

Total Synthesis of (–)-Balanol, All Stereoisomers, Their *N*-Tosyl Analogues, and Fully Protected Ophiocordin: An Easy Route to Hexahydroazepine Cores from Garner Aldehydes

Ajay Kumar Srivastava and Gautam Panda*^[a]

Abstract: Total syntheses of (–)-balanol and all of its stereoisomers starting from easily available Garner aldehydes are described. Diastereoselective Grignard reactions on Garner aldehydes and ring-closing metatheses are the key steps for the construction of hexahydroazepine subunits. The benzo-

phenone subunits were constructed through coupling of suitably functionalized aromatic aldehyde and bromo

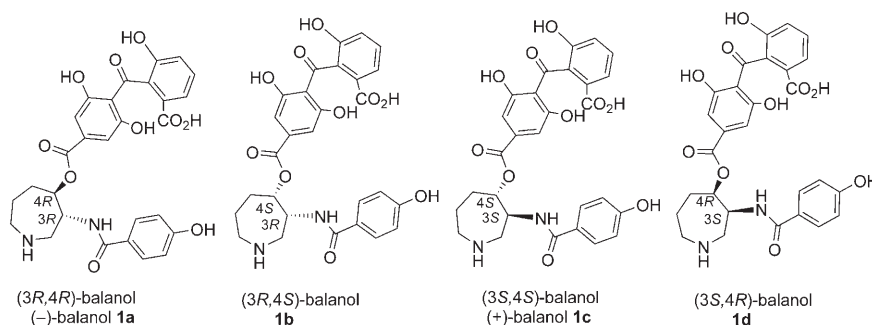
Keywords: balanol • metathesis • natural products • Protein kinase C inhibitors • total synthesis

components. The synthetic route constitutes a convenient and scalable reaction sequence to generate all of the stereoisomers of balanol. The methodology is explored further for the synthesis of *N*-tosyl analogues of balanol and of fully protected ophiocordin.

Introduction

Protein kinase C (PKC) is a Ca^{2+} - and phospholipid-dependent enzyme that phosphorylates serine and threonine residues in a wide variety of cellular proteins.^[1] PKC mediates the regulation of cardiac muscle function by a variety of neurotransmitters, hormones, and extracellular signaling molecules.^[2] As PKC plays an important role in signal transduction, cell proliferation, cell differentiation, and gene expression,^[3] the discovery of specific inhibitors of PKC would provide potential chemotherapeutic agents^[4–7] encompassing a wide spectrum of diseases: cancer, disorders of the central nervous and cardiovascular systems, diabetes, asthma, rheumatoid arthritis, and HIV infection. Some PKC inhibitors are currently in clinical trials for various types of cancer.^[8–10]

Balanol (**1a**), an unusual metabolite isolated by Kulanthaivel et al.^[11–13] from the fungus *Verticillium balanoides*

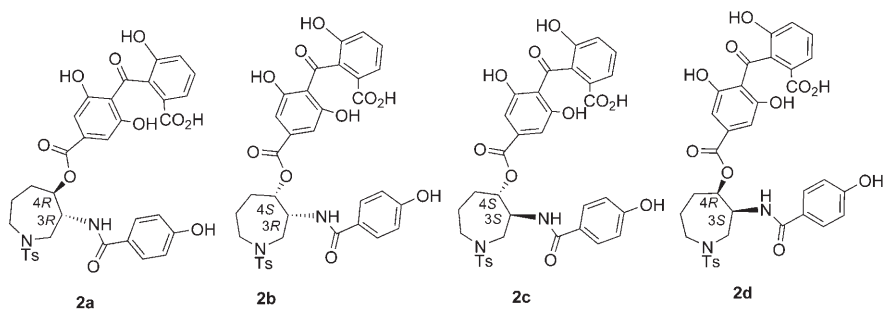


collected from *Pinus palustris* needle litter in 1993, and later by Ohshima et al. from *Fusarium merismoids* in 1994,^[12] inhibits almost all PKC isoforms in the 4–5 nanomolar range. Ophiocordin (**3**),^[14,15] a regioisomer of (–)-balanol (**1a**), was isolated from *Cordyceps ophioglossoides* in 1977 and serves as an antibiotic with antifungal activity. While several efforts to achieve selectivity among PKC isoforms have been undertaken,^[16–35] there is still a constant need for more selective and potent PKC inhibitors.

In our endeavors to develop some novel anticancer agents we have recently reported various benzannulated heterocycles synthesized from naturally abundant amino acids.^[36] In continuation of our program for nonbenzannulated heterocycles, we became interested in achieving the synthesis of two azepane-containing natural products (–)-balanol and ophiocordin as well as their analogues.

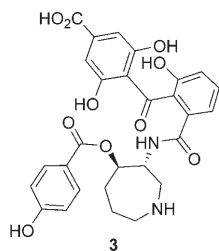
[a] A. K. Srivastava, Dr. G. Panda
Medicinal and Process Chemistry Division
Central Drug Research Institute, Lucknow, UP, 226001 (India)
Fax: (+91) 522-2623-938
E-mail: gautam_panda@cdri.res.in

Supporting information for this article is available on the WWW under <http://www.chemeurj.org> or from the author.



The isolation and structure elucidation of balanol (**1a**) was immediately followed by six total syntheses of the compound.^[37–46] Key to Nicolaou's group's asymmetric synthesis of balanol was chiral allylation of a substituted serinal with Brown's reagent ($(\text{Ipc})_2\text{B-allyl}$).^[39] An anionic homo-Fries rearrangement strategy to the benzophenone subunit and construction of the azepane unit from 3-hydroxylysine was the key step for **1a** from Lampe's and Hughes' group.^[38] Tanner's group used regio- and stereoselective opening of chiral epoxides and aziridines for the synthesis of **1a**.^[42] Ring expansion of piperidin-4-ones into azepane ring systems and further modification to give **1a** has also been reported.^[41] A radical cyclization approach to the hexahydroazepine ring and a biomimetic route to the benzophenone fragment of **1a** have been described by Naito's group.^[46] Apart from

these, syntheses of the 3-amino-hexahydroazepin-4-ol ring of balanol and suitable analogues have also been reported, because of its potent PKC inhibitory properties.^[47–63] Here we report for the first time total syntheses of all stereoisomers of balanol, along with their *N*-tosyl analogues **2a–d** and also of fully protected ophiocordin, that follow a different conceptual design rooted in a flexible and diversity-oriented approach based on ring-closing metathesis (RCM)^[48,51] and diastereoselective nucleophilic addition steps on Garner aldehydes.^[64]

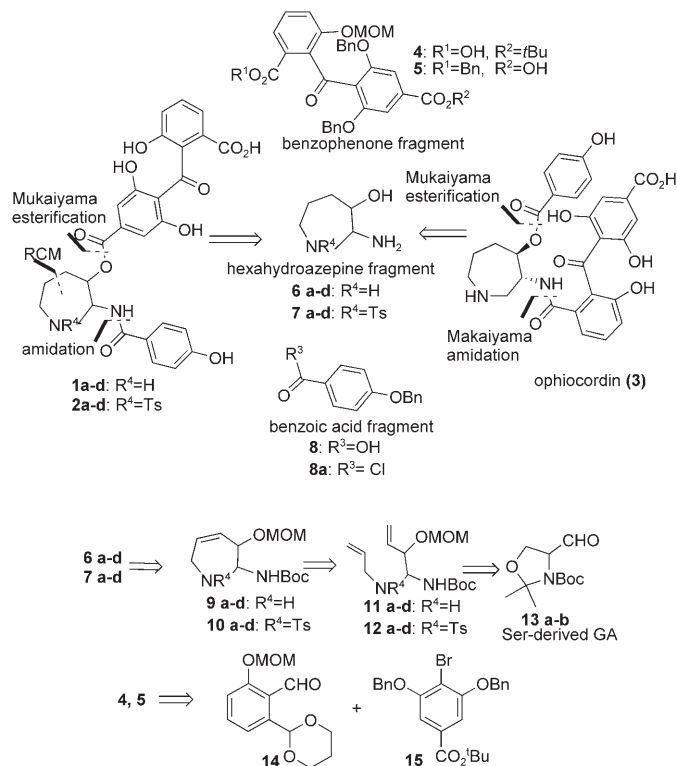


Results and Discussion

Retrosynthetic analysis and strategy: Retrosynthesis (Scheme 1) illustrates disconnection of the ester and amide linkages of **1a–d** and **2a–d** to afford the substituted hexahydroazepine units **6a–d** and **7a–d**, which can be easily accessed from their tetrahydroazepine precursors **9a–d** and **10a–d**, respectively (Scheme 1, bottom). These should in turn be obtainable through RCM^[65] of the pendant vinyl groups of **11a–d** and **12a–d**, respectively. We envisioned that the divinyl derivatives **11a–d** and **12a–d** should be easily accessible from Garner aldehydes **13a–b** by diastereoselective nucleophilic addition followed by expedient func-

tional group transformations. Similarly, the disconnection of the ester and amide linkages of ophiocordin **3** would also afford the hexahydroazepine subunit **6a** and acid **4**.

The highly congested tetra-*ortho*-substituted benzophenone fragments **4** and **5** should be preparable by coupling of



Scheme 1. Retrosynthetic analysis.

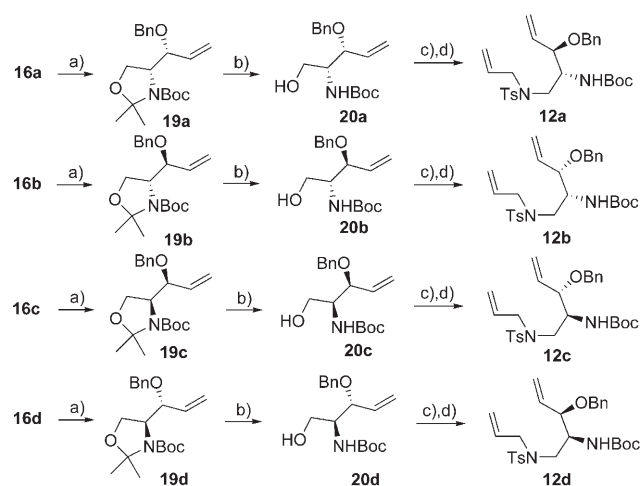
aldehyde **14** with bromo derivative **15** followed by MnO_2 oxidation and functional group interconversions, while fragments **8** and **8a** should be preparable in good yields from *p*-hydroxybenzoic acid. The hexahydroazepine and aromatic domains can be coupled by Mukaiyama esterification and amidation procedures to generate fully protected precursors for target compounds. Finally total synthesis of **1a–d**, **2a–d**, and **3** should be accomplished through global deprotection of their fully protected precursors.

Synthesis of the divinyl derivatives 11a–d and 12a–d: Our synthesis started with the preparation of diastereomerically pure alcohol precursors **16a–d** (Scheme 2). Addition of vinylmagnesium bromide to freshly prepared^[64] (*R*)-Garner aldehyde (**13a**) at -78°C delivered a mixture of *syn*-**16a** and *anti*-**16b** allylic alcohols in 1:6 diastereomeric ratio.^[66] The two diastereomers were separated by flash chromatography.

Similarly, addition of vinylmagnesium bromide to (*S*)-Garner aldehyde (**13b**) furnished *syn*-**16c** and *anti*-**16d**. To enhance the yields of *syn* alcohols the major *anti* alcohols **16b** and **16d** were converted into their corresponding *syn* alcohols **16a** and **16c**, respectively, by a Mitsunobu approach.^[67] Other methods to acquire *syn* alcohols as the major products by addition of vinylolithium^[68] (generated in situ from tetravinyltin and methylolithium) and zinc bromide on Garner aldehyde were not suitable for scaling-up purposes, due to the lower stabilities of the reagents. Diastereomerically pure allylic alcohols **16a–d** were converted into their corresponding MOM ethers **17a–d** by treatment with MOM chloride in quantitative yields. Selective removal of the isopropylidene groups of **17a–d** with catalytic amounts of PTSA in methanol secured **18a–d**, respectively. Further tosylation of the resulting alcohols, followed by replacement of tosyloxy groups with allylamine at 65 °C in a sealed tube, furnished amines, which were protected as benzyl carbamates to afford the divinyl derivatives **11a–d** (Scheme 2).

Similarly, alcohols **16a–d** were converted into their corresponding benzyl ether derivatives **19a–d** by treatment with NaH and benzyl bromide in THF at 0 °C (Scheme 3). Opening of the isopropylidene rings of **19a–d** furnished alcohols **20a–d**, respectively, which were further tosylated. The tosyloxy derivatives of **20a–d** were treated with allylamine in sealed tube to afford amine derivatives, which were further converted into their corresponding divinyl sulfonamides **12a–d** through tosyl protection of their amino functionalities.

Synthesis of amido alcohols 22a–d and 24a–d: Ring-closing metatheses of the diastereomerically pure divinyl derivatives **11a–d** and **12a–d** in the presence of Grubbs' first-generation



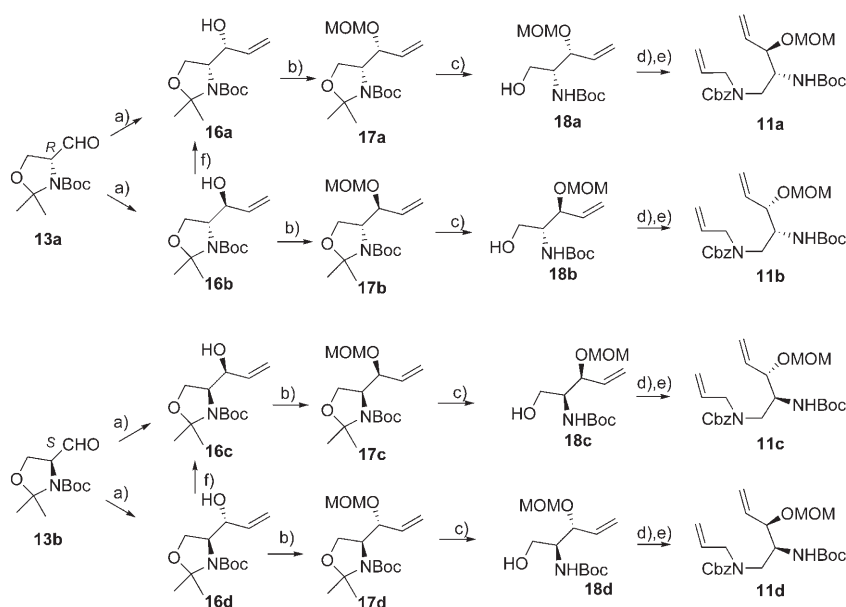
Scheme 3. Synthesis of divinyl derivatives **12a–d**. a) BnBr, NaH, THF, 0 °C → RT; b) PTSA, MeOH, 0 °C → RT; c) i) TsCl, Et₃N, CH₂Cl₂, 0 °C, ii) allylamine, MeOH, 65 °C; d) TsCl, Et₃N, CH₂Cl₂, 0 °C.

catalyst delivered the tetrahydroazepines **9a–d** and **10a–d**, respectively, in quantitative yields (Scheme 4). Reduction of the double bonds in **9a–d** by hydrogenation at atmospheric pressure in THF furnished the hexahydroazepine cores **21a–d**. Simultaneous removal of MOM and Boc with 50 % TFA in CH₂Cl₂ afforded the amino alcohols, which were further coupled with *p*-benzyloxybenzoyl chloride in Et₃N/CH₂Cl₂ to provide their corresponding amido alcohols **22a–d**.

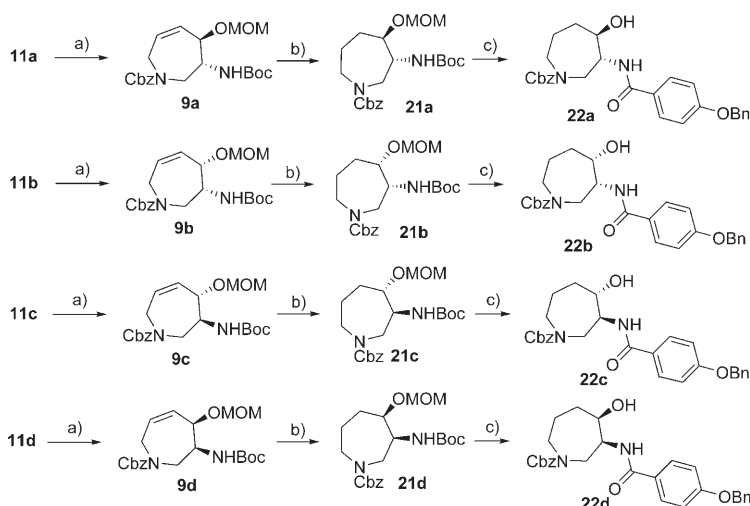
Similarly, to achieve the synthesis of amido alcohols **24a–d**, tetrahydroazepines **10a–d** were converted into **23a–d** through simultaneous Boc removal and double bond reduction followed by debenzoylation with 10 % Pd/C in methanol and HCl under pressure (Scheme 5). Amines **23a–d** were further coupled with *p*-benzyloxybenzoyl chloride after regeneration of amine with triethylamine in CH₂Cl₂ at 0 °C to provide amido alcohols **24a–d** in good yields.

Synthesis of the benzophenone fragments 4 and 5:

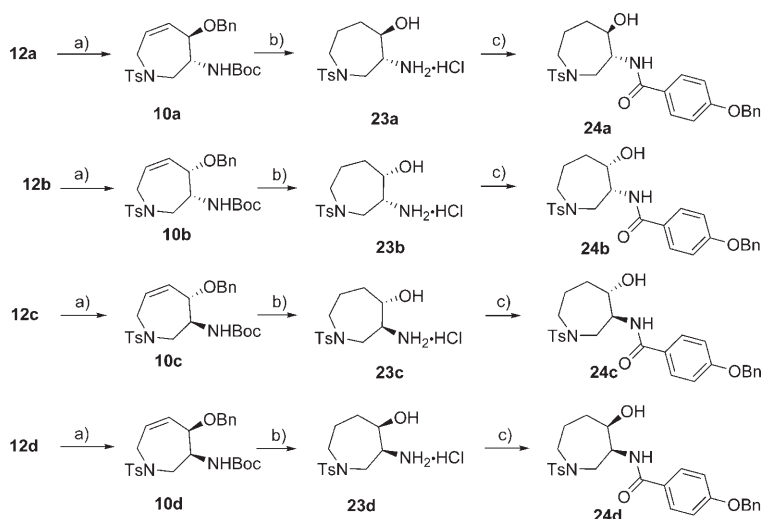
The benzophenone fragments of balanol and ophiocordin were synthesized by a modification of the procedure of Hollinshead et al.^[69] In the reported procedure, *m*-hydroxybenzaldehyde was converted into aldehyde **29** (Scheme 6) in five steps with the use of dibromotetrafluoroethane as a brominating agent in one of the intermediate steps. To reduce the number of steps and to avoid the use of dibromotetrafluoroethane, MOM-protected alde-



Scheme 2. Synthesis of divinyl derivatives **11a–d**. a) Vinylmagnesium bromide, THF, −78 °C; b) MOMCl, DIPEA, CH₂Cl₂, 0 °C → RT; c) PTSA, MeOH, 0 °C → RT; d) i) TsCl, Et₃N, CH₂Cl₂, 0 °C, ii) allylamine, MeOH, 65 °C; e) CbzCl, Et₃N, THF, 0 °C; f) *p*-nitrobenzoic acid, DEAD, PPh₃, THF; ii) K₂CO₃, MeOH, RT.



Scheme 4. Synthesis of amido alcohols **22a–d**. a) Grubbs' catalyst (1st gen), CH_2Cl_2 , 45°C ; b) $\text{H}_2/\text{Pd-C}$, THF, RT; c) i) TFA, CH_2Cl_2 , RT, 4 h s, ii) *p*-benzyloxybenzoyl chloride, CH_2Cl_2 , Et_3N .



