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Preparation of (3*S*,4*S*)-1-Benzhydryl-3-[(5*R*)-1′-hydroxyethyl]-4-acyl-2-azetidinones from (2*R*,3*R*)-Epoxybutyramide Precursors

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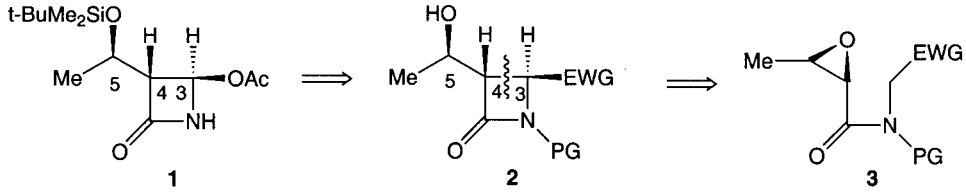
Abstract—The N-(phenacyl)-**8a** and N-(pivaloylmethyl)-**8b** derivatives of N-(benzhydryl)-(2*R*,3*R*)-*cis*-2,3-epoxybutyramide were prepared from sodium (2*R*,3*R*)-*cis*-2,3-epoxybutanoate **4**. Under basic conditions they gave S_Ni reactions leading to the formation of four-, six- and seven-membered heterocycles, namely the azetidin-2-ones **9a**, **b** (C-alkylation), the 2,3-dehydro-morpholin-5-ones **10a**, **b** (O-alkylation), and the 4,5,6,7-tetrahydro-4-aza-oxepin-5-ones **12a, b** (O-alkylation). The structures were confirmed by NMR analysis. Other rearrangement products, **13a** and **14b**, were also isolated.

Introduction

The pharmaceutical development of carbapenems, an important class of β-lactam antibiotics,[1] is connected to the availability of appropriate synthetic precursors, such as the chiral azetidinone **1**: (3*R*,4*R*)-4-acetoxy-3-[(5*R*)-1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone.[2]

Amongst the various strategies explored for the construction of this versatile building block,[3] one is based on the C-3/C-4 ring closure via an intramolecular nucleophilic substitution of (2*R*,3*R*)-epoxy-butyramide precursors **3** derived from L-threonine (Scheme 1).[4–11] The structures **3** are equipped with an electron-withdrawing group (EWG) able to stabilise a carbanionic intermediate, and with a nitrogen-protecting group (PG) that could be cleaved from the β-lactams **2** by oxidation with ceric ammonium nitrate, i.e. 4-methoxybenzyl-, 2,4-dimethoxybenzyl-, or most usually, 4-methoxyphenyl-(=*p*-anisyl) groups. This method, starting from a low cost, naturally occurring chiron,[12,13] generates the three chiral centres of the β-lactam precursors **2** in the required absolute configuration.

In our laboratory, we became interested in a modification of the previous strategy making use of a nitrogen-protecting group cleavable by hydrogenolysis. Our previous experience in the related β-lactamiminium derivatives led us to consider the benzhydryl group.[14] Accordingly, we prepared the precursors **8** (Scheme 2) and examined their transformation into the corresponding β-lactams. During this work, we found unexpected cyclization- and rearrangement products described in this article.



Scheme 1.

Keywords: epoxide ring-opening; intramolecular nucleophilic substitution; O/C-alkylation; β-lactam.

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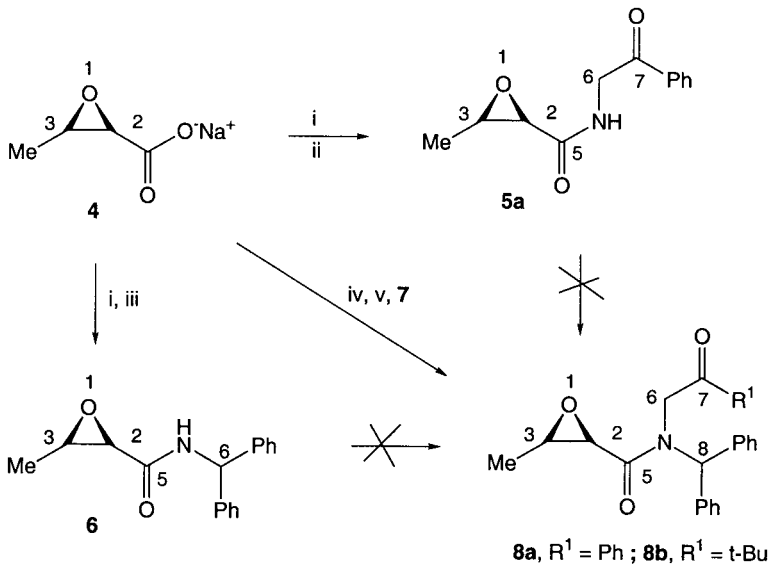
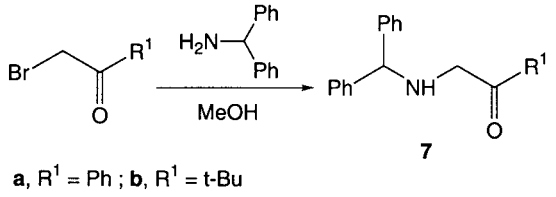


Scheme 2. Reagents and conditions: (i) *t*-BuCOCl, CH_3CN, 20°C; (ii) $HCl{\cdot}H_2NCH_2COPh$, Et_3N, CH_3CN, 20°C; (iii) $HCl{\cdot}H_2NCHPh_2$, Et_3N, CH_3CN, 20°C; (iv) $(COCl)_2$, THF, −15°C; (v) **7**, pyridine, THF, −15 to 20°C.

