Synthesis of Polycyclic β-Lactams from D-Glucose Derived Chiral Template via Substrate-Controlled Radical Cyclization

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

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

The increasing bacterial resistance to the commercially available β-lactam antibiotics through the cleavage of strained β-lactam ring by β-lactamase enzyme attracted chemists toward the synthesis of stable polycyclic β-lactams of non-classical structures.[1,2] 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 regarding the regio and stereochemistry of radical cyclization.[5] Hexenyl radical cyclization is very efficient and well studied for mechanistic as well as synthetic applications.[3] The stereochemical outcome of such kind of cyclization can be predicted by Beckwith's transition state model.[6] According to this model and Baldwin's rules 5-*exo* cyclization is more common than 6-*endo* cyclization. In case of heptenyl radical cyclization also, the examples of 6-*exo* cyclizations are well known,[7] while 7-*endo* cyclizations are very rare.[8] 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.[9] The β-lactams with radical acceptor and radical progenitor appendages at appropriate sites have been used for radical cyclization. We have also employed this methodology for diastereospecific synthesis of novel polycyclic β-lactams[9m,n] wherein the radical progenitor and the radical acceptor are appended at C-3 and C-4 positions, respectively, on the β-lactam ring skeleton.

In our recent communication we have reported highly stereoselective and substrate-controlled synthesis of polycyclic β-lactams from glucose derived chiral template via 6-*exo* and 7-*endo* heptynyl type radical cyclization.[10] The β-lactams with N-1 propargyl group as a radical acceptor and iodo group as a radical progenitor on a sugar part, which is anchored to β-lactam ring at C-4, are used for the construction of polycyclic ring structure. In this paper we wish to report the detailed account of this work.

We selected D-glucose derived chiral templates for the synthesis of β-lactams with suitably sited radical progenitor and acceptor appendages using Staudinger reaction (Scheme 1), as these templates are known to show high level of diastereoselectivity for β-lactam formation.[11] Diacetonide **1** was prepared from D-glucose, following a known procedure,[12] by stirring with acetone in the presence of anhydrous zinc chloride and phosphoric acid. The 3-hydroxy diacetonide **1** was converted into 3-iodo derivative **2** by triphenylphosphine, iodine and imidazole.[13] The selective deprotection of acetonide by 10% H_2SO_4 in MeOH gave monoacetonide **3,** which on oxidative cleavage with $NaIO_4$ adsorbed on silica gel furnished chiral iodoaldehyde **4** in quantitative yield.[14] The reaction of iodoaldehyde **4** with allylamine and propargylamine provided imines **5a**,**b** in quantitative yields. However these imines were found to be unstable and used as such for the next reaction. *N*-Allyl imine **5a** underwent smooth cycloaddition reaction (Staudinger reaction) with ketenes derived from substituted acetyl chlorides (phenoxy and benzyloxy acetyl chlorides) and Et_3N, to give a 1:1 diastereomeric mixture of only *cis* β-lactams **6a**,**b** and **7a**,**b** (J = 5–6 Hz for *cis* β-lactam ring protons). Both the diastereomers could be separated by flash column chromatography. The structure and relative stereochemistry was assigned from spectral data and the absolute stereochemistry for β-lactam ring protons of **7a** was further established from the single crystal X-ray analysis as 3*R*, 4*S* based on the known absolute stereochemistry of the carbohydrate moiety (Figure 1).

The iodo-aldehyde **11** was prepared from glucose diacetonide **1** by following the known reaction sequence as shown in Scheme 2.[13,15,16] Aldehyde **11** was reacted with

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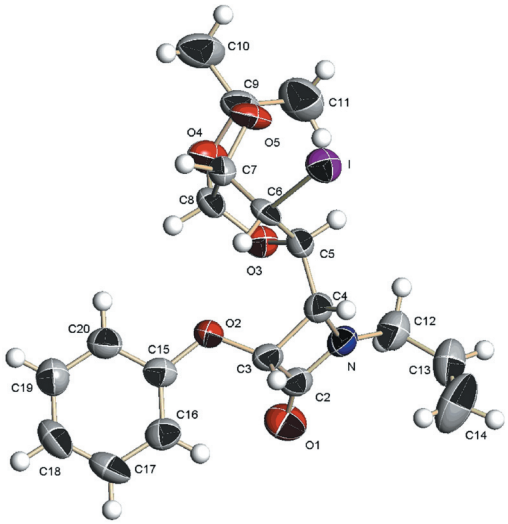
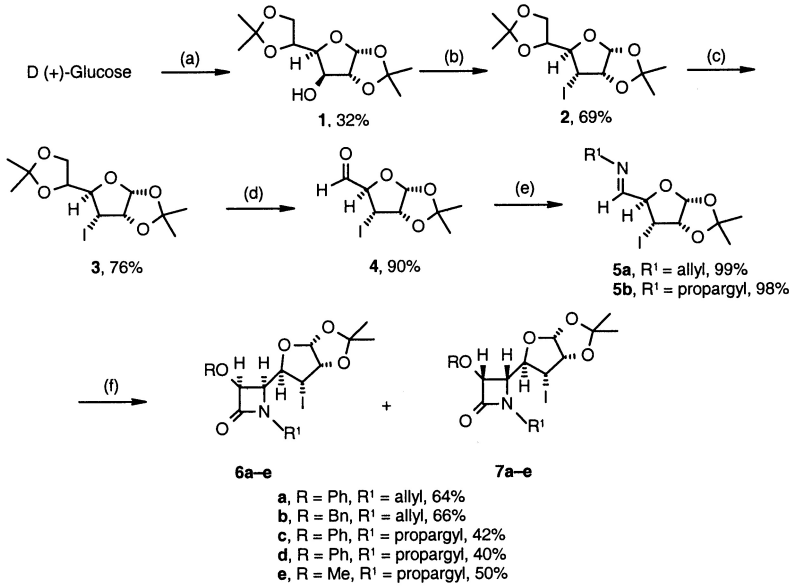


Figure 1 ORTEP diagram of **7a**

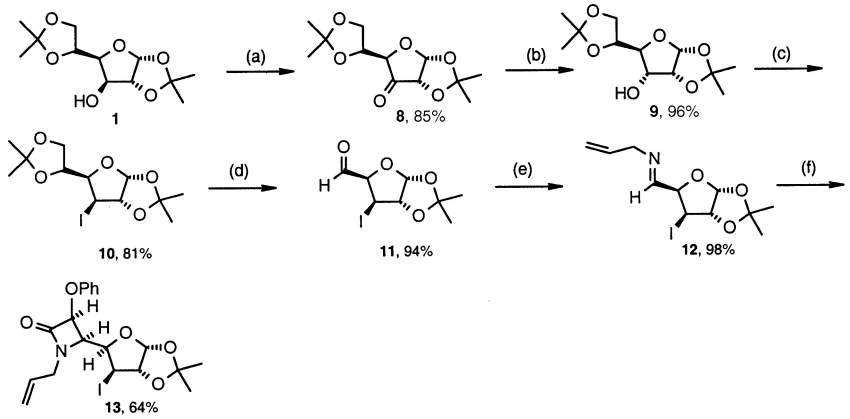
allylamine to give corresponding imine **12** in very good yield, which was directly used for ketene-imine cycloaddition reaction. The cycloaddition reaction was found to be highly diastereoselective and only single *cis* β-lactam **13** was obtained. The observed diastereoselectivity is due to the steric interaction imposed by the bulky iodo group during the ketene-imine cycloaddition reaction.