Scheme 5. Synthesis of amido alcohols **24a–d**. a) Grubbs catalyst (1st gen.), CH_2Cl_2 , 45°C ; b) $\text{H}_2/10\% \text{ Pd-C}$, MeOH/HCl ; c) *p*-benzyloxybenzoyl chloride, CH_2Cl_2 , Et_3N , 0°C .

hyde **14**, which can easily be synthesized in three steps from *m*-hydroxybenzaldehyde,^[69] was used. Coupling of **14** with the anion generated from bromo derivative **15** provided alcohol **25**, which was oxidized to the ketone **26** with MnO_2 . The ketal of **26** was unmasked with catalytic amounts of PTSA in acetone/water 9:1 to provide aldehyde **27**, which was oxidized to the acid **4** required for the synthesis of ophiocordin **3**. Acid **4** was again esterified with benzyl bromide and K_2CO_3 to furnish **28**. Selective hydrolysis of the *tert*-butyl ester component by thermolysis^[38] in quinoline at 195°C delivered acid **5**, required for the synthesis of **1a–d** and **2a–d**.

Coupling of fragments and generation of balanol and analogues: The acid **5** was further coupled with amido alcohols **22a–d** and **24a–d** by Mukaiyama esterification^[70] to provide

the fully protected balanol derivatives **30a–d** and **31a–d**, respectively.

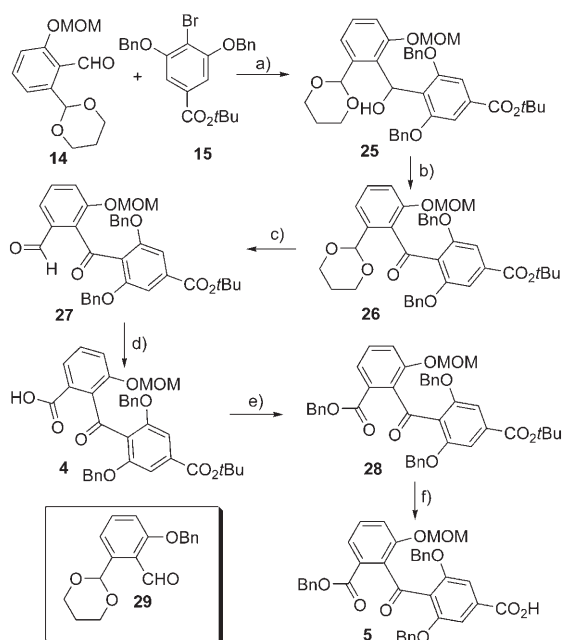
MOM removal in cat HCl/MeOH (Scheme 7), followed by debenzoylation and purification of **30a–d** by Nicolaou's procedure allowed the total syntheses of (–)-balanol (**1a**) and its other stereoisomers **1b–d**. The spectral data and optical purity^[46] of (–)-balanol **1a** were in accordance with the reported properties. Fully protected **31a** was converted into *N*-tosyl balanol **2a** (Scheme 8) by simultaneous removal of MOM and benzyl groups under conditions similar to those described above. Similarly, the syntheses of *N*-tosylbalanols **2b–d** could also be achieved from the advanced precursors **31b–d**.

Synthesis of fully protected ophiocordin (3): To achieve the synthesis of ophiocordin (**3**), hexahydroazepine **21a** was converted into **32** by selective removal of MOM with trimethylsilyl bromide, and this was further esterified with *p*-benzyloxybenzoic acid to deliver **33** by Mukaiyama esterifications (Scheme 9).^[70] Boc removal in $\text{TFA}/\text{CH}_2\text{Cl}_2$ furnished amino ester **34**. Several initial attempts at amide coupling (DCC, DIC, HBTU, TBTU) of amine **34** with acid **4** to achieve **35** were unsuccessful, which might be due to steric hindrance.

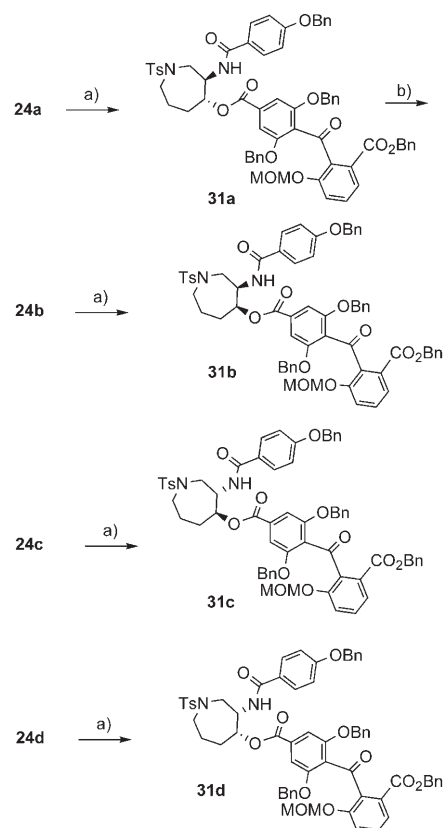
Finally, coupled product **35** was isolated by Mukaiyama amidation,^[71] albeit in poor yield and with recovery of unreacted amine **34**. Ophiocordin **3** may be achieved through final deprotection of fully protected ophiocordin **35**.

Conclusion

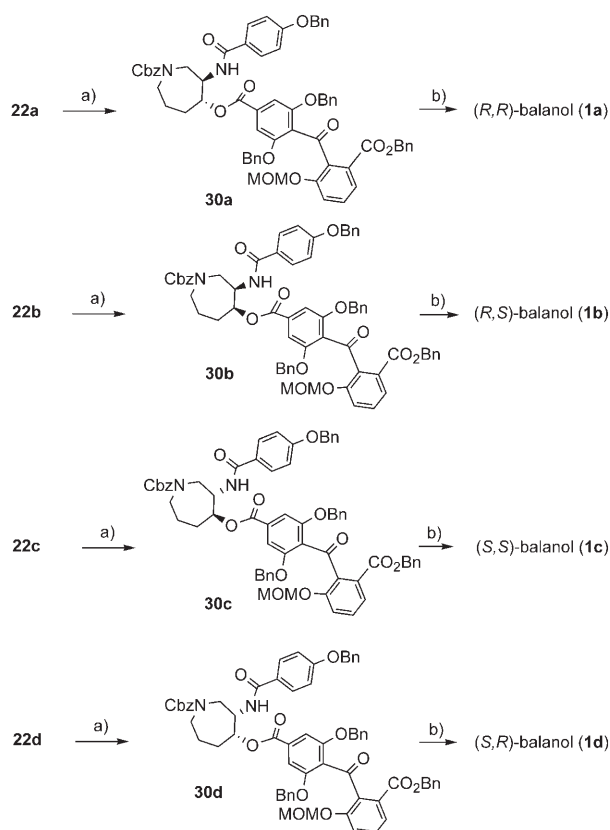
In summary, total syntheses of naturally occurring (–)-(*R,R*)-balanol and its stereoisomers from the easily available (*R*)- and (*S*)-Garner aldehydes have been accomplished for the first time, with overall yields of 9–13% in a stereoselective and regioselective diversity-oriented approach. The attractiveness of the approach lies in its useful nucleophilic



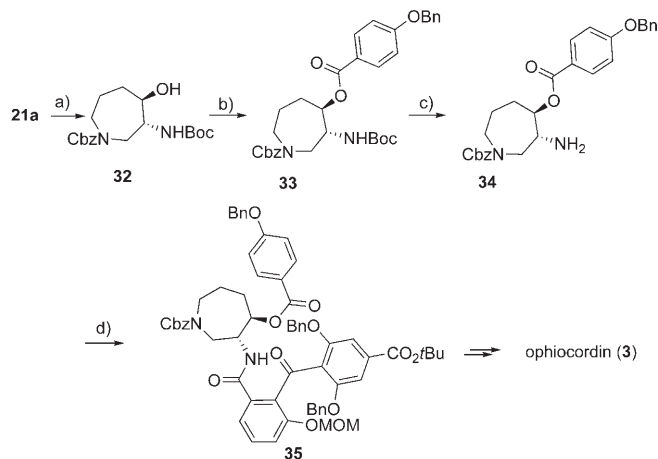
Scheme 6. Synthesis of acids **4** and **5**. a) *n*BuLi, THF, -78°C ; b) MnO_2 , CH_2Cl_2 ; c) PTSA, acetone/water 9:1, reflux; d) NaH_2PO_4 , H_2O_2 , NaClO_2 , acetonitrile; e) benzyl bromide, K_2CO_3 , acetone; f) quinoline, 195°C .



Scheme 8. Synthesis of *N*-tosyl-balanol. a) Acid **5**, 2-chloro-1-methylpyridinium iodide, DMAP, Et_3N , CH_2Cl_2 , RT; b) i) HCl/MeOH , RT; ii) H_2 , Pd/C , THF/water/acetic acid 4:1:1.



Scheme 7. Synthesis of **1a-d**. a) Acid **5**, 2-chloro-1-methylpyridinium iodide, DMAP, Et_3N , CH_2Cl_2 , RT; b) i) HCl/MeOH , RT; ii) H_2 , Pd/C , THF/water/acetic acid 4:1:1.



Scheme 9. Synthesis of fully protected ophiocordin derivative **35**. a) Trimethylsilyl bromide, CH_2Cl_2 , $0^{\circ}\text{C} \rightarrow \text{RT}$; b) *p*-benzyloxybenzoic acid, 2-chloro-1-methylpyridinium iodide, DMAP, Et_3N , CH_2Cl_2 , RT; c) TFA/ CH_2Cl_2 ; d) acid **4**, 2-chloro-1-methylpyridinium iodide, DMAP, Et_3N , CH_2Cl_2 , RT.

addition with high diastereoselectivity, the displacement reaction for access to the divinyl derivatives, and the ruthenium-catalyzed olefin metathesis for the construction of the azepine rings. This easily executed sequence gave access to the key hexahydroazepine building block units **21a-d** and

22a–d, which are well suited for the preparation of several balanol analogues for accessing more selective PKC inhibitors. The synthetic route can also be further exploited for the synthesis of other isosteres of balanols.

Experimental Section

General remarks: Melting points were determined on a COMPLAB melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RXI FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DPX 200 (operating at 200 MHz for ^1H and 50 MHz for ^{13}C) or DPX 300 (operating at 300 MHz for ^1H and 75 MHz for ^{13}C) spectrometers in CDCl_3 and CD_3OD as solvents. Tetramethylsilane (0.00 ppm) served as an internal standard in ^1H NMR, and CDCl_3 (77.0 ppm) in ^{13}C NMR. All spectra were recorded at 25 °C. Coupling constants (J values) are given in Hz. Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded by electron spray ionization (ESI) or fast atom bombardment spectrometry (FAB-MS) on a JEOL SX 102 spectrometer with argon/xenon as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Elemental analyses were done on Varian EL-III CHN analyzer (Germany). Reactions were monitored on silica gel TLC plates (coated with TLC-grade silica gel, obtained from Merck). Detecting agents used (for TLC) were iodine vapors and/or spraying with an aqueous solution of vanillin in 10 % sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (60–120 mesh) procured from Qualigens (India) with freshly distilled solvents. Anhydrous tetrahydrofuran used in Mitsunobu reactions was obtained from Spectrochem and heated at reflux over sodium/benzophenone prior to use.

(1S,4R)-4-(1-Hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (16b): Freshly prepared vinylmagnesium bromide (1 M solution in THF, 175 mL) was added dropwise at –78 °C to a cooled solution of (*R*)-Garner aldehyde (**13a**, 10 g, 38.9 mmol) in anhydrous THF (325 mL). The reaction mixture was stirred for 2 h at the same temperature and was then allowed to warm to room temperature before careful addition of saturated ammonium chloride solution in water. The solution was extracted with ether (500 mL $\times$ 2). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with ethyl acetate in hexane (15 %) as eluent to furnish a mixture of **16a** and **16b** 1:6 as a colorless oil (10.6 g, 94.6 %). $[\alpha]_{\text{D}}^{25} = +27.6$ ($c = 1.47$, chloroform). Pure **16b** was further obtained by flash chromatography on silica gel (8.5 g, 75.8 %). $[\alpha]_{\text{D}}^{25} = +54.6$ ($c = 1.47$, chloroform); $R_f = 0.4$ (ethyl acetate in hexane, 20 %); ^1H NMR (300 MHz, CDCl_3 , 25 °C, TMS): $\delta = 5.87$ – 5.82 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.38 (d, $J = 18$ Hz, 1H; $-\text{CH}=\text{CH}_2$), 5.23 (d, $J = 12$ Hz, 1H; $-\text{CH}=\text{CH}_2$), 4.29–4.18 (brm, 1H; CH-OH), 4.07–4.02 (m, 1H; 4-*H*), 3.99–3.90 (m, 2H; 5-*H*), 1.57 (s, 3H; CH_3), 1.51 (s, 9H; $\text{OC}(\text{CH}_3)_3$), 1.45 ppm (s, 3H; CH_3); ^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{CCl}_4$, 25 °C, TMS): $\delta = 154.9$, 137.9, 117.8, 94.7, 81.1, 75.6, 65.0, 62.3, 28.7, 27.4, 24.7 ppm; IR (neat): $\tilde{\nu} = 3449$, 2982, 2363, 1696 ($-\text{NH}-\text{C}=\text{O}$), 1389, 1287 cm^{-1} ; MS (FAB): m/z (%): 258 (60) $[\text{M}+\text{H}]^+$, 202 (100) $[\text{M}-t\text{Bu}]^+$, 184 (50) $[\text{M}-t\text{Bu}-\text{H}_2\text{O}]^+$; elemental analysis (%) calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_4$: C 60.68, H 9.01, N 5.44; found: C 60.57, H 8.89, N 5.34.

(1R,4R)-4-(1-Hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (16a): Diethyl azodicarboxylate (5.4 g, 0.031 mol) was added dropwise at 0 °C to a stirred solution of alcohol **16b** (4.0 g, 0.015 mol), triphenylphosphine (8.34 g, 0.031 mol), and 4-nitrobenzoic acid (5.2 g, 0.031 mol) in anhydrous THF (100 mL). The reaction mixture was stirred at 0 °C for 15 min and then for 1 h at room temperature. The reaction mixture was concentrated and chromatographed over silica gel to afford the nitrobenzoate as a syrup. Solid K_2CO_3 (3.1 g, 0.022 mol) was added to a solution of the nitrobenzoate (4.5 g, 0.011 mol) in methanol (50 mL) and the reaction mixture was stirred for 30 min at room temperature. After completion of the reaction, solid was filtered off, and the filtrate was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with water followed by brine, dried over anhydrous Na_2SO_4 ,

and concentrated in vacuo. The residue was chromatographed over silica gel with ethyl acetate in hexane (15 %) as eluent to furnish **16a** (2.70 g, 92 %) as a white solid. $R_f = 0.4$ (ethyl acetate in hexane, 20 %); $[\alpha]_{\text{D}}^{25} = +47.9$ ($c = 1.25$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C, TMS): $\delta = 5.89$ – 5.82 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.85 (d, $J = 18$ Hz, 1H; $-\text{CH}=\text{CH}_2$), 5.30 (d, $J = 12$ Hz, 1H; $-\text{CH}=\text{CH}_2$), 4.28 (pseudo t, 1H; CH-OH), 4.19 (brm, 1H; 4-*H*), 4.07–3.90 (m, 2H; 5-*H*), 1.60 (s, 3H; CH_3), 1.57 (s, 9H; $\text{OC}(\text{CH}_3)_3$), 1.46 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C, TMS): $\delta = 154.9$ (C=O), 137.9 ($-\text{CH}=\text{CH}_2$), 117.9 ($\text{CH}=\text{CH}_2$), 96.5 (C-2), 81.2 ($-\text{CH-OH}$), 74.3 ($\text{C}(\text{CH}_3)_3$), 65.0 (C-5), 62.3 (C-4), 28.8 ($\text{C}(\text{CH}_3)_3$), 26.7 ppm (CH_3); IR (neat): $\tilde{\nu} = 3450$, 2981, 2363, 1697 ($-\text{NH}-\text{C}=\text{O}$), 1382, 1260 cm^{-1} ; MS (FAB): m/z (%): 258 (80) $[\text{M}+\text{H}]^+$, 202 (100) $[\text{M}-t\text{Bu}]^+$, 184 (65) $[\text{M}-t\text{Bu}-\text{H}_2\text{O}]^+$; elemental analysis (%) calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_4$: C 60.68, H 9.01, N 5.44; found: C 60.64, H 8.81, N 5.29.

(1R,4S)-4-(1-Hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (16d): This compound was prepared as described for **16b** from (*S*)-Garner aldehyde (**13b**). Yield = 74.3 %; $R_f = 0.4$ (ethyl acetate in hexane, 20 %); $[\alpha]_{\text{D}}^{25} = -32.3$ ($c = 2.1$ in methanol); ^1H NMR (200 MHz, CDCl_3 , 25 °C, TMS): $\delta = 5.91$ – 5.68 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.41–5.13 (m, 2H; $-\text{CH}=\text{CH}_2$), 4.39 (brs, 1H; CH-OH), 4.22 (brs, 1H; 4-*H*), 4.16–3.81 (m, 2H; 5-*H*), 1.55 (s, 3H; CH_3), 1.50 (s, 9H; $\text{OC}(\text{CH}_3)_3$), 1.48 ppm (s, 3H; CH_3); ^{13}C NMR (50 MHz, CDCl_3 , 25 °C, TMS): $\delta = 155.4$, 137.1, 116.6, 94.9, 81.5, 74.6, 65.0, 62.4, 28.7, 26.6, 24.8 ppm; IR (neat): $\tilde{\nu} = 3456$, 2981, 2345, 1689 ($-\text{NH}-\text{C}=\text{O}$), 1376, 1280 cm^{-1} ; MS (ESI): m/z (%): 257 (100) $[\text{M}]^+$, 202 (50) $[\text{M}-t\text{Bu}]^+$, 184 (25) $[\text{M}-t\text{Bu}-\text{H}_2\text{O}]^+$; elemental analysis (%) calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_4$: C 60.68, H 9.01, N 5.44; found: C 60.49, H 8.82, N 5.45.

(1S,4S)-4-(1-Hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (16c): This compound was prepared as described for **16a** from **16d**. Yield = 63 %; $R_f = 0.4$ (ethyl acetate in hexane, 20 %); $[\alpha]_{\text{D}}^{25} = -54.3$ ($c = 2.1$ in methanol); ^1H NMR (300 MHz, CDCl_3 , 25 °C, TMS): $\delta = 5.88$ – 5.81 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.41–5.31 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.22 (d, $J = 10.2$ Hz, 1H; $-\text{CH}=\text{CH}_2$), 4.29 (brs, 1H; CH-OH), 4.18 (s, 1H; 4-*H*), 4.07–3.56 (m, 2H; 5-*H*), 1.56 (s, 3H; CH_3), 1.51 (s, 9H; $\text{OC}(\text{CH}_3)_3$), 1.46 ppm (s, 3H; CH_3); ^{13}C NMR (50 MHz, CDCl_3 , 25 °C, TMS): $\delta = 155.3$, 137.9, 118.1, 94.8, 81.4, 76.0, 65.6, 62.1, 59.7, 28.7, 27.4, 26.7 ppm; IR (neat): $\tilde{\nu} = 3467$, 2981, 2363, 1691 ($-\text{NH}-\text{C}=\text{O}$), 1379, 1280 cm^{-1} ; MS (FAB): m/z (%): 280 (100) $[\text{M}+\text{Na}]^+$, 202 (35) $[\text{M}-t\text{Bu}]^+$, 184 (50) $[\text{M}-t\text{Bu}-\text{H}_2\text{O}]^+$; elemental analysis (%) calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_4$: C 60.68, H 9.01, N 5.44; found: C 60.51, H 8.89, N 5.26.

General Procedure for MOM protection: DIPEA (1.35 mL, 7.78 mmol) was added at 0 °C to a cooled solution of the alcohol (1.0 g, 3.89 mmol) in dry CH_2Cl_2 (15 mL), followed by MOM chloride (0.44 mL, 5.84 mmol). The reaction mixture was stirred at the same temperature for 4 h. After completion of the reaction, solvent was evaporated, and the residue was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The residue was chromatographed over silica gel with ethyl acetate in hexane (5 %) as eluent to furnish the protected alcohol.

