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Synthesis of benzocycloheptene-based amino acid derivatives via a [4+2] cycloaddition reaction as a key step

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Abstract—The seven-membered diene **5** is prepared from 2-butyne-1,4-diol using double orthoester Claisen rearrangement reaction as a key step. The Diels–Alder reaction of the diene **5** with various dienophiles followed by oxidation delivered the benzocycloheptene-based α-amino acid derivatives in very good yields. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Cyclic αα-dialkylated amino acids (αα-AAs) are considered to be a special class of αα-AAs. Surprisingly only the simplest members of this class have been used in the peptide arena.[1,2] This is probably due to the non-availability of the general methods for their synthesis in the literature. In view of these facts we have been engaged in the development of new methodologies for the synthesis of unusual α-amino acids (AAAs) via 'building block approach'.[3]

To expand the building block approach that provides various unusual AAAs via Diels–Alder strategy, it is desirable to develop new methods for the preparation of various dienes containing AAA moiety. During the course of our investigations, few conjugate dienes (**1**–**4**, Fig. 1) embodying AAA unit appeared in the literature.[4–7] Unfortunately there is not much information available about Diels–Alder chemistry of these dienes. Nevertheless, the Diels–Alder reaction of these dienes (except **4**) will not provide cyclic ααAAs, however they can be employed for the synthesis of various phenylalanine (Phe) or phenylglycine (with **3**) analogs (Fig. 1).

2. Strategy

In order to extend the Diels–Alder methodology towards the synthesis of benzocycloheptene derived AAA derivatives, the seven-membered diene building block **5** synthesis was undertaken. The [4+2] cycloaddition reaction of exocyclic diene **5** with suitable dienophiles followed by oxidation is expected to provide the benzocycloheptene based amino acid derivatives (Scheme 1).

3. Results and discussion

The key diene **8** was prepared according to the literature procedure involving a double orthoester Claisen rearrangement as a key step (Scheme 2).[8] Thus the microwave[9] assisted *ortho* Claisen rearrangement of 2-butyne-1,4-diol **7** with triethyl orthoacetate in presence of catalytic amount of propionic acid gave the diethyl 3,4-bismethyleneadipate **8** as a major product. Reduction of compound **8** with $LiAlH_4$ in dry THF gave the corresponding diol **9** in 62% isolated yield. Initially, when the reaction was quenched with ethyl acetate, diacetoxy derivative **10** (60%) was obtained as the sole product. Later on, the diacetoxy derivative **10** was hydrolyzed to diol **9** (88%) using KOH/MeOH conditions (Scheme 2).

Attempts to convert the diol **9** to the corresponding dibromide under PBr_3/ether conditions[10] were not successful. Consequently, the reaction of diol **9** with tosyl chloride in

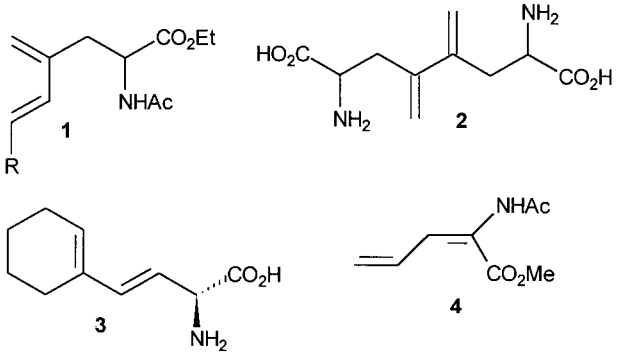

Figure 1.

Keywords: amino acids and derivatives; cycloadditions; dienes; Diels–Alder reaction drugs.

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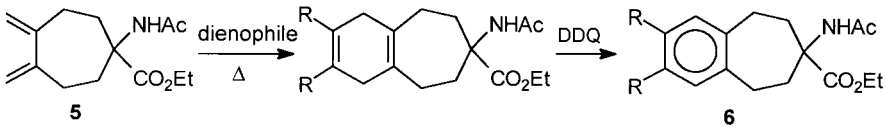
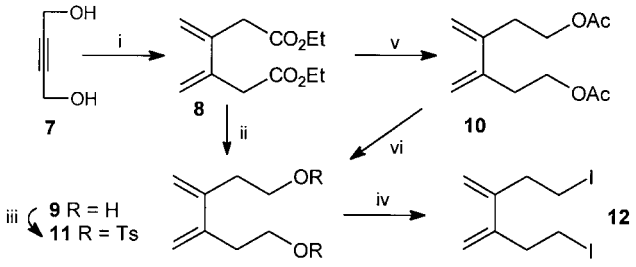


Scheme 1.



