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Stereoselective construction of X-azabicyclo[*m*.2.1]alkanes by [3+2]-cycloaddition of non-stabilized cyclic azomethine ylides: synthesis of enantiopure constrained amino acids and formal total synthesis of optically active epibatidine☆

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Abstract—A new and general strategy for the stereoselective construction of X-azabicyclo[*m*.2.1]alkanes has been developed by the [3+2]-cycloaddition of cyclic azomethine ylides with suitable achiral dipolarophiles. The cyclic azomethine ylides, where the whole of the ylide conjugation is in the ring, have been generated by the sequential double desilylation of the *N*-alkyl-α,α′-bis(trimethylsilyl) cyclic amines utilizing Ag(I)F as one electron oxidant. The structural rigidity of cyclic azomethine ylides has allowed preferential facial discrimination by the dipolarophile resulting into very good *exo*/*endo* selectivity. The *exo*/*endo* selectivity associated with these cycloadditions has been further exploited to access optically pure X-azabicyclo[*m*.2.1]alkanes by carrying out the cycloadditions with the Oppolzer's acryloyl dipolarophile. Application of this methodology is demonstrated by the construction of few constrained amino acids related to azabicyclic structural framework and the formal total synthesis of optically active epibatidine.

1. Introduction

The compounds displaying the X-azabicyclo[*m*.2.1]alkane framework (**1**) are endowed with a variety of biological activities as they represent an important class of ligands for the nicotinic acetylcholine receptors (nAChRs).[1] Therefore, research activities in this area have led to the registration of several nAChRs ligands of this class.[2] For illustration, 7-azabicyclo[2.2.1]heptane derivatives such as **2** and **3** were shown to have local anesthetic[3] and long acting anticholinergic bronchodilator[4] activities, respectively. Epibatidine (**4**) an important analgesic, 200–500 times more potent than morphine with the non-opioid mode of action, isolated by Daly et al.[5] in 1992 from the *Ecuadorian* tree frog *Epipedobates tricolor*, is another important member of this class of compounds (Fig. 1). Recent studies have also suggested that **4** is extremely potent naturally occurring nicotinic acetylcholine receptor known to date.[6] The 8-azabicyclo[3.2.1]octane skeleton (**1b**, *n*=2) is the basic structural feature of all the tropane class of alkaloids.[7] Cocaine (**5**) and its synthetic analogues show high binding affinity to serotonin (5HT) and nor-epinephrine transporters.[8] The profound behavioral and neuronal reinforcing properties of these alkaloids have attracted serious attention by synthetic chemists.[9] In recent years, a resurgence of interest has also surfaced in the synthesis of structural derivatives of **1b** (*n*=2) owing to the recognition of their utility in probing the study of the neurochemistry of cocaine abuse.[10] Anatoxin-a (**6**),[11] the only representative alkaloid possessing the unusual 9-azabicyclo[4.2.1]nonane skeleton (**1c**, *n*=3), is shown to have exquisite potency towards the nAChR.[12] Few other ligands such as PHT (**7**)[13] and UB-165 (**8**)[14] having the 9-azabicyclo[4.2.1]nonane ring systems

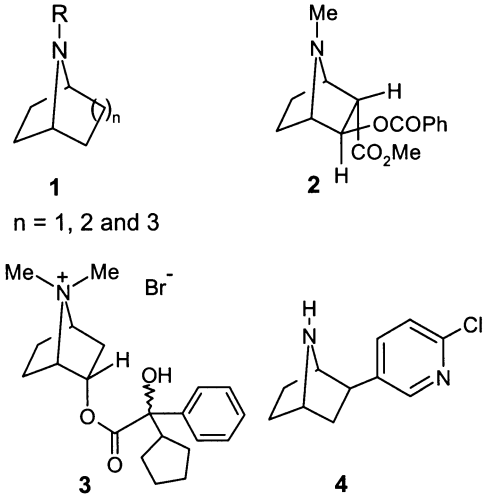

Figure 1.

☆ This report is Part 11 in this series. For part 10, see ref. 44.

Keywords: non-stabilized; azomethine ylides; constrained; enantiopure.

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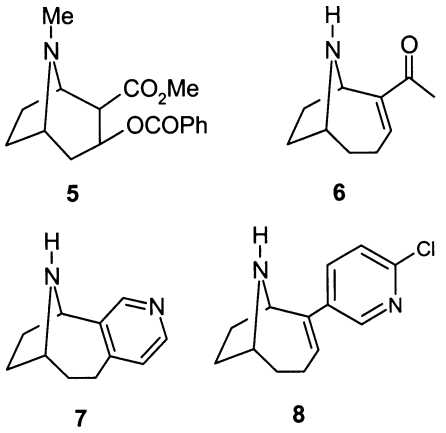
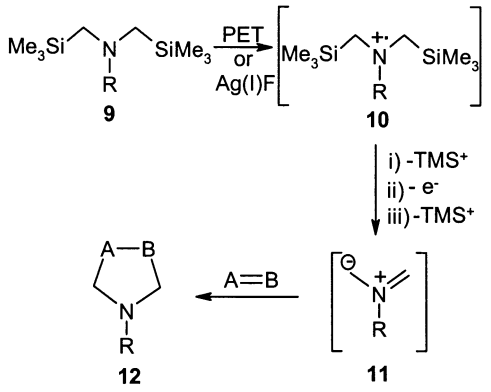


Figure 2.

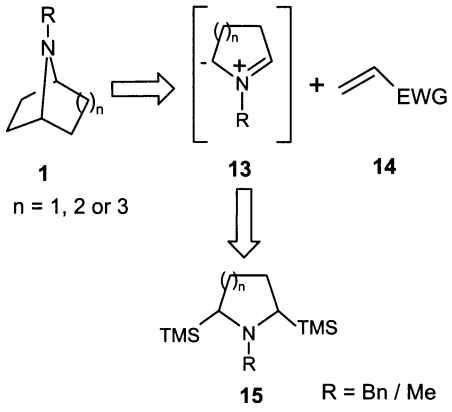
were identified as potent nicotinic ligands and have been shown to possess intermediate potency between **6** and **4** (Fig. 2).

In view of the growing importance of compounds possessing the X-azabicyclo[*m*.2.1]alkane framework as effective nAChR ligands, considerable synthetic efforts have been directed towards the development of new strategies to synthesize these classes of molecules. As a consequence, a diverse array of synthetic approaches have been devised to set-up the individual basic skeleton of the X-azabicyclo-[*m*.2.1]alkane system.[15–17] Although few general synthetic strategies have appeared in the literature[18] to build-up the basic skeleton **1**, they seem to be inappropriate to initiate a complex total synthesis. Therefore, it was imperative to envisage the development of an efficient and general approach for the construction of these structural frameworks.

A closer look at the X-azabicyclo[*m*.2.1]alkane framework (**1**) reveals the presence of a α,α′-pyrrolidine ring system fused to a cyclic amine. As the [3+2]-cycloaddition of a non-stabilized azomethine ylide provides a convenient route for synthesizing a stereo-defined pyrrolidine moiety,[19] cycloaddition of appropriate cyclic azomethine ylides with olefinic dipolarophiles was envisaged to provide an attractive and general strategy for the construction of **1**. Our group have reported[20,21] earlier a very simple strategy of generating non-stabilized azomethine ylides (AMY) by sequential



Scheme 1.



Scheme 2.

double desilylation of *N*,*N*′-bis-trimethylsilylmethyl benzylamine (**9**) initiated by one electron oxidation either by photoinduced electron transfer (PET) processes[20] or by using Ag(I)F[21] as a one-electron oxidant as shown in Scheme 1.

Based on our continuing interest in this area, we designed the following general retrosynthetic route (Scheme 2) for the construction of structural frameworks of **1** and are pleased to disclose herein the full details[22,23] of the strategy for the construction of **1** in racemic as well as in optically pure form and demonstrate the application of this strategy for the construction of enantiopure constrained amino acids and for the formal total synthesis of optically pure epibatidine.

