Tetrahedron 69 (2013) 2184–2192

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Exploring the scope of Bergman Cyclization mediated cascade reaction of alkenyl enediynes: synthesis of [5]helicene and amino acid appended [4]helicenes

Snigdha Roy, Amit Basak *

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

ARTICLE INFO

Article history:
Received 11 October 2012
Received in revised form 21 December 2012
Accepted 26 December 2012
Available online 4 January 2013

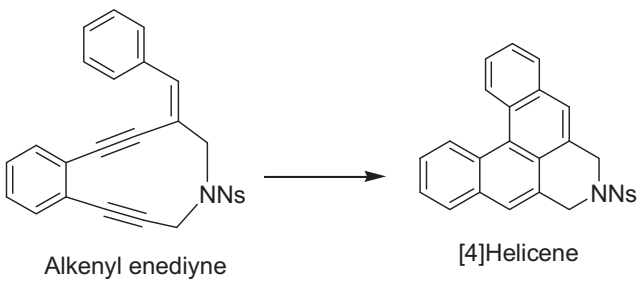
ABSTRACT

Bergman Cyclization mediated cascade radical process is employed for the synthesis of [5]helicenes as well as diastereoselective mixtures of chiral amino acid appended [4]helicenes. Maximum selectivity (2.5:1) was found in case of L-leucine attached cyclic enediyne. Mechanistic considerations for this tandem radical reaction revealed that the major pathway probably involved quenching of the biradical, formed after aryl radical addition to pendant aromatic ring, by the solvent followed by aromatization. Intramolecular H-abstraction by the sp^2-hybridized radical in the central ring or a 1,5-H shift followed by self-quenching could be the other possible ways to lead to the helicenes.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Recently, we have reported[1] a general method for the synthesis of [4]helicenes via a novel cascade radical reaction initiated by Bergman Cyclization[2] starting from alkenyl aromatic enediynes (Scheme 1). Helicenes have attracted lot of attention in materials chemistry[3] as well as catalysts for asymmetric synthesis.[4] All these applications originated from their helical chirality, which arises due to the non-planarity of the aryl rings caused mainly by the steric repulsion between protruding/proximal hydrogens in smaller helicene and inner axial terminal carbon-carbon nonbonded interactions in higher helicenes as shown (Fig. 1). The extent of non-planarity of the aryl groups will be more in higher helicenes as well as for helicenes with bulky substituents replacing the concerned hydrogen(s). Racemization barrier for [4]helicene is calculated[5] to be around 8 kcal/mol at 27 °C whereas in case of the next higher benzologue, i.e., [5]helicene, the barrier rises up to 23 kcal/mol. Incorporation of a simple methyl group at the terminal position can also enhance the barrier energy by about 8–14 kcal/mol.[6] In this paper we wish to report that the method of cascade radical reaction can be extended for the synthesis of [5]helicenes as well as [4] helicenes appended with chiral amino acid substituents at one of the proximal positions (Fig. 2). The diastereoselctivity shown in the latter case is also reported.



Scheme 1. Synthesis of [4]helicene.

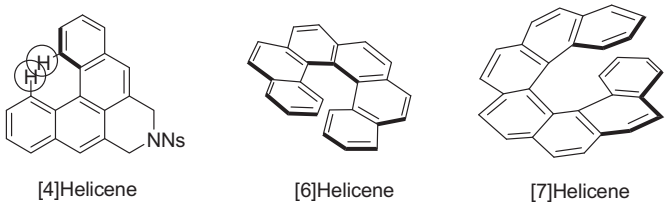


Fig. 1. Different helicenes.

2. Results and discussions

For the synthesis of [5]helicene, 2-naphthaldehyde was taken as the starting substrate. Halo-Wittig[7] reaction followed by DIBAL reduction produced the allyl alcohol **5** (Scheme 2). This was mesylated, substituted with sodium azide and then reduced with triphenylphosphine. Product **7**, an unsaturated amine, was

* Corresponding author. Fax: +91 3222 283300; e-mail address: absk@chem.iitkgp.ernet.in (A. Basak).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.12.064

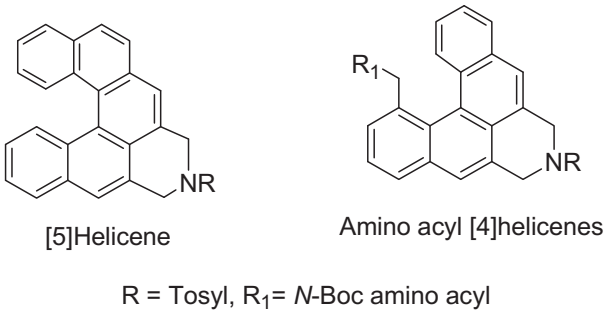
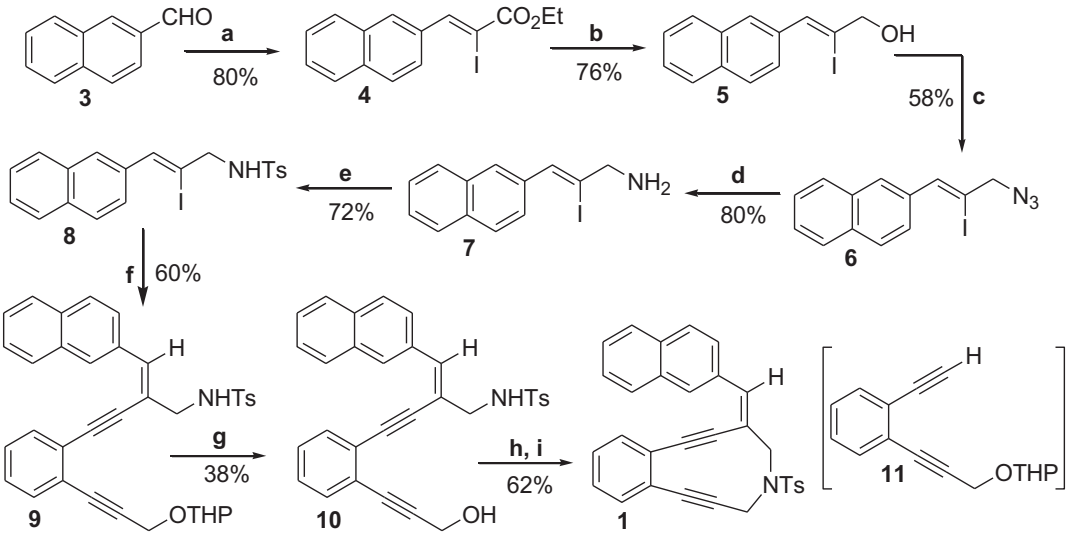


Fig. 2. [5]Helicene and chiral amino acid tagged [4]helicene.

diastereoselectivity of the cascade reaction. All these five chiral enediynes were characterized by NMR and mass spectral data.

With all the required cyclic enediynes in hand, the final tandem cyclization was attempted. At first, compound **1** was subjected to the cyclization condition as described for [4]helicene,[1] which involved heating at 90 °C in dry DMSO (Scheme 4). The reaction was found to be complete in 8 h. Column purification of the crude reaction mixture gave a gummy liquid whose ^{1}H and ^{2}H NMR spectra (Fig. 3) clearly proves the formation of [5]helicene, **21**. In case of chiral amino acid tagged cyclic enediyne, temperature had to be raised to induce the cyclization. Thus, each of these chiral enediyne was heated at 120 °C in dry DMF for 7–9 h (Scheme 5). ^{1}H NMR spectrum of the crude reaction mixture indicated the formation of



Reagents and conditions: a) i) $Ph_3P^+CH_2CO_2Et.Br^-$, I_2, K_2CO_3, CH_3OH, 0 °- 5 °C, 1.5 h, ii) **3**, Tetrabutyl ammonium bromide, K_2CO_3, 40 °C, 18 h; b) DIBAL-H, CH_2Cl_2, -78 °C, 3 h; c) i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, ii) NaN_3, DMF, r.t., 2 h; d) PPh_3, THF-H_2O, r.t., 7 h; e) TsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 h; f) $Pd(PPh_3)_4$, CuI, **11**, Et_3N, THF, r.t., 10 h; g) Pyridinium *p*-toluene sulfonate, EtOH, r.t., 6 h; h) MsCl, Et_3N, CH_2Cl_2, 0 °C, 5 min; i) K_2CO_3, DMF, r.t., 4 h.

