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1β-Methylthienamycin : Some Stereocontrolled Approaches towards the Key Intermediate

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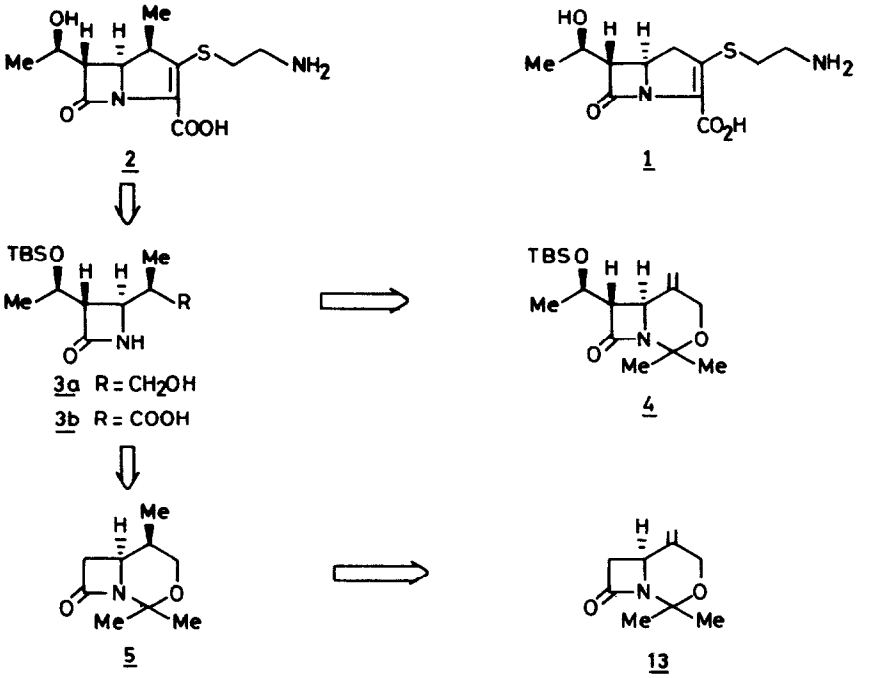
Abstract: Two stereocontrolled approaches towards a precursor of 1 β-methylthienamycin, have been accomplished by involving stereospecific hydrogenation of **13** and stereoselective hydroboration oxidation of **9.** The latter compounds were obtained from the easily accessible chiral building block **7.** The hydroboration-oxidation approach was extended to **18** in which the optically active 1R- (1-hydroxy ethyl) side-chain was incorporated. The highly stereoselective hydroboration-oxidation reaction of **9** is explained by considering Houk's models.

Since the discovery[1] of penicillin, no class of antibiotics has received such overwhelming attention, on so many fronts. Over the years, several new classes of β-lactam antibiotics have been isolated[2], however, the most significant discovery in recent years is, perhaps, the isolation[3] of thienamycin (**1**) belonging to the carbapenem group of antibiotics. The profound interest in thienamycin (**1**) arose because of its unusual structural and functional framework. In spite of these qualities, thienamycin could not be regarded[4] as a potential clinical drug apparently due to chemical susceptibility and metabolic sensitivity towards renal dehydropeptidase (DHP-1). The efforts to enhance the chemical and metabolic stabilities of thienamycin (**1**) by structural modification were intensified. The Merck group[5] in 1984 introduced a simple analogue of **1**, namely 1-β methylthienamycin (**2**). The stability of **2** at higher dose levels was quite pronounced and further it was not prone to metabolism by DHP-I. The antibiotic activity of **2** was compatible with **1**[6]. This discovery has encouraged several synthetic chemists to establish a general and practical route to **2.** The synthetic studies[7] made on carbapenem antibiotics, particularly during the synthesis of thienamycin (**1**), could in principle be extended to 1-β-methylthienamycin (**2**), the main emphasis[8], therefore, was directed on developing a stereocontrolled route for introducing the β-methyl group at position 1 of **2.** The stereochemical approaches reported for **2** mainly involved aldol condensations[9] and cycloaddition reactions[10]. However, the search is on[11] to develop a simple and practical route which can be used for large-scale preparation.

It is noteworthy that the catalytic reduction of an unsaturated derivative **4** occurs[5] with high degree of stereospecificity, leading to the advanced intermediate **3a** with the desired stereochemistry (Scheme 1). The reduction was indeed expected to take place from the less hindered α face as revealed by the molecular model (A). In spite of this valuable observation

by the Merck group, the methods described by them as well as by others[12] for the key intermediate **4** could not be applied to large scale preparation and therefore we felt, the scope and need to develop alternate but simple protocols for compounds of the type **4** (or **13**) still existed. Our studies directed towards the advanced intermediate **3**, based on the above observation, are described. In addition, an alternative approach to the intermediates (**5** and **3**) useful for **2**, that involves a stereoselective hydroboration-oxidation reaction, is also dealt with in this report.

