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Chemoenzymatic Preparation of a Key Intermediate for Carbapenem Synthesis Starting from Asymmetrized *Bis*(hydroxymethyl)acetaldehyde (BHYMA*)

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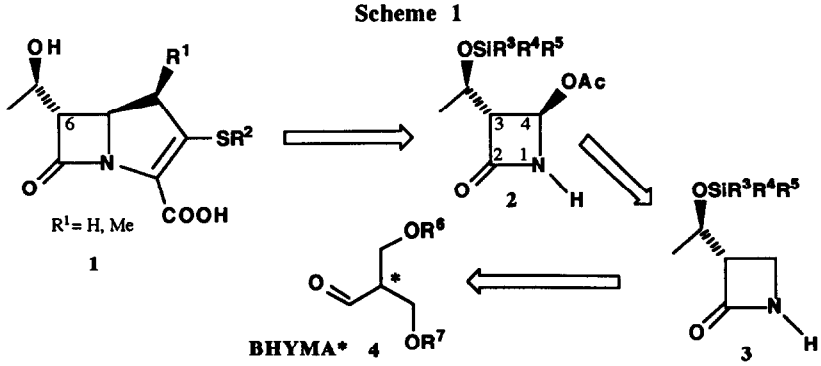
Abstract: 4-Unsubstituted 2-azetidinones **3a,b**, which are useful intermediates for the synthesis of carbapenem antibiotics, have been enantiospecifically and diastereoselectively prepared starting from asymmetrized *bis*(hydroxymethyl)acetaldehyde (BHYMA*) **4**, a new chiral building block obtained through biological methods. The key steps are the highly diastereoselective addition of Me_2CuLi to **4** (diast. ratio = 95 : 5), and the regioselective deblocking of tBuMe$_2$Si ether in the presence of a (iPr)$_3$Si ether, by using a novel methodology.

4-Acetoxyazetidinones **2** (Scheme 1) are very important building blocks, useful for the synthesis of a large variety of pharmacologically important carbapenem antibiotics, represented by the general formula **1**, and characterized by the presence at position 6 of an 1-hydroxyethyl side chain. Therefore many methods for the preparation of **2** in enantiomerically and diastereomerically pure form have been developed.[1] The catalytic[2] or electrochemical[3] oxidation of 4-unsubstituted β-lactams **3** has recently emerged as a new efficient entry into these important intermediates. However, only few methods for the stereoselective production of **3** are presently known.[4]

We now report a novel synthesis of **3** starting from asymmetrized *bis*(hydroxymethyl)acetaldehyde

Scheme 1



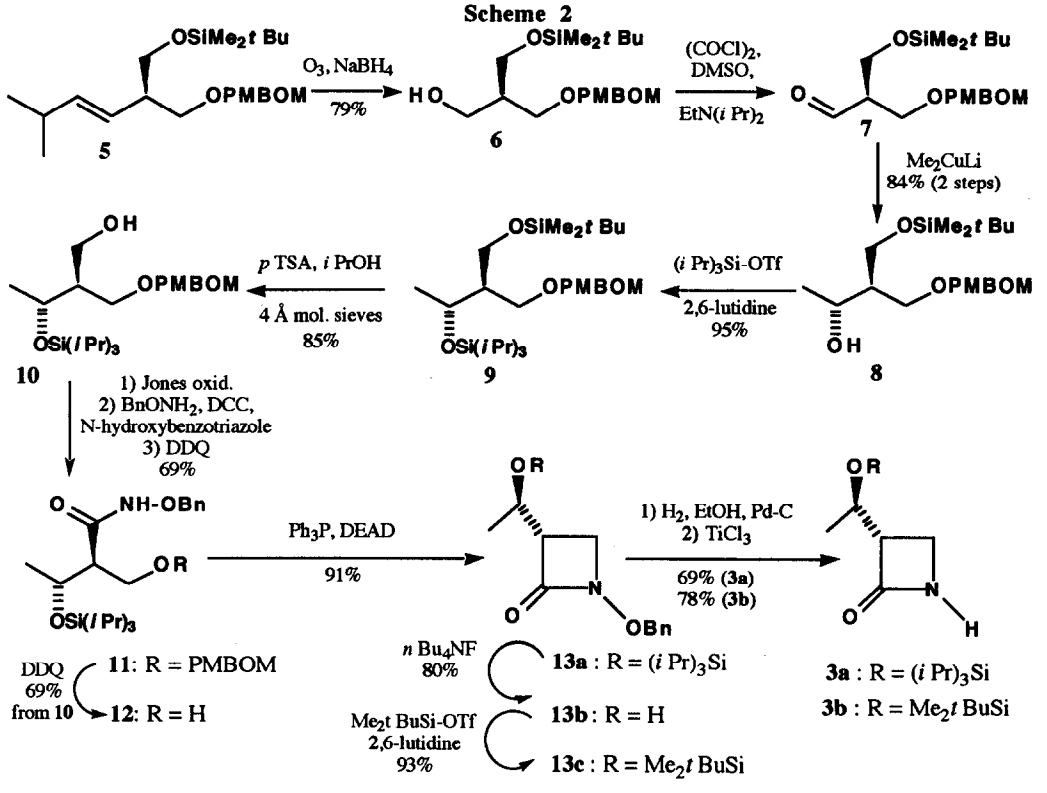
(BHYMA*) **4**, which is a new versatile chiral building block, readily accessible in high enantiomeric excess (97%) through pig pancreatic lipase catalyzed asymmetrization of a prochiral diacetate.[5]