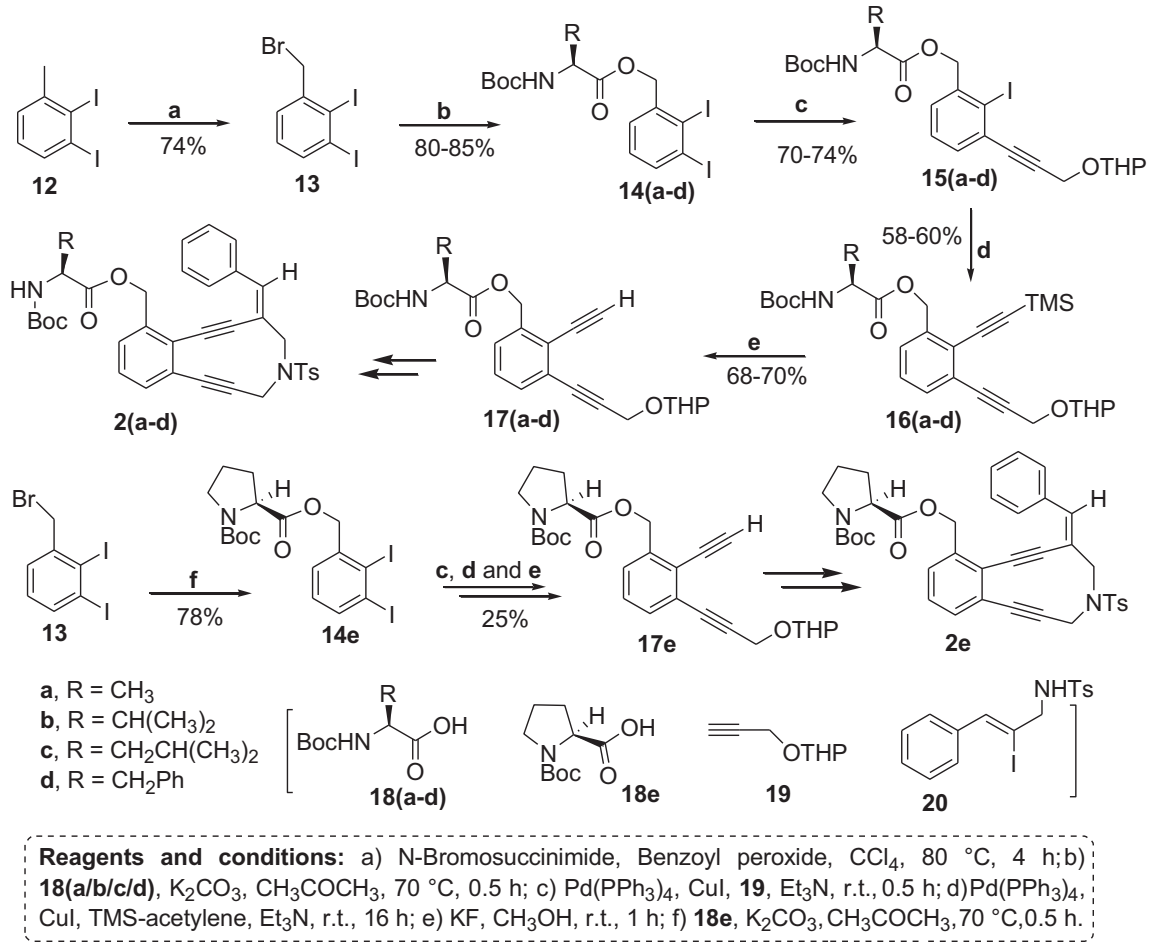
Scheme 2. Synthesis of cyclic enediyne **1**.

protected as tosyl to form the sulfonamide **8**. Final Sonogashira coupling[8] between this sulfonamide and the previously prepared[9] enediyne **11** provided the intermediate **9**, which on deprotection, mesylation followed by intramolecular cyclization under high dilution[10] produced the desired cyclic enediyne **1**. NMR and mass spectral analysis were in full agreement with its structure.

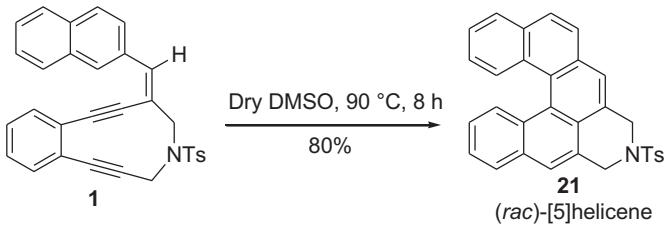
For diastereoselective synthesis of amino acid appended chiral [4] helicenes, 2,3-diiodotoluene (Scheme 3) was first subjected to benzylic bromination with NBS and benzoyl peroxide in carbon tetrachloride. Reaction with *N*-Boc protected amino acids with potassium carbonate in dry acetone produced the *N*-Boc aminoacyl methyl 2,3-diiodobenzene **14**(**a**–**e**). Sequential Sonogashira coupling with THP-protected propargyl alcohol and then with TMS-acetylene followed by silyl deprotection produced the terminal alkyne derivatives **17**(**a**–**e**). The latter on Sonogashira coupling with iodo alkene **20** (prepared from benzaldehyde following procedure similar to that of **8**) followed by a sequence of steps (Supplementary data) finally provided the cyclic enediynes appended with *N*-Boc protected chiral amino acids **2**(**a**–**e**).[11] Five different amino acids were incorporated to see the effect of different amino acid side chains on the two diastereomers in unequal proportions. Unfortunately, the diastereomers could not be separated by column chromatography. The formation of helicenes was confirmed on the basis of NMR and mass spectral analysis.

Based on the ^{1}H NMR [Fig. 4(A–D)], the diastereomeric ratio for each set of chiral amino acid attached [4]helicenes was calculated. These are compiled in Table 1. For leucine attached diastereomers **22c** and **23c**, ^{1}H NMR failed to resolve any signal. In this case, the diastereomeric ratio was calculated from the corresponding HPLC profile using CHIRALCEL OD-H column (250 mm×4.6 mm) (Fig. 4E). The fact that there was no equilibration between the diastereomers via rotation around the chiral axis under ambient conditions was confirmed by recording the VT-NMR on valine based [4]helicenes. It clearly showed that the signals did not coalesce even after heating up to 60 °C thus pointing to a much slower equilibration as compared to NMR time scale (Fig. 5).

From these results, it is quite evident that although the synthesis of the aminoacyl helicenes was successful, the diastereoselectivity of the reaction was rather poor in spite of the variation in steric bulk of the amino acid side-chain. The maximum selectivity with the dr



Scheme 3. Synthesis of aminoacyl enediynes **2**(**a**–**e**).



Scheme 4. Synthesis of [5]helicene.

value of 2.5:1.0 was obtained in case of leucine attached cyclic enediyne (**22c**+**23c**). The reason for poor stereoselectivity may possibly be due to the quite remote positioning of the stereogenic centre.

The proposed mechanism of the cascade radical reaction leading to the formation of [5]helicene and also the substituted [4]helicenes is somewhat different from the earlier one.[1,12] In these cases, the radical formed via addition of the aryl radical to the naphthalene or benzene moiety[13,14] is not in a position to abstract H from the benzene ring **A** because of either steric constraint or absence of such hydrogen. Thus the biradical in either case is quenched by H-abstraction from the solvent (*Step IIIa*) followed by aromatization under the reaction condition to provide the final product (Scheme 6). An alternative mechanism has also been shown where, after the intramolecular radical addition in *Step II*, the sp^2-carbon based radical in the newly generated biradical, can abstract the considerably labile hydrogen atom at the **D**/**E** ring junction probably in an intramolecular fashion (*Step IIIb*).[15] This particular C–H bond dissociation energy should be lower than that of the 1,4-CHD or DMF. So, a direct aromatization of rings **E** and **D** may easily take place along with quenching of **B** ring sp^2 radical to lead to the final product. An alternate way to view this process is to have a 1,5H-shift (*Step IIIc*) followed by self-quenching. However, such 1,5 H-shift is unlikely to be concerted due to geometric constraint.[16] The possibility of abstracting the benzylic hydrogen in case of amino acid appended helicenes was ruled out by lack of deuterium incorporation at the benzylic carbon when the reaction was carried out in a mixed solvent system of MeOH-d_4 (20%) in dry DMF.