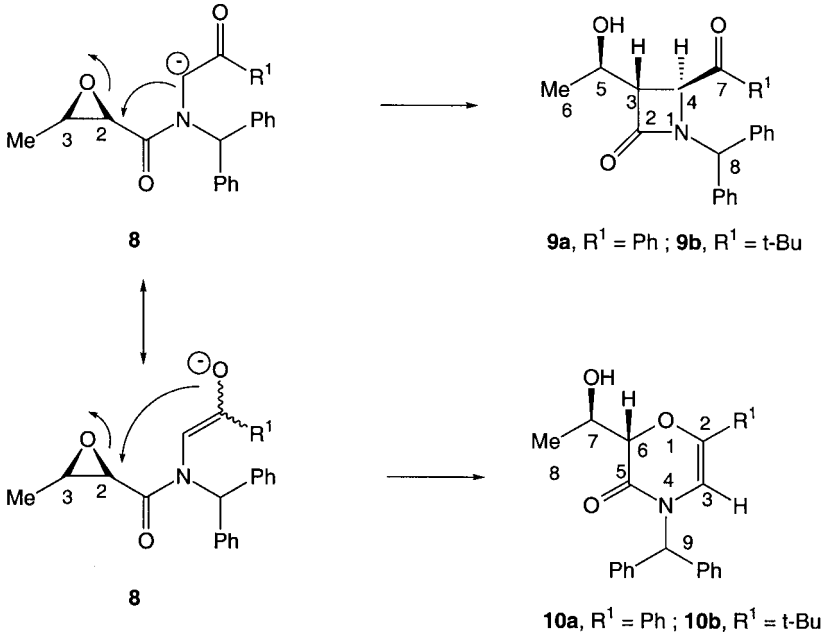


Scheme 3.

Results

(2*R*,3*R*)-*cis*-2,3-Epoxybutanoate **4** was prepared from L-threonine according to known procedures,[12,13] adapted for large quantities (100 g scale). The enantiomeric purity of **4** has been established by chiral GC analysis, after derivatization into the corresponding isopropyl ester.[13]

From the examination of several conditions for direct activation of the salt **4** ($SOCl_2$/THF; $SOCl_2$+pyridine/benzene; $(COCl)_2$+pyridine/THF; 2,3,5-trichlorobenzoyl chloride/DMF; *i*-butyl chloroformate/DMF or CH_3CN; pivaloyl chloride+pyridine/CH_3CN), we selected two methods allowing the further coupling of amines in good yields, i.e. the in situ formation of an acid chloride with oxalyl chloride, or a mixed anhydride with pivaloyl chloride. Thus, after appropriate activation, **4** was reacted with 2-aminoacetophenone or benzhydrylamine to furnish, respectively, the epoxybutyramides **5a** or **6** in good yields (Scheme 2). All attempts to transform either **5a** or **6** into the



Scheme 4.

Table 1. Ratio of products from ^{1}H NMR analysis of the crude mixtures (%) (examination of the 5.0–6.5 δ spectral domain)

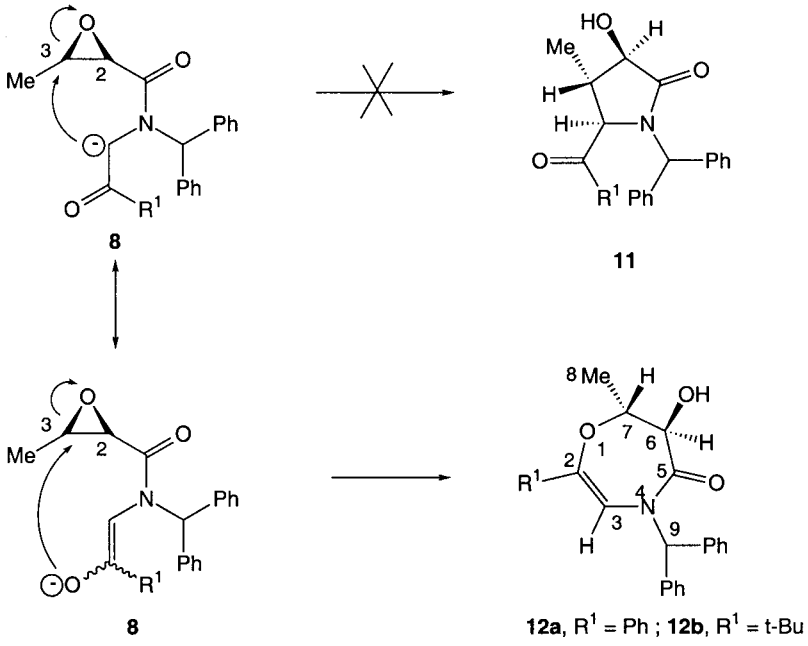
Entry	R^1 (**8**); conditions	**9**	**10**	**12**	**13**	**14**
1	**a**, Ph; K_2CO_3, DMF, 100°C, 17 h	16	56	21	7	–
2	**a**, Ph; Li_2CO_3, DMF, 100°C, 17 h	34	38	18	10	–
3	**a**, Ph; LiHMDS, THF, 0°C, 2 h	57	21	20	2	–
4	**b**, *t*-Bu; K_2CO_3, DMF, 100°C, 17 h	55	35	8	–	<2
5	**b**, *t*-Bu; Li_2CO_3, DMF, 100°C, 17 h	62	24	9	–	5
6	**b**, *t*-Bu; LiHMDS, THF, 0°C, 2 h	>90	<2	>2	–	–

required precursor **8a** by the appropriate N-alkylation reaction (R–X/base/DMF) failed. Also, the treatment of **5a** under various basic conditions (LiHMDS, LiOH, Li_2CO_3, basic Al_2O_3) did not lead to the formation of the corresponding N-unprotected β-lactam. Therefore, we developed a convergent synthesis towards the N-protected precursors **8** using N-(benzhydryl) aminoketones **7** (Scheme 3).

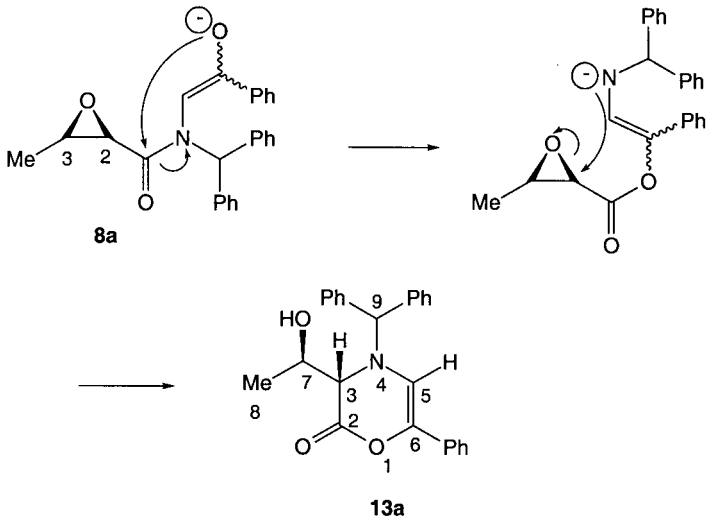
Compounds **7a** and **7b** were easily prepared by reaction of diphenylaminomethane with 2-bromoacetophenone and 1-bromopinacolone, respectively, in methanol solution. Activation of **4** with oxalyl chloride in THF at −15°C, followed by addition of pyridine and **7a**, **b** led to the recovery of **8a**, **b** in 80% yield (Scheme 2). Compounds **8a**, **b** showed the presence of two rotamers in the NMR spectra recorded in $CDCl_3$, splitting practically all the signals. This could be due to a restricted rotation around the C(O)–N amide bond. As a matter of fact, recording the ^{1}H NMR spectrum of **8a** in DMSO-d_6 at 99°C (300 MHz) gave one singlet at 6.8 δ attributed to the benzhydryl proton H-8; after cooling to 19°C, splitting of the signal occurred, giving two distinct singlets at 6.73 and 6.88 δ.

