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SYNTHESIS OF RIGID BICYCLOHETEROCYCLIC SCAFFOLDS FROM VINCE'S LACTAM (ENZYMATIC RESOLUTION OF VINCE'S LACTAM)

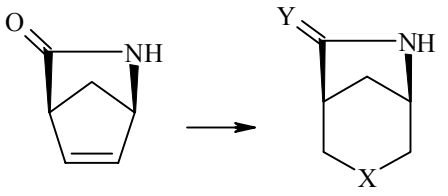
Mukund K. Gurjar,* Smritilekha Bera, Rohini R. Joshi, and Ramesh A. Joshi

National Chemical laboratory, Pune 411 008, India

Abstract- Vince's lactam, on oxidative cleavage and reduction, produced the 3,5-dihydroxymethylpyrrolidin-2-one derivative. This precursor has been utilized in intramolecular cyclization reactions to design some unique diaza-, oxaaza-, and thiaaza-bicyclic molecules as potential scaffolds in combinatorial chemistry.

INTRODUCTION

In an era of diversity oriented organic synthesis[1] for drug like small molecular libraries, structural complexity and diversity have proved absolutely essential to identify new targets. To accomplish this goal, rigid molecules as scaffolds have been incorporated during an assembly of small molecule library through combinatorial synthesis.[2] Therefore, design and synthesis of new scaffolds[3] inheriting rigidity and diversity, have attracted unprecedented significance particularly in new pharmaceutical and agrochemical discovery.[4]



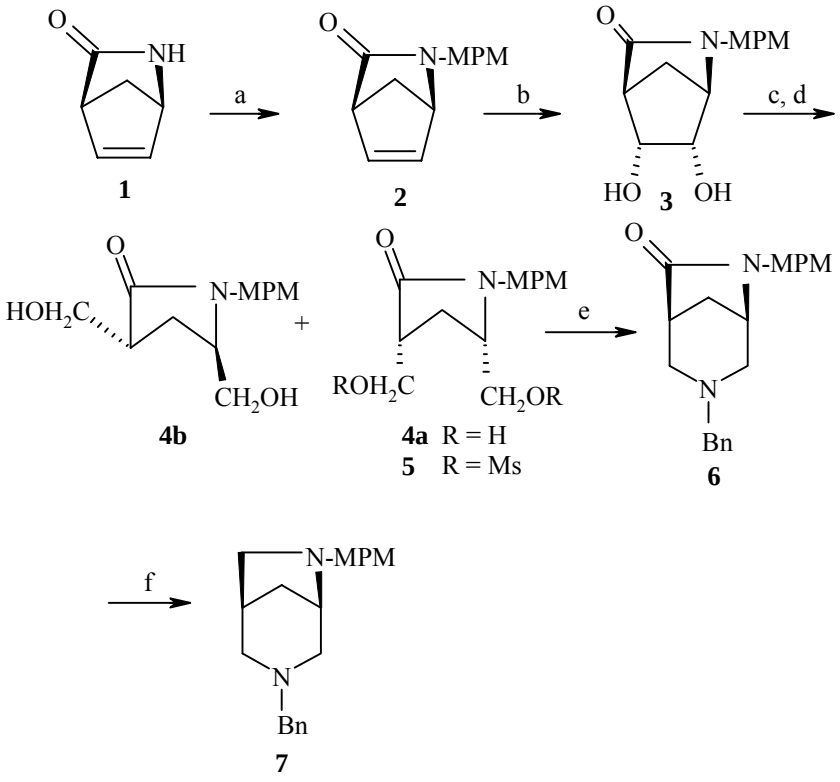
X = N, S, O
Y = O or H,H

We have realized that cheap and commercially available Vince's lactam could be an ideal precursor to rationally design some novel and unique bicyclo-heterocyclic molecules which can serve as scaffolds in combinatorial chemistry.[5] Our strategy was founded on the cleavage of the cyclopentene ring of Vince's lactam while keeping the lactam ring intact. This strategy has enabled us to synthesise some bicyclo-

[3.2.1]-heterocyclic ring system as described in this report. In addition, a new enzymatic route to resolve racemic Vince's lactam that could produce both (+)- or (-)-isomers with more than 99 % ee has been dealt with.

Vince's lactam[6] (**1**) was converted into the *N*-(*p*-methoxybenzyl) derivative (**2**) by treatment with sodium hydride and *p*-methoxybenzyl bromide. Subsequent oxidative cleavage of carbon carbon double bond was accomplished in two steps. For example, compound (**2**) was treated with catalytic OsO_4 in presence of 4-methylmorpholine *N*-oxide to provide the diol (**3**). Treatment of **3** with sodium periodate in aqueous methanol gave a rather unstable dialdehyde which was immediately reduced with $NaBH_4$ in methanol to produce a diastereomeric mixture of 3,5-dihydroxymethylpyrrolidin-2-ones (**4**). The ^1H NMR spectrum and HPLC analysis of **4** revealed the presence of 4:1 mixture of *cis*- and *trans*-diol derivatives (**4a** and **4b**). The mixture was subjected to liquid chromatography to give the pure *cis*-product (**4a**) whose stereo-structure was established at a later stage.

