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Synthesis of Four-Membered Ring Spiro-β-lactams by Epoxide Ring-Opening

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A variety of hydroxy epoxides have been obtained from well defined hydroxy-alkenyl derivatives. Their subsequent intramolecular ring-opening allowed unprecedented classes of spiro-lactams to be obtained. The effect of the epoxide stereochemistry and of the reaction temperature on the regioselective formation of five- or four-membered ring spiro derivatives was explored. This transformation is part of a program directed towards the synthesis of polyfunctionalized β-lactams as cholesterol absorption inhibitors (CAIs).

Introduction

The β-lactam ring represents the fundamental pharmacophore group for a wide range of compounds showing biological efficacy, but activity can nevertheless be enhanced or addressed by suitable functionalization at side chains at the C3 and C4 position in the ring. While the various natural or synthetic β-lactams are best known for their high antibacterial activities,[1] examples of azetidin-2-ones have recently been applied as enzyme inhibitors of proteases.[2] In this context, spiro-β-lactams that are new and interesting due to their structural features and to their bioactivity have recently been reported. Interest in these molecules has been stimulated by the recent application of spiro-β-lactam-based structures as antiviral agents,[3] β-turn mimetics[4] and cholesterol absorption inhibitors (CAIs).[5]

The synthesis of these compounds has generally been performed by ketene-imine cycloaddition, though a recent paper by Alcaide et al.[6] reports an alternative strategy through intramolecular metal-catalysed cyclization of unsaturated alcohols. Our synthetic approach takes advantage of the easy regioselective ring-opening of an epoxide to afford unprecedented classes of oxetane four-membered rings or tetrahydrofuran spiro-β-lactams that, to the best of our knowledge, have not yet been reported.

Epoxides are among the most useful synthetic intermediates in organic synthesis, albeit a conversion of an alkene into an epoxide is usually part of a more extensive molecular transformation. Indeed, the regio- and stereoselective ring-opening of oxiranes provides a convenient way to prepare polyfunctionalized compounds.[7] Moreover, the stereochemical outcome of the epoxidation of a double bond by *m*-chloroperbenzoic acid (MCPBA) is strongly influenced by steric factors.[8] It is well known that allylic and homoallylic alcohols can be epoxidized with peracids with good stereoselectivity, due to complex formation between the peroxy acid and the unsaturated alcohol.

A variety of hydroxy epoxides have therefore been obtained by starting from well defined hydroxy-alkenyl derivatives. Their transformation into the corresponding spiro-lactams is reported here as a part of a program directed towards the synthesis of polyfunctionalized β-lactams as cholesterol absorption inhibitors.

Results and Discussion

Treatment of 3-(but-1′-enyl)-3-(1′′-hydroxybenzyl)azetidin-2-ones[9] **1a**–**d** with MCPBA allowed the *trans* epoxides **2a**–**d** to be obtained with high levels of diastereoselectivity. The pure major isomers could be generally isolated either by flash chromatography on silica gel or by reversed-phase preparative HPLC (Scheme 1).

The use of Lewis acids in the ring-opening of epoxides is well documented in the literature.[10] Initially we used $TiCl_4$, $AlMe_2Cl$ and $Yb(OTf)_3$ in catalytic amounts as promoters of intramolecular cyclization of **2a**, but the unreacted starting material was recovered in almost quantitative yield. Finally, when the reaction was carried out in the presence of one equivalent of boron trifluoride–diethyl ether at room temperature,[11] the ring-opening occurred in high yield and with good regioselectivity, giving the unprecedented oxetane **3a** in 90/10 regioisomeric ratio with respect to its tetrahydrofuran regioisomer **4a**. The same regioisomeric ratio was observed both in the reaction performed at –20 °C and in the one carried out at room temperature. The ^1H NMR patterns and the HPLC-MS analyses for **3a** and **4a** are consistent with the spiro structures.