BHYMA* **4** indeed possesses four of the five carbon atoms present in our target **3**, an asymmetric centre (corresponding to that at C-3 in **3**), and three oxygenated functionalities which could be suitably manipulated in order to afford the β-lactam moiety and the protected secondary alcohol. The remaining carbon atom and asymmetric centre could derive from a stereoselective nucleophilic addition of CH_3^- to the carbonyl group of **4**.

The choice of R^6 and R^7 protecting groups in **4** was made not only on the basis of the projected pathway, but also in order to maximize the diastereoselectivity in the nucleophilic methyl addition. In fact it should be pointed out that in **4** the two hydroxymethyl branches are differentiated only by the protecting groups. We have already demonstrated[6] that good results in *"protecting group controlled"* additions to BHYMA* can be achieved by operating under conditions which favour a cyclic chelated transition state, and employing a protecting group capable to favour chelation, like an acetal (*"chelating protecting group"*) and another one (typically a silyl ether) which, on the contrary, depresses the Lewis basicity of the ethereal oxygen (*"non-chelating protecting group"*).

Thus we chose (*R*) aldehyde **7**, where the R^6 and R^7 protecting groups were dimethyl-*tert*-butylsilyl and *p*-methoxybenzyloxymethyl, this latter being a protection which can be conveniently removed under oxidative conditions[7] (Scheme 2). Preparation of **7** was carried out starting from the already described[5] alkene **5**. In this case, direct transformation of **5** into **7** through ozonolysis followed by treatment with dimethyl sulfide gave erratic results, leading often to extensive aldehyde decomposition.[8] Better overall yield, and a more reproducible behaviour were achieved by a two-step sequence, involving reduction to the alcohol **6**, followed by reoxidation, using a modification of Swern methodology.[9,10] Condensation of **7** with dimethyl lithium cuprate proceeded in good overall yield and with excellent diastereoselectivity (95 : 5) to give adduct **8**, which

Scheme 2



was expected from a chelation control.[14] This result is in agreement with previous examples of dialkyl lithium cuprate additions to BHYMA* aldehydes **4**.[6a,b]

At this point the main problem was to convert the secondary alcohol **8** into the hydroxamate **11**. This transformation could be in principle accomplished in two ways: **a**) by deblocking the silyl ether in **8** to give a diol, followed by selective oxidation of the primary alcohol to the corresponding carboxylic acid, or **b**) by protecting the secondary alcohol and selectively deblocking the primary silyl ether. Since the first strategy gave unsatisfactory yields, due to poor selectivity in the Pt/O_2 oxidation[16] of the diol, we turned our attention to the second one. Thus, after protection of the secondary hydroxyl in **8** as the tri-*iso*-propylsilyl ether, we studied the selective removal of the dimethyl-*tert*-butylsilyl ether.

Using the classical methods for silyl ether removal (nBu$_4$NF, pTSA in EtOH, HF), the selectivity turned out to be only moderate, and the yields of **10** were always lower than 50%. Even using methods reported to afford good to excellent selectivity in the deblocking of silyl ethers of different bulkiness,[17] like pyridinium p-toluenesulfonate in EtOH,[17a] or the newly developed method which employs H_2SiF_6 with or without HF,[17b] the yields were still unsatisfactory.[18] Searching for a new methodology best suited for our case, we eventually found out that good selectivity could be achieved by the use of pTSA in anhydrous *iso*-propyl alcohol. We think that the reason for this selectivity relies in the bulkiness of the *iso*-propyl alcohol which makes difficult the attack to the protonated tri-*iso*-propylsilyl ether. The rate is indeed sensibly lower compared to the analogous reaction in absolute EtOH. The presence of small amounts of water increases sensibly the rate, but at the expense of selectivity. Thus, in order to insure the anhydricity of the medium, powdered 4 Å molecular sieves were added to the reaction mixture. We guess that this method could prove to be of general application for the selective removal of silyl ethers.

