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Synthesis of β-Lactam Fused Enediynes by Intramolecular Kinugasa Reaction: Comparison of Reactivity with Monocyclic Analogues

Amit Basak (Corresponding author)

Department of Chemistry, Indian Institute of Technology

Kharagpur 721 302, India

Tel: 91-3222-283-301 E-mail: absk@chem.iitkgp.ernet.in

Runa Pal

Department of Chemistry, Indian Institute of Technology

Kharagpur 721 302, India

Sanket Das

Department of Chemistry, Indian Institute of Technology

Kharagpur 721 302, India

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Abstract

β-lactam fused enediynes have been successfully synthesized by intramolecular Kinugasa reaction in moderate yields. DSC studies indicated significant influence of the β-lactam ring upon the reactivity of enediynes. None of the β-lactam fused enediynes (under ring opening conditions) as well as the 11-membered monocyclic enediyne as the tosylate salt showed any cleavage of plasmid DNA. Interestingly, the 10-membered enediyne as the tosylate salt cleaved both single and double strands of plasmid DNA at micromolar concentration.

Keywords: Enediynes, β-lactam, Kinugasa reaction, Hybrid, Plasmid DNA

1. Introduction

N-containing cyclic enediynes including the β-lactam fused ones, are potential candidates for evaluation as antitumor and antibiotic agents.[10] The N-atom in monocyclic enediynes serves as a handle for incorporation of various appendages. The advantage of using β-lactam as a molecular lock[10, 6] lies in the fact that it imparts the strain to the fused enediyne system, thereby preventing it from undergoing Bergman cyclisation[4] and the 4-membered lactam can be easily opened up by neucleophiles (thiol) or enzymes like transpeptidase or β-lactamase or under basic conditions for activation. Because of the instability of both the β-lactam ring as well as the cyclic enediynes, the previously reported synthesis of these "lactendiynes" by Guanti *et al.*[1] (*via* route a and b) and our group[3] (via route a and c) and may not be the ideal choice (Scheme 1). The concerted formation of both enediyne and β-lactam rings via route d, has the advantage of not handling the sensitive β-lactam or cyclic enediyne until the last step. In a preliminary communication[11], we have reported the one step synthesis of β-lactam fused enediynes *via* Kinugasa reaction.[5, 8] In this paper, we describe the full experimental details for the synthesis of both the aromatic and non-aryl β-lactam fused enediynes (1-8) along with their reactivity (thermal and biological) which were compared with the corresponding monocyclic enediynes 10-11. Incidentally, the enediyne 9, a counterpart of the aromatic enediyne **7** could not be prepared.

<Space for Scheme 1>

Kinugasa reaction is a simple [3+2] cycloaddition between a nitrone and *in situ* generated Cu (I) - acetylide producing both *cis* and *trans* isomers. The reaction has the advantage for its mild condition and also the availability of large repertoire of nitrones and alkynes makes it quite attractive. In 2003 Fu *et al.*[12] first reported the intramolecular Kinugasa reaction. Ours is only the second report of intramolecular Kinugasa reaction applied to the synthesis of β-lactam fused enediynes.

<Space Figure 1>

Since intramolecular Kinugasa reaction is the final step, the construction of an acyclic enediyne with one arm carrying the nitrone while the other terminal acetylene was required. The synthesis of the oxacyclic enediynes were first attempted because of easy accessibility of the precursor. For 1 the following steps are involved: i) Sonogashira coupling[13] to construct the acyclic enediyne framework ii) O-propargylation, iii) generation of the nitrone by functional group modification. The final Kinugasa reaction was carried out by dissolving the nitrone 17 in deoxygenated acetonitrile at 0 ^{o}C (c 0.003M) followed by addition of cuprous iodide (0.5 eq) and triethyl amine (1 eq) and stirring for 24 h at 15 ^{o}C. The desired β-lactams 1 and 2 were isolated by careful chromatography over Si-gel and finally purified by hplc (ODS column, H_2O/MeOH, 5%). A third slower running compound characterized as the elimination product 5 was isolated (Scheme 2). It is interesting to note that the higher homologous nitrone 23 when subjected to similar conditions produced only the *cis* and the *trans* β-lactams 3 and 4 respectively; no such elimination product was isolated (Scheme 3).

<Space for Scheme 2-7>

We then turned our attention to the synthesis of the 11-membered enediyne systems 6 and 33. For this the precursor nitrone 32 was prepared as shown in Scheme 4. When this nitrone was subjected to Kinugasa reaction conditions, two β-lactam containing products were isolated. One is the *trans* fused system 6 and the other was the elimination product 7. Gratifyingly the reaction was much cleaner and the yields were better than what were obtained in case of the synthesis of the oxacycles. Similar strategy has been adopted to synthesize the non-aromatic β-lactam fused enediynes. The nitrone 44 under Kinugasa reaction condition gave only one product namely the *trans* fused hydroxyl-containing isomer 8 (Scheme 5). No elimination product 9 could be isolated. Perhaps the incorporation of double bond in the 11-memebered enediyne framework makes the system too unstable for isolation. It was unfortunate to note that all our attempts to induce the intramolecular Kinugasa reaction for the synthesis of the 10-membered β-lactam fused enediyne 46 were not successful; the nitrone 45 discomposing under the reaction conditions.

For the synthesis of monocyclic enediynes 10-11, our reported method* based on intramolecular N-alkylation was used. Both the 10 and 11-membered cyclic enediynes were deprotected and the free amines were isolated as the tosylate salts 10c and 11c.

1.1 Characterization

The structures of both the compounds were determined by NMR, IR and mass spectroscopic data. The stereochemistry was confirmed by extensive decoupling experiments. Thus for compound 2, upon irradiation of the H-5 methylene, the signal for the H-4 appearing as a broad signal in the range δ 4.17-4.14, collapsed to a narrow singlet with half-width of 2.3 Hz, which indicated *trans* stereochemistry.[9] For the compound 1, similar irradiation collapsed the signal for the H-4 into a doublet of coupling constant 5 Hz confirming the *cis* stereochemistry. For this compound the H-3 and H-4 protons appeared in the range of δ 3.86-3.70 as complex multiplet. For the elimination product 5 characteristic[2] broad singlets at δ 5.75 and 5.21 for the exomethylene hydrogens appeared.

The structures of the *trans* fused β-lactam 6 and the elimination product 7 were confirmed by decoupling experiment, ^{13}C and HRMS analysis. For compound 6 the carbinol proton came at δ 4.89 as doublet with J = 10.0 Hz, the NCH_2Ph appeared as separate double doublets at δ 4.71 and 4.08 (J = 15.0 Hz). H-4 appeared as a multiplet at δ 3.51 and H-3 as a dd at δ 3.36 with J values of 15.0 and 2.5 Hz. The coupling constant of 2.5 Hz indicated trans configuration. In the decoupling experiment, upon irradiation of H-13 the H-3 proton signal appeared as multiplet and irradiation of H-3 proton H-13 appeared as singlet and H-4 became a triplet. The assignments of chemical shifts and the coupling between the different protons is the elimination compound 7 has also been unambiguously settled by extensive decoupling experiments. The characteristic double bonded proton H-13 appeared at δ 6.28 as doublet with J value 1.5 Hz and H-4 at δ 3.98 as multiplet. Upon irradiation of H-4, H-13 changed to singlet and on irradiation of H-13, the pattern of H-4 changed to a dd confirming the elimination compound. Apparently the diastereomer 33 having *trans* relationship between the H-3 and carbinol OH, undergoes elimination under the reaction conditions which cannot happen for the major isomer 6.

The assignments of aliphatic β-lactam fused enediyne 8 were similarly done by decoupling experiment, ^{13}C and HRMS. In ^{1}H spectra characteristics H-3, H-4 proton appeared at δ 3.22 as dd (J = 2.5 Hz) and 3.38 as multiplet, NCH_2Ph appeared at δ4.63, 3.98 as a separate double doublets with coupling constant 14.8 Hz. The CHOH proton resonates at δ 4.75 as doublet (J = 10.4 Hz). The corresponding aromatic analogue was similarly characterized.

1.1.1 Thermal reactivity

The thermal reactivity of both the aliphatic and aromatic β-lactam fused enediynes (6-8) was then studied. The onset temperatures for BC were determined using Differential Scanning Calorimetric measurements (DSC). The enediynes 6 and 7 showed the onset temperature of BC at 207 ^{o}C and 192 ^{o}C respectively.

The slight lowering of onset temperature of elimination compound can be attributed to be due to the incorporation of endocyclic double bond into the enediyne framework; however, the effect is not very significant. For the corresponding

aliphatic analogue 8 the exothermic rise started at ~ 79 ^{o}C. This experimental result is in agreement with the fact that on going from aromatic to corresponding aliphatic analogue there is a substantial drop in onset temperature and thus lowering the activation barrier of BC. The reactivity of the β-lactam fused enediyne was then compared with the 11-membered N-substituted enediyne which revealed little difference in reactivity as recorded by DSC. The various onset temperatures for BC are shown in Table 1.

1.1.2 DNA Cleavage Activity

The higher reactivity of the β-lactam fused aliphatic enediyne prompted us to check whether it possesses any DNA-cleaving activity. Gel electrophoresis experiment carried out at 37 ^{o}C, however, revealed no such activity even at millimolar concentration. Since the free amine as salts are activated towards BC, the tosylate salt of the 11-membered enediynyl amine was also prepared and the onset temperature for BC was recorded which came out to be 100 ^{o}C. Although there is considerable lowering of activation barrier, the extent of lowering is not sufficient to bring down the reactivity to the level of room temperature. Consequently, it also failed to show any DNA-cleavage activity. Interestingly, the tosylate salt of the corresponding 10-membered enediynyl amine having a half life of 12 h at 30 ^{o}C turned out to be a potent DNA cleaving agent at micromolar concentration; the cleavage also produced significant proportion of Form III corresponding to double strand cleavage (Figure 2).

