# A novel synthesis of β-lactam fused cyclic enediynes by intramolecular Kinugasa reaction†

**Runa Pal and Amit Basak***

*Received (in Cambridge, UK) 24th April 2006, Accepted 24th May 2006*
*First published as an Advance Article on the web 7th June 2006*
**DOI: 10.1039/b605743h**



**A general synthetic route to β-lactam-fused enediynes by intramolecular Kinugasa reaction has been successfully developed. The method has widened the scope of Kinugasa reaction in the synthesis of sensitive systems like the one described in this communication.**

The Kinugasa reaction,[1] a one-step synthesis of β-lactams *via* [3 + 2] cycloaddition between a nitrone and an *in situ* generated Cu(I)-acetylide, has attracted considerable attention in recent years.[2] The reaction usually produces a mixture of *cis* and *trans* β-lactams and studies have shown that the *trans* isomer originates from the *cis* isomer.[3] The asymmetric version of the reaction is a relatively new development. Miura *et al.*[4] achieved moderate enantioselectivity using a bisoxazoline-based catalyst. More recently, Lo and Fu[5] reported a catalytic method proceeding with high enantioselectivity using a chiral ferrocene ligand. We have also reported[6] a highly diastereoselective Kinugasa reaction based on the chiral auxiliary approach. The Kinugasa reaction offers several advantages, which include mild reaction conditions and the availability of a large repertoire of alkynes and nitrones. Crafting of these functionalities on two arms of the same molecule to facilitate an intramolecular reaction is comparatively easier than the widely used Staudinger reaction[7] which requires the use of an acyl halide, a more reactive functionality. The recent report of the intramolecular Kinugasa reaction by Shintani and Fu[8] has encouraged us to explore the possibility of synthesizing β-lactam-fused enediynes employing such a strategy. The latter class of molecules has gained importance because of the ability of the β-lactam ring to act as a molecular lock[9,10] in stabilizing the otherwise unstable enediyne moiety. Moreover, opening of the ring by a suitable nucleophile can trigger Bergman cyclizaton[11] if the enediyne ring size is appropriate.[12] In this communication, we report the synthesis of β-lactam fused enediynes (lactendiynes) **1–5** (Fig. 1) by intramolecular Kinugasa reaction. In addition, we have also synthesized the unsaturated β-lactam based enediynes **6–7**. Our report demonstrated the potential of this reaction in the synthesis of delicately functionalized ring systems.

One can conceive three possible strategies for the synthesis of β-lactam fused enediynes in Scheme 1. Pathways **a** and **b** both involve the formation of enediyne on to a preformed β-lactam ring. Pathway **c** reverses the sequence by forming the β-lactam on to a cyclic enediyne. The third alternative pathway as represented

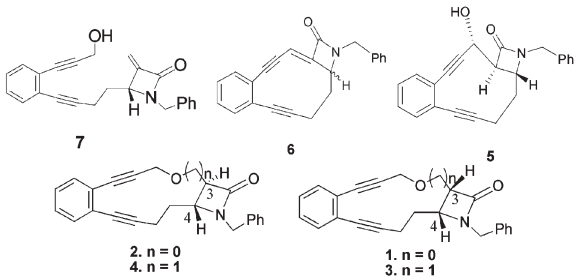
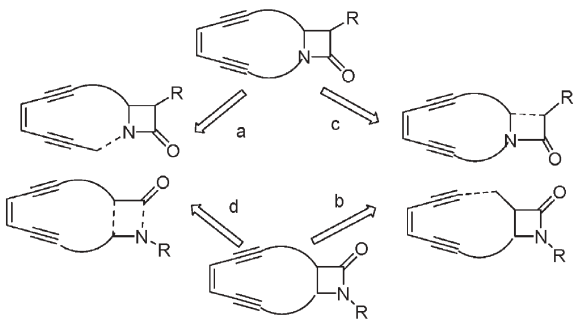



**Fig. 1** Design of macrocyclic enediynes.

in **d** involves the concerted formation of both the enediyne and β-lactam rings. Both 1,4- or 3,4-fused systems have been synthesized in Guanti's laboratory[13] following pathways **a** and **b**. We have also reported[14] the synthesis of 1,4-fused systems *via* route **a** as well as **c**. Pathway **d** has not been explored as yet although it has the advantage of not handling the sensitive β-lactam or cyclic enediyne until the last step. For synthesis following pathway **d**, intramolecular Kinugasa reaction to generate both the systems in one step is certainly a possibility. The outcome of the latter strategy brightened when it has been shown[15] from our laboratory that isooxazoline fused enediynes could be synthesized using an intramolecular 1,3-dipolar cycloaddition involving a nitrone and an alkene, both belonging to the same enediyne system.