2. Results and discussion

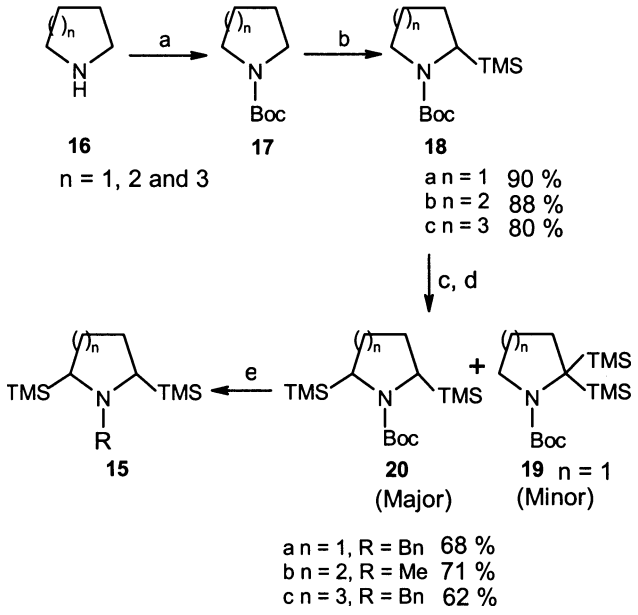
2.1. Synthesis of α,α′-bis-trimethylsilyl cyclic amines (15)

The designed precursors **15** for the generation of **13** were prepared[24] from the corresponding cyclic amines **16** by following the general reaction sequences as shown in Scheme 3.

Since generation of the non-stabilized azomethine ylides **13** involves electron transfer processes[20,21] of the amine functionality, it was necessary to transform **20a–c** into their corresponding *N*-alkyl derivatives **15** as no ylide generation could be achieved directly from **20**.

2.2. Construction of racemic X-azabicyclo[*m*.2.1]alkanes by [3+2]-cycloaddition reaction

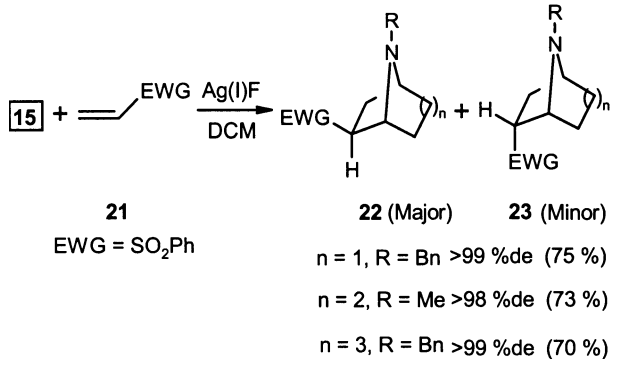
Phenyl vinyl sulfone (**21**) was chosen as a suitable dipolarophile for the cycloaddition reaction due to the ease of isolation and purification of the cycloadducts. A typical cycloaddition reaction involved slow addition of a solution of **15** in dry DCM to a stirring mixture of Ag(I)F and **21** under an argon atmosphere. The progress of the reaction was followed by the deposition of silver mirror on the wall of the reaction flask and the reaction mixture was allowed to stir for an additional 2 h. The reaction mixture was filtered through a plug of Celite and evaporation of the



Scheme 3. *Reagents and conditions*: (a) Boc-N_3, Et_3N, Dioxan, 90–95%; (b) TMEDA, *s*-BuLi, TMSCl, −78°C, 80–90%; (c) TMEDA, *s*-BuLi, TMSCl, −50 to −30°C, 1 h (*n*=1 and 2), 68–71%; −40°C, 5 h (for *n*=3), 62%; (d) TFA, DCM, quantitative; (e) $PhCH_2Cl$, K_2CO_3, CH_3CN (for *n*=1 and 3), 80–85%; HCHO, $NaBH_3CN$, CH_3CN, gl. CH_3COOH (for *n*=2), 80%.

filtrate gave crude mixture of the cycloadducts. Purification of the crude residue by silica-gel column chromatography gave cycloadducts **22** and **23** in 70–75% yield. The diastereomeric ratio of **22/23** was determined by HPLC analysis and was found to be excellent (>98% de) in each case. Pure cycloadducts **22** were obtained by careful column chromatography (Scheme 4).

These ylides where all of the ylide conjugation is in the ring, are rigid and restrict the facial attack of the dipolarophile resulting in the excellent *exo*/*endo* selectivity. The major cycloadduct **22** was fully characterized and the *endo*-relative stereochemistry of H_2 in **22** was determined by detailed ^1H NMR decoupling and ^1H COSY experiments, thereby indicating the *exo*-orientation of the phenyl sulfonyl group in all the cycloadducts. For illustration, in **22a** the proton H_2 at δ 3.18 (dd, J=9.4, 4.8 Hz) was found to couple only with the adjacent two H_{3exo} and H_{3endo}, but not with the bridgehead H_1. This observation is in line with the ^1H NMR



Scheme 4.

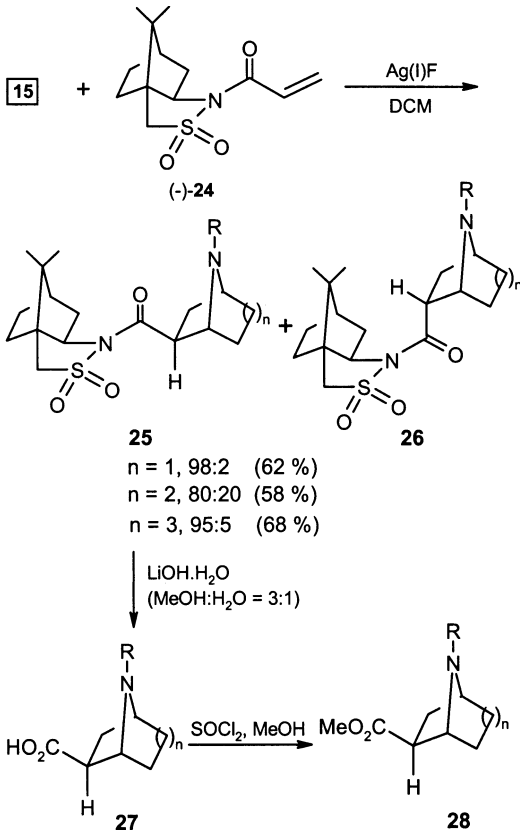
patterns of the norbornane system[25] where no coupling is observed between bridgehead and adjacent *endo* hydrogens due to a dihedral angle close to 90°.

2.3. Construction of optically pure X-azabicyclo-[*m*.2.1]alkanes

In spite of the growing interest prevailing in the synthesis of compounds possessing X-azabicyclo[*m*.2.1]alkane frameworks, there remains an absence of a general asymmetric protocol to construct the basic skeleton. Although, a few asymmetric approaches to construct the individual basic skeleton have been reported,[26–28] no effort has been made to provide a general strategy for the asymmetric construction of these structural frameworks.

Taking advantage of the high *exo*/*endo* selectivity in the cycloaddition of **15** with phenyl vinyl sulfone, we envisaged that such cycloadditions with a suitable chiral dipolarophile having excellent facial selectivity may provide a new and general synthetic methodology to access optically pure X-azabicyclo[*m*.2.1]alkanes. As Oppolzer's chiral acryloyl sultam[29] has been used widely as an efficient dipolarophile in asymmetric cycloaddition reactions, we decided to evaluate the facial selectivity of this dipolarophile in our [3+2]-cycloaddition reaction for the construction of **1** in optically pure form. The dipolarophile (−)-**24** was prepared essentially by following the reported literature[30] procedure. The cyclic AMYs **13**, generated from **15** by the reaction of Ag(I)F in dry DCM as described above, underwent smooth [3+2]-cycloaddition reaction with (−)-**24** giving rise to cycloadducts **25** and **26** in 58–68% overall yield. The diastereomeric ratio (*exo*/*endo*) of the cycloadducts was determined by comparing the integration values of the proton α to the amide functionality from each ^1H NMR spectrum. The two diastereomers were separated carefully by flash column chromatography. These cycloadducts were characterized by IR, ^1H NMR, ^{13}C NMR, mass and HRMS analyses. It should be noted that the ^1H NMR spectra of cycloadducts in $CDCl_3$ were not very helpful in establishing the relative stereochemistry of diastereomeric cycloadducts due to overlapping signals. Better resolution was obtained by adding varying amounts of C_6D_6 in $CDCl_3$. The relative stereochemistry of the H_2 proton in both the cycloadducts **25** and **26** was confirmed by a similar analogy as described earlier. It has been found that in all the major cycloadducts **25**, the H_2 proton is *endo*-oriented, a diagnostic feature for the *exo*-orientation of the amide functionality (Scheme 5).

