Synthesis of Novel Polycyclic β-Lactams from D-Glucose via Unusual Substrate-Controlled Radical Cyclization

A. Jayanthi,[a] Vedavati G. Puranik,[b] A. R. A. S. Deshmukh*[a]

[a] Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune – 411 008, India

[b] Division of Physical Chemistry, National Chemical Laboratory, Pune – 411 008, India
Fax +91(20)25893153; E-mail: arasd@dalton.ncl.res.in

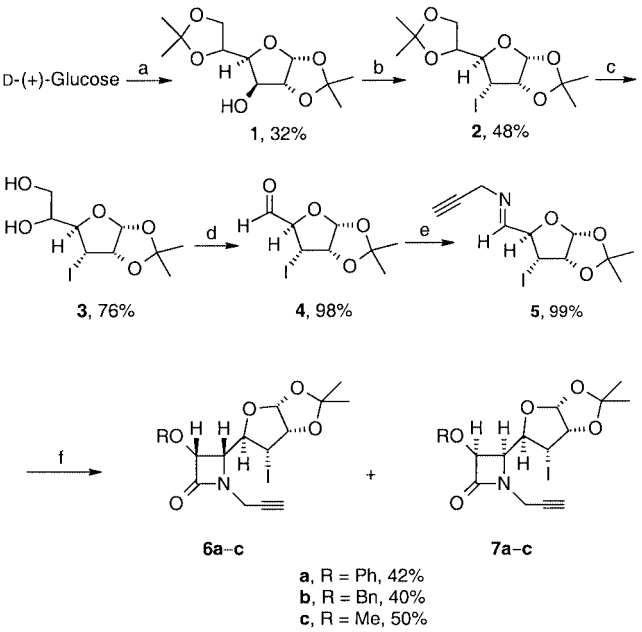
Received 30 January 2004

Dedicated to Dr. S. Rajappa on his 70th birthday

Abstract: A highly stereoselective and substrate-controlled synthesis of polycyclic β-lactams from D-glucose derived chiral template via intramolecular free radical cyclization is described. The cyclization is highly substrate dependant, proceeding via 6-*exo* and 7-*endo* heptynyl type radical cyclization with the radical acceptor at N-1 and the radical progenitor on a sugar moiety, anchored to the β-lactam ring at C-4.

Key words: azetidin-2-ones, polycyclic β-lactams, radical cyclization, tributyltin hydride

The increasing bacterial resistance to the commercially available β-lactam antibiotics through the cleavage of strained β-lactam ring by β-lactamase enzymes motivated chemists to synthesize stable fused polycyclic β-lactams of non-classical structure.[1,2] Presently the construction of polycyclic ring structures by free radical cyclization has been accepted as a useful synthetic methodology, especially in the total synthesis of natural products.[3,4] The large body of research and systematic studies that have gone into this subject have led to the evolution of certain principles and guidelines[5] regarding the regio and stereochemistry of radical cyclization. Hexenyl and hexynyl radical cyclizations are more efficient and well studied for mechanistic as well as synthetic applications.[3] The stereochemical outcome of these kind of cyclizations can be predicted by using Beckwith's transition state model.[6] According to this model and Baldwin's rules, 5-*exo* is more common than 6-*endo* cyclization in both the cases. However, in case of heptynyl radical cyclization, the examples of 6-*exo* cyclizations are well known[6c–g] while 7-*endo* cyclizations are very rare.[6h,i] Considering the high sensitivity of β-lactam antibiotics to nucleophilic reagents, several groups have employed radical cyclization methodology for the construction of fused polycyclic structures by using β-lactam with radical acceptor and radical progenitor appendages.[7] In a recent publication we have employed this methodology for diastereospecific synthesis of novel polycyclic β-lactams[7m,n] wherein radical progenitor and radical acceptor are appended at C-3 and C-4 positions, respectively, on the β-lactam ring skeleton. We report herein our results on highly stereoselective and substrate-controlled synthesis of polycyclic β-lactams via 6-*exo* and 7-*endo* heptynyl type radical cyclization with a radical acceptor at N-1 of β-lactam and a radical progenitor on a sugar part, which is anchored to β-lactam ring at C-4. We selected D-glucose derived chiral template for the synthesis of β-lactams with suitably sited radical progenitor and acceptor appendages (Scheme 1) using Staudinger reaction, as they were known to show high level of diastereoselectivity for β-lactam formation.[8]