We first examined the cyclization of **8a** (R^1=Ph) into the corresponding β-lactam **9a** (Scheme 4) by using the experimental conditions recommended in the literature for the treatment of similar precursors **3** (Scheme 1) equipped with a benzoyl group (EWG=COPh), i.e. K_2CO_3 in DMF with heating (PG=*p*-anisyl; 75% yield of **2**[8,11]) and LiHMDS (lithium hexamethyldisilazide), at low temperature, in benzene (PG=CH(OEt)Ph; 71% yield of **2**[10]) or in THF (PG=*p*-anisyl; 67% yield of **2**[11]). Our results, collected in Table 1, showed that the treatment of **8a** with K_2CO_3 led to the formation of β-lactam **9a** as a minor product (16% yield), while the use of Li_2CO_3 slightly improved the formation of the desired product **9a** (34% yield). The best results were obtained with LiHMDS as the base, giving 57% of **9a**. In all cases, the β-lactam **9a** was accompanied with a mixture of three side-products (HPLC and NMR analyses of the crude mixtures), which could be separated and isolated as pure materials by careful column-chromatography (see R_f values in Experimental).

The structure of **9a** (single stereoisomer) was fully confirmed by the spectroscopic data in good agreement with the literature;[7,10] in particular, the *trans* β-lactam protons appeared at 3.11 δ (H-3, dd) and 5.07 δ (H-4, d) in the ^{1}H NMR spectrum, with a typical coupling constant value of 2.3 Hz. Two carbonyl stretches were found in the IR spectrum, at 1741 cm^{-1} (β-lactam) and 1685 cm^{-1} (PhCO). The structures of the three side-products, eluted before the β-lactam **9a**, were attributed on the basis of ^{1}H and ^{13}C NMR data (see Experimental): **10a** (Scheme 4) and **12a** (Scheme 5) correspond to intramolecular O-alkylation products of the C-2 and C-3 carbon atoms, respectively, of the epoxide ring, while **13a** (Scheme 6) results from an intramolecular transesterification followed by N-alkylation of the C-2 carbon atom of the epoxide ring. As a matter of fact, in these three structures, the benzoyl group (PhCO) was absent, i.e. a doublet near 7.7 δ (2H, J~8 Hz) for the *ortho*-aromatic protons in the ^{1}H NMR spectra, and a quaternary carbon near 200 ppm for the carbonyl in the ^{13}C NMR spectra. On the other hand, a vinylic proton (s, H-3 or H-5) was clearly visible in the ^{1}H NMR spectra at 6.07 δ in compound



Scheme 5.



Scheme 6.

10a, 5.72 δ in compound **12a**, and 6.24 δ in compound **13a**. Moreover, the structures showed in ^{13}C NMR only one carbonyl function corresponding to an amide (C-5 at 163.6 ppm in **10a** and 172 ppm in **12a**) or an ester (C-2 at 164 ppm in **13a**), and two vinylic carbons corresponding to an α,β-hetero-substituted double bond (C-2 at 140 ppm in **10a** and 145 ppm in **12a** and C-3 at 104 ppm; C-5 and C-6 at 104 ppm and 140 ppm in **13a**). The typical features of the 1′-hydroxyethyl side-chain were found in **10a** and **13a**, but not in **12a**. Accordingly, in the ^1H NMR spectra, H-7 of **13a** appeared as a quartet of doublets of doublets (4.4 δ, coupling with Me-8, H-3 and OH) and H-7 of **12a** appeared as a quartet of doublets (4.8 δ, coupling with Me-8 and H-6). Consistent with the previous assignments, H-3 in **13a** was a doublet (4.5 δ, coupling with H-7), while H-6 in **12a** was a doublet of doublets (4.7 δ, coupling with H-7 and OH).

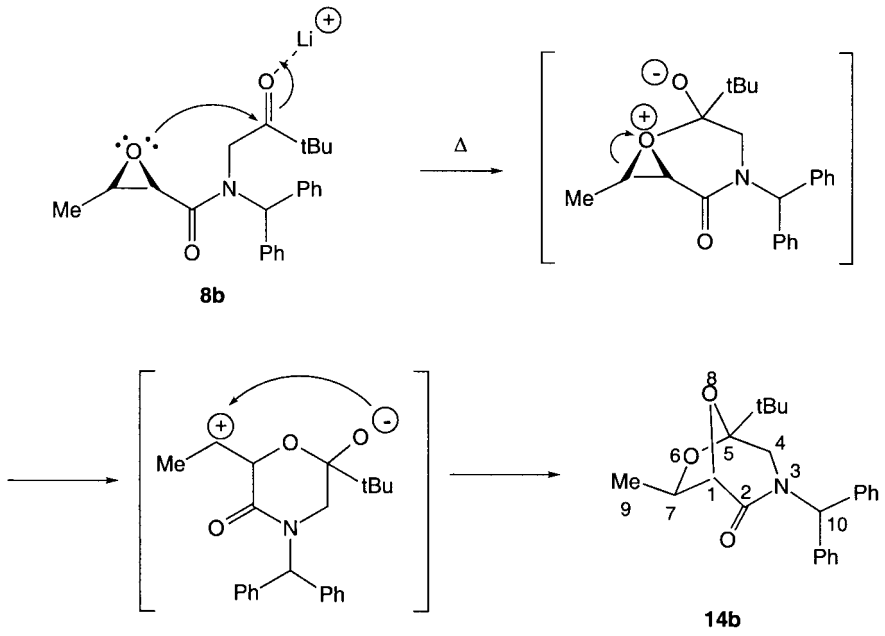
The spectral characteristics of **10a** were similar to those of **13a**. At this stage, the structure of **10a** could be definitively confirmed by the X-ray diffraction analysis of a single crystal; the compound is one stereoisomer with the (6*S*, 7*R*) configuration.[15]

