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Synthesis of a New Rigid Quinone-Amino Acid and Diels-Alder Extension to Higher Quinones

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Electron deficient cyclic α–amino acid derivatives bearing 1,4-benzoquinone and 1,4-anthraquinone side chains were synthesized by a novel route. The common precursor, 2-amino-4,7-dimethoxy-indan-2-carboxylic acid, may be incorporated into a peptide prior to the final oxidation and annelation reactions.

Quinones of diverse varieties play important roles as components of the biological electron transport chains in both photosynthetic and respiratory membrane systems. In addition quinones have been incorporated into numerous synthetic donor-acceptor molecules as part of extensive research on artificial photosynthesis.[1)]

As an important new synthetic target we recognized that an amino acid bearing a quinone side chain would enable peptide assembly strategies in the construction of new donor/acceptor molecular architectures, and further that such an amino acid could serve as a useful building block for higher ring systems via Diels-Alder methodology.[2)] Furthermore, a design featuring a rigid link to the peptide backbone would allow the critical quinone functionality to be installed into confirmationally constrained peptides of diverse potential applications. Only a few quinone amino acids of any kind are known. Glutathione adds to tetrachloro-1,4-benzoquinones via an addition elimination mechanism to give thioether-linked benzoquinone bearing amino acids.[3a)] The quinone of the known compound 2,4,5-trihydroxy-phenylalanine (Topa) has been explored as a potential intermediate in dopachrome synthesis within the melanin biosynthetic pathway.[3b)] The recent discovery of topa as a key redox cofactor in amine oxidases has raised new questions about the diversity and function of quinone redox cofactors and the scope of quinone amino acids in natural polypeptides.[3c)] However, there are no reports on practical synthetic routes to deliver new quinone based α–amino acids, and the rigidly held cyclic quinone amino acids reported here are without precedent.

In recent years numerous synthetic methods have become available to synthesize acyclic α-amino acids,[4)] while only a very limited number of methods[5)] are available for cyclic α–amino acids, with the exception of the simplest five and six membered ring compounds. Recently, we demonstrated[6)] a useful variation of the Stork methodology[7)] to synthesize cyclic α–amino acids containing sensitive functionalities. In this communication we report the synthesis of a rigid and novel benzoquinone based cyclic α-amino acid derivative **9** and its extension to the higher quinone **11** through the Diels-Alder strategy. A simple retrosynthetic analysis of **1** (Fig. 1) indicates that (path **a**) the easily available 1,4-dimethoxy-2,3-dimethyl-benzene **2** is a suitable starting material.

The synthesis of **9** began (Scheme 1) with the commercially available 2,3-dimethyl-hydroquinone **4**. The hydroxyl groups in **4** were protected as methyl ethers in quantitative yield.[8)] When compound **2** was treated with 2.1 equivalents of freshly crystallized N-bromosuccinimide in the presence of benzoyl peroxide, the bis(bromomethyl) compound **5** was obtained in 75% yield. The coupling of **5** with the benzylidene derivative