In conclusion, we have successfully demonstrated the versatility of our previously reported ring annulations by tandem radical process initiated by Bergman Cyclization in synthesizing [5]helicene as well as various amino acid based diastereomeric [4]helicenes in good yields. The diastereoselectivity, however, was far less than satisfactory. Only leucine based helicenes were obtained as a mixture diastereomers with moderate diastereoselectivity. Further studies are currently in progress to improve the diastereoselectivity by directly attaching the stereogenic centre to the ring **A** carbon.

3. Experimental

3.1. General

All reactions were conducted with oven-dried glassware under an atmosphere of argon (Ar) or nitrogen (N_2). All common reagents

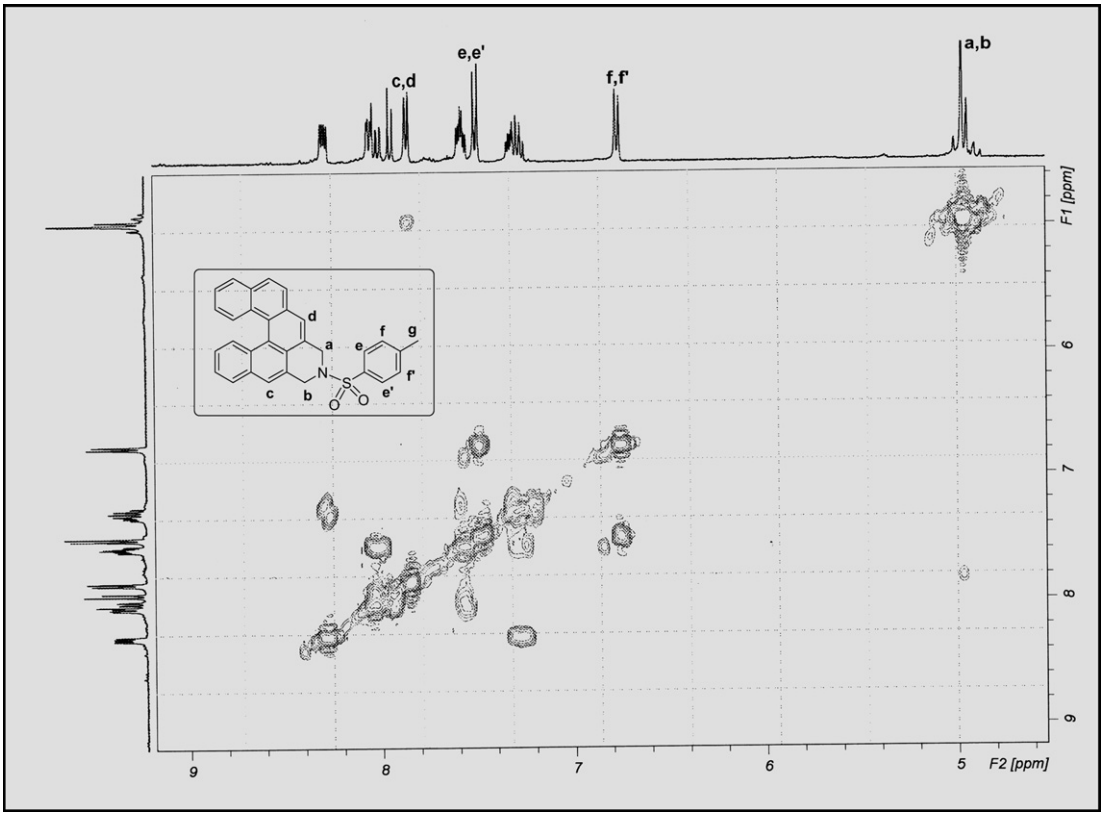
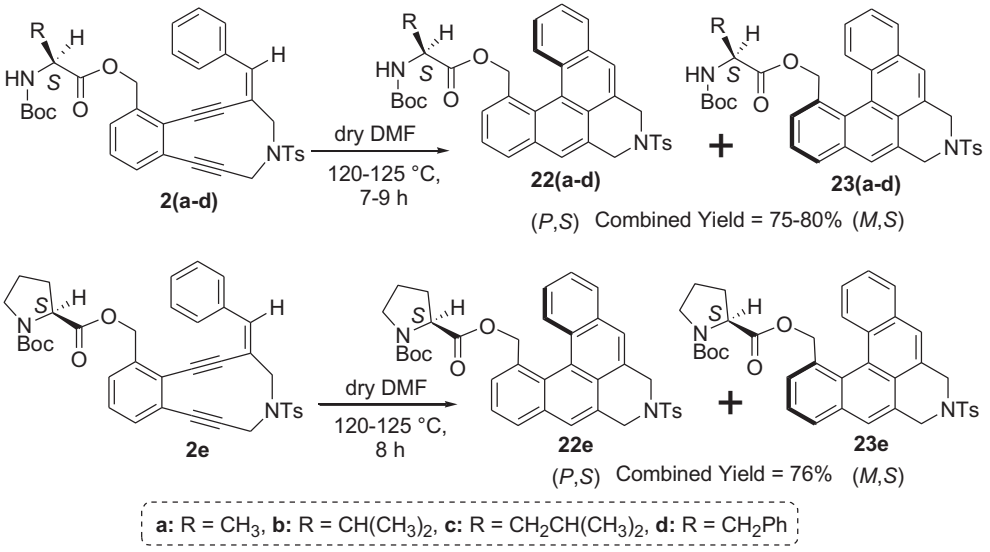


Fig. 3. ^{1}H-^{1}H COSY spectrum (400 MHz, CD_3COCD_3) of [5]helicene **21** (δ 9.2–4.5).



Scheme 5. Synthesis of diastereomeric mixture of chiral amino acid attached [4]helicenes.

were commercial grade reagents and used without further purification. The solvents were dried by standard methods and purified by distillation before use. All crude products were purified by silica gel column chromatography (60–120 mesh) with petroleum ether/ethyl acetate (PE/EA) as eluent and characterized by IR, NMR, and mass spectrometry unless otherwise mentioned. ^{1}H and ^{13}C NMR spectra of all compounds were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ solvent unless otherwise noted. Infrared (FTIR) spectra were recorded as thin films on potassium bromide plates (solid sample), or in chloroform solvent (liquid sample) using Perkin Elmer Spectrum Rx1 spectrometer and are expressed as %-transmission (cm^{-1}). ESI-MS and HRMS were recorded using a Waters LCT mass spectrometer.

3.2. General synthesis of α,β-unsaturated ester (4, 20b) via Halo-Wittig reaction

(Ethoxycarbonylmethyl)triphenylphosphonium bromide salt (1.3 g, 3.0 mmol) was first dissolved in dry MeOH (50 mL) and cooled to −5 °C. Molecular iodine (1.5 g, 6.0 mmol) and freshly

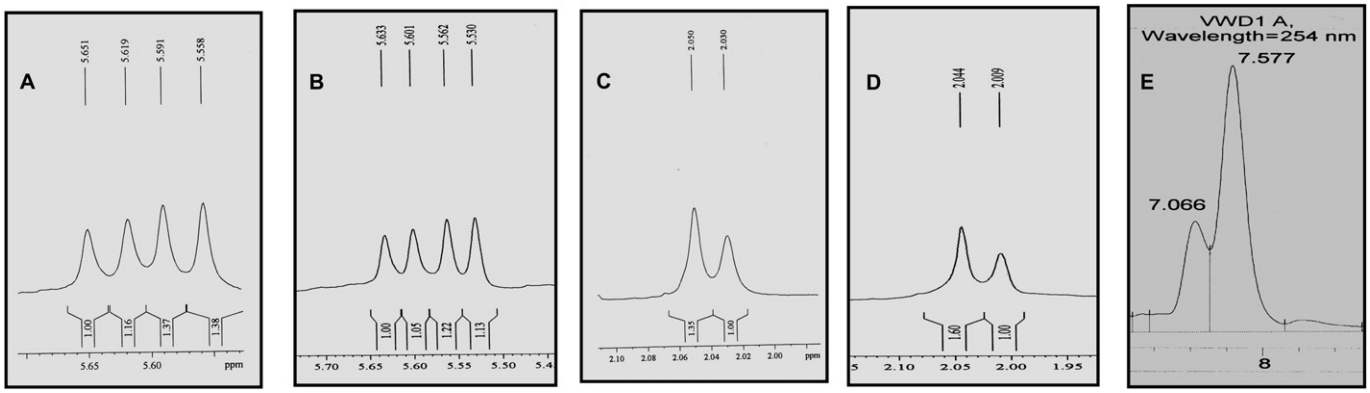


Fig. 4. ^{1}H NMR of pair of doublets for one of the CH_2 protons of **22a** and **23a** (A), **22b** and **23b** (B), two singlets for tosyl methyl protons of **22d** and **23d** (C), **22e** and **23e** (D); HPLC profile of **22c** and **23c** (E) (solvent system=1% CH_3CN in 99% MeOH, flow rate=1 mL/min).

