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Synthesis of Constrained α-Amino Acid Derivatives *via* Diels-Alder Approach

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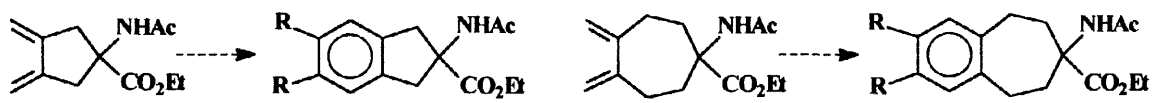
Abstract: Synthesis of new five and seven membered outer ring diene building blocks containing α-amino acid moiety and their usage in the preparation of the constrained amino acid derivatives is described.

Keywords: Alkynes; Amino acids; Diels-Alder reaction; Dienes.

In recent years, constrained α-amino acids (AAAs) have gained widespread use in peptide design. In particular, α,α-disubstituted AAAs are used as a means of controlling secondary structure of peptides [1]. The most extensively investigated member of this class of α-amino acid is Aib (α-aminoisobutyric acid) which has been shown to induce turns (3_{10}) or helices (α-helices) [2]. A logical extension of these studies involving Ac_6c (1-aminocyclo hexane-1-carboxylic acid) has indicated that this AAA residue stabilizes folded/helical structures similar to Aib [3]. Chasing and co-workers synthesized [4] several 2-indanyl-glycine derivatives for analyzing the binding pockets of Phe^7 (S_7) and Phe^8 (S_8), two important aromatic residues for pharmacological properties of substance P (SP). Due to these reasons, availability of several constrained AAA derivatives is valuable for designing constrained analogs of bioactive peptides.



1 3 2 4

As part of our interest in the preparation of constrained AAAs *via* building block approach [5] we have examined the possibility of preparing various dienes containing AAA moiety. In this paper, we report a simple synthesis of outer ring dienes **1** and **2** and their utility in the preparation of various AAA derivatives (e.g., **3** and **4**) *via* Diels-Alder reaction [6]. In addition, the potential for preparing peptides with these dienes appeared worthy of investigation.

We initially focused our attention on the preparation of diene **1** from ethyl 2,2-bis(2-bromoallyl)-glycinate, readily available by dialkylation/hydrolyis of ethyl N-(diphenyl-methylene)glycinate with 2,3-dibromopropene under solid-liquid phase-transfer conditions [7].

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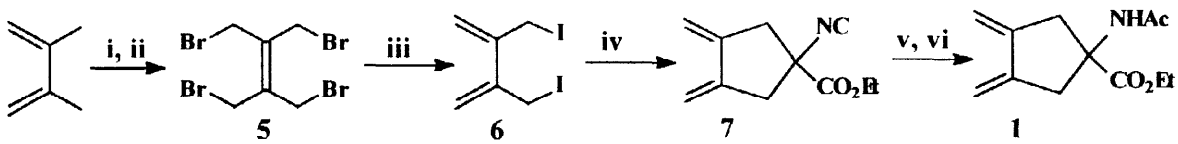
Unfortunately, palladium-induced reductive coupling reaction with polymer supported triphenylphosphine gave several products in our hands. A variety of conditions were probed for this purpose and met with little success [9].

The synthesis of **1** started with the known diiodo compound **6** **(Scheme 1)**. Addition of bromine to 2,3-dimethyl-1,3-butadiene at 0 °C in carbon tetrachloride gave dibromide (highly lacrymator, bp: 60-62 °C/0.2 mm) which upon reaction with NBS in carbon tetrachloride provided the tetrabromide **5** (mp: 152-154 °C). The reductive debromination of **5** with potassium iodide and sodium thiosulphate in acetone gave 2,3-bis(iodomethyl)-1,3-butadiene **6** [10]. Although diene **6** polymerizes readily in the solid state, solution of **6** in ether (0.1 molar) was stable for several months at 0 °C. Reaction of **6** with ethyl isocyanoacetate under mild reaction conditions [11] using NaH/DMSO-ether gave compound **7**. Attempts to purify this isonitrile derivative by silica gel column chromatography results in extensive decomposition. So, it was decided to hydrolyze and protect the resulting amino ester to obtain the diene building block **1** [mp: 93-95 °C, ^{13}C NMR, 75 MHz, $CDCl_3$: δ 14.0 (q), 23.1 (q), 43.4 (t), 61.5 (t), 63.4 (s), 106.3 (t), 144.2 (s), 169.9 (s), 172.4 (s)]. The overall yield of **1** from ethyl isocyanoacetate is 30%.



