

Synthesis of (1'*R*,3*S*,4*S*)-3-[1'-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(cyclopropylcarbonyloxy)azetidin-2-one

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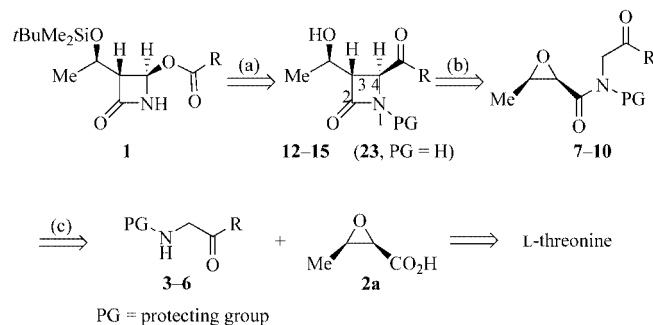
The novel carbapenem precursor **1e** has been synthesized from L-threonine, cyclopropyl methyl ketone and benzhydrylamine (for the introduction of the azetidinone *N*-protecting group). Two independently prepared building blocks – sodium (2*R*,3*R*)-2,3-epoxybutyrate as a mixed salt with NaBr (**2b**) and *N*-(benzhydryl)aminomethyl cyclopropyl ketone (**4e**) – were coupled to give (2*R*,3*R*)-*N*-(benzhydryl)-*N*-(2-cyclopropyl-2-oxoethyl)-2,3-epoxybutyramide (**8e**). This key intermediate gave a regio- and stereoselective C3–C4 ring closure on LiHMDS treatment in THF at 0 °C to yield (1'*R*,3*S*,4*S*)-4-cyclopropylcarbonyl-1-diphenylmethyl-3-(1-hydroxyethyl)azetidin-2-one (**13e**). *N*-Deprotection of **13e**

was performed by photochemical bromination and subsequent hydrolysis. The resulting (1'*R*,3*S*,4*S*)-4-(cyclopropylcarbonyl)-3-(1-hydroxyethyl)azetidin-2-one (**23e**) reacted in a Baeyer–Villiger oxidation with a total control of the regioselectivity (due to the poor migratory aptitude of the cyclopropyl group) to furnish (1'*R*,3*S*,4*S*)-3-(1-hydroxyethyl)-4-(cyclopropylcarbonyloxy)azetidin-2-one (**24e**), subsequent *O*-silylation achieving the total synthesis of **1e** (title compound).

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Introduction

(1'*R*,3*S*,4*S*)-4-Acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (**1**, R = Me; Scheme 1) still remains the most popular key intermediate for the synthesis of thienamycin and carbapenem derivatives, and other novel antibiotics that might defeat bacterial resistance.^[1]



Scheme 1. Retrosynthetic scheme: (a)–(c) see text.

A tremendous amount of effort has been devoted to the search for efficient preparations of this chiral azetidinone **1**, with possible industrial developments.^[2] Three commercial

synthesis of **1** are now available from the Japanese companies Kaneka, Nippon Soda and Takasago International. Their respective strategies for the construction of the four-membered heterocycle (azetidinone) rely on: (i) the [2+2] cycloaddition of chlorosulfonyl isocyanate (CSI) to (3*R*,1*E*)-3-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyloxy)-butene,^[3] (ii) CSI addition to (3*R*,1*E*)-3-(*tert*-butyldimethylsilyloxy)-1-(phenylthio)but-1-ene,^[4] and (iii) the N1–C2 cyclization of (2*R*,3*R*)-2-(aminomethyl)-3-hydroxybutanoic acid.^[5] In both cycloaddition approaches the alkene chirality is provided by the microbial hydroxylation of methyl butanoate, while in the cyclization method the chiral precursor is the result of catalytic hydrogenation of methyl 2-acetyl-3-(benzoylamino)propanoate in the presence of a chiral Ru catalyst.^[6]

Many other strategies (e.g., [2+2] cycloadditions of ketenes to Schiff bases, [2+2] cycloadditions of ester enolates to Schiff bases, N1–C4 cyclizations and C3–C4 cyclizations) have been disclosed and extensively discussed,^[2] but none has been developed for the production of **1** on a large scale. In this context, a communication from Hanessian et al. attracted our attention:^[7] azetidinone **1** (R = Ph) was prepared by the C3–C4 cyclization of a 2,3-epoxybutyramide precursor obtained from L-threonine. The retrosynthetic scheme (Scheme 1) was based on three key steps: (a) a Baeyer–Villiger oxidation to introduce the C4 functionality, performed preferably after cleavage of PG (*N*-deprotection), (b) C3–C4 cyclization by intramolecular nucleophilic attack on the epoxide, and (c) the coupling of an α -amino ketone synthon onto (2*R*,3*R*)-2,3-epoxybutyric acid. In our opin-

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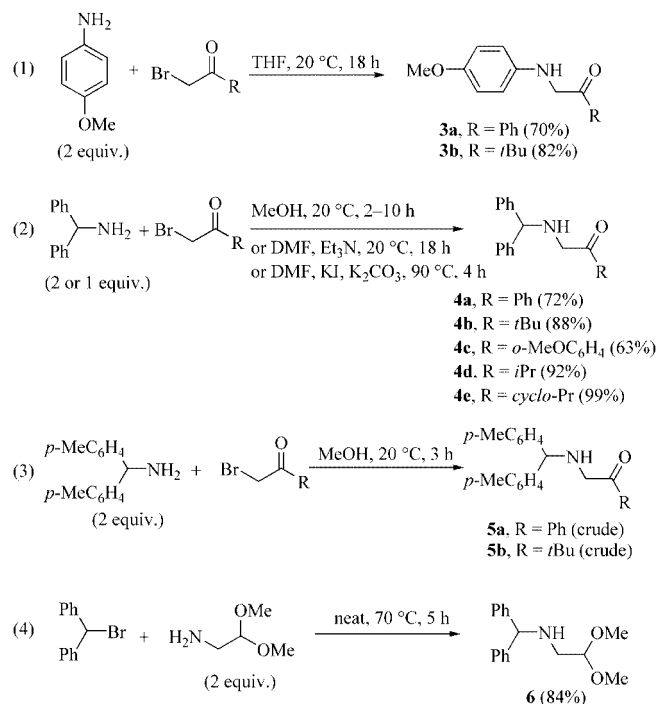
ion, this route offers interesting features for potential development (cheap chiral starting material, high stereocontrol, good yields, limited number of steps, smooth conditions, ...), provided that the *N*-protecting group can be modified. Indeed, in the original paper, the authors made use of the *p*-methoxyphenyl (PMP) group, which requires suprachromic amounts of CAN (ceric ammonium nitrate) to be cleaved.^[8] We therefore decided to revisit Hanessian's synthesis, but replacing the *N*-(*p*-methoxyphenyl) (PMP) substituent with an *N*-benzhydryl or *N*-(*p,p'*-dimethoxy)-benzhydryl group, which should enable deprotection by hydrogenation or acidic hydrolysis.^[9] What was expected to be a trivial structural modification proved to bring major changes in the chemical reactivity and selectivity of the C3–C4 cyclization key step with it,^[10] so the experimental conditions and the nature of the substituent *R* were adapted. Other surprises, however, also arose from the deprotection step^[11] and the Baeyer–Villiger oxidation.^[12] Here we fully describe our adventures in this azetidinone story and the happy ending we were able to find for the synthesis of **1**, thanks to the discovery of a novel method of *N*-benzhydryl deprotection and the use of the cyclopropyl substituent to direct the Baeyer–Villiger rearrangement (Scheme 1; *R* = *cyclo*-Pr and PG = CHPh₂).

Results and Discussion

According to the retrosynthetic plan shown in Scheme 1, the chiral building block required to start the synthesis of azetidinone **1** is (2*R*,3*R*)-2,3-epoxybutyric acid (**2a**). This acid is poorly stable and not easily prepared on a large scale, so we adapted previous methods^[13–16] and prepared a mixed salt **2b** with sodium carboxylate and sodium bromide (1:1) (Scheme 5, Part A). L-Threonine was thus treated with KBr and NaNO₂ in 2.5 M H₂SO₄ to produce the corresponding α -bromo acid derivative with retention of configuration.^[17] This compound, extracted with ethyl acetate, was then cyclized by treatment with 2 equiv. of NaOH in water. Epoxide **2b** was obtained directly by concentration of the aqueous phase. This salt **2b** could be stored at room temperature without degradation; it was found by DTA (differential thermal analysis) to be stable to 100 °C. As a result of the S_N2 mechanism, a single stereoisomer (2*R*,3*R*) of epoxybutyrate was formed. The enantiomeric purity of **2b** was monitored by GC after derivatization as the isopropyl ester.^[18]

The second building block on the pathway to azetidinone **1** are *N*-protected (PG) α -amino ketones (**3–6**) (Scheme 1). Such compounds were readily available from α -bromo ketones and *p*-anisidine [PG = C₆H₄OMe, Scheme 2, Equation (1)], benzhydrylamine [PG = CHPh₂, Scheme 2, Equation (2)], or bis(*p*-methoxyphenyl)methylamine^[19] [PG = CH(C₆H₄OMe)₂, Scheme 2, Equation (3)]. THF was the best solvent^[20] for performing the substitution of Equation (1) with 2 equiv. of *p*-anisidine (1 equiv. acting as a base); indeed, by the procedure of Tachdjian et al.^[21] in diethyl ether we obtained a 75:25 mixture of mono- and

dialkylated anilines. Products **3a** (*R* = Ph) and **3b** (*R* = *t*Bu) were recovered after precipitation of the hydrobromide salt from hexane, filtration and concentration of the organic phase. Two different methods allowed the preparation of synthons **4** [Equation (2)], working either in methanol with 2 equiv. of benzhydrylamine or in DMF with 1 equiv. of benzhydrylamine and 1 equiv. of another added base (organic or inorganic). Compounds **4a** (*R* = Ph) and **4b** (*R* = *t*Bu) were readily obtained and isolated by the first method, because they precipitated in methanol, while benzhydrylamine hydrobromide remained soluble. Compounds **5a** (*R* = Ph) and **5b** (*R* = *t*Bu) were prepared similarly [Equation (3)]. The second method [Equation (2)] was used for the synthesis of **4c** (*R* = *o*-MeOC₆H₄) with triethylamine as a base and of **4d** (*R* = *i*Pr) and **4e** (*R* = *cyclo*-Pr) with potassium carbonate as a base and potassium iodide to activate the substrate. In these cases an aqueous workup was required to eliminate the salts. Lastly, the masked α -amino aldehyde **6** was prepared as shown in Equation (4) (Scheme 2): benzhydryl bromide and 2 equiv. of 2-aminoethanal dimethyl acetal were allowed to react at 70 °C without solvent, with the product being isolated after aqueous workup and distillation.