Scheme 1 *Reagents and conditions*: (a) Ref.[9]; (b) PPh_3, I_2, imidazole, toluene, reflux, 17 h; (c) 0.8% H_2SO_4 in MeOH, r.t., 24 h; (d) 0.65 M $NaIO_4$ on SiO_2, CH_2Cl_2, r.t., 1 h; (e) $HC{\equiv}CCH_2NH_2$, $MgSO_4$, CH_2Cl_2, r.t., 3–4 h; (f) $ROCH_2COCl$, Et_3N, CH_2Cl_2, 0 ° C to r.t., 12–15 h.

To study the intramolecular radical cyclization we prepared azetidin-2-ones, with *N*-propargyl substituent as radical acceptor and iodo group as radical progenitor appendage, from commercially available D-glucose (Scheme 1). Diacetonide **1** was prepared from D-glucose, following a known procedure,[9] by stirring with acetone in the presence of anhydrous zinc chloride and phosphoric acid. This was converted into 3-iodo derivative **2** by triphenylphosphine, iodine and imidazole.[10] The selective

SYNLETT 2004, No. 7, pp 1249–1253
Advanced online publication: 10.05.2004
DOI: 10.1055/s-2004-822920; Art ID: G00304ST

deprotection of acetonide by 0.8% H_2SO_4 in MeOH gave **3,** which on oxidative cleavage with $NaIO_4$ adsorbed on silica gel furnished chiral iodoaldehyde **4** in quantitative yield.[11] The chiral imine **5** prepared from iodoaldehyde **4** and propargyl amine was found to be unstable and used as such for the next reaction. This imine underwent smooth cycloaddition reaction (Staudinger reaction) with ketenes derived from substituted acid chlorides (phenoxy, benzyloxy and methoxy acetyl chlorides) and Et_3N, to give 1:1 diastereomeric mixture of only *cis* β-lactams **6a–c** and **7a–c** (J = 4–6 Hz for *cis* β-lactam ring protons). However, both the diastereomers could be separated by flash column chromatography or crystallization from MeOH. The structure and relative stereochemistry was assigned from spectral data[12] and the absolute stereochemistry for β-lactam ring protons of **6a** was further established from the single crystal X-ray structure analysis as 3*R*, 4*S* based on the known absolute stereochemistry of the carbohydrate moiety (Figure 1).[13]

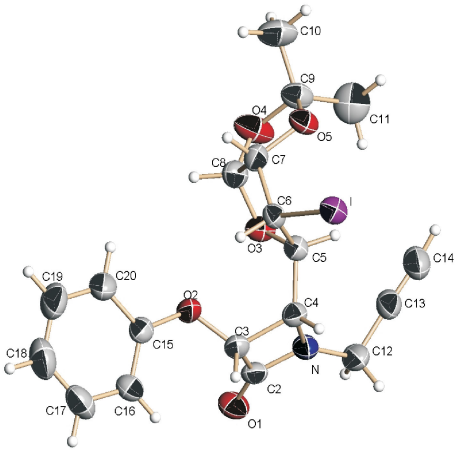
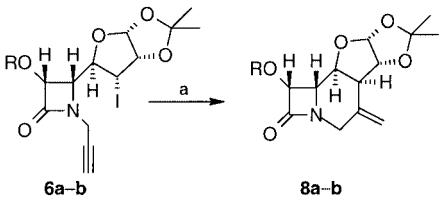


Figure 1 ORTEP diagram of **6a**



Scheme 2 *Reagents and conditions*: (a) Bu_3SnH, AIBN, toluene, reflux, 6 h.