Assuming that the O-alkylation processes (direct attack of the epoxide, or transesterification) should be less favourable in the case of the precursor **8b** (R^1=*t*-Bu) for electronic and steric reasons, we treated this non-conjugated and hindered ketone as above, with K_2CO_3, Li_2CO_3, or LiHMDS (Table 1). As expected, the β-lactam **9b** resulting from the C-alkylation of the C-2 carbon atom of the epoxide ring was the major product in all cases (Scheme 4). In the presence of K_2CO_3 and Li_2CO_3, the O-alkylation products **10b** (Scheme 4) and **12b** (Scheme 5) were also formed, but under treatment with LiHMDS, **8b** was transformed into the β-lactam **9b** in more than 90% yield. The products were separated and isolated as pure compounds by careful column-chromatography (see R_f values in Experimental). A weakly polar rearrangement product **14b** (Scheme 7), not found during the basic treatment of **8a**, was isolated in a few percent yield. No product resulting from a transesterification process (like **13** in Scheme 6) could be detected.

The structural assignments of **9b**, **10b** and **12b** were made, on the basis of NMR data, by analogy with the related compounds **9a**, **10a** and **12a**. Moreover, the structure of **12b** was unambiguously confirmed by the X-ray diffraction analysis of a single crystal; the compound is one stereoisomer with the (6*R*,7*S*) configuration.[15] Compound **14b** (Scheme 7), isolated in the first elution fractions from chromatography in less than 5% yield, is devoid of a hydroxyl function; in the ^1H NMR spectrum, it shows a typical AB pattern corresponding to two protons of a CH_2 group adjacent to a nitrogen atom (H-4 at 2.9 δ and H-4′ at 3.3 δ with J=11.8 Hz). Since these protons appear less deshielded than the related H-6 and H-6′ protons of the precursor **8b** (4.2–4.9 δ, J=17.3 Hz), we concluded that they are not adjacent to a carbonyl function (CO–*t*-Bu). Accordingly, in the ^{13}C NMR, only one carbonyl function was found at 167 ppm corresponding to an amide. The bridged tricyclic structure **14b** was fully confirmed by selective H/C decoupling experiments; the ketal-type carbon C-5 appeared at 110 ppm.

Discussion

The intramolecular ring-opening of chiral expoxides is a stereochemically controlled S_Ni process useful for the preparation of various carbocycles[16–18] and heterocycles.[19–24] The epoxide function behaves as an ambident electrophile that can be attacked by nucleophiles on the C-2 or C-3 position of the small ring. In our case, the internal nucleophile is an enolate, thus also an ambident function, that could attack with either its carbon- or oxygen atom, leading theoretically to the possible formation of four products allowed by Baldwin's rules,[25] as illustrated in Schemes 4 and 5. In our hands, three products were isolated, **9**, **10** and **12**, corresponding, respectively, to C-nucleophilic attack on the epoxide C-2 position, O-nucleophilic attack on the epoxide C-2 position, and O-nucleophilic attack on the epoxide C-3 position. Compounds **11** resulting fom C-nucleophilic attack on the epoxide C-3 position were never isolated nor detected in the crude reaction mixtures from the ^1H NMR analyses. If formed, they must only be



Scheme 7.

present in less than 2% yield (limit of detection of the analytical method). The precursor **8a** (R^1=Ph) also underwent a base-catalysed intramolecular transesterification, leading to the final rearrangement product **13a** (Scheme 6) in low yield. The same reaction did not occur with the precursor **8b** (R^1=*t*-Bu), most probably for steric reasons. On the other hand, this compound **8b** displayed a reactive unconjugated carbonyl function susceptible to intramolecular nucleophilic attack of the epoxide oxygen atom (Scheme 7), leading to the bridged rearrangement product **14b**. Since **8b** was thermally stable in pure hot DMF, we speculated that the rearrangement could be catalysed by lithium cations present in the basic reactive medium.

Most of the previous syntheses of β-lactams **2** based on the cyclization of precursors **3** (Scheme 1) made use of anion-stabilising groups favouring C-nucleophilic attack (EWG=CO_2–*t*-Bu;[7] CN;[6] SO_2Ph);[4] the corresponding β-lactams **2** were isolated in relatively good yields (60–80%), and the authors did not mention the formation of any 5-, 6- or 7-membered heterocyclic side-products. At low temperature of cyclization, some (3*S*,4*R*)-*cis* stereoisomer of β-lactam **2** could be a minor product (kinetic control instead of thermodynamic control). Also, the course of the reaction seemed to be independent on the nature of the N-protecting group (PG=aryl- or benzyl type). Reactions making use of the benzoyl group (EWG=COPh) were scarcely described in the literature;[8,10,11] precursors **3** equipped with *p*-anisyl[8,11] or phenylethoxymethyl protecting groups[10] gave similar yields of β-lactams **2** (67–75%). The only reported side-product, isolated in about 10% yield, was a bicyclic hemiketal derived from the (3*S*,4*R*)-*cis* stereoisomer of **2**.[11]

We found that the N-benzhydryl bulky protecting group dramatically changed the course of the cyclization reaction of **8a**, favouring the formation of O-alkylation products (**10a**, **12a**) and transesterification product (**13a**) over the desired azetidinone (**9a**) (C-alkylation). Replacing the benzoyl substituent (R^1=Ph) with the pivaloyl group (R^1=*t*-Bu) reversed the O/C chemoselectivity, allowing the formation of azetidinone **9b** as the major product. In this case, the non-conjugated enolate reacts preferentially with its C-nucleophilic site on the oxirane C-2 position. However, the absence of C-alkylation on the oxirane C-3 position (product **11**, Scheme 5), in all cases, remains surprising. A recent study[26] devoted to the intramolecular cyclization of enolate derived from 1-phenyl-5,6-epoxy-hexan-1-one reported similar observations: only the O-alkylation products (6-phenyl-2-hydroxymethyl-3,4-dihydro-2H-pyran and 7-phenyl-3-hydroxy-2,3,4,5-tetrahydro-oxepine) were formed, while the C-alkylation products were not found (1-benzoyl-2-hydroxymethyl-cyclobutane and 1-hydroxy-3-benzoylcyclopentane). Dianions of acetoacetic esters reacted with epibromohydrin derivatives at the γ-position to form enolate intermediates[27] which subsequently cyclize, affording exclusively the O-alkylation products of the epoxide moiety. In the previous examples, the product selectivity remains unexplained by the authors.

