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A Trans Olefin Replacement of the Disulfide Bridge Found in Cyclic Peptides: Synthesis of 6,6-Pentamethylene-2-amino-$\Delta^{4,5}$-suberic Acid.

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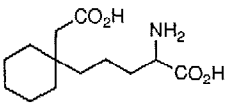
Key Words: disulfide replacements; dicarba replacement; *trans* olefin replacement; alkylation of glycine equivalent; vasopressin antagonists

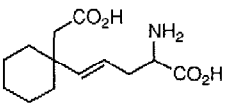
Abstract: *Substitution of the sulfur atoms in the disulfide bridge of cyclic peptides with a trans olefin incorporates the features of a dicarba replacement while introducing a greater torsional restriction The synthesis of the differentially protected racemic 6,6-pentamethylene-2-amino-$\Delta^{4,5}$-suberic acid (2) is described as an example of such a replacement.*

A common method of restricting the conformational mobility of a linear peptide is to convert it into a corresponding cyclic analog. Typically this is accomplished by formation of a cyclic disulfide where the disulfide bridge joins two cysteine or substituted cysteine residues (e.g. penicillamine) that are inserted into the linear peptide of interest[1]. Among the problems that arise when this particular cyclic constraint is used are 1) the chemical and metabolic stability of the disulfide bond and 2) the inherent flexibility of the disulfide torsion angle. The latter occurs because a disulfide within a cyclic peptide can exist in either of two possible rotamer forms[2]. The chemical and metabolic stability problems have been addressed by replacing the two sulfur atoms of the bridge with methylene groups to give the corresponding dicarba analogues[3-5]. The dicarba replacement however allows for considerable flexibility in the bridge between the side chains[5]. A further constraint could be introduced by replacing the methylene groups of the dicarba bridge with a *trans* olefin. The introduction of the *trans* olefin would fix a key torsion angle of the bridge and limit the conformations available to the resulting cyclic peptide. A test of the feasibility of such a replacement would require the synthesis of a representative pseudo-dipeptide whose side chains have been bridged by a *trans* olefin.

Our interest in cyclic dicarba vasopressin antagonists[5], which incorporate the unnatural amino acid, 6,6-cyclopentamethylene-2-aminosuberic acid (**1**)[6], led us to chose 6,6-pentamethylene-2-amino-$\Delta^{4,5}$-suberic acid (**2**) as our initial target molecule. Synthesis of this unnatural amino acid **2** required the incorporation of a spiro-cyclohexane, an isolated *trans* olefin and an amino group onto a differentially protected suberic acid framework. Our synthetic plan was predicated on the synthesis of the desired side chain as an electrophile which could then be added to the enolate of a suitably protected glycine equivalent.