The pure diastereomer **6a** when treated with tributyltin hydride in the presence of AIBN in toluene under refluxing condition underwent radical cyclization to give kinetically controlled stable *exo-dig* cyclized tetracyclic product **8a** (Scheme 2) via 1,6-bond coupling of hept-6-ynyl radical.[14] The presence of olefinic methylene peak down in the ^{13}C DEPT experiment at 113.5 ppm and single crystal X-ray analysis[15] of **8b** (Figure 2) confirmed the

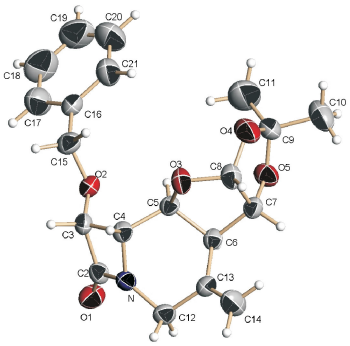
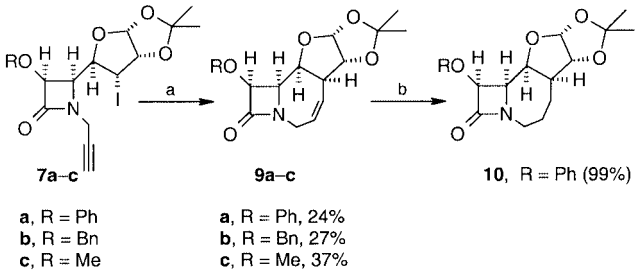


Figure 2 ORTEP diagram of **8b**

exo-dig cyclization and relative stereochemistry of C3, C4 and C6 was assigned as 3*R*, 4*S* and 6*R*.



Scheme 3 Reagents and conditions: (a) Bu_3SnH, AIBN, toluene, reflux, 6h; (b) H_2, Pd/C (10%).

On the other hand, when alpha diastereomer **7a** is subjected to radical cyclization under similar reaction conditions, the radical attacks the terminal carbon regiospecifically to give *endo-dig* cyclized product **9a** (Scheme 3). IR and NMR spectral data[14] established the structure of **9a**. However, the compound could not be obtained in crystalline form for the single crystal X-ray analysis. Therefore, it was subjected to catalytic hydrogenation at room temperature using Pd/C (10%) and 60 psi H_2 pressure to get white crystalline compound. The absence of CH_3 signal, which was expected for the *exo*-cyclization, and the appearance of three-methylene carbon peaks in ^{13}C DEPT spectrum of cyclized product **10** and 2D NMR studies revealed *endo-dig* radical cyclization of **9a**.[16]

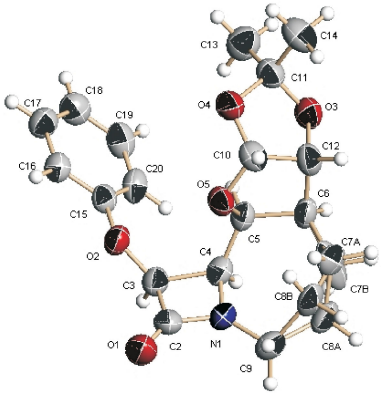
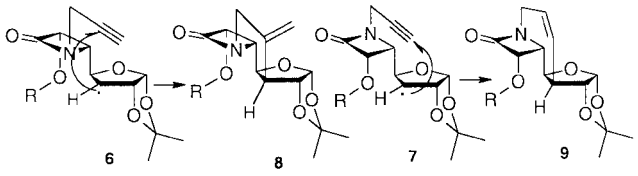


Figure 3 ORTEP diagram of **10**

This is in contrast with the normally expected *exo*-radical cyclization of hept-6-ynyl system.[6c–g] Single crystal X-ray analysis[17] of **10** further confirmed the structure and the absolute stereochemistry at the newly formed centers was established as 3*S*, 4*R*, 8*S* based on the known absolute stereochemistry of 6*R*, 7*R*, 9*S* of sugar moiety. The carbon atoms C7 and C8 are disordered and occupy two positions at C7A, C7B and C8A, C8B with 0.7 and 0.3 occupancies respectively, as shown in the ORTEP diagram (Figure 3).