Both the reactivity and C/O-selectivity of enolates depend on the nature of the solvent and the counter-ion influencing the degree of ion-pair dissociation.[28,29] The formation of a strong ion-pair with the lithium counter-ion tends to increase the C-versus the O-enolate reactivity in weakly polar solvents such as THF.[29] The use of DMF as a polar solvent reduces this counter-ion effect. In this case, the nature of the leaving group of the alkylating reagent (i.e. the epoxide) will exercise the major influence on the C/O-selectivity; generally, soft electrophiles favour the C-alkylation process, and hard electrophiles the O-alkylation one.[28] Our observations are in good agreement with the hard character of the epoxide reagent. Accordingly, the best conditions to obtain high yield of azetidinone **9** (C-alkylation) from precursor **8** make use of lithium hexamethyldisilazide as the base, in THF solution. However, steric (low

hindrance) and electronic factors (conjugated carbonyl) still allow the occurrence of side-reactions (O-alkylation and transesterification) in the case of precursor **8a** (R^1=Ph; Table 1, entry 3), but not with precursor **8b** (R^1=*t*-Bu: Table 1, entry 6).

Experimental

The melting points were determined with an Electrothermal microscope and are uncorrected. The specific rotations (±0.5) were determined on a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). The IR spectra were taken with a Bio-Rad FTS 135 instrument, and calibrated with polystyrene (1601 cm^{-1}). The ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300 (at 300 MHz for proton and 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); the attributions were firmly established by selective decoupling experiments. The mass spectra were obtained on a Finnigan-MAT TSQ-70 instrument at 70 eV (electronic impact (EI) mode), or with a Xenon ION TECH 8 KV (fast atom bombardment (FAB) mode). The microanalyses were performed at the Christopher Ingold Laboratories of the University College London. The HRMS were performed at the University of Liège (Belgium) on a VG-AutoSpec-Q equipment (Fisons Instruments, Manchester).

Thin-layer chromatography was carried out on silica gel 60 plates F254 (Merck, 0.2 mm thick); visualisation was effected with UV light, iodine vapour, or a spray of potassium permanganate (3 g) and potassium carbonate (20 g) in aqueous acetic acid (1%, 300 mL). Column-chromatography (under medium pressure) was carried out with Merck silica gel 60 of 230–240 mesh ASTM. The HPLC analyses were performed with a Beckman equipment, System Gold, 126P Solvent module, 168 Detector, from Analis (Belgium). We used a Hypersil Elite C18 Column (100 Å, 5 μm; 250×4.6 mm^2) thermostatised at 25°C and eluted with a gradient of acetonitrile/water, from 50:50 to 0:100 during 30 min (detection at 254 nm). The following retention times were recorded (min): **8a**: 9.53; **8b**: 10.38; **9a**: 8.35; **9b**: 8.75; **10a**: 11.80; **10b**: 13.18; **12a**: 13.53; **12b**: 15.58.

(2*R*,3*R*)-*cis*-2,3-Epoxybutanoate (4). This compound (sodium salt) was prepared according to the known procedures[12,13] and used without purification: ^1H NMR (200 MHz, D_2O) δ 1.37 (d, 3H, *J*=5.6 Hz), 3.36 (dq, 1H), 3.55 (d, 1H, *J*=4.5 Hz).

***N*-(Phenacyl) (2*R*,3*R*)-*cis*-2,3-epoxybutyramide (5a).** To a suspension of **4** (2.0 g, 8.81 mmol) in dry CH_3CN (17 mL), stirred at 18°C under argon atmosphere, was added dropwise pivaloyl chloride (1.085 mL, 8.81 mmol). After 5 h 45 min of stirring, the mixture was successively treated with 2-aminoacetophenone hydrochloride (1.19 g, 8.81 mmol) (the temperature was maintained below 20°C) and with triethylamine (2.58 mL, 18.5 mmol) added dropwise during 30 min. After 3 h of stirring, the mixture was filtered and the filtrate was poured into ice-cold water (25 mL). The aqueous solution was extracted with ethyl acetate (3×30 mL). The organic phases were gathered, washed with brine (3×30 mL), and concentrated under reduced pressure to give crude **5a** (1.558 g, 81% yield). Pure product was recovered by crystallisation from *t*-butyl methyl ether/ethyl acetate (0.96 g, 50% yield): mp 135–136°C (white crystals);$[\alpha]_D$=+23.3 (*c*=0.242, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (d, 3H, *J*=5.8 Hz, H-4), 3.32 (qd, 1H, *J*=5.8, 4.4 Hz, H-3), 3.56 (d, 1H, *J*=4.4 Hz, H-2), 4.69 (dd, 1H, *J*=19.4, 4.4 Hz, H-6), 4.91 (dd, 1H, *J*=19.4, 5.5 Hz, H-6′), 7.11 (br s, 1H, NH), 7.49 (t, 2H, *J*=7.7 Hz), 7.62 (t, 1H, *J*=7.7 Hz), 7.96 (d, 2H, *J*=7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.01 (C-4), 45.41 (C-6), 54.33 (C-3), 55.23 (C-2), 127.78, 128.81, 134.06, 134.18, 167.67 (C-5), 193.29 (C-7). Anal. Calcd for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.61; H, 5.85; N, 6.37%.

***N*-(Benzhydryl) (2*R*,3*R*)-*cis*-2,3-epoxybutyramide (6).** Amide **6** was prepared following the procedure described for **5a**, starting from **4** (10 g, 44 mmol) and aminodiphenylmethane hydrochloride (9.15 g, 45 mmol). Precipitation from *t*-butyl methyl ether gave **6** as an amorphous white solid (6.4 g, 54% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 3H, *J*=5.5 Hz, H-4), 3.31 (dq, 1H, *J*=5.5, 5.4 Hz, H-3), 3.58 (d, 1H, *J*=5.4 Hz, H-2), 6.32 (d, 1H, *J*=8.7 Hz, H-6), 6.84 (d, 1H, NH), 7.15–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0 (C-4), 54.8 (C-3), 55.2 (C-2), 56.2 (C-6), 125–130 (CH Ar), 140.8, 141, 166.7 (C-5).