(1R,4R)-4-(1-Methoxymethoxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (17a): Yield = 84 %; $R_f = 0.62$ (ethyl acetate in hexane, 10 %); $[\alpha]_{\text{D}}^{25} = +72.4$ ($c = 0.915$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C, TMS): $\delta = 5.77$ – 5.71 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.31–5.22 (m, 2H; $-\text{CH}=\text{CH}_2$), 4.71 (d, $J = 6.6$ Hz, 1H; $-\text{CH}_2-\text{O}-\text{CH}_3$), 4.56 (d, $J = 6.6$ Hz, 1H; $-\text{CH}_2-\text{O}-\text{CH}_3$), 4.39–4.28 (brm, 1H; 4-*H*), 4.08 (dd, $J = 8.4, 1.2$ Hz, 1H; $-\text{CH-OMOM}$), 4.01–3.87 (m, 2H; 5-*H*), 3.35 (s, 3H; OCH_3), 1.51 (s, 3H; CH_3), 1.49 (s, 3H; CH_3), 1.48 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CDCl_3 , 25 °C, TMS): $\delta = 151.2$ (C=O), 134.3 ($-\text{CH}=\text{CH}_2$), 117.9 ($-\text{CH}=\text{CH}_2$), 93 ($\text{O}-\text{CH}_2-\text{O}$), 78.7 (CH-OMOM), 62.7 ($\text{C}(\text{CH}_3)_3$), 58.9 (C-4), 57.9 ($\text{O}-\text{CH}_3$), 54.6 (C-5), 28.4 ($\text{C}(\text{CH}_3)_3$), 27.1 (CH_3), 25.6 ppm (CH_3); IR (neat): $\tilde{\nu} = 3861$, 3821, 2932, 2362, 1700, 1386, 1169, 1098, 1033 cm^{-1} ; MS (ESI): m/z (%): 301.9 (89) $[\text{M}]^+$, 245.9 (100) $[\text{M}-t\text{Bu}]^+$, 202.1 (12) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{15}\text{H}_{27}\text{NO}_5$: C 59.78, H 9.03, N 4.65; found: C 59.68, H 8.93, N 4.56.

(1S,4R)-4-(1-Methoxymethoxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (17b): Yield = 81 %; $R_f = 0.64$ (ethyl acetate in hexane, 10 %); $[\alpha]_{\text{D}}^{25} = +61.4$ ($c = 0.376$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C, TMS): $\delta = 5.76$ – 5.68 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.35–5.22 (m, 2H;

-CH=CH₂), 4.63 (d, *J* = 6.6 Hz, 1H; -CH₂-O-CH₃), 4.56 (d, *J* = 6.6 Hz, 1H; -CH₂-O-CH₃), 4.41–4.26 (brm, 1H; -CH-OMOM), 4.09–3.76 (m, 3H; 4-*H* and 5-*H*), 3.37 (s, 3H; OCH₃), 1.61 (s, 3H; CH₃), 1.51 (s, 3H; CH₃), 1.45 ppm (s, 9H; OC(CH₃)₃); ¹³C NMR (50 MHz, CDCl₃, 25 °C, TMS): δ = 152.7, 135.9, 120.5, 94.1, 85.5, 80.2, 70.2, 64.7, 60.2, 55.9, 28.6, 27.7, 26.6 ppm; IR (neat): $\tilde{\nu}$ = 3860, 3821, 2912, 2361, 1710, 1386, 1169, 1068, 1033 cm⁻¹; MS (ESI): *m/z* (%): 301.9 (89) [M]⁺, 245.9 (100) [M-*t*Bu]⁺, 202.1 (12) [M-*t*Boc]⁺; elemental analysis (%) calcd for C₁₅H₂₇NO₅: C 59.78, H 9.03, N 4.65; found: C 59.71, H 8.90, N 4.51.

(1S,4S)-4-(1-Methoxymethoxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (17c): Yield = 82%; *R*_f = 0.6 (ethyl acetate in hexane, 10%) [α]_D²⁵ = -77.4 (*c* = 0.715 in CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 5.74–5.67 (m, 1H; -CH=CH₂), 5.31–5.22 (m, 2H; -CH=CH₂), 4.71 (d, *J* = 6.6 Hz, 1H; -CH₂-O-CH₃), 4.56 (d, *J* = 6.6 Hz, 1H; -CH₂-O-CH₃), 4.39–4.28 (brm, 1H; 4-*H*), 4.08 (dd, *J* = 8.4, 1.2 Hz, 1H; -CH-OMOM), 4.01–3.87 (m, 2H; 5-*H*), 3.35 (s, 3H; O-CH₃), 1.51 (s, 3H; CH₃), 1.49 (s, 3H; CH₃), 1.46 ppm (s, 9H; OC(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = 151.1, 134.3, 127.4, 117.8, 93.0, 88.1, 78.6, 72.1, 63.1, 58.6, 54.4, 27.0, 27.5 ppm; IR (neat): $\tilde{\nu}$ = 3851, 3821, 2942, 2262, 1732, 1380, 1098, 1033 cm⁻¹; MS (ESI): *m/z* (%): 301.9 (89) [M]⁺, 245.9 (100) [M-*t*Bu]⁺, 202.1 (12) [M-*t*Boc]⁺; elemental analysis (%) calcd for C₁₅H₂₇NO₅: C 59.78, H 9.03, N 4.65; found: C 59.69, H 8.89, N 4.60.

(1R,4S)-4-(1-Methoxymethoxy-allyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (17d): Yield = 83.4%; *R*_f = 0.6 (ethyl acetate in hexane, 10%); [α]_D²⁵ = -66.4 (*c* = 0.776 in CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 5.75–5.70 (m, 1H), 5.30–5.24 (m, 2H), 4.68 (d, *J* = 6.6 Hz, 1H), 4.53 (d, *J* = 6.6 Hz, 1H), 4.38–4.35 (brm, 1H), 4.13–3.88 (m, 3H), 3.34 (s, 3H; OCH₃), 1.55 (s, 3H; -CH₃), 1.48 (s, 3H; -CH₃), 1.44 ppm (s, 9H; OC(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = 151.1, 134.3, 117.9, 92.6, 78.8, 64.9, 62.7, 58.8, 54.4, 50.9, 27.0, 25.6 ppm; IR (neat): $\tilde{\nu}$ = 3900, 3811, 2932, 2342, 1700, 1356, 1160, 1098, 1033 cm⁻¹; MS (ESI): *m/z* (%): 301.6 (79) [M]⁺, 245.6 (100) [M-*t*Bu]⁺, 202.1 (32) [M-*t*Boc]⁺; elemental analysis (%) calcd for C₁₅H₂₇NO₅: C 59.78, H 9.03, N 4.65; found: C 59.73, H 8.93, N 4.59.

General Procedure for benzyl protection: Washed NaH (1.86 g, 7.78 mmol) was added at 0 °C to a cooled solution of the alcohol (1.0 g, 3.89 mmol) in dry THF (15 mL), followed by benzyl bromide (800 mg, 4.67 mmol). The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, methanol was added dropwise to neutralize excess NaH, and solvent was evaporated. The residue was diluted with ethyl acetate, washed with water followed by brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was chromatographed over silica gel to furnish the protected product.

(4R,6R)-4-(1-Benzyloxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (19a): Yield = 78%; *R*_f = 0.5 (ethyl acetate in hexane, 6%); [α]_D²⁵ = +59.4 (*c* = 0.711 in CHCl₃); ¹H NMR (200 MHz, CDCl₃, 25 °C, TMS): δ = 7.32 (s, 5H; ArH), 5.96–5.61 (m, 1H; -CH=CH₂), 5.32–5.24 (m, 2H; -CH=CH₂), 4.62 (d, *J* = 11.6 Hz, 1H; -CH₂-Ph), 4.36 (d, *J* = 11.6 Hz, 1H; -CH₂-Ph), 4.11–4.03 (m, 2H; 4-*H*, -CHOBn), 3.90 (brs, 2H; 5-*H*), 1.59 (s, 3H; -CH₃), 1.51 (s, 3H; -CH₃), 1.46 ppm (s, 9H; -OC(CH₃)₃); ¹³C NMR (50 MHz, CDCl₃): δ = 152.8 (C=O), 138.3 (-CH=CH₂), 136.4, 128.1, 128.3, 119.7, 118.1 (-CH=CH₂), 94.3 (C-2), 81.4, 80.4, 71.2 (C(CH₃)₃), 65.6, 64.8, 60.2, 60.8 (C-4), 28.1, 27.4, 25.9, 23.1 ppm; IR (neat): $\tilde{\nu}$ = 3984, 3876, 3712, 3537, 2979, 1838, 1699, 1384, 1170, 1084 cm⁻¹; MS (FAB): *m/z* (%): 348 (29) [M+H]⁺, 292 (45) [M-*t*Bu]⁺, 248 (51) [M-*t*Boc]⁺, 234 (85) [M-Bn+Na]⁺, 91 (100) [PhCH₂]⁺; elemental analysis (%) calcd for C₂₀H₂₉NO₄: C 69.14, H 8.41, N 4.03; found: C 68.97, H 8.34, N 3.99.

(4R,6S)-4-(1-Benzyloxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (19b): Yield = 76.8%; *R*_f = 0.51 (ethyl acetate in hexane, 6%); [α]_D²⁵ = +46.4 (*c* = 0.738 in CHCl₃); ¹H NMR (200 MHz, CDCl₃, 25 °C, TMS): δ = 7.27 (s, 5H; ArH), 5.91–5.67 (m, 1H; -CH=CH₂), 5.30–5.21 (m, 2H; -CH=CH₂), 4.59 (d, *J* = 11.6 Hz, 1H; -CH₂-Ph), 4.33 (d, *J* = 11.6 Hz, 1H; -CH₂-Ph), 4.11–3.89 (m, 4H; 4-*H*, 5-*H*, -CHOBn), 1.51 (s, 3H; -(CH₃)₂), 1.46 (s, 9H; -(CH₃)₂), 1.43 ppm (s, 3H; -OC(CH₃)₃); ¹³C NMR (50 MHz, CDCl₃+CCl₄): δ = 152.7 (C=O), 138.7 (-CH=CH₂), 136.9, 135.5, 128.7, 120.6, 119.4 (-CH=CH₂), 94.1, 81.6, 80.0, 79.4, 71.2,

65.5, 64.0, 60.6, 28.8, 27.3, 25.4 ppm; IR (neat): $\tilde{\nu}$ = 3984, 3876, 3712, 3537, 2979, 1838, 1699, 1384, 1170, 1084 cm⁻¹; MS (FAB): *m/z* (%): 348 (27) [M+H]⁺, 292 (65) [M-*t*Bu]⁺, 248 (100) [M-*t*Boc]⁺; elemental analysis (%) calcd for C₂₀H₂₉NO₄: C 69.14, H 8.41, N 4.03; found: C 68.87, H 8.04, N 3.96.

(4S,6S)-4-(1-Benzyloxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (19c): Yield = 79%; *R*_f = 0.6 (ethyl acetate in hexane, 10%); [α]_D²⁵ = -53.4 (*c* = 1.714 in CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 7.34 (s, 5H; ArH), 5.89–5.78 (m, 1H; -CH=CH₂), 5.33–5.26 (m, 2H; -CH=CH₂), 4.63 (d, *J* = 11.6 Hz, 1H; -CH₂-Ph), 4.33 (d, *J* = 11.6 Hz, 1H; -CH₂-Ph), 4.16–3.98 (m, 2H; 4-*H*, -CHOBn), 3.92–3.88 (m, 2H; 5-*H*), 1.51 (s, 3H; -CH₃), 1.46 (s, 9H; -OC(CH₃)₃), 1.43 ppm (s, 3H; -CH₃); ¹³C NMR (50 MHz, CDCl₃): δ = 152.9 (C=O), 138.8 (-CH=CH₂), 136.8, 128.8, 128.3, 119.7, 118.9 (-CH=CH₂), 94.6 (C-2), 81.7, 80.6, 71.2 (C(CH₃)₃), 65.6, 64.8, 60.6, 60.4 (C-4), 28.8, 27.4, 25.4, 23.6 ppm; IR (neat): $\tilde{\nu}$ = 3981, 3876, 3612, 3537, 2979, 1830, 1702, 1384, 1170, 1084 cm⁻¹; MS (ESI): *m/z* (%): 360.3 (29) [M+Na]⁺, 292.3 (45) [M-*t*Bu]⁺, 248.3 (100) [M-*t*Boc]⁺; elemental analysis (%) calcd for C₂₀H₂₉NO₄: C 69.14, H 8.41, N 4.03; found: C 69.00, H 8.24, N 3.79.

(4S,6R)-4-(1-Benzyloxyallyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (19d): Yield = 78.5%; *R*_f = 0.54 (ethyl acetate in hexane, 8%); [α]_D²⁵ = -49.8 (*c* = 2.025 in CHCl₃); ¹H NMR (200 MHz, CDCl₃, 25 °C, TMS): δ = 7.32 (s, 5H; ArH), 5.89–5.78 (m, 2H; -CH=CH₂), 5.32–5.23 (m, 1H; -CH=CH₂), 4.61 (d, *J* = 11.6 Hz, 1H; -CH₂-Ph), 4.35 (d, *J* = 11.6 Hz, 1H; -CH₂-Ph), 4.15–4.02 (m, 2H; 4-*H*, -CHOBn), 3.90 (brs, 2H; 5-*H*), 1.59 (s, 3H; -CH₃), 1.49 (s, 3H; -CH₃), 1.46 ppm (s, 9H; -OC(CH₃)₃); ¹³C NMR (50 MHz, CDCl₃, 25 °C, TMS): δ = 152.9, 138.8, 136.8, 128.7, 128.3, 119.6, 118.8, 94.6, 81.6, 80.4, 71.2, 65.6, 64.7, 60.6, 30.1, 28.8, 27.3 ppm; IR (neat): $\tilde{\nu}$ = 3967, 3871, 3712, 3537, 2979, 1838, 1699, 1374, 1170, 1084 cm⁻¹; MS (FAB): *m/z* (%): 348 (29) [M+H]⁺, 292 (45) [M-*t*Bu]⁺, 248 (51) [M-*t*Boc]⁺, 234 (85) [M-Bn+Na]⁺, 91 (100) [PhCH₂]⁺; elemental analysis (%) calcd for C₂₀H₂₉NO₄: C 69.14, H 8.41, N 4.03; found: C 68.94, H 8.24, N 3.94.

General Procedure for acetonide deprotection: A catalytic amount of PTSA (100 mg) was added to a solution of an acetonide (0.9 g, 2.99 mmol) in methanol (10 mL) and the reaction mixture was stirred at room temperature for 3 h. Methanol was removed at low temperature, the residue was dissolved in ether, and the organic layer was washed with NaHCO₃ (5%) followed by brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel with ethyl acetate in hexane (40%) as eluent to furnish the deprotected product.

(1R,2R)-(1-Hydroxymethyl-2-methoxymethoxybut-3-enyl)-carbamic acid *tert*-butyl ester (18a): Yield = 87%; *R*_f = 0.33 (ethyl acetate in hexane, 30%); [α]_D²⁵ = +82.8 (*c* = 0.433 in CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 5.83–5.71 (m, 1H; -CH=CH₂), 5.37–5.23 (m, 3H; -CH=CH₂, NH), 4.61 (dd, *J* = 23.7, 6.6 Hz, 2H; OCH₂OCH₃), 4.28 (pseudo t, *J* = 5.4 Hz, 1H; CH-OMOM), 3.91 (dd, *J* = 11.7, 4.2 Hz, 1H; 1-*H*), 3.64 (d, *J* = 9.6 Hz, 2H; CH₂OH), 3.39 (s, 3H; OCH₃), 2.79 (brs, 1H; OH), 1.45 ppm (s, 9H; OC(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = 154.5 (C=O), 133.6, 117.7, 94.8, 93.3, 78.2, 77.5, 60.7, 54.4, 53.4, 27.1 ppm; IR (neat): $\tilde{\nu}$ = 3446, 2977, 2363, 1634 cm⁻¹; MS (FAB): *m/z* (%): 261 (43) [M+H]⁺, 261 (100) [M]⁺, 205 (80) [M-*t*Bu]⁺, 162 (65) [M-*t*Boc]⁺; elemental analysis (%) calcd for C₁₂H₂₃NO₅: C 55.16, H 8.87, N 5.36; found: C 55.10, H 8.78, N 5.29.

(1R,2S)-(1-Hydroxymethyl-2-methoxymethoxy-but-3-enyl)-carbamic acid *tert*-butyl ester (18b): Yield = 84%; *R*_f = 0.31 (ethyl acetate in hexane, 30%); [α]_D²⁵ = +89.8 (*c* = 0.476 in CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 5.83–5.72 (m, 1H; -CH=CH₂), 5.37–5.28 (m, 3H; -CH=CH₂, NH), 4.61 (dd, *J* = 23.7, 6.6 Hz, 2H; OCH₂OCH₃), 4.30 (pseudo t, *J* = 5.4 Hz, 1H; CH-OMOM), 3.91 (dd, *J* = 11.7, 4.2 Hz, 1H; 1-*H*), 3.64 (d, *J* = 9.6 Hz, 2H; CH₂OH), 3.39 (s, 3H; OCH₃), 2.80 (brs, 1H; OH), 1.45 ppm (s, 9H; OC(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = 154.8, 133.2, 117.7, 93.4, 78.3, 77.7, 60.8, 54.5, 53.4, 28.3, 27.0 ppm; MS (ESI): *m/z* (%): 284.1 (48) [M+Na]⁺, 261.9 (100) [M]⁺, 205.9 (86) [M-*t*Bu]⁺, 162.0 (68) [M-*t*Boc]⁺; elemental analysis (%) calcd for C₁₂H₂₃NO₅: C 55.16, H 8.87, N 5.36; found: C 55.10, H 8.78, N 5.29.

(1S,2S)-(1-Hydroxymethyl-2-methoxymethoxy-but-3-enyl)-carbamic acid *tert*-butyl ester (18c): Yield = 86%; *R*_f = 0.33 (ethyl acetate in hexane,

30%); $[\alpha]_D^{25} = -59.7$ ($c = 0.438$ in CHCl_3); $^1\text{H NMR}$ (200 MHz, CDCl_3 , 25°C, TMS): $\delta = 5.87\text{--}5.69$ (m, 1H; $-\text{CH}=\text{CH}_2$), 5.39–5.29 (m, 3H; $-\text{CH}=\text{CH}_2$, NH), 4.61 (dd, $J = 23.7$, 6.6 Hz, 2H; OCH_2OCH_3), 4.29 (pseudo t, $J = 5.4$ Hz, 1H; CH-OMOM), 3.93 (d, $J = 8.88$ Hz, 1H; 1-H), 3.68 (d, $J = 7.42$ Hz, 2H; CH_2OH), 3.40 (s, 3H; OCH_3), 2.90 (brs, 1H; OH), 1.45 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (50 MHz, CDCl_3 , 25°C, TMS): $\delta = 155.8$, 134.7, 119.0, 94.5, 79.6, 78.7, 61.9, 55.7, 54.6, 28.3 ppm; MS (ESI): m/z (%): 284.1 (43) $[\text{M}+\text{Na}]^+$, 261.9 (100) $[\text{M}]^+$, 205.9 (82) $[\text{M}-t\text{Bu}]^+$, 162.0 (79) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_5$: C 55.16, H 8.87, N 5.36; found: C 55.10, H 8.78, N 5.29.

