Direct alkylation of the two nitrogen atoms first with a two-carbon bridge to close the ring followed by reaction with the appropriate methyl synthon, or vice-versa (first methylation followed by ring-closure), although a conceptually simple approach, is totally impractical because of undesired N-polyalkylated products.

An alternate to the direct alkylation involving a protective group strategy was not considered. Initially we prepared tetrahydroquinoxaline derivative **3** starting from 4,5-dimethyl-*o*-phenylenediamine **3a** and glyoxal by condensation using sodium bisulfite (*via* **5**,[4] 85% yield) followed by reductive methylation. Attempted bromination at the benzylic positions of **3** resulted in rapid oxidation of the substrate. This finding suggested that proper protection or masking of the electronically rich tetrahydroquinoxaline side chain functionality was needed. It occurred to us that an excellent way to circumvent this problem was the use of the quinoxaline system which is a natural form of protected tetrahydroquinoxaline moiety.

Benzylic bromination of **5** was effected with NBS in CCl_4 using AIBN as a radical initiator. The required dibromide **6**[4] is obtained in 53% yield by flash chromatography. The unwanted byproducts (most likely mono and tribromide) were not characterized completely. Dibromide **6** is sensitive to heat and light and must be stored at low temperature (freezer).

Scheme 1



i) NBS, AIBN ii) $CNCH_2COOEt$, K_2CO_3, PTC iii) 1 N HCl
iv) $PhCH_2OCOCl$, aq NaOH, v) TMSCl, $(iPr)_2NEt$-(^{t}Boc)$_2$O vi) $NaBH_4$, CF_3COOH, THF, 30 min then aq. HCHO vii) 1 N NaOH viii) 10% NaOH, PTC or $CNCH_2COOEt$, 10% NaOH, PTC

Coupling of **6** with ethyl isocyanoacetate [6] in presence of NaH in diethylether/DMSO at room temperature gave **7**[4] in low and irreproducible yields (5-25%). Change of reaction conditions or usage of various base combinations (KO^{t}Bu, LDA, NaHMDS, KHMDS) for the coupling reaction was of no help. We have evaluated 30 different conditions for this purpose. Later on, we have tried various benzylidene derivatives of glycine ester(s) with various bases (KO^{t}Bu, LDA, NaHMDS, KHMDS) and found none of the desired coupling product.

At this juncture we reasoned out that the phase-transfer catalysis (PTC) method may be a good alternative for the coupling reaction because the highly base-sensitive dibromide **6** may be less in contact with the base under these conditions. When we attempted the coupling reaction of **6** with ethyl isocyanoacetate using conventional PTC conditions (aq. NaOH, methylenechloride, tetrabutylammonium hydrogen sulfate) we found the formation of cyclic ether **12** [♣] (46% yield) and no coupling product was observed (Scheme 1). We also conducted a blank experiment (i.e., in the absence of ethyl isocyanoacetate) under the same conditions and found the ether **12** was formed in 84% yield. By switching over to solid-liquid PTC conditions (K_2CO_3, acetonitrile, tetrabutylammonium hydrogen sulfate) [7] the coupling product **7** was observed in 38% isolated yield. We have repeated this reaction several times on 1 mmol scale and the yields are consistent. On a 2 mmol scale the yield is 30%.

A mild acidic hydrolysis of **7** (1 N HCl in ethanol) gave the amino ester derivative **8** in 87-94% yield. Amino group of **8** was protected in 85% yield to give Boc derivative **10**[♣] using Meienhofer procedure.[8] Then, the ester **10** was hydrolyzed to the corresponding acid **13**[♣] (90% yield) under saponification conditions. Alternatively, amino group in **8** was protected as a benzyloxycarbonyl (Z) to generate **9**[♣] (50% yield) which was methylated in a reductive fashion to afford **11**[♣] (50 % yield).

In conclusion, the amino acid derivative prepared here is the first of its class and the strategy developed here may be useful in the synthesis of electronically interesting cyclic α-amino acid derivatives.

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♣ Selected Spectral data:

(**5**): ^{1}H NMR ($CDCl_3$, 250 MHz), δ 2.5 (s, 6H), 7.84 (s, 2H), 8.74 (s, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz), δ 20.4, 128.4, 140.7, 142.0, 144.1.

(**6**): ^{1}H NMR ($CDCl_3$, 250 MHz), δ 4.88 (s, 4H), 8.0 (s, 2H), 8.8 (s, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz), δ 29.5, 131.9, 138.5, 142.8, 146.0.

(**7**): ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.38 (t, *J*=7.1, 3H), 3.70 (part of ABq, *J*=16.8, 2H), 3.9 (part of ABq, *J*=16.8, 2H), 4.36 (q, *J*=7.1, 2H), 7.98 (s, 2H), 8.82 (s, 2H).^{13}C NMR ($CDCl_3$, 75.43 MHz), δ 13.9, 45.6, 63.4, 68.5, 124.8, 141.4, 142.9, 144.6, 159.8, 167.7

(**9**): ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.19 (t, *J*=7.1, 3H), 3.57 (part of ABq, *J*=16.8, 2H), 3.81 (part of ABq, *J*=17.0, 2H), 4.20 (q, *J*=7.3, 2H), 5.1 (s, 2H), 5.44 (s, 1H), 7.31 (s, 5H), 7.88 (s, 2H), 8.76 (s, 2H).

(**10**): ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.26 (t, *J*=7.1, 3H), 1.48 (s, 9H), 3.5 (part of ABq, *J*=17.0, 2H), 3.81(part of ABq, *J*=17.2, 2H), 4.24 (q, *J*=7.0, 2H), 5.16 (s, 1H), 7.9 (s, 2H), 8.77 (s, 2H).

(**11**): ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.21 (br t, 3H), 2.82 (s, 6H), 3.05 (part of ABq, *J*=17.0, 2H), 3.28 (s, 4H), 3.55 (part of ABq, *J*=17.0, 2H), 4.20 (br q, 2H), 5.07 (s, 2H), 5.3 (s, 1H), 6.35 (s, 2H), 7.32 (s, 5H).

(**12**): ^{1}H NMR ($CDCl_3$, 300 MHz), δ 5.3 (d, *J*=0.9, 4H), 7.95 (s, 2H), 8.83 (s, 2H). **Mass**: M^+ 172.

(**13**): ^{1}H NMR (DMSO-d_6, 500 MHz), δ 1.37 (s, 9H), 3.46 (part of ABq, *J*=17.5, 2H), 3.64 (part of ABq, *J*=17.0, 2H), 7.56 (s, 1H), 7.88 (s, 2H), 8.84 (s, 2H), 12.6 (br s, 1H).

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