Jones oxidation gave an acid which was directly converted into benzyl hydroxamate **11** by the DCC/N-hydroxybenzotriazole method. Oxidative deblocking of PMBOM group with DDQ afforded β-hydroxyhydroxamate **12**, which was ready for cyclization under Miller conditions to give N-benzyloxy β-lactam **13a**.[19] Finally, removal of the N-benzyloxy group under reductive conditions,[20] gave the target compound **3a** in 29% overall yield from alcohol **6**. Since **3a** was not reported in the literature, we have also converted N-benzyloxyazetidinone **13a** into **3b**, through interchange of protecting groups followed by reductive removal of benzyloxy group. The enantiomeric excess of these products was checked at the level of alcohol **13b** through the preparation of both diastereomeric Mosher's esters[13] and ^{1}H n.m.r. analysis, which showed an e.e. of 95%.[21,22]

In conclusion we have demonstrated that BHYMA* **4** can be a valuable chiral building block for the synthesis of β-lactams of the thienamycin family. Extension to more functionalized intermediates of this class is in progress.

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EXPERIMENTAL

In n.m.r. spectra, a * means that the value was obtained through double resonance experiments. All n.m.r. were measured in $CDCl_3$ at 200 MHz. (H) or 50 MHz. (C) in ppm (δ scale). Coupling constants are reported in Hertz. Attribution of ^{13}C signals was made also with the aid of DEPT and HETCOR experiments. I.r. spectra were taken in $CHCl_3$ solution. All reactions employing dry solvents were carried out under a nitrogen atmosphere. Polarimetric values were measured at 20°C. Tlc analyses were carried out on silica gel plates, which were developed by spraying a solution of $(NH_4)_4MoO_4$•4 H_2O (21g) and $Ce(SO_4)_2$•4 H_2O (1g) in H_2SO_4 (31 cc) and H_2O (469 cc) and warming. R_f were measured after an elution of 7-9 cm. Chromatographies were carried out on 70-230 mesh silica gel using the "flash" methodology.[23] Petroleum ether

(40-60°C) is abbreviated as PE. In extractive work-up aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. Preparation of alkene **5** is described in ref. 5.

(*R*) 3-[[(*t*-Butyldimethyl)silyl]oxy]-2-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-1-propanol 6. (Caution : ozone is toxic and ozonides are potentially explosive. This reaction must be carried out under a hood and behind a safety shield). A solution of alkene **5** (3.20 g, 7.83 mmol) in dry MeOH (60 mL) and dry CH_2Cl_2 (40 mL) was cooled to -78°C. Ozone was bubbled into the solution until persistence of a grey/blue colour. After further bubbling of O_2 for 5 min, Me_2S (2 mL) was added. After 5 min the mixture was put under nitrogen, and treated rapidly with solid $NaBH_4$ (888 mg, 23.50 mmol). After 15 min, the mixture was warmed to rt and stirred until complete aldehyde reduction was detected by tlc. The solution was treated with saturated aqueous NH_4Cl, and most MeOH removed in vacuo. The resulting suspension was diluted with water and extracted thrice with Et_2O to give, after chromatography (PE : Et_2O 1:1), pure **6** as an oil (2.30 g, 79%). R_f 0.37 (PE : Et_2O 1:1). Anal.: found C, 61.35; H, 9.20. $C_{19}H_{34}O_5Si$ requires C, 61.58; H, 9.25%. $[\alpha]_D$ (c 2, $CHCl_3$)= 0°. ^1H n.m.r.: δ 0.07 [6H, s, $Si(CH_3)_2t$ -Bu]; 0.88 [9H, s, $SiMe_2C(CH_3)_3$]; 1.20[1H, t, O*H*, J= 5.0]; 2.03 [1H, heptuplet, C*H*-CH_2OH, J= 5.4]; 3.67 [2H, d, CH_2OR, J= 6.2]; 3.67-3.87 [4H, m, CH_2OR + CH_2OH]; 3.81 [3H, s, CH_3O]; 4.53 [2H, s, CH_2Ar]; 4.73 [2H, s, O-CH_2-O]; 6.89 [2H, d, aromatics ortho to OMe, J= 8.7]; 7.28 [2H, d, armatic meta to OMe, J= 8.7]. ^{13}C n.m.r.: δ -5.57 [$Si(CH_3)_2$]; 18.18 [CMe_3]; 25.85 [$C(CH_3)_3$]; 42.86 [*C*-CH_2OH]; 55.29 [OCH_3]; 63.52, 64.22, 67.17, 69.08 [CH_2OH, CH_2O, Ar-CH_2O]; 94.58 [O-CH_2-O]; 113.85 [*C* ortho to MeO]; 129.54 [*C* meta to MeO]; 129.75 [*C*-CH_2]; 159.28 [*C*-OMe].