1.1.3 Experimental

Synthesis of 2-{5-[2-(3-Prop-2-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-ynyloxy}-tetrahydro-pyran (14)

To a suspension of sodium hydride (60% suspension in mineral oil, before using it was washed with petroleum ether to remove the oil, 250 mg, 10.4 mmol) in THF, solution of 3-{2-[5-(Tetrahydro-pyran-2-yloxy)-pent-1-ynyl]-phenyl}-prop-2-yn-1-ol (13) (1.55 gm, 5.20 mmol) in THF (15 ml) was added dropwise at 0 ^{o}C and the solution was stirred for 30 minutes at 0 ^{o}C. Propargyl bromide (537µl, 6.24 mmol) dissolved in THF was added dropwise. The mixture was stirred for 4 hours at room temperature. Evaporation in vacuum gave solid mass which was quenched with NH_4Cl and extracted with EtOAc (50 ml). The organic layer was washed with brine (50 ml) and dried over Na_2SO_4. Evaporation in vacuum gave an oil from which the title compound (14) was isolated by column chromatography (Si-gel, PE: EA = 25:1) as a yellowish oil; Yield: 1.49 gm, 85%; State*:* yellow oil; ν_{max} (neat) 3293, 3014, 2947, 2117, 1719, 1508, 1480, 1443, 1347, 1269 and 1028 cm^{-1}; δ_H 1.96-1.52 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (pyran)], 2.48 (1H, t, *J* = 2.4 Hz, OCH_2CCH), 2.59 (2H, t, *J* = 7.0 Hz, $CCCH_2CH_2$), 3.62-3.45 [2H, m, -OCH_2CH_2 (pyran)], 3.96-3.82 (2H, m, CH_2CH_2OTHP), 4.38 (2H, d, *J* = 2.4 Hz, OCH_2CCH), 4.55 (2H, s, $CCCH_2O$), 4.62 [1H, t, *J* = 2.8 Hz, OCH (pyran)], 7.28-7.16 (2H, m, Ar-H), 7.44-7.37 (2H, m, Ar-H); δ_C 16.5, 19.4, 25.4, 28.8, 30.6, 56.1, 57.2, 62.1, 65.9, 74.9, 79.0, 79.4, 85.8, 87.3, 93.9, 98.7, 124.6, 126.5, 127.2, 127.3, 131.7, 131.8; Mass (ESI) m/z 336 (M^+).

Synthesis of 5-[2-(3-Prop-2-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-yn-1-ol (15)

To a solution of compound 14 (1.50 gm, 4.46 mmol) in dry ethanol (20 ml) pyridinium *p*-toluene sulfonate (PPTS) (112 mg, 0.45 mmol) was added and stirred for 8 h at room temperature. Solvent was removed under vacuum and the title compound (15) was isolated by column chromatography (Si-gel, PE: EA= 3:1) as a very pale yellow viscous liquid; Yield: 876 mg, 78%; State: pale yellow; ν_{max} (neat) 3447, 2960, 2224, 1709, 1262, 1185, 1097, 760 and 667 cm^{-1}; δ_H 1.94-1.87 (2H, m, $CCCH_2CH_2CH_2OH$), 2.52 (1H, t, *J* = 2.4 Hz, OCH_2CCH), 2.63 (2H, t, *J* = 6.7 Hz, $CCCH_2CH_2CH_2OH$), 3.90 (2H, t, *J* = 6.2 Hz, CH_2CH_2OH), 4.41(2H, d, *J* = 2.4 Hz, OCH_2CCH), 4.59 (2H, s, $CCCH_2O$), 7.29-7.24 (2H, m, Ar-H), 7.45-7.41 (2H, m, Ar-H); δ_C 15.9, 31.0, 56.3, 57.3, 61.3, 75.1, 78.9, 79.7, 85.9, 87.3, 93.8, 124.6, 126.4, 127.3, 128.2, 131.7, 131.9; Mass (ESI) m/z 252 (M^+).

Synthesis of 5-[2-(3-Prop-2-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-ynal (16)

To a solution of 5-[2-(3-Prop-2-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-yn-1-ol 15 (791 mg, 3.14 mmol) in dry DCM (15 ml),) PCC (1.01 gm, 4.71 mmol) was added and stirred for 3 h at room temperature under argon. The mixture was filtered thorough silica gel bed, which was thoroughly washed with DCM and the combined filtrate and washings were evaporated. The titled compound 16 was isolated by column chromatography (Si gel, PE: EA = 7:1) as a pale brown oil; Yield: 510 mg, 65%; State: pale brown oil; ν_{max} (neat) 3448, 2919, 2226, 1718, 1218, 1078 and 761 cm^{-1}; δ_H 2.47 (1H, t, *J* = 2.4 Hz, OCH_2CCH), 2.79 (4H, s, CH_2CH_2CHO), 4.38 (2H, d, *J* = 2.4 Hz, OCH_2CCH), 4.54 (2H, s, $CCCH_2O$), 7.26-7.21 (2H, m, Ar-H), 7.42-7.36 (2H, m, Ar-H), 9.87 (1H, s, CH_2CHO); δ_C 12.8, 42.4, 56.2, 57.2, 74.9, 78.9, 79.9, 85.6, 87.5, 92.0, 124.8, 125.9, 127.5, 128.2, 131.8, 131.9, 200.4; Mass (ESI) m/z 250 (M^+).

Synthesis of 5-[2-(3-Prop-2-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-ynyl-N-benzyl nitrone (17)

To a solution of 5-[2-(3-Prop-2-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-ynal (16) (550 mg, 2.20 mmol) in dry MeOH (20 ml) N-benzyl hydroxylamine (406 mg, 3.30 mmol) was added and stirred for 2 h at room temperature under argon atmosphere. Evaporation in vacuum gave an oily residue from which title compound 17 was isolated by column chromatography (Si-gel, PE: EA = 1:4) as brown oil; Yield: 625 mg, 80%; State: brown oil; δ_H 2.49 (1H, t, *J* = 2.0 Hz,

OCH_2CCH), 2.87-2.74 (4H, m, $CCCH_2CH_2CH_2$), 4.31 (2H, d, J = 2.2 Hz, OCH_2CCH), 4.48 (2H, s, $CCCH_2O$), 5.04 (2H, s, NCH_2Ph), 7.45-7.17 [10H, m, Ar-H, CHN (O) CH_2Ph]; δ_C 15.8, 26.1, 43.0, 56.3, 57.3, 68.9, 75.2, 78.9, 80.4, 85.7, 87.5, 92.2, 124.7, 125.8, 127.6, 128.2, 128.8, 128.8, 129.2, 129.3, 131.8, 132.4; Mass (ESI) m/z 355 (M^+).

Synthesis of Sulfuric acid methyl ester 3-{2-[5-(tetrahydro-pyran-2-yloxy) -pent-1-ynyl]-phenyl}-prop-2-ynyl ester (18)

To a solution of 3-{2-[5-(Tetrahydro-pyran-2-yloxy)-pent-1-ynyl]-phenyl}-prop-2-yn-1-ol (13) (1.26 gm, 4.23 mmol) in CH_2Cl_2 (20 ml) at 0 ^oC, methane sulfonyl chloride (490 µl, 6.34 mmol) and triethyl amine (882 µl, 6.34 mmol), were added. The reaction mixture was stirred for 15 mins at room temperature after which it was poured into water (50 ml) and extracted with CH_2Cl_2 (2 x 50 ml). The organic layer was washed with water (2 x 50 ml), dried and then evaporated. The residue on chromatography (Si-gel, hexane: EtOAc = 2:1) furnished the title compounds (18) as pale yellow oil; Yield: 1.41 gm, 85%; State: pale yellow oil; δ_H 1.97-1.58 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (pyran)], 2.60 (2H, t, J = 7.0 Hz, $CCCH_2CH_2CH_2$), 3.14 (3H, s, OSO_2CH_3), 3.61-3.45 (2H, m, OCH_2CH_2OTHP), 3.91-3.85 (2H, m, $CCCH_2CH_2CH_2OTHP$), 4.62 (1H, t, J = 2.8 Hz, OCH-Pyran), 5.03 (2H, s, CH_2OMs), 7.26-7.19 (2H, m, Ar-H), 7.40-7.36 (2H, m, Ar-H); Mass (ESI) m/z 392 (M^+).

Synthesis of 2-{5-[2-(3-Bromo-prop-1-ynyl)-phenyl]-pent-4-ynyloxy}-tetrahydro-pyran (19)

To a solution of mesylate 18 (1.4 gm, 3.57 mmol) in dry THF (20 ml) at 0 ^oC, LiBr (463 mg, 5.36 mmol) was added to it and stirred at 0 ^oC for 3 h. After completion of the reaction it was poured onto a saturated solution of $NaHCO_3$ (25 ml). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude oil was purified *via* chromatography (Si-gel, hexane: EtOAc = 25:1) to yield the bromide compound 19; Yield: 1.03 gm, 80%; State: yellow oil; δ_H 1.98-1.58 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (pyran)], 2.60 (2H, t, J = 7.0 Hz, $CCCH_2CH_2CH_2$), 3.61-3.45 (2H, m, OCH_2CH_2OTHP), 3.91-3.85 (2H, m, $CCCH_2CH_2CH_2OTHP$), 4.23 (2H, s, $CCCH_2Br$), 4.62 [1H, t, J = 2.8 Hz, OCH (Pyran)], 7.26-7.19 (2H, m, Ar-H), 7.40-7.36 (2H, m, Ar-H); δ_C 15.3, 16.6, 19.5, 25.5, 28.9, 30.7, 62.2, 65.9, 79.3, 85.7, 87.5, 94.4, 98.8, 124.5, 126.8, 127.2, 128.4, 131.8, 132.0; Mass (ESI) m/z 363, 361 (M^+).

