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STEREOSPECIFIC SYNTHESIS OF CHIRAL PRECURSORS OF THIENAMYCIN FROM L-THREONINE

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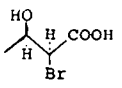
Abstract—L-Threonine was transformed, stereospecifically, to a versatile β-lactam (**5a**) in 3 steps. This β-lactam was further converted to a key intermediate (**25**) for the synthesis of thienamycin and its biologically active analogues. Furthermore, the compound **5a** was changed to iodides (**18** and **23**), cyanides (**19** and **24**), chloromethylketone (**26**) and aldehydes (**30** and **31**) which appear to have a latent potential as precursors for the syntheses of the carbapenems.

In 1976, a Merck research group reported the discovery of a novel β-lactam antibiotic, namely thienamycin,[1] having no traditional amide functionality on the C-6 side chain. Subsequently, many closely related compounds, i.e. such carbapenems as olivanic acid (epithienamycin), PS-5, carpetimycin, asparenomycin, etc., have been discovered as naturally occurring products.[2] Among these, thienamycin itself exhibits the strongest antibiotic activity[3] against many kinds of bacteria including *Pseudomonas* species and also the greatest stability to β-lactamases. For the industrial production of thienamycin by means of fermentation, however, there are serious limitations, due to its strong antibiotic activity, which hinders *Streptomyces cattlea* (one of the thienamycin producing bacteria), and also its instability, which hampers its efficient recovery from the fermentation broth. These facts have spurred many organic chemists into attempts to establish a practical synthetic method for thienamycin and its biologically active analogues. However, there are six major problems requiring solution in order to attain this goal: (i) even though methods for optical resolution, asymmetric synthesis or utilization of a naturally occurring source are available, a choice of an inexpensive chiral starting material is necessary (e.g. L-aspartic acid,[4] penicillin,[5] cephalosporin,[6] L-threonine,[7] D-*allo*-threonine,[7a] (R) - 3 - amino - 4 - (methoxycarbonyl)butyric acid,[8] D-glucose,[9] D-glucosamine,[10] etc); (ii) the elaboration of the three contiguous chiral centers in a stereocontrolled manner; (iii) the construction of the unstable carbapenem bicyclic system; (iv) choice of the protecting groups for hydroxy, carboxy, amino and amide, or finding some way to dispense with the protecting groups; (v) finding suitable methods with few steps and high overall yield; (vi) avoiding undesirable steps in the synthetic process in large-scale production, particularly with a view to the effluent treatment problem. Since it was unrealistic for us to expect to solve these problems at a single stroke, we decided to look initially for possible solutions to the second item while at the same time taking into consideration the first, fifth and sixth items. As a result, having been able to establish a route to chiral key intermediates for carbapenem-synthesis, we wish here to report the route and some modifications.

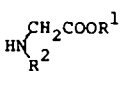
Treatment of (2S, 3R) - 2 - bromo - 3 - hydroxybutyric acid (**1**), obtained easily from L-threonine,[11] with *tert*-butyl N-2,4-dimethoxybenzylglycinate (**2a**, R^1 = t-Bu, R^2 = 2,4-dimethoxybenzyl) by use of N,N-dicyclohexylcarbodiimide (DCC) as a dehydrative coupling reagent gave an amide **3a** (R^1 = t-Bu, R^2 = 2,4-dimethoxybenzyl) in 84% yield. The other analogues (**3b–e**) were also obtained by the condensation of **1** and the corresponding amines (**2b–e**). Azetidinone ring formation of **3a** was accomplished by use of two equivalents of lithium hexamethyldisilazide in tetrahydrofuran (THF) via cis-epoxide (**4**) to give **5a**; $[\alpha]_D^{24}$ + 20.1° (c = 2.5, $CHCl_3$); in 61% yield. If necessary, we can easily isolate the cis-epoxide (**4**) which also cyclized to **5a** by the same treatment. In this reaction, the reaction temperature influences the ratio of products. When this reaction was carried out at −78°, the reaction products were trans-isomer (**5a**) and cis-isomer (**6**) in 28% and 4.8% yield respectively, accompanied by 50% recovery of epoxide (**4**). On the other hand, when the same reaction was run at 20–23°, only one product (**5a**) was afforded without yielding cis-isomer (**6**). It is assumed that the conformational isomer (**A**) of the reaction intermediate is preferred to **B**, which would be more hindered sterically (Scheme 2). Moreover, there was no epimerization from **6** to **5a** or from **5a** to **6** on treatment with lithium hexamethyldisilazide in THF at 20–23°, and both compounds were stable under this condition. Therefore, a kinetic control is operative in this reaction.

The other isomers (**3b–e**) also afforded the corresponding azetidin-2-ones (**5b–e**) under the same treatment (Scheme 1). Compound **5a** was further transformed to thienamycin intermediates (Scheme 3).

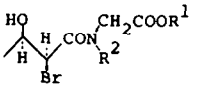
Protection of the hydroxy group of **5a** by t-butyldimethylsilyl chloride and 4-dimethylaminopyridine in dimethylformamide (DMF) gave **7a** in 97% yield. Saponification of **7a** in ethanol at 50° for 18 h with the same equivalent of 1N NaOH gave a carboxylic acid (**8**) in 92% yield as a viscous oil. The carboxylic acid (**8**) was converted to an acid chloride (**9**) on treatment with oxalyl chloride in THF, and



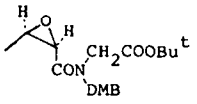
1



2a-e



3a-e



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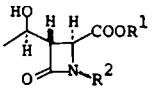
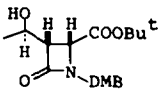


5a-e

27. R^1=H, R^2=DMB

32. R^1=Bu^t, R^2=H



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a. R^1=Bu^t, R^2=DMB

b. R^1=CH_2Ph, R^2=DMB

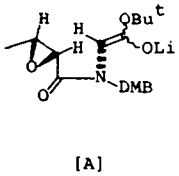
c. R^1=Me, R^2=DMB

d. R^1=Bu^t, R^2=CH_2Ph

e. R^1=Bu^t, R^2=p-methoxyphenyl

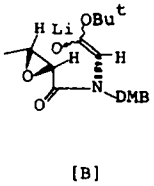
DMB=2,4-dimethoxybenzyl

Scheme 1.



[A]

5a

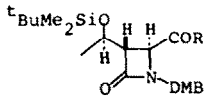


[B]

6

Scheme 2.

successive treatment with etherial diazomethane gave a corresponding diazoketone (**10**) in 66% yield from **7a**. Wolff rearrangement of **10** in water or benzylalcohol by irradiation (generated by 450 W high pressure mercury–vapour lamp, through a pyrex filter) proceeded with retention of configuration at C-4 position to afford a homologated carboxylic acid (**11**, m.p. 136–138°) or its benzyl ester (**12**) in 81 or 46% yield, respectively. When this reaction was carried using silver benzoate as a catalyst, a mixture of cis- and trans-isomers was obtained. On the other hand, treatment of **10** in methanol with silver oxide as a catalyst, gave a β-lactam ring cleavage product (**33**) in 71% yield, exclusively. Catalytic hydrogenation of benzyl ester (**12**) in ethyl acetate using 10% palladium on carbon also afforded **11** in 96% yield. Treatment of the acid **11** with oxalyl chloride in THF yielded carboxylic acid chloride (**13**), which was further transformed to a mixture of diazomethyl ketone (**14**) and chloromethyl ketone (**15**) on treatment with etherial diazomethane. Treatment of this mixture in THF with hydrogen chloride gave **15**, in 33% yield from **11**, accompanied by evolution of nitrogen. Other derivatives were also obtained from **7a** and **7b** as follows. The esters **7a** and **7b** were reduced to an alcohol (**16**) by sodium borohydride in ethanol in 53% and quantitative yields, respectively. The t-butylester (**7a**) offered little resistance to sodium borohydride reduction, but the methyl ester (**7b**) was reduced smoothly. Mesylation of **16** in methylene chloride with mesyl chloride and triethylamine gave **17** in 98% yield, which was treated with sodium iodide in acetone to afford an iodide (**18**) in 82% yield. Treatment of **18** with potassium cyanide in DMF at 50° for 15 h gave **19** in 93% yield. Deprotection of the 2,4-dimethoxybenzyl group in **19** according to a reported method[12] by use of potassium persulfate–dipotassium hydrogen phosphate in acetonitril–water (1:1) gave **24** (m.p. 97.5–98.5°; $[\alpha]_D^{25}$ − 19.0° (c = 2.00, EtOH)) in 83% yield. This