Scheme 1

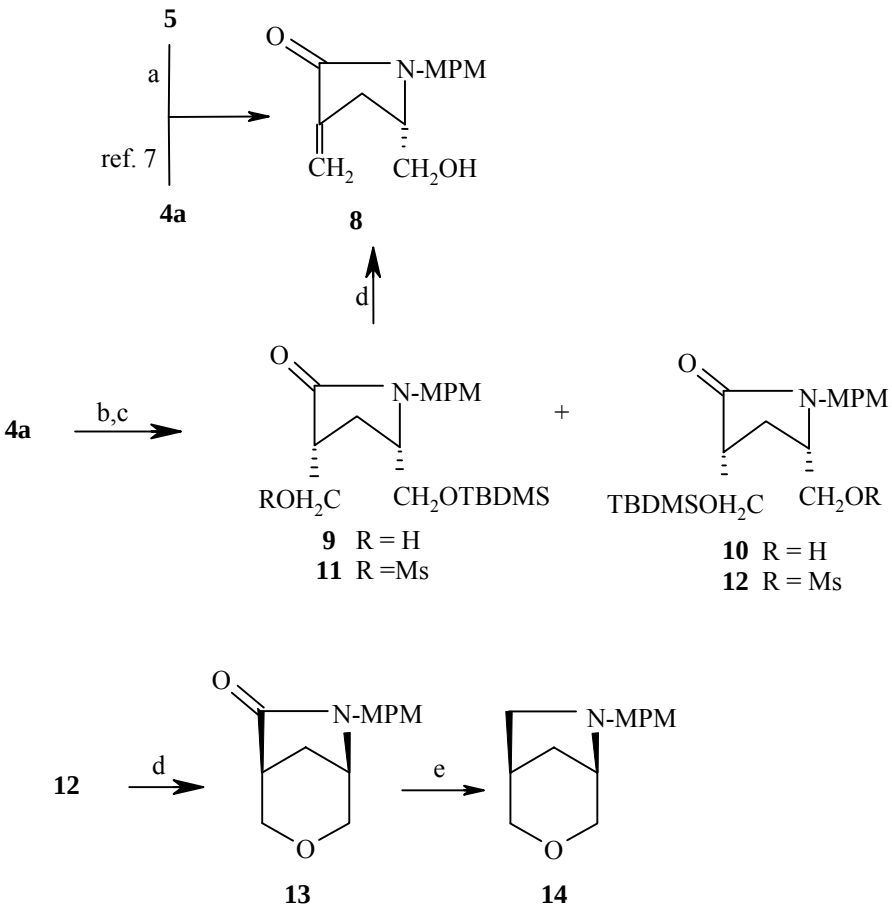


Reagents and conditions: a) NaH, *p*-methoxybenzyl bromide, Bu_4NI, rt, 1 h. b) OsO_4, NMO, acetone-water, rt, 15 h. c) $NaIO_4$, methanol-water, 0 ^{0}C, 45 min; $NaBH_4$, methanol-water, rt, 30 min. d) MsCl, Et_3N, DMAP, 30 min. e) $PhCH_2NH_2$, $NaHCO_3$, toluene, reflux, 19 h. f) $H_3B.SMe_2$, THF, 0 ^{0}C-rt, 16 h.

Treatment of the diol (**4**a) with $MeSO_2Cl$ and Et_3N gave the dimesylate (**5**) in whose ^1H NMR spectrum, the two characteristic singlets due to methyl group were located at 2.99 ppm and 3.07 ppm while rest of the spectrum was consistent with the assigned structure.

The first nucleophilic displacement reaction on the dimesylate (**5**) was performed with benzylamine containing excess of $NaHCO_3$ in refluxing toluene for 12 h to give the diazabicyclo-lactam derivative (**6**) in 80% yield. The ^1H, ^{13}C NMR, and MS spectroscopic data of **6** were in consistent with the assigned structure. The reduction of the amino bond was effected with 2 M solution of $Me_2S.BH_3$ in THF to give diazabicyclic derivative (**7**) whose structure was supported by ^1H-, ^{13}C NMR and MS spectra and elemental analysis. It is pertinent to mention that the cyclisation of **5** clearly substantiates the assignment of *cis*-structure to the parent compound (**4a**). The *trans*- product would have resisted the cyclisation step.