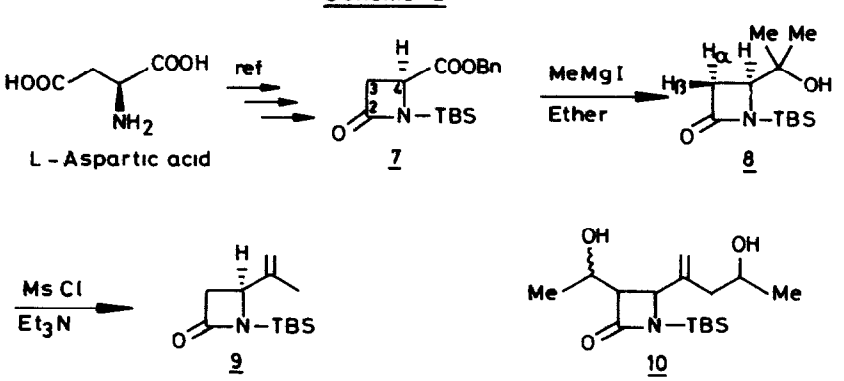
Scheme-1



RESULTS AND DISCUSSION

The N-(tert-butyldimethylsilyl)4-benzyloxycarbonyl-2-azetidinone (**7**), chosen for the present study, was prepared[13] from L-aspartic acid in three high-yielding steps. Treatment

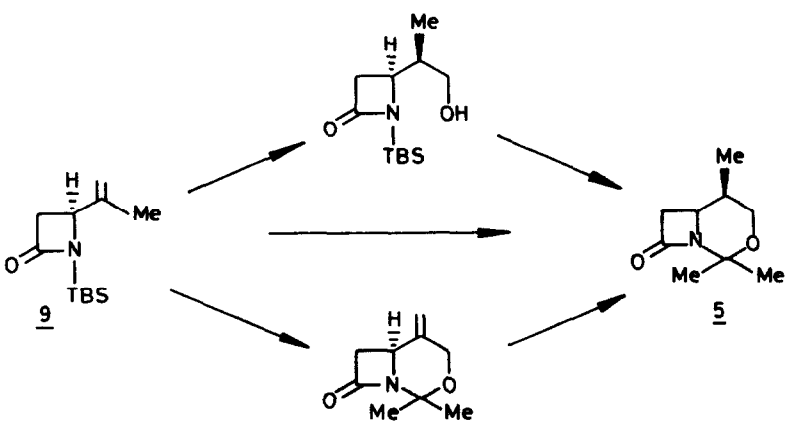
Scheme-2



of **7** with excess methylmagnesium iodide afforded the dimethyl carbinol derivative **8** (84%) (Scheme 2). The ^{1}H-NMR spectrum of **8** was compatible with its structure as the characteristic singlet due to the two methyl groups was located in the upfield region at 1.00 ppm. The tertiary carbinol derivatives undergo facile dehydration reaction and many reagents[14] have been reported for this transformation. We observed that the dehydration of **8** could be efficiently and neatly carried out by using 4 equivalents of mesyl chloride and 8 equivalents of triethylamine in methylene chloride at room temperature for 5 h to afford **9** in 82% yield. The characteristic signals of the isopropenyl, methyl group and terminal olefinic protons in the ^{1}H-NMR spectrum of **9** indicated the assigned structure.

At this stage we had two choices to initiate our synthetic plan: either to introduce the 1-hydroxyethyl side chain at position 3 of **9** by adopting the well established procedure[15], or to manipulate the isopropenyl substituent present at position 4 to the corresponding 1-methyl-2-hydroxyethyl derivative. We considered the first choice and accordingly, **9** was made to react with LDA (1.5 equivalents) at -78° C followed by addition of acetaldehyde to give **10** as the major product. The ^{1}H-NMR spectrum of **10** was not amenable to firs order analysis due to the presence of a diastereomeric mixture. However, in the upfield region the conspicious absence of the methyl singlet of isopropenyl group was noted. In addition, multiplets due to methyls of two hydroxyethyl substituents were observed at 1.1-1.3 ppm. The rest of the spectrum revealed resonances at δ 5.35 (m, 2H, $=CH_2$), 4.9 (m, 1H), 4.75 (m, 1H), 4.1 (m, 1H), 3.7 (m, 1H), 1.6-1.7 (m, 2H). Although the aldol condensation is known to occur at a carbon α to the carbonyl function of the β -lactam derivative, it appears that in the present case metallation[16] also took place at the remote γ position. This undesired course of reaction implied that with the isopropenyl group present at position 4 in **9**, the introduction of 1-hydroxyethyl group at C-3 was not advisable. This led us to consider the second choice of modifying the isopropenyl group in a stereocontrolled fashion to realise the 1-methyl-2-hydroxyethyl group. Consequently, we examined two approaches as delineated in scheme 3.

