A New Method of *N*-Benzhydryl Deprotection in 2-Azetidinone Series

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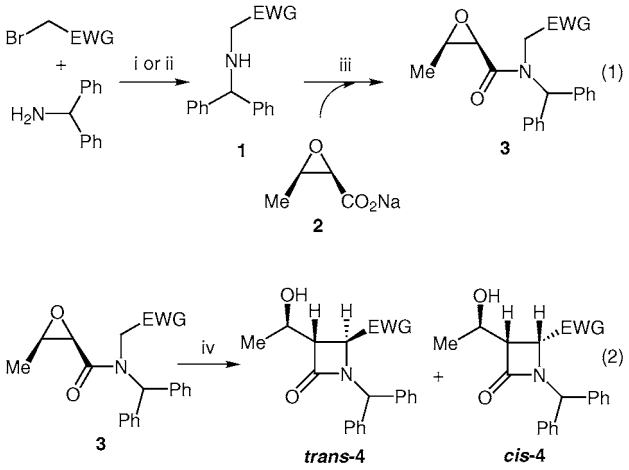
Abstract: A mild and efficient procedure for the selective cleavage of *N*-benzhydryl protecting group of β-lactams is described. The protected 2-azetidinones **4**, precursors of carbapenems, were treated with a stoichiometric amount of *N*-bromosuccinimide and a catalytic amount of bromine under sun light irradiation in CH_2Cl_2–H_2O mixture at 20 °C for 3 hours. The *N*-benzhydrol intermediates **6**, which could be isolated, were then hydrolyzed with *p*-TsOH in aqueous acetone to furnish β-lactams **7** and benzophenone quantitatively.

Key words: antibiotics, halogenation, protecting groups, benzhydryl derivatives, stable hemiaminals

The importance of 2-azetidinones (β-lactams)[1] is widely recognized as key intermediates for the synthesis of antibiotics,[2] as well as versatile synthons for the preparation of β-amino acid derivatives.[3] Enantiomerically pure 2-azetidinones are now accessible via different routes based on cyclization, [2+2] cycloaddition, or cyclocondensation strategies.[4] Because of their excellent stability towards β-lactamases and enhanced activity, carbapenems, a new class of β-lactam antibiotics, have attracted much attention over the last twenty years.[5] Recently, we revisited the synthesis of 3-[1′-(*R*)-hydroxyethyl]azetidin-2-one intermediates of carbapenems, by applying the C-3/C-4 ring-closure method from (2*R*,3*R*)-epoxybutyramide precursors.[6] We were interested in the replacement of the habitual *p*-anisyl *N*-1 protecting group[5a,7] with the benzhydryl group. Indeed, the cleavage of *p*-anisyl substituent requires supra-stoichiometric amount[5] of ceric ammonium nitrate (CAN) as selective oxidant,[8] a method which uses a toxic reagent, and is not really compatible with large scale synthesis. The other useful *N*-1 protecting groups of 2-azetidinones are trialkylsilyl residues, 2,4-dimethoxybenzyl and di(*p*-methoxyphenyl)methyl substituents, the last ones being removable also by CAN oxidation or under strongly acidic treatments.[5a,9]

In this paper, we describe the incorporation of *N*-1 benzhydryl group into β-lactams using the commercially available benzhydrylamine for the preparation of synthons **1** [Scheme 1, (1)], and the further *N*-1 deprotection of β-lactams **4** resulting from the coupling of **1** with chiral epoxide **2**,[10] followed by basic cyclization [Scheme 1, equation (2)][6] (Table 1). Our method relies upon the ease with which photobromination of the diphenylmethyl moiety can be performed.[11]



Scheme 1 Synthesis of β-lactams. *Reagents and conditions*: (i) benzhydrylamine (2 equiv), MeOH, r.t.,overnight; (ii) benzhydrylamine (1 equiv), K_2CO_3 (1.1 equiv), Kl (1.1 equiv), DMF, reflux, 5 h; (iii) a) **2** (1.2 equiv), $(COCl)_2$ (1.3 equiv), THF, –5 °C, 2 h; b) pyridine (2 equiv), **1a**–**d**, THF, –5 °C, 2 h; (iv) LiHMDS (1.1 equiv), THF, 0 °C, 3 h.

Table 1 Yields of Isolated Compounds (%)

Product	EWG	**1** (Method)	**3**	**4**	*trans:cis*
a	CO*t*-Bu	88 (i)[6]	46[6]	90[6]	100:0
b	COPh	86 (i)[6]	55[6]	57[6]	100:0
c	CO_2*t*-Bu	95 (ii)	67	69	100:0
d	CN	90 (ii)	41	47	52:48

We have previously reported the preparation of epoxide intermediates **3a** and **3b**, and their transformation into 2-azetidinones **4a** and **4b**, respectively, equipped with pivaloyl- and benzoyl-EWG (electron-withdrawing) groups at position C-4;[6] side products (six- and seven-membered ring derivatives) of the S_Ni reaction were also isolated.[12] According to the same strategy, based on the seminal work of Hanessian,[7] we have now synthesized β-lactams **4c** and **4d** with *tert*-butyloxycarbonyl and cyano substitu-