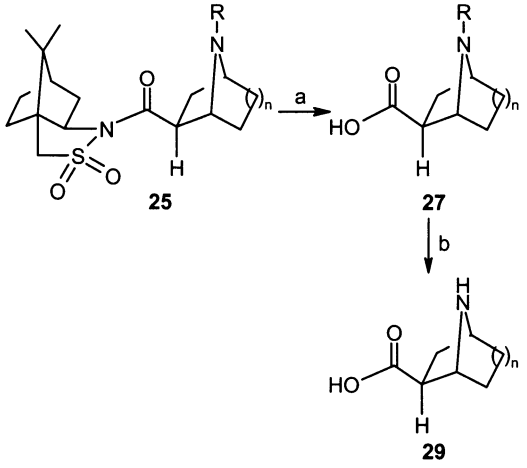
The success of our asymmetric [3+2]-cycloaddition methodology in the chiral synthesis of X-azabicyclo-[*m*.2.1]alkanes was evaluated after the hydrolytic removal of the chiral auxiliary from the major diastereomeric cycloadducts **25** and measuring the optical rotation of the corresponding methyl esters. The chiral auxiliary from cycloadducts **25** was removed by warming with $LiOH{\cdot}H_2O$ in $MeOH/H_2O$ (3:1) for 45 min and the crude acids **27**, thus obtained, were isolated as their corresponding methyl esters **28** by treating with $SOCl_2$ in dry MeOH at 0°C. The optical purity of **28** was further confirmed by chiral HPLC analysis.



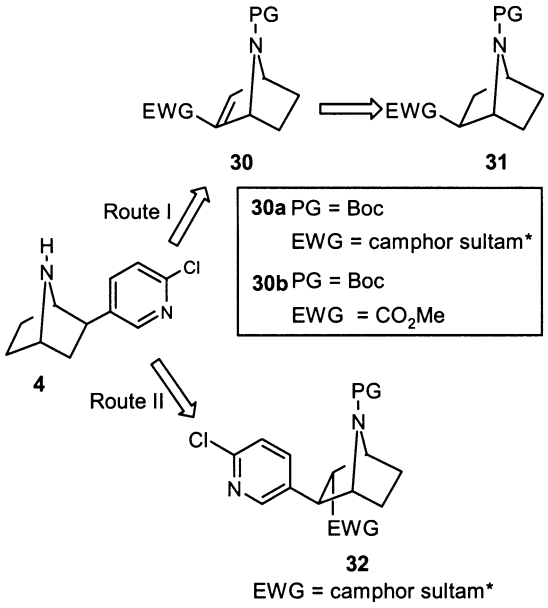
Scheme 5.

2.4. Synthesis of optically pure conformationally constrained amino acids

Constrained amino acids are introduced in to the sequences of bioactive peptides[31] to provide local constraints[32] for restricting the rotation of the N–C, C–C(O), C(O)–NH bonds and side chain conformations by covalent or non-covalent steric interactions. Such modifications are known[33] to improve significantly the physical and pharmacological properties of bioactive peptides and peptidomimetics including improvement in their affinities and



Scheme 6. *Reagents and conditions*: (a) $LiOH{\cdot}H_2O$, $MeOH/H_2O$ (3:1), 60°C, 45 min 90–95%; (b) H_2 (80 psi), Pd/C, MeOH, rt, 90–92% for n=1, 3; α-chloro ethyl chloroformate, *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalene diamine, 1,2-dichloroethane (for n=2), then MeOH, reflux, 68%.



Scheme 7.

selectivity for biological receptors/acceptors. Incorporation of conformationally constrained amino acid analogues such as X-azabicyclo[*m*.2.1]alkane amino acids, containing the pendent side chain of the parent amino acid, to the backbone of a peptide might produce an effective peptidomimetics. To date, however, only two such types of peptidomimetics have been reported.[34,35]

Considering the structural homology of this particular class of amino acids with the cycloadducts **25**, we became interested in gaining access to a few of these constrained amino acids to show the diverse synthetic applications of these cycloadducts. Thus, we approached this problem with a desire to utilize the major diastereomeric cycloadducts to generate a few potential peptidomimetic groups that could be appropriate in solid phase peptide synthesis by virtue of their rigid and chemically inert structures. The rigidity inherent in these constrained acids should significantly bind the conformation of the resultant peptide, thereby stabilizing the specific conformational motifs. Towards this goal, the major diastereomeric cycloadducts **25** were first hydrolyzed to their corresponding acids that on subsequent *N*-dealkylation gave constrained amino acids **29** as shown in Scheme 6.

Hydrolysis of the amide functionality in the cycloadducts **25** was successfully carried out with $LiOH{\cdot}H_2O$ in $MeOH/H_2O$ (3:1), as described in the previous section. N-Debenzylation of the corresponding acids **27a** and **27c** was carried out smoothly, almost in quantitative yield, by hydrogenolysis using Pd/C and H_2 (70 psi) in MeOH. *N*-Demethylation of the corresponding acid **27b** was carried out in 68% yield by refluxing with the α-chloroethyl chloroformate[36] in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalene diamine followed by refluxing with MeOH.

2.5. Formal total synthesis of optically active epibatidine

Due to intriguing structural features and important biological

activities of epibatidine (**4**), its synthesis has attracted intense research activities.[24,37] All the synthetic strategies related to the synthesis of **4** involve a key step of constructing the 7-azabicyclo[2.2.1]heptane framework starting from different precursors. Remarkably, in spite of the intense research activities associated with the synthesis of **4**, approaches concerning with its synthesis in optically pure form are limited.[26] However, all these approaches involve multi-step reaction sequences and suffer from overall poor yield.

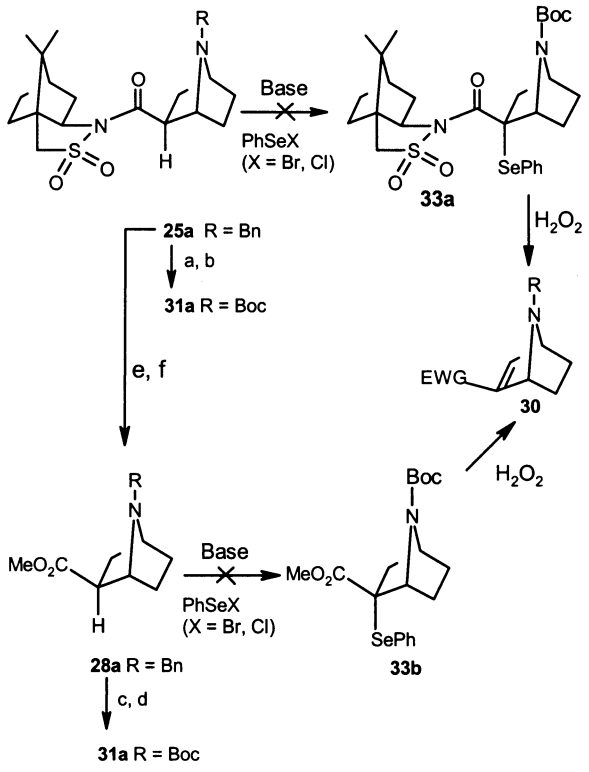
Having demonstrated the validity of our [3+2]-cycloaddition methodology for the construction of the enantiopure X-azabicyclo[*m*.2.1]alkane framework,[23] it was realized that this novel methodology could be exploited for the total synthesis of epibatidine (**4**) in optically pure form. Towards this goal, we envisaged two complementary (asymmetric approaches) retrosynthetic approaches as shown in Scheme 7.