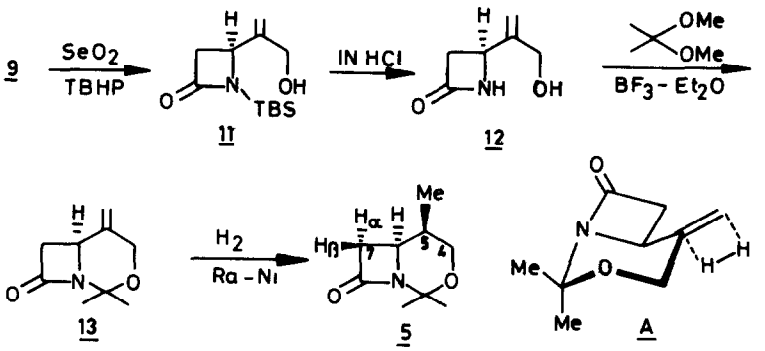
Scheme-3



The allylic oxidation of olefins in the presence of TBHP and a catalytic amount of SeO_2 is one of the most reliable approaches[17] for the direct insertion of the OH group at

the allylic carbon. We felt this reaction could be exploited to introduce the required OH group at position 5 of **9**. Treatment of **9** with 2 equivalents of TBHP and 0.5 equivalents of SeO_2 in CH_2Cl_2 at room temperature for 48 h gave **11** in 83% yield (based on recovered unreacted starting material) (Scheme 4). Structure of the product **11** was clearly suggested by its ^{1}H-NMR spectrum in which the signals due to the hydroxymethyl group were located at 4.1 ppm while the vinylic methyl singlet of **9** was conspicuously absent in the upfield region. Our next concern was to prepare the isopropylidene derivative **13** from **11**.

Scheme - 4

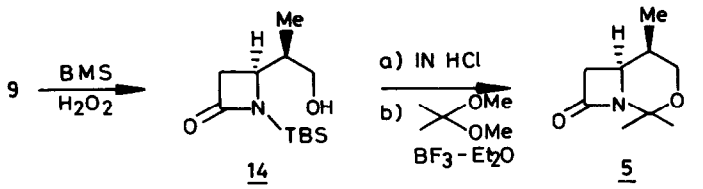


Treatment of **11** with 1N HCl in methanol successfully deprotected the TBS group to give the amino alcohol **12** which was not characterised but subjected to a treatment of dimethoxypropane in the presence of BF_3:Et_2O at room temperature to give **13**.

The catalytic hydrogenation[5] of an exocyclic double bond as present in **4** has been systematically studied by the Merck Group with variable catalyst and solvents. The best stereoselectivity of reduction was observed with Ra-Ni (EtOAc) in MeOH at normal temperature and pressure. We employed the same condition for the reduction of **13** and obtained **5** as exclusive product as judged by ^{1}H-NMR spectrum. The structure of **5** was unambiguously assigned by its ^{1}H-NMR spectrum in which the characteristic coupling constants: $J_{4a,5e}$=2.5, $J_{4e,5e}$=2.2 and $J_{4a,4e}$=12.2 Hz between the protons located at C-4 and C-5 were in agreement with the reported values[18].

The stereoselective hydroboration-oxidation of a prochiral isopropenyl group containing an adjacent chiral center is currently being investigated[19]. The stereochemical outco-e of this study is profoundly influenced by steric and electronic factors and also by nature of the hydroborating agent. Therefore we perceived that it could be interesting to study the hydroboration reaction of **9** in which the isopropenyl group is flanked by the chiral β-lactam ring system. So far studies on stereoselective hydroborations of α-chiral allylic amines have not been fully[20] estimated although their potential as viable routes to chiral amino alcohols could be promising. We also viewed that in case this reaction is successful it would form an alternate and short approach to the key intermediate **5**. Thus compound **9** when treated with 2M solution of borane-methylsulfide complex in THF, followed by oxidation with H_2O_2-NaOAc yielded 61% of **14** (Scheme 5). With 1M borane THF complex, compound **9** furnished only 30% of **14**. Similarly the hydroboration-oxidation reaction of **9** with 9-BBN was also