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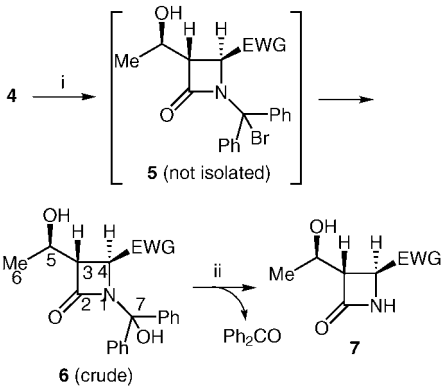
ents, respectively, at this position (Table 1). Reaction of benzhydrylamine with *tert*-butyl bromoacetate and bromoacetonitrile, respectively, gave secondary amines **1c**[13] and **1d**,[14] purified by recrystallization from methanol. Activation of sodium (2*R*,3*R*)-*cis*-2,3-epoxybutanoate (**2**)[10] with oxalyl chloride in THF at low temperature, followed by addition of pyridine and **1c**,**d** led to the isolation of **3c**,**d** in 40–70% yield, after chromatography on silica gel. Compound **3c** showed the presence of two rotamers in the NMR spectra ($CDCl_3$), splitting practically all the signals, as a result of restricted rotation around the C(O)–N amide bond. In contrast, compound **3d** showed broad signals characteristic of rotamers in rapid equilibrium; recording the NMR spectra at –55 °C allowed the detection of the signals of both the rotamers (see experimental). The best conditions of cyclization, previously determined,[6] were applied. Thus, epoxyamides **3c**,**d** were treated with lithium hexamethyldisilazide (LiHMDS) in THF at 0 °C to furnish β-lactams **4c**,**d** in 50–70% yield after purification. The cyclization of **3c** into **4c** occurred similarly to that of **3a**,**b**,[6] giving only the *trans*-diastereoisomer **4c**. This most probably results from the steric control due to a bulky EWG-substituent when the third asymmetric center (C-4) was induced. Accordingly, in the case of **3d**, the cyclization into **4d** (EWG = CN) was no longer stereoselective: an equimolar mixture of *trans* and *cis* β-lactams was recovered, as revealed by the typical ^{1}H NMR coupling constants of H-3 and H-4 (J_{trans} = 2.4 Hz and J_{cis} = 5.4 Hz). Such loss of stereoselectivity has been previously mentioned for small EWG groups at position C-4.[15]

Traditionally, the removal of a benzhydryl protecting group from O- or N-functionalities has been achieved via hydrogenation or under vigorous acidic conditions;[9] ether and esters derivatives being more easily cleaved than the corresponding amines and amides. Thus, we first applied various conditions of catalytic hydrogenation to compound **4a** [Pd/C, $Pd(OH)_2$/C, $Pd/BaSO_4$, $Pd/CaCO_3$ or Raney Ni, in EtOAc, EtOH, HOAc or DMF, under 50 psi H_2, during several hours], but without success: the *N*-benzhydryl azetidinone was recovered unchanged. In the case of compound **4b**, prolonged hydrogenation provoked the reduction of the benzoyl moiety (into hydroxybenzyl and benzyl groups), without any N-deprotection. Disappointing results were also obtained when submitting **4a** to acidic conditions (HCO_2H or CF_3CO_2H, neat or in the presence of anisole; HBr–HOAc); the benzhydryl group was never removed, and under prolonged reaction times, modifications of the hydroxyl function of the C-3 sidechain appeared (such as formylation and trifluoroacetylation). Therefore, we turned to a totally different strategy making use of the sensitivity of benzylic derivatives towards free radical bromination.[11] Our plan was to selectively produce bromobenzhydryl intermediates **5** (Scheme 2) and to further hydrolyze them into benzhydrol derivatives **6**, the acid-catalyzed decomposition of which would lead to N-deprotected azetidinones **7** and benzophenone.

Table 2 Deprotection Conditions of **4a**

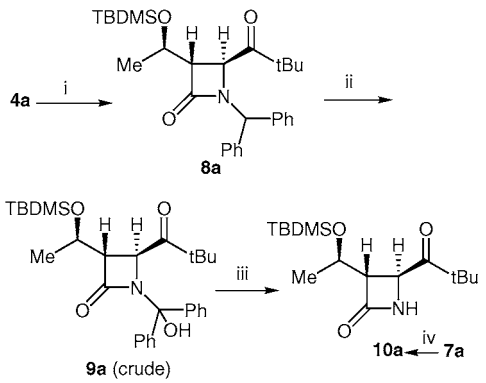
Entry	Conditions	Results[a]
1	NBS, AIBN (catal.), PhCl, 120 °C, 3 h	degradation[b]
2	NBS, AIBN (catal.), CCl_4, 70 °C, 3 h	degradation[b]
3	NBS, AIBN (catal.), PhCl, 20 °C, dark, 24 h	**4a** (no reaction)
4	NBS, PhCl, white light (120 W), 20 °C, 30–90 min	**4a** + **5a** + degradation[b]
5	NBS, PhCl, fume hood lamp, 20 °C, 24 h	degradation[b]
6	NBS, PhCl–H_2O (10:1), fume hood lamp, 20 °C, 24 h	**6a** (>95%)
7	NBS, CH_2Cl_2–H_2O (10:1), fume hood lamp, 20 °C, 24 h	**6a** (>95%)
8	NBS, Br_2 (catal.), CH_2Cl_2–H_2O (5:1), *h*ν, 20 °C, 3 h	**6a** (>95%)
9	NBS, Br_2 (catal.), CH_2Cl_2–H_2O (5:1), dark, 20 °C, 3 h	**4a** (no reaction)
10	Br_2, CH_2Cl_2–H_2O (5:1), *h*ν, 20 °C, 3 h	**6a** (ca. 85%) + degradation

[a] ^{1}H NMR analysis of the crude mixtures.
[b] The β-lactam ring was broken.



Scheme 2 Benzhydryl group deprotection (unprotected substrates). *Reagents and conditions*: (i) NBS (1.2 equiv), CH_2Cl_2–H_2O 5:1, Br_2 (0.1 equiv), r.t., hν, 3 h; (ii) *p*TsOH (1 equiv), CH_3CN–H_2O 1:1, r.t., dark, overnight

Treatment of **4a** with *N*-bromosuccinimide[16] (NBS) was thus considered under various conditions (Table 2). We first used azobis(isobutyro)nitrile (AIBN) as free radical initiator. Reaction took place at higher temperatures (entries 1,2), and after aqueous workup, we could identify the presence of benzophenone in the crude mixtures, indicating that the sequence of reactions outlined in Scheme 2 could occur, at least partially! But the reaction further



Scheme 3 Benzhydryl group deprotection (O-protected substrate). *Reagents and conditions*: (i) TBDMSCl (5 equiv), imidazole (10 equiv), DMF, r.t., 2 d; (ii) NBS (1.2 equiv), CH_2Cl_2–H_2O 5:1, Br_2 (0.1 equiv), r.t., hν, 3 h; (iii) *p*TsOH (1 equiv), CH_3CN–H_2O or acetone–H_2O 1:1; r.t.; dark, overnight; (iv) TBDMSCl (2 equiv), imidazole (5 equiv), DMF, r.t., 16 h.