Scheme 2

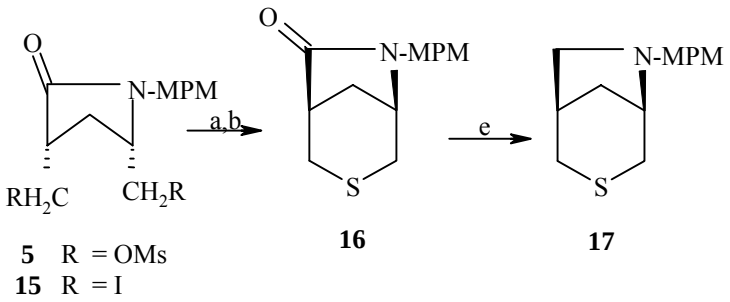


Reagents and conditions: a) NaOH, MeCN -water, reflux, 2 h. b) TBDMSCl, imidazole, 0 ^{0}C, 30 min c) MsCl, Et_3N, DMAP, 0 ^{0}C, 15 min. d) Bu_4NF, THF, 0 ^{0}C, 3 h. e) $H_3B.SMe_2$, THF, 0 ^{0}C - rt, 16 h.

Our next target was turned to synthesis the oxaaza bicyclic derivatives (**13**) and (**14**) for which the diol (**4a**) was subjected to Mitsunobu reaction.[7] The isolated compound of the above reaction did not correspond to the expected product (**13**). Based on the ^{1}H NMR and ^{13}C NMR spectroscopic data, a simple dehydrated structure (**8**) was proposed. For instance, the olefinic protons were located at 5.32 and 5.97 ppm. The signals due to ring methylene showed a down field shift and observed at 2.72 ppm. In the ^{13}C NMR spectrum, the olefinic carbons were observed at 114.6 and 138.7 ppm. The reaction of the dimesylate (**5)** with 2 N NaOH in refluxing MeCN also gave the eliminated product (**8**).

In order to circumvent this problem it was apparent that a monomesyl derivative of **4a** has to be prepared. The reaction of **4a** with TBDMSCl in presence of imidazole in CH_2Cl_2 gave the monosilylated derivative (**10**) (35%) and the regiomeric product (**9**) (50%). The compound (**9**) was mesylated and then treated with Bu_4NF solution to give (**8**) identical with the product described above. However, compound (**10**) on mesylation and exposure to Bu_4NF solution in THF gave the oxaaza bicyclic derivative (**13**). The ^{1}H and ^{13}C NMR and MS spectroscopic data of **13** were consistent with the assigned structure. The reduction of **13** with $Me_2S.BH_3$ gave **14**.

Scheme 3



Reagents and conditions: a) NaI, acetone, reflux, 14 h. b) Na_2S, DMSO-MeCN (1:5), reflux, 6 h. c) H_3B-SMe_2, 0 ^{0}C-rt, 14 h.

Our final target was to introduce sulfur for preparing thiaaza bicyclic derivatives. Thus treatment of the dimesylate (**5**) with sodium sulfide in DMSO-MeCN produced the thiaaza bicyclic derivative (**16**) in low yield. We observed that conversion of dimesylate derivative (**4a**) into the corresponding diiodide (**15**) followed by treatment with Na_2S in DMSO-MeCN produced (1**6**) in good yield. The carbonyl group was reduced with $H_3B.SMe_2$ complex to give heterocyclic thiaaza compound (**17**).

In order to make the scaffolds described above in optically pure forms, we desired the synthesis of chiral Vince's lactam. Both the enantiomers of Vince's lactam were prepared with more than 99 % ee enzymatic resolution[8] using two new strains. For instance, *k. citrophila* provided (-)-Vince's lactam while *A. viscous* produced (+)-Vince's lactam.

In conclusion, we have some novel and unique scaffold molecules starting from easily accessible Vince's lactam.

EXPERIMENTAL

NMR spectra were recorded on Bruker AC 200, MSL 300 or DRX 500 MHz instruments in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. EIMS spectra were recorded on a Finnigan MAT – 1020. Microanalysis was carried out on Carbo–Elba elemental analyzer. Melting points were measured on a Buchi B-540 apparatus and are uncorrected. Solvents were distilled over drying agents under argon or nitrogen. All reactions were monitored by thin-layer chromatography carried out on 0.25 m E. Merck silica gel plates (60F-254) using UV light as visualizing agent and anisaldehyde in ethanol as developing agent. Silica gel (60–120) was purchased from Acme Chemical Company. Microbial strains were procured from ATCC (American Type Culture Collection) and NCIM (National Collection of Industrial Microorganism).