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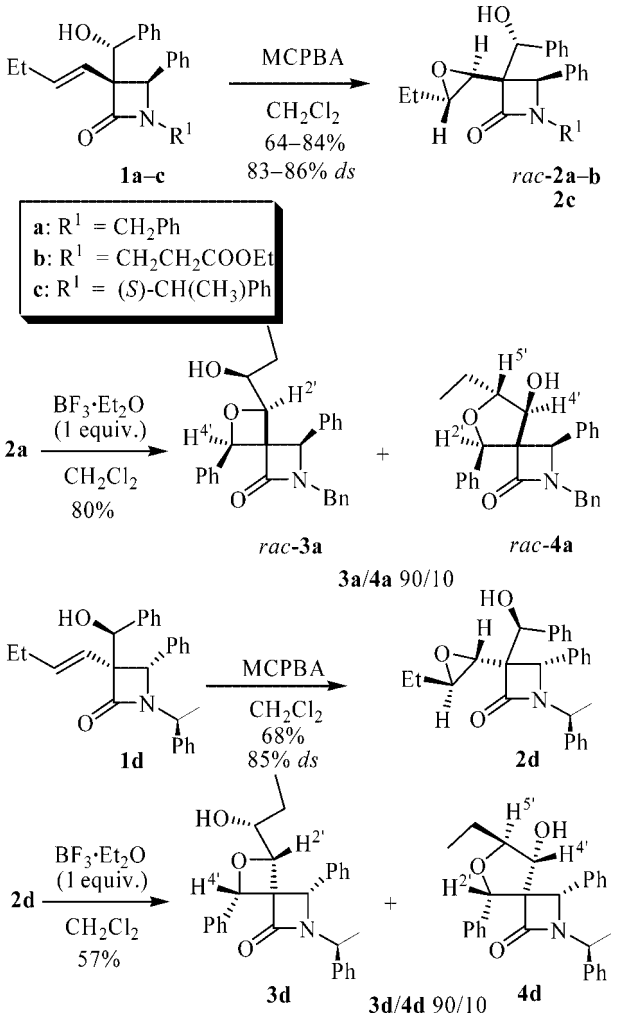


Scheme 1. $BF_3{\cdot}Et_2O$-induced ring-opening of epoxide **2**.

A NOESY-1D[12] analysis performed on **3a** showed a strong enhancement of the $H^{2'}$ signal when $H^{4'}$ was irradiated and a medium nOe effect on H^4, thus suggesting a *cis* relationship between the two hydrogen atoms $H^{2'}$ and $H^{4'}$. These observations allowed the (4*R**,2′*R**,3′*S**,4′*R**) relative configuration to be attributed to the bicyclic compound **3a**, corresponding to a (1′*S**,2′*S**) configuration of the ring stereocenters in the starting epoxide **2a** (Figure 1).

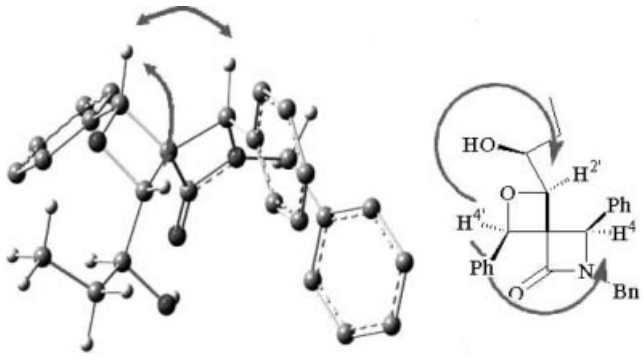
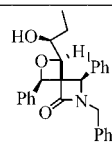
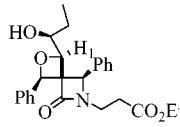
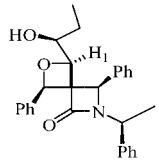
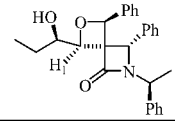


Figure 1. NOESY-1D enhancements for compound **3a**.

Similarly high regioselectivity was observed on repetition of the same reaction on the examples **2b** and **2c** (Table 1). Compound **2b** afforded the four-membered ring compound **3b** in 75% yield and as almost exclusively one regioisomer (Table 1, Entry 2), while the same treatment of **2c** afforded a lower regioisomeric ratio (Entry 3). In a similar way, enantiomerically pure (1′′*S*,1′*R*,2′*R*)-**2d**, containing the same configurational feature, afforded the corresponding spiro derivative **3d** in a 90:10 regioisomeric ratio (Entry 4). Compounds **3a**–**d** are characterized by a typical IR adsorption of the β-lactam carbonyl group in the 1719–1724 cm^{-1} range, while **4a**–**d** showed IR absorption in the 1743–1750 cm^{-1} range. These values were used as diagnostic for ring size determination in these classes of compounds. Moreover, comparison of the ^1H NMR spectra showed complete regularity in the chemical shifts of the starting epoxides and of the products, thus allowing the relative and absolute configuration to be attributed to all the members of this class.[13]

Table 1. $BF_3{\cdot}Et_2O$-induced ring-opening of epoxide **2**.