The unique feature associated with β-lactams **6**, **7** and **13** is the presence of iodo group as radical progenitor at C-4 and presence of *N*-allyl side chain on azetidin-2-one nucleus as radical acceptor. This is an ideal system to study tributyltin hydride mediated radical cyclization.

The β-lactam **6a** when treated with tributyltin hydride in presence of AIBN in refluxing toluene underwent smooth radical cyclization to give tetracyclic compound **14** in moderate yield. The ^{1}H and ^{13}C NMR data revealed the formation of *endo* radical cyclized product **14**, which was further confirmed by single crystal X-ray analysis. The



Scheme 1 *Reagents and conditions:* (a) $ZnCl_2$, acetone, H_3PO_4, r.t., 30 h; (b) PPh_3, I_2, imidazole, toluene, reflux, 17 h; (c) 10% H_2SO_4, MeOH, r.t., 6 h; (d) 0.65 M $NaIO_4$ on SiO_2, CH_2Cl_2, r.t., 1 h; (e) R^1NH_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



Scheme 2 *Reagents and conditions:* (a) PCC, 3 Å MS, neutral alumina/CH_2Cl_2, r.t., 15 h; (b) $NaBH_4$, EtOH–H_2O (7:3), 0 °C to r.t., 2 h; (c) PPh_3, I_2, imidazole, toluene, reflux, 17 h; (d) i) 10% H_2SO_4, MeOH, r.t., 4 h, ii) 0.65 M $NaIO_4$ on SiO_2, CH_2Cl_2, r.t., 1 h; (e) allyl amine, $MgSO_4$, CH_2Cl_2, r.t., 3 h; (f) $PhOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C to r.t., 12 h

absolute stereochemistry at the newly formed centre was established as 6*S* based on known absolute stereochemistry of 7*R*, 8*R* of the sugar moiety. The carbon atoms C13 and C14 are disordered and occupy two positions at C13A, C13B and C14A, C14 B with 0.7 and 0.3 occupancy respectively as shown in the ORTEP diagram (Figure 2).

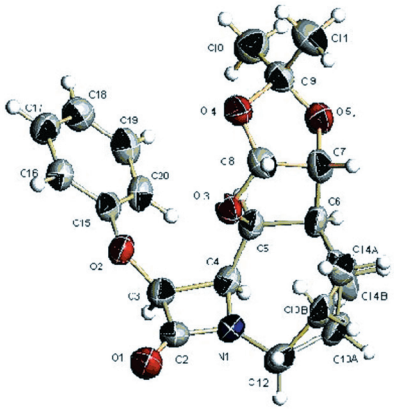
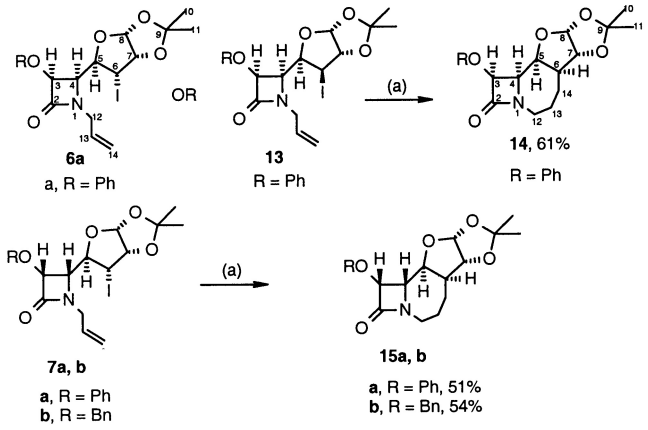


Figure 2 ORTEP diagram of **14**

β-Lactam **13** also gave the same cyclized product **14** as in case of **6a** through a common radical intermediate, when subjected to tributyltin hydride mediated radical cyclization. The other diastereomers **7a**,**b** under similar reaction conditions gave *endo*-cyclized tetracyclic β-lactams **15a**,**b** in moderate yields (Scheme 3). The structures of **15a** and **15b** were established from IR, ^{1}H and ^{13}C NMR spectral data.



Scheme 3 *Reagents and conditions:* (a) Tributyl tinhydride, AIBN, toluene, reflux, 6 h

N-Propargylimine **5b** when reacted with ketenes generated from acid chloride (phenoxy, benzyloxy and methoxy acetyl chlorides) under Staudinger reaction conditions gave a diastereomeric mixture of β-lactams **6c**–**e** and **7c**–**e** in moderate yields (Scheme 1). Both the isomers were separated by careful column chromatography and structures were established by spectral analyses. The absolute stereochemistry of one of the diastereomers **7c** was established by single crystal X-ray spectral data (Figure 3). After establishing the structure and absolute stereochemistry, both the diastereomers **6c**–**e** and **7c**–**e** were independently subjected to radical cyclization reaction using tributyltin hydride (Scheme 4). The pure diastereomer **6c** when treated with tributyltin hydride in the presence of AIBN in refluxing toluene underwent radical cyclization to give *endo-dig* cyclized product **16a**. ^{1}H and ^{13}C NMR spectral data established the structure of **16a**. However, this compound could not be obtained in crystalline form to get the single crystal X-ray analysis. Therefore, it was subjected to catalytic hydrogenation at room temperature using Pd/C (10%) and H_2 (60 psi pressure) to get white crystalline compound **14**. 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 **14** and 2D NMR studies revealed *endo-dig* radical cyclization of **6c**. The spectral data was found to be identical with the compound obtained from the cyclization of *N*-allyl β-lactam **6a**.

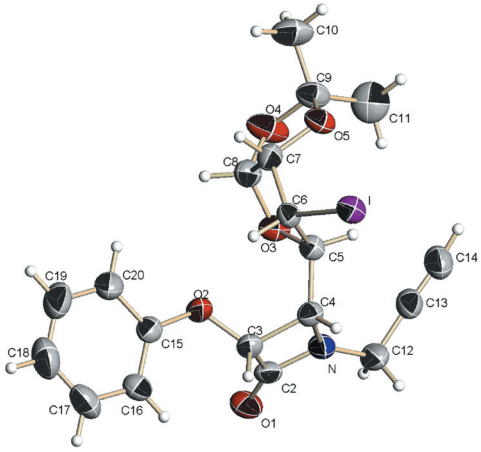
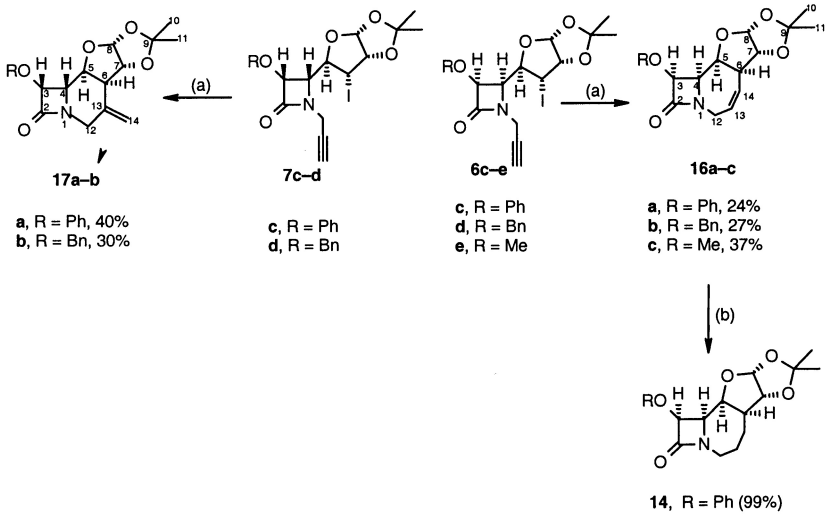