(1S,2R)-(1-Hydroxymethyl-2-methoxymethoxy-but-3-enyl)-carbamic acid tert-butyl ester (18d): Yield = 89%; $R_f = 0.31$ (ethyl acetate in hexane, 30%); $[\alpha]_D^{25} = -65.4$ ($c = 0.384$ in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 5.84\text{--}5.73$ (m, 1H; $-\text{CH}=\text{CH}_2$), 5.38–5.30 (m, 3H; $-\text{CH}=\text{CH}_2$, NH), 4.61 (dd, $J = 23.7$, 6.6 Hz, 2H; OCH_2OCH_3), 4.28 (pseudo t, $J = 5.4$ Hz, 1H; CH-OMOM), 3.94 (d, $J = 10.7$ Hz, 1H; 1-H), 3.79–3.64 (m, 2H; CH_2OH), 3.39 (s, 3H; OCH_3), 2.76 (brs, 1H; OH), 1.45 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C, TMS): $\delta = 154.6$, 133.4, 117.8, 93.3, 78.3, 77.6, 60.8, 54.5, 53.3, 27.1 ppm; MS (ESI): m/z (%): 284.1 (43) $[\text{M}+\text{Na}]^+$, 261.9 (100) $[\text{M}]^+$, 205.9 (82) $[\text{M}-t\text{Bu}]^+$, 162.0 (79) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_5$: C 55.16, H 8.87, N 5.36; found: C 55.10, H 8.78, N 5.29.

(1R,2R)-(2-Benzyloxy-1-hydroxymethyl-but-3-enyl)-carbamic acid tert-butyl ester (20a): Yield = 81%; $R_f = 0.4$ (ethyl acetate in hexane, 40%); $[\alpha]_D^{25} = +44.6$ ($c = 0.967$ in CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 200 MHz, 25°C, TMS): $\delta = 7.32$ (s, 5H; ArH), 5.92–5.74 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.41–5.34 (m, 2H; $-\text{CH}=\text{CH}_2$), 5.27 (s, 1H; NH), 4.64 (d, 1H; $J = 11.8$ Hz, $-\text{CH}_2\text{Ph}$), 4.33 (d, $J = 11.8$ Hz, 1H; $-\text{CH}_2\text{Ph}$), 4.07 (brs, 1H; 1-H), 3.94 (d, $J = 10.05$ Hz, 1H; 2-H), 3.67–3.61 (m, 2H; CH_2OH), 1.42 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (50 MHz, CDCl_3 , 25°C, TMS): $\delta = 155.8$, 137.6, 135.1, 128.5, 127.8, 119.2, 82.0, 79.5, 71.1, 61.9, 54.5, 28.3 ppm; IR (neat): $\tilde{\nu} = 3963$, 3857, 3697, 1813, 1706, 1512, 1371, 1170, 1056, 771 cm^{-1} ; MS (FAB): m/z (%): 330 (52) $[\text{M}+\text{Na}]^+$, 252 (98) $[\text{M}-t\text{Bu}]^+$, 208 (82) $[\text{M}-t\text{Boc}]^+$, 91 (100) $[\text{PhCH}_2]^+$; elemental analysis (%) calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_4$: C 66.43, H 8.20, N 4.56; found: C 66.32, H 8.04, N 4.36.

(1R,2S)-(2-Benzyloxy-1-hydroxymethyl-but-3-enyl)-carbamic acid tert-butyl ester (20b): Yield = 86.5%; $R_f = 0.4$ (ethyl acetate in hexane, 40%); $[\alpha]_D^{25} = +54.8$ ($c = 0.967$ in CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 200 MHz, 25°C, TMS): $\delta = 7.73\text{--}7.25$ (m, 5H; ArH), 5.90–5.72 (m, 1H; $-\text{CH}=\text{CH}_2$), 5.45–5.18 (m, 2H; $-\text{CH}=\text{CH}_2$), 4.60 (d, $J = 11.6$ Hz, 1H; $-\text{CH}_2\text{Ph}$), 4.33 (d, $J = 11.6$ Hz, 1H; $-\text{CH}_2\text{Ph}$), 4.10 (brs, 1H), 3.97 (d, $J = 10$ Hz, 1H; 2-H), 3.61 (brs, 2H; $-\text{CH}_2\text{OH}$), 1.42 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (50 MHz, $\text{CDCl}_3+\text{CCl}_4$, 25°C, TMS): $\delta = 156.03$ (C=O), 138.11, 135.75, 128.88, 128.21, 128.13, 127.27, 119.47, 82.29, 79.73, 71.53, 71.01, 62.22, 55.02, 28.81 cm^{-1} ; MS (FAB): m/z (%): 308 (52) $[\text{M}+\text{H}]^+$, 252 (85) $[\text{M}-t\text{Bu}]^+$, 208 (60) $[\text{M}-t\text{Boc}]^+$, 91 (100) $[\text{PhCH}_2]^+$; elemental analysis (%) calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_4$: C 66.43, H 8.20, N 4.56; found: C 66.39, H 8.11, N 4.31.

(1S,2S)-(2-Benzyloxy-1-hydroxymethyl-but-3-enyl)-carbamic acid tert-butyl ester (20c): Yield = 84%; $R_f = 0.4$ (ethyl acetate in hexane, 40%); $[\alpha]_D^{25} = -49.3$ ($c = 0.967$ in CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 200 MHz, 25°C, TMS): $\delta = 7.37\text{--}7.26$ (m, 5H; ArH), 5.89–5.77 (m, 1H), 5.41–5.27 (m, 3H), 4.64 (d, $J = 11.2$ Hz, 2H), 4.33 (d, $J = 11.2$ Hz, 1H), 4.07 (s, 1H), 3.94 (d, $J = 8.6$ Hz, 1H), 3.67–3.62 (m, 2H), 1.42 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (50 MHz, CDCl_3 , 25°C, TMS): $\delta = 155.8$, 137.6, 135.0, 128.5, 127.8, 119.2, 82.0, 79.5, 71.0, 61.9, 54.4, 28.3 ppm; MS (FAB): m/z (%): 330 (52) $[\text{M}+\text{Na}]^+$, 252 (98) $[\text{M}-t\text{Bu}]^+$, 208 (82) $[\text{M}-t\text{Boc}]^+$, 91 (100) $[\text{PhCH}_2]^+$; elemental analysis (%) calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_4$: C 66.43, H 8.20, N 4.56; found: C 66.22, H 8.14, N 4.39.

(1S,2R)-(2-Benzyloxy-1-hydroxymethyl-but-3-enyl)-carbamic acid tert-butyl ester (20d): Yield = 88%; $R_f = 0.4$ (ethyl acetate in hexane, 40%); $[\alpha]_D^{25} = -51.8$ ($c = 0.953$ in CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz, 25°C, TMS): $\delta = 7.37\text{--}7.33$ (m, 5H), 5.91–5.79 (m, 1H), 5.43–5.32 (m, 2H), 4.67 (d, $J = 11.2$ Hz, 1H), 4.35 (d, $J = 11.2$ Hz, 1H), 4.12 (s, 1H), 4.00–3.96 (brm, 1H), 3.73–3.64 (m, 2H), 1.45 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 154.5$ (C=O), 133.6, 135.0, 128.5, 127.9, 119.2, 82.2, 79.1, 71.2, 62.1, 54.4, 28.3 ppm; MS (ESI): m/z (%): 330.1 (52) $[\text{M}+\text{Na}]^+$, 252.1 (80) $[\text{M}-t\text{Bu}]^+$, 208 (100) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_4$: C 66.43, H 8.20, N 4.56; found: C 66.32, H 8.04, N 4.36.

sis (%) calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_4$: C 66.43, H 8.20, N 4.56; found: C 66.34, H 8.12, N 4.44.

General Procedure for the preparation of divinyl derivatives 11a–d: The starting compound (250 mg, 0.96 mmol) was taken up in dry CH_2Cl_2 (15 mL) and the mixture was cooled to 0°C. Triethylamine (0.2 mL, 1.44 mmol) was added, followed by tosyl chloride (220 mg, 1.15 mmol), and the reaction mixture was stirred at 0°C for 4 h. After completion of the reaction, solvent was evaporated and the residue was dissolved in ether. The organic layer was washed with water, followed by brine, and dried on Na_2SO_4 . Column chromatography over silica gel gave the tosylated product (350 g, 88%), which was stirred in a glass pressure bomb with allylamine (5 mL) in methanol (5 mL) at 65°C for 6 h. The reaction mixture was concentrated, and the residue was dissolved in THF. Triethylamine (1.0 mL) was added at 0°C, followed by benzyl chloroformate (170 mg, 0.99 mmol). The reaction mixture was stirred for 3 h. After completion of the reaction it was diluted with ethyl acetate and organic layer was washed with water, followed by brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The residue was chromatographed over silica gel with ethyl acetate in hexane (25%) as eluent to furnish the pure divinyl product.

(2R,3R)-Allyl-(2-tert-butoxycarbonylamino-3-methoxymethoxy-pent-4-enyl)-carbamic acid benzyl ester (11a): Overall yield = 59%; $R_f = 0.4$ (ethyl acetate in hexane, 20%); $[\alpha]_D^{25} = +9.2$ ($c = 0.426$ in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.34$ (s, 5H; ArH), 5.82–5.66 (m, 2H), 5.31–5.12 (m, 4H), 5.15 (s, 2H), 4.67–4.52 (m, 2H), 4.21–4.05 (m, 2H), 3.91–3.88 (m, 1H), 3.79–3.71 (m, 1H), 3.39 (s, 3H; OCH_3), 3.35–3.26 (m, 2H), 1.44 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (50 MHz, CDCl_3 , 25°C, TMS): $\delta = 155.8$ (C=O), 154.3 (C=O), 135.4, 133.7, 132.2, 127.2, 126.9, 126.6, 117.4, 115.6, 94.9, 93.3, 77.7, 77.1, 66.25, 65.9, 54.4, 51.6, 48.1, 44.4, 28.4 ppm; IR (neat): $\tilde{\nu} = 3447$, 2932, 2362, 1704, 1640, 1464, 1243 cm^{-1} ; MS (ESI): m/z (%): 457.1 (53) $[\text{M}+\text{Na}]^+$, 434.9 (50) $[\text{M}]^+$, 378.8 (42) $[\text{M}-t\text{Bu}]^+$, 335.2 (100) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_6$: C 63.57, H 7.89, N 6.45; found: C 63.55, H 7.68, N 6.25.

(2R,3S)-Allyl-(2-tert-butoxycarbonylamino-3-methoxymethoxy-pent-4-enyl)-carbamic acid benzyl ester (11b): Overall yield = 58%; $R_f = 0.4$ (ethyl acetate in hexane, 20%); $[\alpha]_D^{25} = +11.2$ ($c = 0.413$ in CHCl_3); $^1\text{H NMR}$ (200 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.36$ (s, 5H; ArH), 5.86–5.74 (m, 2H), 5.30–5.11 (m, 4H), 5.16 (s, 2H), 4.69–4.55 (m, 2H), 4.21–4.27 (m, 2H), 4.12–3.81 (m, 1H), 3.79–3.73 (m, 1H), 3.38 (s, 3H; OCH_3), 3.35–3.26 (m, 2H), 1.40 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); MS (ESI): m/z (%): 457.1 (100) $[\text{M}+\text{Na}]^+$, 434.9 (50) $[\text{M}]^+$, 378.8 (40) $[\text{M}-t\text{Bu}]^+$, 335.2 (20) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_6$: C 63.57, H 7.89, N 6.45; found: C 63.48, H 7.79, N 6.47.

(2S,3S)-Allyl-(2-tert-butoxycarbonylamino-3-methoxymethoxy-pent-4-enyl)-carbamic acid benzyl ester (11c): Overall yield = 63%; $R_f = 0.4$ (ethyl acetate in hexane, 20%); $[\alpha]_D^{25} = -10.7$ ($c = 0.236$ in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.38$ (s, 5H; ArH), 5.78–5.70 (m, 2H), 5.36–5.08 (m, 4H), 5.14 (s, 2H), 4.67–4.51 (m, 2H), 4.21–4.04 (m, 2H), 3.94–3.79 (m, 1H), 3.78–3.74 (m, 1H), 3.39 (s, 3H; OCH_3), 3.35–3.26 (m, 2H), 1.44 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C, TMS): $\delta = 155.9$, 154.6, 135.4, 133.5, 132.1, 127.1, 126.4, 117.4, 116.0, 115.5, 93.5, 77.8, 77.4, 66.2, 66.0, 54.4, 51.5, 51.2, 48.6, 48.1, 44.3, 43.5, 27.1 ppm; MS (ESI): m/z (%): 457.1 (53) $[\text{M}+\text{Na}]^+$, 378.8 (60) $[\text{M}-t\text{Bu}]^+$, 335.2 (100) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_6$: C 63.57, H 7.89, N 6.45; found: C 63.42, H 7.73, N 6.35.

(2S,3R)-Allyl-(2-tert-butoxycarbonylamino-3-methoxymethoxy-pent-4-enyl)-carbamic acid benzyl ester (11d): Overall yield = 60%; $R_f = 0.41$ (ethyl acetate in hexane, 20%); $[\alpha]_D^{25} = -13.7$ ($c = 0.209$ in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.33$ (s, 5H; ArH), 5.78–5.70 (m, 2H), 5.36–5.08 (m, 4H), 5.14 (s, 2H), 4.67–4.51 (m, 2H), 4.20–4.07 (m, 2H), 3.95–3.88 (m, 1H), 3.79–3.74 (m, 1H), 3.39 (s, 3H; OCH_3), 3.35–3.26 (m, 2H), 1.40 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C, TMS): $\delta = 155.6$, 154.6, 135.4, 133.4, 133.3, 132.1, 127.1, 126.6, 126.4, 117.9, 117.4, 115.5, 93.3, 77.9, 77.1, 65.9, 54.4, 51.6, 48.1, 44.3, 28.4, 27.0 ppm; MS (ESI): m/z (%): 457.1 (40) $[\text{M}+\text{Na}]^+$, 434.9 (40) $[\text{M}]^+$, 378.8 (80) $[\text{M}-t\text{Bu}]^+$, 335.2 (100) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_6$: C 63.57, H 7.89, N 6.45; found: C 63.42, H 7.73, N 6.35.

calcd for $C_{23}H_{34}N_2O_6$: C 63.57, H 7.89, N 6.45; found: C 63.39, H 7.81, N 6.37.

General Procedure for the preparation of divinyl derivatives 12a–d: The starting compound was taken up in dry CH_2Cl_2 and cooled at 0°C. Triethylamine was added, followed by tosyl chloride. The reaction mixture was stirred at the same temperature for 3 h. After completion of the reaction, solvent was evaporated, and the residue was dissolved in ether. The organic layer was washed with water, followed by brine, and dried on anhydrous Na_2SO_4 . Column chromatography over silica gel gave the tosylated product, which was heated in a steel bomb with allylamine and methanol at 65°C for 10–12 h. The reaction mixture was concentrated, and the residue was dissolved in CH_2Cl_2 . Triethylamine was added at 0°C, followed by TsCl. The reaction mixture was stirred for 3 h. After completion of the reaction the mixture was diluted with ethyl acetate, and the organic layer was washed with water, followed by brine, and dried over sodium sulfate. Chromatography over silica gel gave the divinyl product.

(3R,4R)-(1-[[Allyl-(toluene-4-sulfonyl)-amino]-methyl]-2-benzyloxy-but-3-enyl)-carbamic acid *tert*-butyl ester (12a): Overall yield=65%; $R_f=0.4$ (ethyl acetate in hexane, 15%); m.p. 105°C; $[\alpha]_D^{25}=+6.3$ ($c=1.850$ in $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.69$ (d, $J=8.1$ Hz, 2H; ArH), 7.37–7.23 (m, 7H; ArH), 5.89–5.70 (m, 1H; 5-H), 5.67–5.48 (m, 1H; 8-H), 5.38–5.29 (m, 2H; 6-H), 5.19–5.11 (m, 2H; 9-H), 5.00 (d, $J=7.08$ Hz, 1H; NH), 4.63 (d, $J=11.97$ Hz, 1H; $-CH_2Ph$), 4.34 (d, $J=12.0$ Hz, 1H; $-CH_2Ph$), 4.03 (pseudo t, 1H), 3.92–3.83 (m, 3H), 3.52 (dd, $J_1=10.47$ Hz, $J_2=14.6$ Hz, 1H), 3.15 (dd, $J_1=4.68$ Hz, $J_2=14.6$ Hz, 1H), 2.44 (s, 3H; CH_3), 1.45 ppm (s, 9H; $-OC(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=159$ (C=O), 143, 139, 137, 135, 131, 130, 129, 127, 127.7, 120.1, 118.5, 81.3, 78, 71, 51, 50, 46, 30, 27.7, 21.8 ppm; IR (neat): $\tilde{\nu}=3953.1$, 3906.5, 3755.2, 3375.0, 2980.3, 2932.4, 2369.0, 1690.7, 1597.5, 1534.4, 1352.8, 1159.5, 1091.4, 1046.1, 988.7, 921.8, 808.5, 759.0, 704.0, 661.8, 550.5 cm^{-1} ; MS (FAB): m/z (%): 501 (15) $[M+H]^+$, 445 (30) $[M-tBu]^+$, 401 (100) $[M-tBoc]^+$; elemental analysis (%) calcd for $C_{27}H_{36}N_2O_5S$: C 64.77, H 7.25, N 5.60; found: C 64.52, H 7.20, N 5.44.

(3R,4S)-(1-[[Allyl-(toluene-4-sulfonyl)-amino]-methyl]-2-benzyloxy-but-3-enyl)-carbamic acid *tert*-butyl ester (12b): Overall yield=64%; $R_f=0.4$ (ethyl acetate in hexane, 15%); m.p. 112°C; $[\alpha]_D^{25}=+11.23$ ($c=0.824$ in $CHCl_3$); 1H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.66$ (d, $J=8.1$ Hz, 2H; ArH), 7.32–7.24 (m, 7H; ArH), 5.89–5.68 (m, 1H; 5-H), 5.61–5.40 (m, 1H; 8-H), 5.37–5.26 (m, 2H; 6-H), 5.18–5.08 (m, 2H; 9-H), 4.95 (d, $J=6.2$ Hz, 1H; NH), 4.61 (d, $J=11.8$ Hz, 1H; $-CH_2Ph$), 4.34 (d, $J=11.8$ Hz, 1H; $-CH_2Ph$), 4.0 (pseudo t, $J=4.5$ Hz, 1H; 3-H), 3.82–3.76 (m, 3H), 3.51–3.39 (m, 1H), 3.18–3.08 (m, 1H), 2.43 (s, 3H; CH_3), 1.42 ppm (s, 9H; $-OC(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=156$ (C=O), 143, 138, 137, 135, 132, 130, 129, 128, 127.7, 120.1, 119, 81.3, 79, 71, 52, 51, 46, 30, 28, 21.9 ppm; IR (neat): $\tilde{\nu}=3377$, 3315, 3247, 2812, 2374, 1596, 1350, 1163, 763, 663, 553 cm^{-1} ; MS (FAB): m/z (%): 501 (15) $[M+H]^+$, 445 (30) $[M-tBu]^+$, 401 (100) $[M-tBoc]^+$; elemental analysis (%) calcd for $C_{27}H_{36}N_2O_5S$: C 64.77, H 7.25, N 5.60; found: C 64.68, H 7.18, N 5.53.

(3S,4S)-(1-[[Allyl-(toluene-4-sulfonyl)-amino]-methyl]-2-benzyloxy-but-3-enyl)-carbamic acid *tert*-butyl ester (12c): Overall yield=69%; $R_f=0.41$ (ethyl acetate in hexane, 15%); m.p. 102°C; $[\alpha]_D^{25}=-6.76$ ($c=0.700$ in $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.68$ (d, $J=8.3$ Hz, 2H; ArH), 7.39–7.28 (m, 7H; ArH), 5.86–5.71 (m, 1H; 5-H), 5.61–5.49 (m, 1H; 8-H), 5.38–5.29 (m, 2H; 6-H), 5.19–5.11 (m, 2H; 9-H), 5.00 (d, $J=8.67$ Hz, 1H; NH), 4.62 (d, $J=11.8$ Hz, 1H; $-CH_2Ph$), 4.36 (d, $J=11.8$ Hz, 1H; $-CH_2Ph$), 4.04 (pseudo t, $J=4.6$ Hz, 1H; 3-H), 3.92–3.80 (m, 3H), 3.51 (dd, $J_1=10.5$ Hz, $J_2=14.5$ Hz, 1H), 3.16 (dd, $J_1=3.84$ Hz, $J_2=14.6$ Hz, 1H), 2.44 (s, 3H; CH_3), 1.42 ppm (s, 9H; $-OC(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=156.2$ (C=O), 143.6, 138.6, 137.5, 135.4, 133, 130.1, 128.7, 128.0, 127.6, 119.9, 119.2, 81.3, 79.7, 74.4, 71.3, 52.4, 51.1, 46.2, 28.8, 21.9 ppm; IR (neat): $\tilde{\nu}=3960.1$, 3907.0, 3859.8, 3372.9, 2369.4, 1595.9, 1352.0, 1159.3, 1091.9 cm^{-1} ; MS (ESI): m/z (%): 523.1 (100) $[M+Na]^+$, 445.1 (30) $[M-tBu]^+$, 401.1 (50) $[M-tBoc]^+$; elemental analysis (%) calcd for $C_{27}H_{36}N_2O_5S$: C 64.77, H 7.25, N 5.60; found: C 64.71, H 7.20, N 5.52.