(*R*)-3-[[(*t*-Butyldimethyl)silyl]oxy]-2-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-propanal 7. A solution of $(COCl)_2$ (1.04 mL, 11.94 mmol) in dry CH_2Cl_2 (35 mL) was cooled to -78°C, and treated with a 2.8 M solution of DMSO in dry CH_2Cl_2 (6.83 mL, 19.12 mmol). After 10 min, a solution of alcohol **6** (1.77 g, 4.78 mmol) in CH_2Cl_2 (5 mL) was added. After 10 min N-ethyl di-*iso*-propylamine (5.83 mL, 33.5 mmol) was introduced, and the mixture allowed to react at -78°C until complete at tlc (usually 6-7 h or overnight). The reaction was quenched at -78°C with 5% aqueous $NH_4H_2PO_4$ (15 mL) followed by 1 M HCl (10 mL). After warming to rt, the pH was adjusted to 3 with 1 M HCl, and the aqueous phase extracted with Et_2O. The organic extracts, washed with saturated NaCl, and evaporated to dryness, gave crude **7** (single spot in tlc) as a colorless oil, used immediately (or after 1 night at -30°C) as such for the next reaction. R_f 0.47 (PE : Et_2O 7:3).

(2*R*,3*R*)-4-[[(*t*-Butyldimethyl)silyl]oxy]-3-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-2-butanol 8. (This reaction was carried out under a helium atmosphere). A suspension of CuI (5.46 g, 28.70 mmol) in dry Et_2O (50 mL) was cooled to -50°C and treated with a 1.6 M solution of MeLi in Et_2O (32.9 mL, 52.6 mmol). The temperature was allowed to rise to -20°C during 1 h. After being stirred at -20°C for 10 min, the brown mixture was cooled to -70°C, and treated with a solution of crude aldehyde **7** (obtained from 4.78 mmol of alcohol **6**) in Et_2O (7 mL). After 1 h at -70°C, the temperature was allowed to rise slowly (during 1 h 30 min) to -20°C. The reaction was then quenched with saturated aqueous NH_4Cl, transferred into a beaker, adjusted to pH 9 with 10% NH_4OH, and stirred in air atmosphere until all the Cu(I) salts passed in solution. The blue aqueous phase was acidified to pH 7 with 2 N HCl, and extracted with Et_2O to give a crude product. ^1H n.m.r. analysis of this crude mixture in the presence of Yb(FOD)$_3$ indicated, by integration of the CH_3Si signals, a diastereomeric ratio of 95 : 5. Chromatography (PE : Et_2O 55:45) furnished compound **8**, as an oil, contaminated with traces of its (2*S*,3*R*) diastereoisomer (which had a very close R_f) (1.55 g, 84%). R_f 0.33 (PE : Et_2O 55:45). Anal.: found C, 62.75; H, 9.3. $C_{20}H_{36}O_5Si$ requires C, 62.46; H, 9.43%. $[\alpha]_D$ = -2.7° (c 1.88, $CHCl_3$). ^1H n.m.r.: δ 0.07 [6H, s, $Si(CH_3)_2t$ -Bu]; 0.89 [9H; s; $SiMe_2C(CH_3)_3$]; 1.25 [3H; d; CH_3CH; J= 6.5]; 1.81 [1H, hexuplet, $CHCH_2OSi$, J= 5.2]; 3.32 [1H, d, O*H*, J= 4.5]; 3.77[2H, d, CH_2O, J= 5.9];

3.81 [3H, s, CH_3O]; 3.78 e 3.85 [2H, AB part of an ABx syst., CH_2O, J_{AB}= 9.9, J_{AX}= 5.0, J_{BX}= 5.1]; 3.97-4.12 [1H, m, CHOH]; 4.54 [2H, s, CH_2Ar]; 4.73 [2H, s, OCH_2O]; 6.88 [2H, d, aromatics ortho to OCH_3, J= 8.7]; 7.28 [2H, d, aromatics meta to OCH_3, J= 8.7].

