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Synthesis Of Highly Functionalized Homochiral Azetidines And Azetidine-2-Carboxylic Esters

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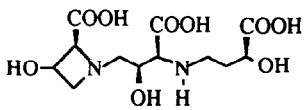
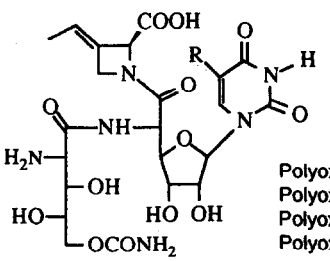
Key Words : Polyhydroxylated azetidines, 2-carbomethoxy-3-hydroxy-azetidines, 2-hydroxymethyl-3-azetidinone

Abstract : Homochiral (*2S, 3S*)-3-benzyloxy-2-formyl-azetidines **2**, (*2S, 3S*)-3-benzyloxy-2-carbomethoxy-azetidines **3** and the highly strained (*2S*)-N-*p*-methoxyphenyl-2-silyloxymethyl-3-azetidinone **4** were successfully synthesized starting from diethyl-L-tartrate. The suitably functionalized azetidine ring is formed in a single synthetic operation with minimum protecting group chemistry.

Functionalized azetidine-2-carboxylic acids such as 2-carboxy-3-hydroxy-azetidine, the azetidine moiety of 3-hydroxy mugineic acid, a typical phytosiderophore[1], or such as polyoximic acid: (*2S,E*)-3-ethylidene-azetidine-2-carboxylic acid[2], a constituent of tripeptidyl polyoxins (nucleoside antibiotics with fungicidal properties) are met in the nature.

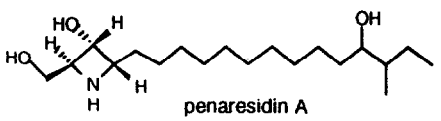


3-hydroxy mugineic acid

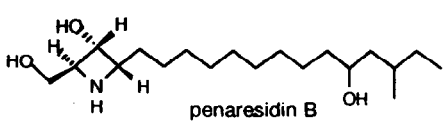


Polyoxin A, R=CH_2OH
Polyoxin F, R=COOH
Polyoxin H, R=CH_3
Polyoxin K, R=H

Natural polyhydroxylated azetidines are also encountered although they are not as widespread as are the pyrrolidines derivatives. Recently two sphingosine-derived azetidine alkaloids, possessing potent actomyosin ATPase-activating activity were isolated from marine sponge and their structure was elucidated[3].



penaresidin A

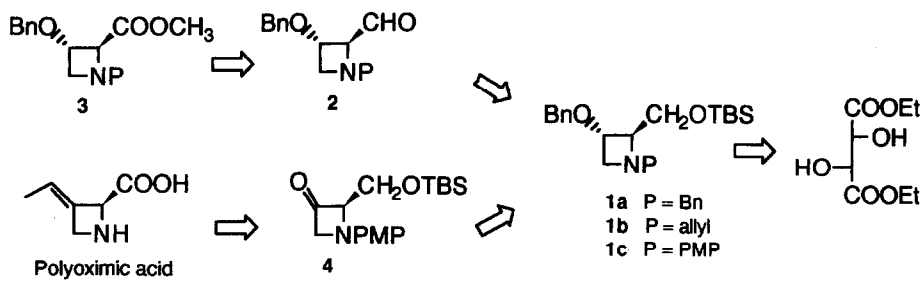


penaresidin B

We have recently published a new approach towards mugineic acid[4], but to our knowledge no synthesis of (2*S*, 3*S*)-2-carboxy-3-hydroxy-azetidine, the azetidine moiety of 3-hydroxy mugineic acid has been reported. Concerning polyoxins, whereas for the acyclic unusual polyhydroxy amino acid named polyoxamic acid several syntheses have been published, including the one we have developed starting from L-arabinose[5], there are only few reports concerning attempts to synthesize polyoximic acid[6]. Recently however a synthesis of racemic polyoximic acid was reported starting from Boc-glycine[7].

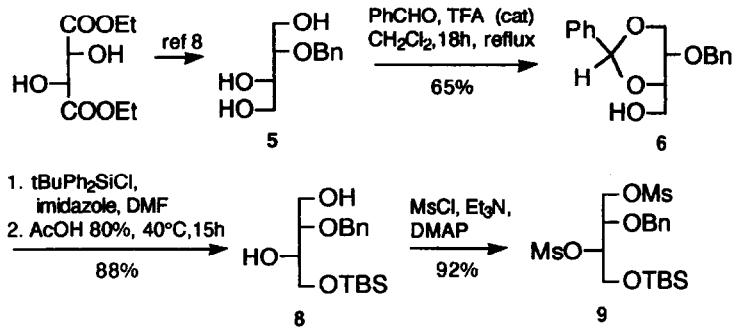
In connection with our interest in the synthesis of homochiral polyhydroxylated nitrogen heterocycles we report herein starting from diethyl-L-tartrate the syntheses through a flexible way, of differently functionalized azetidines including the synthesis of 3-hydroxy-azetidine-2-carboxylic acid derivatives. The azetidine ring is elaborated by nitrogen nucleophilic substitution of a 1,3-activated tetrol derived from diethyl-L-tartrate.