Table 1
Diastereomeric ratio for the amino acid based helicenes

Starting enediyne	Diastereomers	L-Amino acid used	Reaction time (h)	Combined yield (%)	Diastereomeric ratio (dr) from NMR
2a	**22a**+**23a**	Alanine	7	75	1.3:1.0
2b	**22b**+**23b**	Valine	7.5	80	1.2:1.0
2c	**22c**+**23c**	Leucine	8.5	77	2.5:1 (from HPLC)
2d	**22d**+**23d**	Phenyl alanine	8	78	1.4:1.0
2e	**22e**+**23e**	Proline	9	76	1.6:1.0

activated K_2CO_3 (414 mg, 3.0 mmol) were successively added to it and stirred for 1.5 h strictly maintaining the temperature between −5 and 5 °C. A brown colored suspension was obtained into which aldehyde **3**/**20a** (2.6 mmol), tetrabutyl ammonium bromide (TBAB) (0.13 mmol,) and K_2CO_3 (0.42 mmol) were added consecutively. The reaction pot was removed from the low temperature immersion bath (set at −5 °C) and heated in an oil bath kept at 40 °C. After every 2 h of heating, K_2CO_3 (0.42 mmol) was added for another two times and the heating was continued for next 10–16 h. On completion, MeOH was evaporated under vacuum and the crude reaction mass was subjected to column purification.

3.3. General synthesis α,β-unsaturated alcohol (5, 20c)

The unsaturated ester **4**/**20b** (1.5 mmol) was dissolved in dry DCM (25 mL) and cooled at −78 °C. DIBAL (3 equiv) was added to this solution drop wise and stirred for 3–4 h at the same

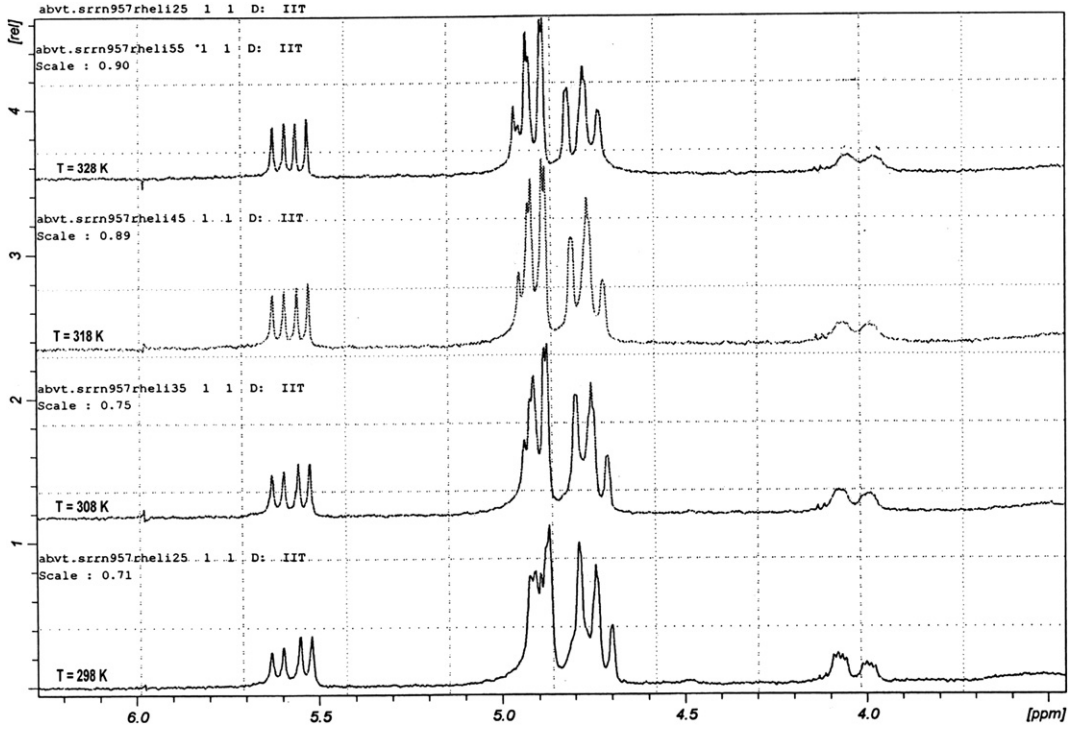
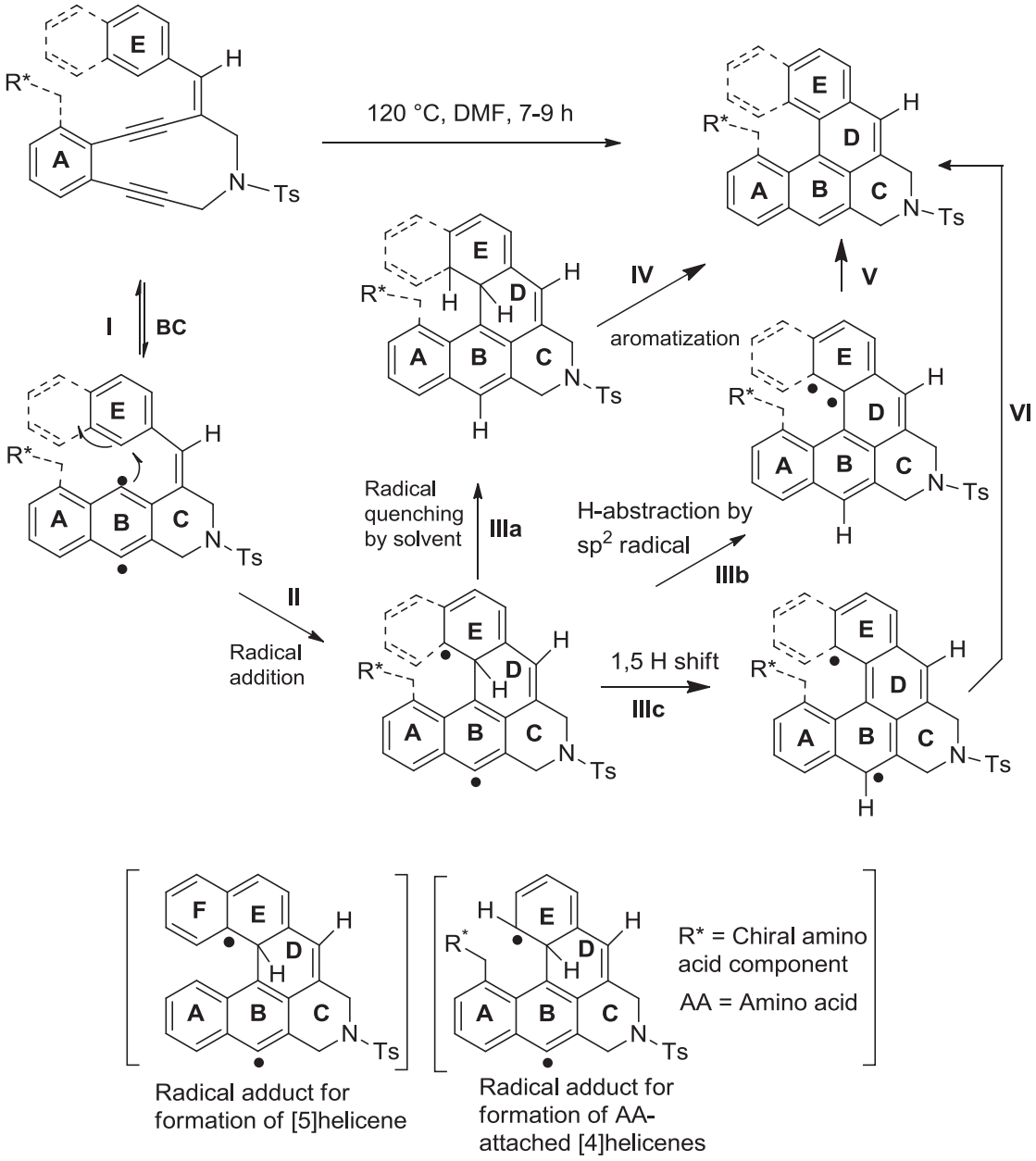


Fig. 5. VT-NMR (400 MHz, $CDCl_3$) of diastereomeric mixture of L-valine amino acid attached [4]helicenes (**22b**+**23b**).