It was envisaged that enantiopure **25a** could easily be transformed into a non-racemic 7-azabicyclo[2.2.1]hept-2-ene system **30** (EWG=CO_2Me/camphor sultam*) (Route I) on which the Michael addition of 5-(2-chloro) lithiopyridine would provide an easy access to enantiopure epibatidine. Since nucleophilic addition in the norbornene system is known[38] to give an adduct with an *exo*-orientation, it was reasonable to assume that Michael addition of 5-(2-chlorolithiopyridine) on to **30** would lead to the correct isomer of enantiopure epibatidine. Towards this end, the cycloadduct **25a** was converted to its corresponding *N*-Boc derivative **31a** following *N*-debenzylation by stirring with an equal wt. of Pd/C in HCOOH/MeOH (5:95 by volume).[39] It is interesting to mention that N-debenzylation of **25a** by catalytic hydrogenation (Pd/C, H_2 or $Pd(OH)_2$/C, H_2) was unsuccessful. Our attempt to create unsaturation in the azabicyclic ring involving **33a** via incorporating a SePh group α to the sulfonamide moiety of **25a** followed by oxidative elimination[40] failed as we could not convert **31a** to **33a** in spite of using a variety of different bases (e.g. LDA, KHMDS, etc.) to generate the anion. Alternatively, we also tried to obtain **30b** (EWG=CO_2Me) via the corresponding **33b**, but this approach also failed in spite of our best effort. Therefore, we decided to abandon this route at this stage (Scheme 8).

In order to pursue the synthesis of enantiopure epibatidine via Route II, a chiral dipolarophile (−)-**35** was first synthesized by a novel Heck-coupling reaction[41] of the 2-chloro-5-iodopyridine[42] **34** onto Oppolzer's acryloyl chiral dipolarophile **24** (Scheme 9).

A typical cycloaddition reaction of cyclic AMY **13** with the dipolarophile (−)-**35** gave two cycloadducts **36** and **37** with good *exo*/*endo* selectivity (9:1) as shown in Scheme 10.

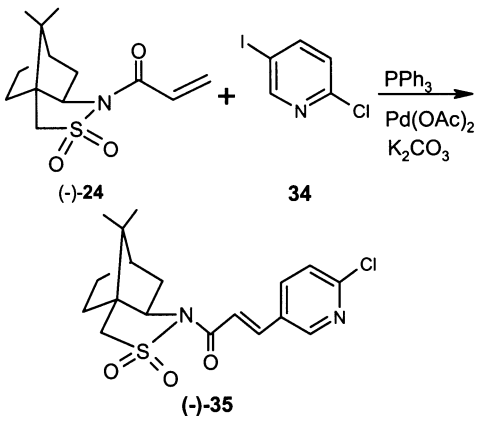
The two diastereomers were separated by careful flash column chromatography. They were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and HRMS analyses. The ratio of two diastereomeric cycloadducts was determined from their crude ^{1}H NMR spectrum by comparing the integration values of H_2 and/or H_3. The stereochemical orientation of the amide functionality and the chloropyridinyl moiety was



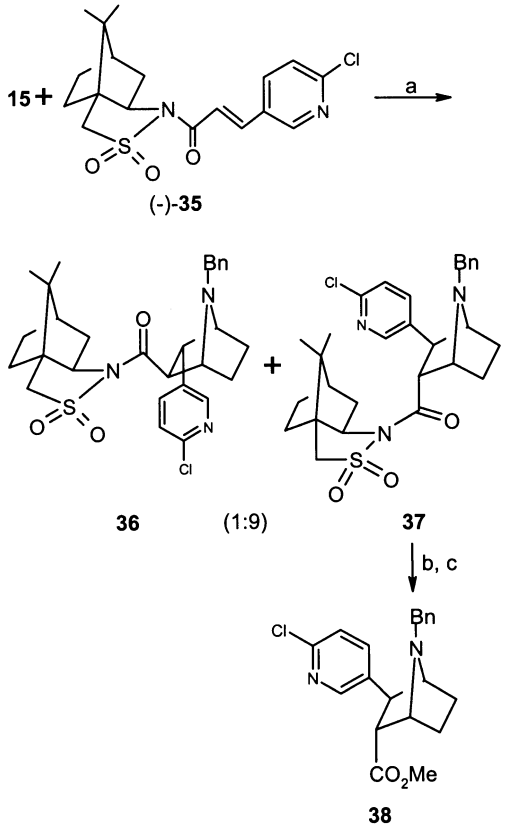
Scheme 8.

determined by decoupling experiment and ^{1}H COSY experiment.

The synthetic potential of the major cycloadduct **37** towards the enantioselective synthesis of epibatidine was visualized by removing the chiral auxiliary followed by simple chemical manipulation of the functional groups. Although, the cycloaddition of the corresponding **35** without a chiral auxiliary had given the major cycloadduct **36** in which the 2-chloropyridyl moiety was *endo*-oriented, the reversal of *exo*/*endo* ratio in this case was a pleasant surprise. However, at this stage we do not have any reasonable explanation for the formation of compound **37** as the major cycloadduct. The conversion of **38** (EWG=CO_2Et) to epibatidine has already been earlier reported[24] by us.



Scheme 9.



Scheme 10. *Reagents and conditions*: (a) Ag(I)F, DCM; (b) $LiOH{\cdot}H_2O$, THF/H_2O (3:1), 45°C, 1 h, (c) MeOH, $SOCl_2$.

3. Conclusion

In summary, we have developed a new and general methodology for the construction of X-azabicyclo[*m*.2.1]alkanes in the racemic as well as in the optically pure form by the [3+2]-cycloaddition of cyclic azomethine ylides with a suitable dipolarophile. The application of this methodology is demonstrated in the synthesis of conformationally constrained amino acids and in the formal total synthesis of enantiopure epibatidine.

4. Experimental

4.1. General

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110°C) that was dried under argon. All organic layers obtained from extractions were dried over anhydrous Na_2SO_4. Solvents for anhydrous reactions were dried according to the procedures reported in the literature.[43] All the commercial reagents were obtained from Aldrich Chemical Co. Silica gel for column chromatography was 60–120 or 230–400 mesh obtained from S.D. Fine Chemical, India or SRL, India. All melting points were uncorrected in degree Celsius and were recorded on a Thermonik melting point apparatus. IR spectra were recorded on a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^{1}H NMR spectra were recorded using TMS as internal reference on Bruker AC-200, Bruker MSL-300, DRX-500 instruments using $CDCl_3$ and/or C_6D_6 as solvent. Chemical shifts are reported in δ. ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker MSL-300 instruments operating at 50.32 and 75.3 MHz, respectively. Mass spectra were recorded on Finnigan-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV. HPLC analyses were carried out on Perkin–Elmer Model 135C equipped with Diode-array detector using either Merck Purospher RP-18e or Daicel Chiralpak OD-R column.

N-Alkyl-α,α′-bis (trimethylsilyl)-cyclic amines (**15a**–**b**) were obtained from the corresponding *N*-*tert*-butoxy-carbonyl cyclic amines (**17**) by the strategy reported by us earlier.[24] Compound **15c** was also prepared by following the identical approach. **15c**: IR (neat): 2921, 2850, 1450, 1245 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 18H), 1.58–165 (m, 2H), 1.78–1.98, (m, 6H), 2.38–2.48 (m, 2H), 3.78 (d, *J*=13.6 Hz, 1H), 3.88 (d, *J*=13.6 Hz, 1H), 7.30–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ −1.5, 27.8, 29.2, 29.6, 51.9, 58.1, 126.5, 127.7, 127.8, 129.8, 141.2. MS (*m*/*z*, relative intensity): 333 (M^+, 1), 318 (6), 260 (100), 188 (38), 91 (32), 73 (29). Anal. calcd for $C_{19}H_{35}NSi_2$: C, 68.46; H, 10.51; N, 4.20. Found: C, 68.32; H, 10.33; N, 4.11.