(3*S, 6*R**)-*N*-(4-Methoxybenzyl)-1-azabicyclo[2.2.1]hept-4-en-2-one (2):**

To a suspension of NaH (60 % dispersion in oil, 3.3 g, 82.6 mmol) in dry DMF (100 mL) at 0 ^{0}C, a solution of Vince's lactam (**1**) (6.6 g, 60.5 mmol) in DMF (30 mL) was added followed by Bu_4NI (0.3 g). After 30 min, *p*-methoxybenzyl bromide (13.3 g, 66.5 mmol) was introduced and stirred at rt for 1 h. After addition of water, the mixture was extracted with CH_2Cl_2 and washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel using EtOAc-hexane (4:1) to give **2** (12.9 g, 93 %) as an oil: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.03 (m, 1 H), 2.27 (m, 1 H), 3.35 (br s, 1 H), 3.80 (s, 3 H), 3.98 (d, 1 H, *J* = 14.0 Hz), 4.00 (br s, 1 H), 4.31 (d, 1 H, *J* = 14.0 Hz), 6.50 (s, 2 H), 6.82 (d, 2 H, *J* = 8.0 Hz), 7.09 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 46.5, 53.0, 54.4, 57.5, 61.8, 113.3, 127.7, 129.0, 136.1, 139.1, 158.5, 178.8; MS: m/z 229 (M^+). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.11. Found: C, 72.90; H, 6.45; N, 6.11.

(3*S, 6*R**)- *N*-(4-Methoxybenzyl)-4,5-dihydroxy-1-azabicyclo[2.2.1]heptan-2-one (3):**

A mixture of **2** (15.0 g, 65.5 mmol), 50 % aq NMO solution (5.4 mL, 196.5 mmol), OsO_4 (80 mg, 0.281 mmol) in toluene (2 mL), acetone (40 mL) and water (60 mL) was stirred at rt for 18 h. Saturated $NaHSO_3$ solution was introduced to quench the reaction. After 1 h, solid was filtered, washed with water and CCl_4 and recrystallized from methanol to give **3** (13 g, 75 %): mp 205 ^{0}C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.68 (br d, 1 H, *J* = 9.5 Hz), 1.89 (br d, 1 H, *J* = 9. 2 Hz), 2.44 (s, 1 H), 3.60 (m, 1 H), 3.73 (s, 3 H), 4.02 (d, 1 H, *J* = 16.0 Hz), 4.29 (d, 1 H, *J* = 15.2 Hz), 4.90 (d, 1 H, *J* = 5.1 Hz), 5.06 (d, 1 H, *J* = 5.1 Hz), 6.90 (d, 2 H, *J* = 8.0 Hz), 7.17 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 33.9, 43.7, 52.2, 55.3, 62.3, 68.3, 69.4, 114.2, 129.3, 158.8, 174.4; MS: m/z 263 (M^+). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.46. Found: C, 63.59; H, 6.20.

(3*S, 6*R**)-*N*-(4-Methoxybenzyl)-3,5-*bis*-hydroxymethylpyrrolidin-2-one (4a):**

A mixture of **3** (4.2 g, 16.0 mmol), $NaIO_4$ (6.7 g, 31.14 mmol), water (50 mL), and methanol (200 mL) was stirred at rt for 30 min and filtered. To the filtrate $NaBH_4$ (0.9 g, 23.8 mmol) was added. After stirring for 20 min, the reaction mixture was concentrated, diluted with water, extracted with CH_2Cl_2 and washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with EtOAc-MeOH (1:1) to give **4a** (3.5 g, 83 %) as an oil. (**4a**) **:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.10 (m, 2 H), 2.70 (m, 1 H), 3.47 (m, 4 H), 3.69 (m, 1 H), 3.74 (s, 3 H), 4.04 (d, 1 H, *J* = 8.9 Hz), 4.87 (d, 1 H, *J* = 14.7 Hz), 6.77 (d, 2 H, *J* = 8.0 Hz), 7.09 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.9, 43.7, 55.1, 57.1, 61.8, 62.5, 114.0, 128.2, 129.0, 158.9, 176.8; MS: m/z 265 (M^+). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.39; H, 7.17; N, 5.28. Found: C, 63.62; H, 7.28; N, 5.12.

(3*S, 6*R**)-*N*-(4-Methoxybenzyl)-3,5-*bis*-(methansulfonyloxymethyl)pyrrolidin-2-one (5):**