Scheme 2. Synthesis of α -amino ketone reagents.

Different conditions were explored to perform the coupling reactions between epoxybutyrate **2b** and amino ketones **3–6**, with use of various activation reagents such as thionyl chloride, oxalyl chloride, pivaloyl chloride, isobutyl chloroformate and 2,4,6-trichlorobenzoyl chloride. Our aim was to produce the acid chloride (or mixed anhydride) of **2b** in situ, without proceeding through the unstable acid **2a**. Oxalyl chloride afforded the best results as coupling agent (Table 1). Treatment of **2b** with the *p*-anisidine derivatives

3a and **3b** gave moderate yields of epoxybutyramides **7a** (R = Ph) and **7b** (R = *t*Bu), bearing the PMP protecting group previously used by Hanessian et al.^[7] (Entries 1–2). On the other hand, moderate to good yields were collected with the benzhydrylamine derivatives **4a** to **4e** (Entries 3–7), with epoxybutyramides **8a** (R = Ph), **8b** (R = *t*Bu), **8c** (R = *o*-MeOC₆H₄), **8d** (R = *i*Pr) and **8e** (R = *cyclo*-Pr) being purified either by column chromatography on silica gel or by crystallization. The preparation of compound **9** (R = H) required two steps: the coupling of **2b** and **6** to give the intermediate **11** in 70% yield after chromatography (Figure 3) and acidic hydrolysis in a two-phase system (Entry 8). The precursors **10a** (R = Ph) and **10b** (R = *t*Bu), protected with the bis(*p*-methoxyphenyl)methyl group, were prepared similarly, but in low yields after purification (Entries 9–10).

Table 1. Coupling to epoxybutyrate: i: **2b** (1.2 equiv.), (COCl)₂ (1.2 equiv.), THF, –5 °C, 2 h; ii: pyridine (3 equiv.), amine **3–6** (1 equiv.), 1 h at –5 °C and 2 h at 20 °C.

Entry	PG	R	Yield (%)	Compd.
1	<i>p</i> -MeOC ₆ H ₄ (PMP)	Ph	44	7a
2	<i>p</i> -MeOC ₆ H ₄ (PMP)	<i>t</i> Bu	40	7b
3	Ph ₂ CH	Ph	64	8a
4	Ph ₂ CH	<i>t</i> Bu	73	8b
5	Ph ₂ CH	<i>o</i> -MeOC ₆ H ₄	45	8c
6	Ph ₂ CH	<i>i</i> Pr	76	8d
7	Ph ₂ CH	<i>cyclo</i> -Pr	83	8e
8	Ph ₂ CH	H	69 ^[a]	9
9	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	Ph	29	10a
10	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	<i>t</i> Bu	34	10b

[a] Protected reagent **6** was used for the coupling, followed by acidic hydrolysis (CHCl₃, H₂O, TFA, 3 h, 20 °C).

The NMR spectra of the epoxybutyramides recorded at 25 °C showed interesting features: the PMP derivatives **7** each appeared as a single rotamer giving one set of signals. The presence of two rotamers in rapid equilibrium was not considered as an alternative hypothesis because the spectra did not show any splitting of the signals when recorded at lower temperature (CDCl₃, –50 °C and acetone, –85 °C). On the other hand, the diarylmethyl derivatives **8–10** showed splitting of all the signals, characteristic of a slowing down of the rotation around the amide bond (Table 2).

Table 2. ¹H NMR spectroscopic data for epoxybutyramides.

Compd. (Table 1)	Conformer ratio	$\delta(\text{CH}_2)$		J_{AB} [Hz]		$\delta(\text{CHAr}_2)$	
		major	minor	major	minor	major	minor
7a ^[7]	–	4.87:5.42		17.3		–	
7b ^[55]	–	4.41:4.84		17.5		–	
8a	53:47	4.71:4.86	4.68:5.28	17.3	18.7	6.71	7.15
8b	56:44	4.23:4.45	4.23:4.98	17.4	19.3	6.62	7.22
8c	50:50	4.65:4.82	4.71:5.11	18.0	18.9	6.65	7.15
8d	54:46	4.14:4.31	4.12:4.82	17.7	19.2	6.62	7.20
8e	58:42	4.26:4.42	4.25:4.82	17.1	20.1	6.61	7.20
11	70:30	3.54:3.61	3.60	15.6	–	6.55	7.13
9	69:31	4.00:4.12	4.20:4.40	17.6	19.1	6.66	7.17
10a ^[56]	58:42	4.66:4.86	4.66:5.24	17.1	18.8	6.58	6.72
10b	68:32	4.18:4.44	4.22:4.92	17.3	18.8	6.48	6.76

Two conformers are thus visible in solution at room temperature, and their structures were attributed by 2D NOESY (nuclear Overhauser and exchange spectroscopy) experiments performed at 0 °C (Figure 1). The major rotamer showed the CH₂COR moiety away from the epoxide. Interestingly, in the solid state, **8b** has been “frozen” in the form of the minor conformer (X-ray structure^[64]).

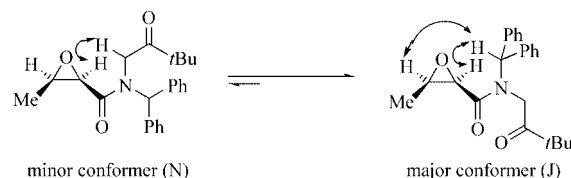


Figure 1. Rotamers of **8b** with NOESY correlations indicated.

The next step of our synthesis of **1** was the cyclization of the epoxybutyramide precursors to azetidinones **12–15** under basic conditions [Scheme 1, step (b)]: the carbanion formed by abstraction of a hydrogen atom α to the COR group could attack the epoxide moiety intramolecularly. Both the nucleophilic and electrophilic parts of the reagents being ambident functions, four cyclized products could be formed in principle:^[10] the azetidinones **A** (enolate *C*-alkylation at the C2 atom of the epoxide ring), the 5,6-dehydromorpholin-3-ones **B** (enolate *O*-alkylation at the C2 atom of the epoxide ring), the 4,5,6,7-tetrahydro-4-azaoxepin-5-ones **C** (enolate *O*-alkylation at the C3 atom of the epoxide ring) and the pyrrolidin-2-ones **D** (enolate *C*-alkylation at the C2 atom of the epoxide ring). Experimentally, three products, **A**, **B** and **C**, were isolated and carefully identified, with ratios depending on the nature of the *N*-protecting group (PG), the nature of the R substituent and the experimental conditions (Table 3).

First of all we reproduced the synthesis of Hanessian et al.,^[7] with the same experimental conditions and starting material and, fortunately, found the same result (Entry 1): treatment of epoxybutyramide **7a** (PG = PMP and R = Ph) with potassium carbonate in DMF at high temperature furnished the azetidinone **12a**^[7] as the only identified cyclized product (isolated pure product: 76% yield). Similarly, precursor **7b** (PG = PMP and R = *t*Bu) exclusively gave the azetidinone **12b** (isolated pure product: 81% yield) (Entry 2).

Table 3. Cyclization of epoxybutyramides.

Entry	PG	R	Cond. ^[a]	Ratio ^[b] (Compd.)			
				A	B	C	Other
1	<i>p</i> -MeOC ₆ H ₄ (PMP)	Ph	i	100 (12a)	—	—	—
2	<i>p</i> -MeOC ₆ H ₄ (PMP)	<i>t</i> Bu	i	100 (12b)	—	—	—
3	Ph ₂ CH	Ph	i	16 (13a)	56 (16a)	21 (19a)	7
4	Ph ₂ CH	Ph	ii	34 (13a)	38 (16a)	18 (19a)	10
5	Ph ₂ CH	Ph	iii	57 (13a)	21 (16a)	20 (19a)	2
6	Ph ₂ CH	<i>t</i> Bu	i	55 (13b)	35 (16b)	8 (19b)	2
7	Ph ₂ CH	<i>t</i> Bu	ii	62 (13b)	24 (16b)	9 (19b)	5
8	Ph ₂ CH	<i>t</i> Bu	iii	100 (13b)	—	—	—
9	Ph ₂ CH	<i>o</i> -MeOC ₆ H ₄	iii	31 (13c)	12	57 (19c)	—
10	Ph ₂ CH	<i>i</i> Pr	iii	85 (13d)	15	—	—
11	Ph ₂ CH	<i>cyclo</i> -Pr	iii	88 (13e)	—	7 (19e)	5
12	Ph ₂ CH	H	i	—	76 (17)	24 (20)	—
13	Ph ₂ CH	H	ii	2 (14)	64 (17)	20 (20)	14
14	Ph ₂ CH	H	iii	2 (14)	98 (17)	—	—
15	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	Ph	i	21 (15a)	64 (18a)	15 (21a)	—
16	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	Ph	ii	30 (15a)	47 (18a)	23 (21a)	—
17	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	Ph	iii	41 (15a)	29 (18a)	30 (21a)	—
18	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	<i>t</i> Bu	i	61 (15b)	27 (18b)	6 (21b)	6
19	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	<i>t</i> Bu	ii	65 (15b)	28 (18b)	3 (21b)	4
20	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	<i>t</i> Bu	iii	74 (15b)	19 (18b)	—	7

[a] i: K₂CO₃, DMF, 100 °C, 18 h; ii: Li₂CO₃, DMF, 100 °C, 18 h; iii: LiHMDS, THF, 0 °C, 3 h. [b] Determined by ¹H NMR spectroscopy of the crude mixtures (rel. %).