4.1.1. [3+2]-Cycloaddition reaction. A two neck flask, equipped with a magnetic stir bar and argon gas balloon, was charged with Ag(I)F (1.3 g, 10.25 mmol) (dried previously under vacuum at 40°C) and with a solution of dipolarophile **21** (1.03 g, 6.15 mmol) in 30 mL of dry DCM. Compound **15** (4.10 mmol) dissolved in 15 mL of dry DCM was introduced into the reaction flask drop-wise over a period of 15 min. The color of the reaction mixture gradually turned dark brown with the concomitant deposition of the silver on the surface of the reaction flask in the form of a mirror and the progress of the reaction was periodically monitored by TLC. After stirring for 6 h, the reaction mixture was filtered through a small plug of Celite and the solvent was evaporated to give a brown residue. Purification of the crude residue by silica gel (60–120) column chromatography gave **22** with 70–75% cycloaddition yield. **22a** (gummy paste): IR ($CHCl_3$): 3040, 1230, 1160 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.35–1.45 (m, 1H), 1.72–1.85 (dd, *J*=9.4, 4.3 Hz, 1H), 1.85–2.15 (m, 3H), 2.18–2.28 (m, 1H), 3.18 (dd, *J*=9.4, 4.8 Hz, 1H), 3.26–3.38 (m, 1H), 3.40 (d, *J*=13.5 Hz, 1H), 3.48 (d, *J*=13.5 Hz, 1H), 3.76 (d, *J*=4.8 Hz, 1H), 7.02–7.15 (m, 2H), 7.22–7.35 (m, 3H), 7.47–7.72 (m, 3H), 7.83–8.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 50.32 MHz): 25.8, 27.2, 33.8, 51.2, 58.8, 61.4, 68.9, 127.1, 128.4, 128.6, 129.2, 129.4, 133.5, 139.1, 139.4. MS (*m*/*z*, relative intensity): 327 (M^+, 22), 186 (100), 158 (70), 91 (68). Anal. calcd for $C_{19}H_{21}NO_2S$: C, 69.72; H, 6.42; N, 4.28; S, 9.78. Found: C, 69.56; H, 6.22; N, 4.18; S, 9.54. **22b** (gummy paste): IR (neat): 3400, 2930, 2880, 1670, 1450 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.46–1.76 (m, 3H), 1.82–2.10 (m, 4H), 2.55 (s, 3H), 2.50–2.65 (dd, *J*=12.2, 7.3 Hz, 1H), 3.32–3.40 (m, 1H), 3.62 (dd, *J*=9.7, 7.3 Hz, 1H), 3.75 (bs, 1H), 7.55–7.75 (m, 3H), 7.79–8.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 50.32 MHz): 16.9, 27.0, 28.2, 30.8, 38.4, 61.6, 62.3, 69.0, 128.5, 129.3, 133.6, 139.6. MS (*m*/*z*, relative intensity): 265 (M^+, 65), 124 (100), 97 (15), 84 (18). Anal. calcd for $C_{14}H_{19}NO_2S$: C, 63.39; H, 7.16; N,

5.28; S, 12.07. Found: C, 63.19; H, 7.09; N, 5.11; S, 12.01. **22c** (gummy paste): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.25–1.45 (m, 4H), 1.60–1.70 (m, 2H), 1.75–1.90 (m, 3H), 2.62–2.70 (m, 1H), 3.50 (t, J=5.5 Hz, 1H), 3.60 (dd, J=9.7, 4.3 Hz, 1H), 3.85 (s, 1H), 3.87 (d, J=13.5 Hz, 1H), 3.97 (d, J=13.5 Hz, 1H), 7.30 (t, J=7.2 Hz, 1H), 7.38 (t, J=7.5 Hz, 2H), 7.45 (d, J=7.2 Hz, 2H), 7.62 (t, J=7.0 Hz, 2H), 7.70 (t, J=7.5 Hz, 1H), 7.98 (d, J=9.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ 24.2, 25.2, 29.7, 35.0, 36.2, 59.4, 63.9, 64.0, 73.6, 126.8, 128.2, 128.6, 129.2, 133.4, 140.7. MS (*m*/*z*, relative intensity): 355 (M^+, 6), 298 (1), 214 (100), 186 (3), 158 (4), 91 (53), 77 (14). Anal. calcd for $C_{21}H_{25}NO_2S$: C, 70.98; H, 7.04; N, 3.94; S, 9.01. Found: C, 70.78; H, 6.98; N, 3.78; S, 8.95.