A mixture of **4a** (1.8 g, 6.8 mmol), Et_3N (3.6 mL), DMAP (50 mg, 0.409 mmol), $MeSO_2Cl$ (1.3 mL, 17.0 mmol) was stirred at rt for 15 min, diluted with CH_2Cl_2 and washed with water(50mL), and brine, dried (Na_2SO_4) and concentrated. The residue was triturated with EtOAc-hexane (2:3) to give **5** (2.5 g, 87 %): mp 115 ^{0}C (Recrystalized from EtOAc-Hexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 1 H), 2.89, 2.95 (2 s, 6 H), 3.07 (m, 2 H), 3.64 (m,1 H), 3.71 (s, 3 H), 4.09 (m, 2 H), 4.21 (dd, 1 H, *J* = 3.1, 12.1 Hz), 4.32 (dd, 1 H, *J* = 3.1, 10.7 Hz), 4.56 (dd, 1 H, *J* = 4.5, 10.7 Hz), 4.92 (d,1 H *J* = 15.1 Hz), 6.83 (d, 2 H, *J* = 8.0 Hz), 7.10 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.5, 36.9, 37.9, 40.7, 44.4, 54.1, 55.2, 68.5, 69.1, 114.2, 127.7, 129.1, 159.3, 172.6; MS: m/z 421 (M^+). Anal. Calcd for $C_{16}H_{23}NO_8S_2$: C, 45.59; H, 5.46; N, 3.32; S, 15.19. Found: C, 45.56; H, 5.26; N, 3.28; S, 14.82.

(3*S, 6*R**)-1-(4-Methoxybenzyl)-5-benzyl-1,5-diazabicyclo[3.2.1]octan-2-one (6):**

A solution of **5** (5.8 g, 13.8 mmol), benzylamine (1.47 g, 13.8 mmol), and $NaHCO_3$ (2.76 g, 27.6 mmol) in toluene (50 mL) was heated under reflux for 19 h and concentrated. The residue was partitioned between EtOAc-water. The organic layer was dried (Na_2SO_4), concentrated and chromatographed on silica gel using EtOAc-hexane (2:3) to give **6** (3.8 g, 82 %) as a syrup: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (d, 1 H, *J* = 11.1 Hz), 1.95 (d, 1 H, *J* = 11.1 Hz), 2.05 (m, 1 H), 2.18 (d, 1 H , *J* = 9.7 Hz), 2.46 (t,1 H, *J* = 4.1 Hz), 2.70 (m, 1 H), 3.09 (m, 1 H), 3.32 (t, 1 H, *J* = 4.1 Hz), 3.49 (ABq, 2 H, *J* = 13.9 Hz), 3.67 (s, 3 H), 3.69 (d, 1 H, *J* = 13.9 Hz), 4.79 (d, 1 H, *J* = 13.9 Hz), 6.69 (d, 2 H, *J* = 7.2 Hz), 7.01 (d, 2 H, *J* = 7.2 Hz), 7.20 (s, 5 H); ^{13}CNMR ($CDCl_3$, 50 MHz) δ 35.7, 40.7, 43.9, 50.0, 53.3, 53.8, 54.8, 60.9, 113.7, 128.0, 129.1, 137.4, 158.7, 176.3; MS: m/z 336 (M^+). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.00 ; H, 7.14; N, 8.33. Found**:** C, 74.52; H, 7.38; N, 8.32.

(3*S, 6*R**)-1-[4-Methoxybenzyl]-5-benzyl-1,5-diazabicyclo[3.2.1]octane (7):**

To a stirred solution of **6** (0.4 g, 1.2 mmol) in dry THF (10 mL) was added a 2 M solution of $Me_2S.BH_3$ in THF (1.8 mL, 3.6 mmol) under nitrogen at 0 ^{0}C. The reaction was stirred for 12 h, quenched with methanol and concentrated. The residue was chromatographed on silica gel with EtOAc-hexane (3:7) to give **7** (0.34 g, 89 %) as a syrup: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (d, 1 H, *J* = 12.3 Hz), 2.01 (d, 2 H, *J* = 12.3 Hz), 2.20 (d, 1 H, *J* = 9.2 Hz), 2.29 (m, 1 H), 2.75 (d, 2 H, *J* = 12.3 Hz), 2.93 (d, 1 H, *J* = 12.3 Hz), 3.15 (m, 2 H), 3.52 (ABq, 2 H, *J* = 12.3 Hz), 3.76 (s, 3 H), 3.89 (ABq, 2 H, *J* = 12.3 Hz), 6.83 (d, 1 H, *J* = 8.0 Hz), 7.2-7.5 (m, 7 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.7, 36.5, 53.8, 54.2, 54.9, 55.9, 56.6, 58.7, 62.1, 113.5, 126.9, 127.9, 128.9, 129.7, 130.8, 138.5, 158.4; MS: m/z 322 (M^+). Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.26; H, 8.07. Found: C, 77.8; H, 8.34.

