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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. © 1998 Elsevier Science Ltd. All rights reserved.

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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 (3₁₀) or helices (α helices) [2]. A logical extension of these studies involving Ac₆c (1-aminocyclo hexane-1carboxylic 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 Phe⁷ (S₇) and Phe⁸ (S₈), 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.



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(2bromoallyl)-glycinate, readily available by dialkylation/hydrolyis of ethyl N-(diphenylmethylene)glycinate with 2,3-dibromopropene under solid-liquid phase-transfer conditions [7]. 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, ¹³C NMR, 75 MHz, CDCl₃: 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%.



Scheme 1: i) Br₂, CCl₄ / 0 °C ii) NBS, AIBN, CCl₄ / reflux iii) KI, Na₂S₂O₃ 5H₂O, acetone/45 °C iv) CNCH₂CO₂Et, NaH, DMSO-ether/10 °C v) HCl, EtOH vi) Ac₂O, DMAP, CH₂Cl₂

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, ¹³C NMR, 75 MHz, CDCl₃: 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,

S. No.	Synthesis of A Dienophile	AAAs Using Diene Building Block Aromatized Product	s 1 and 2 <i>via</i> 1 % Yields ^a	¹ H NMR Data ^b
· 1	CO2Me CO2Me	MeO2C NHAC MeO2C CO2E	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	Ts 	Ts NHAC CO2Et	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			e 89 Øt	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	CO ₂ Me CO ₂ Me	MEO2C MEO2C NHAc CO2Et	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	Ts 	Ts NHAc CO ₂ Br	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)

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

a Yields refer to combined isolated yields for both the Diels-Alder and DDQ products. b 300 MHz, CDCl₃, δ . Coupling constants (J) are in Hz.



v) CNCH₂CO₂Et, K₂CO₃, ⁿBu₄NHSO₄, CH₃CN/Δ vi) HCl, EtOH vii) Ac₂O, DMAP, CH₂Cl

these quinones (entry no. 3 and 6) may find useful applications in designing artificial photosynthetic 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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References:

- [1] Wysong CL, Yokum TS, McLaughlin, Hammer RP. Chemtech. 1997:26.
- [2] Balaram P. Curr. Opin. Struct. Biol. 1992;2:845.
- [3] Toniolo C, Crisma M, Fabiano N, Melchiorri P, Negri L, Krause JA, Eggleston DS. Int. J. Peptide Protien Res 1994;44:85.
- [4] Josien H, Lavielle S, Brunissen A, Saffroy M, Torrens Y, Beaujouan J-C, Glowinski J, Chassaing, G. J. Med. Chem. 1994;37:1556.
- [5] Kotha S, Brahmachary E. Tetrahedron Lett. 1997;38:3561.
- [6] Carruthers W. Cycloaddition Reactions in Organic Synthesis, Oxford: Pergamon Press, 1990; Fringuelli F, Taticchi
 A. Dienes In The Diels-Alder Reaction, New York: John Wiley, 1990.
- [7] Moreno-Manas M, Pleixats R, Roglans, A. Liebigs Ann. 1995:1807; Kotha S, Brahmachary, E. Bioorg. & Med. Chem. Lett. 1997;7:2719 and references cited therein.
- [8] Grigg R, Stevenson P, Workun T. Tetrahedron 1988;44;2049 and references cited there in.
- [10] Hamon DPG, Spurr PR. Synthesis 1981:873 and references cited therein.
- [11] Kalvin D, Ramalingam K, Woodard R. Synth. Commn. 1985;15:267.
- [12] Srikrishna A, Nagaraju S, Kondaiah P. Tetrahedron 1995;51:1809.
- [13] Kotha S, Kuki A. Chem. Lett. 1993:299: Tamiaki H, Maruyama K. Chem. Lett. 1993;1499.
- [14] Simpkins NS, Sulphones in Organic Synthesis, Oxford: Pergamon Press, 1990.
- [15] Fu PP, Harvey RG. Chem. Rev. 1978;78:317.