(2*R*,3*R*)-1-[[(*t*-Butyldimethyl)silyl]oxy]-2-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-3-[(tri-*i*-propylsilyl)oxy]butane 9. A solution of alcohol **8** (1.43 g, 3.72 mmol) in dry CH_2Cl_2 (40 mL) was cooled to 0°C, and treated with 2,6-lutidine (1.30 mL, 11.15 mmol) and with tri-*i*-propylsilyl triflate (2.00 mL, 7.44 mmol). After 2 h, the reaction was quenched with saturated aqueous NH_4Cl. Extraction with Et_2O gave, after chromatography (PE : Et_2O 95:5) pure **9** as an oil (1.91 g, 95%). R_f 0.75 (PE : Et_2O 8:2). Anal.: found C, 64.6; H, 10.6. $C_{29}H_{56}O_5Si_2$ requires C, 64.39, H, 10.43%. $[\alpha]_D$= + 0.7° (c 1.95, $CHCl_3$). ^1H n.m.r.: δ 0.03 [6H, s, $(CH_3)_2Si$]; 0.88 [9H, s, $(CH_3)_3CSi$]; 1.06 [21H, s, $Si(CH(CH_3)_2)_3$]; 1.19 [3H, d, CH_3CH, J= 6.4]; 1.87 [1H, hexuplet, $CHCH_2O$, J= 5.7]; 3.63-3.76[2H, m, CH_2O]; 3.63 e 3.78 [2H, AB part of an ABX syst., CH_2O, J_{AB}= 9.9, J_{AX}= 6.8, J_{BX}= 5.5]; 3.81 [3H; s; CH_3O]; 4.24 [1H, dd, CH_3CH; J= 4.4(d) and 6.4(q)]; 4.52 [2H, s, CH_2Ar]; 4.71 [2H, s, OCH_2O]; 6.88 [2H, d, aromatics ortho to CH_3O, J= 8.7]; 7.28 [2H, d, aromatics meta to CH_3O, J= 8.7].

(2*S*,3*R*)-2-[[[(*p*-Methoxybenzyl)oxy]methoxy]methyl]-3-[(tri-*i*-propylsilyl)oxy]butan-1-ol 10. A solution of *bis*-silylether **9** (624 mg, 1.153 mmol) in dry *iso*-propyl alcohol (15 mL) was treated with 4 Å powdered molecular sieves (activated overnight in oven at 250°C) (50 mg) and stirred at rt for 15 min. The mixture was cooled to 0°C and treated with 1 M solution of *p*-toluenesulfonic acid monohydrate in *i*-PrOH (3.69 mL, 3.69 mmol). The reaction was followed in tlc. When the starting material and (2*S*,3*R*) 2-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-1,3-butanediol [R_f 0.37 (PE : AcOEt 1:9)] appeared to be present in the same amount (usually after 20-24 h), the reaction was quenched by addition of saturated aqueous $NaHCO_3$, saturated with NaCl, and extracted with Et_2O to give, after chromatography (PE : Et_2O 95:5 → 50 : 50; then AcOEt), starting **9** (111 mg, 17.8%), pure **10** as an oil (344 mg, 69.8%), and (2*S*,3*R*) 2-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-1,3-butanediol (25.5 mg, 8.7%). The yield of **10**, based on unrecovered substrate, was 85%. R_f 0.32 (PE : Et_2O 1:1). Anal.: found C, 64.4; H, 10.1. $C_{23}H_{42}O_5Si$ requires C, 64.75; H, 9.92%. $[\alpha]_D$= -4.1° (c 1.77, $CHCl_3$). ^1H n.m.r.: δ 1.08 [21H, d, $((CH_3)_2CH)_3Si$]; 1.23 [3H, d, CH_3CH, J=6.4]; 2.12-2.30 [1H, m, $CHCH_2O$]; 3.12 [1H, dd, CH_2OH, J= 4.2 and 6.4]; 3.52 e 3.55 [2H, AB part of an ABx syst., $CH_2OPMBOM$, J_{AB}= 9.8, J_{AX}= 6.2, J_{BX}= 7.2]; 3.70-4.00 [2H, m, CH_2OH, it becomes AB part of an ABx syst. on D_2O addition, δ 3.73 and 3.86, J_{AB}= 10.9, J_{AX}= 7.4, J_{BX}= 5.2]; 3.81 [3H, s, CH_3O]; 4.28 [1H, dq, CHOSi, J= 4.1(d), J= 6.4(q)]; 4.52 [2H, s, CH_2Ar]; 4.70 [2H, s, OCH_2O]; 6.88 [2H, d, aromatics ortho to CH_3O, J=8.8]; 7.28 [2H, d, aromatics meta to CH_3O, J= 8.8].