Synthesis of 2-{5-[2-(3-But-3-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-ynyloxy}-tetrahydro-pyran (20)

To a suspension of sodium hydride (80 mg, 3.33 mmol) in THF, solution of 3-butyn-1-ol (251 µl, 3.33 mmol) in THF (5 ml) was added dropwise at 0 ^oC and it was stirred for 30 minutes at 0 ^oC. Then 2-{5-[2-(3-Bromo-prop-1-ynyl)-phenyl]-pent-4-ynyloxy}-tetrahydro-pyran (19) (1 gm, 2.77 mmol) dissolved in THF (15 ml) was added dropwise. It was stirred for 4 hours at room temperature. Evaporation in vacuum gave a solid mass which was quenched with NH_4Cl and extracted with EtOAc (50 ml). The organic layer was washed with brine (50 ml) and dried over Na_2SO_4. Evaporation in vacuum gave an oil from which the title compound 20 was isolated by column chromatography (Si-gel, PE: EA = 25:1) as a yellowish oil; Yield: 679 mg, 70%; State: yellow liquid; ν_{max} (neat) 3293, 3014, 2947, 2117, 1719, 1508, 1480, 1443, 1347, 1269 and 1028 cm^{-1}; δ_H 1.95-1.54 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (pyran)], 2.00 (1H, t, J = 2.8 Hz, OCH_2CCH), 2.62-2.49 (4H, m, $CCCH_2CH_2CH_2$, OCH_2CH_2CCH), 3.59-3.54 [2H, m, OCH_2CH_2 (pyran)], 3.93-3.74 (4H, m, CH_2CH_2OTHP, OCH_2CH_2CCH), 4.47 (2H, s, OCH_2CCH), 4.62 [1H, t, J = 2.8 Hz, OCH (pyran)], 7.25-7.20 (2H, m, Ar-H), 7.41-7.37 (2H, m, Ar-H); δ_C 16.6, 19.5, 19.7, 25.5, 29.0, 30.7, 58.9, 62.1, 65.9, 67.6, 69.4, 79.5, 81.1, 85.5, 88.2, 93.9, 98.8, 124.9, 126.5, 127.2, 128.1, 131.8, 131.9; Mass (ESI) m/z 350 (M^+).

Synthesis of 5-[2-(3-But-3-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-yn-1-ol (21)

Procedure same as 15; Yield: 297 mg, 78%; State: pale yellow; ν_{max} (neat) 3447, 2960, 2224, 1709, 1262, 1185, 1097, 761, 667 cm^{-1}; δ_H 1.91-1.77 (2H, m, $CCCH_2CH_2CH_2OH$), 1.99 (1H, t, J = 2.6 Hz, OCH_2CCH), 2.61-2.49 (4H, m, $CCCH_2CH_2CH_2OH$, OCH_2CH_2CCH), 3.89-3.72 (4H, m, CH_2CH_2OH, OCH_2CH_2CCH), 4.47 (2H, s, $CCCH_2O$), 7.24-7.19 (2H, m, Ar-H), 7.43-7.35 (2H, m, Ar-H); δ_C 16.1, 19.7, 31.2, 58.9, 60.4, 67.9, 69.6, 79.8, 81.0, 85.5, 88.1, 93.8, 124.9, 126.4, 127.3, 128.2, 131.8, 132.0; Mass (ESI) m/z 266 (M^+).

Synthesis of 5-[2-(3-But-3-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-ynal (22)

Procedure same as 16;Yield: 323 mg, 65%; State: pale brown oil; ν_{max} (neat) 3448, 2919, 2226, 1718, 1218, 1078, 761 cm^{-1}; δ_H 2.00 (1H, t, J = 2.4 Hz, OCH_2CH_2CCH), 2.59-2.50 (2H, m, OCH_2CH_2CCH), 2.79 (4H, s, CH_2CH_2CHO), 3.77 (2H, t, J = 7.0 Hz, OCH_2CH_2CCH), 4.47 (2H, s, $CCCH_2O$), 7.25-7.21 (2H, m, Ar-H), 7.41-7.36 (2H, m, Ar-H), 9.87 (1H, s, $-CH_2CHO$); δ_C 12.6, 19.4, 42.1, 58.6, 67.4, 69.1, 80.1, 80.7, 84.9, 87.9, 91.6, 124.6, 125.6, 127.2, 127.8, 131.5, 131.6, 200.1; Mass (ESI) m/z 264 (M^+).

Synthesis of 5-[2-(3-But-3-ynyloxy-prop-1-ynyl)-phenyl]-pent-4-ynyl-N-benzyl nitrone (23)

Procedure same as 17; Yield: 447 mg, 80%; State: brown oil; δ_H 1.99 (1H, t, J = 2.6 Hz, OCH_2CH_2CCH), 2.55-2.47 (2H, m, $CCCH_2CH_2CH_2$), 2.81-2.71 (4H, m, $CCCH_2CH_2$, OCH_2CH_2CCH), 3.73 (2H, t, J = 7.0 Hz, OCH_2CH_2CCH), 4.41 (2H, s, $CCCH_2O$), 4.93 (2H, s, NCH_2Ph), 6.96 [1H, t, J = 8.4 Hz, CHN (O) CH_2Ph], 7.45-7.22 (9H, m, Ar-H); δ_C 11.6, 15.4, 21.8, 25.3, 54.6, 63.5, 65.2, 76.1, 76.7, 80.9, 83.9, 88.0, 95.2, 120.6, 121.6, 123.3, 123.8, 123.9, 124.6, 124.9,

127.6, 127.7, 128.4; Mass (ESI) m/z 369 (M^+).

Synthesis of {2-[5-(Tetrahydro-pyran-2-yloxy)-pent-1-ynyl]-phenyl}-propynal (24)

To a solution of alcohol (13) (900 mg, 3.01 mmol) in dry DCM was added Dess- Martin reagent (1.54 gm, 3.62 mmol) under argon atmosphere and the mixture stirred at room temperature in the dark for 4 h. The reaction mixture was diluted with ethyl acetate and the oxidant quenched with a saturated solution of $Na_2S_2O_3$. The organic layer was washed (sat. $NaHCO_3$), dried over Na_2SO_4, filtered and concentrated. Evaporation in vacuum gave oil from which the title compound (24) was isolated by column chromatography (Si-gel, PE: EA = 15:1) as a brown oil. Yield: 858 mg, 96%; State: yellow oil; ν_{max} (neat) 3016, 2945, 2187, 1719, 1656, 1354, 1216, 1032, 759 cm^{-1}; δ_H 1.96-1.52 [8H, m, $CCCH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.61 (2H, t, J = 7.0 Hz, $CCCH_2CH_2CH_2$), 3.61-3.45 [2H, m, OCH_2CH_2 (pyran)], 3.96-3.80 (2H, m, CH_2OTHP), 4.62 [1H, t, J = 2.8 Hz, O-CH (pyran)], 7.80-7.35 (4H, m, Ar-H), 9.46 (1H, s, CCCHO); Mass (ESI) m/z 296 (M^+).

Synthesis of 1-{2-[5-(Tetrahydro-pyran-2-yloxy)-pent-1-ynyl]-phenyl}-5-trimethylsilanyl-penta-1, 4-diyn-3-ol (25)

Dry degassed THF (70 ml) was placed in a two neck round bottom flask under argon atmosphere and temperature was reduced to 0 ^oC. Trimethylsilyl acetylene (1.023 ml, 7.39 mmol) was added and then n-butyllithium soln. in hexane (1.6 M in hexane) 4.62 ml (3 equivalent) was added dropwise. The mixture was stirred at 0 ^oC under argon atmosphere for 20 minutes. The aldehyde 24 (730 mg, 2.46 mmol) dissolved in dry degassed THF (5 ml) was added dropwise at that condition. Reaction was continued for 30 minutes at 0 ^oC and then quenched with aq. NH_4Cl soln. (30 ml). The mixture was poured into EtOAc (200 ml) and the organic layer was washed with saturated $NaHCO_3$ soln. followed by brine (100 ml each) and dried over Na_2SO_4 and then evaporated. Evaporation in vacuum gave oil from which the title compound (25) was isolated by column chromatography (Si-gel, PE: EA = 10:1) as a brown oil; Yield: 826 mg, 85%; State: brown oil; ν_{max} (neat) 3432, 2946, 2206, 1623, 1443, 1293, 1137, 994 cm^{-1}; δ_H 0.06 (9H, s, TMS), 1.98-1.67 [8H, m, $CCCH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.69-2.57 (2H, m, $CCCH_2CH_2CH_2$), 3.75-3.54 [2H, m, OCH_2CH_2 (OTHP)], 4.28-3.78 (2H, m, $CCCH_2CH_2CH_2OTHP$), 4.78 [1H, bs, OCH (pyran)], 5.36 (1H, bs, CHOH), 7.29-7.16 (2H, m, Ar-H), 7.48-7.34 (2H, m, Ar-H); δ_C 19.1, 35.3, 37.7, 44.7, 48.4, 49.7, 72.1, 75.0, 80.9, 85.1, 99.4, 102.1, 109.6, 113.0, 117.6, 121.8, 144.1, 146.6, 146.9, 147.8, 151.5, 152.0; Mass (ESI) m/z 394 (M^+).