The next experiments were somewhat disappointing. The replacement of the PMP protecting group by the benzhydryl group resulted in the formation of mixtures of cyclized products when epoxybutyramides **8a** (PG = Ph₂CH and R = Ph) and **8b** (PG = Ph₂CH and R = *t*Bu) were treated with K₂CO₃ in hot DMF (Entries 3 and 6). However, the amount of azetidinone **13** was higher with the R substituent being *t*Bu (**13b**, 55%) rather than phenyl (**13a**, 16%). In the case of the bis(*p*-methoxyphenyl)methyl protecting group, the results were in the same range [Entries 15 and 18; PG = (*p*-MeOC₆H₄)₂CH and R = Ph or *t*Bu]. At this stage we speculated that the nature of the base and the counter-cation might significantly modify the enolate reactivity and the C/O-alkylation selectivity: a soft cation should favour O-alkylation while a hard cation should favour C-alkylation.^[22] Indeed, by using lithium carbonate as a base in hot DMF we increased the amounts of azetidinones: 34% of **13a** instead of 16% with K₂CO₃ (Entry 4; PG = Ph₂CH and R = Ph), 62% of **13b** instead of 55% (Entry 7; PG = Ph₂CH and R = *t*Bu), 30% of **15a** instead of 21% [Entry 16; PG = (*p*-MeOC₆H₄)₂CH and R = Ph], and 65% of **15b** instead of 61% [Entry 19; PG = (*p*-MeOC₆H₄)₂CH and R = *t*Bu]. This effect is even more pronounced with lithium hexamethyldisilazide (LiHMDS) as a base in THF, a less polar solvent in which the ionic pairs are more intimate. The amounts of azetidinones were 57% of **13a** (Entry 5; PG = Ph₂CH and R = Ph), 100% of **13b** (Entry 8; PG = Ph₂CH and R = *t*Bu), 41% of **15a** [Entry 17; PG = (*p*-MeOC₆H₄)₂CH and R = Ph], and 74% of **15b** [Entry 20; PG = (*p*-MeOC₆H₄)₂CH and R = *t*Bu]. Comparison between Entries 5 and 8 and Entries 17 and 20 pointed to the effect of the R substituent on the enolate reactivity. The C-alkylation

was favoured by the presence of the *tert*-butyl substituent (steric effect), while the presence of the phenyl group increased the ratio of O-alkylation (electronic effect). Hence, extension of the mesomeric effect (R = *o*-MeOC₆H₄) led to 31% of azetidinone **13c** (Entry 9) instead of 57% (R = Ph). The steric effect was also demonstrated further by replacement of the *t*Bu group with the smallest substituent, a hydrogen atom. Under all tested conditions, treatment of epoxybutyramide **9** with a base gave O-cyclized products and azetidinone **14** only as traces (≤ 2%; Entries 12–14; PG = Ph₂CH and R = H). With the isopropyl and cyclopropyl substituents, on the other hand, high yields (85–88%) of azetidinones **13d** and **13e**, respectively, were collected on treatment of the precursors **8d** and **8e** with LiHMDS in THF (Entries 10 and 11; PG = CHPh₂ and R = *i*Pr or *cyclo*-Pr). Quantitative formation of azetidinone (**13b**), however, could be observed only when R was *tert*-butyl and PG benzhydryl (Entry 8).

The structures of the cyclized products **12–15** (A), **16–18** (B) and **19–21** (C) (Table 3) were assigned from the ¹H and ¹³C NMR spectroscopic data and, in some cases, X-ray diffraction analyses of single crystals.^[23–25] Three protons are characteristic in azetidinones **12–15**: namely, Ha on the 1-hydroxyethyl chain, giving a signal (dq) at δ = 4.2–4.3 ppm, Hb on the β-lactam ring (C3), giving a doublet of doublets at δ = 2.9–3.1 ppm, and Hc on the β-lactam ring (C4), giving a doublet at δ = 4.5–5.1 ppm (Figure 2, Table 4). The coupling constant of 2–2.5 Hz between Hb and Hc is typical of *trans* stereochemistry. The absolute configurations of the chiral centres were inferred from the known chirality of the starting material and the S_N2i mechanism of epoxide substitution (inversion of configuration) and were con-

firmed by X-ray data.^[25] In the ^{13}C NMR spectrum, the β -lactam carbonyl signal is visible at $\delta = 164$ –167 ppm, and the ketone carbonyl signal at $\delta = 200$ –211 ppm, whilst the IR spectra show the typical β -lactam stretching at 1740–1760 cm^{-1} . Azetidinones **12**–**15** (Table 4) were obtained exclusively as the *trans* stereoisomers and the side-products arising from the *cis* stereoisomers ($\approx 10\%$), described by Kugelman et al.^[26] (PG = PMP and $\text{R} = \text{C}_6\text{H}_4\text{X}$), were not formed in our hands.

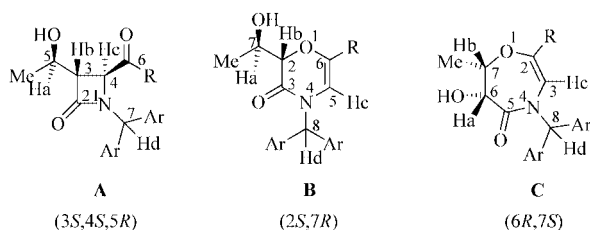


Figure 2. Atom numbering considered in Tables 4–6.

The dehydromorpholinones **16**–**18** (**B**) (Table 3) each show signals of three characteristic protons in the ^1H NMR spectrum (Figure 2, Table 5): Ha on the 1-hydroxyethyl

chain giving the same pattern as the corresponding proton in azetidinones **A** ($\delta = 4.3$ –4.5 ppm), Hb on the morpholine heterocycle giving a doublet at $\delta = 4.2$ –4.5 ppm, and the olefinic proton Hc giving a singlet at $\delta = 5.4$ –6 ppm (doublet for $\text{R} = \text{H}$). The presence of a $\text{C}=\text{C}$ double bond is visible in the ^{13}C NMR with signals at $\delta = 100$ –103 ppm (C5) and $\delta = 130$ –150 ppm (C6). The stereochemical assignment, in agreement with the reaction mechanism, was confirmed by X-ray data.^[23]

The tetrahydroazaoxepinones **19**–**21** (**C**) (Table 3) are also each characterized by three protons (Figure 2, Table 6): Ha on the heterocycle ($\delta = 4.4$ –4.8 ppm), Hb also on the heterocycle ($\delta = 4.4$ –4.9 ppm) and the olefinic proton Hc ($\delta = 5$ –6 ppm), and by the $\text{C}=\text{C}$ double bond (C2 at $\delta = 130$ –150 ppm and C3 at $\delta = 100$ –110 ppm). Here the X-ray diffraction analysis was again useful for structural and stereochemical assignment.^[24]

Our results could be interpreted in terms of Baldwin's rules^[27–29] and conformational (rotamers around the amide bond) and configurational [*(E)*/*(Z)*-enolates] considerations. Of the four possible cyclization processes: three are allowed by Baldwin's rules (4-*exo*-tet, 6-*exo*-tet and 7-*endo*-tet) whilst one is disfavoured (5-*endo*-tet), and indeed, this last process has not been observed experimentally. The cycliza-

Table 4. NMR spectroscopic data for azetidinones (Figure 2).