5 6 7 1

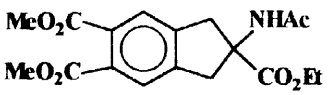
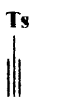
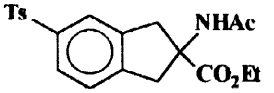
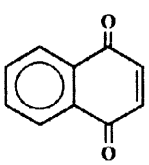
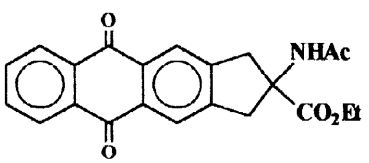
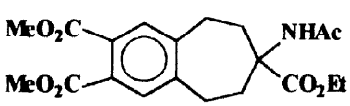
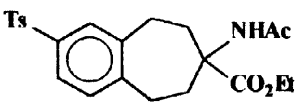
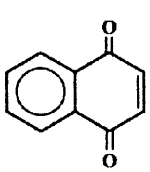
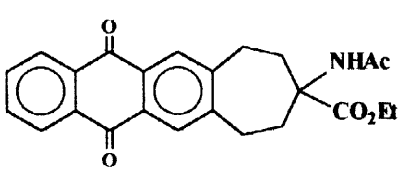
Scheme 1: i) Br_2, CCl_4 / 0 °C ii) NBS, AIBN, CCl_4 / reflux iii) KI, $Na_2S_2O_3$ $5H_2O$, acetone/ 45 °C iv) $CNCH_2CO_2Et$, NaH, DMSO-ether/10°C v) HCl, EtOH vi) Ac_2O, DMAP, CH_2Cl_2

The synthesis of seven membered outer ring diene is outlined in **Scheme 2.** Microwave assisted double ortho ester Claisen rearrangement of 2-butyne-1,4-diol **8** with triethyl orthoacetate and propionic acid in DMF gave diene ester **9** as the major product [12]. Reduction (inverse addition of LAH) of the diester **9** gave diol **10.** On storage (0 °C, within 1-2 weeks) complete polymerization of the diol was observed. But it can be stored for longer period as ethyl acetate solution containing small amount of hydro-quinone. Attempts to prepare dibromide from this diol using phosphorus tribromide was unsuccessful. However the required diiodo compound **11** was obtained *via* tosylation and Finkelstein iodination sequence. Reaction of **11** with ethyl isocyanoacetate under phase-transfer conditions gave the coupling product **12.** Hydrolysis, and DMAP assisted acylation gave the diene building block **2** [mp: 68-69 °C, ^{13}C NMR, 75 MHz, $CDCl_3$: δ 14.2, 23.5, 29.7, 35.8, 61.3, 61.9, 111.0, 149.6, 169.9, 173.8].

Having the two dienes **1** and **2** in hand, we then examined the Diels-Alder reactions of these dienes with the readily available 2π-components. Reaction of dienes **1** and **2** with various dienophiles and subsequent aromatization reaction results are summarized in **Table 1.** Since quinones are important as the biological electron transport chains in photosynthetic systems,