Scheme 6. Mechanism of formation of helicenes.

temperature under nitrogen. The reaction was quenched with a saturated Rochelle salt solution (15 mL) and diluted with DCM (20 mL). Resultant thick reaction mixture was filtered through a Celite bed to have a clear biphasic layer from which the organic layer was separated, washed with water and brine solution, dried over Na_2SO_4, and concentrated.

3.4. Mesylation of primary alcohol (5a, 10a, 20d, and 26)

Dry DCM (20 mL) solution of compound **5**/**10**/**20c**/**25** (0.30 mmol) was first cooled to 0 °C. MsCl (1 equiv) and dry Et_3N (1.2 equiv) were added successively to the solution drop wise and stirred for 5 min. Progress of the reaction was carefully monitored by TLC and on completion, rapid quenching was done with addition of water to avoid over mesylation. The organic layer was washed with a dilute solution of $NaHCO_3$ (10 mL) to remove excess MsCl. Due to the stability problem, the crude mesylates of compounds **10** and **25** were subjected to the next reaction condition without further column purification.

3.5. Synthesis of azide (6, 20e)

To a dry DMF (10–15 mL) solution of the mesylate **5a**/**20d** (0.32 mmol), NaN_3 (1.5 or 3.0 equiv, depending on mono or di substitution) was added and stirred for 6–8 h at room temperature. Afterward, it was quenched with water and extracted with EtOAc (3×10 mL). The combined organic layers were washed with water and brine solution, dried over Na_2SO_4, and concentrated.

3.6. Synthesis of 2-iodo-3-naphthalen-2-yl-allylamine (7, 20f)

Azide derivative **6**/**20e** (700 mg, 2.26 mmol) was dissolved in THF (25 mL). PPh_3 (1.18 gm, 4.51 mmol) and 3–4 drops of water were added to the solution and stirred for 6 h at room temperature.

After THF evaporation, the crude reaction mass was subjected to column purification (8% MeOH in DCM).

3.7. Tosylation of primary amine (8, 20)

Primary amine (**7**/**20f**) (7.72 mmol) was first dissolved in dry DCM (20 mL) at 0 °C under nitrogen atmosphere and then TsCl (1.0 equiv) and Et_3N (1.2 equiv) were added successively at this same temperature. The reaction mixture was stirred for next 1.5–2.0 h while the temperature increased up to room temperature. Progress of the reaction was monitored by TLC. On completion, it was quenched with water and diluted with more DCM (10 mL). The organic layer was separated, washed with water and brine solution, dried over Na_2SO_4, and concentrated.

*3.7.1. N-(2-Iodo-3-naphthalen-2-yl-allyl)-4-methyl-benzenesulfonamide (**8**).* Light brown colored solid; R_f (PE/EA=4:1) 0.50; yield: 72%; mp: 90–92 °C; δ_H (200 MHz): 7.84–7.75 (m, 7H), 7.53–7.46 (m, 2H), 7.29–7.25 (m, 2H), 7.00 (s, 1H), 5.30 (t, *J*=6.4 Hz, 1H), 4.17 (dd, *J*=6.5, 1.2 Hz, 2H), 2.37 (s, 3H); δ_C (50 MHz): 143.8, 137.7, 136.9, 134.3, 133.1, 129.9, 128.3, 127.9, 127.6, 126.7, 126.5, 126.2, 101.4, 56.6, 21.7.

*3.7.2. N-(2-Iodo-3-phenyl-allyl)-4-methyl-benzenesulfonamide (**20**).* White solid; R_f (PE/EA=5:1) 0.60; yield: 76%; mp: 55–56 °C; δ_H (200 MHz): 7.79 (d, *J*=8.0 Hz, 2H), 7.33–7.28 (m, 6H), 6.85 (s, 1H), 5.29 (t, *J*=6.5 Hz, 1H), 4.10 (dd, *J*=6.0, 1.2 Hz, 2H), 2.38 (s, 3H); δ_C (50 MHz): 143.8, 137.6, 136.9, 129.9, 128.6, 128.5, 128.2, 127.5, 101.1, 56.5, 21.7.

3.8. Sonogashira coupling of iodo alkene with terminal alkyne (9, 24)

Iodo alkene **8**/**20** (0.9 mmol) was dissolved in dry THF (15 mL) followed by the addition of dry Et_3N (10 mL). After degasification of the solution for 0.5 h, $Pd(PPh_3)_4$ (0.03 equiv) was added to it and stirred for 5 min under nitrogen atmosphere. CuI (0.1 equiv) and alkyne **11**/**17** (1.2 equiv) were added to it with 5 min interval and stirred for 8–12 h at room temperature. On completion, it was quenched with a saturated NH_4Cl solution (15 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were washed with water and brine solution, dried over Na_2SO_4, and concentrated.

3.9. Synthesis of 1-bromomethyl-2,3-diiodobenzene (13)

2,3-Diiodotoluene (**12**) (800 mg, 2.33 mmol), NBS (500 mg, 2.79 mmol), and benzoyl peroxide (670 mg, 2.34 mmol) were taken in distilled CCl_4 (40 mL) and refluxed for 4 h. On completion, the reaction mixture was evaporated to dryness and subjected to column chromatography without any further washing (purification: PE).

3.10. General synthesis of ester [14(a–e)]

N-Boc protected amino acid **18** (**a**/**b**/**c**/**d**/**e**) (3.50 mmol) and the bromide **13** (3.50 mmol) were dissolved in dry acetone (30 mL) and freshly dried K_2CO_3 (1.2 equiv) was added to it. Total solution was refluxed for 0.5 h. On completion, acetone was evaporated and the crude mass was taken in EtOAc (25 mL). The resultant solution was washed with water and brine solution, dried over Na_2SO_4, and concentrated.

3.11. Sonogashira coupling with THP-protected propargyl alcohol [15(a–e)]

In a dry degassed Et_3N (15 mL) solution of compound **14**, tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] (264 mg, 0.23 mmol) was added. After 10 min of stirring, CuI (145 mg, 0.76 mmol) and THP-protected propargyl alcohol (1 mL, 7.65 mmol) were added successively with 5 min interval. The whole mixture was stirred for 0.5 h at room temperature under nitrogen atmosphere. On completion, a saturated NH_4Cl solution (10 mL) was poured into the reaction pot and extracted with EtOAc (3×10 mL). The combined organic layers were washed with water and brine solution, dried over Na_2SO_4, and concentrated.

3.12. Sonogashira coupling with TMS-acetylene [16(a–e)]

Same procedure as described for the synthesis of **15**(**a**–**e**). The reaction mixture was stirred for a longer time of 16 h at room temperature.

3.13. Removal of TMS group [17(a–e)]

To a dry MeOH (15 mL) solution of compound **16**(**a**–**e**) (600 mg, 1.44 mmol), KF (440 mg, 7.2 mmol) was added and stirred for 1 h at room temperature under nitrogen atmosphere. On completion, the solvent was evaporated under reduced pressure and subjected to column purification.

3.14. Deprotection of THP group [10, 25(a–e)]

The THP-protected alcohol [**9**/**24**(**a**–**e**)] (0.37 mmol) was dissolved in commercial grade EtOH (10–20 mL) and PPTS (0.1 equiv) was added. Resulting reaction mixture was stirred for 6 h at room temperature. The solvent was removed under vacuum and the crude reaction mass was subjected to column purification without any further washing.

3.15. General synthesis of cyclic enediyne [1, 2(a–e)]

Mesylate **10a**/**26**(**a**–**e**) (~0.18 mmol), in its crude form, was dissolved in perfectly dry DMF (~65 mL) maintaining a high dilution of the solution (~3.0×10^{-3} mmol/mL) and freshly activated K_2CO_3 (3 equiv) was added to it. The whole mixture was stirred for next 4 h at room temperature. On completion, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (4×15 mL). The combined organic layers were thoroughly washed with water and brine solution, dried over Na_2SO_4, and concentrated.