evolved to the destruction of the β-lactam ring (NMR analysis). At room temperature (entry 3), no reaction occurred. In order to avoid high temperatures, we tried to photochemically activate the reaction (entry 4) : the transformation of **4a** into **5a** (and **6a**, after aqueous workup) was observed by NMR, together with the gradual appearance of unidentified degradation products. At complete conversion of **4a** (after 90 min), the yield of desired products **6a** was very low versus degradation. Reducing the irradiation power, we slowed down the reaction rate, but did not avoid the product degradation (entry 5). At this stage, we assumed that the initially formed benzhydrylamine derivative **5a** should be unstable under radical conditions, and that its trapping in situ (by hydrolysis for instance) would lead to a cleaner transformation. Indeed, the addition of 10% water[17] in the chlorobenzene solution of entry 5 completely changed the evolution of the reaction: the benzhydrol derivative **6a** was smoothly formed and isolated as the sole product (entry 6). The same reaction could be performed in dichloromethane–water solution (entry 7), a solvent more appropriate for the dissolution of all types of precursor **4**. At last, we found that the photochemical bromination with NBS could be significantly accelerated by the addition of a catalytic amount of molecular bromine (entry 8). Under irradiation, bromine was well the free-radical initiator, since no reaction took place in the dark (entry 9). The use of a nearly equimolar amount of bromine (instead of NBS + Br_2 catalysis) in CH_2Cl_2–H_2O, under the irradiation of the fume hood lamp, also led to the formation of **6a**, within 3 hours, but in slightly lower yields (entry 10).

Compound **6a** has been well characterized by ^{1}H NMR (disappearance of the benzhydryl proton at δ = 5.69 and appearance of the OH proton at δ = 5.12 as a broad signal) and ^{13}C NMR spectroscopy (NCOH at 87.4 ppm). Moreover, the structure of this intermediate was unambiguously confirmed by X-ray diffraction analysis of a monocrystal.[18] Such a functionality (stable *O*,*N*-hemiaminal) was rarely described in the previous literature. It was observed as secondary product in the Baylis–Hillman reaction with acrylamide,[19a,b] or in a few natural products: spergualin[19c] and zampanolide.[19d] The authors[19a,d] advanced as hypothesis that this function was stabilized by an extensive intramolecular hydrogen bonding network.

The quantitative decomposition of **6a** into NH-free β-lactam **7a** required the treatment with *p*-toluenesulfonic acid in aqueous acetonitrile or acetone (homogeneous medium). Otherwise, **7a** was very slowly formed when the crude product **6a** was left at room temperature in the dark for several days. Compound **7a** was purified by column-chromatography on silica gel (removal of benzophenone) or by extraction with water. This novel method of *N*-benzhydryl deprotection (Table 2, entry 8) could be readily applied to the other precursors **4b**, **4c**, and **4d** (Scheme 2). The corresponding NH-azetidinones **7a**,[20] **7b**,[20,21] **7c**[22] and **7d** are previously described compounds, except **7d** (*cis* and *trans* compounds).

We have controlled that our deprotection procedure works also on OH-masked precursors, as usually recommended in the carbapenem chemistry. Thus, azetidinone **4a** was transformed into *tert*-butyldimethylsilyloxy derivative **8a** (Scheme 3), and further treated with NBS in wet chlorobenzene under light to give alcohol **9a** and then hydrolyzed in acidic medium into **10a** in 95% yield. Azetidinone **10a** was identical to a sample obtained by silylation of **7a**.

The search of an alternative method to the CAN cleavage of N-protective groups of β-lactams have led us propose an original two-step reaction (optionally conducted in a one-pot procedure) in which a *N*-benzhydryl substituent is transformed into a *N*-benzhydrol group with NBS/H_2O/Br_2 (cat.)/hν, and the resulting *O*,*N*-hemiaminal is then acid-hydrolyzed. Our procedure is practical, quantitative, and clean; as a supplementary advantage, the method can be run on the free hydroxyl precursors **4**, as well as on the corresponding silylated derivatives with the same excellent yields. Other options to replace CAN deprotection were the oxidation of *p*-methoxyphenyl group by means of silver cation in the presence of persulfate anion as cooxidant,[23] or by using electrochemical methods.[20,24] In our opinion, the photohalogenation-hydrolysis of a *N*-benzhydryl substituent constitutes a valuable deprotection method of amides (lactams) which could be a useful complement of the well-established orthogonal protective group strategy in peptide synthesis.[25,26] β-Lactams **7c** and **7d** are precursors of the corresponding 2-azetidinone-4-carboxylic acid, a known intermediate for carbapenem synthesis.[27]

Melting points were determined with an electrothermal microscope and are uncorrected. Specific rotations (±0.2) were determined on a Perkin-Elmer 343 polarimeter (concentration in g/100mL). IR spectra were taken with a Bio-Rad FTS 135 instrument and calibrated with polystyrene (1601 cm^{-1}). The ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200–300 (at 200–300 MHz for proton and 50–75 MHz for carbon), or Bruker AM-500 spectrometers (at

500 MHz for proton and 125 MHz for carbon); the chemical shifts are reported in ppm downfield from tetramethylsilane (internal standard). Mass spectra were obtained on a Finnigan-MAT TSQ-70 instrument at 70 eV (chemical ionization mode). Microanalyses were performed at the Christopher Ingold Laboratories of the University College London, UK. HRMS were recorded at the University of Mons, Belgium (Prof. R. Flamang).

TLC was carried out on silica gel 60 plates F254 (Merck, 0.2 mm thick); visualization was effected with UV light. Column chromatography (under medium pressure) was carried out with Merck silica gel 60 of 230–240 mesh ASTM. Compounds **1a**, **1b**, **3a**, **3b**, **4a** and **4b** were fully described in Ref.[6]

tert-Butyl(diphenylmethylamino)ethanoate (1c)[13]

To a solution of benzhydrylamine (7.6 mL, 44.1 mmol, 1 equiv) in anhyd DMF (160 mL) were added K_2CO_3 (6.70 g, 48.5 mmol, 1.1 equiv) and KI (8.16 g, 49.1 mmol, 1.1 equiv). The suspension was stirred and brought to reflux. *tert*-Butyl bromoacetate (8.63 g, 44.3 mmol, 1 equiv) was then added dropwise during 15 min. A white precipitate appeared. After 5 h, the precipitate was filtered off and the solution was diluted with EtOAc (200 mL), washed with brine (3 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. A yellow solid was obtained which could be used without further purification (13.34 g, ca. 100%). A pure sample was obtained by recrystallization from MeOH; light brown crystals; mp 75.5–76.5 °C.