Synthesis of 1-{2-[5-(Tetrahydro-pyran-2-yloxy)-pent-1-ynyl]-phenyl}-penta-1,4-diyn-3-ol (26)

To a solution of the silylated compound 25 (700 mg, 1.78 mmol) in dry methanol (50 ml), potassium flouride (205 mg, 3.54 mmol) was added and the mixture was stirred for 4 h at room temperature under argon atmosphere. Evaporation in vacuum gave oil from which the title compound (26) was isolated by column chromatography (Si-gel, PE: EA = 10:1) as a brown oil; Yield: 458 mg, 80%; State*:* brown oil; δ_H 1.97-1.54 [(8H, m, $CCCH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.65-2.55 (3H, m, $CCCH_2CH_2$, CHOHCCH), 3.76-3.75 [2H, m, OCH_2CH_2 (OTHP)], 4.15-3.85 (2H, m, OCH_2CH_2 (OTHP)], 4.75 (1H, bs, OCH (pyran)], 5.37 (1H, bs, CHOH), 7.29-7.19 (2H, m, Ar-H), 7.46-7.35 (2H, m, Ar-H); δ_C 16.2, 18.8, 25.2, 28.1, 30.3, 51.9, 61.5, 65.6, 72.1, 79.7, 81.5, 82.7, 89.5, 93.7, 97.9, 124.3, 125.1, 126.4, 128.0, 131.6, 132.3; Mass (ESI) m/z 322 (M^+).

Synthesis of tert-Butyl-(1-ethynyl-3-{2-[5-(tetrahydro-pyran-2-yloxy)-pent-1-ynyl] -phenyl}-prop-2-ynyloxy) -diphenyl-silane (27)

To a solution of 26 (650 mg, 2.02 mmol) in dry CH_2Cl_2 (50 ml), imidazole (342 mg, 5.04 mmol) and then TBDPS-Cl (613 µl, 2.42 mmol) were added at room temperature. After addition of DMAP (25 mg, 0.20 mmol), the mixture was stirred for 3 h. It was then poured into CH_2Cl_2 (100 ml) and the organic layer was washed with 0.1 (N) HCl and brine (100 ml each), dried over Na_2SO_4 and then evaporated. Evaporation in vacuum gave oil from which the title compound (27) was isolated by column chromatography (Si-gel, PE: EA = 25:1) as a brown oil; Yield: 904 mg, 80%; State: brown oil; δ_H 1.10 (9H, s, t-Bu of TBDPS), 1.96-1.56 [8H, m, $CCCH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.35 (2H, t, J = 6.9 Hz, $CCCH_2CH_2CH_2$), 2.50 (1H, d, J = 2.4 Hz, CCH), 3.75-3.70 [2H, m, OCH_2CH_2 (pyran)], 4.15-3.80 (2H, m, CH_2OTHP), 4.68 [1H, bs, OCH (pyran)], 5.37 (1H, d, J = 2.1 Hz, CHOTBDPS), 7.38-7.30 (10H, m, Ar-H), 7.70-7.64 (4H, m, Ar-H); δ_C 19.0, 19.2, 24.8, 25.5, 26.0, 27.9, 31.5, 52.3, 62.3, 64.8, 71.9, 77.8, 80.1, 81.4, 90.6, 97.9, 120.8, 121.5, 122.8, 127.5, 127.6, 127.8, 127.8, 128.1, 128.3, 128.7, 129.6, 129.6, 130.5, 131.8, 134.6; Mass (ESI) m/z 560 (M^+).

Synthesis of 5-{2-[3-(tert-Butyl-diphenyl-silanyloxy)-penta-1, 4-diynyl]-phenyl}-pent-4-yn-1-ol (28)

Procedure same as 15; Yield: 680 mg, 80%; State: yellow oil; ν_{max} (neat) 3435, 2377, 2067, 1638 cm^{-1}; δ_H 1.11 (9H, s, t-Bu of TBDPS), 1.79 (2H, m, $CCCH_2CH_2CH_2$), 2.51 (2H, t, J = 7.2 Hz, $CCCH_2CH_2$), 2.56 (1H, d, J = 2.4 Hz, CCH), 3.80 (2H, t, J = 6.2 Hz, $CH_2CH_2CH_2OH$), 5.36 (1H, d, J = 2.1 Hz, CHOTBDPS), 7.47-7.21 (10H, m, TBDPS), 7.84-7.77 (4H, m, Ar-H); δ_C 16.1, 19.3, 26.7, 31.0, 54.4, 61.5, 72.3, 79.6, 81.4, 83.2, 89.5, 93.9, 124.7, 126.6, 127.2, 127.7, 127.7, 128.3, 129.9, 130.0, 131.6, 132.1, 132.5, 132.8, 135.9, 135.9; Mass (ESI) m/z 476 (M^+).

5-{2-[3-(tert-Butyl-diphenyl-silanyloxy)-penta-1,4-diynyl]-phenyl}-pent-4-ynal (29)

Procedure same as described for 24; Yield: 1.14 gm, 95%; State: yellow oil; ν_{max} (neat) 3433, 2377, 1638, 772 cm^{-1}; δ_H

1.11 (9H, s, t-Bu of TBDPS), 2.53 (1H, d, J = 2.2 Hz, CCH), 2.68 (4H, s, CH_2CH_2CHO), 5.35 (1H, bs, CHOTBDPS), 7.43-7.22 (10H, m, Ar-H of TBDPS), 7.84-7.77 (4H, m, Ar-H), 9.75 (1H, s, $CCCH_2CH_2CHO$); δ_C 32.3, 38.8, 46.1, 62.0, 73.8, 91.7, 99.3, 100.8, 102.5, 109.1, 111.8, 144.2, 145.6, 146.9, 147.1, 147.2, 147.4, 147.8, 149.3, 149.5, 151.1, 151.5, 152.7, 152.9, 155.3, 220.0; Mass (ESI) m/z 474 (M^+).

Synthesis of 1-[2-(5, 5-Dimethoxy-pent-1-ynyl)-phenyl]-penta-1, 4-diyn-3-ol (30)

A solution of silylated compound (750 mg, 1.58 mmol) in 3% methanolic HCl (12N) (10 ml) was treated and the mixture was stirred for 2 h at room temperature. It was then partitioned between EtOAc and water (50 ml each). The organic layer was washed with saturated solution of $NaHCO_3$, brine solution and dried (Na_2SO_4) and concentrated under vacuum at room temperature. After purification by column chromatography (Si-gel, PE: EA = 2:1), compound 30 was isolated as a pale yellow oil; Yield: 335 mg, 75%; State: pale yellow oil; ν_{max} (neat) 3433, 2377, 1637, 1219, 771 cm^{-1}; δ_H 2.00-1.90 (2H, m, $CCCH_2CH_2CH_2$), 2.54 (2H, t, J = 6.6 Hz, $CCCH_2CH_2CH_2$), 2.57 (1H, d, J = 2.2 Hz, CHOHCCH), 3.37 (6H, d, J = 3.0 Hz, OCH_3), 5.02 [1H, t, J = 5.8 Hz, CH $(OMe)_2$], 5.35 (1H, bs, CHOH), 7.37-7.19 (2H, m, Ar-H), 7.47-7.38 (2H, m, Ar-H); δ_C 15.3, 30.8, 52.3, 52.5, 72.7, 78.9, 81.5, 81.9, 92.8, 97.6, 102.8, 124.2, 125.0, 126.5, 128.6, 130.6, 133.2; Mass (ESI) m/z: 282 (M^+).

Synthesis of 5-[2-(3-Hydroxy-penta-1,4-diynyl)-phenyl]-pent-4-ynal (31)

A solution of the compound 30 (600 mg, 2.13 mmol) in THF (30 ml) containing aqueous HCl (2M, 3 ml) was stirred for 6 hours at room temperature. The mixture was quenched with saturated $NaHCO_3$ (30 ml), and extracted with EtOAc. Drying over Na_2SO_4 and evaporation gave the yellow oily material which was purified by column chromatography (Si-gel, PE: EA = 1:1). Yield: 427 mg, 85%; State: yellow oil ; ν_{max} (neat) 3433, 2079, 1637, 771 cm^{-1}; δ_H 2.60 (1H, d, J = 2.0 Hz, CHOHCCH), 2.80 (4H, s, CH_2CH_2CHO), 5.40 (1H, d, J = 2.4 Hz, CHOH), 7.28-7.17 (2H, m, Ar-H), 7.44-7.34 (2H, m, Ar-H), 9.86 (1H, s, CH_2CH_2CHO); δ_C 12.6, 41.9, 51.9, 73.9, 80.9, 82.6, 87.3, 89.2, 92.4, 124.1, 126.0, 126.6, 128.7, 130.7, 133.2, 202.1; Mass (ESI) m/z: 236 (M^+).

5-[2-(3-Hydroxy-penta-1,4-diynyl)-phenyl]-pent-4-ynyl-N-benzyl nitrone (32)

Yield: 686 mg, 95%; State: brown oil; δ_H 2.55 (1H, d, J = 2.4 Hz, CCH), 2.88-2.68 (4H, m, $CCCH_2CH_2$), 4.95 (2H, s, NCH_2Ph), 5.29 (1H, d, J = 2.2 Hz, CHOH), 6.89 [1H, m, $CH{=}N(O)CH_2Ph$], 7.44–7.18 (9H, m, Ar-H); δ_C 16.2, 26.2, 58.7, 68.8, 72.2, 80.8, 81.5, 81.6, 90.7, 92.6, 125.1, 125.8, 127.6, 128.2, 128.7, 128.8, 129.5, 131.4, 131.6, 132.1, 141.6; Mass (ESI) m/z: 341 (M^+).