4.1.2. Asymmetric [3+2]-cycloaddition reaction. Cycloaddition of **15** with (−)-24 was carried out in a similar manner as described above. Purification of the crude residue by silica gel (60–120) column chromatography gave mixture of stereoisomers (*exo* and *endo*) in 58–68% overall yield. The two isomers were separated by careful flash column chromatography. **25a**: mp 135–137°C. IR ($CHCl_3$): 3018, 1683 cm^{-1}. ^{1}H NMR (C_6D_6, 500 MHz): δ 0.52 (s, 3H), 0.70–0.78 (m, 1H), 0.88–0.95 (m, 1H), 1.05 (s, 3H), 1.20–1.30 (m, 1H), 1.40–1.45 (m, 2H), 1.55–1.65 (m, 2H), 1.75–1.85 (m, 2H), 1.94–1.98 (m, 1H), 2.01–2.08 (m, 2H) 2.30 and 2.35 (d, J=4.0, 4.4 Hz, 1H), 2.85 (d, J=13.6 Hz, 1H), 2.92 (d, J=13.6 Hz, 1H), 3.18 (t, J=4.4 Hz, 1H), 3.55 (d, J=13.5 Hz, 1H), 3.68 (d, J=13.5 Hz, 1H), 3.80 (t, J=5.6 Hz, 1H), 4.23 (bs, 1H), 4.30 (dd, J=5.6, 3.8 Hz, 1H), 7.2 (t, J=7.3 Hz, 1H), 7.35 (t, J=7.5 Hz, 2H), 7.55 (d, J=7.6 Hz, 2H). ^{13}C NMR (C_6D_6, 125 MHz): δ 19.1, 20.1, 24.6, 25.9, 28.5, 29.5, 31.8, 38.3, 44.2, 46.9, 47.4, 47.8, 51.6, 52.1, 60.2, 63.6, 64.8, 126.5, 127.9, 128.6, 139.9, 172.5. MS (*m*/*z*, relative intensity): 428 (M^+, 17), 337 (5), 214 (9), 186 (29), 159 (86), 91 (100), 68 (9). HRMS: calculated for $C_{24}H_{32}N_2O_3S$: 428.2133, observed: 428.2134. **26a**: mp 133–135°C. IR (neat): 3019, 1683 cm^{-1}. ^{1}H NMR (C_6D_6: $CDCl_3$, 500 MHz): δ 0.42 (s, 3H), 0.92–0.99 (m, 1H), 1.02–1.08 (m, 2H), 1.23 (s, 3H), 1.32–1.48 (m, 2H), 1.55–1.70 (m, 1H), 1.85–1.95 (m, 1H, 2.05–2.35 (m, 6H), 2.95 (d, J=13.6 Hz, 1H), 3.08 (d, J=13.6 Hz, 1H), 3.32 (t, J=4.3 Hz, 1H), 3.68 (d, J=13.3 Hz, 1H), 3.72 (d, J=13.3 Hz, 1H), 3.75 (t, J=5.5 Hz, 1H), 4.08–4.15 (m, 1H), 4.35 (t, J=4.1 Hz, 1H), 7.25–7.35 (m, 3H), 7.55 (d, J=7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ 19.9, 20.8, 24.2, 26.5, 28.6, 29.6, 32.9, 38.8, 44.6, 45.8, 47.8, 48.3, 51.4, 53.2, 60.4, 63.6, 65.7, 126.8, 128.2, 128.7, 140.3, 173.7. MS (*m*/*z*, relative intensity): 428 (M^+, 15), 337 (7), 214 (9), 186 (30), 159 (86), 91 (100), 68 (9). **25b**: mp 165–167°C. IR (neat): 3018, 2927, 1689 cm^{-1}. ^{1}H NMR (C_6D_6/$CDCl_3$=1:1, 500 MHz): δ 0.70 (s, 3H), 1.05 (s, 3H), 1.12–1.28 (m, 3H), 1.40–1.80 (m, 9H), 1.92–1.95 (m, 2H), 2.30 (s, 3H), 2.78–2.85 (m, 1H), 2.95 (d, J=13.6 Hz, 1H), 3.08 (d, J=13.6 Hz, 1H) 3.17–3.20 (m, 1H), 3.37 (bs, 1H), 3.42 (dd, J=7.6, 4.3 Hz, 1H), 3.75 (t, J=5.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ 16.1, 19.4, 20.4, 26.1, 28.3, 28.4, 28.8, 29.1, 32.4, 38.1, 39.0, 44.2, 47.3, 47.8, 52.8, 61.7, 65.3, 67.3, 174.4. MS (*m*/*z*, relative intensity): 366 (M^+, 10), 152 (24), 124 (61), 97 (100), 82 (29). HRMS: calculated for $C_{19}H_{30}N_2O_3S$: 366.1977, observed: 366.1967. **26b**: mp 169–171°C. IR (neat): 3018, 2928, 1690 cm^{-1}. ^{1}H NMR (C_6D_6/$CDCl_3$=1:1, 500 MHz): δ 0.72 (s, 3H), 1.05 (s, 3H), 1.20–1.30 (m, 3H), 1.40–1.75 (m, 9H), 1.80–2.10 (m, 2H), 2.12–2.20 (m, 1H), 2.21 (m, 3H), 2.95–3.10 (m, 3H), 3.65 (t, J=5.6 Hz, 1H), 3.75 (m, 1H), 4.15 (dd, J=7.9, 5.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ 15.1, 19.8, 20.6, 26.4, 26.9, 28.4, 31.4, 32.8, 38.5, 41.1, 44.6, 46.4, 47.67, 47.9, 53.0, 61.8, 65.5, 65.7, 171.3. MS (*m*/*z*, relative intensity): 366 (M^+, 11), 152 (25), 124 (65), 97 (100), 82 (30). **25c**: mp 205–207°C. IR (neat): 3028, 1669, 1425 cm^{-1}. ^{1}H NMR (C_6D_6, 500 MHz): δ 0.52 (s, 3H), 0.68–0.75 (m, 1H), 0.82–0.90 (m, 1H), 1.08 (s, 3H), 1.17–1.25 (m, 1H), 1.37–1.45 (m, 3H), 1.62–1.70 (m, 1H), 1.78–2.18 (m, 8H), 2.33–2.43 (m, 1H), 2.48–2.57 (m, 1H), 2.87 (d, J=13.7 Hz, 1H), 2.92 (d, J=13.7 Hz, 1H), 3.22 (bs, 1H), 3.63 (d, J=13.4 Hz, 1H), 3.80 (t, J=5.5 Hz, 1H), 3.94 (d, J=13.4 Hz, 1H), 4.20 (t, J=4.1 Hz, 1H), 4.45 (dd, J=8.9, 3.6 Hz, 1H), 7.10–7.30 (m, 3H), 7.50–7.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ 19.7, 20.6, 24.6, 26.4, 29.5, 31.5, 32.6, 34.9, 36.1, 38.6, 44.3, 47.4, 47.7, 48.1, 53.0, 61.2, 62.6, 65.5, 66.7, 126.4, 127.8, 128.2, 140.9, 172.3. MS (*m*/*z*, relative intensity): 456 (M^+, 7), 242 (6), 214 (100), 186 (11), 91 (66), 81 (49), 69 (98). HRMS: calculated for $C_{26}H_{36}N_2O_3S$: 456.2446, observed: 456.2442. **26c**: mp 210–212°C. IR ($CHCl_3$): 3025, 1669, 1428 cm^{-1}. ^{1}H NMR (C_6D_6/$CDCl_3$=1:1, 500 MHz): δ 0.46 (s, 3H), 0.58–0.88 (m, 3H), 1.10 (s, 3H), 1.28–1.45 (m, 4H), 1.75–2.08 (m, 8H), 2.3–2.45, (m, 2H), 2.78 (d, J=13.5 Hz, 1H), 2.82 (d, J=13.5 Hz, 1H), 3.15–3.27 (m, 1H), 3.65 (dd, J=5.6, 4.2 Hz, 1H), 3.75 (d, J=13.6 Hz, 1H), 3.95 (d, J=13.6 Hz, 1H), 4.25–4.45 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ 19.7, 20.5, 24.4, 24.8, 26.4, 31.3, 32.2, 32.7, 34.7, 38.5, 44.6, 47.6, 47.9, 48.6, 52.9, 61.1, 62.9, 65.3, 66.4, 126.4, 127.8, 128.2, 140.9, 171.7. MS (*m*/*z*, relative intensity): 456 (M^+, 7), 242 (6), 214 (100), 186 (12), 91 (65), 81 (49), 69 (95).

4.1.3. Preparation of X-alkyl-2-*exo*-carbomethoxy-X-azabicyclo[*m*.2.1] alkanes (28). A solution of **25** (1.10 mmol) in 12 mL MeOH/H_2O (3:1) mixture containing LiOH·H_2O (4.6 mg, 1.10 mmol) was warmed to 45°C while stirring. After 45 min, mixture was cooled and the resulting solution was extracted with EtOAc (3×5 mL) to remove the sultam chiral auxiliary. The aqueous layer was acidified to pH 6–7 by careful addition of 3N HCl under an ice-cold condition. The crude acid **27**, thus obtained, by evaporating the aqueous layer was used as such without further purification for the next step. The crude acid **27** was dissolved in 15 mL of dry MeOH and was transferred to a 25 mL flask equipped with argon gas balloon. The freshly distilled $SOCl_2$ (0.7 mL, excess) was added to that solution at 0°C over a period of 15 min. The solution was allowed to stir at this temperature for 4 h and it was allowed to stir afterwards for 6 h at rt. The solution was evaporated to dryness and dry $CHCl_3$ (20 mL) was added to it. The ammonia gas was passed through this suspension until basic (pH 8). The suspension was filtered and the evaporation of the solution gave crude methyl ester **28**. Purification of the crude mixture by the column chromatography afforded optically pure methyl ester **28** in 82–85% yield. **28a**: IR ($CHCl_3$): 2954, 1731, 1215 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35–1.42 (m, 2H), 1.60 (dd, J=12.2, 9.2 Hz, 1H), 1.82–1.95 (m, 2H), 2.22–2.36 (m, 1H), 2.45 (dd, J=9.2, 4.9 Hz, 1H),