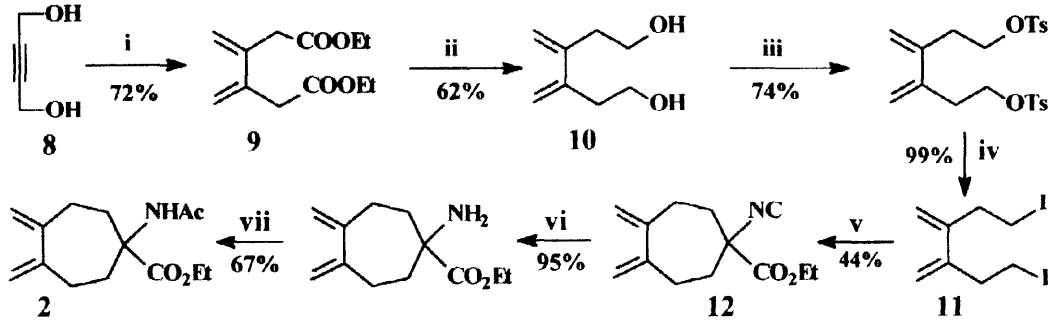
Table: 1

Synthesis of AAAs Using Diene Building Blocks 1 and 2 *via* Diels-Alder Reaction.

S. No.	Dienophile	Aromatized Product	% Yields [a]	^{1}H NMR Data [b]
1			97	1.2 (t, J=7.1, 3H), 1.9 (s, 3H), 3.3 (1/2 ABq, J=17.2, 2H), 3.6 (1/2 ABq, J=17, 2H), 3.9 (s, 6H), 4.2 (q, J=7.1, 2H), 6.1 (s, 1H), 7.5 (s, 2H)
2			96	1.2 (t, J=7.1, 3H), 1.9 (s, 3H), 2.4 (s, 3H), 3.3 (dd, J=17.2, 11.9, 2H), 3.58 (t, J=17, 2H) 6.2(s, 1H), 7.2-7.3 (m, 3H), 7.7-7.8 (m, 4H)
3			89	1.2 (t, J=7.1, 3H), 2.0 (s, 3H), 3.5 (1/2 ABq, J=17.4, 2H), 3.7 (1/2 ABq, J=17.2, 2H), 4.2 (q, J=7.14, 2H), 6.2 (s, 1H), 7.8 (dd, J=5.7, 3.3, 2H), 8.1 (s, 2H), 8.3 (dd, J=5.6, 3.3, 2H)
4			99	1.2 (t, J=7.1, 3H), 2.0 (s, 3H), 1.9-2.3 (m, 4H), 2.7-3 (m, 4H), 3.9 (s, 6H), 4.1 (q, J=7.1, 2H), 5.7 (s, 1H), 7.5 (s, 2H)
5			92	1.2 (t, J=7.1, 3H), 2.0 (s, 3H), 1.9-2.3 (m, 4H), 2.4 (s, 3H), 2.7-2.9 (m, 4H), 4.1 (q, J=7.1, 2H), 5.7 (s, 1H), 7.2-7.3 (m, 3H), 7.6-7.8 (m, 4H)
6			74	1.2 (t, J=7.1, 3H), 2.0 (s, 3H), 2.1-2.4 (m, 4H), 2.9-3.1 (m, 4H), 4.2 (q, J=7.1, 2H), 5.7 (s, 1H) 7.7 (dd, J=5.7, 3.3, 2H), 8.0 (s, 2H), 8.3 (dd, J=5.7, 3.4, 2H)

a Yields refer to combined isolated yields for both the Diels-Alder and DDQ products.

b 300 MHz, $CDCl_3$, δ. Coupling constants (J) are in Hz.



Scheme 2: i) $CH_3C(OC_2H_5)_3$ / DMF μv ii) $LiAlH_4$, THF iii) TsCl, pyridine/0 °C iv) NaI, acetone/Δ v) $CNCH_2CO_2Et$, K_2CO_3, $^nBu_4NHSO_4$, CH_3CN/Δ vi) HCl, EtOH vii) Ac_2O, DMAP, CH_2Cl

these quinones (entry no. 3 and 6) may find useful applications in designing artificial photo-synthetic probes [13]. Similarly alkynyl sulphone group (entry no. 2 and 5) provides an additional handle for further synthetic manipulation [14]. The typical reaction conditions consists of treating the diene and dienophile in benzene at ambient temperatures and the resulting adducts were treated with DDQ [15] in benzene at reflux temperature. The crude product was purified by neutral alumina column chromatography.

Since cyclic structures are at the heart of many challenging compounds, the preparation of dienes **1** and **2** and demonstration of DA strategy reported here may find useful applications in peptide design and peptide modifications.

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