Synthesis of 2-(7-Chloro-hept-6-en-4-ynyloxy)-tetrahydro-pyran (34)

To a solution of *cis*-dichloroethylene (1 ml, 13.24 mmol) in dry degassed benzene (20 ml) at room temperature, Pd $(PPh_3)_4$ (453 mg, 0.40 mmol) and n-$BuNH_2$ (3.93 ml, 52.95 mmol) were added and stirred for 5 mins under argon. CuI (503 mg, 2.65 mmol) was then added and the solution was stirred for 20 min followed by addition of THP protected 4-Pentyn 1-ol (2.43 gm, 14.55 mmol). The reaction was carried out for 2 hours. The mixture was then partitioned between EtOAc and aqueous NH_4Cl (2 x 100 ml each). The combined organic layers were washed with aqueous NH_4Cl (2 x 70 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The product 34 was isolated as brown oil by column chromatography (Si-gel, PE: EA = 15: 1); Yield: 2.72 gm, 90%; State: brown oil; δ_H 1.89-1.51 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.49 (2H, t, J = 7.0Hz, $CCCH_2CH_2CH_2$), 3.54-3.43 [2H, m, OCH_2CH_2 (pyran)], 3.89-3.76 (2H, m, CH_2OTHP), 4.59 [1H, t, J = 2.8 Hz, OCH (pyran)], 5.81 (1H, td, J = 1.9, 7.3 Hz, CHCHCl), 6.27 (1H, d, J = 7.4 Hz, CHCl); δ_C 16.5, 19.4, 25.4, 28.7, 30.6, 62.1, 65.8, 74.8, 98.5, 98.8, 112.4, 126.9; Mass (ESI) m/z: 228 (M^+).

Synthesis of 10-(Tetrahydro-pyran-2-yloxy)-dec-4-ene-2,6-diyn-1-ol (35)

Procedure same as described for 34; Yield: 2.32 gm, 88%; State*:* brown oil; δ_H 1.89-1.49 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.53 (2H, t, J = 6.0 Hz, $CCCH_2$), 3.64-3.52 [2H, m, OCH_2CH_2 (pyran)], 4.09-3.83 (2H, m, CH_2OTHP), 4.40 (2H, s, $CCCH_2OH$), 4.73 [1H, t, J = 3.0 Hz, OCH (pyran)], 5.77 (2H, s, CHCH); δ_C 16.4, 18.9, 25.4, 28.2, 30.4, 51.3, 61.6, 65.2, 78.9, 82.4, 94.9, 97.7, 98.3, 118.2, 120.5; Mass (ESI) m/z: 248 (M^+).

Synthesis of 10-(Tetrahydro-pyran-2-yloxy)-dec-4-ene-2, 6-diynal (36)

Procedure same as described for 24; Yield: 1.13 gm, 95%; State: yellow oil; δ_H 1.94-1.24 [8H, m, $CCCH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.58 (2H, t, J = 6.9 Hz, $CCCH_2CH_2CH_2$), 3.57-3.46 [2H, m, OCH_2CH_2 (pyran)], 3.93-3.80 (2H, m, CH_2OTHP), 4.60 [1H, t, J = 3.2 Hz, O-CH (pyran)], 5.87 (1H, d, J = 10.8 Hz, $CHCHCCCH_2CH_2$), 6.13 (1H, dt, J = 2.4, 8.4 Hz, CHCHCCCHO), 9.34 (1H, s, CCCHO); δ_C 16.8, 19.4, 25.4, 28.5, 30.6, 62.1, 65.7, 84.4, 91.7, 94.3, 98.8, 103.0, 114.9, 132.1, 176.5; Mass (ESI) m/z 246 (M^+).

Synthesis of 12-(Tetrahydro-pyran-2-yloxy)-1-trimethylsilanyl-dodec-6-ene-1, 4, 8-triyn-3-ol (37)

Procedure same as described for 25; Yield: 1.19 gm, 85%; State: brown oil; δ_H 0.18 (9H, s, TMS-H), 1.86-1.56 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.54 (2H, t, J = 6.1 Hz, $CCCH_2CH_2CH_2$), 3.64-3.58 [2H, m, OCH_2CH_2 (pyran)],

4.21-3.90 (2H, m, CH_2OTHP), 4.77 [1H, t, *J* = 3.2 Hz, OCH (pyran)], 5.26 (1H, bs, CHOH), 5.81 (2H, s, CH=CH); Mass (ESI) m/z 344 (M^+).

Synthesis of 12-(Tetrahydro-pyran-2-yloxy)-dodec-6-ene-1, 4, 8-triyn-3-ol (38)

Procedure same as that of 26; Yield: 506 mg, 80%; State: yellow oil; δ_H 1.89-1.52 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.63-2.49 (3H, m, $CCCH_2CH_2CH_2$, CHOHCCH), 3.65-3.58 [2H, m, OCH_2CH_2(OTHP)], 4.19-3.93 (2H, m, $CH_2CH_2CH_2OTHP$), 4.98-4.78 (1H, m, OCH (pyran)], 4.97 (1H, d, *J* = 8.8 Hz, CHOH), 5.25 (1H, d, *J* = 4.8 Hz, $CH=CHCCCH_2CH_2$), 5.86-5.77 (1H, m, CH=CHCCCHOH); δ_C 16.3, 18.5, 25.3, 27.9, 30.3, 52.0, 61.2, 65.1, 72.1, 79.0, 81.2, 81.4, 92.7, 97.6, 97.8, 117.6, 121.6; Mass (ESI) m/z 272 (M^+).

Synthesis of tert-Butyl-[1-ethynyl-10-(tetrahydro-pyran-2-yloxy)-dec-4-ene-2,6-diynyloxy]-diphenyl-silane (39)

Procedure same as 27; Yield: 1.05 gm, 80%; State: yellow oil; δ_H 1.15 (9H, s, t-Bu of TBDPS), 1.76-1.41 [8H, m, $CCCH_2CH_2CH_2$, $CH_2CH_2CH_2$ (Pyran)], 2.37 (2H, t, *J* = 6.9 Hz, $CCCH_2CH_2CH_2$), 2.43 (1H, d, *J* = 2.4 Hz, CCH), 3.40-3.36 [2H, m, OCH_2CH_2 (pyran)], 3.75-3.70 (2H, m, CH_2OTHP), 4.49 [1H, t, *J* = 3.2 Hz, OCH (pyran)], 5.19 (1H, bs, CHOH), 5.66 (1H, dd, *J* = 1.2, 10.8 Hz, $CH=CHCCCH_2CH_2$), 5.76 (1H, d, *J* = 10.8 Hz, CH=CHCCCHOTBDPS), 7.38-7.30 (5H, m, Ar-H), 7.71-7.64 (5H, m, Ar-H); δ_C 19.3, 19.4, 25.4, 26.5, 26.6, 28.8, 30.6, 54.3, 62.1, 65.9, 72.3, 78.1, 81.1, 81.6, 92.7, 98.7, 117.3, 121.3, 121.4, 127.4, 127.6, 127.6, 127.7, 129.9, 130.0, 132.6, 134.8; Mass (ESI) m/z 510 (M^+).

Synthesis of 10-(tert-Butyl-diphenyl-silanyloxy)-dodec-6-ene-4, 8, 11-triyn-1-ol (40)

Procedure same as 15; Yield: 802 mg, 80%; State: yellow viscous oil; δ_H 1.15 (9H, s, t-Bu of TBDPS), 1.74 (2H, t, *J* = 6.4 Hz, $CCCH_2CH_2CH_2$), 2.45 (2H, t, *J* = 4.8 Hz, $CCCH_2CH_2CH_2$), 2.52 (1H, d, *J* = 2.4 Hz, CHOHCCH), 3.75 (2H, d, *J* = 6.4 Hz, $CH_2CH_2CH_2OH$), 5.25 (1H, d, *J* = 1.6 Hz, CHCCH), 5.73 (1H, d, *J* = 10.8 Hz, $CH=CHCCCH_2CH_2$), 5.82 (1H, td, *J* = 1.6, 11.2 Hz, CH=CHCCCH), 7.45-7.38 (5H, m, Ar-H), 7.77-7.75 (5H, m, Ar-H); δ_C 16.3, 19.3, 26.7, 30.9, 54.3, 61.5, 72.3, 78.5, 81.2, 81.7, 92.7, 98.3, 117.6, 121.4, 127.6, 127.7, 129.6, 129.9, 130.0, 132.5, 132.7, 135.9; Mass (ESI) m/z: 426 (M^+).

Synthesis of 10-(tert-Butyl-diphenyl-silanyloxy)-dodec-6-ene-4, 8, 11-triynal (41)

Procedure same as described for 24; Yield: 946 mg, 95%; State: brown oil; δ_H 1.09 (9H, s, t-Bu of TBDPS), 2.50 (1H, d, *J* = 2.1 Hz, CHOHCCH), 2.62 (4H, s, CH_2CH_2CHO), 5.27 (1H, d, *J* = 1.6 Hz, CHCCH), 5.77 (2H, dd, *J* = 1.6, 5.3 Hz, CH=CH), 7.49-7.33 (5H, m, Ar-H), 7.79-7.75 (5H, m, Ar-H), 9.71 (1H, s, CH_2CH_2CHO); δ_C 13.0, 19.3, 26.7, 42.5, 54.3, 74.3, 78.8, 81.2, 81.5, 93.0, 96.4, 118.1, 120.9, 127.6, 127.7, 129.8, 129.9, 132.6, 132.7, 135.8, 135.9, 200.2; Mass (ESI) m/z: 424 (M^+).