IR (neat): 3320 (NH), 1734 (C=O), 1455 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.1–7.5 (m, 10 H_{arom}), 4.88 (s, 1 H, Ph_2CH), 3.28 (s, 2 H, $NHCH_2CO_2Bu$), 2.1 (br s, 1 H, NH), 1.46 (s, 9 H, *t*-C_4H_9).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.7, 143.5, 128.5, 127.4, 127.1, 81.1, 66.7, 50.0, 28.2.

MS (EI): *m*/*z* (%) = 297.2 ([M]$^+$·, 0.6), 182.0 ([Ph_2CHNH]$^+$, 100), 167.1 ([Ph_2CH]$^+$, 17), 105.1 (70), 77.0 ([Ph]$^+$, 67).

N-(Diphenylmethyl)aminoacetonitrile (1d)[14]

To a solution of benzhydrylamine (5.4 mL, 31.4 mmol, 1 equiv) in anhyd DMF (120 mL) were added K_2CO_3 (4.79 g, 34.7 mmol, 1.1 equiv) and KI (5.74 g, 34.6 mmol, 1.1 equiv). The suspension was stirred and brought to reflux. Bromoacetonitrile (3.77 g, 31.4 mmol, 1 equiv) was then added dropwise during 15 min. The mixture turned darker and a small white precipitate was formed. After 5 h, the precipitate was filtered off and the organic solution was diluted with EtOAc (100 mL), washed with brine (3 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. A dark solid was recovered which could be used without further purification (6.96 g, 99%). A pure sample was obtained by recrystallization from MeOH; light brown crystals; mp 69–71 °C.

IR (neat): 3338 (NH), 2244 (C≡N), 1453 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.2–7.5 (m, 10 H_{arom}), 5.08 (s, 1 H, Ph_2CH), 3.52 (s, 2 H, $NHCH_2CN$), 2.1 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 141.7, 128.8, 127.6, 127.3, 117.4, 65.8, 35.3.

MS (EI): *m*/*z* (%) = 222.0 ([M]$^+$·, 77), 196.0 ([$Ph_2CHNHCH_2$]$^+$, 10), 182.0 ([Ph_2CHNH]$^+$, 27), 167.0 ([Ph_2CH]$^+$, 85), 144.8 ([PhCHNHCH$_2$CN]$^+$, 100), 77.0 ([Ph]$^+$, 30).

Epoxyamides 3; General Procedure

To a stirred suspension of **2** (1.1 equiv) in anhyd THF (4 mL/mmol of **2**) at –6 °C under argon was added dropwise oxalyl chloride (1.3 equiv). A strong gaseous evolution was observed. The mixture was stirred for 2 h at –6 °C. Pyridine (3 equiv) was then added dropwise, followed by the amine **1** (1 equiv). The mixture was stirred for 1 h at –6 °C and then allowed to warm up to r.t. during 1 h. The crude mixture was diluted with EtOAc, washed with sat. aq $NaHCO_3$ (3 ×), dried ($MgSO_4$) and concentrated under reduced pressure. The solid obtained was then purified by chromatography on silica gel (hygroscopic compounds).

tert-Butyl (2′*R*, 3′*R*)-2-[*N*-(Diphenylmethyl)-*N*-(2′,3′-epoxybutanoyl)amino]ethanoate (3c)

Starting from **1c** (1.14 g, 3.8 mmol) and following the general procedure, a white foam (0.98 g, 67%) was obtained after chromatography (eluent: cyclohexane–EtOAc, 5:1); R_f 0.18; mp 90–92 °C; $[\alpha]_D^{20}$ +57.2 (*c* = 0.458, $CHCl_3$).

IR (neat): 3321 (OH), 1723 (C=O ester), 1660 (C=O amide) cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz, two rotamers in a 55:45 ratio): δ (major rotamer) = 7.1–7.4 (m, 10 H_{arom}), 6.61 (s, 1 H, Ph_2CH), 4.07 (d, 1 H, *J* = 16.9 Hz, NCH_2CO), 3.93 (d, 1 H, *J* = 16.9 Hz, NCH_2CO), 3.60 (d, 1 H, *J* = 4.4 Hz, H-2′), 3.29 (dq, 1 H, *J* = 4.4, 5.3 Hz, H-3′), 1.38 (d, 3 H, *J* = 5.3 Hz, CH_3), 1.25 (s, 9 H, *t*-C_4H_9). δ (minor rotamer) = 7.1–7.4 (m, 11 H_{arom} and Ph_2CH), 4.47 (d, 1 H, *J* = 18.4 Hz, NCH_2CO), 3.94 (d, 1 H, *J* = 18.4 Hz, NCH_2CO), 3.67 (d, 1 H, *J* = 4.4 Hz, H-2′), 3.29 (dq, 1 H, *J* = 4.4, 5.3 Hz, H-3′), 1.35 (d, 3 H, *J* = 5.3 Hz, CH_3), 1.21 (s, 9 H, *t*-C_4H_9).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.4, 168.0, 167.1, 138.9, 138.8, 127.9–129.6, 64.6, 61.4, 55.7, 55.1, 54.3, 47.3, 47.2, 28.3, 15.1, 14.5.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 464.3 (14), 382.1 ([M + H]$^+$, 0.6), 298.1 ([$Ph_2CHNH_2CH_2CO_2Bu$]$^+$, 31), 183.0 (100), 166.9 ([Ph_2CH]$^+$, 83).

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 71.97; H, 7.12; N, 4.07.

(2*R*,3*R*)-*N*-(Diphenylmethyl)-*N*-cyanomethyl-2,3-epoxybutanoamide (3d)

Starting from **1d** (1.21 g, 5.4 mmol) and following the general procedure, a white foam (0.69 g, 41%) was obtained after trituration with acetone; R_f 0.22 (EtOAc–CH_2Cl_2, 10:1); mp 146.5–148.0 °C; $[\alpha]_D^{20}$ +51.7 (*c* = 0.750, $CHCl_3$).