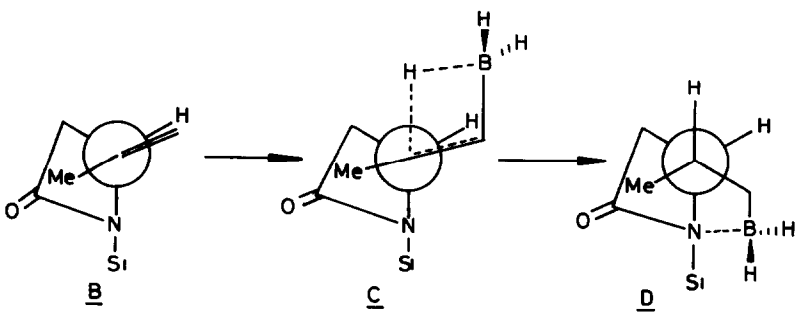
Scheme-5



attempted but this reaction was found to be extraordinarily sluggish and after several hours only traces of **14** were formed. The steric interference of the TBS group and the bulky nature of the hydroborating reagent could perhaps be responsible for the lack of any reactivity. In order to establish the stereochemistry at the newly generated centre of **14**, its conversion into **5** was sought. Thus the removal of the TBS group in the presence of 1N HCl followed by isopropylidination as reported above gave **5** whose ^{1}H-NMR and optical rotation were in agreement with the data for the sample prepared above.

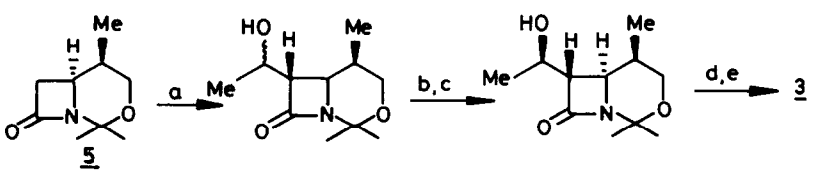
To provide a rationale for the highly stereoselective hydroboration reaction described above, Houk's perpendicular model was considered[21] (Scheme 6). Houk's conformer model 'B' perhaps explains the direction of the borane attack on the double bond of **9** and leads to the transition state 'C'. The intermediate 'D' arising from the transition state 'C' on oxidation provides the product **14** stereoselectively.

Scheme-6



The next aim was to incorporate the chiral side-chain and although several modifications have been suggested, the intrinsic chemistry in all these modificatios essentially follows the work of the Merck group[5]. This approach was adopted to prepare the key intermediate **3b** (Scheme 7).

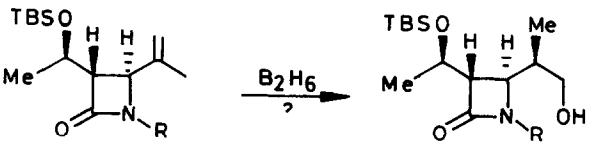
Scheme-7



a) LDA, THF, -78°C, CH_3CHO, 5min , b) TFAA - DMSO, 0°C, 16h , c) K-Selectride, Et O, 0 5h , d) TBS-Cl, DMF, Imi , e) Jones reagent

Inspired by the success of introducing the β-methyl group at position 1 of **3b** using the hydroboration-oxidation reaction of the isopropenyl derivative **9**, we formulated an extension of this approach to an another β-lactam intermediate **15** in which the 1-hydroxy ethyl side chain has already been incorporated (Scheme 8). Thus compound **15** was prepared by the literature procedure[22]. Subsequent Grignard reaction of **15** with excess methylmagnesium iodide in ether gave a number of compounds as judged by TLC. Although, we could not offer any explanation for the failure but predicted that the substituents such as t-butyl ester and N-2,4-dimethoxybenzyl groups, may perhaps be the factors responsible. Therefore, replacing the tert-butyl ester with methyl ester and N-2,4-dimethoxybenzyl with N-TBS groups were envi-