7a. R=OBu^t

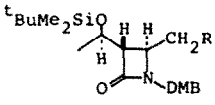
7b. R=OMe

8. R=OH

9. R=Cl

10. R=CHN_2

30. R=H



11. R=COOH

12. R=$COOCH_2Ph$

13. R=COCl

14. R=$COCHN_2$

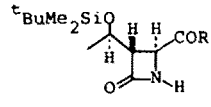
15. R=$COCH_2Cl$

16. R=OH

17. R=OSO_2Me

18. R=I

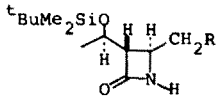
19. R=CN



20a. R=OBu^t

20b. R=OMe

31. R=H



21. R=OH

22. R=OSO_2Me

23. R=I

24. R=CN

25. R=$COOCH_2Ph$

26. R=$COCH_2Cl$

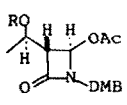
Scheme 3.

method for cleavage of the 2,4-dimethoxybenzyl group was attempted on compounds **5a**, **7a**, **7b**, **12**, **15**, **16**, and **18** which were converted to the corresponding free amides **32** (76%), **20a** (82%), **20b** (69%), **25** (56%), **26** (57%), **21** (60%), and **23** (41%), respectively. Another approach to the iodide (**23**) is as follows: Sodium borohydride reduction of **20a** and **20b** gave **21** in 89% and quantitative yields, respectively, as a crystalline solid (m.p. 89–90°), which was further mesylated with mesyl chloride and triethylamine in methylene chloride to give **22** in 83% yield. Compound **22** was converted to a corresponding iodide (**23**) in 83% yield by treatment with sodium iodide in acetone. Treatment of **23** with potassium cyanide in DMF as described in the conversion of **18** to **19** failed to afford cyanide **24**.

Alternatively, an effective method for synthesis of benzyl ester (**25**) via N-protected **12** was developed. In the above mentioned route, diazoketone **10** for Wolff rearrangement was prepared on treatment of acid chloride (**9**) with diazomethane. This route, however, was not suitable for large-scale preparation due to the necesssity of using highly toxic and explosive diazomethane. To avoid this route, t-butyl ester (**5a**) was converted to carboxylic acid (**27**) on treatment with trifluoroacetic acid. Applying essentially the Merck procedure,[46] treatment of **27** in DMF-acetic acid with 1 equivalent of lead tetraacetate at 60–70° for 5 min gave acetate **28** which was successively silylated with t-butyldimethylsilyl chloride and 4-dimethylamino pyridine in DMF to give **29** (23.6% from **5a**) as a viscous oil. Treatment of acetate **29** in dichloromethane with 1-benzyloxy-1-trimethylsilyloxyethylene in the presence of catalytic amount of trimethylsilyl trifluoromethanesulfonate at room temperature for 16 h according to Barrett's method[13] gave **12** in 37% yield which was easily converted to **25**. The benzyl ester (**25**) had already been correlated to thienamycin.[14] Thus we accomplished a formal total synthesis of thienamycin from L-threonine.

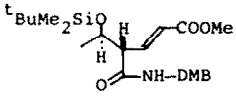
Moreover, C-4 formyl derivatives having the same correct three contiguous configurations as those of thienamycin were obtained. Either reduction of acid chloride (**9**) with bis(triphenylphosphine)copper(I) tetrahydroborate[15] or Pfitzner–Mofatt oxidation of alcohol **16** with DMSO–DCC–H_3PO_4 gave an aldehyde (**30**) in 60 or 92% yield, respectively. On the other hand, it was difficult to obtain in good yield the corresponding N-free aldehyde (**31**) by oxidation of **21** or by 2,4-dimethoxybenzyl deprotection of **30**. However, reduction of methyl ester (**20b**) with sodium bis(2-methoxyethoxy)aluminium hydride at −78° in THF gave **31** in 78% yield, which was unstable for standing for long periods at room temperature and easily dimerized with bases such as triethylamine. Also, the nitrogen protecting groups, 2,4-dimethoxybenzyl and p-methoxyphenyl (in the case of **5e**) were easily cleaved by ceric ammonium nitrate (CAN)[16] at any stage. For example, treatment of both compounds **5a** and **5e** with CAN in acetone–water gave **32** in 57% and 53% yields, respectively.

We believe that these aldehydes (**30** and **31**), iodides (**18** and **23**), cyanides (**19** and **24**) and chloromethylketone (**26**) are potential precursors for the carbapenem synthesis.



28. R=H

29. R=$SiBu^tMe_2$



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DMB=2,4-dimethoxybenzyl

EXPERIMENTAL

All m.ps are uncorrected. Optical rotations were obtained using a Perkin–Elmer 241 Polarimeter. ^{1}H NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The IR absorption spectra were determined on a Jasco IR A-2 spectrophotometer, and mass spectra were obtained on a JMS-01SG mass spectrometer. Preparative TLC was performed on silica gel plates (Merck 60 PF_{254}). Elemental analyses were performed by the Analytical Center of Analytical and Metabolic Research Laboratories, Sankyo Company, Limited.

t-Butyl N-(2,4-dimethoxybenzyl)glycinate (**2a**). A mixture of 2,4-dimethoxybenzylamine hydrochloride (101.8 g, 0.50 mol), t-butyl bromoacetate (110 g, 0.564 mol) and Et_3N (150 g, 1.49 mol) in THF (2.5 L) was refluxed for 1 h. After cooling, the reaction mixture was filtered to remove Et_3N.HCl which was washed with a small volume of THF. The combined filtrates were concentrated *in vacuo* to give an

oily residue which was chromatographed on silica gel (1.5 kg). Elution with cyclohexane–EtOAc (1:3) gave **2a** (81.7 g, 58%) as an oil; NMR ($CDCl_3$) δ 1.46 (9H, s), 2.00 (1H, s, NH), 3.27 (2H, s), 3.73 (2H, s), 3.89 (3H, s), 3.91 (3H, s), 6.3–6.5 (2H, m), 7.10 (1H, d, J = 9 Hz).

Preparation of **2b–2e**. The same reaction in the case of 2,4-dimethoxybenzylamine and benzylbromoacetate, 2,4-dimethoxybenzylamine and methyl chloroacetate, benzylamine and t-butyl bromoacetate, and p-anisidine and t-butyl bromoacetate gave corresponding secondary amines **2b**, **2c**, **2d** and **2e**, respectively.

Physical data: **2b**: NMR ($CDCl_3$) δ 2.31 (1H, s, NH), 3.38 (2H, s), 3.72 (2H, s), 3.76 (6H, s), 5.08 (2H, s), 6.26–6.45 (2H, m), 7.06 (1H, d, J = 9 Hz), 7.30 (5H, s); IR ν_{max}(film) 1740, 1613, 1590 cm^{-1}. **2d**: NMR ($CDCl_3$) δ 1.43 (9H, s), 1.88 (1H, s, NH), 3.25 (2H, s), 3.74 (2H, s), 7.23 (5H, s). **2e**: NMR ($CDCl_3$) δ 1.45 (9H, s), 3.67 (6H, s, NH, CH_2, OCH_3), 6.43 (2H, d, J = 9 Hz), 6.69 (2H, d, J = 9 Hz).