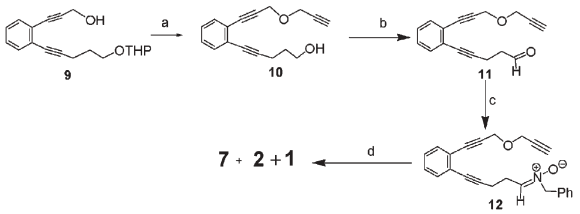
We first attempted to synthesize the enediyne **1**, the reason being the easy access to the precursor. The retrosynthesis of the enediyne **1** (shown as an example in Scheme 2), involves the following important steps: (i) the construction of the acyclic enediyne framework by Sonogashira coupling,[16] (ii) O-propargylation, (iii) functional group modification to generate the nitrone and (iv) an intramolecular Kinugasa reaction. The nitrone **12** essentially existing in the *Z*-form, was subjected to Kinugasa reaction




**Scheme 1** Possible approaches to β-lactam fused enediynes.

*Bioorganic Laboratory, Department of Chemistry, Indian Institute of Technology, Kharagpur, India. E-mail: absk@chem.iitkgp.ernet.in; Fax: 91 3222 282252; Tel: 91 3222 283300*
† Electronic supplementary information (ESI) available: NMR spectra. See DOI: 10.1039/b605743h

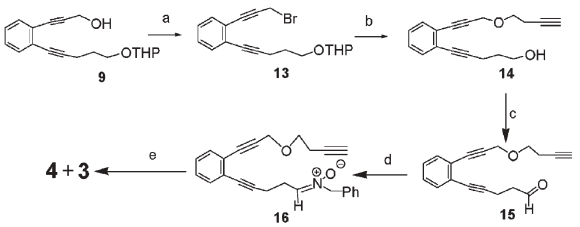
 



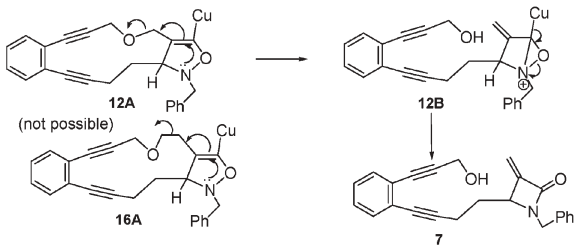
**Scheme 2** Synthesis of enediynes **1** and **2**. *Reagents and conditions*: (a) (i) NaH, propargyl bromide, THF, rt (85%); (ii) PPTS, EtOH (78%); (b) PCC, DCM, rt (65%); (c) $PhCH_2NHOH$, MeOH (80%); (d) CuI, $Et_3N$, $CH_3CN$. Overall yield: 55%, *trans* = 30%, *cis* = 10%, elimination product = 15%.

conditions with some modification. Thus it was dissolved in deoxygenated acetonitrile at 0 °C at a high dilution (0.003 M) and treated with cuprous iodide (0.5 eq.) and triethylamine (1 eq.). The mixture was stirred for 24 h while the temperature was kept within the range of 15–20 °C. The desired β-lactams **1** and **2** were isolated by careful chromatography over Si-gel using hexane–ethyl acetate of increasing polarity as eluent. The structures of both the compounds were determined by NMR, IR and mass spectrometric data.[18] The stereochemistry was confirmed by extensive decoupling experiments. Thus for compound **2**, upon irradiation of the H-5 methylene, the signal for the H-3 which appeared as a broad signal, collapsed to a narrow singlet with half-width of 2.3 Hz, which indicated *trans* stereochemistry .[19] For compound **1**, similar irradiation collapsed the signal for the H-3 into a doublet of coupling constant 5 Hz confirming the *cis* stereochemistry. A third slower running compound was isolated which was characterized (appearance of characteristic[17] broad singlets at $\delta$ 5.75 and 5.21 for the exomethylene hydrogens) as the elimination product **7**. The other nitrone **15** when subjected to similar reaction conditions gave only *cis* and *trans* β-lactams **3** and **4**, respectively (Scheme 3). The structures of these compounds were also confirmed by extensive decoupling experiments.