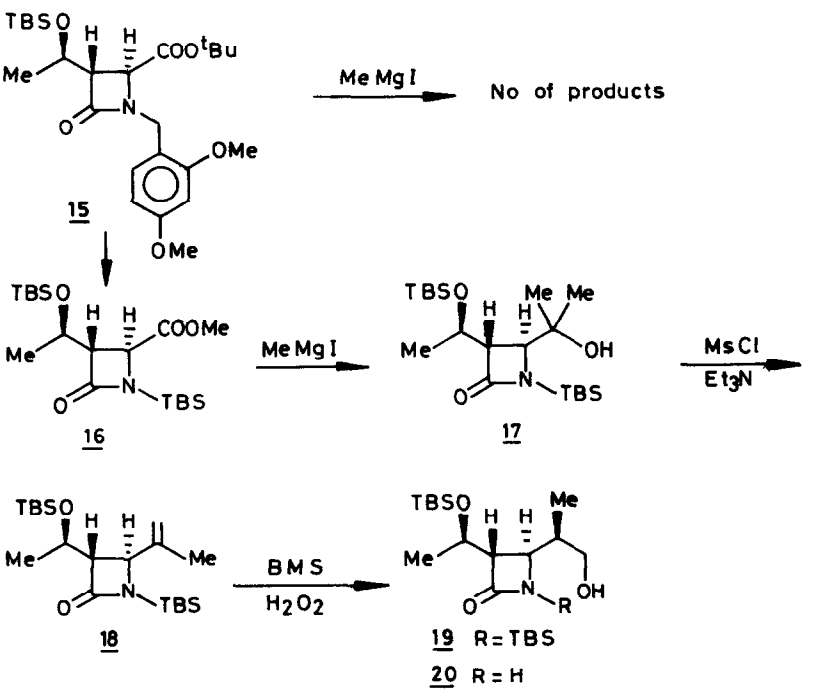
Scheme - 8



6 19

saged. Compound **15** was hydrolysed in the presence of 1N aqueous NaOH for 16 h and then the corresponding acid was treated with diazomethane in ether to obtain the methyl ester. Consequently, the methyl ester was treated with $K_2S_2O_8$ in KH_2PO_4 buffer in 1:1 mixture of water acetonitrile at reflux temperature to give **16** after being protected as TBS derivative. It was gratifying to note that the Grignard reaction of **16** occurred smoothly giving rise to

Scheme-9



the dimethyl carbinol derivative **17** (83%). As described earlier, the elimination reaction of **17** in the presence of mesyl chloride and triethylamine then provided the product **18** (81%). Subsequent hydroboration-oxidation reaction of **18** with 2M borane-methylsulfide-H_2O_2-NaOAc in THF, gave a 64% yield of **19**. In order to assign the structure of **19** without any doubt, the N-TBS group was selectively cleaved in the presence of 1N HCl in methanol to give the known compound **20** whose optical rotation and ^{1}H-NMR spectra were in close agreement with the reported data[11]. (Scheme 9)

In conclusion, we would like to stress, that the two approaches reported above are indeed suitable, due to their simplicity, for large-scale preparation of 1-β-methylthienamycin. The reactions involved are straightforward, using simple reagents, but they provide a high degree of stereoselectivity.

EXPERIMENTAL SECTION

General Procedures

^{1}H-NMR spectra were recorded at 80 MHz or 90 MHz, 200 MHz or 300 MHz instruments using deuterio chloroform as solvent. Infra Red spectra were recorded with a Perkin-Elmer spectrophotometer. Optical rotations were measured on a JASCO DIP 360 or 370 polarimeter. Low resolution and high resolution mass spectra were recorded on VG Micromass 7070H instrument. Column chromatography was done on silica gel 60. Solvents were distilled before use and light petroleum refers to the fraction. b.p. 60-80°C.

(4S)-N-(tert-Butyldimethylsilyl)-4-[1-hydroxy)-1-(methyl)ethyl]-azetidin-2-one (8) : To a solution of methyl magnesium iodide [prepared from 2.28 g (93.8 mmol) of magnesium and (13.7 g) methyl iodide)] in dry ether (50 mL) at 0 °C under nitrogen, was added **7** (12.0 g, 37.6 mmol) in dry ether (100 mL) over a period of 30 min. After 15 h, the reaction was quenched with saturated NH_4Cl solution. The ether layer was separated and aqueous layer was extracted with ether. The combined extract was dried (Na_2SO_4) concentrated and the residue purified over silica gel with ethyl acetate-light petroleum (1:4) as an eluent to afford **8** (7.66 g, 84%) as an oil. **8:** $[\alpha]_D$ -26.7° (c 1, $CHCl_3$). ^{1}H-NMR (90 MHz): δ 0.03 (2s, 6 H $(CH_3)_2Si$), 0.75 (s, 9 H, $(CH_3)_3CSi$), 1.00 (s, 6 H, 2xCH_3), 2.35 (dd, 1 H, J = 3.2 Hz, J = 16 Hz, H-3β), 2.82 (dd, 1 H, J = 6.4 Hz, J = 16 Hz, H-3α), 3.39 (dd, 1 H, J = 3.2 Hz, J = 6.4 Hz, H-4). IR ($CHCl_3$): 3580, 1720 cm^{-1}, MS (m/e): 186 (M^+-57).