(2*S*, 3*R*) - *N* - (2,4 - *Dimethoxybenzyl*) - *N* - (*t* - *butoxycarbonylmethyl*) - 2 - *bromo* - 3 - *hydroxybutyramide* (**3a**). To a stirred solution of (2S, 3R) - 2 - bromo - 3 - hydroxybutyric acid[10] (**1**, 54.8 g, 0.30 mol) and **2a** (84.4 g, 0.30 mol) in THF (700 mL), DCC (61.8 g, 0.30 mol) was added at 20–25°. After 15 min, the precipitated DCC–H_2O was removed by suction filtration, and washed with a small volume of benzene. The combined filtrates were concentrated *in vacuo*, and chromatographed on silica gel (2 kg, eluted with cyclohexane–EtOAc = 2:1) to give **3a** (112 g, 84%) as a viscous oil; MS *m/z* 445 (M^+, ^{79}Br), 366, 348, 293, 281; IR ν_{max}(film) 3430, 1740, 1640, 1615, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (3H, d, J = 6 Hz), 1.45 (9H, s), 3.81 (6H, s), 3.9–5.0 (6H, m), 6.35–6.60 (2H, m), 7.05 (1H, d, J = 8.5 Hz); and a by-product, (2S, 3R) - N - (2 - bromo - 3 - hydroxybutyryl) - N,N′ - dicyclohexylurea (10.5 g, 9.0%), as a crystalline solid in the less polar fraction.

Preparation of **3b–3e**. Condensation of (2S, 3R) - 2 - bromo - 3 - hydroxybutyramide and each of **2b**, **2c**, **2d** and **2e** with DCC according to the same procedure described above gave corresponding amides **3b** (containing a small amount of the other conformer), **3c**, **3d** (as *ca* a 1:1 mixture of conformers) and **3e**, respectively. Physical data of **3b–3e**: **3b**: NMR ($CDCl_3$) δ 1.27 (3H, d, J = 6 Hz), 3.70 (3H, s), 3.77 (3H, s), 4.0–5.0 (6H, m), 5.06 (2H, s), 6.3–6.5 (2H, m), 7.02 (1H, d, J = 9 Hz), 7.35 (5H, s). **3c**: NMR ($CDCl_3$) δ 1.29 (3H, d, J = 6 Hz), 3.70 (3H, s), 3.82 (6H, s), 3.9–5.0 (7H, m), 6.35–6.53 (2H, m), 7.05 (1H, d, J = 9 Hz); IR ν_{max}(film) 3440, 1745, 1640, (broad), 1613, 1588 cm^{-1}. **3d**: NMR ($CDCl_3$) δ 1.23, 1.26 (each 3H, d, J = 6 Hz), 1.40, 1.45 (each 9H, s), 3.8–4.8 (7H × 2, m), 7.23 (5H × 2, bs). **3e**: NMR ($CDCl_3$) δ 1.12 (3H, d, J = 6 Hz), 1.48 (9H, s), 3.83 (2H, s), 3.97, 4.40 (2H, AB-q, J = 17 Hz), 4.01 (1H, m), 4.08 (1H, d, J = 3 Hz), 6.90 (2H, d. J = 9 Hz), 7.33 (2H, d, J = 9 Hz).

(2*S*, 3*R*) - *N* - (2,4 - *Dimethoxybenzyl*) - *N* - (*t* - *butoxycarbonylmethyl*) - 2,3 - *epoxybutyramide* (**4**). To a stirred solution of **3a** (253 mg, 0.567 mmol) in THF (3 mL), DBU (172 mg, 1.13 mmol) was added at room temp. After 4 h, the reaction mixture was diluted with EtOAc, washed with 10% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue. Chromatography on preparative silica gel TLC plates (developed with cyclohexane–EtOAc = 1:1, R_f = 0.375) gave **4** (175 mg, 85%); $[\alpha]_D^{24}$ + 60.8° (c = 2.00, $CHCl_3$); MS *m/z* 365 (M^+); IR ν_{max}(film) 1745, 1665, 1615, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (3H, d, J = 6 Hz), 1.44 (9H, s), 3.36 (1H, qd, J = 6, 10 Hz), 3.81 (6H, s), 3.94 (1H, d, J = 10 Hz), 3.70, 4.18 (2H, AB-q, J = 2, 9 Hz), 6.47 (1H, d, J = 2 Hz), 7.05 (1H, d, J = 9 Hz).

[3*S* - [3α(*S**),4β]] - *t* - *Butyl* 1 - (2,4 - *dimethoxybenzyl*)-3 - (1 - *hydroxyethyl*) - 2 - *azetidinone* - 4 - *carboxylate* (**5a**). To a stirred solution of **3a** (44.6 g, 0.10 mol) in THF (600 mL) under nitrogen, half of an $LiN(SiMe_3)_2$ solution (prepared by addition of n-BuLi solution (150 mL of 1.6 M n-hexane solution, 0.24 mol) into a solution of $HN(SiMe_3)_2$ (37.2 g, 0.23 mol) in THF (400 mL) at ice cooling or room temp) was added over 15 min at 0–5°. After 15 min, the temperature was elevated to 20°, and the second half of the $LiN(SiMe_3)_2$ solution was added to the resulting solution at 20–25°. After 1 h, the reaction mixture was quenched with 10% HCl and diluted with EtOAc. The organic layer was washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil which was chromatographed on silica gel (1.2 kg). Elution with cyclohexane–EtOAc (1:2) gave **5a** (22.2 g, 61%) as a viscous oil; $[\alpha]_D^{24}$ + 20.1° (c = 2.25, $CHCl_3$); IR ν_{max}(film) 3430, 1760, 1745, 1615, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (3H, d, J = 6 Hz), 1.45 (9H, s), 2.83 (1H, bs, OH), 3.10 (1H, dd, J = 2.5, 4 Hz), 3.79 (6H, s), 3.88 (1H, d, J = 2.5 Hz), 4.11 (1H, m), 4.14, 4.61 (2H, AB-q, J = 14 Hz), 6.40 (1H, dd, J = 2, 9 Hz), 6.41 (1H, d, J = 2 Hz), 7.11 (1H, d, J = 9 Hz); MS *m/z* 365 (M^+), 337, 321, 309, 265, 237, 153.