(3*S, 6*R**)-*N*-(4-Methoxybenzyl)-3-methansulphonyloxymethyl-5-(*tert*-butyldimethylsilyloxy-methyl)pyrrolidin-2-one (12) and (3**S*, 6*R**)-*N*-4-methoxybenzyl-5-methansulphonyloxymethyl-3-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-2-one (11):**

Compound (**4a**) (6.23 g, 23.5 mmol), imidazole (2.41 g, 35.5 mmol), and TBDMSCl (3.54 g, 23.5 mmol) in CH_2Cl_2 (50 mL) was stirred for 1 h at 0 ^{0}C and concentrated. The residue was chromatographed on silica gel with EtOAc-hexane(1:3). The first compound to be eluted was **10** (3.1 g, 35 %) which was treated with Et_3N (1.46 mL, 11.05 mmol), DMAP (45 mg, 0.368 mmol), $MeSO_2Cl$ (0.42 mL, 5.5 mmol) in CH_2Cl_2 (10 mL) at 0 ^{0}C for 25 min. The reaction mixture was diluted with water and organic layer was separated. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel by eluting with EtOAc-hexane (1:3) to give **12** (2.4 g, 95 %) as a syrup. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 6 H), 0.86 (s, 9 H), 1.81 (m,1 H), 2.29 (m, 1 H), 2.58 (m, 1 H), 2.79 (s, 3 H),

3.48 (m, 1 H), 3.68 (m, 1 H), 3.73 (s, 3 H), 4.09 (m, 3 H), 4.23 (d, 1 H, *J* = 14.8 Hz), 4.68 (d, 1 H, *J* = 14.8 Hz), 6.78 (d, 2 H, *J* = 8.1 Hz), 7.13 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.9, 25.8, 36.9, 43.7, 44.6, 54.5, 54.9, 62.1, 69.7, 113.9, 128.6, 129.0, 158.9, 174.6; MS: m/z 457 (M^+). Anal. Calcd for $C_{21}H_{35}NO_6SSi$: C, 55.14; H, 7.65; S, 7.0. Found: C, 54.80; H, 7.58; S, 6.92.

Further elution gave **9** (4.5 g, 50 %) which was mesylated with mesyl chloride (1.5 mL, 19.6 mmol) and Et_3N (5 mL) as described above, to give **11** (3.2 g, 83 %) as an oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.03 (s, 6 H), 0.84 (s, 9 H), 1.93 (m, 1 H), 2.24 (m, 1 H), 2.67 (m, 1 H), 2.89 (s, 3 H), 3.65-3.74 (m, 3 H), 3.74 (s, 3 H), 3.93 (m, 2 H), 4.08 (d, 1 H, *J* = 14.5 Hz), 4.92 (d,1 H, *J* = 14.5 Hz), 6.80 (d, 2 H, *J* = 8.6 Hz), 7.14 (d, 2 H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.7, 25.7, 37.5, 42.6, 44.3, 54.5, 55.2, 62.4, 68.2,114.3, 127.9, 129.2, 154.3, 176.2. MS: m/z 457 (M^+). Anal. Calcd for $C_{21}H_{35}NO_6SSi$: C, 55.14; H, 7.65; S, 7.0. Found: C, 54.60; H, 7.53; S, 6.92.

(5*S)-*N*-(4-Methoxybenzyl)-3-methylene-5-hydroxymethylpyrolidin-2-one (8):**

To a solution of **11** (2.0 g, 4.4 mmol) in THF (20 mL) was added 1 M solution of Bu_4NF in THF (6.6 mL, 6.6 mmol). The mixture was stirred at rt for 2 h. After addition of saturated NH_4Cl, the organic layer was separated, concentrated and chromatographed on silica gel eluting with EtOAc-hexane (3:2) to give **8** (0.97 g, 90 %). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.72 (m, 2 H), 3.52 (m, 2 H), 3.77 (s, 3 H), 3.82 (m, 2 H), 4.12 (d,1 H, *J* = 14.9 Hz), 4.93 (d, 1 H, *J* = 14.7 Hz), 5.33 (t, 1 H, *J* = 2.1 Hz), 5.98 (t, 1 H, *J* = 2.7 Hz), 6.81 (d, 2 H, *J* = 8.8 Hz), 7.16 (d, 2 H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.7, 43.5, 54.3, 54.6, 61.1, 113.2, 114.6, 127.6, 128.6, 138.8, 158.2, 167.9; MS: m/z 247 (M^+). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.01; H, 6.88; N, 5.66. Found**:** C, 67.68; H, 6.88; N, 5.49.

Compound (**8**) (96%) was also obtained from **5** by refluxing with 2 N NaOH in MeCN for 2 h.