Compd. (Table 3)	$\delta(\text{Ha})$ (mult, J [Hz])	$\delta(\text{Hb})$ (mult, J [Hz])	$\delta(\text{Hc})$ (mult, J [Hz])	$\delta(\text{Hd})$ (mult)	$\delta(\text{C2})$	$\delta(\text{C3})$	$\delta(\text{C4})$	$\delta(\text{C5})$	$\delta(\text{C6})$	$\delta(\text{C7})$
12a ^[7]	4.33 (quint, 6.4)	3.19 (dd, 2.4, 6.4)	5.54 (d, 2.4)	–	–	not determined				
2b ^[55]	4.26 (dq, 6.3, 6.9)	3.05 (dd, 2.1, 6.9)	4.97 (d, 2.1)	–	163.6	62.6	55.5	66.6	211.0	–
13a	4.31 (dq, 5.2, 6.3)	3.11 (dd, 2.5, 5.2)	5.07 (d, 2.3)	5.59 (s)	167.1	62.3	55.3	65.2	197.6	62.5
13b	4.21 (dq, 5.4, 6.4)	2.89 (dd, 2.1, 6.4)	4.52 (d, 2.1)	5.69 (s)	166.9	61.9	55.3	66.2	212.7	62.8
13c	4.22 (m)	3.14 (dd, 2.5, 4.6)	5.14 (d, 2.5)	5.88 (s)	167.4	62.1	58.6	64.3	199.9	62.5
13d	4.22 (dq, 5.4, 6.6)	2.89 (dd, 2.4, 5.4)	4.34 (d, 2.4)	5.85 (s)	166.8	61.2	57.9	65.1	211.5	62.5
13e	4.26 (m)	3.09 (dd, 2.4, 4.8)	4.41 (d, 2.4)	5.95 (s)	167.1	61.5	59.9	64.4	208.0	62.1
15a	4.26 (dq, 5.1, 6.2)	3.08 (dd, 2.2, 5.1)	5.07 (d, 2.2)	5.82 (s)	–	not determined				
15b	4.17 (m)	2.87 (dd, 2.0, 5.9)	4.50 (d, 2.0)	5.57 (s)	167.1	61.7	55.3	66.2	213.0	55.8
22a	4.29 (m)	3.07 (m)	5.21 (d, 2.0)	–	–	not determined				
22b	4.26 (dq, 6.3, 6.6)	2.87 (dd, 2.1, 6.3)	4.69 (d, 2.1)	–	166.7	60.8	57.2	66.2	216.0	87.4
22d	4.28 (dq, 5.6, 6.3)	2.84 (dd, 2.5, 5.6)	4.60 (d, 2.5)	–	166.4	60.6	59.1	65.0	213.9	87.6
22e	4.22 (dq, 5.1, 5.8)	2.95 (dd, 2.5, 5.1)	4.62 (d, 2.5)	–	166.7	60.7	60.5	64.5	209.7	87.6
23a ^[57]	4.32 (quint, 6.3)	3.23 (ddd, 2.5, 4.0, 6.3)	5.07 (d, 2.5)	–	167.6	63.7	54.5	66.4	196.6	–
23b	4.24 (quint, 6.3)	3.21 (m, 2.4, 6.3)	4.58 (d, 2.1)	–	169.0	64.1	52.6	65.9	213.0	–
23d	4.29 (quint, 6.0)	3.11 (m)	4.42 (d, 3.0)	–	168.4	63.4	55.3	64.6	212.3	–
23e	4.33 (dq, 4.4, 6.0)	3.22 (ddd, 1.6, 2.7, 4.4)	4.45 (d, 2.7)	–	167.2	63.7	57.3	65.0	207.6	–
24d	4.24 (quint, 6.0)	3.24 (dd, 1.2, 6.0)	5.84 (s)	–	167.2	63.9	75.9	65.2	177.6	–
24e	4.09 (dq, 5.7, 6.3)	3.15 (dd, 1.5, 5.7)	5.90 (s)	–	166.8	64.3	76.5	66.0	175.0	–
25b ^[58]	4.28 (dq, 3.5, 6.3)	3.21 (ddd, 1.1, 2.5, 3.5)	4.18 (d, 2.5)	–	168.6	63.4	49.9	64.0	170.5	–
25d	4.34 (dq, 3.3, 6.3)	3.31 (dd, 2.4, 3.3)	4.29 (d, 2.4)	–	168.3	64.0	50.0	64.5	170.8	–
1d	4.22 (dq, 3.6, 6.3)	3.19 (dd, 1.5, 2.4)	5.82 (s)	–	166.4	65.0	75.2	64.0	177.3	–
1e	4.22 (dq, 3.6, 6.3)	3.19 (dd, 1.2, 3.6)	5.83 (s)	–	166.4	63.9	75.0	65.0	175.0	–

Table 5. NMR spectroscopic data for dehydromorpholinones (Figure 2).

Compd. (Table 3)	$\delta(\text{Ha})$ (mult, J [Hz])	$\delta(\text{Hb})$ (mult, J [Hz])	$\delta(\text{Hc})$ (mult, J [Hz])	$\delta(\text{Hd})$ (mult)	$\delta(\text{C2})$	$\delta(\text{C3})$	$\delta(\text{C5})$	$\delta(\text{C6})$	$\delta(\text{C7})$	$\delta(\text{C8})$
16a	4.50 (m)	4.50 (m)	6.07 (s)	7.10 (s)	79.3	163.6	103.7	139.7	66.7	59.7
16b	4.37 (ddq, 4.1, 6.4, 6.6)	4.21 (d, 4.1)	5.30 (s)	7.00 (s)	79.9	164.2	101.8	151.1	67.3	60.2
17	4.52 (dq, 2.7, 6.6)	4.48 (d, 2.7)	5.88 (d, 6.9)	7.15 (s)	76.7	171.6	100.7	132.7	72.8	61.7
18a	4.45 (m)	4.45 (m)	6.05 (s)	6.96 (s)	–	not determined				
18b	4.37 (m)	4.26 (d, 4.1)	5.45 (s)	6.90 (s)	79.1	166.5	100.8	150.5	66.6	54.8

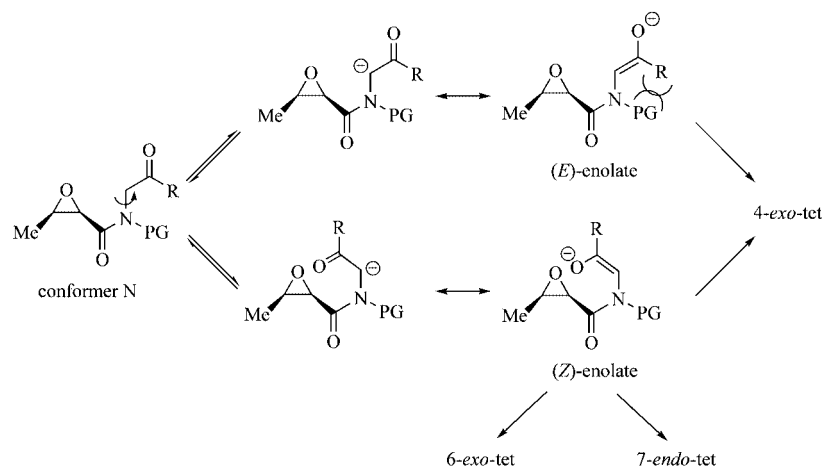
Table 6. NMR spectroscopic data for tetrahydroazaoxepinones (Figure 2).

Compd. (Table 3)	$\delta(\text{Ha})$ (mult, J [Hz])	$\delta(\text{Hb})$ (mult, J [Hz])	$\delta(\text{Hc})$ (mult, J [Hz])	$\delta(\text{Hd})$ (mult)	$\delta(\text{C2})$	$\delta(\text{C3})$	$\delta(\text{C5})$	$\delta(\text{C6})$	$\delta(\text{C7})$	$\delta(\text{C8})$
19a	4.70 (dd, 4.0, 4.2)	4.85 (dq, 4.2, 6.5)	5.72 (s)	7.19 (s)	145.1	104.6	171.8	80.7	71.5	62.2
19b	4.57 (dd, 4.6, 5.2)	4.69 (dq, 4.6, 6.3)	5.05 (s)	7.09 (s)	155.8	102.0	171.4	81.5	70.4	61.6
19c	4.88 (t, 5.3)	4.99 (quint., 5.9)	6.17 (s)	7.17 (s)	143.7	110.8	171.8	83.3	70.4	61.9
19e	4.54 (m)	4.54 (m)	4.99 (s)	7.12 (s)	146.8	99.3	171.3	79.5	71.2	61.6
20	4.40 (d, 4.0)	4.36 (dq, 4.0, 6.5)	6.18 (d, 4.4)	7.01 (s)	130.0	107.4	163.6	79.5	66.8	59.3
21a	4.66 (br. s)	4.80 (dq, 6.4)	5.71 (s)	7.12 (s)			not determined			
21b	4.55 (t, 5.1)	4.68 (dq, 5.1, 6.4)	5.07 (s)	6.98 (s)			not determined			

tion could occur from only one of the two possible conformers around the N–C(O) amide bond (see Figure 1) in the epoxybutyramide precursors: namely the N conformer. Since the enolate stereochemistry [(*E*) or (*Z*)] should influence the selectivity of ring closure, the nature of the protecting group (PG) plays a crucial role. An (*E*)-enolate could only provide a four-membered heterocycle while a (*Z*)-enolate could cyclize to six-, seven- but also four-membered heterocycles (Scheme 3). With PG = PMP, only one isomer of the enolate [(*E*)-enolate] is obtained and the 4-*exo*-tet process was observed in all cases, while with the nonconjugated and bulkier benzhydryl group, the three allowed processes were in competition. In this latter case, the (*E*)-enolate is probably less stable than its (*Z*) isomer, due to steric interactions between the PG and R groups. Thus, under reversible conditions of enolate formation (K_2CO_3 , DMF, Δ), the reaction should proceed mostly via the (*Z*)-enolate, giving three kinds of cyclized products. On the other hand, under nonreversible conditions of enolate formation (LiHMDS, THF, 0 °C), the (*E*)-enolate should be formed more rapidly, giving the expected azetidinone as the major (or unique) product. The (*E*)/(*Z*) ratios of the enolates and the reactivities of the ionic pairs are obviously also influenced by the nature of solvent and the temperature, but these parameters were chosen according to the base (mainly for solubility reasons). Lastly, we performed control experiments to ensure that the cyclization step was nonreversible: each cyclized product (**13b**, **16b**, **19b**), placed individually under basic conditions, (Li_2CO_3 , DMF, 100 °C, 2 d) was found to

be stable: the mixture of all cyclized products was never regenerated. Our results thus solely reflect the ratios of (*E*)/(*Z*)-enolates initially formed and their possibility to equilibrate or not. Surprisingly, the question of selectivity for intramolecular cyclization of epoxyenolate derivatives was poorly documented in previous literature.^[30–31] Crotti et al.^[32–33] recently studied the effect of the chain length separating a terminal epoxide from a benzoyl moiety on the product distribution under basic conditions: the 4,5- and 6,7-epoxides gave *C*-alkylation products (3-*exo*-tet, 5-*exo*-tet, 6-*endo*-tet), while the 5,6-epoxides furnished mainly *O*-alkylation products (6-*exo*-tet, 7-*endo*-tet). In only one case (bicyclic epoxide) has the disfavoured 5-*endo*-tet cyclization been observed.^[33] Huang^[34] mentioned this type of cyclization as a special case when the epoxide was substituted with a phenyl group.