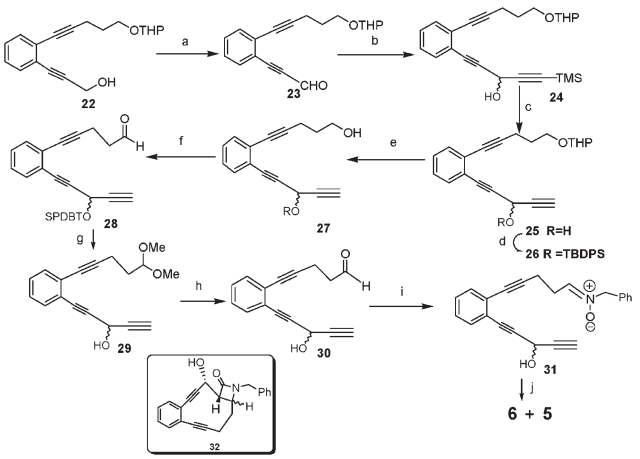
Since both **1** and **2** are stable towards triethylamine, **7** must have been produced during the collapse of the isooxazoline intermediate formed by initial cycloaddition.[20] The mechanism of formation of **7** is shown in Scheme 4, which is based on the elimination of propargyl alcohol in a SN′-fashion. This mechanism is supported by the fact that when the higher homologous nitrone **16** was subjected to Kinugasa reaction conditions, no elimination product was observed because that would involve breakage of the C–C bond.



**Scheme 3** Synthesis of enediynes **3** and **4**. *Reagents and conditions*: (a) (i) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C (85%); (ii) LiBr, THF (80%); (b) NaH, homopropargyl alcohol, THF (70%); (c) PCC, DCM, rt (65%); (d) $PhCH_2NHOH$, MeOH (80%); (e) CuI, $Et_3N$, $CH_3CN$. Overall yield: 60%, *trans* = 45%, *cis* = 15%.



**Scheme 4** Possible mechanism of formation of **7**.



**Scheme 5** Synthesis of enediynes **5** and **6**. *Reagents and conditions*: (a) (i) Dess–Martin oxidation (>90%); (b) TMS–acetylene, BuLi, THF, 0 °C (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, $Et_3N$, MeCN. Overall yield: 65%, *trans* : elimination product = 4 : 1.

Having been successful in the synthesis of β-lactam fused oxaenediynes, we turned our attention to utilize this approach in the synthesis of carbocyclic enediynes of smaller size which would be more meaningful to do as enediynes having ring size of 9 or 10 spontaneously cyclize under ambient conditions. For the synthesis of 10-membered enediyne, we performed the Kinugasa reaction with the bis-acetylenic system. Unfortunately our attempts failed, we could not isolate any β-lactam containing products. The conjugated bis-acetylenic system is perhaps less reactive towards the Kinugasa reaction. Our attention was then diverted to synthesize the 11-membered enediyne system **5**. For this the precursor nitrone **31** was prepared in 10 steps as shown in Scheme 5. When this nitrone was subjected to Kinugasa reaction conditions, to our satisfaction we could isolate two β-lactam containing products. One is the *trans* fused system **5** and the other was the elimination product **6**. Gratifyingly the reaction was much cleaner and the yields were better than what were obtained in case of the synthesis of the oxacycles; the selectivity was also high. For the structure of the major product **5**, the large coupling constant between the carbinol hydrogen and H-3 and the small coupling constant between H-3 and H-4 indicated the geometry as shown. Both the structures were confirmed by extensive decoupling experiments, $^{13}C$ and HRMS analysis. Apparently the diastereomer **32** having *trans* relationship between the H-3 and carbinol

OH, undergoes elimination under the reaction conditions which cannot happen for the major isomer **5**.

In conclusion, we have successfully developed a general synthetic route to β-lactam-fused enediynes by an intramolecular Kinugasa reaction. The method has widened the scope of the Kinugasa reaction in the synthesis of sensitive systems like the one described in this communication. The mechanism of formation of an elimination product was also successfully established.