Preparation of **5b–5e**. Each solution of **3b**, **3c**, **3d** and **3e** in THF was treated as described above to give **5b** (40%), **5c** (33%), **5d** (52%) and **5e** (46%), respectively. Physical data of **5b–5e**. **5b**: NMR ($CDCl_3$) δ 1.21 (3H, d, J = 6 Hz), 2.32 (1H, bs, OH), 3.16 (1H, dd, J = 2.5, 4 Hz, C_3–H), 3.64 (3H, s), 3.74 (6H, s), 3.97 (1H, d, J = 2.5 Hz, C_4–H), 4.08 (1H, m), 4.10, 4.60 (2H, AB-q, J = 14 Hz), 5.10 (2H, s), 6.35–6.55 (2H, m), 7.07 (1H, d, J = 9 Hz), 7.36 (5H, s). **5c**: NMR ($CDCl_3$) δ 1.23 (3H, d, J = 6 Hz), 2.54 (1H, bs, OH), 3.16 (1H, dd, J = 2.5, 5 Hz, C_3–H), 3.70 (3H, s,), 3.75 (3H, s), 3.77 (3H, s), 3.98 (1H, d, J = 2.5 Hz, C_4–H), 4.09 (1H, m), 4.11, 4.60 (2H, AB-q, J = 14 Hz), 6.36 (1H, dd, J = 2, 9 Hz), 6.36 (1H, dd, J = 2, 9 Hz), 6.36 (1H, d, J = 2 Hz), 7.10 (1H, d, J = 9 Hz); IR ν_{max}(film) 3430, 1745 (broad), 1693, 1590 cm^{-1}. **5d**: m.p. 83.5–84.5° (from i-Pr_2O); $[\alpha]_D^{24}$ − 7.3° (c = 2.01, EtOH); MS *m/z* 306 (M^+ + 1), 277, 248, 204, 176, 160. NMR ($CDCl_3$) δ 1.25 (3H, d, J = 6 Hz), 1.44 (9H, s), 3.20 (1H, dd, J = 2.5, 3.5 Hz, C_3–H), 3.99 (1H, d, J = 2.5 Hz, C_4–H), 4.15, 4.80 (AB-q, J = 15 Hz), 4.25 (1H, dq, J = 3.5, 6 Hz), 7.26 (5H, s); IR ν_{max}(KBr) 3420, 1754, 1733 cm^{-1}. (Calc for $C_{17}H_{23}O_4N$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.85; H, 7.63; N, 4.62%.) **5e**: m.p. 118–120° (from i-Pr_2O); $[\alpha]_D^{24}$ − 97.5° (c = 1.33, EtOH); MS *m/z* 321 (M^+), 265. NMR ($CDCl_3$) δ 1.32 (3H, d, J = 6 Hz), 1.45 (9H, s), 1.70 (1H, bs, OH), 3.28 (1H, dd, J = 2.5, 4 Hz, C_3–H)), 3.75 (3H, s), 4.30 (1H, m), 4.44 (1H, d, J = 2.5 Hz, C_4–H), 6.77 (2H, d, J = 9 Hz), 7.18 (2H, d, J = 9 Hz); IR ν_{max}(Nujol) 3510, 1759, (shoulder), 1750, 1740 cm^{-1}. (Calc for $C_{17}H_{23}O_5N$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.46; H, 7.11; N, 4.36%.)

A mixture of [3*S* - [3α(*S**),4β]] - *and* [3*S* - [3α(*S**),4α]] - *t* - *butyl* 1 - (2,4 - *dimethoxybenzyl*) - 3 - (1 - *hydroxyethyl*)-2 - *azetidinone* - 4 - *carboxylate*, (**5a**) *and* (**6**).

(i) The amide (**3a**) was treated as described above, except that the second half of the $LiN(SiMe_3)_2$ solution was added to the resulting epoxide (**4**) at −78°, to give **5a** (22%), **6** (3%) and **4** (40%).

(ii) To a solution of **4** (270 mg, 0.75 mmol) in THF (5 mL) under nitrogen, $LiN(SiMe_3)_2$ solution {prepared by addition of n-BuLi solution (0.65 mL of 1.6 M n-hexane solution, 1 mmol) into a solution of $HN(SiMe_3)_2$ (161 mg, 1 mmol) in THF (5 mL) at room temp} was added dropwise at −78°. After 3 h stirring, the reaction mixture was quenched with excess AcOH, and diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oily mixture which was separated on a preparative silica gel plate. Development with cyclohexane–EtOAc (1:2) gave trans-isomer (**5a**, 75 mg, 28%, R_f = 0.314), cis-isomer (**6**, 13 mg, 4.8%, R_f = 0.407); $[\alpha]_D^{25}$ + 13.1° (c = 0.75, $CHCl_3$); MS *m/z* 365 (M^+), 337, 321, 309, 153; IR ν_{max}(film) 3430, 1760, 1745, 1615, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (3H, d, J = 6 Hz), 1.53 (9H, s), 2.60 (1H, bs, OH), 3.30 (1H, dd, J = 5.5, 10 Hz), 3.81 (6H, s), 3.95 (1H, d, J = 5.5 Hz), 4.12, 4.69 (2H, AB-q, J = 14 Hz), 6.43 (1H, dd, J = 2, 9 Hz), 6.45 (1H, d, J = 2 Hz), 7.12 (1H, d, J = 9 Hz), and the recovered epoxide (**4**, R_f = 0.535, 135 mg, 50%).

[3*S* - [3α(*S**),4β]] - *t* - *Butyl* 1 - (2,4 - *dimethoxybenzyl*)-3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 2 - *azetidinone* - 4 - *carboxylate* (**7a**). To a solution of **5a** (10.4 g, 28.4 mmol) in DMF (25 mL) was added t-butyldimethylsilyl chloride

(5.15 g, 34.1 mmol) and 4-dimethylaminopyridine (4.20 g, 34.4 mmol). The mixture was stirred overnight at room temp, and diluted with EtOAc. The whole was washed with 5% HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$, and concentrated to give an oily mixture which was separated on a silica gel column. Elution with cyclohexane–EtOAc (4:1) gave **7a** (13.2 g, 96.7%) as an oil; NMR ($CDCl_3$) δ 0.05 (6H, s), 0.77 (9H, s), 1.15 (3H,d, J = 6 Hz), 1.47 (9H, s), 3.04 (1H, dd, J = 2.5, 4 Hz, C_3–H), 3.77 (6H, s), 3.96 (1H, d, J = 2.5 Hz, C_4–H), 4.26 (1H, dq, J = 4, 6 Hz), 4.19, 4.51 (2H, AB-q, J = 14 Hz), 6.39 (1H, dd, J = 2, 9 Hz), 6.40 (1H, d, J = 2 Hz), 7.10 (1H, d, J = 9 Hz).

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 2 - *azetidinone* - 4 - *carboxylic acid* (**8**). A solution of **7a** (2.4 g, 5 mmol) in EtOH (13 mL) and 1N NaOH (6 mL) was stirred for 18 h at 50–55°. After checking on the disappearence of **7a** with TLC, the reaction mixture was acidified with 5% HCl, and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 2.2 g of a crude acid (**8**) characterized as its methyl ester. The crude 100 mg of **8** was esterified with CH_2N_2, and purified on a preparative silica gel TLC plate to give 92 mg of methyl ester (**7b**). Accordingly, the crude acid (2.2 g), which was employed for the next reaction without further purification, contained more than 1.96 g of **8** (92.5% yield); NMR ($CDCl_3$) δ 0.06 (6H, s), 0.78 (9H, s), 1.24 (3H, d, J = 6 Hz), 3.27 (1H, t, J = 3 Hz, C_3-H), 3.83 (6H, s), 4.19 (1H, d, J = 3 Hz, C_4–H), 4.28, 4.62 (2H, AB-q, J = 14 Hz), 4.32 (1H, m), 6.46 (1H, dd, J = 2, 9 Hz), 7.16 (1H, bs, COOH), 7.20 (1H, d, J = 9 Hz).

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 2 - *azetidinone* - 4 - *carboxylic acid chloride* (**9**). To a solution of the crude acid (2.1 g), obtained above, in THF (20 mL) was added oxalyl chloride (1.0 mL). After a reaction time of 2 h with stirring at 25°, the reaction mixture was concentrated *in vacuo* to give an acid chloride (**9**, 2.1 g), which was employed for the next reaction.

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 4 - *diazoacetyl* - 2 - *azetidinone* (**10**). To an excess etherial CH_2N_2 solution was added gradually a solution of **9** (2.1 g) in THF (20 mL) at 0–5° with stirring. After 30 min, the reaction mixture was concentrated *in vacuo* to give an oily residue which was chromatographed on a silica gel (40 g) column. Elution with cyclohexane–EtOAc (2:1) gave a diazomethylketone (**10**, 1.42 g, 66% yield from **7a**); IR ν_{max}(film) 2110, 1760, 1645, 1615, 1590, 1510 cm^{-1}; NMR ($CDCl_3$) δ 0.03 (6H, s), 0.84 (9H, s), 1.22 (3H, d, J = 6.5 Hz), 3.05 (1H, dd, J = 2, 2.5 Hz, C_3–H), 3.78 (3H, s), 3.81 (3H, s), 4.06 (1H, d, J = 2.5 Hz, C_4–H), 4.0–4.5 (1H, m), 4.20, 4.48 (2H, AB-q, J = 14 Hz), 5.30 (1H, s), 6.40 (1H, dd, J = 2, 9 Hz), 6.40 (1H, d, J = 2 Hz), 7.13 (1H, d, J = 9 Hz).