(4S)-N-(tert-Butyldimethylsilyl)-4-[1-(methyl)vinyl]-azetidin-2-one (9) : To an ice cooled mixture of **8** (7.66 g, 31.5 mmol) and triethylamine (35 mL, 252 mmol) in dry CH_2Cl_2 (80 mL) was added methanesulfonyl chloride (14.4 g, 126.0 mmol). After 5 hrs. the reaction was poured over ice-water and extracted with dichloromethane. The organic layer was washed with saturated sodium carbonate, water, dired (Na_2SO_4), concentrated and the resulting residue was chromatographed on silica gel by using ethyl acetate-light petroleum (5:95) as eluent to give **9** (5.81 g, 82%) as an oil. **9:** $[\alpha]_D$ -16.8° (c 0.8, $CHCl_3$). ^{1}H-NMR (300 MHz): δ 0.02 (s, 3 H, CH_3Si), 0.18 (s, 3 H, CH_3Si), 0.86 (s, 9 H, $(CH_3)_3CSi$), 1.65 (s, 3 H, CH_3), 2.68 (dd, 1 H, J = 1.5 Hz, J = 15 Hz, H-3β), 3.09 (dd, 1 H, J = 5 Hz, J = 15 Hz, H-3α), 4.0 (m, 1 H, H-4), 4.8-5.0 (br.s, 2 H, =CH_2) IR (Neat): 1720 cm^{-1}. HRMS Calcd. for $C_{11}H_{20}NOSi$ 210.1312,

found 210.1319 (M^+-15).

(4S)-N-(tert-Butyldimethylsilyl)-4-[1-(hydroxymethyl)vinyl]-azetidin-2-one (11) : A mixture of SeO_2 (0.49 g, 4.44 mmol), t-butylhydroperoxide (1.60 g, 17.76 mmol) and dichloromethane (15 mL) was stirred for 30 min. at room temperature and then cooled to 0 °C. Compound **9** (2.0 g, 8.88 mmol) was then added and stirring continued for 48 h at room temperature. The solid material was filtered and the filtrate washed with 5% aqueous sodium bicarbonate, brine, dried (Na_2SO_4) and concentrated to give a residue which was purified by column chromatography on silica gel with ethyl acetate-light petroleum (3:7) to give **11** (1.18 g, 55%), 83% based on recovered **9**) as an oil. **11**: $[\alpha]_D$ -88° (c 0.8, $CHCl_3$), ^{1}H-NMR (300 MHz):δ 0.02 (s, 3 H, CH_3Si), 0.18 (s, 3 H, CH_3Si), 0.90 (s 9 H, $(CH_3)_3CSi$), 2.80 (dd, 1 H, J = 2.5 Hz, J = 15.5 Hz, H-3β), 3.20 (dd, 1 H, J = 5.5 Hz, J = 15.5 Hz, H-3α), 4.1 (m, 3 H, H-4, CH_2OH), 5.2 (m, 2 H, CH_2=); IR (Neat): 3450, 1720 cm^{-1}; MS (m/e): 184 (M^+-57). Analysis calcd. for $C_{12}H_{23}NO_2Si$: C, 59.75; H, 9.60. Found: C, 59.61; H, 9.49.

(6S)-1-Aza-3-oxa-2,2-dimethyl-4-methylenebicyclo[4.2.0]octan-8-one (13) : A mixture of **11** (1.0 g, 4.14 mmol), IN HCl (1 mL) in methanol (7 mL) was stirred at room temperature for 1 h. The reaction mixture was basified with solid sodium bicarbonate, filtered and concentrated. The crude product was purified on silica gel column with ethyl acetate-light petroleum (1:1) as solvent to give **12** (0.48 g).

To **12** (0.48 g, 3.77 mmol), 2,2-dimethoxypropane (1 mL) in dry dichloromethane (8 mL) was added BF_3:OEt_2 (0.05 mL) at room temperature. After stirring for 30 min, the solution was neutralised with triethylamine. It was concentrated and chromatographed on silica gel with dichloromethane to afford **13** (0.57 g, 82.3%) as an oil, **13**: $[\alpha]_D$ -112° (c 0.9, $CHCl_3$). ^{1}H-NMR (80 MHz): δ 1.41, 1.68 (2s, 6 H, $(CH_3)_2C$), 2.82 (dd, 1 H, J = 1.5 Hz, J = 14 Hz, H-7β), 3.21 (dd, 1 H, J = 5.5 Hz, J = 14 Hz, H-7α), 4.0 (m, 3 H, H-4a, 4b, H-6), 4.90, 5.05 (2xbr.s, 2 H, CH_2=), MS (m/e): 167 (M^+).

(6S,5R)-1-Aza-3-oxa-2,2,5-trimethylbicyclo[4.2.0]octan-8-one (5) (by hydrogenation of 13) : A solution of **13** (0.50 g, 2.99 mmol) and Raney Ni (0.6 g, washed with ethyl acetate) in methanol (20 mL) was hydrogenated at normal pressure and temperature for 4 h. The catalyst was filtered and concentrated to get **5** (0.45 g, 90%) as an oil. **5**: $[\alpha]_D$ +34.6° (c 0.5, $CHCl_3$). ^{1}H-NMR (300 MHz): δ 1.1 (d, 3 H, J = 7 Hz, 5-CH_3), 1.4, 1.7 (2s, 6 H, $(CH_3)_2$C-2), 1.9 (m, 1 H, H-5), 2.83 (dd, 1 H, J = 2.2 Hz, J = 15 Hz, H-7β), 2.90 (dd, 2 H, J = 4.5 Hz, J = 15 Hz, H-7α), 3.61 (dd, 1 H, J = 2.5 Hz, J = 12.2 Hz, H-4a), 3.8 (m, 1 H, H-6), 3.93 (dd, 1 H, J = 2.2 Hz, J = 12.2 Hz, H-4b), MS (m/e): 154 (M^+-15).