3.42 (t, J=5.9 Hz, 1H), 3.50 (d, J=13.7 Hz, 1H), 3.60 (d, J=13.7 Hz, 1H), 3.65 (bs, 1H), 3.7 (s, 3H), 7.20–7.35 (m, 5H). MS (*m/z*, relative intensity): 245 (M^+, 54), 230 (2), 216 (10), 186 (31), 158 (84), 91 (100), 65 (26). HRMS: calculated for $C_{15}H_{19}NO_2$: 245.1415, observed: 245.1411. **28b**: IR ($CHCl_3$): 2925, 2851, 1712 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35–1.6 (m, 4H), 1.75–1.95 (m, 3H), 2.25 (s, 3H), 2.45 (m, 1H), 2.85 (dd, J=9.8, 5.9 Hz, 1H), 3.17–3.27 (m, 1H), 3.55 (bs, 1H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): 16.5, 29.2, 29.8, 30.0, 39.8, 46.6, 51.5, 61.8, 65.3, 176.0. MS (*m/z*, relative intensity): 183 (M^+, 10), 168 (<1), 152 (9), 140 (28), 124 (47), 96 (95), 82 (100). HRMS: calculated for $C_{10}H_{17}NO_2$: 183.1259, observed: 183.1258. **28c**: IR ($CHCl_3$): 2927, 1731, 1225 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): 1.25–1.45 (m, 4H), 1.60–1.85 (m, 5H), 2.52–2.65 (m, 1H), 2.83 (dd, J=8.9, 3.6 Hz, 1H), 3.45–3.62, (m, 2H), 3.70 (s, 3H), 3.85 (s, 2H), 7.25–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ 24.4, 25.1, 33.1, 34.7, 36.1, 51.2, 51.7, 60.2, 64.1, 67.6, 126.6, 128.1, 128.2, 140.6, 177.2. MS (*m/z*, relative intensity): 273 (M^+, 56), 258 (1), 242 (10), 214 (100), 158 (45), 186 (21), 91 (92), 65 (19). HRMS: calculated for $C_{17}H_{23}NO_2$: 273.1728, observed: 273.1726.

4.1.4. Preparation of constrained amino acids 29a–c. The hydrolysis of **25** with $LiOH{\cdot}H_2O$ in $MeOH/H_2O$ (3:1) to obtain corresponding acids **27** is already described. N-Debenzylation of acids **27a** and **27c** was carried out by the hydrogenation over Pd/C (10%, 20 mg) in MeOH at rt for 24 h. The reaction mixture was filtered; the filtrate was evaporated to give corresponding amino acids **29a** and **29c** in almost quantitative yield (90–92%) as a white crystalline solid.

The crude acid **27b** (0.20 g, 3.82 mmol) was treated with α-chloroethyl chloroformate (0.165 g, 7.69 mmol) in the presence of proton sponge (*N,N,N′,N′*-tetramethyl-1,8-naphthalene diamine) (0.365 g, 3.82 mmol) in 1,2-dichloroethane (15 mL) and the mixture was refluxed for 6 h. Dry HCl was bubbled into the reaction mixture, resulting precipitate was filtered off and the filtrate was evaporated under reduced pressure. The resulting viscous liquid was dissolved in dry MeOH (10 mL) and was refluxed for 1 h. The mixture was washed with $CHCl_3$ (3×5 mL) and the resultant mass was basified to obtain **29b** (0.068 g) in 68% yield. **29a**: $[\alpha]_D^{25}=-5.27°$ (*c* 1.2, MeOH), mp 238–241°C. IR (nujol): 3417, 2968, 1635, 1209 cm^{-1}. ^1H NMR (D_2O) (200 MHz): 1.75–1.90 (m, 2H), 1.95–2.10 (m, 3H), 2.15–2.25 (m, 1H), 3.40 (dd, J=8.8, 4.2 Hz, 1H), 4.25–4.35 (m, 1H), 4.45 (t, J=5.6 Hz, 1H). MS (*m/z*, relative intensity): 141 (M^+, 75), 124 (56), 112 (32), 96 (95), 67 (100). Anal. calcd for $C_7H_{11}NO_2$: C, 59.57; H, 7.80; N, 9.92. Found: C, 59.32; H, 7.71; N, 9.80. **29b**: $[\alpha]_D^{25}=-04.76°$ (*c* 0.78, MeOH), mp 210–215°C. IR (Nujol): 3419, 1648 cm^{-1}. ^1H NMR (D_2O): δ 1.25–1.65 (m, 6H), 1.90–2.15 (m, 2H), 2.70 (dd, J=7.9, 4.3 Hz), 3.75–3.82 (m, 1H), 3.87 (t, J=5.2 Hz, 1H). MS (*m/z*, relative intensity): 155 (M^+, 65), 140 (25), 126 (12), 110 (27), 82 (100), 68 (17). Anal. calcd for $C_8H_{13}NO_2$: C, 61.93; H, 8.38; N, 9.03. Found: C, 61.78; H, 8.21; N, 9.01. **29c**: $[\alpha]_D^{25}=-9.18°$ (*c* 1.1, MeOH), mp 225–227°C. ^1H NMR (D_2O): δ 1.25–1.55 (m, 4H), 1.65–1.85 (m, 6H), 2.25 (dd, J=7.6, 3.9 Hz, 1H), 2.90–3.05 (m, 2H). MS (*m/z*): 169 (M^+, 65), 96 (65), 87 (100), 65 (82). Anal: calcd for $C_9H_{15}NO_2$: C, 63.90; H, 8.87; N, 8.28. Found: C, 63.66; H, 8.63; N, 8.18.

4.1.5. Preparation of 7-(*tert*-butoxycarbonyl)-2-*exo*-bornane-2,10-sultam-7-azabicyclo-[2.2.1]heptane 31a. To a solution of **25a** (0.5 g, 1.16 mmol) in 50 mL of 5% HCOOH–MeOH was added Pd/C (0.5 g) and the resultant suspension was stirred at rt for 36 h. The reaction mixture was filtered, the filtrate was evaporated and the crude amine was dissolved in 30 mL of dry DCM and treated with a solution of $(Boc)_2O$ (0.305 g, 1.40 mmol) in 10 mL DCM followed by Et_3N (0.8 mL) under argon atmosphere. The resulting mixture was stirred for 18 h and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/EtOAc (7:3) to afford 0.62 g of **31a** (82%) as a white solid, mp 173–175°C. IR ($CHCl_3$): 2945, 1679 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 0.95 (s, 3H), 1.12 (s, 3H), 1.32–1.60 (m, 4H), 1.45 (s, 9H), 1.65–1.95 (m, 6H), 2.05–2.15 (m, 3H), 3.40 (d, J=13.6 Hz, 1H), 3.50 (d, J=13.6 Hz, 1H), 3.55 (dd, J=7.9, 4.3 Hz, 1H), 3.90 (t, J=5.6 Hz, 1H), 4.20 (t, J=4.8 Hz, 1H), 4.60–4.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 19.9, 20.1, 24.8, 26.4, 28.0, 29.0, 31.5, 32.9, 34.45, 38.8, 44.8, 47.0, 48.1, 53.5, 57.5, 58.9, 66.2, 79.0, 154.5, 171.2. MS (*m/z*, relative): 438 (M^+, 5), 365 (15), 338 (100), 135 (17), 83 (25). Anal. calcd for $C_{22}H_{34}N_2O_4S$: C, 60.27; H, 7.76; N, 6.39; S, 7.30. Found: C, 60.13; H, 7.47; N, 6.36; S, 7.27.

4.1.6. Preparation of 31b. To a solution of **28a** (0.5 g, 0.4 mmol) in 30 mL of ethanol was added palladium hydroxide (50 mg) and the resultant suspension was hydrogenated (50 psi, rt) for 2 days. The reaction mixture was worked-up as mentioned above and was converted to its N-Boc derivative to afford 0.48 g of **31b** (92%) as a colorless oil. $[\alpha]_D^{25}=-12.1$ (*c* 1.06, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 1.38–1.42 (m, 2H), 1.43 (s, 9H), 1.61 (dd, J=12.4, 8.9 Hz, 1H), 1.71–1.82 (m, 2H), 2.25–2.29 (m, 1H), 2.55 (dd, J=8.9, 5.1 Hz, 1H), 3.70 (s, 3H), 4.29–4.35 (m, 1H), 4.45–4.52 (m, 1H). ^{13}C NMR ($CDCl_3$, 50.32 MHz): 28.1, 28.7, 29.3, 33.1, 47.3, 51.9, 55.8, 59.1, 99.5, 154.7, 173.6. MS (*m/z*, relative intensity): 255 (M^+, 0.9), 196 (25), 169 (52), 96 (42), 69 (100). Anal. calcd for $C_{13}H_{21}NO_4$: C, 61.17; H, 8.23; N, 5.49. Found: C, 61.01; H, 8.11; N, 5.23.