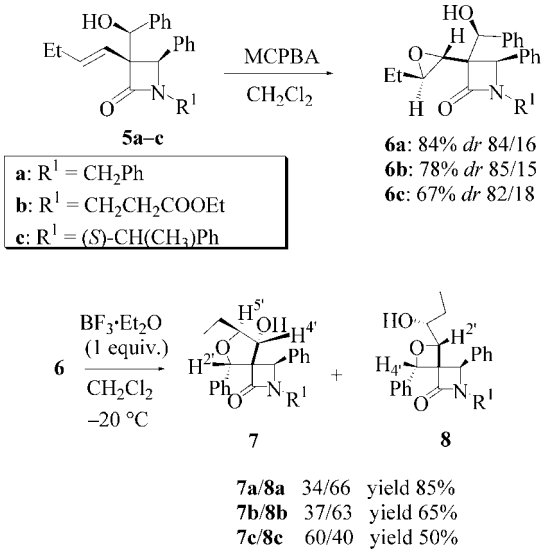
Entry	Start. material	Product **3**	% Yield[a]	Regioisomeric ratio[b] **3/4**
1	**2a**		80	90/10
2	**2b**		75	>99/1
3	**2c**		60	72/28
4	**2d**		57	90/10

[a] Yields correspond to products isolated by flash chromatography on silica gel. [b] Product distribution was determined by ^1H NMR integration at 300 MHz on the crude mixture and confirmed by isolation of pure compounds.

On the other hand, the regioselectivity of the ring-closure is strongly influenced by the stereochemistry of the starting epoxide, as shown by further examples that we have examined.

Treatment of **5a**–**c**[9] with MCPBA (Scheme 2) afforded the *trans*-epoxides **6a**–**c** in high diastereomeric ratios. In the presence of one equivalent of $BF_3{\cdot}Et_2O$ in CH_2Cl_2,[11] the intramolecular ring-opening reaction of **6a** worked very well at –20 °C, affording the spiroderivatives **7a** and **8a** in a 34:66 regioisomeric ratio and in 85% yield. On repetition of the same reaction with **6b**, the spiro derivatives **7b** and

8b were obtained in a 37:63 ratio. The boron-catalysed intramolecular ring-opening of enantiomerically pure **6c** performed at –20 °C occurred with low regioselectivity, but in this case the major product was the tetrahydrofuran **7c** (**7c**/**8c** = 60:40) (Scheme 2). The same reaction performed at +40 °C gave enhanced regioselectivity, affording **7c** and **8c** in an 80:20 ratio.



Scheme 2. $BF_3{\cdot}Et_2O$-induced ring-opening of epoxide **6**.

In order to evaluate the dependence of the regiochemistry on the temperature, **6a** was treated under different conditions. Although the total yields of **7a** and **8a** remained more or less unchanged over the –20 to +40 °C range, the regioisomeric ratio was strongly enhanced in favour of **7a** (Table 2).

Table 2. Dependence of the regioselectivity of the reaction of **6a** on the temperature.

Entry[a]	Temp. (°C)	Yield (%)	**7a/8a**
1	–40	–	–
2	–20	85%	34:66
3	+20	>95%	57:43
4	+40	>95%	73:27

[a] The reaction was performed in CH_2Cl_2 in the presence of 1 equiv. of $BF_3{\cdot}Et_2O$ and was stopped after 1 hour.