Scheme 4

A drastic change in the mode of radical cyclization is observed with the change in stereochemistry of β-lactam nucleus (Scheme 4). We believe that the steric control of bulky substituents at C3 and sugar moiety at C4 positions of azetidin-2-one ring help in tuning the regioselectivity of cyclization. The electrostatic repulsion between the β-lactam ring nitrogen and the furanose ring oxygen atoms may be responsible for *endo* radical cyclization in **7** (Scheme 4). Radical addition to the triple bond was also stereospecific and the newly formed C-C bond directed *anti* to the acetonide group presumably due to the steric interactions between the β-lactam ring and the acetonide group. This unusual behavior in the mode of radical cyclization was not observed in the case of *N*-allyl β-lactams. Further study on intramolecular radical cyclization of various substituted *N*-allyl as well as *N*-propargyl substrates is in progress.

In conclusion, tributyltin hydride-AIBN mediated radical cyclization of *N*-propargyl β-lactams was studied and the observed products unambiguously proved the cyclization to be stereospecific and substrate controlled, either *6-exo* or *7-endo* depending on the stereochemistry of the β-lactam ring.

Acknowledgment

The authors thank DST for financial support and CSIR for research fellowships to AJ.

References

(1) For selected reviews, see: (a) Setti, E. L.; Micetich, R. G. *Curr. Med. Chem.* **1998**, *5*, 101. (b) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, **1993**. (c) Neuhaus, F. C.; Georgeopapadakou, N. H. In *Emerging Targets in Antibacterial and Antifungal Chemotherapy*; Sutcliffe, J.; Georgeopapadakou, N. H., Eds.; Chapman and Hall: New York, **1992**. (d) Alcaide, B.; Almendros, P. *Curr. Org. Chem.* **2002**, *6*, 245.

(2) (a) Hook, V. *Chem. Ber.* **1997**, *33*, 34. (b) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333. (c) Davies, J. *Science* **1994**, *264*, 375. (d) Spratt, B. G. *Science* **1994**, *264*, 388.

(3) (a) *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, **2002**. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, **1996**. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, **1986**. (d) Giese, B.; Kopping, B.; Göbel, J.; Dickhaut, G.; Thoma, G.; Trach, F. *Org. React.* **1996**, *48*, 301.

(4) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(5) Mustafi, D.; Makinen, M. W. *J. Am. Chem. Soc.* **1995**, *117*, 6739.

(6) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (b) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aus. J. Chem.* **1983**, *36*, 545. (c) Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022. (d) Sharma, G. V. M.; Sreenivasa Rao, V. *Tetrahedron Lett.* **1990**, *31*, 4931. (e) Gomez, A. M.; Moreno, E.; Valverde, S.; Lopez, J. C. *Tetrahedron Lett.* **2002**, *43*, 5559. (f) Gomez, A. M.; Moreno, E.; Valverde, S.; Lopez, J. C. *Tetrahedron Lett.* **2002**, *43*, 7863. (g) Gomez, A. M.; Moreno, E.; Valverde, S.; Lopez, J. C. *Tetrahedron: Asymmetry* **2003**, *14*, 2961. (h) Dupuy, C.; Crozet, M.-P.; Surzur, J.-M. *Bull. Soc. Chim. Fr.* **1980**, 361. (i) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841.

(7) (a) Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2689. (b) Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1982**, *23*, 2505. (c) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (d) Knight, J.; Parsons, P.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, 78. (e) Just, G.; Sacripante, G. *Can. J. Chem.* **1987**, *65*, 104. (f) Kametani, T.; Chu, S.-D.; Itoh, A.; Maeda, S.; Honda, T. *Heterocycles* **1988**, *27*, 875. (g) Kametani, T.; Chu, S.-D.; Itoh, A.; Maeda, S.; Honda, T. *J. Org. Chem.* **1988**, *53*, 2683. (h) Rocker, P. J.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 6176. (i) Bosch, E.; Bachi, M. D. *J. Org. Chem.* **1993**, *58*, 5581. (j) Banik, B. K.; Subbaraju, G. V.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1996**, *37*, 1363. (k) Alcaide, B.; Rodriguez-Campos, I. M.; Rodriguez-Lopez, J.; Rodriguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377. (l) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, *5*, 3795. (m) Joshi, S. N.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron: Asymmetry* **2001**, *12*, 3073. (n) Joshi, S. N.; Phalgune, U. D.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron Lett.* **2003**, *44*, 1827.