(3*S, 6*R**)-1-(4-Methoxybenzyl)-5-oxa-1-azabicyclo[3.2.1]octan-2-one (13):**

Compound (**12**) (2.1 g, 4.6 mmol) and 1 M solution of Bu_4NF in THF (6.8 mL, 6.8 mmol) was stirred at rt for 2 h and concentrated. The residue was partitioned between extracted with ethylacetate and water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel eluting with EtOAc-hexane (3:2) to give **13** (0.97 g, 85 %) as a syrup: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.83 (d, 1 H, *J* = 10.7 Hz), 2.29 (m, 2 H), 2.47 (br s, 1 H), 2.70 (m,1 H), 3.45 (d,1 H, *J* = 11.4 Hz), 3.58 (d, 1 H, *J* = 11.4 Hz), 3.79 (s, 3 H), 3.98 (m, 1 H), 4.04 (d, 1 H, *J* = 14.9 Hz), 4.82 (d, 1 H, *J* = 14.9 Hz), 6.84 (d, 2 H, *J* = 9.3 Hz), 7.19 (d, 2 H, *J* = 9.3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.2, 40.9, 42.8, 53.6, 53.8, 62.9, 65.8, 112.8, 127.54 ,127.9, 157.9, 173.9; MS: m/z 247 (M^+). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.01; H, 6.88; N, 5.66. Found: C, 67.91; H, 6.65; N, 5.41.

(3*S, 6*R**)-1-(4-Methoxybenzyl)-5-oxa-1-azabicyclo[3.2.1]octane (14):**

Compound (**13**) (0.18 g, 0.73 mmol) in THF (3 mL) and $Me_2S.BH_3$ (2 M in THF 0.73 mL, 1.45 mmol) were stirred at rt for 12 h and then worked up as described above to give **14** (0.14 g, 82 %) as a syrup: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.72 (d, 1 H, *J* = 10.8 Hz), 2.05 (m, 1 H), 2.24 (m, 1 H), 2.83 (m, 1 H), 2.99 (d, 1 H, *J* = 9.4 Hz), 3.01 (m, 1 H), 3.11 (m,1 H), 3.43 (d, 1 H, *J* = 11.5 Hz), 3.79 (s, 3 H), 3.89 (m, 4 H), 6.83 (d, 2 H, *J* = 8.9 Hz), 7.34 (d, 2 H, *J* = 8.9 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.6, 35.2, 36.4, 55.1, 60.3, 62.3, 66.7, 73.1, 113.0, 113.7, 126.2, 129.8, 133.9, 159.6; MS: m/z 233 (M^+). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.00. Found: C, 72.31; H, 8.47; N, 6.00.

(3*S, 6*R**)-*N*-(4-Methoxybenzyl)-3,5-*bis*iodomethyl-*N*-pyrrolidin-2-one (15):**

A solution of **5** (4 g, 9.5 mmol) and anhydrous sodium iodide (3.56 g, 23.74 mmol) in dry acetone (30 mL) was heated under reflux for 12 h. The residue was partitioned between EtOAc and water. The organic layer was washed with sodium sulfite solution, brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with EtOAc – hexane (1:9) to give **15** (4.1 g, 89 %) as a syrup: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.53 (m, 1 H), 2.45 (m, 1 H), 2.70-3.08 (m, 1 H), 3.14-3.40 (m, 4 H), 3.53-3.63 (m, 1H), 3.79 (s, 3 H), 3.84 (q, 1 H, *J* = 15.1 Hz), 4.97 (q, 1 H, *J* =15.4 Hz), 6.86 (m, 2 H), 7.11 (q, 2 H, *J* = 8.62 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.7, 33.2 , 41.6, 43.3, 43.7, 53.5, 54.8, 113.8, 126.8, 127.3, 128.8, 129.2, 1 58.8, 172.7; MS: m/z 485 (M^+). Anal. Calcd for $C_{14}H_{17}N\,O_2I_2$ **:** C, 34.63; H, 3.50; N, 2.88. Found**:** C, 34.41; H, 3.46; N, 2.67.

(3*S, 6*R**)-1-(4-Methoxybenzyl)-5-thia-1-azabicyclo[3.2.1]octan-2-one (16):**

Compound (**15**) (1.0 g, 2.1 mmol) and $Na_2S{\cdot}9H_2O$ (0.5 g, 2.1 mmol) in DMSO (2 mL) and MeCN (10 mL) were heated under reflux for 5 h. The reaction mixture was concentrated to remove MeCN, diluted with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with EtOAc-hexane (1:1) to give cyclic product (**16**) (0.43 g, 79 %) as a syrup: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52 (d, 1 H, *J* = 11.0 Hz), 2.10 (m, 1 H), 2.35 (dd, 1 H, *J* = 3.3, 13.7 Hz), 2.5-2.9 (m, 4 H), 3.61 (m, 1 H), 3.71 (s, 3 H), 3.87 (d, 1 H, *J* = 13.7 Hz), 4.87 (d, 1 H, *J* = 13.7 Hz), 6.78 (d, 2 H, *J* = 7.5 Hz), 7.14 (d, 2 H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.6, 29.3, 34.5, 40.0, 43.5, 52.9, 54.9 , 113.7 , 113.9, 128.1, 129.2, 158.8, 175.0; MS: m/z 263 (M^+). Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.87; H, 6.46; N, 5.32; S, 12.16. Found: C, 63.64; H, 6.32; N, 5.32; S, 12.0.