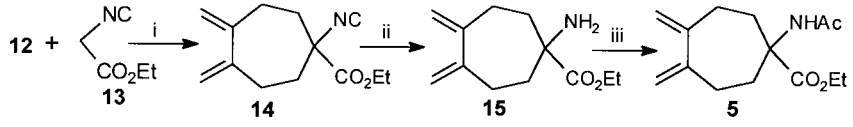
Scheme 2. (i) $HCC(OEt)_3$, AcOH, DMF, μW; (ii) $LiAlH_4$, THF, rt; (iii) TsCl, pyridine, 0°C; (iv) NaI, acetone, 70°C; (v) (1) $LiAlH_4$, THF, (2) EtOAc, rt; (vi) KOH, MeOH, rt.

presence of pyridine gave the ditosylate **11** in 74% yield[11] which, upon reaction with NaI in acetone at reflux, gave the corresponding diiodide **12** (Scheme 2). The diiodide **12** can be purified by silica gel column chromatography and used within a couple of days. It was usually stored at low temperature in diethyl ether solvent. Thus, bis-alkylation of ethyl isocyanoacetate **13** with diiodide **12** under phase transfer catalysis (PTC) conditions gave the required coupling product **14** (Scheme 3). Since the isonitrile derivative **14** was found to be unstable, it was immediately hydrolyzed to the corresponding amino ester **15** using conc. HCl in absolute ethanol. The amino ester **15** was further converted to the *N*-acetyl derivative **5** in 67% yield by using acetic anhydride in dichloromethane (Scheme 3).

The dienes in this series (**9**, **12**, **14**, **15** and **5**) were found to be unstable and can be stored in presence of catalytic amount of hydroquinone at low temperature. Diene **5** was treated with the various dienophiles in refluxing benzene and the resulting adducts were subjected to DDQ oxidation to give the benzocycloheptene derived AAAs in good yields (**16**–**18**, Table 1). Since the Diels–Alder adducts in these cases are contaminated with the corresponding aromatized products as indicated by the ^1H NMR spectral data, we did not made any special attempts to isolate the adducts (Table 1).

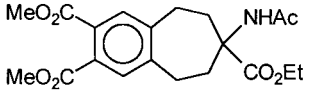
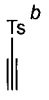
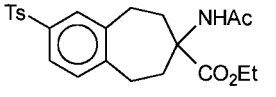
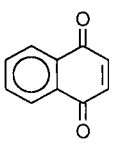
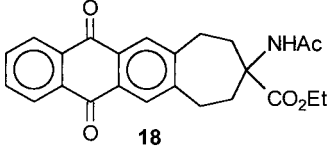
4. Conclusions

To conclude, a new and general synthetic methodology was developed for the synthesis of linearly substituted benzocycloheptene-based ααAA derivatives. The ααAA derivatives prepared here may not be accessible by any other conventional methods such as Bucherer Burg method.[12]



Scheme 3. (i) K_2CO_3, Bu_4NHSO_4, CH_3CN, 70°C; (ii) HCl, EtOH; (iii) Ac_2O, CH_2Cl_2, rt.

Table 1. Synthesis of benzocycloheptene-based α-amino acid derivatives via [4+2] cycloaddition strategy using diene **5**

S. No	Dienophile	Aromatized Product	Yield % [a]
1		 **16**	99
2	 **19**	 **17**	92
3		 **18**	74

[a] Yields refers to combined isolated yields for both the Diels–Alder and DDQ products.
[b] Ts=*p*-toluene sulfonyl.

5. Experimental

5.1. General

Dry diethyl ether, tetrahydrofuran, benzene and toluene were obtained by distilling over benzophenone ketyl. Chloroform, dichloromethane, and acetonitrile were distilled over phosporus pentoxide. Ethyl isocyanoacetate and DDQ were purchased from Aldrich Chemical Co. $LiAlH_4$ was obtained from Fluka.

Precaution. Ethyl isocyanoacetate and electrophiles used in this study are lacrymators and irritants and must be handled with proper care. Some of them are also potent mutagens.