Figure 3 ORTEP diagram of **7c**

On the other hand, when **7d** was subjected to radical cyclization under similar reaction conditions, it gave kinetically controlled stable *exo-dig* cyclized product **17b** via 1,6-bond coupling of hept-6-ynyl radical. The presence of olefinic methylene peak in the ^{13}C DEPT experiment at 113.5 ppm and single crystal X-ray analysis of **17b** confirmed the *exo-dig* cyclization and relative stereochemistry of C3, C4 and C6 was assigned as 3*R*, 4*S* and 6*S* (Figure 4).

A drastic change in the mode of radical cyclization is observed with the change in stereochemistry of β-lactam nucleus. 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 **6c**–**e** (Scheme 5). Radical addition to the triple bond was also stereospecific and the newly formed C–C bond directed *anti* to the acetonide group is presumably due to the steric



Scheme 4 *Reagents and conditions:* (a) Bu_3SnH, AIBN, toluene, reflux, 6 h; (b) H_2, Pd/C (10%)

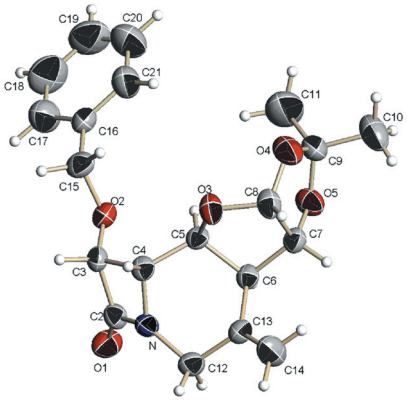


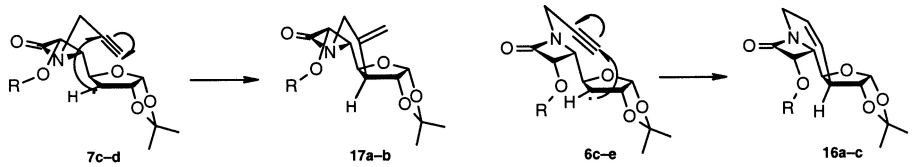
Figure 4 ORTEP diagram of **17b**

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.

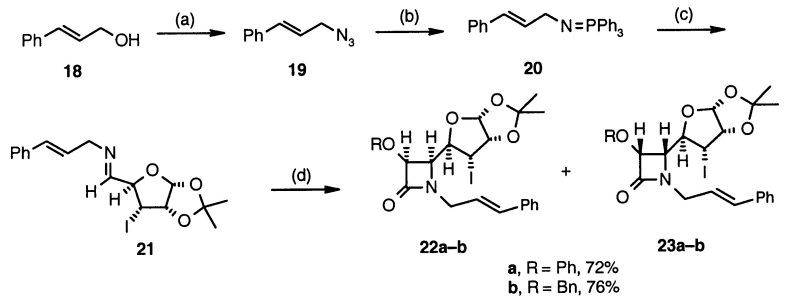
We also studied the radical cyclization of *N*-cinnamyl β-lactams **22** and **23**. These β-lactams were prepared by our recently reported method as shown in Scheme 6.[17] Both the diastereomers **22** and **23** were separated by flash column chromatography and independently subjected to radical cyclization reaction. The β-lactams **22a**,**b** were treated with tributyltin hydride in presence of AIBN in refluxing toluene to give *exo* cyclized products **24a**,**b** with excellent regio and diastereoselectivity. The presence of two double doublets at δ = 3.50 and 2.80 for diastereotopic *N*-CH_2 protons in ^{1}H NMR, two-methylene carbon peaks at δ = 37.34 and 39.07 ppm for $PhCH_2$ and *N*-CH_2, respectively in ^{13}C DEPT spectrum of cyclized product **24a** confirmed the *exo-trig* radical cyclization. The other diastereomers **23a**,**b** gave a 1:1 diastereomeric mixture of *exo-trig* cyclized products **25a**,**b** (Scheme 7). While the *exo*-selectivity in *N*-cinnamyl β-lactams may be attributed to the formation of a stable benzyl radical, the reason for the observed diastereoselectivity is not clear. A possible explanation could be that in the alpha diastereomers **22a**,**b**, the proximity of the acetonide moiety to the reaction site may be responsible for the observed diastereoselectivity. On the contrary, the acetonide moiety in beta isomer **23a**,**b** is far away from the reaction site and thus giving a 1:1 mixture of diastereomers **25a**,**b**.

In conclusion, tributyltin hydride-AIBN mediated radical cyclization of *N*-allyl gave *7-endo* cyclized polycyclic β-lactams while *N*-cinnamyl β-lactams gave *6-exo* cyclized products. In case of *N*-propargyl β-lactams the radical cyclization was found to be highly stereospecific, substrate controlled and gave either *6-exo* or *7-endo* products depending on the stereochemistry of the β-lactam ring.

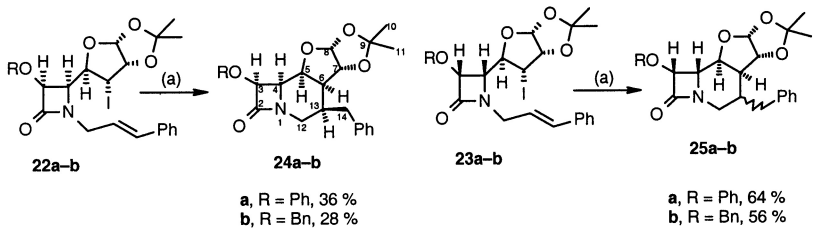
^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Bruker AC 200, Bruker MSL-300 and Bruker DRX-500 spectrometers and chemical shifts are reported in ppm downfield from TMS for ^{1}H NMR. IR spectra were recorded on Shimadzu FTIR-8400 using NaCl optics. The mass spectra were recorded on Finnigan Mat 1020 mass spectrometer at 70 eV. Melting points were de-



Scheme 5



Scheme 6 *Reagents and conditions:* (a) i) Triphosgene, Et_3N, acetone, 0 °C to r.t., 3 h, ii) NaN_3, 0 °C to r.t., 12 h; (b) PPh_3, toluene, reflux, 4 h; (c) **4**, toluene, 0 °C to r.t., 12 h; (d) $ROCH_2COCl$, Et_3N, CH_2Cl_2, –15 °C to r.t., 12 h



Scheme 7 *Reagents and conditions:* Bu_3SnH, AIBN, toluene, reflux, 5–8 h

termined on a Thermonik Campbell melting point apparatus and were uncorrected. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108 elemental analyzer. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions. X-Ray intensity data were collected on a Bruker SMART APEX CCD diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 28.25°.