(2*R*, 3*S*)-3-Benzyloxy-2-silyloxymethyl-N-substituted azetidines **1** have been synthesized from diethyl-L-tartrate with different nitrogen subtituents (benzyl, allyl, paramethoxyphenyl). Alternate selective deprotection of each of the hydroxyl groups of compound **1** enabled on one hand the synthesis of the (2*S*, 3*S*)-2-formyl-3-hydroxy azetidines **2** and of (2*S*, 3*S*)-2-carboxy-3-hydroxy-azetidines protected as their methyl esters **3** and on the other hand, the synthesis of the 2-silyloxymethyl-3-azetidinone **4**. **4** was anticipated as a possible chiral precursor of enantiomerically pure polyoximic acid, requiring the ethylidenation of the carbonyl group and the oxidation of the hydroxymethyl substituent at C-2 into a carboxy group; this assertion being supported by the recently reported synthesis of (±) polyoximic acid[7] which lies on a Wittig-type reaction effected on a 3-azetidinone.



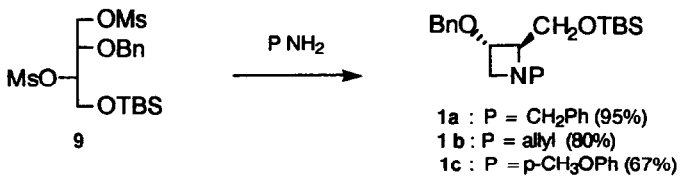
Scheme 1

We have carried out the elaboration of the azetidine framework in one step, through nucleophilic substitution by a primary amine of the suitably functionalized 1,3-dimesylate **9**. The synthesis of **9** was undertaken starting from an optically active tetrol: 2-O-benzyl-L-threitol **5** readily available from the C_2 symmetrical, inexpensive diethyl-L-tartrate[8] (scheme 2). Acetalisation of **5** by benzaldehyde afforded a 7:3 mixture of the 1,3 and 1,2 acetals from which pure 1,3-O-benzylidene-2-O-benzyl-L-threitol **6** was obtained by cristallization in ether. Silylation of **6** resulted in **7**. Hydrolysis of the acetal in compound **7** led to the 1,3 diol **8** which was mesylated with mesyl chloride giving dimesylate **9**. **9** was thus obtained in 53% overall yield starting from **5**. The azetidine framework was then elaborated in one step from **9** in satisfactory yield.



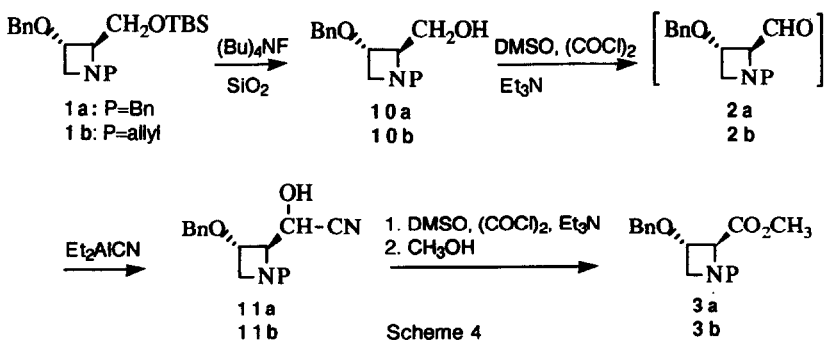
Scheme 2

Nitrogen nucleophilic substitution with inversion of configuration at both C-1 and C-3 of L-threitol was effected by heating **9** in the presence of benzylamine, allylamine or *p*-methoxyaniline, yielding **1a**, **1b**, **1c** in 95%, 80% and 67% yield respectively. The ^{1}H and ^{13}C NMR spectra attested the optical purity of compounds **1**, and the relative configuration of C-2 was verified by NOE difference experiments, effected on **1b**.



Scheme 3

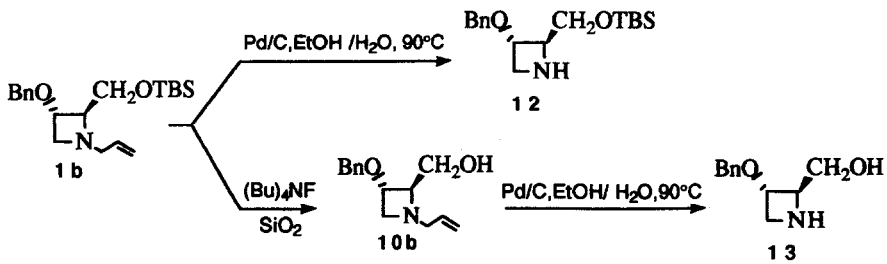
The azetidine **3** (scheme 4) resulted of the desilylation of **1** followed by the oxidation of the resulting alcohol **10**. We needed a mild oxidation procedure compatible with the tertiary amino group and the α-asymmetric center. The high yields and cleanliness of Swern oxidations permit further reactions to be carried out by treatment of the product with additional reagents in the same pot[9]. Tertiary amino alcohol **10** was transformed into the amino ester **3** via a two-step oxidation procedure[10]. **10** was first converted in good yield into the cyanohydrin **11** via Swern oxidation into the intermediate aldehyde **2** followed by diethyl aluminium cyanide addition. Subsequent oxidation of the crude tertiary amino cyanohydrin again under the Swern conditions was slower, it led to a labile acyl cyanide which was converted in-situ into the methyl ester **3** in moderate yield by coupling with methanol.



