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A Diels–Alder approach for the synthesis of highly functionalized benzo-annulated indane-based α-amino acid derivatives via a sultine intermediate

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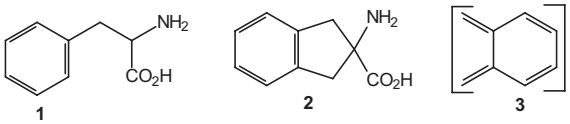
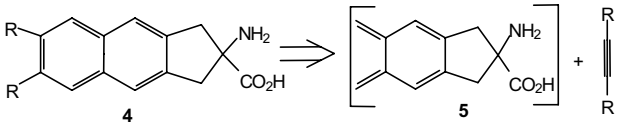
Abstract—The synthesis of various highly functionalized benzo-annulated indane-based α-amino acid (AAA) derivatives are reported via a [4+2] cycloaddition strategy using a sultine derivative, containing an AAA moiety, as a reactive diene component. By adopting this strategy, a new α,α-dialkylated indane-based C_{60} fullerene containing a constrained AAA unit is reported.

The development of new methodologies for the synthesis of unusual α-amino acid (AAA) derivatives has direct impact generating modified peptides suitable for therapeutic studies.[1] The traditional routes such as the Bucherer–Berg (BB) method for synthesizing unusual cyclic AAA derivatives are not suited for a wide substitution pattern. To overcome these problems, we have reported a 'Building Block Approach'[2] that has tremendous flexibility to generate molecular diversity and is also suitable for a combinatorial approach. In this regard, we proposed *o*-xylylene[3] (or *o*-quinodimethane) intermediate **5** containing an AAA moiety as a useful reactive intermediate for the generation of various benzo-annulated indane-based AAA derivatives (e.g., **4**). Indane-based AAA derivatives (e.g., **2**) are a special class of constrained phenylalanine derivatives **1**, used in several instances to modify various biologically active peptides.[4a,b,c] Also, indane-based AAAs are useful building blocks to design 'ladder-like' parallel tapes in crystal engineering studies.[4d]





Scheme 1.

Realization of our proposition as shown in Scheme 1 depends on finding suitable conditions to generate the key precursor **5**. Although there are several methods available for the generation of the parent *o*-xylylene **3**[3] from benzocyclobutene and its related compounds, these methods are not applicable for an intermediate of type **5** due to the presence of the two reactive functional groups, the amino and carboxylic acid groups. Our initial experiments to prepare *o*-xylylene intermediates containing an AAA moiety from benzocyclobutene intermediates were not encouraging.[5] Similarly, efforts to generate **5** from the dibromo derivative **7** were also not successful. In view of our favorable experience with sultine intermediates that can be trapped with a dienophile containing an AAA moiety, we focused our attention towards the generation of **5** via a sultine intermediate. Compounds such as **4** can be synthesized by the BB[6] method starting from a benzo-fused 2-indanone derivative which involves drastic hydrolysis conditions. For this reason, the synthesis of many sensitive substrates is not possible and therefore, only a limited number of derivatives are available. In this

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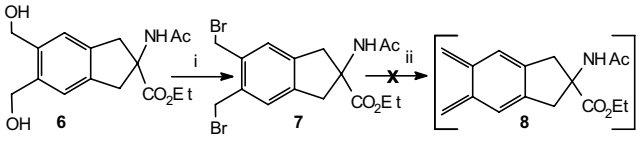
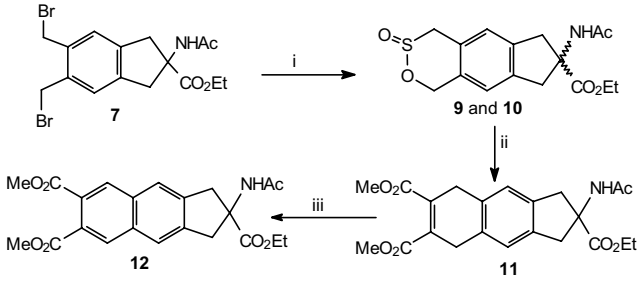
communication, we report our results toward the synthesis of highly functionalized benzo-annulated indane-based (AAA) derivatives such as **4** by trapping a diene derivative related to **5** with various dienophiles, including C_{60} fullerene, via a [4+2] cycloaddition strategy as shown in Scheme 1. A sultine-based approach for the synthesis of polycyclic compounds by the Diels–Alder (DA) strategy is known in the literature.[7] However, there are no reports in the literature where the sultine derivatives also contain an AAA moiety. To expand our 'Building Block Approach' for highly functionalized benzo-annulated indane-based AAA derivatives, generation of **5** via sultine derivative **9** (or **10**) is an attractive proposition due to the wide scope of DA methodology in combinatorial synthesis.[4f] In this regard, recently, we have reported various tetralin-based AAA derivatives.[8]