(3S,4R)-(1-[[Allyl-(toluene-4-sulfonyl)-amino]-methyl]-2-benzyloxy-but-3-enyl)-carbamic acid *tert*-butyl ester (12d): Overall yield=61%; $R_f=0.4$ (ethyl acetate in hexane, 15%); $[\alpha]_D^{25}=-10.23$ ($c=0.727$ in $CHCl_3$); m.p. 115°C; 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.69$ (d, $J=8.3$ Hz, 2H; ArH), 7.37–7.37 (m, 7H; ArH), 5.81–5.71 (m, 1H), 5.62–5.48 (m, 1H), 5.38–5.28 (m, 2H), 5.19–5.11 (m, 2H), 5.01 (d, $J=8.7$ Hz, 1H), 4.63 (d, $J=11.9$ Hz, 1H), 4.37 (d, $J=11.9$ Hz, 1H), 4.03 (pseudo t, $J=4.3$ Hz, 1H), 3.92–3.80 (m, 3H), 3.51 (dd, $J_1=10.5$ Hz, $J_2=14.6$ Hz, 1H), 3.16 (dd, $J_1=3.84$ Hz, $J_2=14.6$ Hz, 1H), 2.44 (s, 3H; CH_3), 1.43 ppm (s, 9H; $OC(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=156.2$, 143.6, 138.6, 137.5, 135.4, 132.9, 130.1, 128.7, 128.0, 127.6, 119.9, 119.2, 81.3, 79.7, 71.3, 52.4, 51.0, 46.2, 28.8, 21.9 ppm; MS (ESI): m/z (%): 523.1 (100) $[M+Na]^+$, 445.1 (40) $[M-tBu]^+$, 401.1 (50) $[M-tBoc]^+$; elemental analysis (%) calcd for $C_{27}H_{36}N_2O_5S$: C 64.77, H 7.25, N 5.60; found: C 64.62, H 7.19, N 5.54.

General Procedure for RCM: Grubbs' catalyst (5 mol %) was added to a solution of the starting compound at reflux in dry CH_2Cl_2 , and the reaction mixture was stirred overnight. After completion of the reaction, solvent was removed and the residue was chromatographed over silica gel to furnish the tetrahydroazepine core.

(3R,4R)-3-*tert*-Butoxycarbonylamino-4-methoxymethoxy-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (9a): Yield=76%; $R_f=0.4$ (ethyl acetate in hexane, 30%); $[\alpha]_D^{25}=-40.5$ ($c=2.1$ in $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.35$ (s, 5H; ArH), 5.98–5.89 (m, 1H), 5.82–5.72 (m, 1H), 5.15 (s, 2H), 4.65–4.54 (m, 2H), 4.35 (d, $J=12.6$ Hz, 1H), 4.20 (dd, $J=17.0$, 3.6 Hz, 2H), 3.91–3.65 (m, 3H), 3.32 (s, 3H; OCH_3), 1.43 ppm (s, 9H; $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta=154.5$, 149.3 (C=O), 129.6, 127.2, 126.7, 126.5, 94.9, 93.9, 78.14, 73.6, 66.1, 54.2, 52.0, 50.2, 47.9, 45.3, 28.42 ppm; IR (neat): $\tilde{\nu}=3860$, 3445, 2932, 2362, 1700, 1636, 1387, 1167, 1099, 1033 cm^{-1} ; MS (ESI): m/z (%): 429.1 (100) $[M+Na]^+$, 407.0 (10) $[M]^+$, 373.1 (12) $[M-tBu+Na]^+$, 307.1 (13) $[M-tBoc]^+$; elemental analysis (%) calcd for $C_{21}H_{30}N_2O_6$: C 62.05, H 7.44, N 6.89; found: C 61.97, H 7.44, N 6.78.

(3R,4S)-3-*tert*-Butoxycarbonylamino-4-methoxymethoxy-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (9b): Yield=78.4%; $R_f=0.4$ (ethyl acetate in hexane, 30%); $[\alpha]_D^{25}=-34.5$ ($c=2.3$ in $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.38$ (s, 5H; ArH), 5.93 (pseudo t, 1H), 5.79–5.77 (m, 1H), 5.15 (s, 2H), 4.71–4.58 (m, 2H), 4.36 (d, $J=12.6$ Hz, 1H), 4.22 (dd, $J=17.0$, 3.6 Hz, 2H), 3.86–3.69 (m, 3H), 3.35 (s, 3H; OCH_3), 1.43 ppm (s, 9H; $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta=154.5$, 135.3, 129.6, 127.2, 126.7, 125.6, 94.0, 78.2, 73.5, 66.1, 63.9, 54.2, 50.2, 47.9, 45.3, 30.6, 28.4, 27.0, 21.3 ppm; MS (ESI): m/z (%): 429.1 (100) $[M+Na]^+$, 407.0 (20) $[M]^+$, 350.1 (10) $[M-tBu]^+$, 307.1 (80) $[M-tBoc]^+$; elemental analysis (%) calcd for $C_{21}H_{30}N_2O_6$: C 62.05, H 7.44, N 6.89; found: C 62.01, H 7.29, N 6.79.

(3S,4S)-3-*tert*-Butoxycarbonylamino-4-methoxymethoxy-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (9c): Yield=78%; $R_f=0.41$ (ethyl acetate in hexane, 30%); $[\alpha]_D^{25}=+48.5$ ($c=2.1$ in $CHCl_3$); 1H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.36$ (s, 5H; ArH), 5.89 (brs, 1H), 5.72 (brs, 1H), 5.23 (s, 2H), 4.69–4.49 (m, 2H), 4.31 (brs, 1H), 4.08 (brs, 2H), 3.82–3.61 (m, 3H), 3.24 (s, 3H; OCH_3), 1.35 ppm (s, 9H; $OC(CH_3)_3$); MS (ESI): m/z (%): 429.1 (100) $[M+Na]^+$, 407.0 (10) $[M]^+$, 373.1 (15) $[M-tBu+Na]^+$, 307.1 (13) $[M-tBoc]^+$; elemental analysis (%) calcd for $C_{21}H_{30}N_2O_6$: C 62.05, H 7.44, N 6.89; found: C 61.89, H 7.19, N 6.75.

(3S,4R)-3-*tert*-Butoxycarbonylamino-4-methoxymethoxy-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (9d): Yield=78.5%; $R_f=0.41$ (ethyl acetate in hexane, 30%); $[\alpha]_D^{25}=+39.5$ ($c=2.2$ in $CHCl_3$); 1H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.36$ (s, 5H; ArH), 5.94–5.92 (m, 1H), 5.79–5.74 (m, 1H), 5.16 (s, 2H), 4.67–4.58 (m, 2H), 4.39 (brs, 1H), 4.20 (d, $J=8.6$ Hz, 2H), 3.91–3.69 (m, 3H), 3.32 (s, 3H; OCH_3), 1.43 ppm (s, 9H; $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta=154.5$, 136.4, 130.1, 129.6, 127.2, 126.7, 94.0, 78.2, 73.5, 66.3, 66.1, 54.3, 50.1, 47.9, 45.3, 28.4, 27.0 ppm; MS (ESI): m/z (%): 429.1 (100) $[M+Na]^+$, 407.0 (10) $[M]^+$, 373.1 (35) $[M-tBu+Na]^+$, 307.1 (13) $[M-tBoc]^+$; elemental analysis (%) calcd for $C_{21}H_{30}N_2O_6$: C 62.05, H 7.44, N 6.89; found: C 61.91, H 7.23, N 6.81.

(3R,4R)-[4-Benzyloxy-1-(toluene-4-sulfonyl)-2,3,4,7-tetrahydro-1H-azepin-3-yl]-carbamic acid *tert*-butyl ester (10a): Yield = 76%; R_f = 0.4 (ethyl acetate in hexane, 25%); $[\alpha]_D^{25} = +7.14$ (c = 0.370 in CHCl_3); ^1H NMR (CDCl_3 , 300 MHz, 25°C, TMS): δ = 7.63 (d, J = 8.0 Hz, 2H; ArH), 7.35–7.23 (m, 7H; ArH), 5.80–5.68 (m, 2H; 5-H, 6-H), 4.43 (dd, J_1 = 12 Hz, J_2 = 22 Hz, 2H; $-\text{CH}_2\text{Ph}$), 4.37 (brs, 1H), 4.29 (brs, 1H; 4-H), 3.76 (brs, 2H; 2-H, 7-H), 3.48–3.32 (m, 2H; 2'-H, 7'-H), 2.38 (s, 3H; CH_3), 1.48 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CDCl_3): δ = 156.1 (C=O), 143.9, 138.2, 136.1, 133.4, 130.2, 128.8, 128.1, 127.6, 80.1, 71.2, 51.9, 50.2, 48.4, 32.3, 30.1, 28.8, 27.1, 23.1, 21.9, 14.5 ppm; IR (neat): $\tilde{\nu}$ = 3980, 3950, 3711, 1838, 1716, 1500, 1365, 1163, 764, 673 cm^{-1} ; MS (FAB): m/z (%): 473 (15) $[\text{M}+\text{H}]^+$, 417 (70) $[\text{M}-\text{tBu}]^+$, 373 (90) $[\text{M}-\text{tBoc}]^+$, 91 (100) $[\text{PhCH}_2]^+$; elemental analysis (%) calcd for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_6\text{S}$: C 63.54, H 6.82, N 5.93; found: C 63.51, H 6.73, N 5.85.

(3R,4S)-[4-Benzyloxy-1-(toluene-4-sulfonyl)-2,3,4,7-tetrahydro-1H-azepin-3-yl]-carbamic acid *tert*-butyl ester (10b): Yield = 79%; R_f = 0.42 (ethyl acetate in hexane, 25%); $[\alpha]_D^{25} = +4.21$ (c = 0.190 in CHCl_3); ^1H NMR (200 MHz, CDCl_3 , 25°C, TMS): δ = 7.64 (d, 2H; J = 8.2 Hz, ArH), 7.28–7.20 (m, 7H; ArH), 5.96–5.71 (m, 2H; 5-H, 6-H), 4.82 (d, J = 8 Hz, 1H; NH), 4.52 (dd, J_1 = 11.2 Hz, J_2 = 22.0 Hz, 2H; $-\text{CH}_2\text{Ph}$), 4.39–4.29 (m, 2H; 3-H, 4-H), 3.77 (m, 2H; 2-H, 7-H), 3.61–3.34 (m, 2H; 2'-H, 7'-H), 2.41 (s, 3H; CH_3), 1.43 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CDCl_3 , 25°C, TMS): δ = 155.8 (C=O), 143.5, 138.2, 136.5, 133.4, 130.1, 128.7, 128.1, 127.6, 96.6, 79.8, 71.1, 51.8, 50.2, 48.4, 28.8, 21.9 ppm; IR (neat): $\tilde{\nu}$ = 3980, 3950, 3711, 1838, 1716, 1500, 1365, 1163, 764, 673 cm^{-1} ; MS (FAB): m/z (%): 473 (65) $[\text{M}+\text{H}]^+$, 417 (70) $[\text{M}-\text{tBu}]^+$, 373 (90) $[\text{M}-\text{tBoc}]^+$, 91 (100) $[\text{PhCH}_2]^+$; elemental analysis (%) calcd for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_6\text{S}$: C 63.54, H 6.82, N 5.93; found: C 63.45, H 6.78, N 5.79.

(3S,4S)-[4-Benzyloxy-1-(toluene-4-sulfonyl)-2,3,4,7-tetrahydro-1H-azepin-3-yl]-carbamic acid *tert*-butyl ester (10c): Yield = 82%; R_f = 0.4 (ethyl acetate in hexane, 25%); $[\alpha]_D^{25} = -8.20$ (c = 0.256 in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ = 7.67 (d, J = 8.2 Hz, 2H; ArH), 7.38–7.28 (m, 7H; ArH), 5.85–5.73 (m, 2H; 5-H, 6-H), 4.91 (d, J = 8.4 Hz, 1H; NH), 4.56 (dd, J_1 = 11.7 Hz, J_2 = 25.0 Hz, 2H), 4.43 (s, 1H), 4.35 (brs, 1H), 3.79 (d, J = 3.3 Hz, 2H), 3.56–3.42 (m, 2H), 2.43 (s, 3H; CH_3), 1.47 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CDCl_3 , 25°C, TMS): δ = 156.1 (C=O), 143.9, 138.2, 136.1, 133.4, 130.2, 128.8, 128.1, 127.6, 80.1, 73.8, 73.1, 71.2, 51.9, 50.2, 48.4, 28.7, 21.9 ppm; MS (FAB): m/z (%): 473 (45) $[\text{M}+\text{Na}]^+$, 417 (100) $[\text{M}-\text{tBu}]^+$, 373 (90) $[\text{M}-\text{tBoc}]^+$; elemental analysis (%) calcd for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_6\text{S}$: C 63.54, H 6.82, N 5.93; found: C 63.481, H 6.81, N 5.89.

(3S,4R)-[4-Benzyloxy-1-(toluene-4-sulfonyl)-2,3,4,7-tetrahydro-1H-azepin-3-yl]-carbamic acid *tert*-butyl ester (10d): Yield = 75%; R_f = 0.4 (ethyl acetate in hexane, 25%); $[\alpha]_D^{25} = -5.22$ (c = 0.134 in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ = 7.61 (d, J = 8 Hz, 2H; ArH), 7.32–7.22 (m, 7H; ArH), 5.89–5.68 (m, 2H; 5-H, 6-H), 4.86 (d, J = 9.0 Hz, 1H; NH), 4.52 (dd, J_1 = 12.3 Hz, J_2 = 21 Hz, 2H; $-\text{CH}_2\text{Ph}$), 4.37 (brs, 1H; 3-H), 4.30 (brs, 1H; 4-H), 3.76 (brs, 2H; 2-H, 7-H), 3.47–3.41 (m, 2H; 2'-H, 7'-H), 2.38 (s, 3H; CH_3), 1.41 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CDCl_3 , 25°C, TMS): δ = 143.9 (C=O), 138.1, 136.0, 133.45, 130.2, 128.8, 128.1, 127.56, 80.07, 71.2, 51.9, 50.2, 48.4, 30.1, 28.7, 21.9 ppm; MS (ESI): m/z (%): 496.2 (100) $[\text{M}+\text{Na}]^+$, 417.1 (70) $[\text{M}-\text{tBu}]^+$, 373 (90) $[\text{M}-\text{tBoc}]^+$; elemental analysis (%) calcd for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_6\text{S}$: C 63.54, H 6.82, N 5.93; found: C 63.49, H 6.72, N 5.84.

General Procedure for hydrogenation to prepare 21a–d: The starting compound (500 mg) was taken up in THF (25 mL). Pd/C (10%, 25 mg) was added, and the reaction mixture was stirred under hydrogen at room temperature. The solution was filtered through Celite, and the filtrate was concentrated and passed through a small silica column to furnish the product.

(3R,4R)-3-*tert*-Butoxycarbonylamino-4-methoxymethoxy-azepane-1-carboxylic acid benzyl ester (21a): Yield = 95%; R_f = 0.42 (ethyl acetate in hexane, 30%); $[\alpha]_D^{25} = +19.5$ (c = 0.496 in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ = 7.44–7.30 (m, 5H; ArH), 5.26–5.11 (m, 1H), 5.17 (s, 2H), 4.65 (dd, J = 12.6, 6.6 Hz, 2H), 3.94–3.88 (m, 2H), 3.75–3.67 (m, 2H), 3.43 (s, 3H; OCH_3), 3.33–3.24 (m, 2H), 2.07–1.67 (m, 4H), 1.46 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CDCl_3 , 25°C, TMS): δ = 156.5 (C=O), 155.4 (C=O), 137.4, 128.8, 128.3, 96.4, 79.8, 67.6, 56.3,

53.9, 47.6, 47.2, 30.1, 28.8, 27.6, 20.6 ppm; IR (neat): $\tilde{\nu}$ = 3861, 3754, 3445, 3021, 2364, 1702, 1217, 765 cm^{-1} ; MS (ESI): m/z (%): 431.2 (100) $[\text{M}+\text{Na}]^+$, 399.2 (20) $[\text{M}-\text{OCH}_3+\text{Na}]^+$, 375.2 (12) $[\text{M}-\text{tBu}+\text{Na}]^+$, 309.2 (13) $[\text{M}-\text{tBoc}]^+$; elemental analysis (%) calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_6$: C 61.75, H 7.90, N 6.86; found: C 61.64, H 7.88, N 6.82.

(3R,4S)-3-*tert*-Butoxycarbonylamino-4-methoxymethoxy-azepane-1-carboxylic acid benzyl ester (21b): Yield = 93%; R_f = 0.41 (ethyl acetate in hexane, 30%); $[\alpha]_D^{25} = +26.5$ (c = 0.269 in CHCl_3); ^1H NMR (200 MHz, CDCl_3 , 25°C, TMS): δ = 7.45 (s, 5H; ArH), 5.24–5.09 (m, 1H), 5.16 (s, 2H), 4.66 (dd, J = 12.8, 6.4 Hz, 2H), 3.94–3.88 (m, 2H), 3.75–3.65 (m, 2H), 3.43 (s, 3H; OCH_3), 3.33–3.24 (m, 2H), 2.07–1.66 (m, 4H), 1.45 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CDCl_3 , 25°C, TMS): δ = 156.5, 155.3, 137.2, 128.8, 128.2, 96.6, 96.3, 79.7, 67.6, 67.4, 56.3, 53.8, 47.6, 47.1, 30.0, 28.1, 27.7, 21.6 ppm; MS (ESI): m/z (%): 431.2 (100) $[\text{M}+\text{Na}]^+$, 399.2 (20) $[\text{M}-\text{OCH}_3+\text{Na}]^+$, 375.2 (12) $[\text{M}-\text{tBu}+\text{Na}]^+$, 309.2 (13) $[\text{M}-\text{tBoc}]^+$; elemental analysis (%) calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_6$: C 61.75, H 7.90, N 6.86; found: C 61.71, H 7.86, N 6.76.

(3S,4S)-3-*tert*-Butoxycarbonylamino-4-methoxymethoxy-azepane-1-carboxylic acid benzyl ester (21c): Yield = 95%; R_f = 0.41 (ethyl acetate in hexane, 30%); $[\alpha]_D^{25} = -15.5$ (c = 0.396 in CHCl_3); ^1H NMR (200 MHz, CDCl_3 , 25°C, TMS): δ = 7.42–7.26 (m, 5H; ArH), 5.26–5.15 (m, 1H), 5.14 (s, 2H), 4.66 (dd, J = 12.6, 6.6 Hz, 2H), 3.94–3.67 (m, 4H), 3.39 (s, 3H; OCH_3), 3.33–3.27 (m, 2H), 2.07–1.67 (m, 4H), 1.44 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); MS (ESI): m/z (%): 431.2 (100) $[\text{M}+\text{Na}]^+$, 399.2 (20) $[\text{M}-\text{OCH}_3+\text{Na}]^+$, 375.2 (50) $[\text{M}-\text{tBu}+\text{Na}]^+$, 309.2 (13) $[\text{M}-\text{tBoc}]^+$; elemental analysis (%) calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_6$: C 61.75, H 7.90, N 6.86; found: C 61.71, H 7.79, N 6.80.