5.1.1. 3,4-Bismethylene-1,6-hexanediol (9). A pre-dried three-neck RB flask (250 ml) equipped with an additional funnel was charged with diethyl ester **8**[8] (1.5 g, 6.6 mmol) in dry THF (10 ml). A stirred suspension of $LiAlH_4$ (1.7 g, 44.8 mmol) in dry THF (40 ml) was transferred to the additional funnel with the aid of double ended needle under N_2 pressure, then slowly added to a stirred solution of the reaction mixture over a period of 30 min at rt under N_2 atmosphere. The reaction mixture was then stirred at rt for 4 h. The reaction mixture was very cautiously poured into ice-cold water (40 ml) and extracted with ethyl acetate (100 ml). The combined organic extract was washed with 2 M HCl, water, brine and then dried over $MgSO_4$. Evaporation of the solvent and purification of the crude product by a silica gel column using ethyl acetate/hexane (1:3) as an eluent gave diol **9** (590 mg, 62%) as a colorless liquid. IR (neat): ν_{max} 3345, 1635 cm^{-1}. R_f (50% EtOAc/hexane) 0.301. ^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (br s, 2H), 2.56 (t, J=6.2 Hz, 4H) 3.73 (t, J=6.2 Hz, 4H), 5.09 (s, 2H), 5.18 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 37.6, 61.2, 114.5, 143.8. MS: *m/e* 142 (M^+).

In a separate experiment, when the reaction mixture was quenched with ethyl acetate, diacetoxy derivative **10** was obtained in 60% yield as a light yellow liquid, which was again converted to diol **9** as described in the following experiment. IR (neat): ν_{max} 1740, 1598, 1456 cm^{-1}. R_f (30% EtOAc/hexane) 0.40 ^1H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 6H), 2.60 (t, J=7.1 Hz, 4H), 4.16 (t, J=7.1 Hz, 4H), 5.06 (s, 2H) 5.21 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): 20.9, 33.3, 63.3, 114.3, 142.8, 171.0. MS: *m/e* 226 (M^+).

5.1.2. Hydrolysis of diacetoxy derivative (10) to diol (9). To a solution of **10** (55 mg, 0.24 mmol) in methanol (5 ml) was added finely grounded KOH (32 mg, 0.6 mmol) at rt. The reaction mixture was allowed to stir at rt for 30 min. The solvent was evaporated at reduced pressure and the residue was dissolved in water and extracted with ether. The combined ether extract was washed with water, brine and then dried over $MgSO_4$ Evaporation of the solvent gave diol **9** as a colorless liquid (30 mg, 88%) whose IR and ^1H NMR spectral data were found to be identical to that of the material obtained in the experiment where the $LiAlH_4$ reaction was quenched carefully with water.

5.1.3. Conversion of the diol (9) to ditosylate (11). To a stirred solution of **9** (490 mg, 4.6 mmol) in pyridine (5 ml) was added TsCl (1.21 g, 6.9 mmol) in five portions at 0°C. The reaction mixture was stirred at rt for 3 h and then poured into ice cold water (5 ml). The aqueous solution was extracted with ethyl acetate and the combined organic extract was washed with water, brine and dried over $MgSO_4$. Evaporation of the solvent furnished the ditosylate **11** (1.13 g, 74%) as a crystalline solid. Mp, 99–100°C. R_f (35% EtOAc/hexane) 0.32. IR: (KBr) ν_{max} 3012, 1598 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 6H,), 2.56 (t, J=7.1 Hz, 4H), 4.06 (t, J=7.1 Hz, 4H), 4.96 (s, 2H), 5.08 (s, 2H), 7.34 (d, J=8.4 Hz, 4H), 7.77 (d, J=8.4 Hz, 4H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 21.1, 32.8, 68.2, 114.8, 127.3, 129.3, 132.5, 140.1, 144.3.

5.1.4. 3,4-Bismethylene-1,6-diiodohexane (12). To a stirred solution of ditosylate **11** (1 g, 2.2 mmol) in acetone (50 ml) was added sodium iodide (1.97 g, 14 mmol) and the reaction mixture was heated at 70°C for 8 h. The reaction mixture was cooled and the solvent was evaporated on rotary evaporator at reduced pressure. The residue was dissolved in water and then extracted with ethyl acetate. The combined organic extracts were washed with aq. sodium thiosulfate solution, water, brine and then dried over $MgSO_4$. Evaporation of the solvent and purification of the crude product by a silica gel column using ethyl acetate/hexane (1:49) as an eluent furnished the diiodide **12** (757 mg, 99%) as a light yellow liquid. IR (neat): ν_{max} 3012, 1590, 890 cm^{-1}. R_f (10% EtOAc/hexane) 0.58. ^1H NMR (300 MHz, $CDCl_3$): δ 2.81 (t, J=7.8 Hz, 4H), 3.26 (t, J=7.8 Hz, 4H), 5.06 (s 2H), 5.18 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 4.06, 38.5, 114.4, 144.6.