(2*S*,3*R*) O-Benzyl 2-(hydroxymethyl)-3-[(tri-*i*-propylsilyl)oxy]butanohydroxamate 12. A solution of alcohol **10** (581 mg, 1.36 mmol) in acetone (25 mL), cooled to 0°C, was treated slowly with approximately 30 drops of Jones reagent[24] (prepared from 10 g CrO_3, 8.6 mL 96% H_2SO_4, 14 mL H_2O, and brought up to 40 mL). After 20 min the reaction was quenched with 1 M KH_2PO_4, treated with few mL of 10% $Na_2S_2O_5$., diluted with Et_2O, and filtered through a celite cake. The aqueous phase was adjusted to pH 2, saturated with NaCl, and extracted with Et_2O. Evaporation furnished the crude acid [R_f 0.29 (PE : AcOEt 7:3)], which was used as such for the next reaction. It was taken up in dry CH_3CN (50 mL) and treated, at rt, in sequence, with N-hydroxybenzotriazole hydrate (417 mg, 2.72 mmol), and dicyclohexylcarbodiimide (DCC) (561 mg, 2.72 mmol). After 1 h at rt, triethylamine (0.474 mL, 3.40 mmol) and O-benzylhydroxylamine hydrochloride (327 mg, 2.04) were added. The mixture was stirred overnight at rt, and then filtered, washing the filter with AcOEt. The filtrate was diluted with saturated NaCl, and extracted with AcOEt to give, after silica gel chromatography (PE : AcOEt 75:25), hydroxamate **11** (753 mg, 101%)(R_f 0.53 (PE : AcOEt 70:30), still contaminated by an impurity having silghtly lower R_f and quite difficult to be removed. This partially purified product was used as such for the next reaction. A cleaner sample (but still slightly impure), obtained through a

second chromatography, showed $[\alpha]_D$= + 29.2° (c 1.28, $CHCl_3$). ^1H n.m.r.: δ 1.01 [21H, s, $((CH_3)_2CH)_3Si$]; 1.16 [3H, d, CH_3CH, J= 6.2]; 2.65 [1H, broad q, $CHCH_2OPMBOM$, J= 6.2]; 3.64 [1H, broad dd, CHH-OPMBOM, J= 10.0 and 7.3]; 3.80 [3H, s, CH_3O]; 3.97 [1H; dd; CHH-OPMBOM, J= 10.0 and 7.0]; 4.25 [1H, dq, $CHCH_3$, J_{3-4}=4.7*]; 4.49 [2H, s, CH_2Ar]; 4.69 [2H, s, OCH_2O]; 4.87 and 4.94 [2H, AB syst., $NHOCH_2$, J_{AB}= 11.5]; 6.87 [2H, d, aromatics ortho to CH_3O, J= 8.8]; 7.23 [2H, d, aromatics meta to CH_3O, J= 8.8]; 7.30-7.43 [5H, m, aromatics of phenyl group]; 8.95 [1H, broad s, NH]. The partially purified compound **11**, obtained as above described (753 mg) was dissolved in CH_2Cl_2 (30 mL) and treated with *tert*-butanol (1.50 mL), with a pH 7 0.2 M buffer solution (KH_2PO_4-K_2HPO_4) (1.50 mL), and with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (623 mg, 2.74 mmol). After being stirred for 2 h at rt, the reaction was quenched with saturated aqueous $NaHCO_3$, diluted with Et_2O, and filtered through a celite cake. The phases were separated and the organic layer, after drying, evaporation in vacuo, and chromatography (PE : AcOEt 60:40) gave pure **12** as an oil (370 mg, 69% from **10**). R_f 0.35 (PE : AcOEt 60:40). Anal.: found C, 63.45; H, 9.6; N, 3.45. $C_{21}H_{37}O_4NSi$ requires C, 63.76; H, 9.43; N, 3.54%. ^1H n.m.r.: δ 0.99 [21H, s, $((CH_3)_2CH)_3Si$]; 1.16 [3H, d, CH_3CH, J=6.3]; 2.64 [1H, quintuplet, $CHCH_2OH$, J= 3.8]; 3.11 [1H, broad s, CH_2OH]; 3.55-3.70 [1H, m, CHH-OH]; 3.82-3.98 [1H, m, CHH-OH]; 4.10 [1H, dq, CH_3CH; J_{3-4}=3.9*]; 4.90 and 4.95 [2H, AB syst., $NHOCH_2$, J= 11.6]; 7.30-7.50 [5H, m, aromatics]; 9.33 [1H, broad s, NH].