Synthesis of 12, 12-Dimethoxy-dodec-6-ene-1, 4, 8-triyn-3-ol (42)

Procedure same as that of 30; Yield: 369 mg, 75%; State: yellow oil; δ_H 1.91-1.86 (2H, m, $CCCH_2CH_2CH_2$), 2.48 (2H, t, *J* = 6.4 Hz, $CCCH_2CH_2CH_2$), 2.55 (1H, d, *J* = 2.4 Hz, CHOHCCH), 3.35 (6H, d, *J* = 7.2 Hz, OCH_3), 4.33 (1H, d, *J* = 8.4 Hz, CHOH), 4.93 [1H, t, *J* = 5.6 Hz, $CH(OMe)_2$], 5.27 (1H, d, *J* = 8.4 Hz, CHOH), 5.83 (2H, d, *J* = 2.4 Hz, CH=CH); δ_C 15.4, 30.9, 52.1, 52.3, 72.4, 78.8, 81.0, 81.6, 92.7, 97.9, 102.4, 117.9, 121.5; Mass (ESI) m/z: 232 (M^+).

Synthesis of 10-Hydroxy-dodec-6-ene-4, 8, 11-triynal (43)

Procedure same as 31; Yield: 682 mg, 85%; State: yellow oil; δ_H 2.63 (1H, d, *J* = 2.0 Hz, CHOHCCH), 2.75 (4H, s, CH_2CH_2CHO), 3.75 (1H, d, *J* = 7.6 Hz, CHOH), 5.30 (1H, d, *J* = 6.4 Hz, CHOH), 5.84 (2H, s, CH=CH), 9.86 (1H, s, CH_2CH_2CHO) ; δ_C 13.1, 42.0, 52.1, 72.6, 78.9, 80.8, 81.4, 92.5, 96.5, 118.2, 121.2, 201.9; Mass (ESI) m/z: 186 (M^+).

Synthesis of 10-Hydroxy-dodec-6-ene-4, 8, 11-triynyl-N-benzyl nitrone (44)

Procedure same as 17; Yield: 892 mg, 95%; State: brown oil; δ_H 2.54 (1H, d, *J* = 2.4 Hz, CCH), 2.92-2.76 (4H, m, $CCCH_2CH_2$), 4.95 (2H, s, $-NCH_2Ph$), 5.20 (1H, d, *J* = 7.2 Hz, CHOH), 5.91-5.78 (2H, m, CH=CH), 6.77 (1H, t, *J* = 5.6 Hz, $CH=N(O)CH_2Ph$), 7.43-7.37 (5H, m, Ar-H); δ_C 16.4, 26.3, 51.8, 68.9, 72.2, 80.8, 81.4, 94.0, 96.8, 118.9, 120.6, 128.7, 128.9, 129.1, 129.7, 132.1, 141.0; Mass (ESI) m/z: 291 (M^+).

Synthesis of 5-(2-Buta-1, 3-diynyl-phenyl)-pent-4-ynyl-N-benzyl nitrone (45)

Procedure same as 17; Yield: 883 mg, 90%; State: brown oil; δ_H 2.53 (1H, s, CCCCH), 2.81-2.71 (4H, s, $CCCH_2CH_2$), 4.96 (2H, s, NCH_2Ph), 7.07 [1H, t, *J* = 5.2 Hz, $CH=N(O)CH_2Ph$], 7.52-7.22 (9H, m, Ar-H); δ_C 15.9, 25.8, 68.2, 69.4, 72.4, 74.3, 79.7, 79.8, 93.4, 123.5, 127.3, 127.5, 127.6, 128.8, 128.9, 129.1, 131.67, 131.8, 133.0, 137.6; Mass (ESI) m/z 311 (M^+).

General procedure for intramolecular Kinugasa reaction:

To a solution of different nitrones (1.10 mmol) in deoxygenated acetonitrile (30 ml) at 0 ^oC at a high dilution (0.003 M) under argon at 0 ^oC, Et_3N (1.10 mmol) was added and the mixture was stirred for 30 minutes. Cuprous iodide (0.55 mmol) was added and the solution was stirred for another 5 min at 0 ^oC. The mixture was then stirred for 24 h at room

temperature (15-20 ^{o}C). It was diluted with water (50 ml) and filtered through celite. The celite bed was washed with ethyl acetate (50 ml). The combined filtrate and washings were extracted with ethyl acetate (3 x 50 ml). The organic layer was washed with NH_4Cl, water and brine and dried over Na_2SO_4 and evaporated. The residue, obtained after evaporation, upon chromatography afforded an oil from which the products separated by conventional column chromatography over silica gel using hexane/ ethyl acetate (1:1) as eluent.

7-Benzyl-11-oxa-7-aza-tricyclo[13.4.0.06,9]nonadeca-1(15),16,18-triene-2,13-diyn-8-one (*cis* and *trans* fused) (1 and 2)

Cis: Yield: 10%, overall yield: 55%; State: white solid; ν_{max} (neat) 3423, 2917, 2849, 2362, 2335, 1742, 1652 cm^{-1}; δ_H (200 MHz, d_6-Acetone) 2.63-2.12 (4H, m, $CCCH_2CH_2$), 3.86-3.70 (2H, m, H-3, H-4), 4.27 (2H, d, J = 4.45 Hz, OCH_2CH), 4.52, 4.71 (2H, ABq, J = 17.1 Hz, OCH_2CC), 4.41, 4.63 (2H, ABq, J = 15.6 Hz, NCH_2Ph), 7.38–7.22 (9H, m, Ar-H), δ_C 16.2, 26.3, 44.3, 52.6, 55.4, 58.9, 64.2, 80.8, 86.7, 89.3, 94.2, 125.9, 126.3, 127.5, 127.7, 127.9, 128.0, 128.8, 130.1, 130.5, 135.8, 167.6; HRMS calcd for $C_{24}H_{21}NO_2 + H^+$ 356.1651 found 356.1653.

Trans: Yield: 30%, overall yield: 55%; State: white solid; ν_{max} (neat) 3423, 2917, 2849, 2362, 2335, 1742, 1652 cm^{-1}; δ_H 1.91-1.83 (2H, m, $CCCH_2CH_2$), 2.58-2.43 (2H, m, CH_2CC), 3.06-3.04 (1H, m, H-3), 4.07-4.03 (2H, m, OCH_2CH), 4.17-4.14 (1H, m, H-4), 4.46, 4.36 (2H, ABq, J = 15.6 Hz, OCH_2CC), 4.60, 4.25 (2H, ABq, J = 16.9 Hz, NCH_2Ph), 7.38-7.12 (9H, m, Ar-H), δ_C 16.0, 29.4, 44.6, 53.7, 54.9, 58.7, 64.2, 81.1, 85.0, 88.9, 91.1, 125.2, 125.4, 127.3, 127.5, 127.7, 127.8, 128.4, 130.7, 131.4, 136.0, 167.2; HRMS calcd for $C_{24}H_{21}NO_2 + H^+$ 356.1651 found 356.1642.

7-Benzyl-12-oxa-7-aza-tricyclo[14.4.0.06,9]icosa-1(16),17,19-triene-2,14-diyn-8-one (*cis* and *trans* fused) (3 and 4)

Cis: Yield: 15%, overall yield: 60%; State: white solid; ν_{max} (neat) 1747 cm^{-1}, δ_H 2.36-1.63 (5H, m, 1H of $CCCH_2CH_2$, $CCCH_2CH_2$, OCH_2CH_2), 2.67-2.50 (1H, m, $CCCH_2CH_2$), 3.68-3.53 (2H, m, H-3, OCH_2CH_2), 3.96-3.81 (2H, m, H-4, OCH_2CH_2), 4.45, 4.30 (2H, d, J = 18.3 Hz, OCH_2CC), 4.53, 4.22 (2H, ABq, J = 15.5 Hz, NCH_2Ph),7.38-7.19 (9H, m, Ar-H); δ_C 16.9, 24.5, 26.9, 44.1, 50.1, 55.1, 58.8, 67.8, 81.1, 85.0, 89.1, 92.2, 125.4, 127.2, 127.3, 127.6, 127.6, 127.6, 128.4, 128.5, 130.9, 131.2, 169.1; HRMS calcd. for $C_{25}H_{23}NO_2 + H^+$ 370.1808 found 370.1793.

Trans: Yield: 45%, overall yield: 60%; State: white solid; ν_{max} (neat) 2362, 2335, 1742 cm^{-1}; δ_H 2.53-1.90 (6H, m, $CCCH_2CH_2$, $CCCH_2CH_2$, OCH_2CH_2), 2.90-2.82 (1H, m, H-3), 3.55-3.50 (1H, m, 1H of OCH_2CH_2), 3.85-3.79 (1H, m, H-4), 4.17-4.05 (1H, m, 1H of OCH_2CH_2), 4.44, 4.28 (2H, d, J = 16.3 Hz, OCH_2CC), 4.46, 4.30 (2H, ABq, J = 15.3 Hz, NCH_2Ph), 7.39-7.20 (9H, m, Ar-H); δ_C 16.3, 27.6, 31.0, 44.9, 52.7, 57.5, 58.4, 66.8, 88.7, 92.2, 93.0, 125.4, 126.4, 127.0, 127.6, 128.1, 128.7, 128.8, 131.2, 131.7, 136.5, 169.7; HRMS calcd for $C_{25}H_{23}NO_2 + H^+$ 370.1808 found 370.1821.