Scheme 4

The crude amino aldehydes **2a** and **2b** were characterized by their ^1H NMR spectra; they are formed in quantitative yield, without epimerisation at C-2.

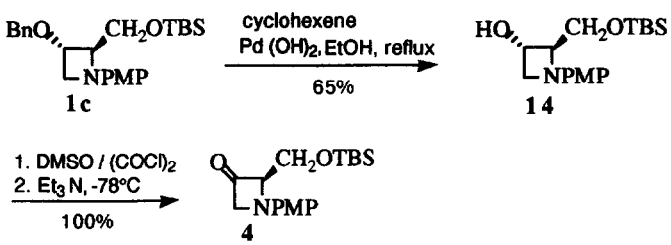
The obtention of the free amino group starting either from ester **3a** or from **3b** was unsuccessful; the N-debenzylation of **3a** by hydrogenolysis on 10% Pd on charcoal or on $Pd(OH)_2$ was not selective and tests of N-deallylation under conventional conditions[11] resulted in the degradation of **3b**. However the N-deallylation of **1b** (scheme 5) gave the unstable NH-azetidine **12** which subsequent benzylation gave **1a** in 75% yield. The 1,3-aminoalcohol **13** resulted from the deallylation of **10b**



Scheme 5

The azetidine **1c** was formed in view of a first approach towards the synthesis of optically active polyoximic acid. The p-methoxyphenyl group was chosen as N-protective group because it is frequently used in β-lactams and can be removed under mild conditions[12]. The oxidation of the hydroxymethyl group, precursor of the carboxy group was planned only after the olefination of a 3-azetidinone in order to prevent the risks of epimerisation and of nucleophilic ring opening[7,13].

Catalytic transfer hydrogenation of **1c** cleanly led to **14** in 65% yield, while the hydrogenolysis of the benzyl ether in the presence of palladium black or of 10% palladium on charcoal was sluggish. Swern oxidation of **14** yielded quantitatively the azetidinone **4**. **4** was purified for characterization purposes but is fairly unstable, it partially decomposes during silica gel chromatography and must be reacted directly after its preparation.



Scheme 6

Further transformations towards Polyoximic acid are now being addressed particularly the olefination of **4** following the recently published Wittig-type reaction[7].

EXPERIMENTAL SECTION

Prior to use, tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from P_2O_5. CH_2Cl_2 and ethyl acetate (AcOEt) were filtered on K_2CO_3 prior to use. ^1H NMR (250MHz) and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Brucker AM 250. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hertz. IR spectra were recorded on a Perkin Elmer 783 Infrared Spectrophotometer. Specific rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) lamp. All reactions were carried out under argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Chromatography was performed with Merck Kieselgel 60 (200-500 μm) or 60H (5-40 μm). Spectroscopic (^1H and ^{13}C NMR) and analytical data were obtained using chromatographically homogeneous samples.

2-O-Benzyl-1,3-O-benzylidene-L-threitol **6**

To a solution of triol **5** (5.5g, 26 mmol) in CH_2Cl_2 (80 mL), benzaldehyde (3.2 mL, 31 mmol) and CF_3COOH (280 μL, 3.6 mmol) were added. After the reaction mixture had been refluxed for 15h, the generated H_2O was removed by distillation as an azeotropic mixture and the remaining solution was washed with a saturated aqueous $NaHCO_3$ solution (10 mL), then with a saturated aqueous $NaHSO_3$ solution (2 x 10 mL) and with brine and dried. Removing of the solvent gave an oily residue of a mixture of isomeric benzaldehyde acetals from which the 1,3-dioxane **6** crystallized after addition of ether (40 mL) as a white solid (5.1g, 65%) : mp 101°C ; $[\alpha]^{20}$ + 47 (*c* 1.48, CH_2Cl_2) ; ^1H NMR δ 2.0 (br s, 1H, OH) ; 3.38 (m, 1H, H-2), 3.68 (m, 1H, H-4), 3.85-4.05 (m, 3H, H-1, H-3, H-4'), 4.44 (dd, 1H, J_{gem} = 13.0 Hz, $J_{1',2}$ = 1.0 Hz, H-1'), 4.46, 4.82 (AB, 2H, J_{AB} = 12.5 Hz, OCH_2Ph), 5.58 (s, 1H, CHPh), 7.20-7.60 (m, $10H_{arom}$) ; Anal. Calcd. for $C_{18}O_{20}O_4$: C, 71.98 ; H, 6.71. Found : C, 71.95 ; H, 6.84.

2-O-benzyl-1,3-O-benzylidene-4-O-tert-butyldiphenylsilyl-L-threitol **7**

A solution of the alcohol **6** (3g, 10.0 mmol), imidazole (1.7g, 25.0 mmol) and *tert*-butyldiphenylchlorosilane (3.9 mL, 15.0 mmol), in DMF (85 mL) was stirred under argon at room temperature for 2h. DMF was evaporated and the residue purified by flash chromatography on silica gel (cyclohexane/EtOAc, 9:1) giving **7** as a colorless oil (4.8g, 90% yield) : $[\alpha]^{20}$ + 22 (*c* 1.68, CH_2Cl_2) ; ^1H NMR δ 1.06 (s, 9H, $C(CH_3)_3$), 3.55 (m, 1H, H-2), 3.80-4.20 (m, 4H, H-1, H-3, H-4, H-4'), 4.44 (dd, 1H, J_{gem} = 12.5 Hz, $J_{1',2}$ = 1.0 Hz, H-1'), 4.59, 4.79 (AB, 2H, J_{AB} = 12.0 Hz, OCH_2Ph), 5.56 (s, 1H, CHPh), 7.20-7.75 (m, $20H_{arom}$).