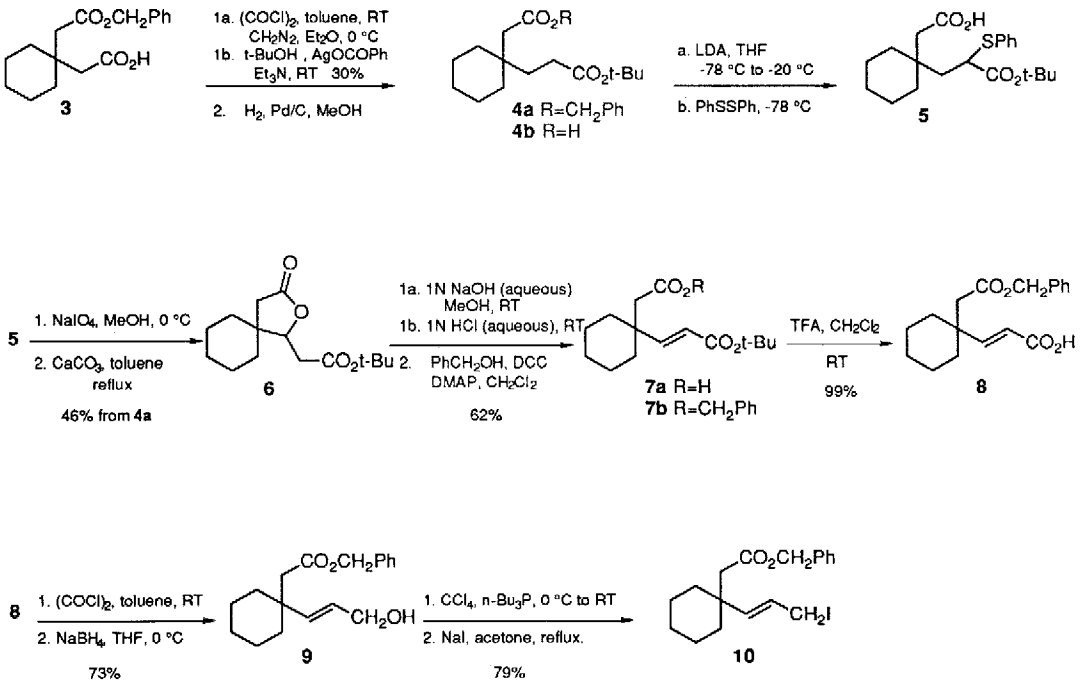


1



2

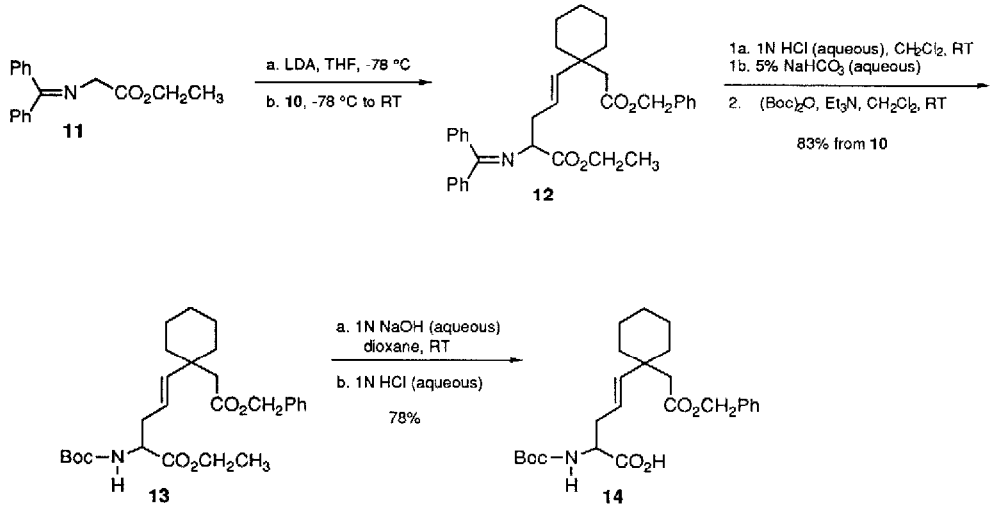
The monobenzyl ester of 1,1-cyclohexanediacetic acid (**3**)[6] was homologated via the diazomethyl ketone to the diester **4a** using Arndt-Eistert methodology[7,8] and then converted to the monoester **4b** via hydrogenolysis of the benzyl ester as shown in Scheme 1[9]. Alkylation of the dianion of **4b** with



Scheme 1

diphenyldisulfide gave a difficult to separate mixture of the desired α-phenylsulfide **5** and unreacted starting material **4b**[10]. Oxidation of the mixture of **5** and **4b** with $NaIO_4$ followed by thermal elimination of the resulting sulfoxides, buffered with $CaCO_3$ to prevent t-butyl ester cleavage,[10] gave the unexpected γ-lactone **6** (46% from **4a**) instead of the desired product **7a** as well as recovered **4b** (26%). Presumably the γ-lactone **6** resulted from a base catalyzed intramolecular lactonization of the intermediate α,β-unsaturated ester **7a**[11]. The γ-lactone **6** was treated with aqueous 1N NaOH in methanol followed by acidification and esterification to give **7b**. The *trans* stereochemistry of the double bond in **7b** was confirmed by ^1H NMR analysis[12]. None of the corresponding *cis* isomer was observed. Selective hydrolysis of **7b** with trifluoroacetic acid gave **8**[13] which was converted to the allylic alcohol **9** by selective sodium borohydride reduction of its acid chloride in tetrahydrofuran. Conversion of the allylic alcohol **9** to the iodide **10** provided the requisite electrophile needed for the alkylation of the glycine equivalent.