4.1.7. Preparation of (−)-35 by Heck-coupling. K_2CO_3 (5.37 g, 0.02 mmol), $Pd(OAc)_2$ (0.25 g, 0.001 mmol) and PPh_3 (0.59 g, 0.002 mmol) were added to a stirring solution of olefin (−)-**24** (3.03 g, 0.01 mmol) and **34** (2.70 g, 0.01 mmol) in 30 mL of dry CH_3CN. The mixture was purged with nitrogen and the mixture was refluxed for 4 h under argon atmosphere. The solvent was removed under reduced pressure and the whole dark-brown mass was taken into $CHCl_3$, the organic layer was washed with 0.1N HCl (3×10 mL) followed by water (2×10 mL) and brine. The crude residue was purified by column chromatography eluting with EtOAc/$CHCl_3$ (2:8) to afford 3.65 g (85%) of **35** as a white solid, mp 225–227°C. IR (Nujol): 3018, 1679, 1334, 1215 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 0.98 (s, 3H), 1.20 (s, 3H), 1.35–1.52 (m, H), 1.87–2.05 (m, 3H), 2.18 (d, J=7.3 Hz, 1H), 3.45 (d, J=13.6 Hz, 1H), 3.55 (d, J=13.6 Hz, 1H), 3.98 (t, J=6.3, Hz, 1H), 7.20 (d,

J=15.6 Hz, 1H), 7.38 (d, J=8.3 Hz, 1H), 7.75 (d, J=15.6 Hz, 1H), 7.9 (dd, J=8.3, 2.4 Hz, 1H), 8.5 (d, J=2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 19.6, 20.6, 26.3, 32.7, 38.2, 44.6, 47.7, 48.5, 52.9, 65.0, 120.2, 124.3, 129.1, 136.6, 139.6, 149.9, 163.1. MS (*m/z*, relative intensity): 381 (M^+, 10), 317 (15), 274 (5), 167 (100), 138 (29), 102 (84), 76 (55). Anal. calcd for $C_{17}H_{21}N_2O_2SCl$: C, 56.76; H, 5.51; N, 7.35; S, 8.4. Found: C, 56.72; H, 5.55; N, 7.78; S, 8.72.

4.1.8. [3+2] Cycloaddition of 15 with (−)-35. A typical cycloaddition of **15** (1.50 g, 4.91 mmol) with **35** (2.24 g, 5.90 mmol) using Ag(I)F (1.54 g, 0.01 mol) followed by column purification of the crude cycloaddition mixture using (60:120) silica gel gave mixture of diastereomeric cycloadducts (**36** and **37**) in a ratio of 9:1 with 64% overall yield. The two diastereomers were separated by careful flash column chromatography eluting with acetone/hexane (2.5:7.5) to afford 1.53 g (58%) of **36** as a white prism shaped solid, mp 237–239°C and further elution with the same polarity of the solvent gave 0.17 g (7%) of **37**. **36**: IR (Nujol): 1683, 1215 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.98 (s, 3H), 1.23 (s, 3H), 1.34–1.43 (m, 2H), 1.45–1.51 (m, 1H), 1.62–1.67 (m, 1H), 1.86–1.95 (m, 4H), 2.01–2.08 (m, 2H), 2.09–2.15 (m, 1H), 3.22 (d, J=4.4 Hz, 1H), 3.37 (d, J=4.8 Hz, 1H), 3.41 (d, J=13.7 Hz, 1H), 3.49 (d, J=13.1 Hz, 1H), 3.53 (d, J=13.1 Hz, 1H), 3.61 (t, J=4.2 Hz, 1H), 3.72 (d, J=13.7 Hz, 1H), 3.90 (t, J=5.1 Hz, 1H), 4.06 (t, J=4.4 Hz, 1H), 7.20 (d, J=8.3 Hz, 1H), 7.21–7.29 (m, 1H), 7.31–7.39 (m, 4H), 7.82 (dd, J=8.3, 2.4 Hz, 1H), 8.3 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): 20.2, 21.2, 22.2, 26.8, 27.2, 33.1, 39.1, 45.1, 47.0, 48.1, 48.6, 52.0, 53.4, 58.6, 64.0, 65.8, 66.2, 124.2, 127.4, 128.7, 128.8, 138.4, 139.6, 139.7, 149.4, 149.7, 171.2. MS (*m/z*, relative intensity): 539 (M^+, 8), 506 (5), 380 (10), 297 (18), 242 (7), 160 (97), 91 (100). HRMS: calculated for $C_{29}H_{34}N_3O_3SCl$: 539.2009, observed: 539.2004. **37**: mp 230–232°C, IR (Nujol): 1683 cm^{-1}. ^{1}H NMR (C_6D_6+$CDCl_3$ 1:1, 500 MHz): δ 0.85 (s, 6H), 1.15–1.35 (m, 3H), 1.65–1.82 (m, 5H), 1.95–2.05 (m, 3H), 3.05 (d, J=4.4 Hz, 1H), 3.12 (d, J=4.8 Hz, 1H), 3.22 (s, 2H), 3.35 (d, J=13.6 Hz, 1H), 3.60 (t, J=6.4 Hz, 1H), 3.63 (d, J=13.6 Hz, 1H), 3.72 (t, J=5.6 Hz, 1H), 4.08 (t, J=4.5 Hz, 1H), 6.95–7.25 (m, 6H), 7.75 (d, J=2.6 Hz, 1H), 8.15 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ 20.2, 21.0, 21.9, 26.8, 27.2, 33.1, 39.0, 44.7, 48.2, 48.7, 49.9, 51.8, 53.4, 57.6, 64.3, 65.9, 65.9, 124.3, 127.3, 128.6, 128.9, 138.2, 139.7, 139.9, 149.1, 149.7, 171.5. MS (*m/z*, relative intensity): 539 (M^+, 5), 506 (5), 380 (12), 297 (18), 242 (5), 160 (97), 91 (100).

4.1.9. Preparation of 38. A solution of **36** (0.5 g, 0.92 mmol) in 24 mL THF/H_2O (3:1) containing $LiOH{\cdot}H_2O$ (0.037 g, 0.93 mmol) was warmed to 45°C for 1 h. THF was evaporated and the aqueous layer was extracted with EtOAc (3×2.0 mL). The aqueous layer was cooled to 0°C, acidified with 1N HCl to pH 6–7, and extracted with $CHCl_3$ (3×3.0 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to obtain the crude acid. The resultant crude acid was converted into corresponding methyl ester **38** in the similar manner as described earlier to obtain 0.29 g (90%) of **38**, $[\alpha]_D^{25}=-16.7°$ (*c* 1.2, MeOH). IR ($CHCl_3$): 1726, 1458, 1112 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.52–1.70 (m, 2H), 1.90–2.30 (m, 2H), 2.85 (t, J=5.1 Hz, 1H), 3.10 (d, J=5.3 Hz, 1H), 3.30 (d, J=4.2 Hz, 1H), 3.6 (s, 2H), 3.70 (s, 3H), 3.60–3.70 (t, J=4.4 Hz, 1H), 7.15–7.45 (m, 6H), 7.80 (dd, J=8.4, 2.6 Hz, 1H), 8.5 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.3 MHz): 21.6, 26.5, 47.3, 51.4, 57.1, 61.3, 66.1, 66.1, 123.3, 126.7, 128.0, 128.2, 137.6, 138.9, 139.7, 148.6, 149.0, 172.2. MS (*m/z*, relative intensity): 356 (M^+, 5), 297 (1), 159 (56), 131 (14), 91 (100), 65 (12). HRMS: calculated for $C_{20}H_{21}N_2O_2Cl$: 356.1290, observed: 356.1292.

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