2-O-Benzyl-4-O-tert-butyldiphenylsilyl-L-threitol **8**

A solution of crude **7** (10 mmol) in acetic acid (65 mL) and water (15 mL) was stirred at 40°C for 15h. The solvent was evaporated and the residue purified by flash chromatography on silica gel (AcOEt/cyclohexane, 40:60) yielding diol **8** as a colorless oil (4.0g, 88% from **6**) : $[\alpha]^{20}$ + 6 (*c* 1.07, CH_2Cl_2) ; ^1H NMR δ 1.08 (s, 9H, $C(CH_3)_3$), 2.08 (s, 2H, OH), 3.63-3.92 (m, 6H, H-1, H-1', H-2, H-3, H-4, H-4'), 4.57, 4.67 (AB, 2H, J_{AB} = 11.5 Hz, OCH_2Ph), 7.20-7.80 (m, 15 H_{arom}) ; Anal. Calcd. for $C_{27}H_{34}O_4Si$: C, 71.96 ; H, 7.60. Found : C, 72.05 ; H, 7.63.

2-O-Benzyl-4-O-tert-butyldiphenylsilyl-1,3-di-O-methylsulfonyl-L-threitol **9**

To a solution of diol **8** (3.57g, 7.9 mmol) in CH_2Cl_2 (50 mL) were added under argon, Et_3N (3.3 mL, 23.8 mmol), MsCl (1.8 mL, 23.8 mmol) and DMAP (213 mg, 1.7 mmol). After 2h stirring at room temperature, H_2O was added (20 mL) and the reaction mixture extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The oily residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 2:1) affording **9** (4.45g, 92%) as a colorless oil : $[\alpha]^{20}$ +0.8 (*c* 2.57, CH_2Cl_2) ; ^1H NMR δ 1.08 (s, 9H, $C(CH_3)_3$), 2.90, 2.94 (2s, 6H, CH_3-SO_2), 3.82-3.99 (m, 2H, H-4, H-4'), 4.04 (m, 1H, H-2), 4.30 (dd, 1H, J_{gem} = 11 Hz, $J_{1,2}$ = 5.0 Hz, H-1), 4.45 (dd, 1H, $J_{1',2}$ = 4.5 Hz, H-1'), 4.59, 4.68 (AB, J_{AB} = 11.5 Hz, OCH_2Ph), 4.76 (m, 1H, H-3) ; 7.20-7.75 (m, 15 H_{arom}) ; ^{13}C NMR δ 19.1 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3$), 37.5, 38.4 (CH_3-SO_2), 62.5, 67.3 (C-1, C-4), 73.6 (CH_2Ph), 75.3, 80.6 (C-2, C-3), 127.9, 128.2, 128.5, 130.1, 132.1, 132.4, 135.4, 135.5, 136.7 (C_{arom}) ; Anal. Calcd. for : $C_{29}H_{38}O_8S_2Si$: C, 57.40 ; H, 6.31. Found : C, 57.55 ; H, 6.37.

(2R, 3S)-1-Benzyl-3-benzyloxy-2-(tert-butyldiphenyl silyloxy) methyl-azetidine **1a**

Dimesylate **9** (1.05g ; 1.7 mmol) in benzylamine (5.5 mL ; 50 mmol) was stirred at 100°C for 8h. The benzylamine was then distilled under reduced pressure and the resulting syrup was added with ether (20 mL), allowing precipitation of the benzylamine salts. The resulting mixture was filtered, concentration of the filtrate yielded an oily residue which was purified by flash column chromatography on silica gel (cyclohexane/EtOAc, 95:5). Azetidine **1a** was obtained as a colorless oil (860 mg, 95%) : $[\alpha]^{20}$ -22 (*c* 3.14, CH_2Cl_2) ; ^1H NMR δ 1.05 (s, 9H, $C(CH_3)_3$), 2.80 (dd, 1H, H-4), 3.33-3.95 (complex, 6H), 3.96 (m, 1H, H-3), 4.39, 4.52 (AB, 2H, J_{AB} = 12.0 Hz, OCH_2Ph), 7.10-7.80 (m, 2OH_{arom}) ; ^{13}C NMR δ 19.2 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 59.0 (NCH_2Ph), 63.1, 65.6 (C-4, OCH_2Si), 71.3, 71.9, 74.6 (OCH_2Ph, C-2, C-3), 120.3, 127.0, 133.5, 135.6, 137.9 (C_{arom}) ; Anal. Calcd. for $C_{34}H_{39}NO_2Si$: C, 78.27 ; H, 7.53; N, 2.68. Found C, 78.11; H, 7.62;.N, 2.68.