IR (neat): 3312 (NH), 2240 (C≡N), 1669 (C=O amide) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz, two rotamers in nearly rapid exchange at 25 °C): δ = 7.3–7.6 (m, 10 H_{arom}), 6.63 (br s, 1 H, Ph_2CH), 4.34 (br m, 2 H, NCH_2CN), 3.81 (br s, 1 H, H-2), 3.46 (br s, 1 H, H-3), 1.49 (br d, 3 H, *J* = 4.8 Hz, CH_3).

^1H NMR ($CDCl_3$, 200 MHz, two rotamers in slow exchange at –55 °C in a 73:27 ratio): δ = 4.36 (d, 1 H, *J* = 16.9 Hz, NCH_2CN), 4.05 (d, 1 H, *J* = 16.9 Hz, NCH_2CN), 3.72 (d, 1 H major, *J* = 4.1 Hz, H-2), 3.62 (d, 1 H minor, *J* = 4.8 Hz, H-2), 3.41 (dq, 1 H, *J* = 4.8 Hz, H-3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 167.3, 137.1, 136.9, 126.9–128.9, 114.8, 64.4, 53.9, 53.7, 32.1, 13.7.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 268.0 ([M – CH_2CN]$^+$, 18), 182.9 ([Ph_2CHNH_2]$^+$·, 92), 166.9 ([Ph_2CH]$^+$, 100).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.08; H, 6.10; N, 8.92.

Azetidinones 4; General Procedure

To a stirred solution of **3** (1 equiv) in anhyd THF (10 mL/mmol of **3**) at 0 °C under argon was added LiHMDS (1.1 equiv). The solution was stirred for 2 h at 0 °C. The reaction was quenched with aq 0.1 N HCl. The mixture was diluted with EtOAc, washed with sat. aq $NaHCO_3$ (3 ×) and brine (3 ×), dried ($MgSO_4$), and concentrated under reduced pressure. The solid obtained was then purified by chromatography on silica gel (hygroscopic compounds).

(3*S*,4*S*,5*R*)-*N*-Diphenylmethyl-3-(1′-hydroxyethyl)-4-(*tert*-butyloxyoxomethyl)azetidin-2-one (4c)

Starting from **3c** (1.29 g, 3.4 mmol, 1 equiv) and following the general procedure, a white foam (0.89 g, 69%) was obtained after chromatography (gradient of elution from cyclohexane–EtOAc 5:1 to cyclohexane–EtOAc 1:1); R_f 0.18 (cyclohexane–EtOAc, 5:2); mp 113.5–115 °C; $[\alpha]_D^{20}$ –2.3 (*c* = 0.259, $CHCl_3$).

IR (neat): 3239 (OH), 1732 (two C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.2–7.4 (m, 10 H_{arom}), 5.90 (s, 1 H, Ph_2CH), 4.26 (dq, 1 H, *J* = 3.6, 6.3 Hz, MeC*H*OH), 4.04 (d, 1 H, *J* = 2.4 Hz, H-4), 3.14 (dd, 1 H, *J* = 2.4, 3.6 Hz, H-3), 1.30 (s, 9 H, *t*-C_4H_9), 1.23 (d, 3 H, *J* = 6.3 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.3, 168.0, 138.9, 138.8, 128.9, 128.7, 128.0, 82.5, 62.7, 62.1, 54.2, 28.3, 21.7.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 382.2 ($[M + H]^+$, 9), 253.0 (20), 182.9 ($[Ph_2CHNH_2]^+\cdot$, 16), 166.9 ($[Ph_2CH]^+$, 100).

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.14; H, 7.05; N, 3.91.

(3*S*,4*S*,5*R*)-*N*-(Diphenylmethyl)-3-(1′-hydroxyethyl)-4-cyanoazetidin-2-one (*trans*-4d) and (3*S*,4*R*,5*R*)-*N*-Diphenylmethyl-3-(1′-hydroxyethyl)-4-cyanoazetidin-2-one (*cis*-4d)

Starting from **3d** (0.22 g, 0.72 mmol) and following the general procedure, after chromatography (gradient of elution from cyclohexane–EtOAc 5:1 to cyclohexane–EtOAc 1:1) *trans*-**4d** (0.053 g, 24%) and *cis*-**4d** (0.051g, 23%) were obtained as yellow solids.

***trans*-4d**

R_f 0.13 (cyclohexane–EtOAc, 5:2); mp 101.0–103.0 °C; $[\alpha]_D^{20}$ +18.0 (*c* = 0.183, $CHCl_3$).

IR (neat): 3308 (OH), 2193 (C≡N), 1772 (C=O) cm^{-1}.

^1H NMR (acetone-d_6, 300 MHz): δ = 7.3–7.45 (m, 10 H_{arom}), 6.08 (s, 1 H, Ph_2CH), 4.52 (br d, 1 H, *J* = 4.2 Hz, OH), 4.36 (d, 1 H, *J* = 2.4 Hz, H-4), 4.20 (ddq, 1 H, *J* = 4.2, 4.5, 6.7 Hz, MeC*H*OH), 3.66 (dd, 1 H, *J* = 2.4, 4.5 Hz, H-3), 1.27 (d, 3 H, *J* = 6.7 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.3, 137.5, 137.3, 128.4–129.4, 117.4, 63.9, 63.8, 62.0, 40.1, 21.9.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 307.1 ($[M + H]^+$, 7), 289.1 ($[M + H - H_2O]^+$, 4), 182.9 ($[Ph_2CHNH_2]^+\cdot$, 100), 166.9 ($[Ph_2CH]^+$, 60), 83.8 (83), 73.0 (78), 60.8 (68).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 73.77; H, 6.08; N, 8.93.

***cis*-4d**

R_f 0.09 (cyclohexane–EtOAc, 5:2); mp 93.5–94.5 °C; $[\alpha]_D^{20}$ –46.2 (*c* = 0.325, $CHCl_3$).

IR (neat): 3459 (OH), 2246 (C≡N), 1763 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.3–7.4 (m, 8 H_{arom}), 7.23 (dd, 2 H_{arom}, *J* = 7.7, 2.0 Hz, *para* H), 6.10 (s, 1 H, Ph_2CH), 4.43 (dq, 1 H, *J* = 8.1, 6.3 Hz, MeC*H*OH), 4.07 (d, 1 H, *J* = 5.4 Hz, H-4), 3.44 (dd, 1 H, *J* = 5.4, 8.1 Hz, H-3), 1.46 (d, 3 H, *J* = 6.3 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.5, 137.1, 129.5, 129.2, 128.6, 116.6, 65.7, 61.8, 60.9, 42.7, 22.1.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 307.1 ($[M + H]^+$, 2), 182.9 ($[Ph_2CHNH_2]^+\cdot$, 8), 166.7 ($[Ph_2CH]^+$, 8), 165.0 (17), 102.8 (25), 100.8 (37), 82.8 (100), 64.8 (23).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 73.46; H, 5.91; N, 8.77.