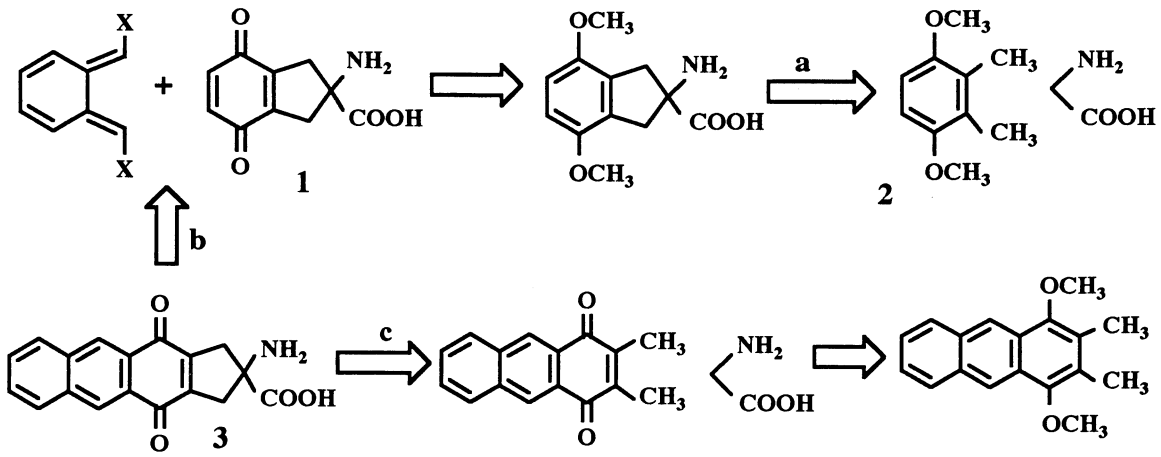
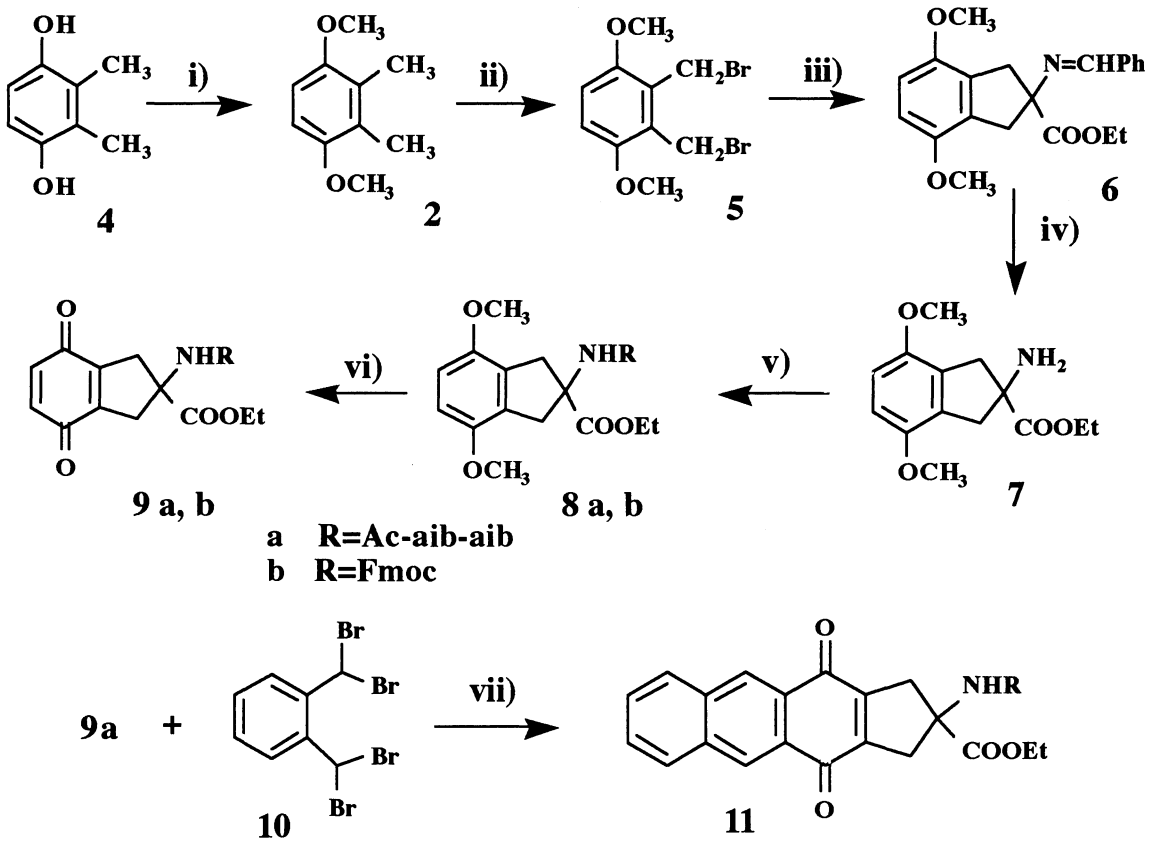


Fig 1.

of glycine ethyl ester in presence of NaHMDS gave **6** which was directly treated with 1M HCl to deliver the key cyclic amino ester **7** (55-60% yield starting from **5**. It was necessary to protect the amino functionality of **7** to effect the desired oxidation to quinone derivatives such as **9.** However, we determined that a simple amide functionality suffices to provide the needed protection. Since we were interested in preparing aib (α-aminoisobutyric acid) peptides of **1** we directly treated **7** with a C-activated N-protected aib di-peptide (the oxazolone)[9] to give the tripeptide **8a**. Ceric ammonium nitrate[10] treatment of **8a** in acetonitrile-water mixture gave **9a**. The simple Fmoc derivative[11] **8b** of the dimethoxy amino ester can also be oxidized to the corresponding quinone amino ester **9b** without any difficulty. The protected amino acid **9** possesses the desired quinone functionality rigidly linked to the peptide backbone, and can serve as a component of peptides of unique design.

For the synthesis of the 1,4-anthraquinone amino acid [12] **3** path **b** appeared to be superior to path **c** due to the ready availability of the starting material **2** and the transformations demonstrated above. Thus, treatment of the protected tripeptide **9a** with α,α,α',α'-tetrabromo-o-xylene **10** in presence of sodium iodide gave the required 1,4-anthraquinone **11** in 20% yield. It is well established that ortho-xylylenes (o-quinodimethanes) serve as diene intermediates in annelations of this type.[13]

In conclusion the two rigid quinone amino acid derivatives (**9, 11**) prepared here are the first examples of their class.[14] Since Diels-Alder methodology[2] has a virtually unlimited potential to construct diverse ring systems, the strategy developed here may be useful in the synthesis of various other electronically interesting cyclic α-amino acids. Our results using **9** in synthesis of polycyclics and peptides will be reported in due course. In the present synthetic approach, both the oxidation of the dimethoxy-xylene ring to the benzoquinone and the subsequent Diels-Alder elaboration to the anthraquinone are performed after a peptide assembly step. Hence the oxidation and annelation conditions are sufficiently mild to permit this "post-translational modification strategy", which serves to impart flexibility to the synthetic preparation of custom quinone containing peptides.



i) KOH, CH_3I, DMSO ii) NBS, benzoyl peroxide, CCl_4, reflux iii) $EtOOCCH_2N{=}CHPh$ $NaN(TMS)_2$, THF, -78 °C iv) 1 M HCl, RT v) Ac-aib-aib(oxazolone), CH_3CN, reflux vi) $(NH_4)_2Ce(NO_3)_6$ CH_3CN/H_2O (1:1), RT vii) NaI (excess), DMF, 65 °C

Scheme 1.

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