Preparation of Imine 5a and 5b; General Procedure

To a solution of allylamine or propargylamine (5 mmol) in CH_2Cl_2 (20 mL) and anhyd $MgSO_4$ was added a solution of the aldehyde **4** (5 mmol) in CH_2Cl_2. The mixture was stirred for 2–3 h (TLC) at r.t. It was filtered through a celite bed and the filtrate was concentrated to get the imines **5a** or **5b**, which were used as such for the β-lactam formation.

Preparation of β-Lactams 6 and 7; General Procedure

A solution of the acid chloride (phenoxyacetyl chloride, benzyloxyacetyl chloride or methoxyacetyl chloride) (1.5 mmol) in CH_2Cl_2 (30 mL) was added to a solution of the imine **5** (1 mmol) and Et_3N (4.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C. It was then allowed to warm to r.t. and further stirred for 15 h. The reaction mixture was washed with sat. $NaHCO_3$ solution (10 mL) and sat. brine solution (10 mL). The organic layer was then dried over anhyd Na_2SO_4, and solvent was removed under reduced pressure to give a diastereomeric mixture (1:1) of β-lactams **6** and **7** in 64–66% yields. Both the diastereomers were separated by flash column chromatography.

Compound 6a

White solid; mp 89 °C; $[\alpha]_D^{25}$ –25.46 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 1766 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 3.81 (dd, *J* = 6.8, 11.2 Hz, 1 H, H-12), 3.9 (dd, *J* = 3.6, 4.4 Hz, 1 H, H-6), 4.19–4.23 (m, 1 H, H-12), 4.24 (dd, *J* = 3.1, 4.7 Hz, 1 H, H-4), 4.46 (dd, *J* = 3.1, 3.6 Hz, 1 H, H-5), 4.60 (t, *J* = 3.6 Hz, 1 H, H-7), 5.26–5.33 (m, 2 H, H-14), 5.36 (d, *J* = 4.7 Hz, 1 H, H-3), 5.77 (d, *J* = 3.6 Hz, 1 H, H-8), 5.78–5.87 (m, 1 H, H-13), 7.00–7.40 (m, 5 H, aromatic).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 21.9, 26.2, 26.6, 44.4, 56.4, 78.7, 79.8, 80.5, 103.1, 111.8, 115.5, 118.9, 122.0, 129.3, 131.5, 157.1, 165.3.

MS: *m*/*z* = 471 [M^+].

Anal. Calcd for $C_{19}H_{22}INO_5$: C, 48.42; H, 4.71; N, 2.97. Found: C, 48.32; H, 4.62; N, 2.84.

Compound 7a

White crystalline solid; mp 113–114 °C; $[\alpha]_D^{25}$ +155.8 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 1771 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 3.80 (dd, *J* = 3.6, 4.4 Hz, 1 H, H-6), 3.90–4.20 (m, 3 H, H-12, H-4), 4.50–4.70 (m, 2 H, H-5, H-7), 5.10–5.40 (m, 3 H, H-14, H-3), 5.70–5.90 (m, 2 H, H-13, H-8), 6.90–7.40 (m, 5 H, aromatic).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 19.1, 26.7, 43.4, 55.7, 79.7, 80.4, 81.3, 103.1, 112.0, 115.5, 119.0, 122.3, 129.5, 131.3, 157.3, 165.7.

MS: *m*/*z* = 471 [M^+].

Anal. Calcd for $C_{19}H_{22}INO_5$: C, 48.42; H, 4.71; N, 2.97. Found: C, 48.34; H, 4.91; N, 3.19.

Crystal Data for 7a

$C_{19}H_{22}INO_5$, colorless needles grown from *i*-PrOH; *M* = 471.28, crystal dimensions 0.40 × 0.16 × 0.13 mm; crystal system orthorhombic, space group $P2_12_12_1$, a = 8.780 (1), b = 17.749 (1), c = 38.745 (2) Å, V = 6037.9(6) $Å^3$, Z = 12, Dc = 1.555 g/cm^3, μ (Mo Kα) (λ = 0.7107 Å) = 1.619 mm^{-1}, F(000) = 2832, θ = 1.56–25°; T = 293 (2) K, Max. and min. transmission 0.8172 and 0.5637; Reflections collected/unique = 30556/10553 [R(int) = 0.0322]; Completeness to θ = 25.00, 99.5%; Refinement method = Full-matrix least-squares on F^2; Data/restraints/parameters = 10553/0/712; Goodness-of-fit on F^2 = 1.043; Final R indices [I > 2σ (I)] *R*1 = 0.0430, *wR*2 = 0.0855; R indices (all data) *R*1 = 0.0538, *wR*2 = 0.0892.

Compound 6b
Thick oil; $[\alpha]_D^{25}$ +7.89 (*c* = 0.6, $CHCl_3$).

IR ($CHCl_3$): 1755 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 3.70 (dd, *J* = 7.3, 11.5 Hz, 1 H, H-12), 3.85–4.25 (m, 4 H, Ph-C$H_a$$H_b$O, H-4, H-6, H-12), 4.40 (dd, *J* = 2.9, 3.4 Hz, 1 H, H-5), 4.50–5.00 (m, 3 H, H-3, PhC$H_a$$H_b$O, H-7), 5.15–5.35 (m, 2 H, H-14), 5.60–5.95 (m, 2 H, H-13, H-8), 7.10–7.50 (m, 5 H, aromatic).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 21.9, 26.5, 44.2, 56.2, 72.9, 79.1, 80.6, 81.2, 103.2, 111.7, 116.3, 118.8, 127.6, 128.2, 128.5, 131.7, 137.0, 167.1.

MS: *m*/*z* = 485 [M^+].

Anal. Calcd for $C_{20}H_{24}INO_5$: C, 49.50; H, 4.98; N, 2.89. Found: C, 49.67; H, 4.79; N, 2.97.

Compound 7b
Thick oil; $[\alpha]_D^{25}$ +20.15 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 1759 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 3.80 (dd, *J* = 6.9, 11.2 Hz, 1 H, H-12), 3.90–4.20 (m, 3 H, H-12, H-6, H-4), 4.45–4.95 (m, 5 H, PhCH_2O, H-3, H-5, H-7), 5.15–5.35 (m, 2 H, H-14), 5.65–5.90 (m, 2 H, H-13, H-5), 7.10–7.45 (m, 5 H, aromatic).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 19.4, 26.9, 43.7, 56.1, 73.2, 80.2, 81.6, 103.4, 112.2, 119.0, 127.8, 128.0, 128.5, 131.6, 137.1, 167.6.

MS: *m*/*z* = 485 [M^+].

Anal. Calcd for $C_{20}H_{24}INO_5$: C, 49.50; H, 4.98; N, 2.89. Found: C, 49.48; H, 5.12; N, 2.94.

Reaction of Imine 5b with Phenoxyacetyl Chloride
A mixture of β-lactams **6c** and **7c** were obtained from imine **5b** following the above general procedure in 42% overall yield. The crude product was purified by flash column chromatography (10% acetone–petroleum ether) to get pure **6c** as a gummy material (22%). However, the other diastereomer **7c** came as a mixture, which was further purified by crystallization from MeOH to get a white crystalline solid (20%).

Compound 6c
Gummy oil; $[\alpha]_D^{25}$ –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, *J* = 2.5 Hz, 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 = 21.7, 25.6, 25.9, 30.6, 55.2, 73.3, 75.4, 79.1, 79.9, 107.5, 111.2, 113.9, 114.8, 121.5, 128.8, 156.3, 164.1.