5.1.5. Ethyl 4,5-dimethylene-1-isocyanocyclohepta-1-carboxylate (14). A heterogeneous solution of diiodide **12** (494 mg, 1.365 mmol), ethyl isocyanoacetate **13** (153 mg, 1.36 mmol), potassium carbonate (1.5 g, 10.9 mmol) and tetrabutylammonium hydrogensulfate (91 mg, 0.2 mmol) in dry acetonitrile (60 ml) was refluxed for 3.5 days. The reaction mixture was cooled and the solid material was filtered off. The filtrate was evaporated at reduced pressure and the residue left was dissolved in ether (120 ml) and washed with water, brine and then dried over $MgSO_4$. Evaporation of the solvent and purification of the crude product by a silica gel column using ethyl acetate/hexane (1:40) as an eluent gave first unreacted starting material **12** (50 mg). Further elution of the column furnished the isonitrile derivative **14** (107 mg, 36%), as a light brown liquid (40% based on the recovered starting material).

IR (neat): ν_{max}, 2137, 1735, 3105 cm^{-1} R_f (10% EtOAc/hexane) 0.50. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H), 1.92 (m, 2H), 2.16 (dd, J=6.8, 14.0 Hz, 2H) 2.40 (dd, J=6.8, 14.0 Hz, 2H), 2.60 (m, 2H), 4.23 (q, J=7.2 Hz 2H), 4.81 (s, 2H), 5.22 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 13.9, 29.5, 37.7, 62.7, 67.7, 111.7, 131.2, 148.3, 162.3.

5.1.6. Hydrolysis of the isonitrile derivative (14) to amino ester (15). A solution of **14** (80 mg, 0.36 mmol) in absolute ethanol (5 ml) was added conc. HCl (5 drops) at 0°C and the reaction mixture was stirred at rt for 1 h. Then the solvent was evaporated and the residue was dissolved in water (5 ml). The acidic aq. solution was basified by addition of ammonia solution. Then it was extracted with ethyl acetate.

The combined organic extract was washed with water, brine and then dried over $MgSO_4$. Evaporation of the solvent gave pure amino ester **15** (72 mg, 95%) as a colorless liquid which was used in subsequent protection step without further purification. R_f (40% EtOAc/hexane) 0.50.

5.1.7. Ethyl 1-acetamido-3,4-dimethylenecyclohepta-1-carboxylate (5). A solution of the amino ester **15** (50 mg, 0.24 mmol), acetic anhydride (50 mg, 0.5 mmol) and DMAP (10 mg) in dichloromethane (5 ml) was stirred at rt for 1 h. The solvent was evaporated and the crude material was directly charged on a silica gel column. Elution of the column with ethyl acetate/hexane (1:9) mixture gave the acetyl derivative **5** (40 mg, 67%) as a white crystalline solid. Mp, 68–69°C. IR (neat): ν_{max} 1740, 1648 cm^{-1}. R_f (50% EtOAc/hexane) 0.50. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=7.1 Hz, 3H), 2.01 (s, 3H), 1.86–2.05 (m, 2H), 2.17–2.31 (s, 2H), 2.31–2.39 (m, 4H), 4.15 (q, J=7.1 Hz, 2H), 4.78 (d, J=1.5 Hz, 2H), 5.18 (d, J=1.5 Hz, 2H), 5.61 (s, 1H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.2, 23.4, 29.7, 35.8, 61.3, 61.8, 111.0, 149.5, 169.8, 173.8.

5.1.8. Ethyl 3-acetamido-7,8-dicarbomethoxybenzocycloheptane-3-carboxylate (16). A solution of diene **5** (10 mg, 0.04 mmol) and DMAD (5.6 mg, 0.06 mmol) in dry benzene (2 ml) was refluxed for 4 days. Then the solvent was evaporated and the crude product was purified by a silica gel column using ethyl acetate/hexane (2:3) as an eluent to give cycloadduct (15.6 mg, 99.9%) as a white solid. Mp, 144–145°C. Subsequently the cycloadduct (12 mg, 0.03 mmol) and DDQ (7 mg, 0.03 mmol) in dry benzene (3 ml) was refluxed for 48 h. Then, the solvent was evaporated and the crude product was purified by a neutral alumina column using ethyl acetate/hexane (2:3) mixture as an eluent to give **16** (11.8 mg, 99%) as a white sticky solid. UV ($CHCl_3$): λ_{max} ($\in M^{-1}\,cm^{-1}$) 248 (2500) nm. IR (KBr): ν_{max} 3296, 1730, 1660 cm^{-1}. R_f (75% EtOAc/hexane) 0.43. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=7.1 Hz, 3H), 2.06 (s, 3H), 1.99–2.11 (m, 2H), 2.26–2.33 (m, 2H), 2.77–3.00 (m, 4H), 3.89 (s, 6H), 4.15 (q, J=7.1 Hz, 2H), 5.72 (s, 1H), 7.47 (s, 2H). FAB-MS: *m/e* 391 (M^+). HRMS (EI) *m/z* for $C_{20}H_{25}NO_7$ Calcd: 391.1631; Found: 391.1617.