With azetidinones **13** (PG = Ph_2CH) and **15** [PG = (*p*-MeOC₆H₄)₂CH] now available, we examined the *N*-deprotection reaction under standard conditions (Table 7).^[35] No reaction was observed under catalytic hydrogenation conditions for the precursor **13b** (PG = Ph_2CH and R = *t*Bu), nor for the precursor **13a** (PG = Ph_2CH and R = Ph) (Entries 1–2), but in this case, when the conditions were forced, reduction of the benzoyl moiety occurred without concomitant cleavage of the benzhydryl group. Similarly, we were unable to deprotect the precursor **15b** [PG = (*p*-MeOC₆H₄)₂CH and R = *t*Bu] under various sets of acidic conditions (Entry 3). Prolonged reaction times with formic or trifluoroacetic acids resulted in the acylation of the side-chain



Scheme 3. Cyclization processes (the process is named *exo* when the C–C bond of the epoxide is outside the formed cycle and *endo* when the C–C bond of the epoxide is inside the formed cycle).

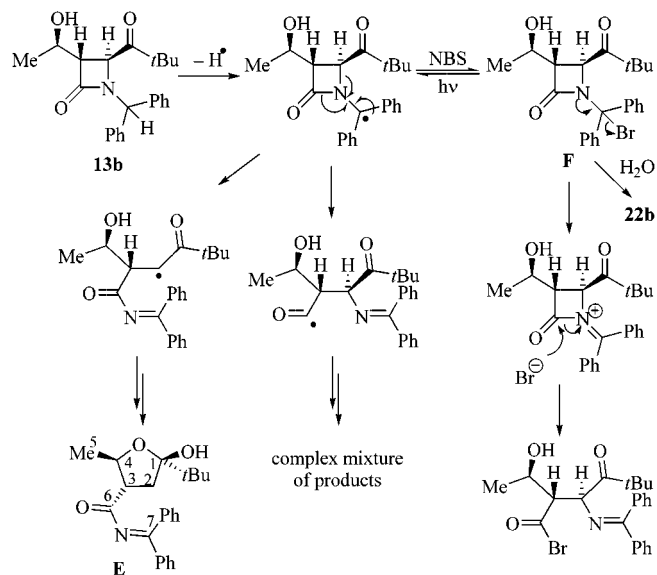
hydroxy group, but without concomitant cleavage of the bis(*p*-methoxyphenyl)methyl substituent.

Table 7. Azetidinone *N*-deprotection.

Entry	PG	R (Cmpd.)	Cond. i	Result; isolated yield (compd.)
1	Ph ₂ CH	<i>t</i> Bu (13b)	H ₂ , various catalysts, solvents, <i>p</i> , <i>T</i> , time, ...	no reaction
2	Ph ₂ CH	Ph (13a)	idem	no <i>N</i> -deprotection but benzoyl reduction
3	(<i>p</i> -MeOC ₆ H ₄) ₂ CH	<i>t</i> Bu (15b)	strong acidic conditions (AcOH, TFA, HBr, HCO ₂ H, ...)	no <i>N</i> -deprotection but OH acylation
4	Ph ₂ CH	<i>t</i> Bu (13b)	NBS, Br ₂ (catal.), hv, CH ₂ Cl ₂ and H ₂ O; then <i>p</i> TosOH, wet acetone	complete <i>N</i> -deprotection; 88% (23b)
5	Ph ₂ CH	Ph (13a)	idem	95% (23a)
6	Ph ₂ CH	<i>i</i> Pr (13d)	idem	92% (23d)
7	Ph ₂ CH	<i>cyclo</i> -Pr (13e)	idem	82% (23e)

These failures prompted us to seek a new deprotection method compatible with the azetidinone stability.^[11] We decided to exploit the proradical character of the benzhydryl motif. Inspired by some precedents involving benzylic cleavages,^[36–40] we treated the β -lactam **13b** with *N*-bromosuccinimide (NBS) in the presence of azobis(isobutyronitrile) (AIBN) as a catalyst (CCl₄ or PhCl, 80–120 °C). At high temperatures, **13b** indeed reacted, but furnished a complex mixture of products (Scheme 4) resulting from azetidinone ring opening (¹H NMR analysis). At room temperature, **13b** was slowly transformed to give a less complex mixture in which the tetrahydrofuran derivative **E** (Scheme 4) was identified by ¹H or ¹³C NMR analysis as the main product [H₂: δ = 1.44 (dd) ppm; H₃: δ = 2.61 (dd) ppm; H₄: δ = 3.87 (dq) ppm; H₅: δ = 0.67 (d) ppm; C₁: δ = 102.0 ppm; C₂: δ = 25.3 ppm; C₃: δ = 56.2 ppm; C₄: δ = 67.9 ppm; C₇: δ = 177.0 ppm]. The first radical formed by H abstraction from the benzhydryl group could suffer β -scission of the N1–C4 bond. This second radical could abstract a proton and the resulting γ -hydroxy ketone should readily cyclize to a hemiketal. In fact, at 20 °C, AIBN did not play any role; the results were the same in the presence or absence of the catalyst, provided that the reaction was performed under light!

We then further considered photoactivation of the bromination reaction of **13b**. Under light, however, the expected product **F** appeared to be unstable (Scheme 4). Fortunately, though, by working in a two-phase system, this intermediate could be quenched by water to furnish the stable β -lactam **22b** quantitatively (Figure 3). We also found that the addition of a catalytic amount of bromine accelerated the photochemical process (Br₂ is more sensitive to light-induced homolytic cleavage than NBS). Accordingly, the selected experimental conditions to transform **13b** into **22b** were as follows: NBS (1.1 equiv.), Br₂ (0.05 equiv.), CH₂Cl₂/H₂O (2:1), 20 °C, with stirring overnight under the irradiation by the fume hood lamp. The benzhydryl derivative **22b** was recovered in the organic phase. This compound



Scheme 4. Postulated routes for the azetidinone degradation.

was identified by ¹H and ¹³C NMR spectroscopy: the characteristic pattern of the Ha, Hb and Hc azetidinone protons (Figure 2) is still present, but the benzhydryl proton Hd has disappeared and two broad singlets attributable to OH protons are visible at δ = 2.50 and 5.12 ppm (hydroxyethyl chain and benzhydryl group, respectively), whilst the signal of the benzhydryl C7 signal at δ = 62.8 ppm has been replaced by a signal at δ = 87.4 ppm (benzhydryl carbon atom). An X-ray diffraction analysis^[25] confirmed our structural attribution. The remarkable stability of the *N*-acyl hemiaminal structure of **22b** was an unexpected result that we tentatively attributed to the involvement of the benzhydryl hydroxy group in an H-bonding network.^[41–43] Thus, intermediate **22b** was not spontaneously hydrolysed in the biphasic reactive medium (CH₂Cl₂/H₂O and HBr formed during the radical bromination); this hydrolysis required subsequent treatment with *p*-toluenesulfonic acid (PTSA) in wet acetone or acetonitrile. The *N*-unsubstituted azetidinone **23b** was recovered in high yield (88% for the two steps of the benzhydryl deprotection; Table 7, Entry 4), together with benzophenone (> 90% yield), which could be recycled for the preparation of benzhydrylamine.

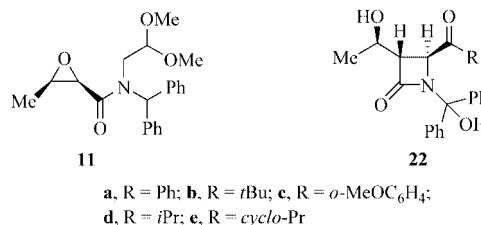


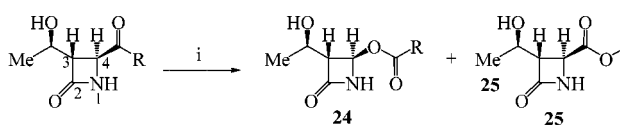
Figure 3. Synthetic intermediates **11** and **22a–e**.

Our two-step procedure for *N*-benzhydryl cleavage on β -lactam cores was successfully applied to compounds **13a**, **13d** and **13e** to furnish the *NH*-azetidinones **23a**, **23d** and **23e**, respectively, in 85–95% yields (Table 7, Entries 5–7); their NMR structural assignments are summarized in

Table 4. The cleavage of *N*-benzhydryl protecting groups from aziridines, via the *N*-benzhydryl intermediates, has recently been explored by Wulff et al.^[44]

The last step of our strategy was the Baeyer–Villiger (B–V) oxidation^[45–46] of precursors **23**, assuming that the required regioisomer **24** (Table 8) would be favoured by the ability of the azetidinyll moiety to stabilize a partial positive charge created at C4. Indeed, as a general rule in B–V rearrangements, it has been established that the more electron-rich substituent should migrate preferentially. Involvement of stereoelectronic effects has also been demonstrated,^[47–48] however, meaning that the preference for migration of one group can in some cases be overturned in favour of the other one, with an intrinsically lower migration aptitude, by appropriate orbital interactions with the peroxocarboxyl leaving group. The migratory aptitude of the azetidinyll group had not previously been systematically studied: in three cases – 4-acetylazetidin-2-one,^[49] 4-benzoylazetidin-2-one,^[50–52] and 4-formylazetidin-2-one^[53] – it was shown that the azetidinyll group migrated preferentially over methyl, phenyl, and even hydrogen, respectively.

Table 8. Baeyer–Villiger oxidation: i: *m*CPBA, CH₂Cl₂, 20 °C, 18 h.