(3S,4R)-3-*tert*-Butoxycarbonylamino-4-methoxymethoxy-azepane-1-carboxylic acid benzyl ester (21d): Yield = 96%; R_f = 0.42 (ethyl acetate in hexane, 30%); $[\alpha]_D^{25} = -29.5$ (c = 0.278 in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ = 7.48–7.29 (m, 5H; ArH), 5.28–5.12 (m, 1H), 5.17 (s, 2H), 4.65 (dd, J = 12.6, 6.6 Hz, 2H), 3.92–3.90 (m, 2H), 3.76–3.66 (m, 2H), 3.43 (s, 3H; OCH_3), 3.42–3.29 (m, 2H), 2.08–1.69 (m, 4H), 1.44 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CDCl_3 , 25°C, TMS): δ = 156.5, 155.3, 137.3, 128.8, 128.2, 96.3, 79.7, 67.5, 56.3, 53.8, 47.6, 47.2, 30.1, 28.7, 27.7, 20.6 ppm; MS (ESI): m/z (%): 431.2 (100) $[\text{M}+\text{Na}]^+$, 399.2 (35) $[\text{M}-\text{OCH}_3+\text{Na}]^+$, 352.2 (55) $[\text{M}-\text{tBu}]^+$, 309.2 (13) $[\text{M}-\text{tBoc}]^+$; elemental analysis (%) calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_6$: C 61.75, H 7.90, N 6.86; found: C 61.71, H 7.82, N 6.79.

General Procedure for preparation of amido alcohols 22a–d: The starting compound was stirred with TFA (50%) at room temperature for 30 min. The solvent was evaporated, and coevaporation was performed with dry CH_2Cl_2 to remove excess TFA. The residue was dissolved in dry CH_2Cl_2 , and triethylamine was added at 0°C, followed by *p*-benzyloxybenzoyl chloride. The reaction mixture was stirred at room temperature for 1 h. Solvent was evaporated, and the residue was dissolved in ethyl acetate. The organic layer was washed with NaHCO_3 (5%), followed by brine, and dried over sodium sulfate. Chromatography over silica gel furnished the amido alcohols.

(3R,4R)-3-(4-Benzyloxybenzoylamino)-4-hydroxyazepane-1-carboxylic acid benzyl ester (22a): Yield = 59%; R_f = 0.3 (ethyl acetate in hexane, 50%); $[\alpha]_D^{25} = -82.85$ (c = 2.1 in methanol); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ = 8.18 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 7.98 Hz, 2H; ArH), 7.47–7.31 (m, 10H; ArH), 7.01 (d, J = 8.19 Hz, 2H; ArH), 5.31 (s, 1H), 5.27–5.19 (m, 2H), 5.15 (s, 2H), 4.45 (s, 1H), 4.22 (d, J = 14.3 Hz, 1H), 4.04–3.94 (m, 2H), 3.19 (d, J = 14.5 Hz, 1H), 3.10–3.04 (m, 1H), 2.05–1.64 ppm (m, 4H); ^{13}C NMR (50 MHz, CDCl_3 , 25°C, TMS): δ = 156.4, 139.3, 135.1, 128.0, 127.4, 127.3, 126.9, 126.5, 126.1, 113.4, 68.81, 66.5, 46.2, 30.6, 28.4, 28.1, 27.7, 21.4 ppm; IR (neat): $\tilde{\nu}$ = 3906.5, 3867, 3820, 3440, 2924, 2857, 2363, 1636, 1427, 1380, 670 cm^{-1} ; MS (FAB): m/z (%): 497.6 (100) $[\text{M}+\text{Na}]^+$; elemental analysis (%) calcd for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_5$: C 70.87, H 6.37, N 5.90; found: C 70.85, H 6.34, N 5.82.

(3R,4S)-3-(4-Benzyloxybenzoylamino)-4-hydroxyazepane-1-carboxylic acid benzyl ester (22b): Yield = 70%; R_f = 0.31 (ethyl acetate in hexane, 50%); $[\alpha]_D^{25} = -73.6$ (c = 0.85 in methanol); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ = 7.20–6.99 (m, 14H; ArH), 5.26–5.14 (m, 4H), 4.45 (s, 1H), 4.33–3.85 (m, 3H), 3.67–3.09 (m, 2H), 3.19 (d, J = 14.5 Hz, 1H), 3.10–3.04 (m, 1H), 2.05–1.62 ppm (m, 4H); ^{13}C NMR (75 MHz, CDCl_3 ,

25°C, TMS): δ = 157.1, 135.1, 131.1, 130.6, 128.0, 127.4, 127.3, 127.0, 126.5, 126.2, 120.9, 113.5, 72.5, 68.9, 66.5, 55.4, 46.1, 30.6, 28.4, 21.4, 20.5, 12.8 ppm; MS (ESI): m/z (%): 497.2 (100) $[M+Na]^+$; elemental analysis (%) calcd for $C_{28}H_{30}N_2O_5$: C 70.87, H 6.37, N 5.90; found: C 70.34, H 6.14, N 5.59.

(3S,4S)-3-(4-Benzyloxybenzoylamino)-4-hydroxyazepane-1-carboxylic acid benzyl ester (22c): Yield = 67%; R_f = 0.32 (ethyl acetate in hexane, 50%); $[\alpha]_D^{25}$ = +79.6 (c = 1.25 in methanol); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 8.20 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 7.98 Hz, 2H; ArH), 7.47–7.31 (m, 10H; ArH), 7.01 (d, J = 8.19 Hz, 2H; ArH), 5.30–5.12 (m, 4H), 4.43 (s, 1H), 4.17 (d, J = 14.3 Hz, 1H), 4.01–3.92 (m, 2H), 3.19 (d, J = 14.5 Hz, 1H), 3.10–3.04 (m, 1H), 2.05–1.60 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 156.2, 135.0, 128.0, 127.4, 127.3, 126.9, 126.5, 126.1, 113.4, 72.3, 68.8, 66.3, 55.3, 46.1, 30.4, 28.4, 21.4, 19.1, 12.9 ppm; MS (ESI): m/z (%): 497.2 (100) $[M+Na]^+$; elemental analysis (%) calcd for $C_{28}H_{30}N_2O_5$: C 70.87, H 6.37, N 5.90; found: C 70.73, H 6.19, N 5.63.

(3S,4R)-3-(4-Benzyloxybenzoylamino)-4-hydroxyazepane-1-carboxylic acid benzyl ester (22d): Yield = 65%; R_f = 0.3 (ethyl acetate in hexane, 50%); $[\alpha]_D^{25}$ = +63.65 (c = 1.25 in methanol); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.81 (d, J = 7.98 Hz, 2H), 7.44–7.28 (m, 10H; ArH), 7.01 (d, J = 8.19 Hz, 2H; ArH), 5.30–5.12 (m, 4H), 4.45 (s, 1H), 4.20 (d, J = 14.3 Hz, 1H), 4.04–3.94 (m, 2H), 3.18 (d, J = 14.5 Hz, 1H), 3.10–3.04 (m, 1H), 2.05–1.63 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 153.6, 138.4, 135.1, 128.0, 127.4, 127.3, 126.9, 126.4, 126.1, 113.4, 68.8, 66.2, 47.8, 46.1, 30.6, 28.4, 27.6, 21.4, 12.8 ppm; MS (ESI): m/z (%): 497.1 (100) $[M+Na]^+$; elemental analysis (%) calcd for $C_{28}H_{30}N_2O_5$: C 70.87, H 6.37, N 5.90; found: C 70.80, H 6.27, N 5.69.

General Procedure for preparation of amido alcohols 24a–d: The starting compound (200 mg, 0.424 mmol) was taken up in methanol and a catalytic amount of HCl was added, followed by Pd/C (10%, 5% w/w). The reaction mixture was stirred under hydrogen in a Parr apparatus at 40 psi pressure. The reaction mixture was filtered through Celite, and the filtrate was concentrated and dissolved in dry CH_2Cl_2 (10 mL). Triethylamine (0.5 mL) was added at 0°C, followed by *p*-benzyloxybenzoyl chloride (170 mg, 0.70 mmol). The reaction mixture was stirred at room temperature for 1 h. Solvent was evaporated, and the residue was dissolved in ethyl acetate. The organic layer was washed with $NaHCO_3$ (5%), followed by brine, and dried over sodium sulfate. Chromatography over silica gel furnished the amido alcohol.

(3R,4R)-4-Benzyloxy-N-[4-hydroxy-1-(toluene-4-sulfonyl)-azepan-3-yl]-benzamide (24a): Yield = 73%; R_f = 0.3 (ethyl acetate in hexane, 60%); m.p. 147°C; $[\alpha]_D^{25}$ = +11.65 (c = 0.156 in $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.97 (d, J = 8.8 Hz, 2H; ArH), 7.70 (d, J = 8.8 Hz, 2H; ArH), 7.51–7.32 (m, 7H; ArH), 7.05 (d, J = 8.8 Hz, 2H; ArH), 5.15 (s, 2H; $-CH_2Ph$), 4.90 (brs, 1H; NH), 4.49 (s, 1H; 3-H), 3.89–3.71 (m, 3H; 2-H, 7-H, 4-H), 2.96–2.88 (m, 2H; 2'-H, 7'-H), 2.46 (s, 3H; CH_3), 2.06–1.95 (m, 6-H), 1.86–1.83 (m, 1H; 5-H), 1.65–1.51 ppm (m, 1H; 5'-H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 168.4, 160.56, 142.78, 135.13, 133.46, 128.69, 128.24, 127.36, 126.84, 126.16, 125.87, 124.46, 113.52, 68.83, 52.01, 47.29, 46.40, 27.24, 21.17, 20.22 ppm; IR (neat): $\tilde{\nu}$ = 3907, 3855, 3804, 3756, 3453, 2933, 2370, 1602, 1347, 1249, 1153, 1092, 756, 660 cm^{-1} ; MS (ESI): m/z (%): 517.3 (35) $[M+Na]^+$, 495.2 (100) $[M+H]^+$; elemental analysis (%) calcd for $C_{27}H_{30}N_2O_5S$: C 65.57, H 6.11, N 5.66; found: C 65.37, H 6.04, N 5.64.

(3R,4S)-4-Benzyloxy-N-[4-hydroxy-1-(toluene-4-sulfonyl)-azepan-3-yl]-benzamide (24b): Yield = 71%; R_f = 0.3 (ethyl acetate in hexane, 60%); m.p. 142°C; $[\alpha]_D^{25}$ = +3.65 (c = 0.245 in $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.92 (d, J = 8.8 Hz, 2H; ArH), 7.69 (d, J = 8.8 Hz, 2H; ArH), 7.47–7.26 (m, 7H; ArH), 7.05 (d, J = 8.8 Hz, 2H; ArH), 5.12 (s, 2H; CH_2Ph), 4.45 (s, 1H; NH), 4.00 (s, 1H; 3-H), 3.88–3.67 (m, 3H; 4-H, 2-H, 7-H), 2.96–2.88 (m, 2H; 2'-H, 7'-H), 2.46 (s, 3H; CH_3), 2.06–1.66 ppm (m, 4H; 5-H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): δ = 169.8, 161.8, 144.1, 136.3, 134.5, 130.0, 129.5, 129.2, 128.6, 128.1, 127.5, 127.1, 127.0, 125.6, 114.7, 70.1, 53.1, 48.5, 47.4, 29.7, 28.4, 27.7, 22.3, 21.6, 14.1 ppm; IR (neat): $\tilde{\nu}$ = 3906.7, 3756.1, 3399.8, 2926.0, 2370.1, 1735.2, 1603.8, 1345.0, 1252.9, 1154.2, 1091.8, 757.2, 659.9, 545.6 cm^{-1} ; MS (FAB): m/z (%): 495 (100) $[M+H]^+$; elemental analysis

(%) calcd for $C_{27}H_{30}N_2O_5S$: C 65.57, H 6.11, N 5.66; found: C 65.53, H 6.10, N 5.38.

(3S,4S)-4-Benzyloxy-N-[4-hydroxy-1-(toluene-4-sulfonyl)-azepan-3-yl]-benzamide (24c): Yield = 75%; R_f = 0.3 (ethyl acetate in hexane, 60%); m.p. 137°C; $[\alpha]_D^{25}$ = -10.72 (c = 0.25 in $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.97 (d, J = 8.8 Hz, 2H; ArH), 7.70 (d, J = 8.8 Hz, 2H; ArH), 7.47–7.28 (m, 7H; ArH), 7.05 (d, J = 8.8 Hz, 2H; ArH), 5.14 (s, 2H; CH_2Ph), 4.48 (s, 1H; NH), 4.10 (s, 1H; 3-H), 3.86–3.67 (m, 3H; 4-H, 2-H, 7-H), 2.97–2.89 (m, 2H; 2'-H, 7'-H), 2.46 (s, 3H; CH_3), 2.16–1.68 ppm (m, 4H; 5-H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 168.4, 160.5, 142.8, 135.1, 133.4, 128.7, 128.2, 127.8, 127.3, 126.8, 126.1, 125.8, 124.4, 120.8, 113.5, 68.8, 51.99, 47.2, 46.3, 28.4, 27.2, 21.1, 20.2 ppm; IR (neat): $\tilde{\nu}$ = 3906.7, 3756.1, 3399.8, 2926.0, 2370.1, 1735.2, 1603.8, 1345.0, 1252.9, 1154.2, 1091.8, 757.2, 659.9, 545.6 cm^{-1} ; MS (ESI): m/z (%): 517.3 (100) $[M+Na]^+$, 495.2 (40) $[M+H]^+$; elemental analysis (%) calcd for $C_{27}H_{30}N_2O_5S$: C 65.57, H 6.11, N 5.66; found: C 65.52, H 6.05, N 5.52.

(3S,4R)-4-Benzyloxy-N-[4-hydroxy-1-(toluene-4-sulfonyl)-azepan-3-yl]-benzamide (24d): Yield = 73%; R_f = 0.31 (ethyl acetate in hexane, 60%); m.p. 141°C; $[\alpha]_D^{25}$ = -3.72 (c = 0.345 in $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.94 (d, J = 8.8 Hz, 2H; ArH), 7.68 (d, J = 8.8 Hz, 2H; ArH), 7.48–7.31 (m, 7H; ArH), 7.02 (d, J = 8.8 Hz, 2H; ArH), 5.16 (s, 2H; CH_2Ph), 4.46 (s, 1H; NH), 4.02 (s, 1H; 3-H), 3.88–3.67 (m, 3H; 4-H, 2-H, 7-H), 2.96–2.90 (m, 2H; 2'-H, 7'-H), 2.43 (s, 3H; CH_3), 2.05–1.82 ppm (m, 4H; 5-H, 6-H); IR (neat): $\tilde{\nu}$ = 3906.7, 3756.1, 3399.8, 2926.0, 2370.1, 1735.2, 1603.8, 1345.0, 1252.9, 1154.2, 1091.8, 757.2, 659.9, 545.6 cm^{-1} ; MS (ESI): m/z (%): 517.3 (100) $[M+Na]^+$, 495.2 (40) $[M+H]^+$; elemental analysis (%) calcd for $C_{27}H_{30}N_2O_5S$: C 65.57, H 6.11, N 5.66; found: C 65.47, H 6.01, N 5.54.

3,5-Dibenzoyloxy-4-[(2-[1,3]dioxan-2-yl-6-methoxymethoxy-phenyl)-hydroxy-methyl]-benzoic acid *tert*-butyl ester (25): *n*-BuLi (4.5 mL, 1.0 M solution in hexane) was added dropwise at -78°C under nitrogen to a solution of bromo compound **15** (2 g, 4.27 mmol) in dry THF. The solution was stirred for 5 min, and then a solution of aldehyde **14** (1.0 g, 3.97 mmol) in THF was added dropwise. The reaction mixture was stirred at the same temperature for 1 h and then at room temperature for 4 h. The reaction was quenched with sat. NH_4Cl solution. The organic layer was separated, and the aq. layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . Chromatography over silica gel afforded alcohol **25** (2.1 g, 79%) as a sticky solid. R_f = 0.3 (ethyl acetate in hexane, 50%); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.45 (d, J = 8.7 Hz, 1H; ArH), 7.44–7.21 (m, 12H; ArH), 7.01 (d, J = 8.7 Hz, 1H; ArH), 6.69 (d, J = 8.7 Hz, 1H; ArH), 6.06 (s, 1H), 5.33 (d, J = 8.9 Hz, 1H), 5.11 (s, 4H), 4.80 (s, 2H), 4.16–4.11 (m, 2H), 3.87 (t, J = 15 Hz, 1H), 3.68 (t, J = 15 Hz, 1H), 2.98 (s, 3H; OCH_3), 2.21–2.09 (m, 1H), 1.58 (s, 9H; $OC(CH_3)_3$), 1.33 ppm (d, J = 14 Hz, 1H); MS (ESI): m/z (%): 665 (59) $[M+Na]^+$, 566.9 (100) $[M-CO_2tBu+Na]^+$; elemental analysis (%) calcd for $C_{38}H_{42}O_9$: C 71.01, H 6.59; found: C 70.71, H 6.54.

3,5-Dibenzoyloxy-4-(2-[1,3]dioxan-2-yl-6-methoxymethoxy-benzoyl)-benzoic acid *tert*-butyl ester (26): Alcohol **2** (1.5 g) was taken up in dry CH_2Cl_2 (50 mL). MnO_2 (1.5 g) was added to it in one portion, and the reaction mixture was stirred for 6 h at room temperature. The solid was filtered through Celite, and the filtrate was concentrated. The residue was chromatographed over silica gel to furnish the oxidized product **26** (1.4 g) as a sticky solid. Yield = 93.6%; R_f = 0.4 (ethyl acetate in hexane, 45%); 1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.50 (d, J = 9.0 Hz, 1H; ArH), 7.39 (t, J = 8.1 Hz, 1H; ArH), 7.30–7.15 (m, 12H; ArH), 7.00 (d, J = 9.0 Hz, 1H; ArH), 5.64 (s, 1H), 5.06 (s, 4H), 4.70 (s, 2H), 4.16–4.11 (m, 2H), 3.80 (t, J = 9.0 Hz, 2H), 2.94 (s, 3H; OCH_3), 2.21–2.17 (m, 1H), 1.58 (s, 9H; $OC(CH_3)_3$), 1.33 ppm (d, J = 14 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): δ = 165.1, 157.5, 154.2, 139.2, 136.7, 133.8, 131.2, 128.8, 128.1, 128.5, 121.3, 115.6, 106.7, 99.9, 94.6, 83.1, 70.8, 67.7, 56.4, 28.5 ppm; IR (neat): $\tilde{\nu}$ = 3954, 3906, 3754, 3428, 2820, 2370, 1595, 1351, 1111 cm^{-1} ; MS (ESI): m/z (%): 663.2 (25) $[M+Na]^+$, 641.1 (100) $[M+H]^+$; elemental analysis (%) calcd for $C_{38}H_{40}O_9$: C 71.23, H 6.29; found: C 71.03, H 6.12.

3,5-Dibenzoyloxy-4-(2-formyl-6-methoxymethoxybenzoyl)-benzoic acid tert-butyl ester (27): Compound **26** (1.2 g, 1.87 mmol) was taken up in acetone/water (25 mL, 9:1 v/v). A catalytic amount of PTSA was added to it, and the reaction mixture was heated at reflux for 30 min. The solvent was evaporated and the residue was diluted with ethyl acetate. The organic layer was washed with water, followed by brine, and dried over anhydrous Na_2SO_4 . Chromatography over silica gel furnished **27** (900 mg) as a white solid. Yield=86%; R_f =0.5 (ethyl acetate in hexane, 45%); m.p.: 65°C. ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ =9.90 (s, 1H; CHO), 7.56–7.10 (m, 15H; ArH), 5.08 (s, 4H), 4.79 (s, 2H), 3.01 (s, 3H; OCH_3), 1.60 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); IR (neat): $\tilde{\nu}$ =3954, 3854, 3777, 3408, 2966, 2368, 1595, 1351, 1161, 1104 cm^{-1} ; MS (ESI): m/z (%): 605.1 (100) $[\text{M}+\text{Na}]^+$, 582.9 (40) $[\text{M}+\text{H}]^+$; elemental analysis (%) calcd for $\text{C}_{35}\text{H}_{34}\text{O}_8$: C 72.15, H 5.88; found: C 71.65, H 5.38.