MS: *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.

Compound 7c
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, *J* = 2.4 Hz, 1 H, H-14), 3.97–4.06 (dd, *J* = 2.5, 17.9 Hz, 1 H, H-12), 4.13 (dd, *J* = 3.6, 4.4 Hz, 1 H, H-6), 4.30 (t, *J* = 4.8, 3.9 Hz, 1 H, H-4), 4.46 (dd, *J* = 3.0, 18.1 Hz, 1 H, H-12), 4.65 (t, *J* = 3.9 Hz, 1 H, H-7), 4.70–4.78 (dd, *J* = 3.6, 3.9 Hz, 1 H, H-5), 5.34 (d, *J* = 4.8 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 = 19.4, 26.8, 26.9, 30.9, 56.3, 74.0, 75.8, 80.1, 80.8, 81.7, 103.4, 112.4, 115.9, 122.7, 129.7, 157.5, 165.6.

MS: *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.

Crystal Data for 7c
$C_{19}H_{20}INO_5$, 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 (Mo Kα) (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.

Reaction of Imine 5b with Benzyloxyacetyl Chloride
A mixture of β-lactams **6d** and **7d** were obtained from imine **5b** following the general procedure in 41% overall yield. The mixture was separated by flash column chromatography (10% acetone–petroleum ether) to get pure **7d** as a gummy material (23%). However, other diastereomer **6d** could not be obtained in pure form either by very careful chromatography or by crystallization. Therefore, this diastereomer was used as such for further reaction.

Compound 7d
Gummy oil; $[\alpha]_D^{25}$ = +101.5 (*c* = 1.4, $CHCl_3$).

IR ($CHCl_3$): 1762 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 2.33 (t, *J* = 2.5 Hz, 1 H, H-14), 3.99–4.13 (m, 3 H, H-4, H-12), 4.44 (dd, *J* = 2.4, 2.4 Hz, 1 H, H-6), 4.70 (m, 5 H, $C_6H_5CH_2O$, H-3, H-7, H-5), 5.77 (d, *J* = 3.4 Hz, 1 H, H-8), 7.36–7.38 (m, 5 H, aromatic).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 20.0, 26.8, 31.3, 57.1, 73.3, 73.7, 75.9, 80.4, 81.7, 103.3, 112.2, 127.9, 128.4, 130.0, 136.8, 167.1.

MS: *m*/*z* = 484 [M + 1].

Anal. Calcd for $C_{20}H_{22}O_5NI$: C, 49.7; H, 4.59; N, 2.30. Found: C, 49.86; H, 4.64; N, 2.48.

Reaction of Imine 5b with Methoxyacetyl Chloride
To a solution of imine **5b** (0.335 g, 1 mmol) and Et_3N (0.45 g, 4.5 mmol) in CH_2Cl_2 (20 mL) was added slowly a solution of methoxyacetyl chloride (0.162 g, 1.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C in 30 min. The reaction mixture was allowed to warm to r.t. and stirred for 15 h. The usual work up afforded an inseparable mixture (0.204 g, 50%) of diastereomers **6e** and **7e**.

IR ($CHCl_3$): 1767 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 6 H, CH_3), 1.58 (s, 6 H, CH_3), 2.34–2.35 (m, 2 H, H-14), 3.58 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.84 (d, *J* = 2.5 Hz, 1 H, H-6), 3.93 (d, *J* = 2.5 Hz, 1 H, H-6), 3.96–4.16 (m, 5 H, H-12, H-4), 4.38 (d, *J* = 2.5 Hz, 1 H, H-5),

4.41–4.48 (m, 2 H, H-4, H-5), 4.57–4.67 (m, 4 H, H-3, H-7), 5.84 (d, *J* = 3.4 Hz, 1 H, H-8), 5.87 (d, *J* = 3.4 Hz, 1 H, H-8).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 19.8, 22.1, 26.6, 26.8, 31.0, 31.2, 56.0, 56.8, 59.5, 73.5, 73.7, 79.1, 80.3, 80.8, 81.7, 83.7, 84.0, 103.3, 112.0, 112.3, 166.6, 167.2.

MS: *m*/*z* = 408 [M + 1].

Preparation of β-Lactam 13

The imine **12** (0.337 g, 1 mmol) on treatment with phenoxyacetyl chloride (0.255 g, 1.5 mmol), in the presence of Et_3N (0.45 g, 4.5 mmol) provided a single diastereomer, which was purified by column chromatography to give *cis*-β-lactams **13** as a thick oil (0.30 g, 64%); $[\alpha]_D^{25}$ +41.97 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 1744 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 6 H, CH_3), 3.55 (dd, *J* = 7.3, 11.8 Hz, 1 H, H-12), 4.20–4.40 (m, 2 H, H-12, H-6), 4.75 (d, *J* = 4.4 Hz, 1 H, H-4), 4.95 (d, *J* = 5.4 Hz, 1 H, H-7), 5.15–5.35 (m, 3 H, H-14, H-5), 5.40 (d, *J* = 4.4 Hz, 1 H, H-3), 5.65–5.90 (m, 1 H, H-13), 5.98 (d, *J* = 5.4 Hz, 1 H, H-8), 6.90–7.40 (m, 5 H, aromatic).

MS: *m*/*z* = 471 [M$^+$].

Anal. Calcd for $C_{19}H_{22}INO_5$: C, 48.42; H, 4.71; N, 2.97. Found: C, 48.66; H, 4.88; N, 2.85.

Radical Cyclization of β-Lactams 6a–e, 7a–e and 13; General Procedure

A solution of Bu_3SnH (0.40 mL, 1.5 mmol) and AIBN (30 mg, 0.18 mmol) in toluene (10 mL) was added to a refluxing solution of β-lactam (1 mmol) and AIBN (30 mg, 0.18 mmol) in toluene (15 mL) over a period of 3 h. The reaction mixture was further refluxed for 2–3 h. After completion of the reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, petroleum ether–EtOAc) to give pure cyclized products **14**–**17**.

Compound 14

Yield: 51%; white solid; mp 174–175 °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), 1.50–1.90 (m, 4 H, H-13, H-14), 2.30–2.40 (m, 1 H, H-6), 3.10–3.20 (m, 1 H, H-12), 3.70–3.80 (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* = 3.6 Hz, 1 H, H-3), 5.85 (d, *J* = 3.6 Hz, 1 H, H-8), 6.90–7.40 (m, 5 H, aromatic).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 23.5, 26.3, 27.7, 42.8, 48.3, 57.6, 75.1, 79.3, 85.3, 104.6, 110.9, 115.4, 121.7, 129.3, 157.2, 164.7.

MS: *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.

Crystal Data for 14

$C_{19}H_{23}NO_5$, 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 (Mo Kα) (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)], *R*1 = 0.0374, *wR*2 = 0.0745; R indices (all data) = *R*1 = 0.0584, *wR*2 = 0.0794.

Compound 15a

Yield: 61%; thick oil; $[\alpha]_D^{25}$ +9.52 (*c* = 0.5, $CHCl_3$).