***N*-(Benzhydryl)-*N*-(phenacyl)amine (7a).** To a suspension of 2-bromoacetophenone (5 g, 25.12 mmol) in dry methanol (35 mL), stirred under argon atmosphere, was added benzhydrylamine (8.66 mL, 50.24 mmol). The mixture was stirred during 5 h at 20°C. The formed solid (86% yield) was filtered, and recrystallised from ethanol (50 mL) to give pure **7a** (5.29 g, 70% yield); mp 130.7°C (white crystals); ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (s, 2H), 2.74 (s, 1H), 7.2–7.6 (m, 13H); 7.87 (d, 2H, *J*= 7.5 Hz); ^{13}C NMR (75 MHz, $CdCl_3$) δ 54.2, 67.2, 127.2–128.6, 133.4, 143.6, 198.0. Anal. Calcd for $C_{21}H_{19}NO$ (301.38); C, 83.69; H, 6.35; N, 4.65. Found: C, 83.64; H, 6.10; N, 4.61%.

***N*-(Benzhydryl)-*N*-(pivaloylmethyl)amine (7b).** This compound (amorphous white solid) was similarly prepared from 1-bromopinacolone, and purified by flash-chromatography on silica gel (CH_2Cl_2/EtOAc, 90:10); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 3.59 (s, 2H), 4.75 (s, 1H), 7.15–7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.96, 43.77, 52.95, 67.73, 127.8, 127.98, 129.18, 144.2, 214.71. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.34; H, 8.28; N, 4.94%. HRMS: 281.1776 (calcd: 281.1780).

***N*-(Benzhydryl)-*N*-(phenacyl) (2*R*,3*R*)-*cis*-2,3-epoxybutyramide (8a).** To a suspension of **4** (2 g, 8.81 mmol) in dry THF (25 mL), stirred at −15°C (bath with ice+NaCl) under argon atmosphere, was added dropwise (with a syringe, through a septum) oxalyl chloride (1.6 mL, 17.5 mmol). The mixture was stirred for 50 min at −12°C. Pyridine (2.2 mL, 27.5 mmol) was added dropwise (with a syringe, through a septum), followed by **7a** (2.65 g, 8.81 mmol). The mixture was stirred for 30 min at −12°C,

then allowed to warm up slowly to room temperature within 50 min. The crude solution was poured into a 50:50 mixture of ethyl acetate and 5% aqueous $NaHCO_3$ (80 mL), and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (3×25 mL). The organic phases were gathered, washed with saturated aqueous ammonium chloride (3×15 mL), dried over $MgSO_4$ and concentrated under vacuum (2.68 g, 79% crude yield). Pure **8a** was obtained by crystallisation from H_2O/EtOH (5:2) (1.87 g, 55% yield): mp 161–162°C (white crystals); $[\alpha]_D$=+9.19 (c=0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; two rotamers in a 53:47 ratio) δ 1.36 and 1.48 (two d, 3H, J=5.8 Hz, H-4), 3.23 and 3.26 (two dq, 1H, J=5.8, 4.4 Hz, H-3), 3.62 and 3.63 (two d, 1H, J=4.4 Hz, H-2), 4.68 and 4.72 (two d, 1H, J=17.3 Hz, H-6), 4.86 and 5.28 (two d, 1H, J=17.3 Hz, H-6′), 6.71 and 7.18 (two s, 1H, H-8), 7.10–7.50 (m, 13H); 7.58 and 7.66 (two d, 2H, J=7.7 Hz) ^{13}C NMR (125 MHz, $CDCl_3$; two rotamers in a 53:47 ratio) δ 13.97 and 14.66 (C-4), 50.42 and 50.62 (C-6), 53.85 and 54.08 (C-3), 54.66 and 55.60 (C-2), 61.14 and 64.19 (C-8), 167.81 and 168.42 (C-5), 191.99 and 193.3 (C-7), 6 quaternary aromatic carbon signals (138.85, 138.60, 138.56, 138.28, 135.22, 134.5) 18 aromatic CH signals (133.29, 132.91, 129.47, 128.85, 128.63, 128.57, 128.48, 128.44, 128.34, 128.31, 128.27, 128.15, 128.05, 128.03, 127.67, 127.47, 127.40, 127.31). Anal. Calcd for $C_{25}H_{23}NO_3$·0.1H_2O: C, 77.56; H, 5.99; N, 3.62. Found: C, 77.61; H, 5.87; N, 3.59%. HRMS: 385.1678 (calcd: 385.1678).

***N*-(Benzhydryl)-*N*-(pivaloylmethyl) (2*R*,3*R*)-*cis*-2,3-epoxybutyramide (8b).** This compound was prepared as above from **4** (2 g, 8.81 mmol) and **7b** (2.48 g, 8.81 mmol). Crystallisation of the crude material from H_2O/EtOH (5:2) gave pure **8b** (1.48 g, 46% yield): mp 157–158°C (white crystals); $[\alpha]_D$=+10.8 (c=1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; two rotamers in a 60:40 ratio) δ 0.89 and 0.85 (two, s, 9H), 1.46 and 1.29 (two d; 3H, J=5.8 Hz, H-4), 3.20 and 3.26 (two dq, 1H, J=5.8, 4.4 Hz, H-3), 3.47 and 3.52 (two, d, 1H, J=4.4 Hz, H-2), 4.23 (d, 1H, J=17.3 Hz, H-6), 4.44 and 4.97 (two, d, 1H, J=17.3 Hz, H-6′), 6.61 and 7.2 (two, s, 1H, H-8), 7.10–7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$; two rotamers in a 60:40 ratio) δ 13.97 and 14.74 (C-4), 26.16 and 26.25, 42.66 and 42.46, 48.82 and 49.36 (C-6), 53.73 and 53.81 (C-3), 54.60 and 55.70 (C-2), 61.02 and 63.96 (C-8), 167.48 and 168.27 (C-5), 206.58 and 208.56 (C-7), 4 quaternary aromatic carbon signals (139.07, 138.75, 138.62, 138.50), 12 aromatic CH signals (129.90, 129.04, 128.60, 128.45, 128.38, 128.36, 128.17, 128.01, 127.96, 127.78, 127.71, 127.24). Anal. Calcd for $C_{23}H_{27}NO_3$ (365.2): C, 75.62; H, 7.43; N, 3.80. Found: C, 75.59; H, 7.57; N, 3.85.