[3*S* - [3α(*S**),4β]] - [1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 2 - *azetidinone* - 4 - *yl*]*acetic acid* (**11**).

(i) A solution of **10** (2.0 g) in dioxane–H_2O (15:13, 140 mL) was irradiated with a high pressure mercury-vapour lamp (450 W) through a pyrex filter for 60 min at 15–20°. After checking the disappearance of diazo-compound, the volume of the reaction mixture was reduced to half *in vacuo*. The residue was diluted with excess 0.1N-NaOH, and the whole was washed with ether to remove non-acidic materials, adjusted to pH 3 with 10% HCl, and extracted with EtOAc. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **11** (1.58 g, 81%) as a crystalline solid; m.p. 136–138° (prisms, from EtOAc–n-hexane); NMR ($CDCl_3$) δ 0.02 (3H, s), 0.04 (3H, s), 0.79 (9H, s), 2.42 (1H, dd, J = 7, 15 Hz), 2.76 (1H, dd, J = 5, 15 Hz), 2.91 (1H, dd, J = 2, 4 Hz, C_3–H), 3.78 (6H, s), 3.8–4.2 (2H, m, C_4–H and CH–OSi), 4.14, 4.40 (2H, AB-q, J = 14.5 Hz), 6.38 (1H, d, J = 2 Hz), 6.38 (1H, dd, J = 2, 9 Hz), 7.13 (1H, d, J = 9 Hz), 9.00 (1H, bs, COOH); IR ν_{max}(Nujol) 3200–2500 (broad), 1740, 1710, 1612, 1588 cm^{-1}. (Calc for $C_{22}H_{35}O_6NSi$: C, 60.38; H, 8.06; N, 3.20. Found: C, 60.26; H, 8.03; N, 3.24%.)

(ii) Catalytic hydrogenation of **12** (44 mg) in EtOAc (2 mL) with 10% palladium on carbon (20 mg) gave **11** (36 mg, 96%) as a crystalline solid.

[3*S* - [3α(*S**),4β]] - *Benzyl*[1 - (2,4 - *dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 2 - *azetidinone* - 4 - *yl*]*acetate* (**12**).

(i) Irradiation of **10** in benzylalcohol (3% solution) under the same conditions as described above, and successive purification on preparative silica gel TLC plates (development with cyclohexane–EtOAc (2:1), R_f = 0.45) gave **12** (46.6%) as a gum; NMR ($CDCl_3$) δ 0.03 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.12 (3H, d, J = 6 Hz), 2.44 (1H, dd, J = 7, 14.5 Hz), 2.75 (1H, dd, J = 5, 14.5 Hz), 2.87 (1H, dd, J = 2, 4 Hz), 3.76 (6H, s), 3.8–4.2 (2H, m), 4.12, 4.38 (2H, AB-q, J = 15 Hz), 5.00 (2H, s), 6.36 (1H, d, J = 2 Hz), 6.36 (1H, dd, J = 2, 9 Hz), 7.12 (1H, d, J = 9 Hz), 7.30 (5H, s); IR ν_{max}(film) 1750–1735, 1615, 1590 cm^{-1}; MS *m/z* 527 (M^+), 470 (M^+–C_4H_9).

(ii) To a solution of **29** (100 mg, 0.23 mmol) in CH_2Cl_2 (1.5 mL) was added 1 - benzyloxy - 1 - trimethylsilyloxyethylene (110 mg, 0.49 mmol) and trimethylsilyl trifluoromethanesulphonate (12 mg, 0.05 mmol) at 20° under nitrogen. After 16 h stirring, the reaction mixture was chromatographed on a preparative silica gel TLC plate (20 × 20 × 0.2 cm). Development with cyclohexane–EtOAc (2:1) gave **12** (45 mg, 37.3%).

(4*S*,5*R*,2*E*) - *Methyl* 4 - (2,4 - *dimethoxybenzylaminocarbonyl*) - 5 - (*t* - *butyldimethylsilyloxy*) - 2 - *hexenoate* (**33**). To a solution of diazoketone (**10**, 223 mg, 0.5 mmol) in MeOH (4 mL) was added Ag_2O (500 mg). The mixture was stirred for 5 h at room temp, concentrated *in vacuo* to give an oily residue, and purified on silica gel preparative TLC plates (developed with cyclohexane–EtOAc (2:1), R_f = 0.474) to give **33** (192 mg, 71%) as a viscous oil; MS *m/z* 451 (M^+), 394 (M^+–C_4H_9); IR ν_{max}(film) 3320, 1728, 1650, 1618, 1592 cm^{-1}; NMR ($CDCl_3$) δ 0.01 (3H, s) 0.04 (3H, s), 0.83 (9H, s), 1.10 (3H, d, J = 6 Hz), 2.94 (1H, dd, J = 4, 9 Hz), 3.69 (3H, s), 3.76 (6H, s), 3.9–4.4 (2H, m), 5.82 (1H, d, J = 16 Hz), 6.22–6.44 (3H, m, aromatic 2H + NH), 6.98 (1H, dd, J = 9, 16 Hz), 7.06 (1H, d, J = 9.5 Hz, aromatic 1H).

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 4 - (2 - *oxo* - 3 - *diazopropyl*) - 2 - *azetidinone* (**14**). To a solution of **11** (219 mg, 0.5 mmol) in THF (4 mL) was added oxalyl chloride (0.2 mL). The mixture was stirred for 12 h at room temp, concentrated *in vacuo* to give an acid chloride (**13**) which was diluted with THF (4 mL), and the resultant solution was added dropwise to an ethereal solution of a large excess of CH_2N_2 at 5°. The mixture was stirred for 30 min at room temp, concentrated *in vacuo*, and chromatographed on a silica gel preparative TLC plate. Development with cyclohexane–EtOAc (1:1) gave **14** (R_f = 0.220, 75 mg, 32.5%) as a viscous oil and **15** (R_f = 0.463, 15 mg, 6.4%) as a viscous oil. Physical data of **14**; NMR ($CDCl_3$) δ 0.03 (6H, s), 0.82 (9H, s), 1.16 (3H, d, J = 6 Hz), 2.34 (1H, dd, J = 7, 15 Hz), 2.64 (1H, dd, J = 6, 15 Hz), 2.83 (1H, dd, J = 2, 4.5 Hz), 3.78 (3H, s), 3.80 (3H, s), 3.7–4.3 (2H, m), 4.27 (2H, s, NCH_2Ar), 5.05 (1H, s, $COCHN_2$), 6.40 (1H, dd, J = 2, 9 Hz), 6.40 (1H, d, J = 2 Hz), 7.14 (1H, d, J = 9 Hz); IR ν_{max}(film) 2115, 1750, 1640, 1615, 1590, 1510 cm^{-1}.

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 4 - (2 - *oxo* - 3 - *chloropropyl*) - 2 - *azetidinone* (**15**). To a solution of **11** (7.5 g, 17.1 mmol) in THF (60 mL) was added oxalyl chloride (5 mL). The reaction mixture was stirred for 5 h at room temp, concentrated *in vacuo* to give an oily acid chloride (**13**), which was dissolved in THF (60 mL). To this solution was added ethereal diazomethane solution at 5–10°. After 30 min stirring, the reaction mixture was concentrated *in vacuo* to give a mixture of **14** and **15**, which was dissolved

in THF (60 mL). The resulting solution was treated with HCl gas at 5–10° for a few min, diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (2:1) gave **15** (2.66 g, 33%); NMR ($CDCl_3$) δ 0.03 (6H, s), 0.76 (9H, s), 1.10 (3H, d, J = 6.5 Hz), 2.50 (1H, dd, J = 6, 15.5 Hz), 2.82 (1H, dd, J = 3.5, 15.5 Hz), 3.66 (6H, s), 4.13 (2H, s), 3.5–4.5 (5H, m), 6.35 (1H, d, J = 2 Hz), 6.35 (1H, dd, J = 2, 9 Hz), 7.05 (1H, d, J = 9 Hz); IR ν_{max}(film) 1750 (shoulder), 1740, 1613, 1590 cm^{-1}; MS *m/z* 412 (M^+–C_4H_9), 394.