The relative configurations of the stereocenters in **7a** were assigned by NOESY-1D-DPFGSE.[12] Irradiation of the $H^{4'}$ proton resulted in the major enhancement of $H^{2'}$, suggesting a *cis* relationship between the two protons, while a minor enhancement with the vicinal $H^{5'}$ was observed; no enhancement of the $H^{5'}$ signal could be observed upon irradiation of $H^{2'}$ (Figure 2). The *trans* relationship between $H^{4'}$ and $H^{5'}$, originating from an *exo* attack on the starting epoxide, was confirmed by the ^1H NMR coupling constant ($J_{1,2}$ = 3.3 Hz).[14]

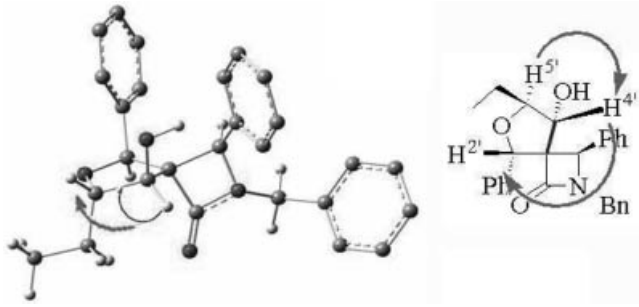


Figure 2. NOESY-1D enhancements for compound **7a**.

From these observations, the relative (4*R**,2′*S**,4′*R**,5′*S**) configuration, as shown in Figure 2 could be attributed to the tetrahydrofuran derivative **7a**. The tetrahydrofuran ring had arisen from the intramolecular ring-opening of the epoxide, which had occurred with inversion of configuration, so the correct relative configuration of **7a** allowed the (1′*R**,2′*R**) relative configuration to be assigned to the stereocenters in the starting epoxide **6a**. The complete regularity in the chemical shifts of the starting epoxides and of the products allowed the absolute configurations to be attributed to **6c**, **7c** and **8c**.[13]

The facility of intramolecular hydroxy participation in epoxide ring-opening is well established[14] and the ring sizes of the newly formed heterocycles, originating from *exo* or *endo* attack, strongly depend on a variety of factors. Examination of models of the two complexes between epoxides **2** and **6** and boron trifluoride[15] revealed that the high regioselectivity of the reaction of **2** could be attributed to the fulfilment of the "collinearity requirement" between the nucleophilic hydroxy group and the C–O bond destined to be broken, as proposed by Stork and co-workers.[16] The collinear arrangement for the intramolecular cyclization resulting in tetrahydrofuran **4** is difficult to achieve, while no distortion is required for the collinear approach for the formation of oxetane spiro derivative **3**. In contrast, examination of the **6**/BF_3 complex shows that only a slight distortion is required for hydroxy approach both to C2′ and to C1′. This small difference between the two pathways accounts for the lower regioselectivity and for the dependence of the mixture compositions on slight changes in reaction temperature (Figure 3).[11]

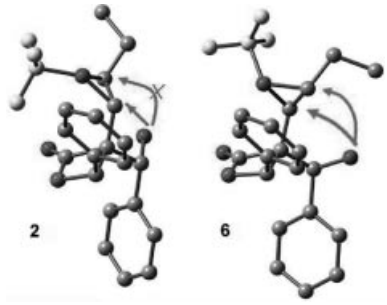


Figure 3. Complexes of epoxides **2** and **6** with boron trifluoride.

Conclusions

In pursuing our research on polyfunctionalized β-lactams as potential inhibitors of cholesterol absorption, we have developed the synthesis of 3-oxiranylazetidin-2-ones in highly stereoselective fashion. The intramolecular ring-opening of β-hydroxy epoxides allowed unprecedented classes of spiro-lactams to be obtained. Oxetane derivatives were obtained as major products from starting epoxides **2a**–**d**, either at room temperature or at low temperature. The same treatment of epoxides **6a**–**c** gave mixtures of oxetanes and terahydrofurans, the compositions of which depended on the reaction temperature. The methodology reported here allowed several moieties linked to the lactam scaffold to be introduced and polyfunctionalized compounds with defined stereochemistry to be obtained by choice of suitable starting materials and reaction conditions. In view of the novel applications of β-lactams, these new structures could represent an interesting class of bioactive compounds. Moreover, these particular spiro-β-lactams are conformationally constrained and for this reason could be usable as scaffolds in the design of medicinally relevant peptidomimetics.