Deprotection of 4; General Procedure

To a solution of **4** (1 equiv) in a biphasic mixture of CH_2Cl_2 and H_2O (5:1, 15 mL CH_2Cl_2/mmol **4**), were added *N*-bromosuccinimide (1.2 equiv) and then Br_2 (0.1 equiv). The mixture was stirred for 3 h at r.t. under the light of the lamp installed in fume hood. The reaction was stopped by addition of an aq 5% solution of $NaHSO_3$ (decolorization). The organic solution was separated and concentrated under reduced pressure to give the azetidinone **6** as a yellow oil. Crude **6** was dissolved in a solution of acetone and H_2O (1:1, 10 mL solution/ mmol **6**) and *p*-toluenesulfonic acid (1 equiv) was added. The solution was stirred overnight in the dark. Solid Na_2CO_3 was then added and the mixture was concentrated under reduced pressure. The residue was extracted with acetone (3 ×) and the organic phase was concentrated under reduced pressure to give the crude azetidinone **7** and benzophenone. The former was further purified by chormatography.

(3*S*,4*S*,5*R*)-*N*-Diphenylhydroxymethyl-3-(1′-hydroxyethyl)-4-pivaloylazetidin-2-one (6a)

Starting from **4a** (0.52 g, 1.4 mmol) and following the general procedure, crude **6a** (0.53 g, crude yield: quantitative) was obtained as an oil.

IR (neat): 3419 (OH), 1752 (C=O), 1707 (C=O), 1451 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.2–7.7 (m, 10 H_{arom}), 5.12 (br s, 1 H, Ph_2CHO), 4.69 (d, 1 H, *J* = 2.1 Hz, H-4), 4.26 (dq, 1 H, *J* = 6.3, 6.6 Hz, MeC*H*OH), 2.87 (dd, 1 H, *J* = 2.1, 6.3 Hz, H-3), 2.50 (br s, 1 H, MeCHO*H*), 1.43 (d, 3 H, *J* = 6.6 Hz, CH_3), 0.84 (s, 9 H, *t*-C_4H_9).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 216.0, 166.7, 142.0, 126.1–130.0, 87.4, 66.2, 60.8, 57.2, 43.7, 25.9, 22.0.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 381.2 ($[M]^+\cdot$, 0.6), 211.1 (7), 182.8 ($[Ph_2CHNH_2]^+\cdot$, 100), 104.8 (11), 99.8 (44).

(3*S*,4*S*,5*R*)-3-(1′-Hydroxyethyl)-4-pivaloylazetidin-2-one (7a)[20]

Starting from crude **6a** (0.53 g) and following the general procedure, a white solid (0.265 g, 95%) was obtained after purification by chromatography on silica gel (eluent: CH_2Cl_2–EtOAc, 10:1, then EtOAc); R_f 0.52 (EtOAc); mp 88.7–89.9 °C; $[\alpha]_D^{20}$ +63.5 (*c* = 0.825, $CHCl_3$).

IR (neat): 3318 (NH, OH), 1752 (C=O), 1707 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.47 (s, 1 H, NH), 4.58 (d, 1 H, *J* = 2.2 Hz, H-4), 4.24 (quint, 1 H, *J* = 6.3 Hz, MeC*H*OH), 3.21 (dd, 1 H, *J* = 2.2, 6.3 Hz, H-3), 2.3 (br s, 1 H, OH), 1.36 (d, 3 H, *J* = 6.3 Hz, CH_3), 1.23 (s, 9 H, *t*-C_4H_9).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 213.0, 169.0, 65.9, 64.1, 52.6, 44.3, 26.6, 22.0.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 200.1 ($[M + H]^+$, 13), 182.2 ($[M + H - H_2O]^+$, 100).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.13; H, 8.70; N, 6.96.

(3*S*,4*S*,5*R*)-*N*-Diphenylhydroxymethyl-3-(1′-hydroxyethyl)-4-benzoylazetidin-2-one (6b)

Starting from **4b** (0.11 g, 0.28 mmol) and following the general procedure, crude **6b** (0.12 g, crude yield: quantitative) was obtained as an oil.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.1–7.9 (m, 15 H_{arom}), 5.94 (br s, 1 H, Ph_2CHO), 5.21 (d, 1 H, *J* = 2.0 Hz, H-4), 4.29 (m, 1 H, MeC*H*OH), 3.07 (m, 1 H, H-3), 1.38 (d, 3 H, *J* = 6.4 Hz, CH_3).

(3*S*,4*S*,5*R*)-3-(1′-Hydroxyethyl)-4-benzoylazetidin-2-one (7b)[20,21]

Starting from the crude product **6b** (0.12 g) and following the general procedure, a white solid (0.059 g, 95%) was obtained after purification by chromatography on silica gel (eluent: CH_2Cl_2, then EtOAc); R_f 0.90 (EtOAc).

IR (neat): 3468 (NH, OH), 1765 (C=O), 1735 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 8.11 (d, 2 H, *J* = 7.1 Hz), 7.2–7.7 (m, 3 H), 6.49 (br s, 1 H, NH), 5.07 (d, 1 H, *J* = 2.5 Hz, H-4), 4.32 (dq, 1 H, *J* = 6.3 Hz, MeC*H*OH), 3.23 (ddd, 1 H, *J* = 6.3, 4.0, 2.5 Hz, H-3), 1.34 (d, 3 H, *J* = 6.3 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 196.6, 167.6, 134.2, 128.7–128.9, 66.4, 63.7, 54.5, 22.1.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 220.1 ($[M + H]^+$, 25), 183.1 (9), 134.0 (10), 117.1 (18), 99.1 ($[PhCO]^+$, 100).