(3*S*,1'*R*)-1-Benzyloxy-3-[[2-(tri-*iso*-propylsilyl)oxy]ethyl]-2-azetidinone 13a. A solution of hydroxamate **12** (350 mg, 0.885 mmol) in dry THF (20 mL) was treated with a preformed solution of Ph_3P (464 mg, 1.770 mmol) and diethyl azodicarboxylate (DEAD) (308 mg, 1.770 mmol) in THF (2.5 mL). After being stirred overnight at rt, the reaction was concentrated in vacuo and chromatographed (PE : AcOEt 86 : 14) to give pure **13a** as an oil (304 mg, 91%). R_f 0.73 (PE : Et_2O 34:66). Anal.: found C, 67.0; H, 9.25; N, 3.65%. $C_{21}H_{35}O_3NSi$ requires C, 66.8; H, 9.34; N, 3.71%. $[\alpha]_D$= -29.3° (c 1.905, $CHCl_3$). ^1H n.m.r.: δ 1.04 [21H, s, $((CH_3)_2CH)_3Si$]; 1.22 [3H, d, CH_3CH, J= 6.2]; 2.85 [1H, dt, $CHCH_2$, J= 5.3(t) and 2.5(d)]; 3.26 e 3.36 [2H, AB part of an ABx syst., CH_2-N, J_{AB}= 4.3, J_{AX}= 2.5, J_{BX}= 5.4]; 4.22 [1H, quintuplet, CH_3CH, J= 6.0]; 4.93 e 4.95 [2H, AB syst., $NOCH_2$, J_{AB}= 11.4]; 7.30-7.50 [5H, m, aromatics].

(3*S*,1'*R*)-3-[[2-(Tri-*iso*-propylsilyl)oxy]ethyl]-2-azetidinone 3a. A solution of **13a** (62 mg, 0.164 mmol) in 96% EtOH (10 mL) was hydrogenated on 10% Pd on carbon (10 mg) for 4 h at rt and under the slight pressure given by a small inflated balloon. Filtration of the catalyst, and evaporation to dryness gave the crude 1-hydroxyazetidinone (R_f 0.15 (PE : Et_2O 30:70), as a solid. It was taken up in MeOH (4.5 mL) and treated, under nitrogen, with a just prepared solution of $TiCl_3$ (30% solution in 2 N HCl)(424 mg, 0.825 mmol) in H_2O (5 mL), neutralized to pH 6 with 1N NaOH. After stirring for 30 min at rt, tlc indicated completion of the reaction. Dilution with saturated NaCl and AcOEt, separation of the phases, and evaporation gave, after chromatography (PE : Et_2O 25 : 75) pure **3a** as a solid (30.7 mg, 69%). R_f 0.23 (PE : Et_2O 30:70). Anal.: found C, 61.65; H, 10.80; N, 5.00. $C_{14}H_{29}O_2NSi$ requires C, 61.94; H, 10.77; N, 5.16%. $[\alpha]_D$= -42.3° (c 1.53, $CHCl_3$). ^1H n.m.r.: δ 1.07 [21H, s, $((CH_3)_2CH)_3Si$]; 1.26 [3H, d, CH_3CH, J= 6.2]; 3.18-3.28 [1H, m, $CHCH_2$]; 3.32 and 3.39 [2H, AB part of an ABx syst., CH_2N, J_{AB}= 5.0, J_{AX}= 2.6, J_{BX}= 5.2]; 4.38 [1H, dq, CH_3CH, J= 4.8(d), J= 6.2]; 5.94 [1H; broad s; NH]. ^{13}C n.m.r.: δ 12.64 [$((CH_3)_2CH)_3Si$]; 18.09 [$((CH_3)_2CH)_3Si$]; 22.79 [CH_3CH]; 37.92 [CH_2N]; 59.67 [$CHCH_2N$]; 65.86 [CH-O]; 169.50 [C=O]. I.R: ν_{max} 3420 (str. NH), 2940 and 2860 (str. CH), 1750 (str. C=O), 1460 e 1370 (bending CH_3), 1145, 1105, 1080, 1010, 965, 940, 920, 880 cm^{-1}.

(3*S*,1'*R*)-1-Benzyloxy-3-[[2-(*tert*-butyldimethylsilyl)oxy]ethyl]-2-azetidinone 13c. A solution of **13a** (322 mg, 0.853 mmol) in dry THF (13 mL) was treated, at rt, with 0.5 M *n*-Bu_4NF•$3H_2O$ in THF (5.12 mL, 2.558 mmol) and stirred for 1 h. Dilution with saturated NaCl and Et_2O, separation of the phases, and chromatography (PE : AcOEt 30:70) gave pure **13b** as an oil (151 mg, 80%). R_f 0.36 (Et_2O). It was taken