Entry	R	Ratio 24/25 (¹ H NMR)	Isolated yield (%)	Compd.
1	Ph ^[7]	100:0	n.d.	24a
2	<i>t</i> Bu	0:100	90	25b
3	<i>i</i> Pr	52:48	n.d.	24d + 25d
4	<i>cyclo</i> -Pr	100:0	89	24e

Treatment of 4-benzoylazetidin-2-one **23a** with *m*-chloroperbenzoic acid (*m*CPBA) in dichloromethane (20 °C, 18 h) quantitatively produced the corresponding 4-benzoyloxyazetidin-2-one **24a** (Table 8, Entry 1), as described by Hanesian.^[7] Under similar conditions, however, the *tert*-butylcarbonyl precursor **23b** gave complete inversion of regioselectivity with the formation of **25b** as the unique product of B–V oxidative rearrangement, with the *tert*-butyl group migrating preferentially over the azetidinyll group (Entry 2). The isomers **24** and **25** could be easily distinguished in the ¹H NMR spectrum thanks to the H4 signal: δ = 5.9 ppm for compound **24a** and δ = 4.2 ppm for compound **25b** (Table 4); the corresponding carbon C4 signals are also typical in the ¹³C NMR spectrum: δ = 76 ppm (**24**) vs. δ = 50 ppm (**25**). As a matter of fact, the isopropyl derivative **23d** represents an intermediate situation producing an equimolar mixture of the regioisomers (**24d** + **25d**, Entry 3) under B–V conditions. Finally, the cyclopropyl derivative fulfilled our expectation! Thanks to the increased electronegativity of the cyclopropane carbon atoms (partial sp² character),^[54] the required regioselectivity was restored and the B–V oxidative rearrangement of **23e** exclusively yielded the 4-(cyclopropylcarbonyloxy)azetidin-2-one **24e**. Thus, in the series of ketones **23**, the experimentally determined order of group migration under B–V conditions is *t*Bu > *i*Pr =

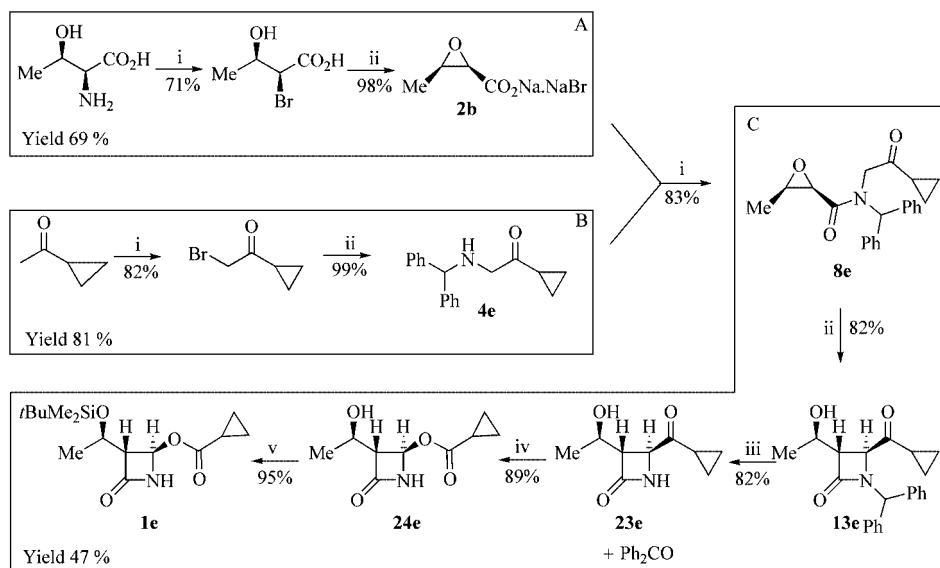
azetidinyll > *cyclo*-Pr = Ph. The particular effect of the cyclopropyl group in relation to the other sterically hindered alkyl groups could be the result of the electronic properties of the exocyclic C–C bond of the cyclopropane ring and the reduced number of C–H bonds involved in the hyperconjugative stabilization of the positive charge. Stereoelectronic effects most probably are not operating in this case.

The continuation of the synthesis towards *O*-protected azetidinones **1** (Scheme 1) was rather straightforward: treatment of **24d–e** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole quantitatively furnished compounds **1d–e** (see Table 4 for NMR spectroscopic data). (1'*R*,3*S*,4*S*)-3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(cyclopropylcarbonyloxy)azetidin-2-one (**1e**, R = *cyclo*-Pr) could be directly engaged in the further synthesis of carbapenems,^[12] or transformed into the commercially available acetoxy derivative **1** (R = Me, Scheme 1) by substitution with acetate.^[12]

Conclusions

At the end of this story, we are able to propose a novel synthesis of the key carbapenem intermediate **1**, by starting from L-threonine (Scheme 5, part A) and cyclopropyl methyl ketone (part B) and using benzhydrylamine for the introduction of the azetidinone *N*-protecting group. The key step is the C3–C4 ring closure of the epoxybutyramide precursor, regio- and stereocontrolled thanks to appropriate choice of the experimental conditions and the steric effects of the cyclopropyl substituent, similar to those of *tert*-butyl (part C). A photohalogenation/hydrolysis sequence allowed the smooth removal of the *N*-benzhydryl protecting group on the azetidinone and the recovery of benzophenone (economy of atoms). The required C4 substitution was achieved through the B–V oxidative rearrangement with total regiocontrol, thanks to the poor migratory aptitude of the cyclopropyl group. The cyclopropyl substituent (R = *cyclo*-Pr in Scheme 1) thus represents the best compromise for control of both the cyclization and the B–V reactions: indeed this group provides strong steric/conformational effects, but poor electron-donating effects.

Practically, two building blocks were independently prepared: sodium (2*R*,3*R*)-2,3-epoxybutyrate (**2b**) and (benzhydrylamino)methyl cyclopropyl ketone (**4e**), obtained in 69% and 81% yields, respectively. Coupling of the two building blocks, cyclization to the azetidinone, *N*-deprotection, B–V oxidation and *O*-silylation were performed in 47% overall yield (Scheme 5). Attempts to change the chronological order of these reaction steps were not successful. The *O*-silylation could be performed on azetidinones **13**, but only under very harsh conditions (LiHMDS, 18-crown-6, 10 equiv. of TBDMSCl), due to the steric effect of the *N*-protecting group. This was also performed in a one-pot process, during workup of the cyclization step with LiHMDS. The B–V oxidation, however, did not work at all in the presence of the bulky *N*-benzhydryl protecting group: neither **13** (free OH), nor the *O*-silylated derivatives reacted with



Scheme 5. Part A: i: NaNO_2 , KBr , $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$, $-10\text{ }^\circ\text{C}$ to $20\text{ }^\circ\text{C}$, 3 h; ii: NaOH , H_2O , $-10\text{ }^\circ\text{C}$ to $20\text{ }^\circ\text{C}$, 18 h. Part B: i: Br_2 , MeOH , $0\text{ }^\circ\text{C}$ to $20\text{ }^\circ\text{C}$; ii: K_2CO_3 , KI , Ph_2CHNH_2 , DMF , $20\text{ }^\circ\text{C}$. Part C: i: $(\text{COCl})_2$, THF , $-5\text{ }^\circ\text{C}$, 2 h, then pyridine, 2 h, $20\text{ }^\circ\text{C}$; ii: LiHMDS , THF , $0\text{ }^\circ\text{C}$, 3 h; iii: NBS , Br_2 (catal.), $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, $h\nu$, $20\text{ }^\circ\text{C}$, 15 h, then PTSA , $\text{acetone}/\text{H}_2\text{O}$, $20\text{ }^\circ\text{C}$, 18 h; iv: $m\text{CPBA}$, CH_2Cl_2 , $20\text{ }^\circ\text{C}$, 18 h; v: TBDMSCl , imidazole , DMF , $20\text{ }^\circ\text{C}$, 48 h.

$m\text{CPBA}$, so N -deprotection has to precede B–V rearrangement and O -protection.

Several advantages of our revisited Hanessian synthesis could be pointed out: (1) the use of a stable form of the chiral starting material (**2b**, mixed salt with NaBr), (2) the use of a novel N -protecting group, deprotection of which was not destructive and did not use cerium salt, (3) the high regio- and stereoselectivities of the two key steps of the reaction sequence, and (4) the introduction of the O -*tert*-butyldimethylsilyl group in the last step of the sequence (TBDMSCl is an expensive reagent) because our conditions of N -benzhydryl cleavage are compatible with a free OH group (which was not the case for PMP cleavage with CAN).

The scaling up of the synthesis of **1e** for potential industrial application is under investigation. Moreover, developments could be expected in fields other than azetidinone chemistry, with the use of benzhydryl as an N -protecting group for amides and lactams, and the use of cyclopropyl as a directing substituent in Baeyer–Villiger rearrangements.