For the synthesis of compound **4**, the required dibromo derivative **7** was prepared from the diol **6**[9] using PBr_3. Several attempts to generate *o*-xylylene intermediate **8** from the dibromide **7** under different reaction conditions[10] were unsuccessful (Scheme 2). Reaction of the dibromide **7** with sodium hydroxy methanesulfinate (rongalite)[11] in the presence of tetrabutylammonium bromide (TBAB) in DMF at 0 °C gave isomeric sultine-based AAA derivatives **9** (mp 180–181 °C) and **10** (mp 198–199 °C) in 72% combined yield (1:1). The two isomers **9** and **10** have very similar IR, ^{1}H NMR, ^{13}C NMR, HRMS, and UV spectra and it was not possible to assign their exact stereochemistry with the available data. Isomers **9** and **10** are presumably diastereoisomers (each as a racemic mixture). Having sultines **9** and **10** in hand, we tested their potential as *o*-xylylene equivalents. Separately, both sultines **9** and **10** were treated with dimethyl acetylenedicarboxylate (DMAD) in xylene at 120 °C to give the DA adduct, which on aromatization under DDQ oxidation conditions gave **12** (Scheme 3).

Along similar lines, the sultine **9** (or **10**) was reacted with various other dienophiles to deliver the corresponding DA adducts, which on subsequent oxidation gave aromatized products (**13**–**16**) (Table 1).[13,14] Since we observed partial aromatization during the DA reactions, no attempts were made to identify the DA adducts.

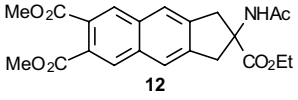
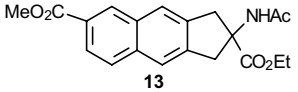
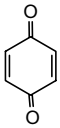
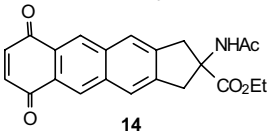
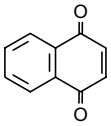
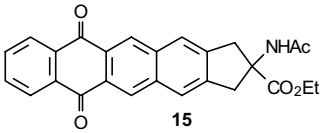
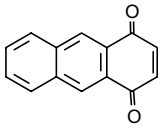
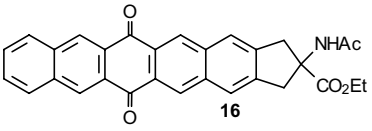


Scheme 2. Reagents and conditions: (i) PBr_3, C_6H_6, rt, 81%; (ii) Dimethyl acetylenedicarboxylate, Zn, ultrasound or NaI, DMF, or Bu_4NI or KI, 18-crown-6.

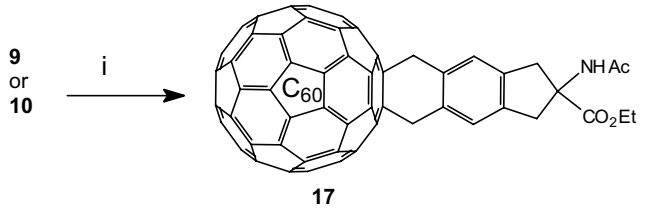


Scheme 3. Reagents and conditions: (i) Rongalite, TBAB, DMF, 0 °C, 72%; (ii) DMAD, toluene, 120 °C; (iii) DDQ, C_6H_6, 80 °C, 78%.

Table 1. List of various benzo-annulated indane-based AAA derivatives prepared by DA/DDQ oxidation strategy

S. No.	Dienophile	DDQ product	Yield[a] (%)
1		 **12**	78
2		 **13**	43
3		 **14**	90
4		 **15**	89
5		 **16**	92

[a] Yields refer to final isolated yields for both the DA reaction and DDQ oxidation.



Scheme 4. Reagents and conditions: (i) C_{60}, toluene, 120 °C.

In view of various applications of fullerene-based AAA derivatives in bioorganic chemistry,[12] we turned our attention to incorporate the AAA moiety in a fullerene system. In this context, sultine **9** (or **10**) was reacted with Buckministerfullerene (C_{60}) in toluene at reflux temperature to give a DA product **17** in 49% yield. NMR spectra and the FAB mass spectral data (M+H, 994) of the adduct **17** were in agreement with the mono-adduct (Scheme 4).

In conclusion, we have shown that *o*-xylylene derivatives containing an AAA moiety derived from sultine **9** (or **10**) can been trapped with various dienophiles. It is worth mentioning that compounds of type **14**–**16** are not accessible by the currently available BB method due to the presence of keto functionalities. Moreover, the synthesis of the starting keto precursor required for the BB method is not a trivial exercise. For the first time, we have demonstrated an easy access to an indane-based fullerene-containing AAA derivative. The methodology reported here may be extended to the synthesis of a new class of benzo-annulated AAA derivatives that may play an important role in the design of biologically active peptides.