(2R, 3S)-1-Benzyl-3-benzyloxy-2-hydroxymethyl-azetidine **10a**

To a solution of azetidine **1a** (472 mg, 0.9 mmol) in THF (25 mL), tetrabutylammonium fluoride on silica gel (1.23g, 1.36 mmol) was added. After 2h stirring at room temperature the mixture was filtered through a celite pad, the filtrate was concentrated and the oily residue purified by flash chromatography on silica gel (cyclohexane/Acetone, 3:2) giving **10a** as a colorless oil (215 mg, 84%) : $[\alpha]^{20}$ + 2.5 (*c* 1.24, CH_2Cl_2) ; ^1H NMR δ 2.70 (br s, 1H, OH) ; 2.87 (dd, 1H, J_{gem} = 7.0 Hz, $J_{3,4}$ = 7.0 Hz, H-4), 3.21-3.39 (m, 3H, CH_2OH, H-2) ; 3.58 (dd, 1H, $J_{3,4'}$ = 7.0 Hz, H-4') ; 3.66, 3.74 (AB, 2H, J_{AB} = 12.5 Hz, NCH_2Ph), 4.15 (ddd, 1H, $J_{2,3}$ = 6.0 Hz, H-3), 4.44 (s, 2H, OCH_2Ph), 7.15-7.45 (m, 10 H_{arom}) ; Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found : C, 76.11; H, 7.52 ; N, 4.87.

(2S, 3S)-1-Benzyl-3-benzyloxy-2-cyanohydroxymethyl-azetidine **11a**

To a solution of oxalyl chloride (86 µL, 1.0 mmol) in CH_2Cl_2 (4.5 mL) at -70°C, under argon, with stirring, was added dropwise DMSO (140 µL, 2.0 mmol). After 10 min, a solution of **10a** (215 mg, 0.76 mmol) in CH_2Cl_2 (0.3 mL) was added and the mixture was allowed to stir for 30 min. The solution was quenched by addition of Et_3N (550 µL, 4.0 mmol) and allowed to stir with warming to -30°C over 40 min. To this mixture was added Et_2AlCN (1.5 mL in 1.0 M solution in toluene) and after stirring for 30 min at -30°C, the solution was

concentrated in vacuo, diluted with EtOAc and H_2O, allowed to stir for 5 min. and filtered through a Celite pad. The layers were separated and the organic phase was washed with H_2O and with brine, dried, and evaporated to give the crude cyanohydrin as an oil. Purification by flash column chromatography.(cyclohexane/EtOAc, 75:25) yielded **11a** (148 mg, 63%), as a 1:1 mixture of two diastereomers. ^1H NMR δ 2.93, 3.01 (2 dd, 1H, $J_{3,4}$ = 6.5Hz, J_{gem} = 7Hz, H-4), 3.45-3.84 (complex, 5H), 3.88 (d, 0.5H,J = 1Hz, H-C-CN), 4.04, 4.20 (2m, 1H, H-3), 4.06 (AB, 0.5H, J_{AB} = 13Hz, NCH_2Ph), 4.37, 4.51 (AB, 2H, J_{AB} = 12Hz, OCH_2Ph), 4.48, 4.61 (AB, 2H, J_{AB} = 12Hz, OCH_2Ph), 7.20-7.50 (m, $10H_{arom}$) ; ^{13}C NMR δ 58.6, 59.2, 60.2, 61.4, 61.8 (C-2, C-4, NCH_2Ph), 69.0, 69.6, 72.1, 73.8, 74.2 (*C*-CN, OCH_2Ph, C-3), 117.6, 118.8 (CN), 127.7, 128.0, 128.3, 128.5, 128.6, 128.8, 136.4, 137.4 (C_{arom}) ; Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found : C, 73.66; H, 6.51 ; N, 9.16

(2S, 3S)-1-Benzyl-3-benzyloxy-2-formyl-azetidine **2a**

Direct filtration and concentration of the mixture after Et_3N quenching, afforded the crude aldehyde **2a** in quantitative yield as an oil (220mg) ; ^1H NMR δ 9.28 (d, 1H, J = 3Hz, HC=O)

(2S, 3S)-1-Benzyl-3-benzyloxy-2-carbomethoxy-azetidine **3a**

To a solution of oxalyl chloride (330 µL, 3.80 mmol) in CH_2Cl_2 (6 mL) at -70°C, under argon, was added dropwise DMSO (530 µL, 7.60 mmol). After 10 min, a solution of crude cyanohydrin **11a** (prepared from 0.76 mmol of **10a**) in CH_2Cl_2 (2 mL) was added dropwise, and this mixture was allowed to stir for 35 min at -60°C. The homogeneous solution was quenched by addition of Et_3N (1.5 mL, 10.7 mmol) and allowed to stir with warming to -35°C over 35 min. To this mixture was added methanol (3.8 mL) and after being stirred at room temperature for 3h, the reaction mixture was concentrated then diluted with EtOAc and H_2O. The layers were separated and the organic phase was washed with H_2O and brine, dried and evaporated to give a pale yellow oil that was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to give methyl ester **3a** as a colorless oil (71 mg, 30%) besides 12% of recovered cyanohydrin : $[\alpha]^{20}$ -51 (*c* 1.83, CH_2Cl_2) ; ^1H NMR δ 2.87 (dd, 1H, J_{gem} = 7.0 Hz, $J_{3,4}$ = 7.0 Hz, H-4), 3.55 (dd, 1H, $J_{3,4'}$ = 6.5 Hz, H-4'), 3.60-3.75 (complex, 5H, H-2, OCH_3, NCH_2Ph) 3.85 (AB, 1H, J_{AB} = 12.5 Hz, NCH_2Ph), 4.27 (m, 1H, $J_{2,3}$ = 6.0 Hz, H-3), 4.45, 4.60 (AB, 2H, J_{AB} = 12.0 Hz, OCH_2Ph), 7.10-7.60 (m, 10 H_{arom}) ; ^{13}C NMR δ 51.9 (OCH_3), 58.2, 62.5 (NCH_2Ph, C-4), 71.4, 72.4 (C-2, C-3, OCH_2Ph), 127.3, 127.9, 128.3, 128.4, 129.0, 136.7, 137.3 (C_{arom}), 171.7 (C=0) ; IR (neat) cm^{-1} : 1740 (st), 1495, 1450, 1435 (md) ; Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29 ; H, 6.80 ; N, 4.50. Found : C, 73.01 ; H, 6.81 ; N, 4.56.