(3*S, 6*R**)-1-[4-Methoxybenzyl]-5-thia-1-azabicyclo[3.2.1]octane (17):**

To compound (**16**) (100 mg, 0.38 mmol) in dry THF (3 mL) was added $Me_2S.BH_3$ (2 M solution in THF 0.57 mL, 1.14 mmol) and the mixture was stirred at rt under nitrogen for 13 h. The residue was quenched

with methanol and concentrated. The residue was purified on silica gel with EtOAc-hexane (1:6) to give (**17**) (74 mg, 78 %) as a syrup: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44 (d, 1 H, *J* = 11.9 Hz), 1.97 (m, 1 H), 2.23 (m, 1 H), 2.53 (m, 2 H), 2.66 (d, 1 H, *J* = 13.3 Hz), 2.99 (m, 2 H), 3.10 (m, 1 H), 3.29 (t, 1 H, *J* = 4.6 Hz), 3.72 (s, 3 H), 3.94 (d, 2 H, *J* = 3 Hz), 6.75 (d, 2 H, *J* = 8.2 Hz), 7.25 (d, 2 H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.1, 31.1, 34.6, 37.0, 53.8, 55.1, 56.2, 56.7, 113.6, 129.7, 159.7; Ms: m/z 249 (M^+). Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.46; H, 7.63; N, 5.62; S, 12.85. Found: C, 67.19; H, 7.49; N, 5.57; S, 12.64.

Procedure for preparation of cells and enzymatic resolution:

i) K. citrophilla (ATCC No.21285) was grown in 10 mL medium containing yeast extract (0.5 g, 5 %), peptone (0.1 g, 1 %), sodium chloride (0.2 g, 2 %), sodium glutamate (0.5 g, 5 %) and phenyl acetic acid (0.2 g, 2 %) at pH 7.2-7.3 for 24 h with shaking at 150 rpm. It was transferred to a 1L flask containing 300 mL medium (yeast extract 15.0 g, peptone 3.0 g, sodium chloride 6.0 g, sodium glutamate 15.0 g, phenyl acetic acid 2.0 g) and incubated at 28-30^{0}C for 24 h on rotary shakers (150 rpm). The whole culture was then harvested by centrifugation and biomass was used for the reaction.

ii) A.viscous (NCIM No. 2451) was grown in 10 mL medium containing beef extract (0.3 g, 3 %), peptone (0.1 g, 1 %) and sodium chloride (0.8 g, 8%) at pH 7.2-7.3 for 24 h with shaking at 150 rpm. It was transferred to 1L flask containing 300 mL medium (beef extract 9.0 g, peptone 3.0 g, sodium chloride 24.0 g) and incubated at 28-30 ^{o}C for 24 h on rotary shakers (150 rpm). The whole culture was then harvested by centrifugation and used for the reaction.

[1*R*,4*S*]-(-)-2-Azabicyclo[2.2.1]hept-5-en-3-one (1):

(±)- **1** (1.0 g, 9.2 mmol) was suspended in phosphate buffer (50 mL, pH 7.5) and then 5 g of wet cell mass of culture *k. citrophilla* (ATCC No.21285) was added. After stirring for 24 h, the cell mass was removed by filtration over a bed of celite. The filtrate was extracted with CH_2Cl_2. Concentration of solvent gave (-)-**1** (0.318 g, 31.8 %); mp 94-95^{o}C, lit.,[8] mp 93-95^{o}C; $[\alpha]_D^{25}$ –552 ^{o} (c 1, CH_2Cl_2), lit.,[8] $[\alpha]_D^{25}$ -557 ^{o} (c 1, CH_2Cl_2), ee = 99.1 %.

[1*S*,4*R*]-(+)-2-Azabicyclo[2.2.1]hept-5-en-3-one (1):

(±)-**1** (1.0 g, 9.2 mmol) was suspended in phosphate buffer (50 mL, pH 7.5) and then 5 g of wet cell mass of culture *A.viscous* (NCIM No.2451) was added. After stirring for 21 h, the cell mass was removed by filtration over a bed of celite. The filtrate was extracted with CH_2Cl_2. Concentration of solvent gave (+)-**1** (0.312 g, 31.2 %); mp 93-95^{o}C, lit.,[8] mp 94-95 ^{o}C; $[\alpha]_D^{25}$ + 554 ^{o} (c 1, CH_2Cl_2), lit.,[8] $[\alpha]_D^{25}$ +557 ^{o} (c 1, CH_2Cl_2), ee = 99.4 %.

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