(3*S*,4*S*,5*R*)-1-Benzhydryl-3-(1′-hydroxyethyl)-4-benzoyl-2-azetidinone (9a). Epoxide **8a** (1.04 g, 2.7 mmol) dissolved in dry DMF (15 mL) was heated at 100°C, under argon atmosphere, in the presence of powdered Li_2CO_3 (1.9 g, 26 mmol) (Table 1, entry 2). After 24 h (stirring), the mixture was poured into a 50:50 solution of ethyl acetate and brine (200 mL), and filtered. The organic layer was separated and washed with brine (3×50 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL). The organic phases were gathered, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel with a 20:1 mixture of CH_2Cl_2 and EtOAc furnished the azetidinone **9a** in the last fractions as a white gum (0.32 g, 30% yield): R_f=0.20 (CH_2Cl_2/EtOAc, 10:1); $[\alpha]_D$=− 13.5 (c=0.222, $CHCl_3$); IR (KBr) ν 3400 (br), 1741, 1685, 1450, 1230, 600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, 3H, J=6.3 Hz, H-6), 2.10 (br s, 1H, OH), 3.11 (dd, 1H, J=2.3, 5.2 Hz, H-3), 4.31 (dq, 1H, J=5.2, 6.3 Hz, H-5), 5.07 (d, 1H, J=2.3 Hz, H-4), 5.59 (s, 1H, H-8), 7.15–7.40 (m, 12H), 7.50 (t, 1H, J=7.7 Hz), 7.70 (d, 2H, J=7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0 (C-6), 55.3 (C-4), 62.3 (C-3), 62.5 (C-8), 65.2 (C-5), 127.6–133.7 (CHAr), 135.3, 138.4, 138.6, 167.1 (C-2), 197.6 (C-7). Mass (D-APCI/LCQ) *m/e* 386 (M+H$^+$, 100%). Anal. Calcd for $C_{25}H_{23}NO_3$·0.3H_2O: C, 76.84; H, 6.04; N, 3.59. Found: C, 76.85; H, 5.94; N, 3.57%.

(3*S*,4*S*,5*R*)-1-Benzhydryl-3-(1′-hydroxyethyl)-4-pivaloyl-2-azetidinone (9b). This compound was obtained as above from **8b** (0.214, 2 g, 0.58 mmol) (Table 1, entry 5). The last fractions from the flash-chromatography (SiO_2; CH_2Cl_2/EtOAc, 20:1) gave **9b** (0.11 g, 58% yield) which crystallised in ethanol: mp 168–170°C (white crystals); R_f=0.15 (CH_2Cl_2/EtOAc, 10:1); $[\alpha]_D$=+41.3 (c=0.995, $CHCl_3$); IR (KBr) ν 3500 (br), 1759, 1704, 1457, 1367, 1115, 899, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.38 (d, 3H, J=6.4 Hz, H-6), 2.04 (br, s, 1H, OH), 2.89 (dd, 1H, J=2.1, 6.4 Hz, H-3), 4.21 (dq, 1H, J=6.4, 6.4 Hz, H-5), 4.52 (d, 1H, J=2.1 Hz, H-4), 5.69 (s, 1H, H-8), 7.20–7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.92 (C-6), 25.80, 43.69, 55.26 (C-4), 61.86 (C-3), 66.23 (C-5), 127.61, 127.72, 128.01, 128.37, 128.55, 138.19, 138.54, 166.93 (C-2), 212.66 (C-7). Anal. Calcd for $C_{23}H_{27}NO_3$·0.2H_2O: C, 74.88; H, 7.43; N, 3.80. Found: C, 74.85; H, 7.53; N, 3.81%. HRMS: 365.1988 (calcd: 365.1991). Higher yield could be obtained as follows (Table 1, entry 6): to a solution of **8b** (0.111 g, 0.3 mmol) in dry THF (5 mL), cooled at 0°C under argon atmosphere, was added in 5 min a 0.5 M solution of LiHMDS in THF (1.3 mL, 0.6 mmol). The mixture was stirred for 2 h at 0°C and 1 h at 20°C, then poured into 1 N HCl (10 mL). Extraction with ethyl acetate (3×15 mL), washing of the organic phase with 5% $NaHCO_3$ (2×10 mL) and brine (10 mL), drying over $MgSO_4$, and concentration gave crude **9b** (100% yield) which could be purified (86% yield) by flash column-chromatography (SiO_2; CH_2Cl_2/ethyl acetate, 10:1).

(6*S*,7*R*)-*N*-Benzhydryl-6-(1′-hydroxyethyl)-2-phenyl-2,3-dehydromorpholin-5-one (10a). This compound, formed together with the azetidinone **9a**, was isolated by chromatography, just before the β-lactam fraction, in about 35% yield: mp 124.5–125.5°C (white crystals); R_f=0.35 (CH_2Cl_2/EtOAc, 10:1); $[\alpha]_D$=+58 (c=0.4, CH_2Cl_2); IR (film) ν 3423, 1676, 1600, 1496, 1448, 1411, 1370, 1196, 1077 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, 3H, J=6.2 Hz, H-8), 2.90 (br s, OH), 4.50 (sharp m, 2H, H-6+H-7), 6.07 (s, 1H, H-3), 7.10 (s, 1H, H-9), 7.22–7.42 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2 (C-8), 59.7 (C-9), 66.65 (C-6), 79.27 (C-7), 103.73 (C-3), 123.58, 127.8, 128.1, 128.4, 128.66, 128.73, 128.77, 132.07, 137.95, 138.17, 139.7 (C-2), 163.6 (C-5); Mass (EI) *m/e* 385.1 ($C_{25}H_{23}O_3N$), 367 (M−H_2O), 167, 165; HRMS: 385.1690 (calcd: 385.1678). Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.92; H,

5.97; N, 3.63. Found: C, 77.76; H, 5.91; N, 3.62%. The structure of **10a** has been fully confirmed by X-ray diffraction analysis of a single crystal.[15]

(6*S*,7*R*)-*N*-Benzhydryl-6-(1′-hydroxyethyl)-2-*tert*-butyl-2,3-dehydromorpholin-5-one (10b). This compound, formed together with the azetidinone **9b**, was isolated from the medium fractions of the flash-chromatography on silica gel (CH_2Cl_2/EtOAc, 20:1) in about 20% yield. Recrystallisation from ethanol gave pure **10b**: mp 161–165°C (white crystals): R_f=0.47 (CH_2Cl_2/EtOAc, 10:1); $[\alpha]_D$=+11.5 (c=0.310, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.37 (d, 3H, J=6.6 Hz, H-8), 3.06 (d, 1H, J=6.4 Hz, OH), 4.21 (d, 1H, J=4.1 Hz, H-6), 4.35 (m, 1H, H-7), 5.3 (s, 1H, H-3), 7.0 (s, 1H, H-9), 7.15–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CdCl_3$) δ 18.68 (C-8), 28.14, 34.78, 60.16 (C-9), 67.32 (C-7), 79.93 (C-6), 101.77 (C-3), 128.36, 128.63, 128.89, 129.24, 129.33, 129.59, 139.06, 139.27, 151.07 (C-2), 164.18 (C-5). Anal. Calcd for $C_{23}H_{27}NO_3{\cdot}0.8H_2O$; C, 72.75; H, 7.54; N, 3.69. Found: C, 72.89; H, 7.31; N, 3.66%. HRMS: 365.1985 (calcd: 365.1991).