Alkylation of the lithium enolate of the glycine equivalent N-(diphenylmethylene)glycine ethyl ester (**11**)[14] with the allylic iodide **10** gave the intermediate imine **12** which was not purified. The crude imine **12** was converted to **13** via mild acid hydrolysis followed by protection with di-t-butyldicarbonate in 83% overall yield as shown in Scheme 2. Selective base hydrolysis of the α-ethyl ester gave racemic **14** suitably protected for use in either solution or solid phase peptide synthesis.[15] The incorporation of **14** into a cyclic vasopressin analogue and the effects of the replacement on biological activity will be the subject of a future publication.[16]



Scheme 2

Acknowledgment: We acknowledge Lewis B. Killmer, Jr. of the Department of Analytical Chemistry and Mary A. Mentzer of the Department of Physical and Structural Chemistry for the mass spectra.

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8. The Arndt-Eistert reaction was routinely run starting with 50 g of the mono-benzyl ester **3**.
9. All compounds gave satisfactory ^{1}H NMR and mass spectral data. The NMR spectra of selective intermediates are given below [^{1}H NMR ($CDCl_3$, 90 MHz)]. **4a**: δ 7.38 (s, 5H), 5.14 (s, 2H), 2.32 (s,

2H), 2.40-1.20 (m, 14H), 1.43 (s, 9H); **6**: δ 4.60 (t, 1H), 2.55-2.40 (m, 4H), 1.10-1.85 (m, 10H), 1.48 (s, 9H); **7b**: δ 7.35 (s, 5H), 6.90 (d, 1H, J = 16 Hz), 5.75 (d, 1H, J = 16 Hz), 5.08 (s, 2H), 2.43 (s, 2H), 2.10-1.10 (m, 10H), 1.47 (s, 9H); **9** δ 7.38 (s, 5H), 5.63 (m, 2H), 5.10 (s, 2H), 4.05 (m, 2H), 2.40 (s, 2H), 2.13 (s, 1H), 1.80-1.20 (br m, 10H); **10** δ 7.38 (s, 5H), 5.78-5.58 (m, 2H), 5.10 (s, 2H), 3.90-3.75 (m, 2H), 2.33 (s, 2H), 1.80-1.13 (m, 10H); **13** δ 7.40 (s, 5H), 5.50-5.07 (m, 3H), 5.12 (s, 2H), 4.50-4.13 (m, 1H), 4.18 (q, 2H, J = 7.5 Hz), 2.57-2.30 (m, 2H), 2.33 (s, 2H), 1.43 (br s, 19H), 1.25 (t, 3H, J = 7.5 Hz); **14** δ 7.40 (s, 5II), 7.23 (s, 1H), 5.70-5.23 (m, 3H), 5.12 (s, 2H), 4.50-4.17 (m, 1H), 2.47 (t, 2H, J = 6 Hz), 2.35 (s, 2H), 1.43 (br s, 19H).

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11. Oxidation and elimination of the corresponding monomethyl ester under neutral conditions gave the expected *trans* olefin containing monomethyl ester.
12. The *trans* stereochemistry of the double bond in **7b** was confirmed by measuring the coupling constant (J = 16.5 Hz) between the two olefinic protons.
13. All attempts to selectively hydrolyze the corresponding methyl-benzyl ester under various conditions gave mixtures of recovered diester, monoester and diacid.
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15. Alkylation of the glycine equivalent with 10.7 mmol of the iodide **10** provided 3.1 g (6.9 mmol) of the selectively protected amino acid **14**.
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