Experimental Section

General: Unless stated otherwise, solvents and chemicals were obtained from commercial sources and were used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). NMR spectra were recorded with 300 or 600 MHz spectrometers. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of $CDCl_3$, set at δ = 7.27 (^{1}H NMR) or δ = 77.0 ppm (^{13}C NMR). Infrared spectra were recorded with an FT-IR spectrometer. Melting points are uncorrected. Microanalyses were performed with a FISONS EA 1108 CHNS-O Instrument. MS analyses were performed on a liquid chromatograph coupled with an electrospray ionization-mass spectrometer (LC-ESI-MS), with H_2O/CH_3CN as solvent at 25 °C (positive scan, *m*/*z* 100–500, fragmentor 70 V). Preparative HPLC separations were performed on a Zorbax Eclipse XDB-C18 PrepHT column (21.2 × 150 mm, particle size 7 μm, flow 12 mL min^{-1}) with water/acetonitrile 30:70 as eluting mixture. Retention factors (R_f) are relative to thin layer chromatography (TLC) performed on plastic sheets coated with silica gel 60-F_{254}, with a 1:1 cyclohexane/ethyl acetate mixture as eluent. Complete characterization for compounds **1a**–**d** and **5a**–**c** is reported in ref.[9a].

Full geometry optimizations were performed with the Gaussian03 package of programs at the DFT B3LYP-STO-3G2 level in order to achieve initial geometries, which were used to generate atomic "am1bcc" charges by use of the "antechamber"3 module in Amber 8.04. MM geometry optimization by use of the GAFF (Generalized Amber Force Field) in the "sander" module of Amber 8.0 was then applied.

General Procedure for the Preparation of Epoxides 2 and 6: *m*-Chloroperbenzoic acid (1.5 mmol, 1.5 equiv., 336 mg of commercial product, 77% purity) was added in one portion to a solution of **1** or **5** (1 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred overnight at room temp. under inert atmosphere and was then diluted with CH_2Cl_2 (10 mL). After having been washed twice with a saturated solution of K_2CO_3 (2 × 10 mL), the organic layer was separated and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The products were purified by preparative HPLC with a Chiralcel OD column [cellulose tris(3,5-dimethylphenylcarbamate) coated on 10 μm silica gel, hexane/*i*PrOH, 9:1, as eluent] or a Chiralcel OJ column [cellulose tris(4-methylbenzoate) coated on 10 μm silica gel, hexane/*i*PrOH, 9:1, as eluent].

Compound 2a: Yield 64% (265 mg), *dr* 85:15, major isomer, yellow oil; R_f = 0.50. ^{1}H NMR ($CDCl_3$): δ = 0.73 (t, ^1J = 7.5 Hz, 3 H, CH_3), 0.90–1.00 (m, 2 H, CH_2CH_3), 1.85 (d, ^1J = 2.1 Hz, 1 H, C*CH*O), 3.25–3.29 (m, 1 H, CH_2CHO), 4.11 (d, ^1J = 15.3 Hz, 1 H, CH_2Ph), 5.05 (d, ^1J = 15.3 Hz, 1 H, CH_2Ph), 5.12 (s, 1 H, N*CH*Ph), 5.48 (s, 1 H, *CH*OH), 6.86–6.89 (m, 2 H, Ph), 7.20–7.40 (m, 11 H, Ph), 7.50–7.60 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.5, 24.4, 44.8, 56.7, 57.2, 59.5, 68.2, 71.5, 127.0, 127.2, 127.5, 127.8, 128.1, 128.4, 128.5, 128.6, 128.8, 133.4, 134.9, 140.0, 169.7 ppm. IR (neat): $\tilde{\nu}$ = 3400, 3063, 3032, 2969, 2924, 1737, 1496, 1454, 1409, 1353, 1287, 1264 cm^{-1}. LC-ESI-MS room temp. 14.2 min, *m*/*z* 414 [M + 1], 436 [M + Na]. $C_{27}H_{27}NO_3$ (413.51): calcd. C 78.42, H 6.58, N 3.39; found C 78.51, H 6.49, N 3.18.