(8) (a) Bose, A. K.; Manhas, M. S.; Hedge, V. R.; Wagle, D. R.; Bari, S. S. *J. Chem. Soc., Chem. Commun.* **1986**, 181. (b) Bose, A. K.; Mathur, C.; Wagle, D. R.; Nagui, R.; Manhas, M. S. *Heterocycles* **1994**, *39*, 491. (c) Hanessian, S.; Desilets, D.; Rancourt, G.; Fosfin, R. *Can. J. Chem.* **1982**, *60*, 2292. (d) Koga, K.; Ikata, N.; Toshino, O. *Chem. Pharm. Bull.* **1982**, *30*, 1929. (e) Bernardo, S. D.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457. (f) Arun, M.; Joshi, S. N.; Puranik, V. G.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron* **2003**, *59*, 2309.

(9) Furniss, B.; Hann Ford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Org. Chem.* **1989**, 5th ed. 654.

(10) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.

(11) Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64.

(12) **General Procedure for the Synthesis of *N*-Propargyl β-Lactams (6a–c and 7a–c)**: To a solution of propargylamine (2 mmol) in CH_2Cl_2 (20 mL), was added an anhyd $MgSO_4$ (4 equiv) and a CH_2Cl_2 solution of iodoaldehyde **4** (2 mmol, in 5 mL) under argon atmosphere at r.t. and stirred for 3–4 h. The mixture was filtered through a pad of celite and the filtrate was concentrated to get the imines **5**, which was found to be unstable and used immediately without further purification.

A solution of the acid chloride (phenoxy or benzyloxy or methoxyacetyl chloride, 1.5 mmol) in anhyd CH_2Cl_2 (10 mL) was added to a solution of the imine (**5**, 1.0 mmol) and Et_3N (4.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon atmosphere. It was then allowed to warm to r.t. and stirred for 15 h. The reaction mixture was then washed with water, sat. $NaHCO_3$ solution, and sat. brine solution. The organic layer was then dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give diastereomeric mixture of *cis* β-lactams **6** and **7** in 1:1 ratio (40–50%). The diastereomers were separated by flash column chromatography using silica gel (230–400 mesh).

6a (Figure 4): White crystalline solid (mp 109–110 °C); $[\alpha]_D^{25}$ +133.0 (*c* = 0.93, $CHCl_3$). IR ($CHCl_3$): 1770 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 2.37 (t, 1 H, H_{14}), 3.97–4.06 (dd, *J* = 2.5, 17.9 Hz, 1 H, H_{12}), 4.10–4.15 (dd, *J* = 3.9, 3.9 Hz, 1 H, H_6), 4.30 (t, *J* = 3.9, 4.9 Hz, 1 H, H_4), 4.41–4.50 (dd, *J* = 2.5, 17.9 Hz, 1 H, H_{12}), 4.65 (t, *J* = 3.5, 3.9 Hz, 1 H, H_7), 4.70–4.78 (dd, *J* = 3.9, 3.9 Hz, 1 H, H_5), 5.34 (d, *J* = 4.9 Hz, 1 H, H_3), 5.88 (d, *J* = 3.5 Hz, 1 H, H_8), 7.02–7.09 (m, 3 H, aromatic), 7.29–7.37 (m, 2 H, aromatic). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 165.6 (C_2), 157.5 (C_{15}), 129.7 (C_{19}, C_{17}), 122.7 (C_{18}), 115.9 (C_{16}, C_{20}), 112.4 (C_9), 103.4 (C_8), 81.7 (C_7), 80.8 (C_5), 80.1 (C_3), 75.8 (C_{14}), 74.0 (C_{13}), 56.3 (C_4), 30.9 (C_{12}), 26.9 (C_{10}), 26.8 (C_{11}), 19.4 (C_6). MS (70 eV): *m*/*z* = 470 [M + 1]. Anal. Calcd for $C_{19}H_{20}NO_5I$: C, 48.63; H, 4.30; N, 2.98. Found: C, 48.49; H, 4.27; N, 2.80.