A. B. thanks DST, Government of India for a research grant. R. P. is grateful to CSIR, Government of India for a senior research fellowship.

## Notes and references


1 M. Kinugasa and S. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 1972, 466–467.

2 (*a*) J. Marco-Contelles, *Angew. Chem., Int. Ed.*, 2004, **43**, 2198–2200; (*b*) A. Basak and R. Pal, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2015–2018.

3 L. K. Ding and W. J. Irwin, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2382–2386.

4 M. Miura, M. Enna, K. Okura and N. Nomura, *J. Org. Chem.*, 1995, **60**, 4999–5004.

5 M. M-C. Lo and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 4572–4573.

6 A. Basak, S. C. Ghosh, T. Bhowmick, A. K. Das and V. Bertolasi, *Tetrahedron Lett.*, 2002, **43**, 5499–5501.

7 *The Organic Chemistry of β-Lactams*, ed. G. I. Georg, VCH, New York, 1992, pp. 295–368.

8 R. Shintani and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4082–4085.

9 Nature uses small epoxide ring as a molecular lock, *e.g.* in dynemicin and kedercidin. For references: (*a*) D. R. Langley, T. W. Doyle and D. L. Beveridge, *J. Am. Chem. Soc.*, 1991, **113**, 4395–4403; (*b*) S. Kawata, S. Ashizawa and S. Hirama, *J. Am. Chem. Soc.*, 1997, **119**, 12012–12013, and references therein.

10 An example of an artificial molecular lock (a cyclic carbonate) was first reported by Nicolaou *et al.*: K. C. Nicolaou, E. J. Sorensen, R. Discordia, C-K. Hwang, R. E. Minto, K. N. Bharucha and R. G. Bergman, *Angew. Chem., Int. Ed. Engl.*, 1992, **104**, 1094–1096.

11 (*a*) R. G. Bergman, *Acc. Chem. Res.*, 1973, **6**, 25–31; (*b*) T. P. Lockhart and R. G. Bergman, *J. Am. Chem. Soc.*, 1981, **103**, 4091–4096.

12 K. C. Nicolaou, G. Zuccarello, Y. Oogawa, E. J. Schweiger and T. Kumazawa, *J. Am. Chem. Soc.*, 1988, **10**, 4866–4868.

13 (*a*) L. Banfi and G. Guanti, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2393–2395; (*b*) L. Banfi and G. Guanti, *Eur. J. Org. Chem.*, 1998, 1543–1548.

14 (*a*) A. Basak, U. K. Khamrai and U. K. Mallick, *Chem. Commun.*, 1996, 749–750; (*b*) A. Basak and S. Mandal, *Tetrahedron Lett.*, 2002, **43**, 4241–4243; (*c*) A. Basak, U. K. Khamrai and J. C. Shain, *Tetrahedron Lett.*, 1997, **38**, 6067–6070.

15 S. C. Ghosh and A. Basak, *Tetrahedron Lett.*, 2005, **26**, 7385–7389.

16 (*a*) K. Sonogashira, Y. Tohoda and N. Hagihara, *Tetrahedron Lett.*, 1975, **50**, 4467–4470; (*b*) S. Takahashi, Y. Kuroyama, K. Sonogashira and N. Hagihara, *Synthesis*, 1980, **8**, 627–630.