(4S)-N-(t-Butyldimethylsilyl)-4-[(1R)-(1-hydroxymethyl)ethyl]-azetidin-2-one (14) : To compound **9** (5.81 g, 25.8 mmol) in dry THF (60 mL) at 0 °C was added 2M BMS solution in THF (9.0 mL). After stirring for 2 h at room temperature, a saturated solution of sodium acetate (2 mL) followed by 30% H_2O_2 (4.4 mL) were added. The stirring was continued for 1.5 h and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried (Na_2SO_4), concentrated and the residue was subjected to chromatographic separation on silica gel with ethyl acetate-light petroleum (2:3) as eluent to give **14** (3.85 g, 61%) as an oil. **14**: $[\alpha]_D$ -13° (c 1, $CHCl_3$). ^{1}H-NMR (300 MHz): δ0.02 (s, 3 H, CH_3Si), 0.18 (s, 3 H, CH_3Si), 0.67

(s, 9 H, $(CH_3)_3CSi$), 0.71 (d, 3 H, J = 6.5 Hz, CH_3), 1.79 (m, 1 H, H-5), 2.58 (dd, 1 H, J = 3.0 Hz, J = 15.6 Hz, H-3β), 2.70 (dd, 1 H, J = 5.6 Hz, J = 15.6 Hz, H-3α), 3.26 (dd, 1 H, J = 6.7 Hz, J = 11.2 Hz, one of CH_2OH), 3.32 (m, 1 H, H-4), 3.47 (dd, 1 H, J = 4.5 Hz, J = 11.2 Hz, one of CH_2OH). IR (Neat): 3400, 1750 cm^{-1}. MS (m/e): 186 (M^+-57). Analysis calcd. for $C_{12}H_{25}NO_2Si$: C, 59.21; H, 10.35. Found: C, 59.10; H, 10.17.

(6S,5R)-1-Aza-3-oxa-2,2,5-trimethylbicyclo[4.2.0]octan-8-one (5) : A mixture of **14** (3.85 g, 15.8 mmol), 1N HCl (3 mL) in methanol (25 mL) was stirred at room temperature for 1 h. The reaction mixture was basified with solid sodium bicarbonate, filtered and concentrated. The resulting crude product was purified on silica gel column with ethyl acetate-light petroleum (1:1) as solvent to give amino alcohol (1.93 g, 95%).

To a solution of the amino alcohol (1.93 g, 14.9 mmol) and 2,2-dimethoxypropane (2 mL) in dry dichloromethane (15 mL) was added BF_3:Et_2O (0.1 mL) at room temperature. The mixture was stirred for 30 min. and then neutralised with Et_3N. It was concentrated and passed through a column of silica gel with dichloromethane to give **5** (2.0 g, 78%). **5**: $[\ ]_D$ +33.6° (c 0.5, $CHCl_3$). ^{1}H-NMR spectra was identical with the spectra of the sample reported above.

(3S,4S)-N-(tert-Butyldimethylsilyl)-3-[(1R)-1-(tert-butyldimethylsilyloxy)-ethyl]-4-[1-(hydroxy)-1-(methyl)ethyl]-azetidin-2-one (17) : To a stirred solution of methylmagnesium iodide [prepared from 0.15 g (6.1 mmol) magnesium and 0.79 g (5.6 mmol) methyl iodide] in dry ether (6 mL) at 0 °C under nitrogen was added compound **16** (0.75 g, 1.8 mmol) in dry ether (5 mL) over 10 min. The reaction was stirred at room temperature for 2 h and then quenched by addition of saturated ammonium chloride solution. The ether layer was separated and the aqueous layer was repeatedly extracted with ether. The combined extracts was dried (Na_2SO_4) and concentrated to give an oily residue which was chromatographed on silica gel column. Elution with ethyl acetate and light petroleum (1:10) gave **17** (0.62 g, 83%) as an oil. **17**: $[\alpha]_D$ - 37.5° (c 0.8, $CHCl_3$). ^{1}H-NMR (200 MHz): δ 0.06, 0.09 (2s, 12 H, 2x$(CH_3)_2Si$), 0.81, 0.90 (2s, 18 H, 2x$(CH_3)_3CSi$), 1.15 (s, 6 H, 2xCH_3), 1.21 (d, 3 H, J = 6 Hz, CH_3-CH-OTBS), 2.65 (dd, 1 H, J = 2.5 Hz, J = 8 Hz, H-3), 3.45 (d, 1 H, J = 2.5, H-4), 4.01 (m, 1 H, CH-OTBS). MS (m/e): 344 (M^+ -57). Analysis calcd. for $C_{20}H_{43}NO_3Si_2$: C, 59.90; H, 10.80. Found: C, 59.82; H, 10.69.