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 4 - *hydroxymethyl* - 2 - *azetidinone* (**16**).

(i) To a solution of **7b** (1.84 g, 4.21 mmol), in 99.5% EtOH (20 mL) was added $NaBH_4$ (600 mg). The mixture was stirred for 4 h at 50°, quenched with 5% HCl at ice–water cooling temp, and extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **16** (1.71 g, quantitatively) as a crystalline solid; m.p. 70.5–71.5° (from n-hexane); $[\alpha]_D^{23}$ – 10.0° (c = 1.00, $CHCl_3$); IR ν_{max}(Nujol) 3350, 1733, 1718, 1615, 1595 cm^{-1}; NMR ($CDCl_3$) δ 0.03 (3H, s), 0.06 (3H, s), 0.85 (9H, s), 1.19 (3H, d, J = 6 Hz), 2.20 (1H, bs, OH), 2.98 (1H, dd, J = 1, 5 Hz), 3.60 (3H, bs, CH_2OH, C_4–H), 3.80 (3H, s), 3.82 (3H, s), 4.15 (1H, dq, J = 5, 6 Hz), 4.32 (2H, bs), 6.42 (1H, d, J = 2 Hz), 6.42 (1H, dd, J = 2, 9 Hz), 7.20 (1H, d, J = 9 Hz). (Calc for $C_{21}H_{35}O_5NSi$: C, 61.52; H, 8.54; N, 3.42. Found: C, 61.26; H, 8.72; N, 3.45%.)

(ii) A suspension of t-butyl ester (**7a**, 120 mg) and $NaBH_4$ (50 mg) in 99.5% EtOH (2 mL) was stirred for 18 h at 70°. The reaction mixture was treated as described above to give an oily mixture, which was separated on a silica gel preparative TLC plate. Development with cyclohexane–EtOAc (1:1) gave **16** (R_f = 0.214, 54 mg, 52.7%) and a carboxylic acid **8** (R_f = 0.0, 20 mg, 18.9%).

(iii) Reduction of **7a** (240 mg, 0.5 mmol) in THF (2 mL) with $LiAlH_4$ (50 mg) for 45 min at 5° and successive treatment of the reaction mixture according to the procedure as described above gave **16** (102 mg, 50%).

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 4 - *methanesulfonyloxymethyl* - 2 - *azetidinone* (**17**). To a solution of **16** (5.20 g, 12.7 mmol) and Et_3N (1.50 g, 14.8 mmol) in CH_2Cl_2 (120 mL) was added mesyl chloride (1.66 g, 1.45 mmol) at 0–5°. After 1 h stirring at room temp, the reaction mixture was concentrated *in vacuo*, and diluted with EtOAc. The whole was washed with 5% HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (1:1) gave **17** (6.07 g, 98%) as a viscous oil; NMR ($CDCl_3$) δ 0.00 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.20 (3H, d, J = 6.5 Hz), 2.90 (3H, s), 2.97 (1H, dd, J = 2, 5 Hz), 3.7–4.4 (12H, m, containing each 3H singlet at δ 3.79 and 3.83), 6.63 (1H, dd, J = 2, 9 Hz), 6.64 (1H, d, J = 2 Hz), 7.39 (1H, d, J = 9 Hz).

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 4 - *iodomethyl* - 2 - *azetidinone* (**18**). A solution of **17** (3.73 g, 7.65 mmol) and NaI (5.0 g, 30 mmol) in acetone (80 mL) was refluxed for 18 h, and concentrated *in vacuo* to given an oily residue which was chromatographed on a silica gel (80 g) column. Elution with cyclohexane–EtOAc (2:1) gave the starting **17** (0.47 g, 13% recovery) and **18** (3.26 g, 82%) as a viscous oil; MS *m/z* 462 (M^+–C_4H_9); NMR ($CDCl_3$) δ 0.03 (3H, s), 0.08 (3H, s), 0.86 (9H, s), 1.30 (3H, d, J = 6 Hz), 2.85 (1H, dd, J = 2, 4.5 Hz), 3.0–3.7 (2H + 1H, m), 3.84 (3H, s), 3.86 (3H, s), 4.19 (1H, dq, J = 4.5, 6 Hz), 4.18, 4.46 (2H, AB-q, J = 14 Hz), 6.45 (1H, d, J = 2 Hz), 6.45 (1H, dd, J = 2, 9 Hz), 7.21 (1H, d, J = 9 Hz).

[3*S* - [3α(*S**),4β]] 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 4 - *cyanomethyl* - 2 - *azetidinone* (**19**). A mixture of **18** (2.00 g, 3.85 mmol) and KCN (1.25 g, 19.25 mmol) in DMF (20 mL) was stirred for 15 h at 50°, poured into H_2O (130 mL), and extracted with EtOAc. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a silica gel (50 g) column. Elution with cyclohexane–EtOAc (7:3) gave **19** (1.50 g, 93%) as a viscous oil; MS *m/z* 418 (M^+), 361 (M^+–C_4H_9); IR ν_{max}(film) 2250 (w), 1750 (broad), 1612, 1590 cm^{-1}; NMR ($CDCl_3$) δ 0.03 (6H, s), 0.80 (9H, s), 1.20 (3H, d, J = 6 Hz), 2.4–2.6 (2H, m), 2.90 (1H, dd, J = 2, 4.5 Hz), C_3–H), 3.6–3.9 (12H + 1H, containing each 3H singlet at δ 3.78 and 3.82), 4.13 (1H, dq, J = 4.5, 6 Hz), 4.27 (2H, s), 6.38 (1H, d, J = 2 Hz), 6.38 (1H, dd, J = 2, 9 Hz), 7.15 (1H, d, J = 9 Hz).

[3*S* - [3α(*S**),4β]] - *t* - *Butyl* 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 2 - *azetidinone* - 4 - *carboxylate* (**20a**). To a solution of **7a** (480 mg, 1 mmol) in MeCN–H_2O (1:1, 32 mL) was added K_2HPO_4 (1.5 g) and $K_2S_2O_8$ (3.0 g). The mixture was stirred at 75° for 1 h under Argon atmosphere, concentrated *in vacuo* to half volume, and extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily mixture, which was separated on silica gel preparative TLC plates (20 × 40 × 0.2 cm). Development with cyclohexane–EtOAc (2:1) gave **20a** (270 mg, 82%) as a viscous oil; NMR ($CDCl_3$) δ 0.08 (6H, s), 0.86 (9H, s), 1.22 (3H, d, J = 6 Hz), 1.46 (9H, s), 3.15 (1H, ddd, J = 1.5, 3, 3 Hz, C_3–H), 4.14 (1H, d, J = 3 Hz, C_4–H), 4.24 (1H, dq, J = 3, 6 Hz), 6.42 (1H, bs, NH).