(3*S*,4*S*,5*R*)-*N*-Diphenylhydroxymethyl-3-(1′-hydroxyethyl)-4-(*tert*-butyloxyoxomethyl)azetidin-2-one (6c)

Starting from **4c** (0.56 g, 1.5 mmol) and following the general procedure for the first step of the deprotection, crude **6c** (0.58 g, crude yield: quantitative) was obtained as an oil.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.2–7.7 (m, 10 H_{arom}), 4.95 (br s, 1 H, Ph_2CO*H*), 4.33 (dq, 1 H, *J* = 3.6, 6.6 Hz, MeC*H*OH), 4.23 (d, 1 H, *J* = 2.6 Hz, H-4), 3.06 (dd, 1 H, *J* = 2.6, 3.6 Hz, H-3), 1.31 (s, 9 H, *t*-C_4H_9), 1.27 (d, 3 H, *J* = 6.5 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.5, 167.2, 142.1, 141.5, 132.4, 130.1, 128.2, 126.8, 88.1, 82.8, 63.9, 61.0, 53.9, 27.9, 21.2.

(3*S*,4*S*,5*R*)-3-(1′-Hydroxyethyl)-4-(*tert*-butyloxyoxomethyl)azetidin-2-one (7c)[22]

Starting from the crude product **6c** (0.58 g) and following the general procedure, a solid was obtained, which was extracted with cyclohexane (6 ×) and acetone (3 ×). The acetone fraction was concentrated under reduced pressure to give a brown oil (0.28 g, 89%).

IR (neat): 3343 (NH, OH), 1765 (C=O), 1744 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 6.75 (br s, 1 H, NH), 4.28 (dq, 1 H, *J* = 3.5, 6.3 Hz, MeC*H*OH), 4.18 (d, 1 H, *J* = 2.5 Hz, H-4), 3.21 (ddd, 1 H, *J* = 1.1, 2.5, 3.5 Hz, H-3), 1.45 (s, 9 H, *t*-C_4H_9), 1.27 (d, 3 H, *J* = 6.3 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 170.5, 168.6, 82.5, 64.0, 63.4, 49.9, 28.0, 21.1.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 216.1 ($[M + H]^+$, 3), 156.8 (100).

(3*S*,4*S*,5*R*)-*N*-Diphenylhydroxymethyl-3-(1′-hydroxyethyl)-4-cyanoazetidin-2-one (*trans*-6d)

Starting from *trans*-**4d** (0.13 g, 0.42 mmol) and following the general procedure for the first step of the deprotection, crude *trans*-**6d** (0.15 g, crude yield: quantitative) was obtained.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.2–7.7 (m, 10 H_{arom}), 4.66 (br s, 1 H, Ph_2CO*H*), 4.30 (d, 1 H, *J* = 2.7 Hz, H-4), 4.29 (dq, 1 H, *J* = 3.0, 6.2 Hz, MeC*H*OH), 3.47 (t, 1 H, *J* = 3.0 Hz, H-3), 1.27 (d, 3 H, *J* = 6.2 Hz, CH_3).

(3*S*,4*S*,5*R*)-3-(1′-Hydroxyethyl)-4-cyanoazetidin-2-one (*trans*-7d)

Crude *trans*-**6d** (0.10 g) was allowed to stand in air for 24 h to give a brown oil, which gave after purification by chromatography on RP-18 gel (eluent: MeCN–H_2O, 1:1) a yellow oil (0.040 g, , 95% from *trans*-**4d**); R_f 0.93 (RP-18, MeCN–H_2O 1:1); $[\alpha]_D^{20}$ –324 (*c* = 0.36, H_2O).

IR (neat): 3332 (NH, OH), 2250 (C≡N), 1767 (C=O) cm^{-1}.

^1H NMR (acetone-d_6, 300 MHz): δ = 7.84 (br s, 1 H, NH), 4.50 (d, 1 H, *J* = 2.4 Hz, H-4), 4.15 (dq, 1 H, *J* = 5.7, 6.7 Hz, MeC*H*OH), 3.63 (dd, 1 H, *J* = 2.4, 5.7 Hz, H-3), 1.28 (d, 3 H, *J* = 6.7 Hz, CH_3).

^{13}C NMR (acetone-d_6, 75 MHz): δ = 166.3, 119.3, 66.9, 64.2, 37.3, 21.6.

MS (CI, CH_4–N_2O, MS-MS): *m*/*z* (%) = 140.9 ($[M + H]^+$, 2), 53.1 (100).

HRMS (CI): *m*/*z* Calcd for $C_6H_9O_2N_2$: 141.0662. Found: 141.0668.

(3*S*,4*R*,5*R*)-*N*-Diphenylhydroxymethyl-3-(1′-hydroxyethyl)-4-cyanoazetidin-2-one (*cis*-6d)

Starting from *cis*-**4d** (0.24 g, 0.77 mmol) and following the general procedure for the first step of the deprotection, crude *cis*-**6d** (0.22 g, 92%) was obtained.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.3–7.6 (m, 10 H_{arom}), 6.75 (br s, 1 H, OH), 4.39 (dq, 1 H, *J* = 8.1, 6.2 Hz, MeC*H*OH), 4.19 (d, 1 H, *J* = 5.4 Hz, H-4), 3.38 (dd, 1 H, *J* = 5.4, 8.1 Hz, H-3), 1.43 (d, 3 H, *J* = 6.2 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 165.9, 141.1, 139.7, 126.6–137.6, 116.3, 89.1, 65.0, 59.2, 41.9, 21.4.

(3*S*,4*R*,5*R*)-3-(1′-Hydroxyethyl)-4-cyanoazetidin-2-one (*cis*-7d)

Crude *cis*-**6d** (0.19 g) was allowed to stand in air for 24 h to give a brown oil, which give after purification by chromatography on RP-18 gel (eluent: MeCN–H_2O, 1:1) a yellow oil (0.057 g, 65% from *cis*-**4d**); R_f 0.61; $[\alpha]_D^{20}$ +17.5 (*c* = 0.332, H_2O).

IR (neat): 3315 (NH, OH), 2248 (C≡N), 1767 (C=O) cm^{-1}.

^1H NMR (acetone-d_6, 300 MHz): δ = 7.96 (br s, 1 H, NH), 4.65 (d, 1 H, *J* = 5.1 Hz, H-4), 4.21 (dq, 1 H, *J* = 9.0, 6.2 Hz, MeC*H*OH), 3.56 (dd, 1 H, *J* = 5.1, 9.0 Hz, H-3), 3.14 (br s, 1H, OH), 1.36 (d, 3 H, *J* = 6.2 Hz, CH_3).