(2R, 3S)-1-Allyl-3-benzyloxy-2-(tert-butyldiphenyl silyloxy) methyl-azetidine **1b**

A solution of dimesylate **9** (1.53g, 2.53 mmol) and allylamine (5.7 mL, 76.0 mmol) in toluene (2 mL) was refluxed (53°C) for 24h. The reaction mixture was concentrated, then diluted with toluene (5 mL) and refluxed for 48h. Evaporation of the solvent and purification by flash column chromatography (cyclohexane/EtOAc, 9:1) yielded azetidine **1b** as a colorless oil (960 mg, 80%) : $[\alpha]^{20}$ -24 (*c* 5.37, CH_2Cl_2) ; ^1H NMR δ 1.06 (s, 9H, $C(CH_3)_3$), 2.75 (dd, 1H, J_{gem} = 7.0 Hz, $J_{3,4}$ = 7.0 Hz, H-4a), 3.00 (dd, 1H, J_{gem} = 13.5 Hz, $J_{1'a,\ 2'}$ = 7.0 Hz, H-1'a), 3.21 (m, H-2), 3.30 (dd, 1H, $J_{1'b,2'}$ = 6.0 Hz, H-1'b), 3.58-3.76 (m, 3H, CH_2OSi, H-4b), 3.93 (m, 1H, $J_{2,3}$ = 6.0 Hz, H-3), 4.40, 4.55 (AB, 2H, J_{AB} = 11.5 Hz, OCH_2Ph), 5.04 (m, 1H, $J_{2',3'cis}$ = 10.0 Hz, H-3'cis), 5.15 (m, 1H, $J_{2',3'\ trans}$ = 17.5 Hz, H-3' trans), 5.71 (m, 1H, H-2'), 7.20-7.80 (15 H_{arom}); ^{13}C NMR δ

19.2 ($C(CH_3)_3$) ; 26.9 ($C(CH_3)_3$) ; 58.8, 61.9 (C-1', C-4) ; 65.8, 71.2 (CH_2OSi, OCH_2Ph) ; 72.1, 74.5 (C-2, C-3) ; 117.2 (C-3') ; 127.6, 128.3, 129.6, 133.5, 133.6, 135.6, 137.9 (C_{arom}) ; 134.6 (C-2'). Anal. Calcd. for $C_{30}H_{37}NO_2Si$: C, 76.39 ; H, 7.91 ; N, 2.97. Found : C, 76.26 ; H, 7.87 ; N, 2.82.

(2R, 3S)-1-Allyl-3 -benzyloxy-2-hydroxymethyl-azetidine **10b**

10b was prepared from **1b** via the procedure given for **10a**. Purification by flash chromatography (cyclohexane/Acetone, 3:2) gave azetidine **10b** in 88% yield as a white solid : $[\alpha]^{20}$ +1 (*c* 1.08, CH_2Cl_2) ; mp 57°C ; ^1H NMR δ 2.77 (dd, 1H, $J_{3,4a}$ = 7.0 Hz, J_{gem} = 7.0 Hz, H-4a) ; 3.07 (dd, 1H, J_{gem} = 13.0 HZ, $J_{1'a,\ 2'}$ = 6.0 Hz, H-1'a) 3.14-3.27 (m, 2H, H-1'b, H-2) ; 3.42, 3.55 (ABX, 2H, J_{AB} = 12.0 Hz, CH_2OH) ; 3.57 (dd, $J_{3,4b}$ = 6.0 Hz, H-4b) ; 4.12 (m, 1H, $J_{2,3}$ = 6.0 Hz, H-3) ; 5.08 (m, 1H, $J_{2',\ 3'cis}$ = 10.0 Hz, H-3'cis) ; 5.17 (m, 1H, $J_{2',\ 3'trans}$ = 17.0 Hz, H-3' trans) ; 5.74 (m, 1H, H-2') ; 7.32(s, $5H_{arom}$). Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found : C, 71.87; H, 8.15; N, 5.88.