IR ($CHCl_3$): 1765 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.50–2.00 (m, 4 H, H-13, H-14), 2.30–2.50 (m, 1 H, H-6), 2.70–2.90 (m, 1 H, H-12), 3.95–4.10 (m, 2 H, H-4, H-12), 4.30 (d, *J* = 3.6 Hz, 1 H, H-7), 4.70 (t, *J* = 4.4 Hz, 1 H, H-5), 5.30 (d, *J* = 4.9 Hz, 1 H, H-3), 5.75 (d, *J* = 3.6 Hz, 1 H, H-8), 6.90–7.40 (m, 5 H, aromatic).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 26.1, 26.3, 28.8, 42.6, 50.6, 60.9, 75.3, 81.00, 87.2, 104.0, 111.1, 115.4, 122.1, 129.3, 156.8, 164.6.

MS: *m*/*z* = 345 [M$^+$].

Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.27; H, 6.62; N, 4.16.

Compound 16a

Yield: 24%; thick oil; $[\alpha]_D^{25}$ +25.38 (*c* = 1.2, $CHCl_3$).

IR ($CHCl_3$): 1762 cm^{-1}.

^{1}H 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, H-5, H-7, H-4, H-12), 5.32–5.57 (m, 3 H, H-13, 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 = 26.6, 41.7, 50.5, 57.5, 74.2, 79.6, 84.5, 104.9, 111.8, 115.5, 122.0, 124.8, 125.8, 129.5, 157.4.

MS: *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.

Compound 16b

Yield: 27%; thick oil; $[\alpha]_D^{25}$ –21.86 (*c* = 0.58, $CHCl_3$).

IR ($CHCl_3$): 1756 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 2.86 (br s, 1 H, H-6), 3.64 (d, *J* = 17.6 Hz, 1 H, H-12), 3.88 (d, *J* = 4.4 Hz, 1 H, H-4), 4.15 (d, *J* = 18.3 Hz, 1 H, H-12), 4.34 (d, *J* = 3.6 Hz, 1 H, H-7), 4.38 (d, *J* = 4.4 Hz, 1 H, H-5), 4.55 (d, *J* = 11.7 Hz, 1 H, $C_6H_5CH_aH_b$), 4.64 (d, *J* = 4.4 Hz, 1 H, H-3), 4.80 (d, *J* = 11.7 Hz, 1 H, $C_6H_5CH_aH_b$), 5.20–5.24 (br d, *J* = 12.4 Hz, 1 H, H-13), 5.37 (d, *J* = 12.4 Hz, 1 H, H-14), 5.72 (d, *J* = 2.9 Hz, 1 H, H-8), 7.17–7.30 (m, 5 H, aromatic).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 26.5, 26.9, 50.4, 41.4, 57.3, 72.9, 74.6, 81.1, 84.5, 104.9, 111.7, 124.7, 126.0, 128.3, 127.8, 137.6, 166.9.

MS: *m*/*z* = 358 [M + 1].

Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.90. Found: C, 67.40; H, 6.62; N, 3.98.

Compound 16c

Yield: 37%; thick oil; $[\alpha]_D^{25}$ –17.04 (*c* = 0.68, $CHCl_3$).

IR ($CHCl_3$): 1758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 3.02 (br s, 1 H, H-6), 3.59 (s, 3 H, OCH_3), 3.79 (d, *J* = 18.7 Hz, 1 H, H-12), 4.06 (d, *J* = 4.4 Hz, 1 H, H-4), 4.27 (d, *J* = 18.6 Hz, 1 H, H-12), 4.46 (d, *J* = 3.7 Hz, 1 H, H-5), 4.56 (d, *J* = 3.7 Hz, 1 H, H-7), 4.58 (d, *J* = 4.4 Hz, 1 H, H-3), 5.38 (d, *J* = 12.7 Hz, 1 H, H-13), 5.53 (d, *J* = 13.1 Hz, 1 H, H-14), 5.83 (d, *J* = 3.7 Hz, 1 H, H-8).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 26.46, 26.91, 41.28, 50.50, 57.13, 59.26, 83.35, 84.45, 104.92, 111.62, 124.61, 125.96, 166.78.

MS: *m*/*z* = 282 [M + 1].

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.80; N, 4.98. Found: C, 59.90; H, 6.96; N, 5.10.

Compound 17a

Yield: 40%; white crystalline solid; mp 109–110 °C; $[\alpha]_D^{25}$ +42.07 (*c* = 2.1, $CHCl_3$).

IR ($CHCl_3$): 1765 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31–1.32 (d, 6 H, CH_3), 2.89 (d, *J* = 4.4 Hz, 1 H, H-6), 3.72 (d, *J* = 14.7 Hz, 1 H, H-12), 3.89 (t, *J* = 3.9, 3.4 Hz, 1 H, H-14), 4.34 (d, *J* = 15.1 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 = 26.4, 45.4, 47.7, 54.9, 75.1, 80.5, 81.8, 104.6, 111.6, 113.5, 115.5, 122.6, 129.6, 137.1, 156.9, 166.3.

MS: *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.

Compound 17b

Yield: 30%; yellow solid; mp 128 °C; $[\alpha]_D^{25}$ +44.7 (*c* = 1.06, $CHCl_3$).

IR ($CHCl_3$): 1759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 2.89 (d, *J* = 5.0 Hz, 1 H, H-6), 3.70–3.63 (m, 2 H, H-4, H-12), 4.28 (d, *J* = 14.7 Hz, 1 H, H-12), 4.72 (d, *J* = 11.0 Hz, 1 H, $C_6H_5CH_aH_bO$), 4.82–4.85 (m, 2 H, $C_6H_5CH_aH_bO$, H-3), 4.99–5.02 (m, 3 H, H-7, H-14), 5.20 (s, 1 H, H-5), 5.96 (d, *J* = 3.2 Hz, 1 H, H-8), 7.26–7.45 (m, 5 H, aromatic).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 26.3, 26.8, 45.4, 47.8, 54.7, 72.8, 75.4, 81.3, 81.8, 111.6, 113.4, 127.9, 128.5, 136.6, 137.5, 168.0.

MS: *m*/*z* = 358 [M + 1].

Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.20; H, 6.49; N, 3.90. Found: C, 67.05; H, 6.60; N, 4.02.

Crystal Data for 17b

$C_{20}H_{23}NO_5$, 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 (Mo Kα) (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)] = *R*1 = 0.0497, *wR*2 = 0.1024; R indices (all data) = *R*1 = 0.0584, *wR*2 = 0.1065.

Hydrogenation of 16a; Typical Procedure

A mixture of tricyclic β-lactam **16a** (13 mg, 0.038 mmol) and Pd/C (10%, 50 mg) was hydrogenated at 60 psi pressure of H_2 for 7 h at r.t. The reaction mixture was filtered through a short bed of celite and solvent was removed under reduced pressure to get **14** as a white crystalline solid (13 mg, 100%), which was further purified by column chromatography (60% EtOAc–petroleum ether). The spectral data was found to exactly identical with the product obtained by radical cyclization of **6a**.