[3*S* - [3α(*S**),4β]] - *Methyl* 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 2 - *azetidinone* - 4 - *carboxylate* (**20b**). The methyl ester (**7b**) was treated as described above to give **20b** (69.3% yield) as a crystalline solid; m.p. 78.5–79.5° (from n-hexane); $[\alpha]_D^{25}$ – 6.0° (c = 1.37, MeOH); NMR ($CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 1.23 (3H, d, J = 6.5 Hz), 3.25 (1H, ddd, J = 1, 3, 3 Hz, C_3–H), 3.77 (3H, s), 4.28 (1H, dq, J = 3, 6.5 Hz), 4.29 (1H, d, J = 3 Hz, C_4–H), 6.30 (1H, bs, HN); IR ν_{max}(Nujol) 3220, 1780 (shoulder), 1772, 1747 cm^{-1}. (Calc for $C_{13}H_{25}O_4NSi$: C, 54.29; H, 8.70; N, 4.87. Found: C, 54.03; H, 8.77; N, 4.90%.)

[3*S* - [3α(*S**),4β]] - 3 - (1 - *t* - *Butyldimethylsilyloxyethyl*) - 4 - *hydroxymethyl* - 2 - *azetidinone* (**21**).

(i) The same treatment of **16** with $K_2S_2O_8$–K_2HPO_4 (2:1) as described in the formation of **20a** from **7a** gave a fair amount of unknown product and **21** (60%) as a crystalline solid; m.p. 89–90° (from n-hexane–ether); $[\alpha]_D^{24}$ – 14.1° (c = 0.625, $CHCl_3$); IR ν_{max}(Nujol) 3250, 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.09 (6H, s), 0.89 (9H, s), 1.21 (3H, d, J = 6 Hz), 2.35 (1H, bs, OH), 2.92 (1H, dd, J = 2, 5 Hz), 3.76 (2H, d, J = 3 Hz), 3.5–3.8 (1H, m), 4.20 (1H, dq, J = 5, 6 Hz), 6.38 (1H, bs, NH). (Calc for $C_{12}H_{25}O_3Si$: C, 55.56; H, 9.71; N, 5.40. Found: C, 56.04; H, 9.88; N, 5.09%.)

(ii) The same treatment of **20a** or **20b** with $NaBH_4$ as described in the formation of **16** from **7b** gave **21** in 88.6% or quantitative yield, respectively.

[3*S* - [3α(*S**),4β]] - 3 - (1 - *t* - *Butyldimethylsilyloxyethyl*) - 4 - *mesyloxymethyl* - 2 - *azetidinone* (**22**). To a suspension of **21** (2.35 g, 9.1 mmol) in CH_2Cl_2 (40 mL) was added Et_3N (1.10 g, 10.9 mmol) and methanesulfonyl chloride (1.15 g, 10 mmol). The mixture was stirred for 1 h at room temp, diluted with EtOAc, washed with 5% HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration *in vacuo* gave **22** (2.54 g, 83%) as a crude viscous oil which was employed for the next reaction without further purification.

[3*S* - [3α(*S**),4β]] - 3 - (1 - *t* - *Butyldimethylsilyloxyethyl*) - 4 - *iodomethyl* - 2 - *azetidinone* (**23**).

(i) The same treatment of **18** with $K_2S_2O_8$–K_2HPO_4 as described in the formation of **20a** from **7a** gave **23** (41%) as a crystalline solid; m.p. 135–136° (from cyclohexane); $[\alpha]_D^{24}$ – 22.5° (c = 2.00, EtOH); NMR ($CDCl_3$) δ 0.09 (6H, s), 0.89 (9H, s), 1.25 (3H, d, J = 6 Hz), 2.84 (1H, ddd, J = 1, 2, 4 Hz, C_3–H), 3.2–3.4 (2H, m), 3.92 (1H, ddd, J = 2, 5, 7 Hz, C_4–H), 4.20 (1H, dd, J = 4, 6 Hz), 6.26 (1H, bs, NH); IR

ν_{max}(Nujol) 3140, 3070, 1762, 1725 cm^{-1}; MS *m/z* 312 (M^+–C_4H_9). (Calc for $C_{12}H_{24}O_2INSi$: C, 39.02; H, 6.55; N, 3.79; I, 34.36. Found: C, 38.94; H, 6.51; N, 3.72; I, 34.08%.)

(ii) A solution of **22** (2.54 g) and NaI (3.37 g, 22.5 mmol) in acetone (60 mL) was refluxed for 24 h. After evaporation of acetone, the residue was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration *in vacuo* gave a crude oil which was purified on a silica gel (80 g) column. Elution with cyclohexane–EtOAc (7:3) gave **23** (2.67 g, 82.7%) as a crystalline solid.

[3*S* - [3α(*S**),4β]] - 3 - (1 - *t* - *Butyldimethylsilyloxyethyl*)-4 - *cyanomethyl* - 2 - *azetidinone* (**24**). The same treatment of **19** with $K_2S_2O_8$–K_2HPO_4, as described in the formation of **20a** from **7a**, gave **24** (83%) as a crystalline solid; m.p. 97.5–98.5° (from ether–n-hexane); $[\alpha]_D^{25}$ − 19.0° (c = 2.00, EtOH); IR ν_{max}(Nujol) 3425, 2270 (w), 1770 cm^{-1}; NMR ($CDCl_3$) δ 0.09 (6H, s), 0.87 (9H, s), 1.23 (3H, d, J = 6.5 Hz), 2.70 (2H, d, J = 6 Hz), 2.94 (1H, dd, J = 2, 4 Hz, C_3–H), 3.96 (1H, dt, J = 2, 6 Hz, C_4–H), 4.22 (1H, dq, J = 4, 6.5 Hz), 6.66 (1H, bs, HN). (Calc for $C_{13}H_{14}O_2N_2Si$: C, 58.17; H, 9.01; N, 10.44. Found: C, 58.15; H, 8.82; N, 10.50%.)

[3*S* - [3α(*S**),4β]] - *Benzyl*[3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 2 - *azetidinone* - 4 - *yl*]*acetate* (**25**). A stirred mixture of **12** (534 mg, 1 mmol), K_2HPO_4 (0.6 g, 3.44 mmol) and $K_2S_2O_8$ (1.8 g, 6.66 mmol) in water–CH_3CN (1:1, 40 mL) was heated at 65–70° for 70 min under argon atmosphere, concentrated *in vacuo*, and extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a silica gel (20 g) column. Elution with PhH–EtOAc (9:1) gave 2,4-dimethoxybenzaldehyde, and elution with EtOAc gave **25** (219 mg, 57%) as a crystalline solid; m.p. 92–93° (recrystallized from n-hexane); NMR ($CDCl_3$) δ 0.06 (6H, s), 0.87 (9H, s), 1.18 (3H, d, J = 6 Hz), 2.6–2.9 (2H + 1H, m), 3.8–4.4 (1H + 1H, m), 5.12 (2H, s), 6.16 (1H, bs, NH), 7.34 (5H, s); $[\alpha]_D^{24}$ + 17.4° (c = 1.75, $CHCl_3$). (Calc for $C_{20}H_{31}O_4NSi$: C, 63.62; H, 8.27; N, 3.71. Found: C, 63.96; H, 8.29; N, 3.68%.)

[3*S* - [3α(*S**),4β]] - 3 - (1 - *t* - *Butyldimethylsilyloxyethyl*)-4 - (2 - *oxo* - 3 - *chloropropyl*) - 2 - *azetidinone* (**26**). Treatment of **15** (470 mg) as described above in the formation of **25** from **12** gave **26** (176 mg, 55.6%) as a viscous oil; NMR ($CDCl_3$) δ 0.05 (6H, s), 1.17 (3H, d, J = 6 Hz), 2.5–3.3 (2H + 1H, m), 3.7–4.4 (4H, m, containing 2H singlet at δ 4.06), 6.40 (1H, bs, NH).

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *hydroxyethyl*) - 2 - *azetidinone* - 4 - *carboxylic acid* (**27**). A solution of **5a** (5.0 g) in CH_2Cl_2 (60 mL) and CF_3COOH (40 mL) was allowed to stand overnight. After checking disappearance of **5a**, the whole was concentrated *in vacuo*, and diluted with EtOAc. The solution was washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*, and dried with a high vacuum pump to give crude **27** (4.2 g) which was employed for next reaction without purification.