Acknowledgements

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References and notes

1. Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720; Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1–19; Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267; Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732; Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585–615; Nájera, C. *Synlett* **2002**, *9*, 1388–1403.
2. Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342–351, and references cited therein.
3. Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proc. Int.* **1991**, *23*, 237–272; Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199–3246, and references cited therein; Mehta, G.; Kotha, S. *Tetrahedron* **2001**, *57*, 625–659.
4. (a) Josien, H.; Lavielle, S.; Brunissen, A.; Saffroy, M.; Torrens, Y.; Beaujouan, J.-C.; Glowinski, J.; Chassaing, G. *J. Med. Chem.* **1994**, *37*, 1586–1601; (b) Torrini, I.; Zecchini, G. P.; Paradisi, M. P.; Lucente, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G.; Spisani, S.; Giuliani, A. L. *Int. J. Peptide Protein Res.* **1991**, *38*, 495–504; (c) Gavuzzo, E.; Lucente, G.; Mazza, F.; Zecchini, G. P.; Paradisi, M. P.; Pochetti, G.; Torrini, I. *Int. J. Peptide Protein Res.* **1991**, *37*, 268–276; (d) Kloster, R. A.; Carducci, M. D.; Mash, E. A. *Org. Lett.* **2003**, *5*, 3683–3686; (e) Tellenbroker, J.; Kuck, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 919–922; (f) Seneci, P. In *Solid-Phase Synthesis and Combinatorial Technologies*; John Wiley and Sons: New York, 2000, and references cited therein.
5. Kotha, S.; Sreenivasachary, N.; Halder, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2565–2568.
6. Trigalo, F.; Biusson, D.; Azerad, R. *Tetrahedron Lett.* **1988**, *29*, 6109–6112.
7. Dittmer, D. C.; Hoey, M. D. *J. Org. Chem.* **1991**, *56*, 1947–1948; Illescas, B.; Martin, N.; Seoane, C.; Cruz, P. la de; Langa, F.; Wudi, F. *Tetrahedron Lett.* **1995**, *36*, 8307–8310; Illescas, M. B.; Martin, N.; Seoane, C.; Orti, E.; Virula, M. P.; Virula, R.; de la Hoz, A. *J. Org. Chem.* **1997**, *62*, 7585–7591; Chung, W.-S.; Lin, W.-J.; Liu, W.-D.; Chen, L.-G. *Chem. Commun.* **1995**, 2537–2539; Chung, W.-S.; Liu, J.-H. *Chem. Commun.* **1997**, 205–206; Liu, J.-H.; Wu, A.-T.; Huang, M.-H.; Wu, C.-W.; Chung, W.-S. *J. Org. Chem.* **2000**, *65*, 3395–3403; Liu, W.-D.; Chi, C.-C.; Pai, I.-F.; Wu, A.-T.; Chung, W.-S. *J. Org. Chem.* **2002**, *67*, 9267–9275.
8. Kotha, S.; Ganesh, T.; Ghosh, A. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1755–1757.
9. Kotha, S.; Brahmachary, E. *Tetrahedron Lett.* **1997**, *38*, 3561–3564.
10. Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030–5032; Thomas, A. D.; Miller, L. L. *J. Org. Chem.* **1986**, *51*, 4160–4169; Hermann, A. D.; Diederich, F.; Thilgen, C.; ter Meer, H.-U.; Meuller, W. H. *Helv. Chim. Acta* **1994**, *77*, 1689–1706; Belik, P.; Guegel, A.; Kraus, A.; Walter, M.; Muellen, K. *J. Org. Chem.* **1995**, *60*, 3307–3310.
11. Jarvis, W. F.; Dittmer, D. C. *J. Org. Chem.* **1983**, *48*, 2784–2786; Jarvis, W. F.; Hoey, M. D.; Finocchio, A. L.; Dittmer, D. C. *J. Org. Chem.* **1988**, *53*, 5750–5756.
12. Ros, T. D.; Prato, M. *Chem. Commun.* **1999**, 663–669; Bianco, A.; Ros, T. D.; Prato, M.; Toniolo, C. *J. Pept. Sci.* **2001**, *7*, 208–219; Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449.
13. General procedure for the Diels–Alder (DA) reaction of the sultine derivative with various dienophiles and subsequent DDQ oxidation of the DA adducts. A solution of sultine (1 equiv) and dienophile (2–3 equiv) in toluene was refluxed until the starting material had been consumed. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography. Elution of the column with ethyl acetate/petroleum ether mixture gave the required DA adduct. Subsequently, the DA adduct (1 equiv) and DDQ (1.5–2 equiv) in dry benzene were refluxed (22–48 h). The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 2% KOH, water, brine, and dried with $MgSO_4$. The solvent was evaporated and the crude product was charged on a silica gel column. Elution of the column with ethyl acetate/petroleum ether gave the desired product.
14. All new compounds were fully characterized by their spectral data. ^{1}H NMR (300 MHz, $CDCl_3$) spectral data of all new compounds are given here. **7** $\delta = 1.25$ (t,