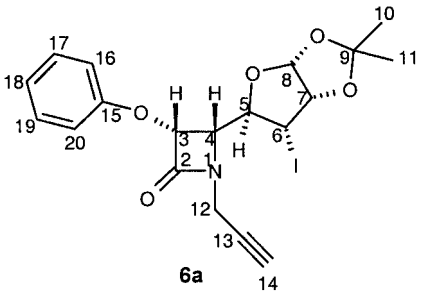


Figure 4

7a (Figure 5): Gummy material; $[\alpha]_D^{25}$ –13.4 (*c* = 1.08, $CHCl_3$). IR ($CHCl_3$): 1769 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 2.40 (t, 1 H, H_{14}), 3.87–4.02 (m, 2 H, H_{12}, H_6), 4.36 (t, *J* = 3.4, 4.9 Hz, 1 H, H_4), 4.43–4.55 (m, 2 H, H_{12}, H_7), 4.64 (t, *J* = 3.4, 3.4 Hz, 1 H, H_5), 5.37 (d, *J* = 4.9 Hz, 1 H, H_3), 5.81 (d, *J* = 3.4 Hz, 1 H, H_8), 7.03–7.12 (m, 2 H, aromatic), 7.31–7.37 (m, 3 H, aromatic). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 164.1 (C_2), 156.3 (C_{15}), 128.8 (C_{19}, C_{17}), 121.5 (C_{18}), 114.8 (C_{16}), 113.9 (C_{20}), 111.2 (C_9), 107.5 (C_8), 79.9 (C_7), 79.1 (C_5), 75.7 (C_3), 75.4 (C_{14}), 73.3 (C_{13}), 55.2 (C_4), 30.6 (C_{12}), 25.9 (C_{10}), 25.6 (C_{11}), 21.7 (C_6). MS (70 eV): *m*/*z* = 470 [M + 1]. Anal. Calcd for $C_{19}H_{20}NO_5I$: C, 48.63; H, 4.30; N, 2.98. Found: C, 48.82; H, 4.11; N, 2.93.

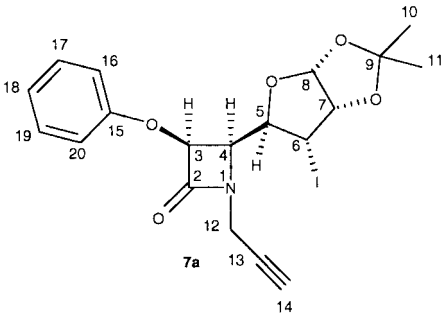


Figure 5

(13) Crystal structure data for **6a**: $C_{19}H_{20}INO_5$, colorless crystals grown from *i*-PrOH; *M* = 469.26; crystal dimensions 0.43 × 0.21 × 0.14 mm; crystal system orthorhombic, space group $P2_12_12_1$; a = 8.104 (2), b = 9.166 (2), c = 26.351 (6) Å; V = 1957.4 (8) $Å^3$; Z = 4; D_c = 1.592 g/cm^3; μ (MoKα) (λ = 0.7107 Å) = 1.664 mm^{-1}; F(000) = 936; θ = 1.55–23.27°; T = 293 (2) K; Max. and min. transmission = 0.8041 and 0.5320; Reflections collected/unique = 8515/2801 [*R*(int) = 0.0181]; Completeness to θ = 23.27 99.6%; Refinement method = Full-matrix least-squares on F^2; Data/restraints/parameters = 2801/0/240; Goodness-of-fit on F^2 = 1.156; Final *R* indices [I>2σ(I)]: *R*1 = 0.0196, *wR*2 = 0.0497; *R* indices (all data): *R*1 = 0.0203, *wR*2 = 0.0501.