*3.15.1. Compound **1**.* White solid; R_f (PE/EA=4:1) 0.40; yield: 80%; mp: 135 °C; δ_H: 8.20 (s, 1H), 7.98–7.97 (m, 1H), 7.96–7.82 (m, 3H), 7.70 (d, *J*=8.0 Hz, 2H), 7.52–7.50 (m, 2H), 7.39–7.33 (m, 2H), 7.30–7.28 (m, 2H), 6.98–6.93 (m, 3H), 4.52 (s, 2H), 4.41 (s, 2H), 2.15 (s, 3H); δ_C: 143.1, 138.4, 138.0, 133.6, 133.5, 133.4, 129.3, 129.2, 128.9, 128.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 126.8, 126.5, 126.3, 116.7, 98.3, 96.8, 94.3, 86.7, 59.3, 42.3, 21.5; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3446, 2923, 2366, 2340, 1750, 1718, 1653, 1622, 1543, 1354, 1335, 1265, 1153, 1122, 1091, 813, 752; HRMS: found 474.1525. $C_{31}H_{23}NO_2S+H^+$ requires 474.1528.

*3.15.2. Cyclic enediyne **2a**.* White solid; R_f (PE/EA=7:1) 0.50; yield: 57%; mp: 126 °C; δ_H: 7.79 (d, *J*=7.6 Hz, 2H), 7.66 (d, *J*=8.0 Hz, 2H), 7.43–7.39 (m, 2H), 7.36–7.33 (m, 2H), 7.30–7.26 (m, 2H), 6.94 (d, *J*=8.0 Hz, 2H), 6.84 (s, 1H), 5.21 (ABq, *J*=31.0, 13.0 Hz, 2H), 5.02–5.00 (m, 1H), 4.47 (ABq, *J*=27.0, 18.6 Hz, 2H), 4.39–4.30 (m, 3H), 2.16 (s, 3H), 1.43 (s, 9H), 1.32 (d, *J*=7.2 Hz, 3H); δ_C: 173.2, 155.3, 143.2, 138.9, 138.6, 137.8, 135.7, 135.6, 129.3, 129.2, 129.0, 128.6, 128.5, 128.4, 127.9, 127.8, 127.7, 116.3, 100.9, 95.7, 94.7, 86.5, 80.1, 65.7, 59.1, 49.5, 42.3, 28.5, 21.4, 18.7; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3399, 2927, 2856, 2363,

2342, 1899, 1740, 1708, 1597, 1496, 1449, 1345, 1261, 1159, 1091, 1068; HRMS: found 625.2369. $C_{36}H_{36}N_2O_6S+H^+$ requires 625.2372.

3.15.3. Cyclic enediyne ***2b****.* Cream colored solid; R_f (PE/EA=5:1) 0.45; yield: 60%; mp: decomposed at 175–177 °C; δ_H: 7.80 (d, *J*=7.6 Hz, 2H), 7.66 (d, *J*=8.4 Hz, 2H), 7.43–7.39 (m, 2H), 7.37–7.32 (m, 2H), 7.28–7.26 (m, 2H), 6.93 (d, *J*=8.0 Hz, 2H), 6.84 (s, 1H), 5.26–5.18 (m, 2H), 5.05–5.03 (m, 1H), 4.52–4.41 (m, 2H), 4.38–4.28 (m, 3H), 2.15 (s, 4H), 1.43 (s, 9H), 0.92 (d, *J*=6.8 Hz, 3H), 0.83 (d, *J*=6.8 Hz, 3H); δ_C: 172.3, 155.8, 143.1, 138.9, 137.8, 135.6, 129.2, 129.1, 129.0, 128.5, 128.3, 128.0, 127.8, 127.7, 127.6, 116.3, 100.9, 95.6, 94.7, 86.5, 80.0, 65.3, 59.1, 58.8, 42.3, 31.4, 28.5, 21.4, 19.2, 17.7; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3394, 2968, 2928, 2364, 2341, 1740, 1714, 1597, 1497, 1451, 1349, 1158, 1092, 1015, 918, 749; HRMS: found 675.2488. $C_{38}H_{40}N_2O_6S+Na^+$ requires 675.2505.

3.15.4. Cyclic enediyne ***2c****.* White solid; R_f (PE/EA=5:1) 0.50; yield: 60%; mp: 160–162 °C; δ_H: 7.80 (d, *J*=7.6 Hz, 2H), 7.67 (d, *J*=8.0 Hz, 2H), 7.44–7.40 (m, 2H), 7.36–7.34 (m, 2H), 7.29–7.26 (m, 2H), 6.94 (d, *J*=8.0 Hz, 2H), 6.84 (s, 1H), 5.26–5.16 (m, 2H), 4.87–4.85 (m, 1H), 4.54–4.46 (m, 2H), 4.42–4.31 (m, 3H), 2.17 (s, 3H), 1.68–1.54 (m, 3H), 1.43 (s, 9H), 0.87–0.86 (m, 6H); δ_C: 173.3, 155.6, 143.1, 139.3, 138.8, 137.7, 135.6, 129.4, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4, 127.8, 127.7, 127.6, 116.2, 100.9, 95.7, 94.6, 86.6, 80.1, 65.5, 59.1, 52.3, 42.3, 41.7, 28.5, 24.9, 23.0, 22.0, 21.4; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3390, 2959, 2925, 2363, 2341, 1742, 1706, 1347, 1274, 1261, 1159, 1091, 750; HRMS: found 667.2840. $C_{39}H_{42}N_2O_6S+H^+$ requires 667.2842.

3.15.5. Cyclic enediyne ***2d****.* Light yellow solid; R_f (PE/EA=7:1) 0.50; yield: 58%; mp: 143–145 °C; δ_H: 7.82 (d, *J*=7.2 Hz, 2H), 7.66 (d, *J*=8.4 Hz, 2H), 7.43–7.39 (m, 2H), 7.36–7.34 (m, 1H), 7.33–7.18 (m, 6H), 7.02–7.01 (m, 2H), 6.91 (d, *J*=7.6 Hz, 2H), 6.86 (s, 1H), 5.21 (ABq, *J*=27.2, 12.8 Hz, 2H), 4.98–4.96 (m, 1H), 4.66–4.64 (m, 1H), 4.54–4.41 (m, 2H), 4.37–4.31 (m, 2H), 3.09, 3.00 (ABq of d, *J*=13.6, 5.8 Hz, 2H), 2.12 (s, 3H), 1.41 (s, 9H); δ_C: 171.8, 155.3, 143.2, 139.0, 137.8, 136.0, 135.7, 135.5, 129.5, 129.3, 129.2, 129.0, 128.8, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.2, 116.3, 101.0, 95.7, 94.8, 86.6, 80.2, 65.6, 59.1, 54.7, 42.3, 38.4, 28.5, 21.4; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3389, 2945, 2364, 2342, 1745, 1695, 1492, 1398, 1342, 1244, 1219, 1165, 1095, 956, 770; HRMS: found 701.2680. $C_{42}H_{40}N_2O_6S+H^+$ requires 701.2685.

3.15.6. Cyclic enediyne ***2e****.* Light brown solid; R_f (PE/EA=5:1) 0.40; yield: 55%; mp: 126–128 °C; δ_H: 7.81–7.78 (m, 2H), 7.66–7.63 (m, 2H), 7.42–7.39 (m, 2H), 7.37–7.32 (m, 2H), 7.27–7.23 (m, 2H), 6.94–6.90 (m, 2H), 6.82–6.81 (m, 1H), 5.28–5.11 (m, 2H), 4.44 (s, 2H), 4.39–4.25 (m, 3H), 3.54–3.33 (m, 2H), 2.14 (s, 4H), 1.89–1.77 (m, 3H), 1.44 (s, 4H), 1.33 (s, 5H); δ_C: 172.9, 172.7, 154.6, 153.9, 143.1, 143.0, 138.6, 137.7, 136.1, 135.8, 135.6, 135.5, 129.3, 129.2, 129.1, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 127.3, 116.3, 116.2, 100.9, 100.7, 95.8, 95.7, 94.7, 94.6, 86.6, 86.5, 80.0, 65.1, 59.2, 59.0, 58.9, 46.7, 46.4, 42.2, 30.9, 28.5, 28.4, 24.4, 23.7, 21.3; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3398, 2943, 2845, 2365, 2335, 1765, 1698, 1578, 1476, 1365, 1187, 960; HRMS: found 673.2344. $C_{38}H_{38}N_2O_6S+Na^+$ requires 673.2348. found 651.2528. $C_{38}H_{38}N_2O_6S+H^+$ requires 651.2529.

3.16. Synthesis of [5]helicene

Cyclic enediyne **1** (~0.08 mmol) was dissolved in perfectly dry DMSO (~15 mL) maintaining the whole solution concentration around 5×10^{-3} mmol/mL. It was heated at 90 °C for 8 h. On completion, the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with water and brine solution, dried over Na_2SO_4, and concentrated.