Preparation of *N*-Cinnamyl β-Lactams 22a, 23a; Typical Procedure

To a solution of cinnamyl azide (0.3 g, 1.88 mmol) in toluene (20 mL), triphenylphosphine (0.493 g, 1.88 mmol) was added and the mixture was refluxed for 4 h. The reaction mixture was then cooled to 0 °C and a solution of iodoaldehyde **4** (0.560 g, 1.88 mmol) in toluene and benzene mixture (4:1, 25 mL) was added and stirred at r.t. for overnight. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL). Et_3N (0.87 g. 8.63 mmol) was added to the mixture and cooled to –15 °C. A solution of phenoxyacetyl chloride (0.48 g, 2.82 mmol) in CH_2Cl_2 (10 mL) was added slowly to the reaction mixture. It was allowed to warm to r.t. and stirred overnight. Usual work-up gave a 1:1 diastereomeric mixture of β-lactams **22a** and **23a** (0.740 g, 72%), which were separated by flash chromatography using 10% acetone–petroleum ether.

Compound 22a

White crystalline solid; mp 112–113 °C; $[\alpha]_D^{25}$ +118.17 (*c* = 0.69, $CHCl_3$).

IR ($CHCl_3$): 1763 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.36 (s, 6 H, CH_3), 4.11–4.13 (m, 3 H, H-12, H-6), 4.24 (dd, *J* = 2.7, 4.1 Hz, 1 H, H-4), 4.60 (t, *J* = 3.7 Hz, 1 H, H-7), 4.66 (dd, *J* = 2.7, 2.8 Hz, 1 H, H-5), 5.35 (d, *J* = 4.1 Hz, 1 H, H-3), 5.89 (d, *J* = 3.7 Hz, 1 H, H-8), 6.19–6.25 (m, 1 H, H-13), 6.63 (d, *J* = 15.6 Hz, 1 H, H-14), 7.05–7.41 (m, 10 H, aromatic).

^{13}C NMR ($CDCl_3$, 125.76 MHz): δ = 19.2, 26.6, 43.2, 56.1, 80.0, 80.5, 81.3, 103.3, 112.1, 115.6, 122.5, 122.6, 126.5, 127.9, 128.5, 129.6, 134.0, 135.9, 157.4, 166.0.

MS: *m*/*z* = 548 [M + 1].

Anal Calcd for $C_{25}H_{26}NO_5I$: C, 54.86; H, 4.79; N, 2.56. Found: C, 54.67; H, 4.60; N, 2.64.

Compound 23a

Thick oil; $[\alpha]_D^{25}$ –1.5 (*c* = 0.43, $CHCl_3$).

IR ($CHCl_3$): 1762 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.90 (t, *J* = 4.0 Hz, 1 H, H-6), 4.00 (dd, *J* = 8.2, 15.7 Hz, 1 H, H-12), 4.24–4.29 (m, 2 H, H-4, H-12), 4.42–4.54 (m, 2 H, H-5, H-7), 5.37 (d, *J* = 5.1 Hz, 1 H, H-3), 5.73 (d, *J* = 3.5 Hz, 1 H, H-8), 6.08–6.12 (m, 1 H, H-13), 6.59 (d, *J* = 16.0 Hz, 1 H, H-14), 6.97–7.40 (m, 10 H, aromatic).

^{13}C NMR ($CDCl_3$, 125.76 MHz): δ = 21.9, 26.3, 26.6, 44.0, 56.0, 56.7, 78.9, 80.0, 80.6, 103.2, 112.0, 115.6, 122.2, 122.7, 126.4, 128.1, 128.6, 129.4, 134.3, 136.0, 157.2, 165.5.

MS: *m*/*z* = 548 [M + 1].

Anal. Calcd for $C_{25}H_{26}NO_5I$: C, 54.86; H, 4.79; N, 2.56. Found: C, 54.62; H, 4.86; N, 2.67.

Preparation of 22b and 23b

By following the same procedure described above, a diastereomeric mixture of β-lactams **22b** and **23b** was obtained in 76% yield. Both the diastereomers were separated by column chromatography.

Compound 22b

Thick oil; $[\alpha]_D^{25}$ +98.5 (*c* = 0.54, $CHCl_3$).

IR ($CHCl_3$): 1753 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 3.88 (t, *J* = 3.6 Hz, 1 H, H-6), 3.98 (dd, *J* = 5.5, 10.1 Hz, 1 H, H-12), 4.03 (dd, *J* = 4.6, 10.1 Hz, 1 H, H-4), 4.10 (dd, *J* = 5.5, 10.1 Hz, 1 H, H-12), 4.38 (t, *J* = 3.2 Hz, 1 H, H-7), 4.49 (dd, *J* = 3.6, 10.1 Hz, 1 H, H-5), 4.61 (d, *J* = 11.5 Hz, 1 H, $PhCH_aH_bO$), 4.72 (d, *J* = 4.6 Hz, 1 H, H-3), 4.83 (d, *J* = 11.5 Hz, 1 H, $PhCH_aH_bO$), 5.62 (d,

J = 3.2 Hz, 1 H, H-8), 6.04–6.10 (m, 1 H, H-13), 6.51 (d, *J* = 15.6 Hz, 1 H, H-14), 7.16–7.29 (m, 10 H, aromatic).

^{13}C NMR ($CDCl_3$, 125.76 MHz): δ = 19.6, 26.7, 43.3, 56.5, 73.3, 80.5, 81.6, 81.7, 103.5, 112.2, 122.9, 126.6, 127.8, 128.0, 128.5, 128.6, 134.1, 136.2, 137.2, 167.5.

MS: *m*/*z* = 562 [M + 1].

Anal. Calcd for $C_{26}H_{28}NO_5I$: C, 55.62; H, 5.03; N, 2.49. Found: C, 55.43; H, 5.25; N, 2.56.

Compound 23b

White solid; mp 142–143 °C; $[\alpha]_D^{25}$ +20.8 (*c* = 0.62, $CHCl_3$).

IR ($CHCl_3$): 1754 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 3.87–4.00 (m, 2 H, H-6, H-12), 4.05 (t, *J* = 4.3 Hz, 1 H, H-4), 4.26 (dd, *J* = 5.8, 15.8 Hz, 1 H, H-12), 4.42–4.53 (m, 2 H, H-5, H-7), 4.73–4.81 (m, 2 H, PhCH_aH$_b$O, H-3), 4.95 (d, *J* = 11.8 Hz, 1 H, PhCH$_a$$H_b$O), 5.80 (d, *J* = 3.5 Hz, 1 H, H-8), 6.03–6.18 (m, 1 H, H-13), 6.55 (d, *J* = 15.8 Hz, 1 H, H-14), 7.27–7.40 (m, 10 H, aromatic).

^{13}C NMR ($CDCl_3$, 125.76 MHz): δ = 21.9, 26.5, 26.6, 43.9, 56.6, 73.1, 79.4, 80.7, 81.5, 103.4, 111.9, 123.0, 126.4, 127.8, 128.1, 128.3, 128.7, 134.3, 136.1, 137.1, 167.3.

MS: *m*/*z* = 562 [M + 1].

Anal. Calcd for $C_{26}H_{28}NO_5I$: C. 55.62; H, 5.03; N, 2.49. Found: C, 55.48; H, 5.22; N, 2.68.

Radical Cyclization of *N*-Cinnamyl-β-lactams 22a; Typical Procedure

To a refluxing solution of iodo β-lactam **22a** (0.231 g, 0.42 mmol) in toluene (40 mL) was added a solution of Bu_3SnH (0.183 g, 0.63 mmol) and AIBN (13 mg) in toluene (20 mL) slowly through a syringe pump in 2 h. The reaction mixture was further refluxed for 4 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash chromatography (10% acetone–petroleum ether). A pale yellow solid was obtained, which was further purified by washing with anhyd EtOH to get *exo* cyclized tetracyclic β-lactam **24a** (64.4 mg, 36%).