(3S,4R)-N-(tert-Butyldimethylsilyl)-3-[(1R)-1-(tert-butyldimethylsilyloxy)-ethyl]-4-[2-(methyl)vinyl]azetidin-2-one (18) · To a mixture of **17** (0.6 g, 1.49 mmol) and triethylamine (1.25 g) in dry CH_2Cl_2 (20 mL) at 0°C was added methanesulfonyl chloride (0.6 g, 5.2 mmol). After 5 h at room temperature, ice was added, followed by extraction with dichloromethane. The organic layer was successively washed with saturated aqueous $NaHCO_3$ solution, water, dried (Na_2SO_4), concentrated and chromatographed on silica gel column by using ethyl acetate-light petroleum (1:20) to give pure **18** (0.46 g, 81%). **18**: $[\alpha]_D$ -31.8° (c 1.2, $CHCl_3$). ^{1}H-NMR (200 MHz): δ0.07, 0.09 (2s, 12 H, 2x$(CH_3)_2Si$), 0.81, 0.93 (2s, 18 H, 2x$(CH_3)_3CSi$), 1.37 (d, 3 H, J = 6.5 Hz, CH_3-CH-OTBS), 1.97 (s, 3 H, CH=CHCH_3), 3.28 (dd, 1 H, J = 2.5 Hz, J = 8 Hz, H-3), 4.37 (d, 1 H, J = 2.5 Hz, H-4), 4.62 (m, 1 H, CH-OTBS), 5.47, 5.65 (two br.s, 2 H, $=CH_2$). MS (m/e): 326 (M^+ -57).

(3S,4R)-(-)-3-[1(R)-1-(tert-Butyldimethylsilyloxy)ethyl]-4-[1(R)-1-(hydroxymethyl)ethyl]azetidin-2-one (20) : To **18** (0.45 g, 1.17 mmol) in dry THF (5 mL) at 0 °C, was added 2M borane-methylsulfide complex in THF (0.5 mL). The reaction mixture was stirred at room temperature for 2 h. Saturated solution of sodium acetate (2 mL) and 30% Hydrogen peroxide solution (1.4 mL) was added at 0°C. Stirring was continued for 1 h at room temperature and then the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was dried (Na_2SO_4) and concentrated. The residue was chromatography on silica gel column with ethyl acetate-light petroleum (1:3) to give **19** (0.30 g, 64%) as an oil. **19**: $[\alpha]_D$ -27.8° (c 0.4, $CHCl_3$). ^{1}H-NMR (200 MHz): δ 0.06, 0.09 (2s, 12 H, 2x$(CH_3)_2$Si), 0.84, 0.90 (2s, 18 H, 2x$(CH_3)_3$CSi), 1.02 (d, 3 H, J = 8 Hz, CH_3), 1.24 (d, 3 H, J = 6 Hz, $\underline{CH_3}$CH-OTBS), 1.91 (m, 1 H, $\underline{CH}$-CH_3), 2.98 (dd, 1 H, J = 2.5 Hz, J = 7.5 Hz, H-3), 3.38 (dd, 1 H, J = 2.5 Hz, J = 5 Hz, H-4), 3.45 (dd, 1 H, J = 5.5 Hz, J = 11 Hz, one of $\underline{CH_2}$OH), 3.65 (dd, 1 H, J = 4.5 Hz, J = 11 Hz, one of $\underline{CH_2}$OH), 3.91 (m, 1 H, $\underline{CH}$-OTBS). MS (m/e): 344 (M^+ - 57). IR (Neat): 3370, 1740 cm^{-1}.

To a solution of **19** (0.10 g, 0.2 mmol) in methanol (5 mL) was added 0.5 mL of 1N HCl. The reaction mixture was stirred for 0.5 h, neutralised with solid bicarbonate and concentrated. The residue was extracted with ethyl acetate (30 mL), concentrated to give an oily residue which was purified on silica gel column with ethyl acetate-petroleum ether (1:1) to give pure **20** (0.022 g, 31%) as an oil. **20**: $[\alpha]_D$ - 20.9° (c 0.55, $CHCl_3$), lit.[11] $[\alpha]_D$ -21.7° (c 0.46, $CHCl_3$).

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