Experimental Section

General: Reagents and solvents were purchased from Acros, Aldrich, Fluka or Rocc. Technical quality solvents were used as eluents in column chromatography and for liquid-liquid extractions. In all other cases P.A. quality solvents were used. Reactions that required anhydrous conditions were performed in glassware flamed under vacuum and cooled in argon. Tetrahydrofuran (THF) was dried with sodium in the presence of benzophenone and then distilled. Dichloromethane was dried by heating at reflux in the presence of calcium hydride and then distilled. DMF and acetonitrile were dried with molecular sieves ($4\text{ \AA}$). Thin layer chromatography was

performed on commercial plates (aluminium sheets coated with silica Merck 5179, 250 mesh, with fluorescent indicator 60F 254, 0.25 mm thickness). Products were revealed with suitable indicators such as phosphomolybdic acid (10% w/v in ethanol) and I_2 vapour or under a UV lamp. Column chromatography was carried out with silica gel 60 (70–230 mesh ASTM) supplied by Merck. ^1H and ^{13}C NMR spectra were obtained with Varian Gemini 200 (at 200 MHz for proton and 50 MHz for carbon), Varian Gemini 300 (at 300 MHz for proton and 75 MHz for carbon), and Bruker AM 500 spectrometers (at 500 MHz for proton and 125 MHz for carbon). Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS) in deuterated chloroform or acetone, and DSS (2,2-dimethyl-2-silapenta-5-sulfonate) in deuterated water. Multiplicity is reported as follows: singlet (s), broad singlet (brs), doublet (d), triplet (t), quadruplet (q), multiplet (m). Coupling constants (absolute values) are expressed in Hertz (Hz). IR spectra were obtained with a BIO-RAD FTS 135 instrument. Only the most significant adsorption bands are reported. Mass spectra were recorded with a Finnigan MAT TSQ-70 instrument. High-resolution mass spectra (HRMS) were obtained from the University of Mons, Belgium (Prof. R. Flamang). Microanalyses (EA) were performed at the Christopher Ingold Laboratories of University College, London (Dr. A. Stones). Melting points were determined with an Electro-thermal microscope and are uncorrected. Rotations were measured with a Perkin–Elmer 241 MC polarimeter fitted with a sodium lamp (concentrations expressed in g/100 mL). Some compounds cited in this paper have been described previously.^[10–12] All compounds are described in Tables 4–6 (NMR spectroscopic data), and Table S1 (Supporting Information). The total synthesis of the title compound (**1e**, Scheme 5) is described fully; the other derivatives were similarly prepared.

Bromomethyl Cyclopropyl Ketone:^[59] Br_2 (11.3 mL, 220 mmol, 1 equiv.) was added in one portion to a cold solution ($-5\text{ }^\circ\text{C}$) of cyclopropyl methyl ketone (20.7 mL, 220 mmol, 1 equiv.) in freshly distilled methanol (100 mL). After 1 h of stirring, water (50 mL)

was added and the mixture was allowed to warm to 20 °C. After stirring overnight, the solution was discoloured. After addition of water (150 mL), the mixture was extracted with diethyl ether (4 × 50 mL), and the organic phase was washed with NaHCO₃ (5%), dried with MgSO₄ and concentrated under reduced pressure to furnish the crude product (37.5 g, yellow liquid; contamination with about 10% of bromomethyl 3-bromopropyl ketone^[60] by ¹H NMR analysis). Distillation (50 °C, 6 × 10⁻³ mbar) afforded pure bromomethyl cyclopropyl ketone (29.5 g, 82% yield) as a colourless liquid; *d* = 1.558 g mL⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.13 (m, 2 H), 1.22 (m, 2 H), 2.32 (tt, *J* = 4.8, 7.8 Hz, 1 H), 4.06 (s, 2 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 12.1, 18.4, 37.7, 201.7 ppm. IR (film): ν̄ = 3012, 2940, 1700, 1383, 1192, 1063, 895 cm⁻¹. EIMS: *m/z* (%) = 163.8 (7) [⁸¹Br, M⁺], 161.9 (7) [⁷⁹Br, M⁺], 153 (37), 122.8 (4), 120.9 (4), 94.7 (3), 92.9 (3), 68.9 (100).

(Benzhydrylamino)methyl Cyclopropyl Ketone (4e): Bromomethyl cyclopropyl ketone (4.5 g, 28 mmol, 1 equiv.) was added at 90 °C to a suspension of finely powdered K₂CO₃ (4.15 g, 30 mmol, 1.2 equiv.), KI (4.95 g, 30 mmol, 1.2 equiv.) and benzhydrylamine (4.78 g, 27 mmol, 0.98 equiv.) in dry DMF (100 mL). This suspension was heated for 4 h and then filtered. The filtrate was diluted with ethyl acetate (100 mL), washed with brine (3 × 50 mL), dried with MgSO₄ and concentrated under vacuum and the solid residue (7.08 g, 98.8% yield) was used without purification in the next step. A pure sample could be obtained by crystallization from methanol; m.p. 82.5–84.0 °C (orange crystals). ¹H NMR (200 MHz, CDCl₃): δ = 0.88 (m, 2 H), 1.06 (m, 2 H), 1.82 (tt, *J* = 4.5, 7.8 Hz, 1 H), 3.66 (s, 2 H), 4.81 (s, 1 H), 7.1–7.4 (m, 10 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 10.7, 18.8, 58.1, 67.0, 126.9, 127.4, 128.5, 143.6, 208.6 ppm. IR (KBr): ν̄ = 3326, 3083, 3060, 3025, 3006, 2880, 2786, 1702, 1451, 1391, 1069, 698 cm⁻¹. EIMS: *m/z* (%) = 265.1 (9) [M⁺], 181.9 (75) [Ph₂CHNH⁺], 167.0 (38) [Ph₂CH⁺], 104.9 (100), 76.9 (63), 68.9 (47). HR-CIMS: calcd. for C₁₈H₂₀NO 266.1545, found 266.1544 [M + H⁺].

(2S,3R)-2-Bromo-3-hydroxybutyric Acid:^[17] A solution of NaNO₂ (9.38 g, 136 mmol, 1.6 equiv.) in water (30 mL) was added dropwise, over 90 min, to a cold (–12 °C) solution of L-threonine (10 g, 84 mmol, 1 equiv.) and KBr (15.48 g, 130 mmol, 1.5 equiv.) in H₂SO₄ (2.5 M, 170 mL). The solution was allowed to warm to 20 °C and stirred for 3 h and the aqueous solution was extracted with ethyl acetate (6 × 50 mL). The organic phase was washed with brine, dried with MgSO₄ and concentrated under vacuum to furnish crude product (10.87 g, 70.7% yield) as a colourless oil. ¹H NMR (200 MHz, CDCl₃): δ = 1.36 (d, *J* = 6.2 Hz, 3 H), 4.19 (dq, *J* = 4.3, 6.2 Hz, 1 H), 4.31 (d, *J* = 4.3 Hz, 1 H), 5.37 (br. s, 1 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 19.9, 52.6, 67.3, 172.1 ppm. IR (film): ν̄ = 3438, 2983, 2936, 1721, 1408, 1381, 1283, 1125, 1026 cm⁻¹. EIMS: *m/z* (%) = 139.8 (24) [CH₃CH(OH)CH₂⁸¹Br⁺], 137.9 (24) [CH₃CH(OH)CH₂⁷⁹Br⁺], 121.7(7), 119.9 (5), 45.0 (100).

(2R,3R)-2,3-Epoxybutyrate Mixed Salt 2b: A solution of NaOH (4.19 g, 103 mmol, 2 equiv.) in water (16 mL) was added dropwise, over 60 min, to a cold (–12 °C) solution of bromothreonine (9.42 g, 52 mmol, 1 equiv.) in water (7 mL). The solution was allowed to warm to 20 °C, stirred for 18 h, diluted with acetone (50 mL) and concentrated under reduced pressure. The residue was dried under high vacuum to furnish **2b** (mixed salt) as a white solid (11.56 g, 97.9% yield). ¹H NMR (200 MHz, D₂O): δ = 1.28 (d, *J* = 5.2 Hz, 3 H), 3.34 (dq, *J* = 5.1, 5.2 Hz, 1 H), 3.53 (d, *J* = 5.1 Hz, 1 H) ppm. ¹³C NMR (50 MHz, D₂O): δ = 15.2, 55.8, 58.5, 177.8 ppm. IR (KBr): ν̄ = 3083, 3012, 2965, 2933, 1611, 1441, 1036, 911, 671 cm⁻¹.

(2R,3R)-N-Benzhydryl-N-(2-cyclopropyl-2-oxoethyl)-2,3-epoxybutyramide (8e): Oxalyl chloride (1.43 mL, 16 mmol, 1.4 equiv.) was

added dropwise at –5 °C to a suspension of finely powdered **2b** (3.36 g, 14.8 mmol, 1.2 equiv.) in dry THF (50 mL) (evolution of gas occurred). After 2 h, pyridine (2.5 mL, 30.9 mmol, 2.5 equiv.) and then amine **4e** (3.09 g, 11.7 mmol, 1 equiv.) were added. After 1 h of stirring at –5 °C, the mixture was allowed to warm to 20 °C, and stirred for 2 h. After dilution with ethyl acetate (50 mL), washing with NaHCO₃ (5%, 3 × 30 mL), drying with MgSO₄ and concentration, crude **8e** was recovered. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate, 7: 3) gave pure **8e** (3.4 g, 83% yield) as a white solid (Table S1). ¹H NMR (300 MHz, CDCl₃, two rotamers in 58.5:41.5 ratio): δ = 0.6–0.8 (m, 4 H), 1.33 (d, *J* = 5.4 Hz, 3 H, minor isomer), 1.40 (d, *J* = 5.7 Hz, 3 H, major isomer), 1.5–1.7 (m, 1 H), 3.25 (m, 1 H), 3.54 (d, *J* = 4.8 Hz, 1 H, minor isomer), 3.59 (d, *J* = 4.5 Hz, 1 H, major isomer), 4.25 (d, *J* = 20.1 Hz, 1 H, minor isomer), 4.26 (d, *J* = 17.1 Hz, 1 H, major isomer), 4.42 (d, *J* = 17.1 Hz, 1 H, major isomer), 4.82 (d, *J* = 20.1 Hz, 1 H, minor isomer), 6.61 (s, 1 H, major isomer), 7.15–7.35 (m + s, 10 H + 1 H, minor isomer) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 10.7, 10.8, 10.9, 11.1, 13.9, 14.5, 17.6, 17.8, 53.5, 53.7, 53.8, 54.5, 55.2, 60.8, 63.9, 127.3–129.2, 138.3, 138.5, 167.4, 167.9, 202.6, 203.6 ppm. IR (KBr): ν̄ = 3062, 3028, 3007, 2930, 1715, 1665, 1449, 1387, 1075, 729, 700 cm⁻¹. CIMS: *m/z* (%) = 350.0 (4) [M + H⁺], 279.1 (12), 267.9 (8), 204.9 (20), 187.0 (16), 166.9 (56) [Ph₂CH⁺], 153.9 (61); 60.9 (100).