$J = 7.1$ Hz, 3H), 1.96 (s, 3H), 3.25 (d, $J = 16.8$ Hz, 2H), 3.61 (d, $J = 16.8$ Hz, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 4.65 (s, 4H), 6.03 (s, 1H), 7.21 (s, 2H). **9** $\delta = 1.24$ (t, $J = 7.3$ Hz, 3H), 1.95 (s, 3H), 3.30 (d, $J = 16.8$ Hz, 2H), 3.53 (d, $J = 15.4$ Hz, 1H), 3.62 (d, $J = 16.8$ Hz, 2H), 4.22 (q, $J = 7.3$ Hz, 2H), 4.40 (d, $J = 15.3$ Hz, 1H), 4.92 (d, $J = 13.5$ Hz, 1H), 5.27 (d, $J = 13.2$ Hz, 1H), 6.11 (s, 1H), 7.12 (s, 1H), 7.14 (s, 1H). **10** $\delta = 1.24$ (t, $J = 7.2$ Hz, 3H), 1.95 (s, 3H), 3.27 (d, $J = 16.8$ Hz, 2H), 3.54 (d, $J = 15.3$ Hz, 1H), 3.63 (d, $J = 16.8$ Hz, 2H), 4.21 (q, $J = 7.2$ Hz, 2H), 4.31 (d, $J = 15.2$ Hz, 1H), 4.92 (d, $J = 13.5$ Hz, 1H), 5.23 (d, $J = 13.5$ Hz, 1H), 6.15 (s, 1H), 7.07 (s, 1H), 7.10 (s, 1H). **12** $\delta = 1.23$ (t, $J = 6.9$ Hz, 3H), 1.95 (s, 3H), 3.49 (d, $J = 16.8$ Hz, 2H), 3.71 (d, $J = 16.8$ Hz, 2H), 3.94 (s, 6H), 4.21 (q, $J = 6.9$ Hz, 2H), 6.11 (s, 1H), 7.67 (s, 2H), 8.11 (s, 2H). **13** $\delta = 1.25$ (t, $J = 7.3$ Hz, 3H), 1.95 (s, 3H), 3.49 (dd, $J = 16.8$, 5.1 Hz, 2H), 3.71 (dd, $J = 17.2$, 7.1 Hz, 2H), 3.97 (s, 3H), 4.23 (q, $J = 7.3$ Hz, 2H), 6.0 (s, 1H), 7.69 (s, 1H), 7.75 (s, 1H), 7.8 (d, $J = 8.4$ Hz, 1H), 8.0 (dd, $J = 8.4$, 1.5 Hz, 1H), 8.53 (s, 1H). **14** $\delta = 1.23$ (t, $J = 7.1$ Hz, 3H), 1.98 (s, 3H), 3.55 (d, $J = 17.4$ Hz, 2H), 3.77 (d, $J = 17.4$ Hz, 2H), 4.23 (q, $J = 7.1$ Hz, 2H), 6.16 (s, 1H), 7.04 (s, 2H), 7.85 (s, 2H), 8.52 (s, 2H). **15** $\delta = 1.25$ (t, $J = 7.3$ Hz, 3H), 1.99 (s, 3H), 3.56 (d, $J = 17.2$ Hz, 2H), 3.78 (d, $J = 17.2$ Hz, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 6.16 (s, 1H), 7.81–7.85 (m, 2H), 7.88 (s, 2H), 8.37–8.41 (m, 2H), 8.75 (s, 2H). **16** $\delta = 1.25$ (t, $J = 7.3$ Hz, 3H), 1.99 (s, 3H), 3.57 (d, $J = 17.2$ Hz, 2H), 3.79 (d, $J = 17.2$ Hz, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 6.11 (s, 1H), 7.70–7.73 (m, 2H), 7.92 (s, 2H), 8.12–8.15 (m, 2H), 8.86 (s, 2H), 8.94 (s, 2H). **17** $\delta = 1.25$ (br s, 3H), 2.03 (s, 3H), 3.47 (d, $J = 16.0$ Hz, 2H), 3.79 (d, $J = 16.0$ Hz, 2H), 4.26 (q, $J = 7.3$ Hz, 2H), 4.40 (d, $J = 14.1$ Hz, 2H), 4.78 (d, $J = 14.1$ Hz, 2H,), 6.14 (s, 1H), 7.51 (s, 1H).