3.16.1. Compound ***21****.* Colorless viscous oil; R_f (PE/EA=5:1) 0.45; yield: 80%; δ_H (acetone-d_6): 8.30–8.28 (m, 2H), 8.06–8.03 (m, 2H), 8.00 (d, *J*=8.4 Hz, 1H), 7.95–7.93 (m, 1H), 7.86 (s, 1H), 7.85 (s, 1H), 7.60–7.55 (m, 2H), 7.50 (d, *J*=8.4 Hz, 2H), 7.34–7.29 (m, 2H), 6.76 (d, *J*=8.0 Hz, 2H), 5.01–4.91 (m, 4H), 1.84 (s, 3H); δ_C: 147.3, 143.6, 134.1, 132.6, 132.0, 131.7, 130.8, 129.2, 129.0, 128.9, 128.3, 128.1, 127.8, 127.6, 127.0, 126.8, 126.4, 126.0, 124.8, 124.6, 124.2, 119.3, 50.2, 50.0, 22.9; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3450, 2934, 1754, 1684, 1653, 1524, 1362, 1238, 1135, 1091, 752; HRMS: found 474.1520. $C_{31}H_{23}NO_2S+H^+$ require 474.1528.

3.17. General synthesis of chiral amino acid tagged [4]helicene [(22+23)(a–e)]

Cyclic enediyne [**2**(**a**/**b**/**c**/**d**/**e**)] (0.04 mmol) was dissolved in dry DMF (10 mL) maintaining a high dilution of the reaction mixture ($3–4\times10^{-3}$ mmol/mL). It was then heated at 125 °C for 7–9 h (different times were required for different substrates, which were monitored by TLC). On completion, the reaction mixture was extracted with EtOAc (4×10 mL). Combined organic layers were washed with water and brine solution, dried over Na_2SO_4 and concentrated.

*3.17.1. Amino acid tagged [4]helicene (****22a****+****23a****).* Yellow solid; R_f (PE/EA=5:1) 0.50; yield: 58%; mp: 125–127 °C; δ_H: 7.97–7.84 (m, 3H), 7.70–7.67 (m, 3H), 7.61–7.52 (m, 5H), 6.82–6.80 (m, 2H), 5.65–5.57 (m, 1H), 4.91–4.70 (m, 6H), 4.15–4.11 (m, 1H), 2.04–2.02 (m, 3H), 1.39–1.37 (m, 9H), 1.25–1.23 (m, 3H), 1.11–1.10 (m, 2H); δ_C: 173.1, 155.1, 143.9, 143.7, 133.9, 133.7, 132.9, 131.7, 130.8, 130.5, 130.3, 129.9, 129.3, 127.8, 127.3, 126.8, 126.6, 126.0, 125.0, 124.7, 124.5, 124.2, 119.3, 80.1, 66.9, 66.8, 50.0, 49.9, 49.3, 49.2, 28.5, 24.9, 22.9, 18.7, 18.6; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3384, 2925, 2854, 1738, 1708, 1597, 1448, 1346, 1219, 1163, 1065, 772; HRMS: found 625.2365. $C_{36}H_{36}N_2O_6S+H^+$ requires 625.2372.

*3.17.2. Amino acid tagged [4]helicene (****22b****+****23b****).* Light orange solid; R_f (PE/EA=5:1) 0.60; yield: 58%; mp: 128–130 °C; δ_H: 7.99–7.94 (m, 1H), 7.92–7.88 (m, 2H), 7.73–7.67 (m, 4H), 7.61–7.52 (m, 4H), 6.81 (m, 2H), 5.62 (d, *J*=13.2 Hz, 0.5H), 5.53 (d, *J*=12.4 Hz, 0.5H), 4.92–4.87 (m, 3H), 4.82–4.70 (m, 3H), 4.08–4.07 (m, 0.5H), 4.00–3.98 (m, 0.5H), 2.03–2.02 (m, 3H), 1.93 (m, 0.5H), 1.87–1.86 (m, 0.5H), 1.38–1.36 (m, 9H), 0.84–0.83 (m, 1.5H), 0.77–0.73 (m, 3H), 0.57–0.55 (m, 1.5H); δ_C: 172.2, 155.8, 155.7, 143.7, 134.0, 133.9, 133.7, 133.6, 132.9, 132.8, 131.7, 130.5, 130.4, 129.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.1, 127.0, 126.8, 126.7, 126.6, 126.5, 126.4, 126.3, 126.0, 125.9, 124.8, 124.5, 79.9, 66.7, 58.6, 58.4, 50.0, 49.9, 31.2, 31.1, 28.5, 21.4, 21.3, 19.2, 17.5, 17.3; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3381, 2965, 2927, 1737, 1712, 1597, 1498, 1346, 1257, 1161, 1091, 957, 758; HRMS: found 675.2530. $C_{38}H_{40}N_2O_6S+Na^+$ requires 675.2505.

*3.17.3. Amino acid tagged [4]helicene (****22c****+****23c****).* Yellow solid; R_f (PE/EA=7:1) 0.45; yield: 58%; mp: 115–117 °C; δ_H: 7.96–7.95 (m, 1H), 7.92–7.88 (m, 2H), 7.71–7.67 (m, 3H), 7.61 (s, 1H), 7.59–7.52 (m, 4H), 6.81–6.80 (m, 2H), 5.64–5.56 (m, 1H), 4.92–4.67 (m, 6H), 4.13–4.09 (m, 1H), 2.02–2.01 (m, 3H), 1.45–1.33 (m, 9H), 0.89–0.77 (m, 8H); δ_C: 173.3, 173.2, 155.5, 147.9, 147.3, 143.7, 138.7, 138.6, 133.9, 133.7, 133.6, 132.9, 131.7, 130.5, 129.1, 127.9, 127.8, 127.7, 127.5, 126.8, 126.7, 126.0, 124.8, 124.7, 124.5, 124.2, 119.3, 80.0, 66.8, 66.7, 52.2, 52.1, 50.0, 49.9, 41.8, 41.6, 28.5, 24.9, 24.8, 23.0, 22.9, 22.0, 21.9, 21.4; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3389, 2957, 2942, 1755, 1702, 1364, 1258, 1159, 1091, 774; HRMS: found 667.2837. $C_{39}H_{42}N_2O_6S+H^+$ requires 667.2842.

*3.17.4. Amino acid tagged [4]helicene (****22d****+****23d****).* Yellow solid; R_f (PE/EA=5:1) 0.45; yield: 58%; mp: 118–119 °C; δ_H: 8.00–7.87 (m, 3H), 7.69–7.53 (m, 7H), 7.48–7.46 (m, 1H), 7.26–7.24 (m, 1H),

7.17–7.09 (m, 2H), 7.02–6.99 (m, 1H), 6.85–6.77 (m, 3H), 5.59–5.51 (m, 1H), 4.98–4.87 (m, 3H), 4.79–4.69 (m, 3H), 4.44–4.42 (m, 0.5H), 4.37–4.35 (m, 0.5H), 2.93–2.75 (m, 2H), 2.05–2.03 (m, 3H), 1.37–1.28 (m, 9H); δ_C: 171.8, 171.6, 155.2, 155.1, 143.7, 143.6, 136.1, 135.9, 133.7, 133.6, 133.5, 132.9, 131.7, 130.5, 129.4, 129.3, 129.1, 129.0, 128.7, 128.6, 128.3, 128.0, 127.9, 127.7, 127.6, 127.4, 127.2, 127.0, 126.9, 126.8, 126.6, 126.4, 126.0, 124.9, 124.8, 124.5, 80.1, 67.0, 66.9, 54.5, 54.3, 50.0, 49.9, 49.8, 38.4, 38.1, 28.4, 21.4, 21.3; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3380, 2959, 2925, 2854, 1738, 1712, 1496, 1453, 1364, 1347, 1250, 1219, 1164, 1091, 1052, 958, 770; HRMS: found 701.2681. $C_{42}H_{40}N_2O_6S+H^+$ requires 701.2685.