^{13}C NMR (acetone-d_6, 75 MHz): δ = 166.3, 118.0, 65.0, 63.3, 39.6, 21.8.

MS (CI, CH_4–N_2O, MS-MS): *m*/*z* (%) = 141.1 ($[M + H]^+$, 2), 53.1 (100).

HRMS (CI) : *m*/*z* Calcd for $C_6H_9N_2O_2$: 141.0662. Found: 141.0669.

(3*S*,4*S*,5*R*)-*N*-Diphenylmethyl-3-(1′-*tert*-butyldimethylsilyloxyethyl)-4-pivaloylazetidin-2-one (8a)

To a solution of **4a** (1.03 g, 2.82 mmol, 1 equiv) in anhyd DMF (50 mL), *tert*-butyldimethylsilyl chloride (2.65 g, 18 mmol, 6 equiv) and imidazole (2.15 g, 32 mmol, 11 equiv) were added. The mixture was stirred at r.t. during 2 d and then diluted with EtOAc (50 mL). The organic phase was washed successively with H_2O (2 × 50 mL) and brine (2 × 50 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography on silica gel (elution with CH_2Cl_2) gave a colorless oil (1.25 g, yield: 93%); R_f 0.08; $[\alpha]_D^{20}$ +20.5 (*c* = 0.41, CH_2Cl_2).

IR (neat): 1768 (C=O), 1710 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.2–7.4 (m, 10 H_{arom}), 5.68 (s, 1 H, Ph_2CH), 4.58 (d, 1 H, *J* = 1.9 Hz, H-4), 4.27 (dq, 1 H, *J* = 5.5, 6.3 Hz, MeC*H*OR), 2.82 (dd, 1 H, *J* = 1.9, 5.5 Hz, H-3), 1.30 (d, 3 H, *J* = 6.3 Hz, CH_3), 0.93 (s, 9 H, *t*-C_4H_9), 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.13 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 213.3, 167.3, 138.8, 128.6, 128.4, 127.7, 66.6, 63.1, 62.9, 54.6, 43.9, 26.1, 26.0, 23.5, 18.1, –3.9, –4.6.

MS (CI, CH_4–N_2O, MS-MS): *m*/*z* (%) = 480.2 ($[M + H]^+$, 42), 422.2 ($[M + H - t\text{-}Bu]^+$, 7), 183.0 ($[Ph_2CHNH_2]^+\cdot$, 100).

Anal. Calcd for $C_{29}H_{41}NO_3Si$: C, 72.61; H, 8.61; N, 2.92. Found: C, 72.58; H, 8.71; N, 2.88.

(3*S*,4*S*,5*R*)-*N*-Diphenylhydroxymethyl-3-(1′-*tert*-butyldimethylsilyloxyethyl)-4-pivaloylazetidin-2-one (9a)

Starting from **8a** (0.13 g, 0.27 mmol, 1 equiv) and following the general procedure for the first step of deprotection, a crude yellow solid (0.11 g, 81%) was obtained.

IR (neat): 3430 (OH), 1779 (C=O) 1713 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.1–7.6 (m, 10 H_{arom}), 5.18 (br s, 1 H, OH), 4.72 (d, 1 H, *J* = 2.2 Hz, H-4), 4.30 (dq, 1 H, *J* = 6.0, 6.3 Hz, MeC*H*OR), 2.78 (dd, 1 H, *J* = 6.0, 2.2 Hz, H-3), 1.33 (d, 3 H, *J* = 6.3 Hz, CH_3), 0.96 (s, 9 H, *t*-C_4H_9), 0.80 [s, 9 H, $SiC(CH_3)_3$], 0.16, 0.15 [2 s, 6 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 216.2, 166.8, 142.1, 141.5, 126.2–129.9, 87.4, 66.6, 62.0, 56.6, 43.8, 26.2, 25.7, 25.3, 18.1, –3.6, –4.5.

(3*S*,4*S*,5*R*)-3-(1′-*tert*-Butyldimethylsilyloxyethyl)-4-pivaloylazetidin-2-one (10a)

Starting from **8a** (0.13 g, 0.27 mmol, 1 equiv) and following the general procedure for the deprotection, a white solid (0.066 g, 95%) was obtained.

***O*-Protection of 7a**

To a solution of **7a** (1.35 g, 6.8 mmol, 1 equiv) in DMF (70 mL) were added *tert*-butyldimethylsilyl chloride (2.04 g, 14 mmol, 2.1 equiv) and imidazole (2.31 g, 34 mmol, 5 equiv). The mixture was stirred under argon at r.t. for 16 h and then diluted with EtOAc (50 mL). The organic phase was washed with brine (3 × 50 mL) and dried ($MgSO_4$). Concentration of the organic extract and flash chromatography of the residue obtained on silica gel (eluent: CH_2Cl_2–EtOAc, 10:1) gave a white solid (1.47 g, 69%); R_f 0.36; mp 108.0–109.0 °C; $[\alpha]_D^{20}$ +32.5 (*c* = 0.815, $CHCl_3$).

IR (KBr): 3158 (NH), 1767 (C=O), 1723 (C=O), 1472 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.96 (br s, 1 H, NH), 4.59 (d, 1 H, *J* = 2.1 Hz, H-4), 4.27 (dq, 1 H, *J* = 6.3, 4.5 Hz, MeC*H*OR), 3.17 (m, 1 H, H-3), 1.26 (d, 3 H, *J* = 6.3 Hz, CH_3), 1.22 (s, 9 H, *t*-C_4H_9), 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.10, 0.09 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.8, 168.6, 65.6, 64.5, 51.3, 44.1, 26.4, 25.8, 23.0, 18.0, –4.4, –4.7.

MS (CI, CH_4–N_2O): *m*/*z* (%) = 627.5 ($[2\ M + H]^+$, 3), 342.3 (23), 314.3 ($[M + H]^+$, 100), 298.2 (17).

Anal. Calcd for $C_{16}H_{31}NO_3Si$: C, 61.30; H, 9.97; N, 4.47. Found: C, 61.49; H, 10.10; N, 4.41.

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