(14) **General Procedure for Intramolecular Radical Cyclization of *N*-Propargyl β-Lactams (6a–b, and 7a–c):** A solution of Bu_3SnH (0.40 mL, 1.5 mmol) and AIBN (15 mg, 0.09 mmol) in toluene (10 mL) was slowly added to a refluxing solution of β-lactam **6a**–**b** or **7a**–**c** (1 mmol) in toluene (20 mL) over a period of 5 h. The reaction mixture was further refluxed for 2–5 h. After completion of the reaction (TLC), the solvent was concentrated and the crude reaction mixture was purified by flash column chromatography (silica gel, petroleum ether–EtOAC) to get pure cyclized product **8a**–**b** or **9a**–**c**.

8a (Figure 6): White crystalline solid (mp 109–110 °C); $[\alpha]_D^{25}$ +42.07 (*c* = 2.1, $CHCl_3$). IR ($CHCl_3$): 1765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.31–1.32 (d, 6 H, CH_3), 2.89 (d, *J* = 4.4 Hz, 1 H, H6), 3.72 (d, *J* = 14.7 Hz, 1 H, H_{12}), 3.89 (t, *J* = 3.4, 3.9 Hz, 1 H, H_4), 4.34 (d, *J* = 14.7 Hz, 1 H, H_{12}), 4.87–4.98 (m, 3 H, H_{14}, H_7), 5.24 (s, 1 H, H_5), 5.37 (d, *J* = 3.9 Hz, 1 H, H_3), 5.87 (d, *J* = 3.9 Hz, 1 H, H_8), 7.00–7.07 (m, 3 H, aromatic), 7.29–7.36 (m, 2 H, aromatic). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 166.3 (C_2), 156.9 (C_{15}); 137.1 (C_{13}), 129.6 (C_{19}, C_{17}), 122.6 (C_{18}), 115.5 (C_{16}, C_{20}), 113.5 (C_{14}), 111.6 (C_9), 104.6 (C_8), 81.8 (C_7), 80.5 (C_3), 75.1 (C_5), 54.9 (C_4), 47.7 (C_6), 45.4 (C_{12}), 26.4 (C_{10}, C_{11}). MS (70 eV): *m*/*z* = 344 [M + 1]. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.50; H, 6.16; N, 4.10. Found: C, 66.33; H, 5.97; N, 4.24.

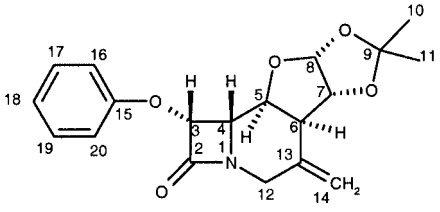


Figure 6

9a (Figure 7): Gummy material; $[\alpha]_D^{25}$ +25.38 (*c* = 1.16, $CHCl_3$). IR ($CHCl_3$): 1762 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 1.14 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 2.99 (br s, 1 H, H_6), 3.86 (d, *J* = 19.0 Hz, 1 H, H_{12}), 4.27–4.44 (m, 4 H,

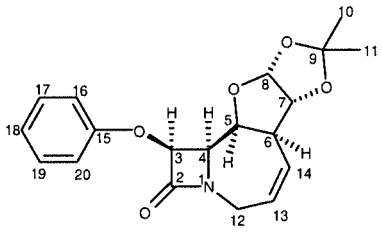


Figure 7

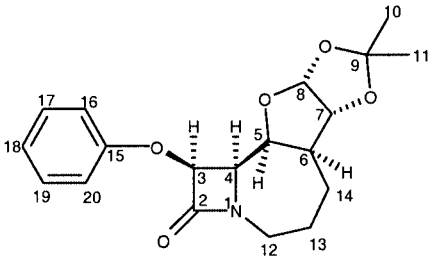


Figure 8

H_5, H_7, H_4, H_{12}), 5.32–5.57 (m, 3 H, H_{13}, H_{14}, H_3), 5.82 (d, J = 3.0 Hz, 1 H, H_8), 6.95–7.05 (m, 3 H, aromatic), 7.28–7.32 (m, 2 H, aromatic). ^{13}C NMR (75.2 MHz, $CDCl_3$): δ = 162.0 (C_2), 157.4 (C_{15}), 129.5 (C_{14}), 125.8 (C_{19}, C_{17}), 124.8 (C_{13}), 122.0 (C_{18}), 115.5 (C_{16}, C_{20}), 111.8 (C_8), 104.9 (C_9), 84.5 (C_7), 79.6 (C_3), 74.2 (C_5), 57.5 (C_4), 50.5 (C_6), 41.7 (C_{12}), 26.9 (C_{10}), 26.7 (C_{11}); MS (70 eV): m/z = 344 [M + 1]. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.62; H, 6.28; N, 4.20.