Compound 24a

White solid; mp 160–161 °C; $[\alpha]_D^{25}$ +25.87 (*c* = 1.55, $CHCl_3$)

IR ($CHCl_3$): 1763 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.37 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 2.31–2.43 (m, 1 H, H-13), 2.54–2.87 (m, 4 H, H-6, H-12, H-14), 3.51 (dd, *J* = 5.5 Hz, 13.3 Hz, 1 H, H-12), 3.90 (t, *J* = 3.9 Hz, 1 H, H-4), 4.76–4.84 (m, 2 H, H-5, H-7), 5.31 (d, *J* = 3.9 Hz, 1 H, H-3), 5.91 (d, *J* = 3.9 Hz, 1 H, H-8), 7.01–7.35 (m, 10 H, aromatic).

^{13}C NMR ($CDCl_3$, 125.76 MHz): δ = 27.1, 27.3, 35.5, 37.3, 39.1, 47.5, 55.0, 72.5, 81.3, 82.00, 106.5, 115.7, 122.5, 126.7, 128.7, 129.0, 129.6, 138.4, 157.0, 165.7.

MS: *m*/*z* = 422 [M + 1].

Anal. Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.45; N, 3.32. Found: C, 71.38; H, 6.60; N, 3.18.

Radical Cyclization of 22b

The radical cyclization of β-lactam **22b** (0.233 g, 0.42 mmol) was carried out using the above procedure and the crude product was purified by chromatography to afford **24b** (50 mg, 28%).

Compound 24b

Pale yellow solid; mp 135–136 °C; $[\alpha]_D^{25}$ +34.14 (*c* = 1.60, $CHCl_3$).

IR ($CHCl_3$): 1760 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.40 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 2.27–2.40 (m, 1 H, H-13), 2.52–2.81 (m, 4 H, H-6, H-12, H-14), 3.45 (dd, *J* = 5.4, 13.3 Hz, 1 H, H-12), 3.65 (t, *J* = 4.3 Hz, 1 H, H-4), 4.71 (s, 2 H, PhCH_2O), 4.67–4.80 (m, 3 H, H-3, H-5, H-7), 5.92 (d, *J* = 4.3 Hz, 1 H, H-8), 7.14–7.38 (m, 10 H, aromatic).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 27.1, 27.5, 35.7, 37.3, 38.8, 47.5, 54.4, 72.6, 72.7, 81.8, 82.1, 105.5, 112.9, 126.6, 128.1, 128.4, 128.6, 129.0, 136.4, 138.5, 166.9.

MS: *m*/*z* = 437 [M$^+$].

Anal. Calcd for $C_{26}H_{24}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.89; H, 6.85; N, 3.40.

Radical Cyclization of 23a

According to the general procedure the radical cyclization of β-lactam **23a** (0.175 g, 0.32 mmol) and purification by column chromatography gave **25a** (86 mg, 64%). It was found to be a diastereomeric mixture (42:58) by ^{1}H NMR spectrum.

Compound 25a

White crystalline solid; mp 165–166 °C.

IR ($CHCl_3$): 1763 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.28 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 2.04 (dd, *J* = 2.8, 11.0 Hz, 1 H, H-13), 2.28–2.30 (m, 1 H, H-13), 2.32–2.64 (m, 4 H, H-6, H-14), 2.75–2.95 (m, 2 H, H-14), 3.06 (d, *J* = 8.0 Hz, 2 H, H-12), 3.66–3.86 (m, 3 H, H-12, H-4), 4.23 (t, *J* = 3.9 Hz, 1 H, H-4), 4.53 (d, *J* = 3.5 Hz, 1 H, H-5), 4.60 (d, *J* = 5.8 Hz, 1 H, H-5), 4.76 (d, *J* = 3.9 Hz, 1 H, H-3), 5.30 (d, *J* = 3.9 Hz, 1 H, H-3), 5.39 (d, *J* = 3.9 Hz, 1 H, H-7), 5.86 (d, *J* = 3.5 Hz, 1 H, H-7), 5.93 (d, *J* = 3.5 Hz, 1 H, H-8), 5.93 (d, *J* = 3.5 Hz, 1 H, H-8), 6.99–7.32 (m, aromatic).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 26.1, 26.4, 26.9, 32.9, 34.8, 36.5, 38.3, 40.2, 40.5, 47.0, 48.0, 52.9, 70.9, 73.9, 79.5, 80.8, 81.5, 82.1, 104.9, 105.5, 111.2, 115.5, 115.6, 122.0, 126.7, 128.6, 128.7 128.9, 129.3, 137.5, 138.6, 157.5, 157.6, 163.9, 168.2.

MS: *m*/*z* = 422 [M + 1].

Radical Cyclization of 23b

β-Lactam **23b** (0.12 g, 0.214 mmol) also gave an inseparable diastereomeric mixture (55:45) of cyclized product **25b** (52 mg, 56%).

Compound 25b

White crystalline solid; mp 190–191 ºC.

IR ($CHCl_3$): 1757 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.26 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.87–1.90 (dd, *J* = 2.8, 11.0 Hz, 1 H, H-13), 1.95–2.03 (m, 3 H, H-13, H-6), 2.26 (dd, *J* = 10.1, 13.8 Hz, 2 H, H-14), 2.40 (t, *J* = 6.0 Hz, 1 H, H-14), 2.47 (dd, *J* = 10.6, 13.8 Hz, 1 H, H-14), 2.64 (dd, *J* = 5.0 Hz, 13.7 Hz, 1 H, H-12), 2.83 (dd, *J* = 4.2 Hz, 12.4 Hz, 1 H, H-12), 2.89–2.95 (m, 2 H, H-12), 3.32 (t, *J* = 3.2 Hz, 1 H, H-4), 3.54 (dd, *J* = 5.0, 13.7 Hz, 1 H, H-12), 4.08 (br s, 2 H, PhCH_2O), 4.24 (d, *J* = 5.5 Hz, 1 H, H-4), 4.46 (d, *J* = 3.7 Hz, 1 H, H-5), 4.50 (d, *J* = 5.0 Hz, 1 H, H-3), 4.52 (d, *J* = 5.0 Hz, 1 H, H-3), 4.66 (d, *J* = 3.2 Hz, 2 H, H-5, H-7), 4.68 (d, *J* = 11.5 Hz, 1 H, PhCH_2O), 4.72 (t, *J* = 3.9 Hz, 1 H, H-7), 4.77 (d, *J* = 11.5 Hz, 1 H, PhCH_2O), 5.86 (d, *J* = 3.6 Hz, 2 H, H-8), 6.99–7.44 (m, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.9, 26.3, 26.5, 27.0, 32.9, 34.9, 36.3, 38.3, 39.9, 40.3, 47.1, 48.3, 53.0, 53.2, 71.4, 73.8, 73.9, 81.0, 81.6, 82.0, 83.6, 105.2, 105.5, 126.5, 126.7, 128.0, 128.4, 128.6, 128.7, 128.8, 128.9, 128.9, 136.8, 137.1, 137.6, 138.7, 165.3, 169.5.

MS: *m*/*z* = 436 [M + 1].

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