(6*R*,7*S*)-*N*-Benzhydryl-6-hydroxy-7-methyl-2-phenyl-4,5,6,7-tetrahydro-4-aza-oxepin-5-one (12a). This compound, formed together with **9a** and **10a**, was isolated from the first fractions of the flash-chromatography on silica gel (CH_2Cl_2/EtoAc, 20:1) in about 15% yield: mp 113–114°C (white crystals); R_f=0.70 (CH_2Cl_2/EtOAc, 10:1); $[\alpha]_D$=+52.5 (c=0.310, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 3H, J=6.5 Hz, H-8), 3.95 (d, 1H, J=4.6 Hz, OH), 4.70 (dd, 1H, J=4.6, 4.3 Hz, H-6), 4.85 (dq, 1H, J=6.5, 4.3 Hz, H-7), 5.72 (s, 1H, H-3), 7.19 (s, 1H, H-9), 7.20–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CdCl_3$) δ 15.5 (C-8), 62.0 (C-9), 71.5 (C-6), 81.0 (C-7), 104.5 (C-3), 125–129 (CH Ar), 136, 138, 139, 145 (C-2), 172 (C-5). Anal. Calcd for $C_{25}H_{23}NO_3{\cdot}0.3H_2O$: C, 76.84; H, 6.04; N, 3.59. Found: C, 76.93; H, 5.80; N, 3.61%. HRMS: 365.1695 (calcd: 365.1678).

(6*R*,7*S*)-*N*-Benzhydryl-6-hydroxy-7-methyl-2-*tert*-butyl-4,5,6,7-tetrahydro-4-aza-oxepin-5-one (12b). This compound, formed together with **9b** and **10b**, was isolated from the first fractions of the flash-chromatography on silica gel (CH_2Cl_2/EtOAc, 20:1) in about 8% yield: mp 105–106.5°C (white crystals); R_f=0.75 (CH_2Cl_2/EtOAc, 10:1); $[\alpha]_D$=+29.8 (c=0.276, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.77 (d, 3H, J=6.3 Hz, H-8), 3.87 (d, 1H, J=5.2 Hz, OH), 4.57 (dd, 1H, J=5.2, 4.6 Hz, H-6), 4.69 (dq, 1H, J=4.6, 6.3 Hz, H-7), 5.05 (s, 1H, H-3), 7.09 (s, 1H, H-9), 7.14–7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.27 (C-8), 28.0, 36.41, 61.61 (C-9), 70.35 (C-6), 81.52 (C-7), 102.03 (C-3), 127.50, 127.81, 128.24, 128.34, 128.51, 128.81, 137.79, 138.86, 155.83 (C-2), 171.39 (C-5). Anal. Calcd for $C_{23}H_{27}NO_3{\cdot}0.2H_2O$: C, 74.88; H, 7.43; N, 3.80. Found: C, 74.82; H, 7.34; N, 3.83%. The structure of **12b** has been fully conformed by X-ray diffraction analysis of a single crystal.[15]

(3*S*,7*R*)-*N*-Benzhydryl-3-(1′-hydroxyethyl)-6-phenyl-5,6-dehydromorpholin-2-one (13a). This compound, formed together with **9a**, **10a** and **12a**, was isolated from the medium fractions of the flash-chromatography on silica gel (CH_2Cl_2/EtOAc, 20:1) in about 9% yield: mp 169–170°C (white crystals); R_f=0.50 (CH_2Cl_2/EtOAc, 10:1); $[\alpha]_D$=+22.4 (c=0.334, $CHCl_3$);^{1}H NMR (500 MHz, acetone-d_6) δ 1.39 (d, 3H, J=6.7 Hz, H-8), 4.05 (d, 1H, J=6.7 Hz, OH), 4.41 (ddq, 1H, J=6.7, 6.7, 4.0 Hz, H-7), 4.54 (d, 1H, J=4.0 Hz, H-3), 6.24 (s, 1H, H-5), 7.12 (s, 1H, H-9), 7.20–7.50 (m, 15H); ^{13}C NMR (125 MHz, acetone-d_6) δ 19.69 (C-8), 60.30 (C-9), 67.05 (C-7), 81.73 (C-3), 104.38 (C-5), 124.54, 128.52, 128.55, 128.73, 129.16, 129.40, 129.45, 129.54, 129.64, 133.90, 139.72 (C-6), 139.57, 139.85, 164.05 (C-2); Mass (D-APCI/LCQ) m/e 386 (M+H+, 27%), 282 (20%), 167 (100%). HRMS: 385.1692 (calcd: 385.1678).

(1*R*,5*S*,7*R*)-3-Benzhydryl-5-*tert*-butyl-7-methyl-6,8-dioxa-3-azabicyclo [3.2.1] octan-2-one (14b). This compound, formed together with **9b**, **10b** and **12b**, was isolated from the first fractions of the flash-chromatography on silica gel (CH_2Cl_2/EtOAc, 20:1) in about 5% yield: (still contaminated with **12b**): R_f=0.80 (CH_2Cl_2/EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.30 (d, 3H, J=6.6 Hz, H-9), 2.93 (d, 1H, J=11.8 Hz, H-4), 3.26 (d, 1H, J=11.8 Hz, H-4′), 4.15 (dq, 1H, J=6.6, 4.6 Hz, H-7), 4.61 (d, 1H, J=4.6 Hz, H-1), 7.13 (s, 1H, H-10); 7.15–7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.77 (C-9), 24.38, 36.37, 47.95 (C-4), 58.45 (C-10), 76.35 (C-7), 79.45 (C-1), 109.87 (C-5), 127.46, 127.54, 128.42, 128.45, 128.55, 128.81, 137.79, 138.17, 166.57 (C-2). HRMS: 365.1982 (calcd: 365.1991).

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