[3*R* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) 3 - (1 - *hydroxyethyl*) - 4 - *acetoxy* - 2 - *azetidinone* (**28**). To a stirred solution of **27** (4.2 g) in DMF (40 mL) and AcOH (10 mL) was added $Pb(OAc)_4$ (6.0 g) at 60° under nitrogen atmosphere. An exothermic reaction accompanied by evolution of CO_2 occurred immediately. After 5 min, the reaction mixture was diluted with EtOAc, washed with water, sat. $NaHCO_3$ and brine, dried over $MgSO_4$. Evaporation *in vacuo* gave a crude oily residue which was chromatographed on a silica gel (100 g) column. Elution with cyclohexane–EtOAc (1:1) gave 2,4-dimethoxybenzaldehyde (39 mg) as a crystalline solid, and elution with EtOAc gave crude **28** (2.11 g) as a viscous oil which was employed for the next reaction without further purification.

[3*R* - [3α(*R**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1-*t* - *butyldimethylsilyloxyethyl*) - 4 - *acetoxy* - 2 - *azetidinone* (**29**). A mixture of **28** (2.11 g), t-butyldimethylsilyl chloride (1.18 g) and 4-dimethylaminopyridine (1.04 g) in DMF (7 mL) was allowed to stand at room temp for 16 h. The reaction mixture was diluted with EtOAc, washed with 5% HCl, water, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily mixture which was separated on a silica gel (100 g) column. Elution with cyclohexane–EtOAc (2:1) gave **29** (1.41 g, overall 23.6% yield from **5a**); NMR ($CDCl_3$) δ 0.02 (6H, s), 0.80 (9H, s), 1.20 (3H, d, J = 6 Hz), 1.88 (3H, s), 3.00 (1H, d, J = 4 Hz, C_3–H), 3.77 (6H, s), 4.14 (1H, dq, J = 4, 6 Hz), 4.27 (2H, s), 6.20 (1H, s, C_4–H), 6.38 (1H, d, J = 2 Hz), 6.38 (1H, dd, J = 2, 9 Hz), 7.14 (1H, d, J = 9 Hz); MS *m/z* 437 (M^+), 422, 381, 380, 338; IR ν_{max}(film) 1775, 1750 (shoulder), 1612, 1590 cm^{-1}.

[3*S* - [3α(*S**),4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*) - 4 - *formyl* - 2 - *azetidinone* (**30**).

(i) To a stirred solution of acid chloride (**9**, 1 mmol) and Ph_3P (524 mg, 1 mmol) in acetone (4 mL) was added $(Ph_3P)_2CuBH_4$ (600 mg, 1 mmol). The mixture was stirred for 1 h at room temp and the precipitate was removed by suction filtration. The filter cake was washed with ether. The combined filtrates were removed *in vacuo* to give an oily residue which was chromatographed on two silica gel preparative TLC plates (20 × 40 × 0.2 cm). Development with cyclohexane–EtOAc (2:1) gave an aldehyde (**30**, R_f = 0.221, 244 mg, 60%) as a viscous oil; NMR ($CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.82 (9H, s), 1.14 (3H, d, J = 6 Hz), 3.00 (1H, dd, J = 2, 2.5 Hz, C_3–H), 3.72 (3H, s), 3.76 (3H, s), 3.96 (1H, dd, J = 2, 4 Hz, C_4–H), 4.15 (1H, dq, J = 2.5, 6 Hz), 4.33 (2H, bs), 6.34 (1H, d, J = 2 Hz), 6.34 (1H, dd, J = 2, 9 Hz), 7.08 (1H, d, J = 9 Hz), 9.35 (1H, d, J = 4 Hz, CHO); IR ν_{max}($CHCl_3$) 1740 (broad), 1610, 1588 cm^{-1}; MS *m/z* 407 (M^+), 350 (M^+–C_4H_9), 151.

(ii) A solution of alcohol (**16**, 1.59 g, 3.88 mmol), DCC (2.40 g, 11.6 mmol) and H_3PO_4 (0.19 g, 1.94 mmol) in DMSO (16 mL) was stirred for 18 h at room temp, and diluted with EtOAc, and the precipitate was removed by suction filtration. The filter cake was washed with a small volume of EtOAc. The combined filtrates were washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oily mixture which was purified on a silica gel (50 g) column. Elution with cyclohexane–EtOAc (1:1) gave **30** (1.45 g, 91.8%).

[3*S* - [3α(*S**),4β]] - 3 - (1 - *t* - *Butyldimethylsilyloxyethyl*)-4 - *formyl* - 2 - *azetidinone* (**31**). To a stirred solution of **20b** (287 mg, 1.00 mmol) in THF (20 mL) was added dropwise a solution of sodium bis(2-methoxyethoxy)aluminium hydride (70% in toluene, 1.0 mL) in THF (10 mL) over 15 min at −78° under nitrogen atmosphere. After 1 h stirring at −78°, the reaction mixture was quenched with AcOH (1 mL) in THF (5 mL), diluted with EtOAc. The solution was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily mixture which was separated on preparative silica gel TLC plates (20 × 40 × 0.2 cm). Development with cyclohexane–EtOAc (1:1) gave starting **20b** (38 mg, 13% recovery, R_f = 0.638) as a solid and **31** (202 mg, 78%, R_f = 0.149) as a viscous oil; NMR ($CDCl_3$) δ 0.07 (3H, s), 0.09 (3H, s), 0.88 (9H, s), 2.24 (3H, d, J = 6 Hz), 3.10 (1H, t, J = 3 Hz, C_3–H), 4.0–4.4 (2H, m), 6.74 (1H, bs, NH), 9.68 (1H, d, J = 3 Hz, CHO). This compound **31** was unstable standing for long periods at room temp and dimerized easily with bases such as Et_3N.

[3*S* - [3α(*S**),4β]] - *t* - *Butyl* 3 - (1 - *hydroxyethyl*) - 2 - *azetidinone* - 4 - *carboxylate* (**32**).

(i) Treatment of **5a** with $K_2S_2O_8$ as described in the formation of **25** from **12** gave **32** (76.2%) as a crystalline solid; m.p. 80–81° (needles from cyclohexane–EtOAc); $[\alpha]_D^{24}$ + 3.1° (c = 0.807, EtOH); MS *m/z* 216 (M^+ + 1), 200; NMR ($CDCl_3$) δ 1.27 (3H, d, J = 6 Hz), 1.47 (9H, s), 3.20 (1H, t, J = 2.5 Hz, C_3–H), 4.17 (1H, d, J = 2.5 Hz, C_4–H), 4.27 (1H, dq, J = 2.5, 6 Hz), 6.65 (1H, bs, NH); IR ν_{max}(KBr) 3380, 3200, 1744, 1733 cm^{-1}. (Calc for $C_{10}H_{17}O_4N$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.96; H, 8.16; N, 6.51%.)

(ii) A solution of ceric ammonium nitrate (1.65 g, 3 mmol) in water (2 mL) was added to a solution of **5a**

(365 mg, 1 mmol) in acetone (3 mL) with stirring at 5°. After 30 min, the reaction mixture was diluted with EtOAc, washed with water, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was chromatographed on a silica gel column. Elution with cyclohexane–EtOAc (1:2) gave **32** (123 mg, 57%) as a crystalline solid.

(iii) The same treatment of [3*S* - [3α(*S**),4β]] - t - butyl 1 - p - methoxyphenyl - 3 - (1 - hydroxyethyl) - 2 - azetidinone - 4 - carboxylate (**5e**, 312.4 mg, 1 mmol) in acetone–water with ceric ammonium nitrate as described above gave **32** (115 mg, 53%) as a crystalline solid.

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