3,5-Dibenzoyloxy-4-(2-carboxy-6-methoxymethoxybenzoyl)-benzoic acid tert-butyl ester (4): A solution of aldehyde **27** (700 mg, 1.2 mmol) and NaH_2PO_4 (50 mg, 0.42 mmol) in acetonitrile/water (16 mL, 6:1 v/v) was cooled to 0°C. H_2O_2 (0.3 mL, 30% solution in water) was added, followed by sodium chlorite (0.44 g). The mixture was stirred for 1 h and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, and the organic layer was washed with water, followed by brine, and dried over Na_2SO_4 . Chromatography over silica gel furnished acid **4** (650 mg, 86%) as a sticky solid. R_f =0.4 (methanol in chloroform, 5%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ =8.31 (s, 1H; ArH), 7.44–7.09 (m, 15H; ArH), 5.07 (dd, J_1 =6.7, J_2 =35 Hz, 2H), 4.95 (s, 4H), 3.22 (s, 3H; OCH_3), 1.59 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , 25°C, TMS): δ =163.2, 157.1, 134.8, 133.6, 129.6, 127.7, 127.1, 127, 126.8, 126.6, 126.2, 126.1, 117.7, 116.6, 105.4, 103.6, 93.1, 92.6, 80.7, 69.5, 54.6, 26.8, 24.1, 21.7, 12.7 ppm; IR (neat): $\tilde{\nu}$ =3906, 3858, 3806, 3755, 3652, 3425, 2976, 2368, 1675, 1593, 1354, 111.9 cm^{-1} ; MS (FAB): m/z (%): 621.1 (100) $[\text{M}+\text{Na}]^+$, 598.9 (70) $[\text{M}+\text{H}]^+$, 542.9 (40) $[\text{M}-t\text{Bu}]^+$; elemental analysis (%) calcd for $\text{C}_{35}\text{H}_{34}\text{O}_9$: C 70.22, H 5.72; found: C 70.02, H 5.51.

Benzyl ester 28: Solid K_2CO_3 (580 mg, 4.2 mmol) was added to a solution of compound **4** (500 mg, 0.84 mmol) in dry acetone (15 mL), followed by benzyl bromide (157 mg, 0.9 mmol). The reaction mixture was heated at reflux at 70°C for 1 h, the solid was filtered off, and the filtrate was concentrated in vacuo. Chromatography over silica gel furnished compound **28** (540 mg, 94%) as a sticky solid. R_f =0.6 (ethyl acetate in hexane, 25%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ =7.39–7.11 (m, 20H; ArH), 5.16 (s, 2H), 4.96 (s, 4H), 4.80 (s, 2H), 3.15 (s, 3H; OCH_3), 1.61 ppm (s, 9H; $\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , 25°C, TMS): δ =189.9, 165.4, 163.5, 157.10, 153.3, 134.9, 134.6, 133.8, 132.7, 130.3, 128.6, 126.9, 126.6, 126.4, 126.0, 121.8, 117.1, 105.7, 93.3, 80.4, 69.6, 65.6, 54.5, 30.6, 28.4, 28.0, 26.8, 21.4, 12.7 ppm; IR (neat): $\tilde{\nu}$ =3956, 3906, 3757, 3425, 2816, 2371, 1595, 1351 cm^{-1} ; MS (FAB): m/z (%): 711.2 (100) $[\text{M}+\text{Na}]^+$, 688.9 (89) $[\text{M}+\text{H}]^+$, 632.9 (20) $[\text{M}-t\text{Bu}]^+$; elemental analysis (%) calcd for $\text{C}_{42}\text{H}_{40}\text{O}_9$: C 73.24, H 5.85; found: C 73.06, H 5.62.

Acid 5: A solution of compound **28** (500 mg) in dry quinoline (5 mL) was heated at 195°C under nitrogen for 1 h. The reaction mixture was diluted with ether. The organic layer was washed with HCl (2N), followed by brine, and dried over anhydrous Na_2SO_4 . Chromatography over silica gel furnished acid **2** (250 mg, 54%) as a sticky brown solid. R_f =0.3 (5% methanol in chloroform); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): δ =12.05 (s, 1H; CO_2H), 7.39–7.08 (m, 20H; ArH), 5.13 (d, J =5.1 Hz, 1H), 4.95 (s, 4H), 4.78 (d, J =5.1 Hz, 1H), 4.58 (s, 2H), 3.60 ppm (s, 3H; OCH_3); MS (ESI): m/z (%): 655.1 (100) $[\text{M}+\text{Na}]^+$, 632.8 (39) $[\text{M}]^+$, 599.0 (9) $[\text{M}-\text{OCH}_3]^+$, 576.8 (10) $[\text{M}-t\text{Bu}]^+$; elemental analysis (%) calcd for $\text{C}_{38}\text{H}_{32}\text{O}_9$: C 72.14, H 5.10; found: C 72.02, H 4.98.

General Procedure for Mukaiyama esterification: Amido alcohol (1 mmol), acid **5** (1 mmol), and 2-chloro-1-methylpyridinium iodide (1.3 mmol) were taken up in dry CH_2Cl_2 (10 mL). Et_3N (1.5 mmol) was added, and the reaction mixture was stirred at room temperature. A catalytic amount of DMAP was added after 30 min, and the mixture was stirred for 1 h. The solvent was removed, and the residue was chromatographed over silica gel to furnish the coupled product.

(3R,4R)-3-(4-Benzoyloxybenzoylamino)-4-[3,5-dibenzoyloxy-4-(2-benzoyloxy-carbonyl-6-methoxymethoxybenzoyl)-benzoyloxy]-azepane-1-carboxylic acid benzyl ester (30a): Yield=82%; R_f =0.4 (ethyl acetate in

hexane, 45%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): (3:1 rotameric mixture) δ =7.64 (d, J =8.7 Hz, 2H; ArH), 7.49–6.81 (m, 30H; ArH), 6.82 (d, J =8.7 Hz, 2H; ArH), 5.31 (d, J =7.9 Hz, 1H), 5.19–4.69 (m, 12H), 3.98 (pseudo t, 1H), 3.71–3.21 (m, 3H), 3.18–3.03 (m, 2H), 3.02 (s, 3H; OCH_3), 2.23–1.64 ppm (m, 4H); IR (neat): $\tilde{\nu}$ =3864, 3447, 2922, 2358, 1638, 1461, 1380, 1256, 764, 670 cm^{-1} ; MS (ESI): m/z (%): 1091.2 (20) $[\text{M}+\text{Na}]^+$, 1089.2 (100) $[\text{M}]^+$, 1089.2 (100) $[\text{M}]^+$; elemental analysis (%) calcd for $\text{C}_{66}\text{H}_{60}\text{N}_2\text{O}_{13}$: C 72.78, H 5.55, N 2.57; found: C 72.71, H 5.52, N 2.49.

(3R,4S)-3-(4-Benzoyloxybenzoylamino)-4-[3,5-dibenzoyloxy-4-(2-benzoyloxy-carbonyl-6-methoxymethoxybenzoyl)-benzoyloxy]-azepane-1-carboxylic acid benzyl ester (30b): Yield=86%; R_f =0.4 (ethyl acetate in hexane, 45%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): (3:1 rotameric mixture)³¹ δ =8.18 (m, 1H), 7.64 (d, J =8.7 Hz, 2H; ArH), 7.46–7.07 (m, 32H; ArH), 6.82 (d, J =8.7 Hz, 2H; ArH), 5.31 (d, J =7.9 Hz, 1H), 5.20–4.76 (m, 12H), 4.18 (brs, 1H), 3.81–3.34 (m, 3H), 3.18–2.98 (m, 2H), 3.08 (s, 3H; OCH_3), 2.16–1.60 ppm (m, 4H); MS (FAB): m/z (%): 1090.2 (45) $[\text{M}+\text{H}]^+$, 1089.2 (100) $[\text{M}]^+$; elemental analysis (%) calcd for $\text{C}_{66}\text{H}_{60}\text{N}_2\text{O}_{13}$: C 72.78, H 5.55, N 2.57; found: C 72.69, H 5.48, N 2.52.

(3S,4S)-3-(4-Benzoyloxybenzoylamino)-4-[3,5-dibenzoyloxy-4-(2-benzoyloxy-carbonyl-6-methoxymethoxybenzoyl)-benzoyloxy]-azepane-1-carboxylic acid benzyl ester (30c): Yield=82%; R_f =0.41 (ethyl acetate in hexane, 45%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): (3:1 rotameric mixture) δ =7.63 (d, J =8.7 Hz, 2H; ArH), 7.58–6.92 (m, 30H; ArH), 6.85–6.77 (m, 2H; ArH), 5.31 (d, J =7.9 Hz, 1H), 5.19–4.61 (m, 12H), 4.00 (pseudo t, 1H), 3.86–3.21 (m, 3H), 3.18–3.03 (m, 2H), 3.02 (s, 3H; OCH_3), 2.34–1.64 ppm (m, 4H); MS (FAB): m/z (%): 1090.1 (70) $[\text{M}+\text{H}]^+$, 1089.2 (100) $[\text{M}]^+$; elemental analysis (%) calcd for $\text{C}_{66}\text{H}_{60}\text{N}_2\text{O}_{13}$: C 72.78, H 5.55, N 2.57; found: C 72.73, H 5.51, N 2.51.

(3S,4R)-3-(4-Benzoyloxybenzoylamino)-4-[3,5-dibenzoyloxy-4-(2-benzoyloxy-carbonyl-6-methoxymethoxybenzoyl)-benzoyloxy]-azepane-1-carboxylic acid benzyl ester (30d): Yield=84%; R_f =0.4 (ethyl acetate in hexane, 45%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): (3:2 rotameric mixture) δ =7.64 (d, J =8.7 Hz, 2H; ArH), 7.39–6.07 (m, 30H; ArH), 6.89 (brs, 2H; ArH), 5.38 (d, J =7.9 Hz, 1H), 5.16–4.74 (m, 12H), 4.02 (pseudo t, 1H), 3.81–3.41 (m, 3H), 3.21–3.03 (m, 2H), 3.02 (s, 3H; OCH_3), 2.15–1.63 ppm (m, 4H; 5.6-H); MS (FAB): m/z (%): 1090.2 (65) $[\text{M}+\text{H}]^+$, 1089.2 (100) $[\text{M}]^+$; elemental analysis (%) calcd for $\text{C}_{66}\text{H}_{60}\text{N}_2\text{O}_{13}$: C 72.78, H 5.55, N 2.57; found: C 72.74, H 5.49, N 2.47.

(3R,4R) derivative (31a): Yield=83%; R_f =0.30 (ethyl acetate in hexane, 40%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): (mix of rotamers 3:2) δ =7.83 (d, J =8.8 Hz, 2H; ArH), 7.69 (d, J =8.8 Hz, 2H; ArH), 7.46–7.04 (m, 27H; ArH), 6.91 (d, J =8.8 Hz, 2H; ArH), 5.32 (d, J =8.3 Hz, 1H), 5.10 (s, 2H; CH_2OCH_3), 4.99 (s, 2H; CH_2Ph), 4.96 (s, 2H; CH_2Ph), 4.81–4.80 (m, 1H), 4.76 (s, 2H; OCH_2Ph), 3.98–3.91 (m, 1H), 3.73 (dd, J_1 =3.99 Hz, J_2 =14.7 Hz, 1H), 3.15 (dd, J_1 =3.3 Hz, J_2 =14.7 Hz, 1H), 3.05 (s, 3H; CH_2OCH_3), 2.97–2.91 (m, 1H), 2.43 (s, 3H; CH_3), 2.32–2.29 (m, 1H), 2.22–2.04 (m, 2H), 1.98–1.83 ppm (m, 2H); IR (neat): $\tilde{\nu}$ =3931.0, 3906.0, 3857.8, 3756.1, 3425.7, 2371.3, 1597.3, 1350.2, 1158.0, 1110.3, 1016.0, 753.5, 695.8 cm^{-1} ; MS (ESI): m/z (%): 1090.2 (60) $[\text{M}+\text{H}]^+$, 1089.2 (100) $[\text{M}]^+$; elemental analysis (%) calcd for $\text{C}_{65}\text{H}_{60}\text{N}_2\text{O}_{13}$: C 70.38, H 5.45, N 2.53; found: C 70.32, H 5.39, N 2.48.

(3R,4S) derivative 31b: Yield=89%; R_f =0.32 (ethyl acetate in hexane, 40%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): (mix of rotamers) δ =7.81 (d, J =8.8 Hz, 2H; ArH), 7.67 (d, J =8.25 Hz, 2H; ArH), 7.38–7.02 (m, 27H; ArH), 6.89 (d, J =8.8 Hz, 2H; ArH), 5.29 (brs, 1H), 5.08 (s, 2H; CH_2OCH_3), 4.97 (s, 2H; CH_2Ph), 4.90 (s, 2H; CH_2Ph), 4.81–4.78 (m, 1H), 4.74 (s, 2H; OCH_2Ph), 3.97–3.90 (m, 1H), 3.71 (dd, J_1 =4.18 Hz, J_2 =14.6 Hz, 1H), 3.14 (dd, J_1 =3.14 Hz, J_2 =14.7 Hz, 1H), 3.06 (s, 3H; CH_2OCH_3), 2.97–2.90 (m, 1H), 2.43 (s, 3H; CH_3), 2.34–2.25 (m, 1H), 2.22–2.09 (m, 2H), 1.98–1.87 ppm (m, 2H); IR (neat): $\tilde{\nu}$ =3931.0, 3906.0, 3857.8, 3756.1, 3425.7, 2371.3, 1597.3, 1350.2, 1158.0, 1110.3, 1016.0, 753.5, 695.8 cm^{-1} ; MS (ESI): m/z (%): 1090.2 (60) $[\text{M}+\text{H}]^+$, 1089.2 (100) $[\text{M}]^+$; elemental analysis (%) calcd for $\text{C}_{65}\text{H}_{60}\text{N}_2\text{O}_{13}$: C 70.38, H 5.45, N 2.53; found: C 70.31, H 5.41, N 2.45.

(3S,4S) derivative 31c: Yield=93%; R_f =0.31 (ethyl acetate in hexane, 40%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): (mix of rotamers) δ =7.81 (d, J =8.8 Hz, 2H; ArH), 7.66 (d, J =8.25 Hz, 2H; ArH), 7.38–7.02

(m, 27H; ArH), 6.89 (d, $J=8.8$ Hz, 2H; ArH), 5.31 (brs, 1H), 5.10 (s, 2H; CH_2OCH_3), 4.98 (s, 2H; CH_2Ph), 4.90 (s, 2H; CH_2Ph), 4.81–4.78 (m, 1H), 4.76 (s, 2H; OCH_2Ph), 3.98–3.89 (m, 1H), 3.72 (dd, $J_1=4.17$ Hz, $J_2=14.8$ Hz, 1H), 3.14 (dd, $J_1=3.36$ Hz, $J_2=14.5$ Hz, 1H), 3.06 (s, 3H; CH_3OCH_3), 2.97–2.90 (m, 1H), 2.43 (s, 3H; CH_3), 2.34–2.25 (m, 1H), 2.22–2.09 (m, 2H), 1.98–1.87 ppm (m, 2H); IR (neat): $\tilde{\nu}=3931.0$, 3906.0, 3857.8, 3756.1, 3425.7, 2371.3, 1597.3, 1350.2, 1158.0, 1110.3, 1016.0, 753.5, 695.8 cm^{-1} ; MS (ESI): m/z (%): 1109.0 (100) $[\text{M}+\text{Na}]^+$; elemental analysis (%) calcd for $\text{C}_{65}\text{H}_{60}\text{N}_2\text{O}_{13}\text{S}$: C 70.38, H 5.45, N 2.53; found: C 70.30, H 5.31, N 2.51.

(3S,4R) derivative 31d: Yield=87%; $R_f=0.31$ (ethyl acetate in hexane, 40%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): (mix of rotamers 3:2) $\delta=7.83$ (d, $J=8.8$ Hz, 2H; ArH), 7.69 (d, $J=8.8$ Hz, 2H; ArH), 7.40–7.09 (m, 27H; ArH), 6.92 (d, $J=8.8$ Hz, 2H; ArH), 5.31 (d, $J=8.3$ Hz, 1H), 5.09 (s, 2H; CH_2OCH_3), 4.98 (s, 2H; CH_2Ph), 4.91 (s, 2H; CH_2Ph), 4.81–4.80 (m, 1H), 4.76 (s, 2H; OCH_2Ph), 3.98–3.92 (m, 1H), 3.73 (dd, $J_1=3.99$ Hz, $J_2=14.7$ Hz, 1H), 3.15 (dd, $J_1=3.3$ Hz, $J_2=14.7$ Hz, 1H), 3.07 (s, 3H; CH_3OCH_3), 2.97–2.91 (m, 1H), 2.45 (s, 3H; CH_3), 2.32–2.29 (m, 1H), 2.22–2.04 (m, 2H), 1.98–1.83 ppm (m, 2H); IR (neat): $\tilde{\nu}=3931.0$, 3906.0, 3857.8, 3756.1, 3425.7, 2371.3, 1597.3, 1350.2, 1158.0, 1110.3, 1016.0, 753.5, 695.8 cm^{-1} ; MS (ESI): m/z (%): 1090.2 (60) $[\text{M}+\text{H}]^+$, 1089.2 (100) $[\text{M}]^+$; elemental analysis (%) calcd for $\text{C}_{65}\text{H}_{60}\text{N}_2\text{O}_{13}\text{S}$: C 70.38, H 5.45, N 2.53; found: C 70.29, H 5.35, N 2.46.

General procedure for deprotection: A catalytic amount of HCl was added to a solution of a fully protected balanol derivative in methanol. The reaction mixture was heated to 50°C and stirred at same temperature for 3 h. The solvent was evaporated, and the residue was debenzylated by Nicolaou's procedure^[39] to afford the balanol derivative.

(3R,4R)-Balanol (1a): $[\alpha]_{\text{D}}^{25}=-107$ ($c=0.252$ in methanol); ^1H NMR (300 MHz, CD_3OD , 25°C, TMS): $\delta=7.60$ (d, $J=8.7$ Hz, 2H; ArH), 7.25 (d, $J=7.8$ Hz, 1H; ArH), 7.17 (t, $J=7.8$ Hz, 1H; ArH), 6.92 (s, 2H; ArH), 6.80 (d, $J=7.8$ Hz, 1H; ArH), 6.76 (d, $J=8.7$ Hz, 2H; ArH), 5.29 (m, 1H; 4-H), 4.32 (brm, 1H; 3-H), 3.42–2.98 (brm, 4H; 2,7-H), 1.84–2.12 ppm (brm, 4H; 5,6-H); MS (ESI): m/z (%): 551.6 (100) $[\text{M}+\text{H}]^+$; elemental analysis (%) calcd for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_{10}$: C 61.09, H 4.76, N 5.09; found: C 60.99, H 4.72, N 5.01.

(3R,4S)-Balanol (1b): $[\alpha]_{\text{D}}^{25}=-64$ ($c=0.252$ in methanol); ^1H NMR (300 MHz, CD_3OD , 25°C, TMS): $\delta=7.60$ (d, $J=8.7$ Hz, 2H; ArH), 7.25 (d, $J=7.8$ Hz, 1H; ArH), 7.17 (t, $J=7.8$ Hz, 1H; ArH), 6.92 (s, 2H), 6.80 (d, $J=7.8$ Hz, 1H; ArH), 6.76 (d, $J=8.7$ Hz, 2H; ArH), 5.30 (m, 1H; 4-H), 4.45 (brm, 1H; 3-H), 3.32–2.97 (brm, 4H; 2,7-H), 2.12–1.78 ppm (brm, 4H; 5,6-H); MS (ESI): m/z (%): 551.2 (100) $[\text{M}+\text{H}]^+$; elemental analysis (%) calcd for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_{10}$: C 61.09, H 4.76, N 5.09; found: C 60.89, H 4.69, N 5.03.