(2S, 3S)-1-Allyl-3-benzyloxy-2-cyanohydroxymethyl-azetidine **11b**

11b was prepared from **10b** via the procedure given for **11a**. Purification by flash chromatography (cyclohexane/EtOAc, 3:1) gave azetidine **11b** (66%), as a 7:3 mixture of diastereomers; ^1H NMR δ 2.85-3.65 (complex, 6H) ; 3.94 (d, 0.7H, J=2Hz, H-C-CN) ; 4.03, 4.22 (2m, 1H, H-3) ; 4.32 (d, 0.3H, J = 3.5Hz, HC-CN) ; 4.39-4.51 (AB, 1.4H, J_{AB} = 12Hz, OCH_2Ph) ; 4.48, 4.62 (AB, 0.6H, J_{AB} = 12Hz, OCH_2Ph) ; 5.10-5.30 (m, 2H, H-3'a, H-3'b) ; 5.65-5.85 (m, 1H, C-2') ; 7.14-7.48 (m, $5H_{arom}$) ; ^{13}C NMR δ 58.4, 58.8, 59.1, 59.7, 60.1 (C-2, C-4, C-1') ; 69.1, 69.6, 72.0, 72.1, 73.7, 74.1 (*C*-CN, C-3, OCH_2Ph) ; 118.6, 118.9 (C-3', CN) ; 128.0, 128.3, 128.5, 128.7, 137.5 (C_{arom}) ; 132.9, 133.4 (C-2'). Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74 ; H, 7.02 ; N, 10.84. Found : C, 69.40 ; H, 7.15 ; N, 10.76.

(2S, 3S)-1-Allyl-3-benzyloxy-2-formyl-azetidine **2b**

The crude aldehyde **2b** was obtained from **10b** in quantitative yield as an oil ; ^1H NMR δ 9.53 (d, 1H, J = 2Hz, HC=O)

(2S, 3S)-1-Allyl-3-benzyloxy-2-carbomethoxy-azetidine **3b**

Ester **12b** was prepared from crude cyanohydrin **11b** via the procedure given for **12a**. Purification by flash chromatography (cyclohexane/Acetone, 9:1) gave recovered cyanohydrin (5%) and the ester **3b** in 40% yield as a colorless oil : $[\alpha]^{20}$ -57 (*c* 2.26, CH_2Cl_2) ; ^1H NMR δ 2.81 (dd, 1H, J_{gem} = 7.0 Hz, $J_{3,4a}$ = 7.0 Hz, H-4a), 3.11, 3.28 (ABX, 2H, J_{AB} = 13.0 Hz, $J_{1',2'}$ = 6.5 Hz, H-1') ; 3.54-3.66 (complex, 2H, H-2, H-4b) ; 3.71 (s, 3H, OCH_3) ; 4.23 (ddd, 1H, J = 6.0 Hz, H-3) ; 4.45, 4.61 (AB, 2H, J_{AB} = 11.5 Hz, OCH_2Ph) ; 5.11 (m, 1H, H-3'cis) ; 5.18 (m, 1H, H-3'trans) ; 5.77 (m, 1H, H-2') ; 7.20-7.40 (s, $5H_{arom}$) ; ^{13}C NMR δ 52.0 (OCH_3) ; 58.1, 61.4 (C-4, C-1') ; 71.4 , 71.5, 72.5 (OCH_2Ph, C-2, C-3) ; 118.3 (C-3') ; 127.8, 128.4 , 137.3 (C_{arom}) ; 133.4 (C-2') ; 171.8 (C=0) ; IR (neat) cm^{-1} : 1740 (st), 1640 (wk), 1495 (wk), 1450, 1435 (md). Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94 ; H, 7.33 ; N, 5.36. Found : C, 68.68 ; H, 7.26 ; N, 5.33.

(2R, 3S)-3-Benzyloxy-2-(tert-butyldiphenyl silyloxy) methyl-azetidine **12**

A solution of the azetidine **1b** (907mg, 1.90mmol) in ethanol and water (12mL, 3:1) was added to 10% Pd on charcoal (181mg) and refluxed under stirring for 15h. After cooling the mixture was filtered through a celite pad,

concentrated under vacuo, purificated by silicagel chromatography (cyclohexane/Acetone, 8:2) affording N-H azetidine **12** as a pale yellow oil (503mg, 61%) ; ^{1}H NMR δ 1.07 (s, 9H, C(CH_3)$_3$) ;1.65 (br s, 1H, NH) ; 3.05 (dd, 1H, $J_{3,4}$ = 5.5Hz, $J_{3,4'}$ = 5.5Hz, H-4) ; 3.38 (m, 1H, H-2) ; 3.46 (dd, 1H, H-4') ; 3.58-3.73 (m, 2H, CH_2OSi) ; 3.88 (m, 1H, H-3) ; 4.40, 4.59 (AB, 2H, J_{AB} = 12Hz, OCH_2Ph) ; 7.20-7.80 (m, 15H_{arom}). Partial degradation occured during the chromatography. Benzylation of the crude derivative **12** gave azetidine **1a** in 75% yield.

(2R, 3S)-3-Benzyloxy-2-hydroxymethyl-azetidine **13**

Refluxing compound **10b** (388mg, 1.66mmol) in ethanol and water (10mL, 3:1) with 10% Pd on charcoal (77mg) for 15h gave after silicagel chromatography (CH_2Cl_2/MeOH/NH_3, 65:10:1) the aminoalcohol **13** as pale yellow, hygroscopic solid (245mg, 76%); ^{1}H NMR δ 2.80-3.10 (complex, 2H, H-4, NH) ; 3.40-3.60 (complex, 4H, CH_2OH, H-2) ; 3.93 (m, 1H, H-4') ; 4.22 (m, 1H, H-3) ; 4.43 (s, 2H, OCH_2Ph) ; 7.20-7.40 (m, 5H_{arom}) ; ^{13}C NMR δ 51.1 (C-4) ; 62.7 (CH_2OH) ; 67.4 (C-2) ; 71.4 (OCH_2Ph) ; 72.8 (C-3) ; 127.9, 128.5, 137.7 (C_{arom}).