7-Benzyl-7-aza-tricyclo[11.4.0.05,8]heptadeca-1(17),4,13,15-tetraene-2,11-diyn-6-one (7)

Yield: 13%, overall yield: 65%; State: white solid; ν_{max} (neat) 2925, 1745 cm^{-1}; δ_H 2.19- 1.97 (2H, m, $CCCH_2CH_2$), 2.63-2.56 (2H, m, $CCCH_2CH_2$), 3.98 (1H, m, $CHCH_2CH_2CC$), 4.82, 4.20 (2H, ABq, J = 15.0 Hz, NCH_2Ph), 6.28 (1H, d, J = 1.5 Hz, CCCH), 7.44-7.20 (9H, m, Ar-H); δ_C 19.9, 28.8, 44.3, 60.9, 80.9, 89.7, 96.3, 96.6, 104.0, 126.4, 127.6, 128.1, 128.4, 128.8, 129.4, 130.0, 130.0, 134.7, 154.6, 167.3; HRMS calcd for $C_{23}H_{17}NO + H^+$ 324.1389 found 324.1429.

7-Benzyl-4-hydroxy-7-aza-tricyclo[11.4.0.05,8]heptadeca-1(17),13,15-triene-2,11-diyn-6-one (6)

Yield: 52%, overall yield: 65%; State: white solid; ν_{max} (neat) 2925, 1735 cm^{-1}; δ_H 2.65-2.25 (4H, m, $CCCH_2CH_2$), 3.36 (1H, dd, J = 2.5 Hz, H-3), 3.51 (1H, m, H-4), 4.71, 4.08 (2H, ABq, J = 15.0 Hz, NCH_2Ph), 4.89 (1H, d, J = 10.0 Hz, CHOH), 7.38-7.23 (9H, m, Ar-H); δ_C 18.1, 30.0, 44.0, 55.5, 63.0, 63.6, 85.5, 81.0, 92.0, 93.5, 125.7, 127.3, 127.6, 128.1, 128.2, 129.1, 129.5, 129.7, 134.9, 168.2; HRMS calcd for $C_{23}H_{19}NO_2 + H^+$ 342.1495 found 342.1526.

12-Benzyl-2-hydroxy-12-aza-bicyclo[9.2.0]tridec-5-ene-3,7-diyn-13-one (8)

Yield: 60%; State: white solid; ν_{max} (neat) 2925, 1735 cm^{-1}; δ_H 2.60-1.95 (4H, m, $CCCH_2CH_2$), 3.22 (1H, dd, J = 2.5 Hz, H-3), 3.38 (1H, m, H-4), 4.63, 3.98 (2H, ABq, J = 14.8 Hz, -NCH_2Ph), 4.75 (1H, d, J = 10.4 Hz, CHOH), 5.76 (2H, s, CH=CH), 7.30-7.16 (5H, m, Ar-H); δ_C 18.6, 30.4, 43.9, 55.4, 63.0, 63.9, 80.5, 84.8, 95.4, 98.1, 120.4, 122.8, 127.8, 128.1, 128.6, 128.9, 129.0, 134.4, 167.6; HRMS calcd for $C_{19}H_{17}NO_2 + H^+$ 292.1338 found 292.1356.

Synthesis of compound 10a

The mesylate (47) (170 mg, 0.4 mmol), dissolved in dry DMF (30 ml) was treated with K_2CO_3 (83 mg, 0.6 mmol) and the mixture was stirred for 3 h at room temperature. It was then partitioned between EtOAc and water (60 ml each). The organic layer was further washed with water (3 x 50 ml), dried and evaporated. From this residue, the title compound (10a) was isolated by column chromatography (Si-gel, PE: EA = 5:1) as yellowish solid; Yield: 119 mg, 90%; State: yellowish solid; δ_H 2.04-1.98 (2H, m, $CH_2CH_2CH_2N$), 2.40 (2H, t, J = 6.0 Hz, $CH_2CH_2CH_2N$), 3.68 (2H, t, J = 7.4 Hz, CH_2CH_2N), 4.34 (2H, s, NCH_2CC), 5.76 (2H, dd, J = 10.0, 18.0 Hz, CHCH), 7.99 (2H, d J = 8.8 Hz, $SO_2CCHCHCNO_2$), 8.38 (2H, d, J = 8.8 Hz, $SO_2CCHCHCNO_2$); δ_C 17.8, 27.8, 39.4, 44.7, 81.9, 87.5, 88.3, 100.4,

120.7, 123.7, 124.5, 128.6, 143.7, 150.2; Mass (ESI) m/z 330 (M^+).

Synthesis of 10b & 10c

To a solution of compound 10a (20 mg, 0.06 mmol) in DMF (6 ml), thiophenol (8 µl, 0.07 mmol) and K_2CO_3 (25 mg, 0.18 mmol) were added and the mixture was stirred for 40 minutes at room temperature. After partitioning between water and EtOAc, the organic layer was evaporated using liquid N_2 in the vacuum pump and the free amine 10b was isolated by column chromatography (Si-gel, 10% CH_3OH in CH_2Cl_2) as a brown oil.Yield: 8 mg, 90%; Immediately the diethyl ether solution of the amine compound 10b was added drop wise to the solution of *p*-toluene sulfonic acid in diethyl ether with few drops of methanol mixture. The reaction mixture was stirred for few minutes until the brownish precipitate appeared. The solid material 10c was isolated as a white solid by washing with diethyl ether by several times.

Spectral data of compound 10b:

δ_H 1.82-1.76 (2H, m, $CH_2CH_2CH_2N$), 2.54 (2H, t, *J* = 6.4 Hz, $CH_2CH_2CH_2N$), 3.29 (2H, t, *J* = 6.0 Hz, CH_2CH_2N), 3.64 (2H, s, NCH_2CC), 5.82 (2H, s, CHCH); δ_C 16.8, 24.8, 39.1, 43.9, 82.4, 85.2, 97.2, 97.5, 121.4, 122.7; Mass (ESI) m/z 145 (M^+).

Spectral data of compound 10c:

δ_H 1.98 (2H, t, *J* = 6.4 Hz, $CH_2CH_2CH_2N$), 2.37 (3H, s, Ar-CH_3), 2.57 (2H, t, *J* = 6.4 Hz, $CH_2CH_2CH_2N$), 3.72 (2H, bs, CH_2CH_2N), 4.10 (2H, s, NCH_2CC), 5.85 (2H, dd, *J* = 10.0, 13.8 Hz, CHCH), 7.16 (2H, d, *J* = 7.6 Hz, $SO_3CCHCHCCH_3$), 7.73 (2H, d, *J* = 8.0 Hz, $SO_3CCHCHCCH_3$); δ_C 16.9, 31.3, 23.0, 37.3, 42.6, 82.9, 86.7, 89.4, 98.3, 120.2, 124.3, 125.8, 128.9, 140.4, 141.4; Mass (ESI) m/z 146 (MH^+).

Synthesis of compound 11b & 11c

The title compound 11b and 11c were prepared from the corresponding cyclic sulphonamide[7, 3c] compound 11a following the same procedure as described for 10b & 10c. The free amine 11b was isolated by column chromatography (Si-gel, 10% CH_3OH in CH_2Cl_2) as a brown oil, Yield: 60%; and 11c was obtained as a brownish solid.

Spectral data of compound 11b

δ_H 2.52 (2H, t, *J* = 5.2 Hz, $CH_2CH_2CH_2N$), 3.26 (2H, t, J = 5.2 Hz, CH_2CH_2N), 3.62 (2H, s, NCH_2CC), 5.85 (2H, s, CHCH); Mass (ESI) m/z 131 (M^+).

Spectral data of compound 11c

δ_H 2.33 (3H, s, Ar-CH_3), 2.86 (2H, t, *J* = 4.4 Hz, CH_2CH_2N), 3.59 (2H, bs, CH_2CH_2N), 4.08 (2H, s, NCH_2CC), 5.89 (2H, d, *J* = 7.6 Hz, CHCH), 7.13 (2H, d, *J* = 7.6 Hz, $SO_3CCHCHCCH_3$), 7.69 (2H, d, *J* = 8.0 Hz, $SO_3CCHCHCCH_3$), 9.50 (2H, bs, NH_2^+); δ_C 19.4, 21.3, 40.4, 49.7, 84.8, 89.8, 91.3, 100.5, 121.8, 124.6, 125.9, 128.9, 140.5, 141.1; Mass (ESI) m/z 132 (MH^+).

2 Conclusion

We have successfully developed a general synthetic route to aromatic and non-aromatic β-lactam-fused enediynes by intramolecular Kinugasa reaction. The method has widened the scope of Kinugasa reaction in the synthesis of sensitive systems like heterocyclic and 11-memebered carbocylic β-lactam fused enediynes. The thermal reactivity of these enediynes indicated very little effect of endocyclic double bonds. The aliphatic enediyne expectedly showed higher reactivity as compared to the aromatic counterparts. There was significant effect of the β-lactam ring on the reactivity of the fused enediynyl system because of larger ring size. The 10-membered monocyclic amine, as the tosylate salt, was found to be a potent DNA-cleaving agent.