(3S,4S)-Balanol (1c): $[\alpha]_{\text{D}}^{25}=+97.8$ ($c=0.331$ in methanol); ^1H NMR (300 MHz, CD_3OD , 25°C, TMS): $\delta=7.60$ (d, $J=8.7$ Hz, 2H; ArH), 7.25 (d, $J=7.8$ Hz, 1H; ArH), 7.17 (t, $J=7.8$ Hz, 1H; ArH), 6.92 (s, 2H), 6.80 (d, $J=7.8$ Hz, 1H; ArH), 6.76 (d, $J=8.7$ Hz, 2H; ArH), 5.19 (m, 1H; 4-H), 4.35 (brm, 1H; 3-H), 3.47–3.03 (brm, 4H; 2,7-H), 2.12–1.74 (brm, 4H; 5,6-H); MS (ESI): m/z (%): 551.5 (100) $[\text{M}+\text{H}]^+$; elemental analysis (%) calcd for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_{10}$: C 61.09, H 4.76, N 5.09; found: C 60.91, H 4.67, N 5.00.

(3S,4R)-Balanol (1d): $[\alpha]_{\text{D}}^{25}=+54$ ($c=0.321$ in methanol); ^1H NMR (300 MHz, CD_3OD , 25°C, TMS): $\delta=7.60$ (d, $J=8.7$ Hz, 2H; ArH), 7.25 (d, $J=7.8$ Hz, 1H; ArH), 7.17 (t, $J=7.8$ Hz, 1H; ArH), 6.92 (s, 2H), 6.80 (d, $J=7.8$ Hz, 1H; ArH), 6.76 (d, $J=8.7$ Hz, 2H; ArH), 5.51 (m, 1H; 4-H), 4.51 (brm, 1H; 3-H), 3.32–3.07 (brm, 4H; 2,7-H), 2.12–1.78 ppm (brm, 4H; 5,6-H); MS (ESI): m/z (%): 551.6 (100) $[\text{M}+\text{H}]^+$; elemental analysis (%) calcd for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_{10}$: C 61.09, H 4.76, N 5.09; found: C 60.94, H 4.70, N 4.91.

N-Tosyl-(R,R)-balanol (2a): Yield=89%; $R_f=0.3$ (MeOH in CHCl_3 , 60%); $[\alpha]_{\text{D}}^{25}=-48.3$ ($c=0.121$ in methanol); ^1H NMR (300 MHz, CD_3OD , 25°C, TMS): $\delta=7.76$ (t, $J=7.9$ Hz, 3H; ArH), 7.66 (d, $J=8.6$ Hz, 1H; ArH), 7.43 (t, $J=7.32$ Hz, 2H; ArH), 7.22 (t, $J=8.5$ Hz, 2H; ArH), 6.94 (d, $J=7.8$ Hz, 1H; ArH), 6.93 (s, 2H; ArH), 6.80 (d, $J=8.7$ Hz, 2H; ArH), 5.38 (d, $J=9.3$ Hz, 1H; 4-H), 4.51 (brm, 1H; 3-H), 3.56 (brs, 2H; 2,7-H), 3.42 (brs, 2H; 2,7-H), 2.44 (s, 3H; CH_3), 2.37–2.21 (brm, 2H; 5,6-H), 1.93–1.87 ppm (brm, 2H; 5,6-H); IR (neat): $\tilde{\nu}=$

3827.8, 3751.1, 3421.7, 2371.3, 1697.3, 1351.2, 1058.0, 1016.0, 753.5, 695.8 cm^{-1} ; MS (ESI): m/z (%): 727.2 (100) $[\text{M}+\text{Na}]^+$; elemental analysis (%) calcd for $\text{C}_{35}\text{H}_{32}\text{N}_2\text{O}_{12}\text{S}$: C 59.65, H 4.58, N 3.98; found: C 59.59, H 4.51, N 3.78.

(3R,4R)-3-tert-Butoxycarbonylamino-4-hydroxy-azepane-1-carboxylic acid benzyl ester (32): Compound **21a** (70 mg, 0.172 mmol) was taken up in dry CH_2Cl_2 (10 mL), trimethylsilyl bromide (0.034 mL, 0.258 mmol) was added at 0°C, and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed, and the residue was dissolved in diethyl ether. The organic layer was washed with aqueous NaHCO_3 , followed by brine, and the organic layer was dried on anhydrous Na_2SO_4 and evaporated in vacuo. The residue was passed through a small silica pad and was used for the next step without further purification. Crude yield: 75%; $R_f=0.4$ (ethyl acetate in hexane, 35%), Crude MS (ESI): m/z (%): 387.2 (100) $[\text{M}+\text{Na}]^+$; elemental analysis (%) calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_5$: C 62.62, H 7.74, N 7.69; found: C 62.58, H 7.67, N 7.59.

(3R,4R)-4-(4-Benzyloxybenzoyloxy)-3-tert-butoxycarbonylamino-azepane-1-carboxylic acid benzyl ester (33): Compound **32** (50 mg, 0.137 mmol), *p*-benzyloxy-benzoic acid (36.2 mg, 0.164 mmol), and 2-chloro-1-methylpyridinium iodide (52.5 mg, 0.206 mmol) were taken up in dry CH_2Cl_2 (5 mL). Triethylamine (0.04 mL, 0.274 mmol) was added, and the reaction mixture was stirred for one hour. After completion of the reaction, solvent was evaporated, and the residue was chromatographed to furnish the pure product **33** as a sticky solid. Yield=75 mg (95%); $R_f=0.6$ (ethyl acetate in hexane, 40%); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta=7.97$ (d, $J=8.7$ Hz, 2H; ArH), 7.93–7.31 (m, 10H; ArH), 6.97 (d, $J=8.7$ Hz, 2H; ArH), 5.28–5.08 (m, 4H), 4.16 (brs, 1H), 3.68–3.50 (brm, 4H), 2.18 (brs, 1H), 1.98–1.61 (brm, 4H), 1.40 ppm (s, 9H; $-\text{OC}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , 25°C, TMS): $\delta=164.3$, 153.7, 138.5, 130.4, 127.4, 127.2, 126.9, 126.6, 126.4, 126.1, 113.3, 78.4, 68.8, 66.3, 66.1, 45.8, 28.4, 27.0 ppm; IR (neat): $\tilde{\nu}=3766$, 3452, 3221, 1736, 1692, 1112, 760 cm^{-1} ; MS (ESI): m/z (%): 597.1 (100) $[\text{M}+\text{Na}]^+$, 575.2 (75) $[\text{M}+\text{H}]^+$, 418 (60) $[\text{M}-t\text{Bu}]^+$, 475.2 (45) $[\text{M}-t\text{Boc}]^+$; elemental analysis (%) calcd for $\text{C}_{33}\text{H}_{38}\text{N}_2\text{O}_7$: C 68.97, H 6.67, N 4.87; found: C 68.91, H 6.59, N 4.74.

Fully protected ophiocordin (35): Compound **33** (25 mg, 0.05 mmol) was taken up in dry CH_2Cl_2 . TFA in CH_2Cl_2 (5%) was added, and the reaction mixture was stirred at room temperature for 2 h. After consumption of all of the starting material, solvent was evaporated. Co-evaporation was performed twice with CH_2Cl_2 to remove the excess TFA. The residue was dried and again dissolved in CH_2Cl_2 . Acid **4** (30 mg, 0.05 mmol) and 2-chloro-1-methylpyridinium iodide (27 mg, 0.105 mmol) were added, followed by tri-*n*-butylamine (0.035 mL, 0.150 mmol), and the reaction mixture was stirred at room temperature. A catalytic amount of DMAP was added after 30 min, and the system was stirred for 1 h. The solvent was removed, and the residue was chromatographed over silica gel to furnish the coupled product **35** (7 mg, 35%). Some starting material **34** was recovered (15 mg). (3:1.5 rotameric mixture); ^1H NMR (600 MHz, CDCl_3 , 25°C, TMS): $\delta=8.02$ (d, $J=12$ Hz, 2H; ArH), 7.49–7.00 (m, 43H; ArH), 5.16–4.92 (m, 10H), 4.22 (brs, 2H), 3.78–3.6 (m, 4H), 3.31 (s, 3H), 3.29 (s, 3H), 2.43–2.31 (m, 1H), 2.21–1.8 (m, 4H), 1.55 ppm (s, 9H); MS (ESI): m/z (%): 1077.2 (10) $[\text{M}+\text{Na}]^+$, 1055.1 (100) $[\text{M}+\text{H}]^+$, 999.1 (15) $[\text{M}-t\text{Bu}]^+$; elemental analysis (%) calcd for $\text{C}_{63}\text{H}_{62}\text{N}_2\text{O}_{13}$: C 71.71, H 5.92, N 2.65; found: C 71.65, H 5.87, N 2.60.

Acknowledgements

This research project was supported by the Department of Science and Technology (SR/S1/OC-23/2005) New Delhi, India. A.K.S. thanks the CSIR for providing a fellowship (NET-SRF). The authors thank Mr. Sandip Kumar Chakraborty and Sanjit Kumar Das for the preparation of starting materials used in this synthesis. This is CDRI communication number 7473.

- [1] H. Toda, W.-G. Ding, Y. Yasuda, F. Toyoda, M. Ito, H. Matsuura, M. Horie, *Br. J. Pharmacol.* **2007**, *150*, 1011.
- [2] Y. A. Mahmoud, *Br. J. Pharmacol.* **2007**, *150*, 200.
- [3] Y. Nishizuka, *Science* **1986**, *233*, 305.
- [4] Y. Nishizuka, *Nature* **1984**, *308*, 693.
- [5] A. Farago, Y. Nishizuka, *FEBS Lett.* **1990**, *268*, 350.
- [6] A. C. Newton, *Annu. Rev. Biophys. Biomol. Struct.* **1993**, *22*, 1.
- [7] S. Stabel, P. J. Parker, *Pharmacol. Ther.* **1991**, *51*, 71.
- [8] D. Bradshaw, C. H. Hill, J. S. Nixon, S. E. Wilkinson, *Agents Actions* **1993**, *38*, 135.
- [9] T. R. Tritton, J. A. Hickman *Cancer Cells* **1990**, *2*, 95.
- [10] P. Cohen, *Nat. Rev. Drug Discovery* **2002**, *1*, 309.
- [11] P. Kulanthaivel, Y. F. Hallock, C. Boros, S. M. Hamilton, W. P. Janzen, L. M. Ballas, C. R. Loomis, J. B. Jiang, B. Katz, J. R. Steiner, J. Clardy, *J. Am. Chem. Soc.* **1993**, *115*, 6452.
- [12] S. Y. Ohshima, M. Katoh, A. Fujii, T. Sano, T. Matsukuma, S. Furumai, T. Fujiu, M. Watanabe, K. Yokose, K. Arisawa, M. Okuda, *J. Antibiot.* **1994**, *47*, 639.
- [13] C. Boros, S. M. Hamilton, B. Katz, P. Kulanthaivel, *J. Antibiot.* **1994**, *47*, 1010.
- [14] H. Kneifel, W. A. König, W. Loeffler, R. Mhller, *Arch. Microbiol.* **1977**, *113*, 121.
- [15] W. A. König, S. Wolker, S. Witt, H. Kneifel, *Microorg.* **1979**, *195*, 2221.
- [16] P. Akamine, Madhusudan, L. L. Brunton, H. D. Ou, J. M. Canaves, N. H. Xuong, S. S. Taylor, *Biochemistry* **2004**, *43*, 85.
- [17] H. M. Crane, D. S. Menaldino, G. E. Jagdmann, J. W. Darges, J. A. Buben, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2133.
- [18] J. M. Defauw, M. M. Murphy, G. E. Jagdmann, H. Hu, J. W. Lampe, S. P. Hollinshead, T. J. Mitchell, H. M. Crane, J. M. Heerding, J. S. Mendoza, J. E. Davis, J. W. Darges, F. R. Hubbard, S. E. Hall, *J. Med. Chem.* **1996**, *39*, 5215.
- [19] A. B. Gustafsson, L. L. Brunton, *Molecular Pharmacol.* **1999**, *56*, 377.
- [20] J. M. Heerding, J. W. Lampe, J. W. Darges, M. L. Stamper, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1839.
- [21] H. Hu, S. P. Hollinshead, S. E. Hall, K. Kalter, L. M. Ballas, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 973.
- [22] H. Hu, J. S. Mendoza, C. T. Lowden, L. M. Ballas, W. P. Janzen, *Bioorg. Med. Chem.* **1997**, *5*, 1873.
- [23] G. E. Jagdmann, J. M. Defauw, Y. S. Lai, H. M. Crane, S. E. Hall, J. A. Buben, H. Hu, P. A. Gosnell, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2015.
- [24] G. E. Jagdmann, J. M. Defauw, J. W. Lampe, J. W. Darges, K. Kalter, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1759.
- [25] K. Koide, M. E. Bunnage, L. G. Paloma, J. R. Kanter, S. S. Taylor, L. L. Brunton, K. C. Nicolaou, *Chem. Biol.* **1995**, *2*, 601.
- [26] Y. S. Lai, D. S. Menaldino, J. B. Nichols, G. E. Jagdmann, F. Mylott, J. Gillespie, S. E. Hall, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2151.
- [27] Y. S. Lai, J. S. Mendoza, F. Hubbard, K. Kalter, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2155.
- [28] Y. S. Lai, J. S. Mendoza, G. E. Jagdmann, Jr., D. S. Menaldino, C. K. Biggers, J. M. Heerding, J. W. Wilson, S. E. Hall, J. B. Jiang, W. P. Janzen, L. M. Ballas, *J. Med. Chem.* **1997**, *40*, 226.
- [29] Y. S. Lai, M. Stamper, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2147.
- [30] J. W. Lampe, C. K. Biggers, J. M. Defauw, R. J. Foglesong, S. E. Hall, J. M. Heerding, S. P. Hollinshead, H. Hu, P. F. Hughes, G. E. Jagdmann, M. G. Johnson, Y. S. Lai, C. T. Lowden, M. P. Lynch, J. S. Mendoza, M. M. Murphy, J. W. Wilson, L. M. Ballas, K. Carter, J. W. Darges, J. E. Davis, F. R. Hubbard, M. L. Stamper, *J. Med. Chem.* **2002**, *45*, 2624.
- [31] J. S. Mendoza, G. E. Jagdmann, P. A. Gosnell, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2211.
- [32] N. Narayana, T. C. Diller, K. Koide, M. E. Bunnage, K. C. Nicolaou, L. L. Brunton, N. H. Xuong, L. F. Ten Eyck, S. S. Taylor, *Biochemistry* **1999**, *38*, 2367.
- [33] J. Setyawan, K. Koide, T. C. Diller, M. E. Bunnage, S. S. Taylor, K. C. Nicolaou, L. L. Brunton, *Mol. Pharmacol.* **1999**, *56*, 370.
- [34] C. F. Wong, P. H. Hunenberger, P. Akamine, N. Narayana, T. Diller, J. A. McCammon, S. Taylor, N. H. Xuong, *J. Med. Chem.* **2001**, *44*, 1530.
- [35] C. F. Wong, J. Kua, Y. K. Zhang, T. P. Straatsma, J. A. McCammon, *Proteins Struct. Funct. Bioinf.* **2005**, *61*, 850.
- [36] J. K. Mishra, G. Panda, *J. Comb. Chem.* **2007**, *9*, 321.
- [37] J. W. Lampe, P. F. Hughes, C. K. Biggers, S. H. Smith, H. Hu, *J. Org. Chem.* **1994**, *59*, 5147.
- [38] J. W. Lampe, P. F. Hughes, C. K. Biggers, S. H. Smith, H. Hu, *J. Org. Chem.* **1996**, *61*, 4572.
- [39] K. C. Nicolaou, M. E. Bunnage, K. Koide, *J. Am. Chem. Soc.* **1994**, *116*, 8402.
- [40] K. C. Nicolaou, K. Koide, M. E. Bunnage, *Chem- Eur. J.* **1995**, *1*, 454.
- [41] C. P. Adams, S. M. Fairway, C. J. Hardy, D. E. Hibbs, M. B. Hursthouse, A. D. Morley, B. W. Sharp, N. Vicker, I. Warner, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2355.
- [42] D. Tanner, A. Almario, T. Högborg, *Tetrahedron* **1995**, *51*, 6061.
- [43] D. Tanner, L. Tedenborg, A. Almario, I. Pettersson, I. Csöreg, N. M. Kelly, P. G. Andersson, T. Högborg, *Tetrahedron* **1997**, *53*, 4857.
- [44] P. Barbier, J. Stadlwieser, *Chimia* **1996**, *50*, 530.
- [45] H. Miyabe, M. Torieda, T. Kiguchi, T. Naito, *Synlett* **1997**, 580.
- [46] H. Miyabe, M. Torieda, K. Inoue, K. Tajiri, T. Kiguchi, T. Naito, *J. Org. Chem.* **1998**, *63*, 4397.
- [47] E. Albertini, A. Barco, S. Benetti, C. De Risi, G. P. Pollini, V. Zanirato, *Tetrahedron* **1997**, *53*, 17177.
- [48] G. R. Cook, P. S. Shanker, S. L. Peterson, *Org. Lett.* **1999**, *1*, 615.
- [49] M. P. Denieul, B. Laursen, R. Hazell, T. Skrydstrup, *J. Org. Chem.* **2000**, *65*, 6052.
- [50] M. P. Denieul, T. Skrydstrup, *Tetrahedron Lett.* **1999**, *40*, 4901.
- [51] A. Fürstner, O. R. Thiel, *J. Org. Chem.* **2000**, *65*, 1738.
- [52] C. Herdeis, R. M. Mohareb, R. B. Nader, F. Schwabenlander, J. Telser, *Tetrahedron: Asymmetry* **1999**, *10*, 4521.
- [53] B. Laursen, M. P. Denieul, T. Skrydstrup, *Tetrahedron* **2002**, *58*, 2231.
- [54] C. E. Masse, A. J. Morgan, J. S. Panek, *Org. Lett.* **2000**, *2*, 2571.
- [55] M. L. Patil, V. H. Deshpande, S. Ramlingam, H. B. Borate, *Tetrahedron* **2004**, *60*, 1869.
- [56] P. Phansavath, S. D. de Paule, V. Ratovelomanana-Vidal, J. P. Genêt, *Euro. J. Org. Chem.* **2000**, 3903.
- [57] S. Raghavan, C. N. Kumar, *Tetrahedron Lett.* **2006**, *47*, 1585.
- [58] D. Riber, R. Hazell, T. Skrydstrup, *J. Org. Chem.* **2000**, *65*, 5382.
- [59] J. P. Storm, C. M. Andersson, *Org. Lett.* **1999**, *1*, 1451.
- [60] M. G. Unthank, N. Hussain, V. K. Aggarwal, *Angew. Chem.* **2006**, *118*, 7224; *Angew. Chem. Int. Ed.* **2006**, *45*, 7066.
- [61] M. H. Wu, E. N. Jacobsen, *Tetrahedron Lett.* **1997**, *38*, 1693.
- [62] J. S. Yadav, C. Srinivas, *Tetrahedron Lett.* **2002**, *43*, 3837.
- [63] J. S. Yadav, C. Srinivas, *Tetrahedron* **2003**, *59*, 10325.
- [64] A. Dondoni, D. Perrone, *Org. Synth.* **2004**, *10*, 320.
- [65] R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117.
- [66] P. Garner, J. M. Park, *J. Org. Chem.* **1988**, *53*, 2979.
- [67] O. Mitsunobu, *Synthesis* **1981**, 1.
- [68] H. Takahata, Y. Banba, H. Ouchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2527.
- [69] S. P. Hollinshead, J. B. Nichols, J. W. Wilson, *J. Org. Chem.* **1994**, *59*, 6703.
- [70] T. Mukaiyama, M. Usui, E. Shimada, K. Saigo, *Chem. Lett.* **1975**, 1045.
- [71] E. Bald, K. Saigo, T. Mukaiyama, *Chem. Lett.* **1975**, 1163.

Received: December 18, 2007
Published online: April 9, 2008