(1'R,3S,4S)-1-Diphenylmethyl-3-(1-hydroxyethyl)-4-(cyclopropylcarbonyl)azetid-2-one (13e): LiHMDS–diethyl ether^[61] (3.10 g, 12.9 mmol, 1.2 equiv.) was added at 0 °C under argon to a solution of **8e** (3.72 g, 10.6 mmol, 1 equiv.) in dry THF (90 mL). After warming up to 20 °C and 3 h of stirring, the reaction was stopped by addition of HCl (1 N, 10 mL). After dilution with ethyl acetate (50 mL), the solution was washed with NaHCO₃ (5%, 3 × 50 mL), dried with MgSO₄ and concentrated under vacuum to furnish crude **13e** (3.78 g, 100% yield). Purification by column chromatography on silica gel (cyclohexane/ethyl acetate, 10:1) gave pure **13e** (3.04 g, 82% yield) as a white solid (Table S1). ¹H NMR (300 MHz, CDCl₃): δ = 0.65–0.85 (m, 4 H), 1.29 (d, *J* = 6.7 Hz, 3 H), 1.81 (tt, *J* = 4.5, 7.5 Hz, 1 H), 3.02 (br. s, 1 H), 3.09 (dd, *J* = 2.4, 4.8 Hz, 1 H), 4.26 (m, 1 H), 4.41 (d, *J* = 2.4 Hz, 1 H), 5.95 (s, 1 H), 7.20–7.40 (m, 10 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 11.6, 12.3, 17.5, 21.8, 59.9, 61.5, 62.1, 64.4, 127.5–128.5, 138.0, 138.4, 167.1, 208.0 ppm. IR (KBr): ν̄ = 3359, 3062, 3023, 2971, 2930, 1742, 1703, 1453, 1381, 1132, 1053, 700 cm⁻¹. CIMS: *m/z* (%) = 350.2 (1) [M + H⁺], 225.8 (4), 167.0 (12) [Ph₂CH⁺], 88.9 (10), 59.0 (100). HR-CIMS: calcd. for C₂₂H₂₄NO₃ 350.1756, found 350.1767 [M + H⁺].

(1'R,3S,4S)-4-(Cyclopropylcarbonyl)-3-(1-hydroxyethyl)azetid-2-one (23e): NBS^[62] (0.99 g, 5.6 mmol, 1.1 equiv.) was added to a mixture of **13e** (1.8 g, 5.1 mmol, 1 equiv.) and Br₂ (1.3 mL of a solution of 0.1 mL Br₂ in 10 mL of CH₂Cl₂; 0.25 mmol, 0.05 equiv.) in CH₂Cl₂ (70 mL) and water (45 mL). The mixture was stirred at room temperature overnight, under irradiation from the fume hood lamp (discoloration occurred). After dilution with CH₂Cl₂ and extraction with NaHSO₃ (5%), the organic phase was concentrated to furnish crude **22e** (1.87 g, 100% yield). ¹H NMR (200 MHz, CDCl₃): δ = 0.7–1.0 (m, 4 H), 1.28 (d, *J* = 6.2 Hz, 3 H), 1.85 (tt, *J* = 4.8, 7.7 Hz, 1 H), 2.95 (dd, *J* = 2.5, 5.1 Hz, 1 H), 4.22 (dq, *J* = 5.1, 5.8 Hz, 1 H), 4.62 (d, *J* = 2.5 Hz, 1 H), 5.63 (br. s, 1 H), 7.1–7.8 (m, 10 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 11.7, 12.4, 17.8, 21.8, 60.5, 60.7, 64.5, 87.6, 126.4–132.3, 141.7, 166.7, 209.7 ppm. Crude **22e** (1.87 g, 5.1 mmol) was dissolved in acetone/water (1:1, 70 mL) containing PTSA (0.94 g, 1.9 mmol, 0.95 equiv.). The mixture was stirred in the dark at room temperature overnight. Concentration under vacuum gave a brown solid (2.77 g) containing PTSA, benzophenone and **23e**. Benzophenone

could be recovered by precipitation from cold water (90–100% yield). Pure *N*-deprotected azetidinone **23e** was obtained by column chromatography on RP-18 (CH₃CN/H₂O, 1:3) as a yellow foam (0.77 g, 82% yield, Table S1). *R*_F = 0.76 (RP-18; CH₃CN/H₂O, 1:3; visualization with phosphomolybdic acid). ¹H NMR (200 MHz, CDCl₃): δ = 1.04 (dt, *J* = 2.9, 7.9 Hz, 2 H), 1.14 (dt, *J* = 2.9, 4.5 Hz, 2 H), 1.41 (d, *J* = 6.3 Hz, 3 H), 2.17 (tt, *J* = 4.5, 7.9 Hz, 1 H), 3.22 (ddd, *J* = 1.6, 2.7, 4.4 Hz, 1 H), 4.33 (dq, *J* = 4.4, 6.3 Hz, 1 H), 4.45 (d, *J* = 2.7 Hz, 1 H), 6.56 (br. s, 1 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 12.0, 12.2, 17.2, 21.9, 57.3, 63.7, 65.0, 167.2, 207.6 ppm. IR (film): ν̄ = 3309, 3012, 2971, 2930, 1750, 1701, 1397, 1127, 994 cm⁻¹. CIMS: *m/z* (%) = 184.3 (5) [M + H⁺], 148.8 (23), 71.6 (34), 60.6 (96), 58.7 (100). HR-CIMS: calcd. for C₉H₁₄NO₃ 184.0974, found 184.0978 [M + H⁺].

(1'*R*,3*S*,4*S*)-4-(Cyclopropylcarbonyloxy)-3-(1-hydroxyethyl)azetidin-2-one (24e): A mixture of **23e** (0.26 g, 1.44 mmol, 1 equiv.) and *m*CPBA^[63] (0.49 g, 2.8 mmol, 2 equiv.) in CH₂Cl₂ (10 mL) was stirred at room temperature overnight. Concentration and column chromatography on silica gel (CH₂Cl₂/ethyl acetate, 3:2) afforded **24e** (0.25 g, 89% yield) as a white solid (Table S1). ¹H NMR (300 MHz, [D₆]acetone): δ = 0.9–1.0 (m, 4 H), 1.27 (d, *J* = 6.3 Hz, 3 H), 1.68 (m, 1 H), 3.15 (dd, *J* = 1.5, 5.7 Hz, 1 H), 4.09 (dq, *J* = 5.7, 6.3 Hz, 1 H), 5.90 (s, 1 H), 7.98 (br. s, 1 H) ppm. ¹³C NMR (75 MHz, [D₆]acetone): δ = 9.0, 9.1, 13.2, 22.1, 64.3, 66.0, 76.5, 166.8, 175.0 ppm. IR (KBr): ν̄ = 3311, 3017, 2973, 2933, 1769, 1732, 1378, 1160, 1034, 862 cm⁻¹. CIMS: *m/z* (%) = 199.9 (25) [M + H⁺], 182.0 (47), 155.9 (100), 113.9 (44), 86.6 (69), 70 (65). HR-CIMS: calcd. for C₉H₁₄NO₄ 200.0923, found 200.0920 [M + H⁺].

(1'*R*,3*S*,4*S*)-3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(cyclopropylcarbonyloxy)azetidin-2-one (1e): TBDMSCl (0.076 g, 0.5 mmol, 4 equiv.) and imidazole (0.09 g, 1.3 mmol, 12 equiv.) were added to a solution of **24e** (0.022 g, 0.11 mmol, 1 equiv.) in dry DMF (3 mL). The mixture was stirred at 20 °C for 2 d. After dilution with ethyl acetate, the solution was washed with brine (3 times), dried with MgSO₄ and concentrated. The residue was dried under high vacuum to give **1e** (0.033 g, 95% yield) as a white solid (Table S1). ¹H NMR (300 MHz, CDCl₃): δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.85 (s, 9 H), 0.94 (ddd, *J* = 3.6, 4.5, 7.8 Hz, 2 H), 1.03 (dt, *J* = 3.6, 4.5 Hz, 2 H), 1.25 (d, *J* = 6.3 Hz, 3 H), 1.63 (tt, *J* = 4.5, 7.8 Hz, 1 H), 3.19 (dd, *J* = 1.2, 3.6 Hz, 1 H), 4.22 (dq, *J* = 3.6, 6.3 Hz, 1 H), 5.83 (s, 1 H), 6.48 (br. s, 1 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = -4.22, 9.14, 9.24, 12.8, 18.0, 22.4, 25.7, 63.9, 65.0, 75.0, 166.4, 175.0 ppm. IR (KBr): ν̄ = 3111, 2954, 2930, 2857, 1779, 1735, 1392, 1161, 1076, 837 cm⁻¹. CIMS: *m/z* (%) = 428.4 (8) [M + SiMe₂tBu⁺], 298.1 (17) [M - CH₃⁺], 269.9 (20), 256.0 (30) [M - C₄H₉⁺], 228.1 (43) [M - OCOC₃H₅⁺], 159.0 (100). HR-CIMS: calcd. for C₁₁H₂₂NSiO₂ 228.1420, found 228.1416 [M - OCOC₃H₅⁺].

Supporting Information (see footnote on the first page of this article): Physical constants and analysis.

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