Synthetic approach to linearly annulated tetralin-based constrained α-amino acid derivatives via Rongalite

Sambasivarao Kotha* and Nimita Gopal Krishna

Department of Chemistry, Indian Institute of Technology – Bombay, Mumbai 400 076, India

Tetralin-based α-amino acid derivatives were assembled through the application of Diels–Alder reaction as a key step. Here, Rongalite has been used to generate the key *o*-xylylene intermediate.

Keywords: Diels–Alder reaction, diversity-oriented approach, Rongalite, tetralin derivatives, unusual α-amino acid derivatives.

Introduction

α,α-DISUBSTITUTED amino acids play a critical role in stability, conformational and biological activity of peptides[1]. Incorporation of these α-amino acids (AAAs) into biologically active peptides enhances their selectivity and efficacy. Unnatural AAAs based on indane **2**, 2-aminotetralin-2-carboxylic acid (Atc) **3** and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) **4** are considered as conformationally restricted AAA analogues of phenylalanine (Phe) **1** (Figure 1) because the amino acid side chain has been fixed by the bridging methylene unit(s). Moreover, the bicyclic nature of these molecules limits the dihedral angle in the N-C(α)-C(β)-C(γ)- and C(α)-C(β)-C(γ)-C(δ)-segments to a small range[2]. The interest in various derivatives of these AAAs propelled their synthetic routes. In several instances, Atc **3** has been incorporated in biologically active peptides to modulate their pharmacological properties[3]. Recently, several derivatives of Atc **3** have been used as immunosuppressants in treatment of transplant rejection, multiple sclerosis, rheumatoid arthritis, etc.[4].

A tetralin unit is a core structural element which can fix the relative position of functional groups to impart greater specificity in biological activity. Daunomycin and adriamycin are clinically important tetralin-based antitumour antibiotics[5]. Compound **6** is an extremely potent competitive inhibitor of system L in murine L1210 leukemia cells[6]. Compound **7** was found to be a far superior ligand than **5** and is expected to show improved delivery to brain and activity against brain tumours[7] (Figure 2).

*For correspondence. (e-mail: srk@chem.iitb.ac.in)

2-Aminotetralin derivatives are novel chemical structural entities owing to their high antifungal activity with low toxicity. For instance, 2-amino-nonyl-6-methoxyltetralin muriate **8** inhibits sterol C-14 reductase in the ergosterol biosynthetic pathway[8].

Results and discussion

Generally, tetralin-based AAA derivatives are assembled by Bücherer–Berg or Strecker method starting from keto derivatives[3]. As the keto precursors are not easy to prepare, this methodology has a few limitations. In this regard, we have shown that *o*-xylylene intermediates[9] are used to prepare tetralin-based AAA derivatives[10]. By selecting suitably functionalized tetralin derivatives, these AAA derivatives can be further expanded to small 'drug-like' molecules via Suzuki–Miyaura cross-coupling strategy[11]. Kotha *et al*. have utilized sultine intermediate such as **9** to generate *o*-xylylene intermediate **10** and subsequently trapped the reactive intermediate in a Diels–Alder (DA) fashion to design novel AAA derivatives

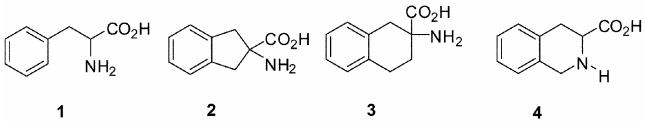


Figure 1. Phenylalanine (Phe) **1** and its constrained analogs.

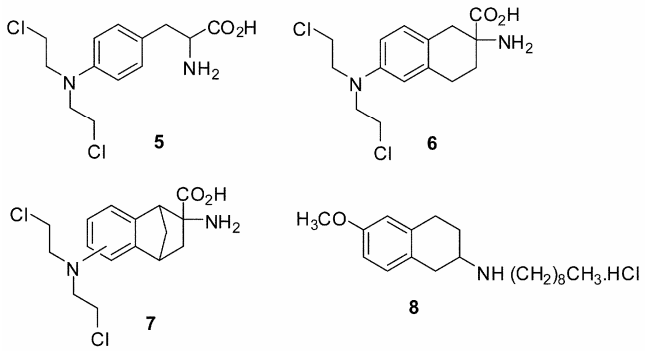
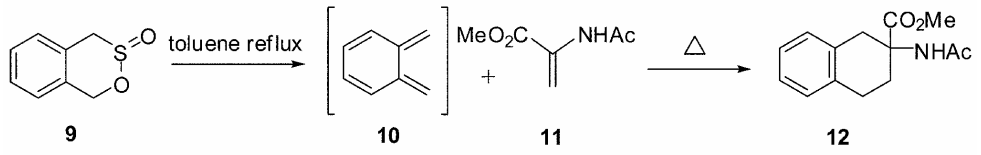
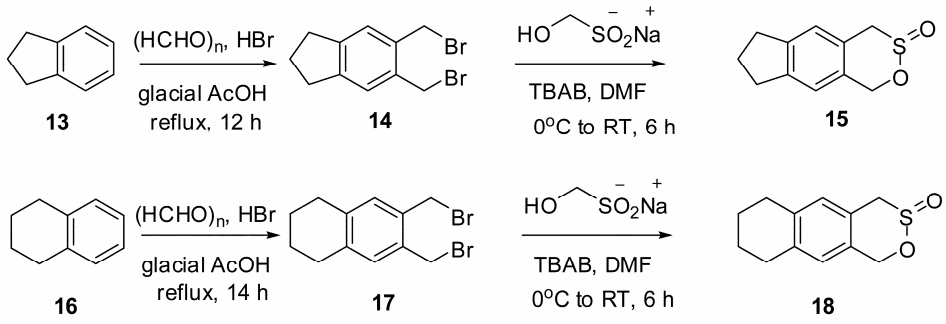