5.1.9. Ethyl 3-acetamido-7-*p*-toluenesulfonylbenzocycloheptane-3-carboxylate (17). A solution of the diene **5** (8.5 mg, 0.03 mmol) and sulfone **19** (6.8 mg, 0.03 mmol) in dry benzene (5 ml) was refluxed for 48 h. Evaporation of the solvent and purification of the crude product by a silica gel column using ethyl acetate/hexane (2:3) as an eluent gave the Diels–Alder adduct (14.1 mg, 94%) as sticky solid. The adduct was dissolved in dry benzene (3 ml), DDQ (12 mg, 0.02 mmol) added, and the mixture was refluxed for 48 h. Evaporation of the solvent and purification of the crude product by a silica gel column using ethyl acetate/hexane (2:3) as an eluent gave the aromatized product **17** (11.3 mg, 94%) as a gummy solid. UV ($CHCl_3$): λ_{max} ($\in M^{-1}\,cm^{-1}$) 248 nm (4300). IR (KBr): ν_{max} 3379, 1736, 1648 cm^{-1}. R_f (70% EtOAc/hexane) 0.33. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J=7.1 Hz, 3H), 2.04 (s, 3H), 1.98–2.22 (m, 2H), 2.26–2.33 (m, 2H), 2.40 (s, 3H), 2.73–2.97 (m, 4H,), 4.15 (q, J=7.1 Hz, 2H), 5.77 (s, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.29 (1/2 ABq, J=8.0 Hz, 2H), 7.63–7.68 (m, 2H), 7.81 (1/2 ABq, J=8.0 Hz, 2H). FAB-MS: *m/e* 431 (M^+). HRMS (EI) *m/z* for $C_{20}H_{18}SO_5$ ($M-C_2H_5NO$) Calcd: 346.1205; Found: 346.1195.

5.1.10. Ethyl 4-acetamido-2,3,6,5-tetrahydro-8*H*-cyclohepta[*b*]-8,13-anthroquinone-4-carboxylate (18). A solution of diene **5** (8.5 mg, 0.03 mmol) and 1,4-naphthoquinone (5.3 mg, 0.03 mmol) in dry benzene (5 ml) was refluxed for 5 days. Then, the solvent was evaporated and the crude product was purified by a silica gel column using ethyl acetate/hexane (2:3) as an eluent to furnish cycloadduct (13.7 mg, 99%) as a light yellow solid. Mp, 258–260°C. The above Diels–Alder adduct (11 mg, 0.02 mmol) and DDQ (12.2 mg, 0.05 mmol) was refluxed in dry benzene for 48 h. Evaporation of the solvent and purification of the crude product by a neutral alumina column using ethyl acetate/hexane (2:3) as an eluent gave aromatized product **18** (8.1 mg, 75%) as a yellow solid. Mp, 255–257°C. UV ($CHCl_3$): λ_{max} ($\in M^{-1}\,cm^{-1}$) 261 (15,000) nm. IR (KBr): ν_{max} 3305, 1736, 1671 cm^{-1}. R_f (80% EtOAc/hexane) 0.38 ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J=7.3 Hz, 3H), 2.08 (s, 3H), 2.01–2.17 (m, 2H), 2.28–2.40 (m, 2H), 2.95–3.12 (m, 4H), 4.19 (q, J=7.1 Hz, 2H), 5.72 (s, 1H), 7.79 (dd, J=5.6, 3.3 Hz, 2H), 8.04 (s, 2H), 8.29 (dd, J=5.6, 3.4 Hz, 2H). FAB-MS: *m/e* 409 (M^+). HRMS (EI) *m/z* for $C_{21}H_{15}O_5$ ($M-C_2H_5NO$) Calcd: 346.1195; Found: 346.1205.

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