(15) Crystal structure data for **8b:** $C_{20}H_{23}NO_5$, colorless crystal from *i*-PrOH; M = 357.39; crystal dimensions 0.21 × 0.19 × 0.06 mm; crystal system monoclinic, space group $P2_1$; a = 9.839 (15), b = 8.148 (12), c = 11.946 (18) Å; V = 945.6 (2) Å^3; Z = 2; D_c = 1.255 g/cm^3; μ (MoKα) (λ = 0.7107 Å) = 0.090 mm^{-1}; F(000) = 380; θ = 1.73–24.99°; T = 293 (2) K; Max. and min. transmission = 0.9943 and 0.9813; Reflections collected/unique = 9089/3324 [R(int) = 0.0320]; Completeness to θ = 24.99 99.8%; Refinement method = Full-matrix least-squares on F^2; Data/restraints/parameters = 3324/1/237; Goodness-of-fit on F^2 = 1.071; Final R indices [I>2σ(I)]: R1 = 0.0497, wR2 = 0.1024; R indices (all data): R1 = 0.0584, wR2 = 0.1065.

(16) Spectral data for hydrogenated product **10** (Figure 8): White crystalline solid (mp 174 °C); $[\alpha]_D^{25}$ +1.88 (c = 0.8, $CHCl_3$). IR ($CHCl_3$,): 1755 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.15 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.5–1.9 (m, 4 H, H_{13}, H_{14}), 2.3–2.4 (m, 1 H, H_6), 3.1–3.2 (m, 1 H, H_{12}), 3.7–3.8 (m, 1 H, H_{12}), 4.17 (d, J = 4.3 Hz, 1 H, H_4), 4.31 (d, J = 3.6 Hz, 1 H, H_7), 4.33 (d, J = 4.3 Hz, 1 H, H_5), 5.36 (d, J = 4.3 Hz, 1 H, H_3), 5.85 (d, J = 3.6 Hz, 1 H, H_8), 6.9–7.4 (m, 5 H, aromatic). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 164.7 (C_2), 157.2 (C_{15}), 129.3 (C_{19}, C_{17}), 121.7 (C_{18}), 115.4 (C_{20}, C_{16}), 110.9 (C_8), 104.6 (C_9), 85.3 (C_7), 79.3 (C_3), 75.1 (C_5), 57.6 (C_4), 48.3 (C_{12}), 42.8 (C_6), 27.7 (C_{14}), 26.3 (C_{10}, C_{11}), 23.5 (C_{13}). MS (70 eV): m/z = 345 [M$^+$]. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.17; H, 6.87; N, 4.27.

(17) Crystal structure data for **10:** $C_{19}H_{23}NO_5$, colorless needles grown from *i*-PrOH; M = 345.38; crystal dimensions 0.47 × 0.24 × 0.19 mm; crystal system orthorhombic, space group $P2_12_12_1$; a = 5.498 (2), b = 14.423 (5), c = 21.601 (8) Å; V = 1712.9 (11) Å^3; Z = 4; D_c = 1.339 g/cm^3; μ (MoKα) (λ = 0.7107 Å) = 0.097 mm^{-1}; F(000) = 736; θ = 1.70–28.22°; T = 293 (2) K; Max. and min. transmission = 0.9814 and 0.9554; Reflections collected/unique = 8380/3863 [R(int) = 0.0227]; Completeness to θ = 28.22°, 94.3%; Refinement method = Full-matrix least-squares on F^2; Data/restraints/parameters = 3863/0/247; Goodness-of-fit on F^2 = 0.837; Final R indices [I>2σ(I)]: R1 = 0.0374, wR2 = 0.0745; R indices (all data): R1 = 0.0584, wR2 = 0.0794.