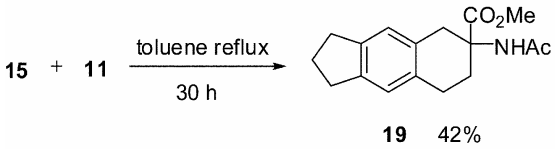
Figure 2. Biologically important phenylalanine **5**- and tetralin-based analogs.



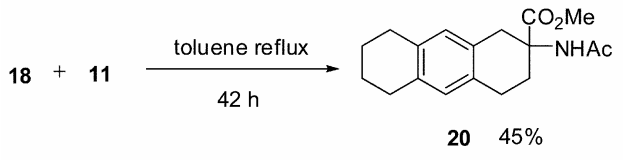
Scheme 1. Diels–Alder approach to Atc derivatives.



Scheme 2. Preparation of sultine intermediates **15** and **18**.



Scheme 3. Preparation of indane-based Atc derivative.



Scheme 4. Preparation of tetralin-based Atc derivative.

(Scheme 1). The building-block approach involving *o*-xylylene intermediate **10** delivered a wide range of tetralin-based AAA derivatives[10].

To further extend this methodology, we now report linearly annulated tetralin-based AAA derivatives. The required bromo precursors were initially prepared by [2 + 2 + 2] cycloaddition as a key step[12]. Alternatively, the bromo precursors **14** and **17** were also assembled by a bromomethylation sequence[13]. Towards this end, we planned to use indane **15** and tetralin **18** based sultines as masked diene equivalents. In this regard, we prepared bis-bromomethylated indane **14** and bis-bromomethylated tetralin **17** by bromomethylation of commercially available indane **13** and tetralin **16**, respectively. Later, the bisbromomethylated compounds were treated with commercially available sodium hydroxymethanesulfinate (Rongalite) in presence of tetrabutylammoniumbromide (TBAB) and N,N′-dimethyl formamide (DMF) at 0°C to room temperature (RT) to generate the corresponding sultines **15** and **18** in 62% and 48% yield respectively (Scheme 2).

When the DA reaction of indane-based sultine **15** was carried out with methyl-2-acetamido acrylate **11** in toluene reflux, the corresponding amino acid derivative **19** was obtained (Scheme 3).

After considerable amount of experimentation, we found that the sultine **18** reacted with methyl-2-acetamido acrylate **11** under toluene reflux conditions to generate the desired DA adduct **20**. It was necessary to simultaneously bubble the reaction mixture with nitrogen to remove the SO_2 as soon as it was generated, for the success of this reaction (Scheme 4).

The structures of the final AAA derivatives **19** and **20** were confirmed by ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectral data. Further, high-resolution mass spectrometry (HRMS) data supported their formation.

Experimental details

Melting points were recorded on Labhosp or Veego melting point apparatus. Infrared (IR) spectra were recorded on Nicolet Impact-400 FTIR spectrometer in KBr/$CHCl_3$. ^{1}H NMR (300 and 400 MHz), ^{13}C NMR (75 and 100.6 MHz) spectral data were determined at RT on a Varian VXR 300 or AX 400 mercury plus in $CDCl_3$ solution. Coupling constants (*J* values) are given in Hertz (Hz). The high-resolution mass measurements were carried out using Micromass Q-T of spectrometer. Analytical thin layer chromatography (TLC) was performed on

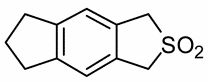
(10 × 5 cm) glass plates coated with Acme's silica gel G or GF 254 (containing 13% calcium sulphate as a binder). Silica gel was coated on glass plates using 'Sandwich Technique'. Column chromatography was performed using Acme's silica gel (100–200 mesh) using double spray bellows for application of pressure and the column was eluted with ethyl acetate–petroleum ether mixture.