(2R, 3S)-3-Benzyloxy-2-(tert-butyldiphenyl silyloxy) methyl-1-p-methoxyphenyl-azetidine **1c**

A solution of dimesylate **9** (1.50g, 2.47 mmol) and paramethoxy-aniline (4.56g, 37 mmol) in toluene (15 mL) is refluxed for 2 days. Concentration under reduced pressure and purification by flash chromatography (cyclohexane/EtOAc, 9:1) gave azetidine **1c** as a white solid (930 mg, 70%) : mp 97°C ; $[\alpha]^{20}$ -34 (*c* 1.58, CH_2Cl_2) ; ^{1}H NMR δ 1.05 (s, 9H, C(CH_3)$_3$) ; 3.47 (m, 1H, H-4) ; 3.74 (s, 3H, OCH_3) ; 3.75-4.20 (m, 4H, CH_2OSi, H-2, H-4') ; 4.24 (m, 1H, H-3) ; 4.43, 4.56 (AB, J_{AB} = 11.5 Hz, OCH_2Ph) ; 6.40-7.73 (m, 19 Harom) ; ^{13}C NMR δ 19.3 (*C*(Me)$_3$) ; 26.9 (C(*C*H3)$_3$) ; 55.8 (OCH3) ; 58.2 (C-4) ; 65.8, 71.7 (*C*H_2OSi, *C*H_2Ph) ; 71.9, 73.7 (C-2, C-3) ; 113.9, 114.5, 127.7, 129.7, 133.1, 133.3, 135.6, 146.4, 152.6 (Carom). Anal. Calcd. for $C_{34}H_{39}NO_3Si$: C, 75.94 ; H, 7.31 ; N, 2.60. Found : C, 76.01 ; H, 7.41 ; N, 2.64.

(2R, 3S)-2-(tert-Butyldiphenyl silyloxy) methyl-3-hydroxy-1-p-methoxyphenyl-azetidine **14**

A mixture of azetidine **1c** (750 mg, 1.39 mmol) and cyclohexene (20 mL) in EtOH (20 mL) was refluxed for 20h with 20% palladium hydroxide on charcoal (500 mg). The catalyst was filtered off and the solvent evaporated to give a yellow oil which was purified by flash chromatography (cyclohexane/EtOAc, 7:3) yielding alcohol **14** as an oil (375 mg, 65%) ; $[\alpha]^{20}$ -47 (*c* 1.37 ; CH_2Cl_2) ; ^{1}H NMR δ 1.04 (s, 9H, C(CH_3)$_3$) ; 3.33 (dd, 1H, J_{gem} = 7.0 Hz, $J_{3,4}$ = 5.5 Hz, H-4) ; 3.73 (s, 3H, OCH_3) ; 3.79 (m, 1H, H-2) ; 3.85-4.0 (m, 2H, CH_2OSi) ; 4.15 (m, 1H, H-4') ; 4.39 (m, 1H, H-3) 6.52-7.73 (m, 14H_{arom}) ; ^{13}C NMR δ 19.2 (*C*(CH_3)$_3$) ; 26.9 (C(*C*H_3)$_3$) ; 55.8 (OCH_3) ; 60.3 (C-4) ; 65.7 (C-2) ; 65.8 (CH_2OSi) ; 75.7 (C-3) ; 113.9, 114.5, 137.7,139.7, 133.1, 133.3, 135.6, 146.4, 152.6 (C_{arom}). Anal. Calcd. for $C_{27}H_{33}NO_3Si$: C, 72.44 ; H, 7.43 ; N, 3.13. Found : C, 72.57 ; H, 7.51 ; N, 3.10.

(2R)-2-(tert-Butyldiphenyl silyloxy) methyl-1-p-methoxyphenyl-3-oxo-azetidine **4**

To a solution of oxalyl chloride (36 µL, 0.42 mmol) in THF (4 mL) at -78°C under argon, with stirring, was added dropwise DMSO (60 µL, 0.86mmol) in THF (500 µL). After 20 min, a solution of alcohol **14** (150 mg, 0.34 mmol) in THF (500 µL) was added and this mixture was allowed to stir for 40 min at -65°C. The solution was quenched by addition of Et_3N (142 µL, 1.0 mmol) and allowed to stir with warming to -50°C over 1h.

Ether (20 mL) was added to the mixture which was filtered and concentrated yielding azetidine **4** quantatively (150 mg) as a colorless oil, which was not further purified, due to its relative instability. IR (neat) cm^{-1} : 1820, 1390, 1250 ; ^1H NMR δ 1.03 (s, 9H, $C(CH_3)_3$) ; 3.74 (s, 3H, OCH_3) ; 3.99 (m, 2H, CH_2OSi), 4.42 (m, 1H, H-4) ; 4.65-4.72 (m, 2H, H-2, H-4') ; 6.61, 6.80 (AB, J = 10 Hz, 4 H_{arom}) ; 7.20-7.70 (m, 10 H_{arom}).

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