up in dry CH_2Cl_2 (10 mL), cooled to 0°C, and treated with 2,6-lutidine (0.159 mL, 1.365 mmol) and *tert*-butyldimethylsilyl triflate (0.235 mL, 1.024 mmol). After 3h the mixture was diluted with saturated aqueous NH_4Cl, extracted with Et_2O, and chromatographed to give pure **13c** as an oil (212 mg, 92.5%, 74% from **13a**). R_f 0.72 (PE : Et_2O 30:70). Anal.: found C, 64.8; H, 8.6; N, 4.1. $C_{18}H_{29}O_3NSi$ requires C, 64.44; H, 8.71; N, 4.17%. ^1H n.m.r.: δ 0.04 and 0.05 [2x3H, 2s, *t* -Bu(CH_3)$_2$Si]; 0.86 [9H, s, Me$_2$(CH_3)$_3$CSi]; 1.15 [3H, d, CH_3CHOSi, J= 6.2]; 2.85 [1H, dt, CHCH$_2$, J= 5.0(t), J= 2.4]; 3.24 and 3.34 [2H, AB part of an ABx syst., CHCH_2N, J_{AB}= 4.2, J_{AX}= 2.5, J_{BX}= 5.3]; 4.08 [1H, dq, CH$_3$CH, J= 6.2(q) e 4.9(d)]; 4.93 and 4.95 [2H; AB syst., NOCH_2, J_{AB}= 11.4]; 7.30-7.50 [5H, m, aromatics].

(3*S*,1'*R*)-3-[[2-(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-azetidinone 3b. It was prepared from **13c** (167 mg, 0.498 mmol) following the same procedure employed for **3a**. Yield= 88.9 mg (white solid) (78%). R_f 0.33 (PE : Et_2O 20:80; detected spraying HBr solution, followed by a ninhydrin solution in *n*BuOH-AcOH)(R_f of 1-hydroxyazetidinone: 0.23). Anal.: found C, 57.8; H, 10.2; N, 6.0. $C_{11}H_{23}O_2NSi$ requires C, 57.60; H, 10.11; N, 6.11%. P.f.= 59.1-62.6°C. $[\alpha]_D$= -58.1° (c 1.51, $CHCl_3$). ^1H n.m.r.: δ 0.08 [6H, s, *t* -Bu(CH_3)$_2$Si]; 0.88 [9H, s, Me$_2$(CH_3)$_3$CSi]; 1.20 [3H, d, CH_3CHOSi, J= 6.2]; 3.18-3.26 [1H, m, C*H*-CON]; 3.29 and 3.35 [2H,AB part of an ABx syst., CHCH_2N, J_{AB}= 5.0, J_{AX}= 2.6, J_{BX}= 5.2]; δ 4.21 [1H, dq, C*H*-CH$_3$, J= 6.2(q) e 4.4(d)]; 5.94 [1H, broad s, N*H*]. ^{13}C n.m.r.: δ -4.98 and -4.27 [*t* -Bu(CH_3)$_2$Si]; 17.96 [Me$_2$((CH_3)$_3$*C*)Si]; 22.54 [CH_3CHOSi]; 25.72 [Me$_2$((CH_3)$_3$C)Si]; 37.67 [CH_2NH]; 59.39 [*C*HCH$_2$NH]; 65.35 [*C*HOSi]; 169.51 [C=O].

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11. A general study on the optimal conditions for avoiding racemization in Swern oxidation of labile aldehydes is in progress and will be reported in due course.
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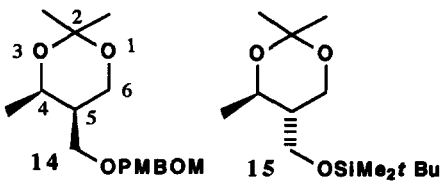
14. The relative configuration of this product was established through its conversion into *cis* and *trans iso*-propylidene derivatives **14** and **15**, whose structure was ascertained by ^1H and ^{13}C nmr. $J_{4,5}$ was indeed = 9.4 Hz. for **15** and 2.7 Hz. for **14**. At ^{13}C the chemical shifts for C-2 and C-5', by comparison with a series of similar compounds,[15] has given further evidence for the assigned relative configuration.



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18. Although we could not detect, under all the conditions tested, the formation of mono-silyl ether deriving from attack to the $(iPr)_3Si$ group, it is more difficult to avoid the formation of diol. Actually, it should be stressed that in our case the removal of the first silyl ether from the primary alcohol strongly relieves the overall steric encumbrance of the molecule, thus facilitating the attack to the secondary silyl ether. On the contrary, the literature methods reported to be efficient for the selective removal of TBDMS groups in the presence of $(iPr)_3Si$, were tested on substrates where the two groups are quite far away from each other (see ref. 17).
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