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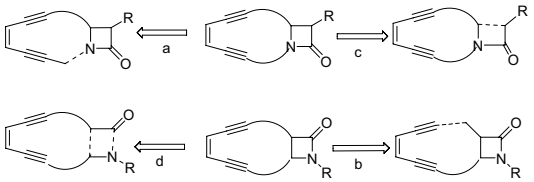
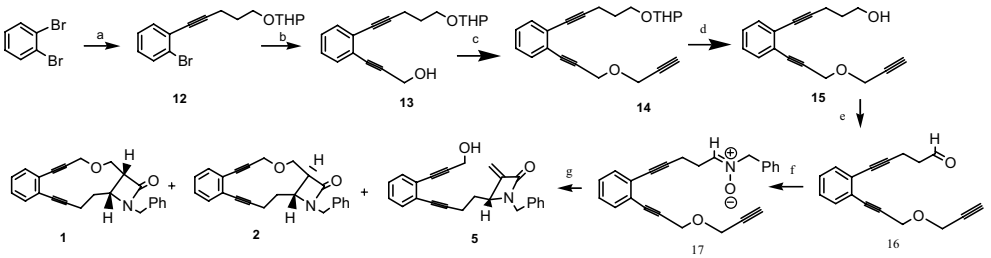
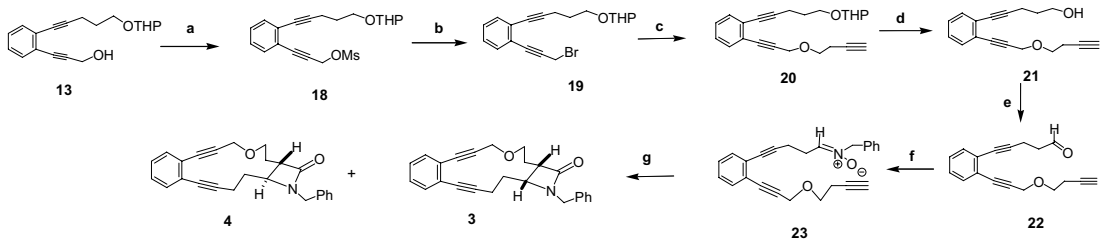


Scheme 1. Possible approaches to - lactam fused enediynes



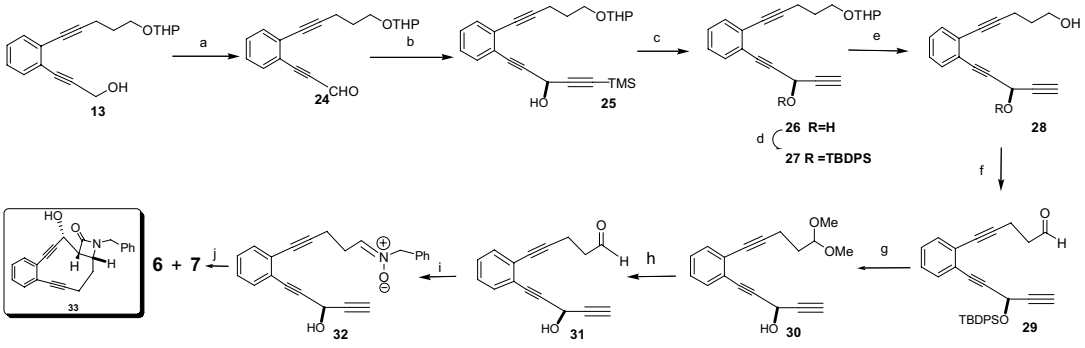
a) THP-protected 4-Pentyn-1-ol, $Pd(PPh_3)_4$, n-$BuNH_2$, reflux; b) Propargyl alcohol, Pd $(PPh_3)_4$, n-$BuNH_2$, reflux (overall 70%); c) NaH, Propargyl bromide, THF, rt, (85%); d) PPTS, EtOH (78%); e) PCC, DCM, rt (65%); f) $PhCH_2NHOH$, MeOH (80%); g) CuI, Et_3N, CH_3CN (overall yield 55%, trans = 30%, cis = 10%, elimination = 15 %)

Scheme 2. Synthesis of enediynes 1, 2 and 5



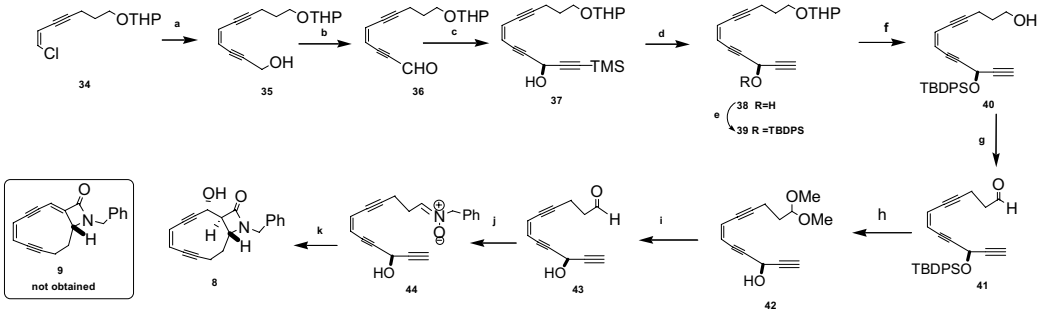
a) MsCl, Et_3N, CH_2Cl_2 , 0 ^oC (85%); b) LiBr, THF (80%); c) NaH, homopropargyl alcohol,THF (70%) d) PPTS, EtOH (78%); e) PCC, DCM, rt. (65%); f) $PhCH_2NHOH$, MeOH (80%); g) CuI, Et_3N, CH_3CN (overall yield 60%, trans = 45%, cis = 15%).

Scheme 3. Synthesis of enediyne 3 and 4



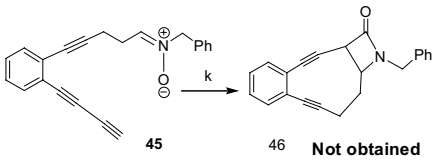
a) Dess-Martin Oxidation (> 90%); b) TMS-acetylene, BuLi, THF, 0 ^oC (85%); c) KF, MeOH (80%); d)TBDPSCl,DMAP,DCM (80%); e) PPTS, EtOH (80%); f) Dess-Martin Oxidation (>90%); g) 3% HCl-MeOH (75%); h) THF-H_2O, HCl (85%); i) $PhCH_2NHOH$, MeOH (>90%); j) CuI, Et_3N, Acetonitrile (overall yield : 65%, trans : elimination product = 4:1)

Scheme 4. Synthesis of 11-membered aryl fused enediynes



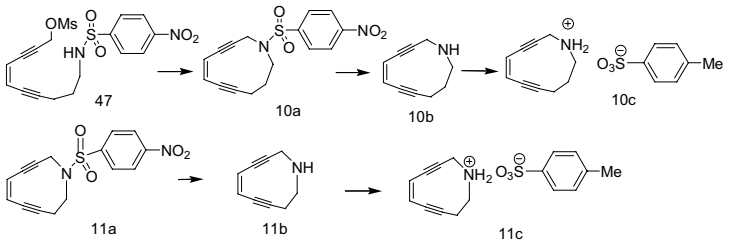
a) propargyl alcohol, $Pd[(PPh)_3]_4$, n-$BuNH_2$, 88%; b) Dess-Martin Oxidation (> 90%); c) TMS-acetylene, BuLi, THF, 0 ^oC (85%); d) KF, MeOH (80%); e)TBDPSCl,DMAP,DCM (80%); f) PPTS, EtOH (80%); g) Dess-Martin Oxidation (>90%); h) 3% HCl-MeOH (75%); i) THF-H_2O, HCl (85%); j) $PhCH_2NHOH$, MeOH (>90%); k) CuI, Et_3N, Acetonitrile (overall yield : 65%, trans : elimination product = 4:1)

Scheme 5. Synthesis of enediyne 8



k) CuI, Et_3N, Acetonitrile.

Scheme 6. Attempted synthesis of 10-memebered β-lactam fused enediyne



Scheme 7. Synthesis of monocyclic enediynes

Table 1. DSC results

Compound number	Onset temperature in ^oC	Compound number	Onset temperature in ^oC
6	207	10a	140
7	192	10c	100
8	79	11c	38

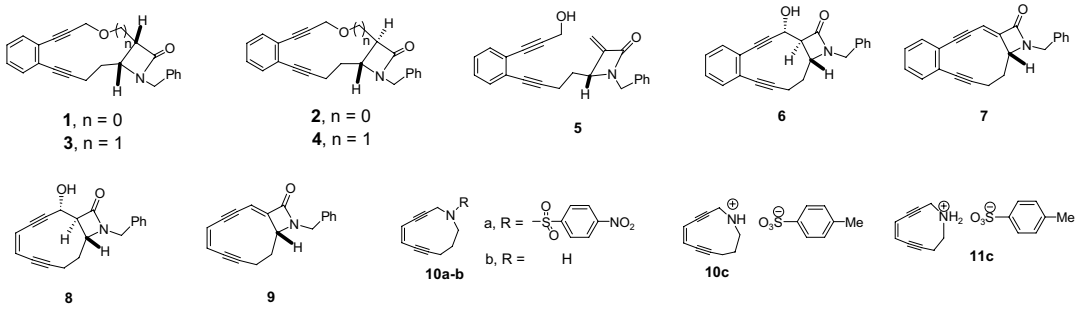


Figure 1. Our target β-Lactam-fused enediynes

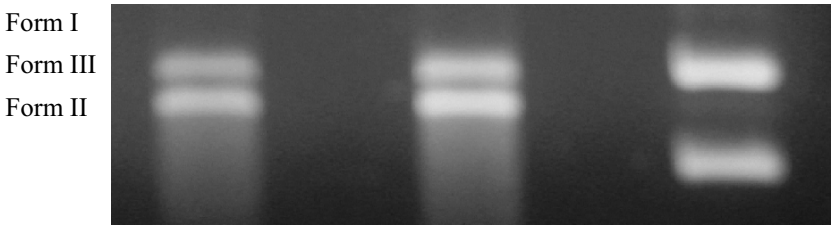


Figure 2. Gel electrophoresis of the tosylate salt 11c