17 A. Basak, H. M. Bdour and G. Bhattacharya, *Tetrahedron Lett.*, 1997, **38**, 2535–2538.

18 *Selected spectral data* (all $^{1}$H and $^{13}$C NMR were recorded at 200 and 50 MHz, respectively, in $CDCl_3$ unless mentioned otherwise). For **1**: $\delta_H$ ($d_6$-acetone): 7.38–7.22 (9H, m), 4.63, 4.41 (2H, ABq, $J$ = 15.6 Hz), 4.71, 4.52 (2H, ABq, $J$ = 17.1 Hz), 4.27 (2H, d, $J$ = 4.45 Hz), 3.86–3.70 (2H, m), 2.63–2.12 (4H, m); $\delta_C$ 167.6, 135.8, 130.5, 130.1, 128.8, 128.0, 127.9, 127.7, 127.5, 126.3, 126.0, 94.2, 89.3, 86.7, 80.8, 64.2, 58.9, 55.4, 52.6, 44.3, 26.3, 16.2; HRMS: calc. for $C_{24}H_{21}NO_2 + H^+$ 356.1651, found 356.1653. For **2**: $\delta_H$ 7.38–7.12 (9H, m), 4.60, 4.25 (2H, ABq, $J$ = 16.9 Hz), 4.46, 4.36 (2H, ABq, $J$ = 15.6 Hz), 4.17–4.14 (1H, m), 4.07–4.03 (2H, m), 3.06–3.04 (1H, m), 2.58–2.43 (2H, m), 1.91–1.83 (2H, m); $\delta_C$ 167.1, 136.0, 131.3, 130.7, 128.4, 127.8, 127.7, 127.5, 127.3, 125.4, 125.2, 91.1, 89.0, 85.0, 81.1, 64.2, 58.7, 54.9, 53.7, 44.6, 29.4, 16.0; HRMS: calc. for $C_{24}H_{21}NO_2 + H^+$ 356.1651, found 356.1642. For **3**: $\delta_H$ 7.38–7.19 (9H, m), 4.53, 4.22 (2H, ABq, $J$ = 15.5 Hz), 4.45, 4.30 (2H, d, $J$ = 18.3 Hz), 3.96–3.81 (2H, m), 3.68–3.53 (2H, m), 2.67–2.50 (1H, m), 2.36–1.63 (5H, m); $\delta_C$ 169.1, 131.2, 130.9, 128.5, 128.4, 127.6, 127.6, 127.6, 127.3, 127.2, 125.4, 92.2, 89.1, 85.0, 81.1, 67.8, 58.8, 55.1, 50.1, 44.1, 26.9, 24.5, 16.9; HRMS: calc. for $C_{25}H_{23}NO_2 + H^+$ 370.1808, found 370.1793. For **4**: $\delta_H$ 7.39–7.20 (9H, m), 4.46, 4.30 (2H, ABq, $J$ = 15.3 Hz), 4.44, 4.28 (2H, d, $J$ = 16.3 Hz), 4.17–4.05 (2H, m), 3.85–3.79 (1H, m), 3.55–3.50 (1H, m), 2.90–2.82 (1H, m), 2.53–1.90 (6H, m); $\delta_C$ 169.7, 136.5, 131.7, 131.2, 128.8, 128.7, 128.1, 127.6, 127.0, 126.4, 125.4, 93.0, 92.2, 88.7, 66.8, 58.4, 57.5, 52.7, 44.9, 31.0, 27.6, 16.3; HRMS: calc. for $C_{25}H_{23}NO_2 + H^+$ 370.1808, found 370.1821. For **5**: $\delta_H$ 7.38–7.23 (9H, m), 4.89 ( 1H, d, $J$ = 10 Hz), 4.71, 4.08 (2H, ABq, $J$ = 15.0 Hz), 3.51 (1H, m), 3.36 (1H, dd, $J$ = 2.5 Hz), 2.65–2.25 (4H, m); $\delta_C$ 168.2, 134.9, 129.7, 129.5, 129.1, 128.2, 128.1, 127.6, 127.3, 125.7, 93.5, 92.0, 81.0, 85.5, 63.6, 63.0, 55.5, 44.0, 30.00, 18.1; HRMS: calc. for $C_{23}H_{19}NO_2 + H^+$ 342.1495, found 342.1526. For **6**: $\delta_H$ 7.44–7.20 (9H, m), 6.28 (1H, d, $J$ = 1.5 Hz), 4.82, 4.20 (2H, ABq, $J$ = 15.0 Hz), 3.98 (1H, m), 2.63–2.56 (2H, m), 2.19–1.97 (2H, m); $\delta_C$ 167.3, 154.6, 134.7, 130.0, 129.4, 130.0, 128.8, 128.4, 128.1, 127.6, 126.4, 104.0, 96.6, 96.3, 89.7, 80.9, 60.9, 44.3, 28.8, 19.9; HRMS: calc. for $C_{23}H_{17}NO + H^+$ 324.1389, found 324.1429.

19 J. L. Luche, H. B. Kagan, R. Parthasarathi, G. Tsoucaris, C. Rongo and C. Zewlar, *Tetrahedron*, 1968, **24**, 1275–1281.

20 A. Basak and S. C. Ghosh, *Synlett*, 2004, 1637–1639.