*3.17.5. Amino acid tagged [4]helicene (**22e**+**23e**).* Light orange solid; R_f (PE/EA=5:1) 0.40; yield: 58%; mp: 170–172 °C; δ_H: 8.00–7.89 (m, 3H), 7.68–7.66 (m, 3H), 7.60–7.50 (m, 5H), 6.85–6.80 (m, 2H), 5.81–5.77 (m, 0.3H), 5.66–5.61 (m, 0.6H), 5.55–5.52 (m, 0.3H), 4.95–4.63 (m, 5H), 4.19–4.04 (m, 2H), 3.34–3.28 (m, 2H), 2.04–2.00 (m, 4H), 1.79–1.63 (m, 6H), 1.41–1.40 (m, 5H), 1.33–1.25 (m, 19H); δ_C: 172.8, 172.6, 154.5, 154.4, 153.9, 143.7, 143.6, 134.2, 134.1, 133.6, 133.5, 132.9, 132.8, 131.7, 131.6, 130.5, 130.4, 129.1, 129.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.1, 126.9, 126.8, 126.7, 126.6, 126.5, 126.4, 126.3, 126.1, 126.0, 124.8, 124.7, 124.5, 80.0, 79.9, 66.6, 66.5, 66.4, 59.2, 59.1, 58.8, 50.0, 49.9, 46.6, 46.4, 46.3, 31.8, 30.8, 30.7, 28.6, 28.4, 28.3, 24.4, 24.3, 23.6, 23.5, 22.9, 21.4; FTIR (KBr, cm^{-1}): $\bar{\nu}$ 3408, 2958, 2925, 2854, 1740, 1689, 1598, 1458, 1401, 1346, 1218, 1161, 1089, 962, 772; HRMS: found 651.2523. $C_{38}H_{38}N_2O_6S+H^+$ requires 651.2529.

Acknowledgements

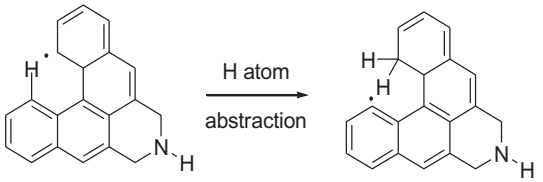
Author A.B. expresses his sincere thanks to Professor I. Alabugin for drawing our attention to the high endothermicity of the aryl–H abstraction and for many other helpful suggestions regarding the mechanism. The authors are also grateful to CSIR, Govt. of India, for research funding and a fellowship (to S.R.) respectively. DST is thanked for the funds for a 400 MHz facility under the IRPHA program and for a JC Bose fellowship (to A.B.). We also thank Professor U. Maitra, IISc, Bangalore, for useful suggestions on the equilibration between the diastereomeric helicenes.

Supplementary data

Full synthetic schemes, detail experimental procedures, spectral data of all new compounds, COSY, NOESY spectra of selected compounds, and copies of ^1H and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.064.

References and notes

1. Roy, S.; Anoop, A.; Biradha, K.; Basak, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8316.
2. (a) Jones, R. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660; (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25; (c) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082; (d) Kar, M.; Basak, A. *Chem. Rev.* **2007**, *107*, 2861.
3. (a) Katz, T. J.; Sudhakar, A.; Teasley, M. F.; Gilbert, A. M.; Geiger, W. E.; Robben, M. P.; Wuensch, M.; Ward, M. D. *J. Am. Chem. Soc.* **1993**, *115*, 3182; (b) Nuckolls, C.; Katz, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 9541; (c) Nuckolls, C.; Katz, T. J.; Katz, G.; Collings, P. J.; Castellanos, L. *J. Am. Chem. Soc.* **1999**, *121*, 79; (d) Katz, T. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1921; (e) Sato, I.; Yamashita, R.; Kadowaki, K.; Yamamoto, J.; Shibata, T.; Soai, K. *Angew. Chem.* **2001**, *113*, 1130; (f) Nuckolls, C.; Shao, R.; Jang, W.-G.; Clark, N. A.; Walba, D. M.; Katz, T. J. *Chem. Mater.* **2002**, *14*, 773; (g) Schmuck, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2448; (h) Vyklicky, L.; Eichhorn, S. H.; Katz, T. L. *Chem. Mater.* **2003**, *15*, 3594; (i) Zak, J. K.; Miyasaka, M.; Rajaca, S.; Lapkowski, M.; Rajca, A. *J. Am. Chem. Soc.* **2010**, *132*, 3246; (j) Rahe, P.; Nimmrich, M.; Grueling, A.; Schütte, J.; Stará, I. G.; Rybáček, J.; Huerta-Angeles, G.; Starý, I.; Rohlfing, M.; Kühnle, A. *J. Phys. Chem. C* **2010**, *114*, 1547; (k) Sahasithiwat, S.; Mophuang, T.; Menbangpung, L.; Kamtonwong, S.; Sooksimuang, T. *Synth. Met.* **2010**, *160*, 1148.
4. (a) Ben Hassine, B.; Gorsane, M.; Geerts-Evrard, F.; Pecher, J.; Martin, R. H.; Castelet, D. *Bull. Soc. Chim. Belg.* **1986**, *95*, 547; (b) Ben Hassine, B.; Gorsane, M.; Pecher, J.; Martin, R. H. *Bull. Soc. Chim. Belg.* **1986**, *95*, 557; (c) Weix, D. J.; Dreher, S. D.; Katz, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 10027; (d) Sato, I.; Yamashima, R.; Kadowaki, K.; Yamamoto, J.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1096; (e) Reetz, M. T.; Sostmann, S. *Tetrahedron* **2001**, *57*, 2515; (f) Yashima, E.; Maeda, K.; Nishimura, T. *Chem.—Eur. J.* **2004**, *10*, 42; (g) Amemiya, R.; Yamaguchi, M. *Org. Biomol. Chem.* **2008**, *6*, 26; (h) Chen, J.; Takenaka, N. *Chem.—Eur. J.* **2009**, *15*, 7268.
5. (a) Janke, R. H.; Haufe, G.; Würthwein, E.-U.; Borkent, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 6031; (b) Grimme, S.; Peyerimhoff, S. D. *Chem. Phys.* **1996**, *204*, 411.
6. (a) Goedicke, C.; Stegemeyer, H. *Tetrahedron Lett.* **1970**, 937; (b) Martin, R. H.; Marchant, M.-J. *Tetrahedron Lett.* **1972**, *35*, 3707; (c) Martin, R. H.; Marchant, M.-J. *Tetrahedron* **1974**, *30*, 347; (d) Meurer, P. P.; Vögtle, F. *Top. Curr. Chem.* **1985**, *127*, 1; (e) Rajca, A.; Miyasaka, M. In *Functional Organic Materials: Syntheses, Strategies, and Applications*; Müller, T. J. J., Bunz, U. H. F., Eds.; Wiley-VCH: Weinheim, 2007; p 547.
7. Zhang, X.; Zhong, P.; Chen, F. *Synth. Commun.* **2004**, *34*, 1729.
8. Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.
9. Two sequential Sonogashira coupling of diiodobenzene with THP-protected propargyl alcohol and TMS–acetylene followed by desilylation provides compound **11**.
10. Basak, A.; Shain, J. C.; Khamrai, U. K.; Rudra, K. R.; Basak, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1955.
11. Breiner, B.; Kaya, K.; Roy, S.; Yang, W.-Y.; Alabugin, I. V. *Org. Biomol. Chem.* **2012**, *10*, 3974.
12. This alternative mechanism induced us to think about the energetics of the mechanism proposed earlier. We also thank Professor Igor Alabugin, Florida State University, for drawing our attention to this aspect. The activation barrier for the H-atom abstraction by the radical in structure X has been calculated to be a 45.1 kcal/mol at the uB3LYP/6-31G** level of theory and the reaction is endothermic by 36.7 kcal/mol (personal communication from Professor Alabugin and Mr. Paul Peterson who have most kindly allowed us to use their result). Presently, we are carrying out a detailed mechanistic reinvestigation on the formation of unsubstituted [4]helicenes. The results will be published in due course.



X Y

13. Radical addition to benzene or quinoline leading to the formation of helicene or azahelicene has been demonstrated: see Harrowven, D. C.; Guy, I. L.; Nanson, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 2242.
14. For some recent work on radical addition to aromatic rings see: (a) Baroudi, A.; Alicea, J.; Flack, P.; Kirincich, J.; Alabugin, I. V. *J. Org. Chem.* **2011**, *76*, 1521; (b) Baroudi, A.; Flack, P.; Alabugin, I. V. *Chem.—Eur. J.* **2010**, *16*, 12316.
15. (a) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Story, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95; (b) Curran, D. P.; Keller, A. I. *J. Am. Chem. Soc.* **2006**, *128*, 13706; (c) Clive, D. L. J.; Peng, J.; Fletcher, S. P.; Ziffle, V. E.; Wingert, D. *J. Org. Chem.* **2008**, *73*, 2330.
16. Alabugin, I. V.; Manoharan, M.; Breiner, B.; Lewis, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 9329.