General procedure for DA reaction of various sultine derivatives with methyl 2-acetamidoacrylate to generate tetralin-based AAA derivatives

A solution of sultine (1 equiv) and methyl 2-acetamidoacrylate **11** (1.5 equiv) in toluene was refluxed until the starting materials had disappeared. At the conclusion of the reaction (TLC monitoring), the solvent was removed at reduced pressure and the crude product was purified by silica gel column chromatography. Elution of the column with ethyl acetate–petroleum ether mixture released the required tetralin-based AAA derivative.

*Synthesis of methyl 6-acetamido-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naphthalene-6-carboxylate (**19**)*

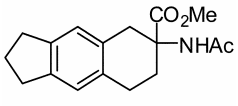
To a solution of indane-based sultine **15** (42 mg, 0.2 mmol) in toluene (10 mL) was added methyl-2-acetamido acrylate **11** (43.4 mg, 0.3 mmol) under nitrogen. Nitrogen gas was also bubbled through the reaction mixture to remove the sulphur dioxide generated during the reaction. The reaction mixture was refluxed for 30 h. Then, the solvent was removed under reduced pressure and the crude material was purified by silica gel column chromatography. Elution of the column with 20% ethyl acetate–petroleum ether resulted in rearranged sulphone **21** as a white solid (12 mg, 28%).



21

R_f = 0.55 (silica gel, 30% EtOAc–petroleum ether). Mp: 206–209°C. IR (KBr) ν_{max}/cm^{-1}: 2948, 1621, 1469. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (quintet, J = 7.3 Hz, 2H), 2.91 (t, J = 7.3 Hz, 4H), 4.32 (s, 4H), 7.15 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 25.50, 32.79, 57.05, 121.99, 128.72, 145.41.

Further elution of the column with 50% ethyl acetate–petroleum ether resulted in the desired product **19** as a white solid (25 mg, 42%).

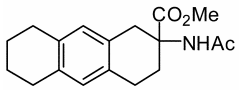


19

R_f = 0.2 (silica gel, 30% EtOAc–petroleum ether). Mp: 168–172°C. IR (KBr) ν_{max}/cm^{-1}: 3289, 2949, 1744, 1659, 1435, 1390, 1214, 1129, 1092. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.02–2.08 (m, 2H), 2.09–2.15 (m, 1H), 2.57–2.71 (m, 1H), 2.86 (t, 4H, J = 6.9 Hz), 2.75–2.81 (m, 2H), 2.93 (d, J = 16.8 Hz, 1H), 3.21 (d, J = 16.8 Hz, 1H), 3.77 (s, 3H), 5.68 (s, 1H), 6.95 (s, 1H), 7.01 (s, 1H). ^{13}C NMR (100.56 MHz, $CDCl_3$): δ 22.9, 23.4, 24.7, 27.8, 29.1, 37.7, 52.7, 58.1, 128.9, 129.4, 129.9, 132.1, 135.3, 135.8, 170.8, 174.5. HRMS (Q–Tof): *m/z* calculated for $C_{17}H_{22}NO_3$ (M + H) 288.1600, found 288.1605.

*Synthesis of methyl 2-acetamido-1,2,3,4,5,6,7,8-octahydroanthracene-2-carboxylate (**20**)*

To a solution of tetralin-based sultine **18** (20 mg, 0.1 mmol) in toluene (5 mL) was added methyl-2-acetamido acrylate **11** (19 mg, 0.14 mmol) under nitrogen. Nitrogen gas was also bubbled through the reaction mixture to remove the sulphur dioxide generated during the reaction. The reaction mixture was refluxed for a period of 42 h. The solvent was removed under reduced pressure and the crude material was purified by silica gel column chromatography. Elution of the column with 40% ethyl acetate–petroleum ether produced the desired compound **20** (12 mg, 45%).



20

R_f = 0.22 (silica gel, 30% EtOAc–petroleum ether). Mp: 177–180°C. IR (KBr) ν_{max}/cm^{-1}: 3310, 2927, 1726, 1682, 1266.4, 1019.8, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78–1.88 (m, 4H), 1.93 (s, 3H), 2.05–2.12 (m, 1H), 2.56–2.61 (m, 1H), 2.78 (dd, J = 5.6 Hz, 4H), 2.80–2.82 (m, 2H), 2.89 (d, J = 16.6 Hz, 1H), 3.17 (d, J = 16.6 Hz, 1H), 3.76 (s, 3H), 5.69 (s, 1H), 6.79 (s, 1H), 6.85 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.3, 23.4, 24.8, 27.8, 29.1, 29.2, 37.9, 52.8, 58.1, 128.9, 129.5, 130.1, 132.2, 135.4, 135.8, 170.3, 174.3. HRMS (Q–Tof): *m/z* calculated for $C_{18}H_{24}NO_3$ (M + H) 302.1748, found 302.1760.

Conclusion

We have designed a simple route for the synthesis of various linearly annulated tetralin-based AAA derivatives based on DA reaction. This building block approach seems to be an attractive strategy for designing various tetralin-based AAA derivatives.

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