Compound 2b: Yield 70% (296 mg), *dr* 86:14, major isomer, yellow oil; R_f = 0.29. ^{1}H NMR ($CDCl_3$): δ = 0.71 (t, ^1J = 7.5 Hz, 3 H, $CHCH_2CH_3$), 1.20–1.30 (m, 2 H, $CHCH_2CH_3$), 1.25 (t, ^1J = 6.9 Hz, 3 H, OCH_2CH_3), 1.79 (d, ^1J = 2.4 Hz, 1 H, C*CH*O), 2.60–2.70 (m, 2 H, CH_2CO), 3.13–3.17 (m, 1 H, CH_2N), 3.27–3.38 (m, 1 H, CH_2CHO), 3.88–3.97 (m, 1 H, CH_2N), 4.11 (q, ^1J = 6.9 Hz, 2 H, OCH_2CH_3), 5.17 (s, 1 H, N*CH*Ph), 5.37 (s, 1 H, *CH*OH), 6.93 (d, ^1J = 7.5 Hz, 2 H, Ph), 7.20–7.40 (m, 6 H, Ph), 7.64 (d, ^1J = 6.9 Hz, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.3, 14.0, 24.2, 32.6, 36.6, 56.3, 57.6, 59.2, 60.9, 67.8, 71.5, 126.6, 126.7, 128.0, 128.1, 128.3, 128.6, 135.0, 139.6, 169.1, 171.3 ppm. IR (neat): $\tilde{\nu}$ = 3422, 2963, 2910, 2851, 1749, 1643, 1460, 1383, 1260, 1024 cm^{-1}. LC-ESI-MS room temp. 12.6 min, *m*/*z* 424 [M + 1], 446 [M + Na]. $C_{25}H_{29}NO_5$ (423.5): calcd. C 70.90, H 6.90, N 3.31; found C 71.02, H 6.86, N 3.58.

Compound 2c: Yield 68% (290 mg), *dr* 83:17, major isomer, yellow oil; R_f = 0.55. [*a*] = –80.0 (*c* = 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.74 (t, ^1J = 7.5 Hz, 3 H, CH_2CH_3), 0.84–0.96 (m, 2 H, CH_2CH_3), 1.75 (d, ^1J = 2.1 Hz, 1 H, C*CH*O), 1.84 (d, ^1J = 7.0 Hz, 3 H, $CHCH_3$), 3.22–3.26 (m, 1 H, CH_2CHO), 4.58 (q, ^1J = 7.0 Hz, 1 H, $CHCH_3$), 4.97 (s, 1 H, N*CH*Ph), 5.38 (s, 1 H, *CH*OH), 6.64–6.77 (m, 2 H, Ph), 7.10–7.40 (m, 11 H, Ph), 7.57 (d, ^1J = 7.2 Hz, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.3, 20.0, 24.3, 54.2, 56.6, 56.8, 59.1, 66.8, 71.7, 126.7, 126.8, 126.9, 127.1, 127.5, 127.74, 127.9, 128.2, 128.4, 135.0, 139.8, 140.9, 169.0 ppm. IR (neat): $\tilde{\nu}$ = 3405, 3063, 3028, 2975, 2927, 1737, 1655, 1454, 1378, 1354, 1053 cm^{-1}. LC-ESI-MS room temp. 14.7 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 78.20, H 6.63, N 3.25.

Compound 2d: Yield 68% (289 mg), *dr* 83:17, major isomer, sticky oil; R_f = 0.60. [*a*] = +44.5 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.74 (t, ^1J = 7.5 Hz 3 H, CH_2CH_3), 1.2–1.4 (m, 2 H, CH_2CH_3), 1.60 (d, ^1J = 7.2 Hz 3 H, $CHCH_3$), 1.80 (d, ^1J = 2.2 Hz, 1 H, C*CH*O), 3.20–3.28 (m, 1 H, CH_2CHO), 4.84 (q, ^1J = 7.2 Hz, 1 H, $CHCH_3$), 5.00 (s, 1 H, N*CH*Ph), 5.36 (s, 1 H, *CH*OH), 6.80–6.90 (m, 2 H, Ph), 7.22–7.65 (m, 13 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.3, 20.2, 24.3, 54.2, 56.5, 58.0, 59.3, 66.5, 71.7, 127.2, 127.3, 127.4, 127.5, 128.1, 128.2, 128.3, 128.4, 133.06, 135.9, 139.5, 167.1 ppm. IR (neat): $\tilde{\nu}$ = 3423, 3062, 3032, 2977, 2934, 1734, 1495, 1454, 1379, 1354, 1265, 1109, 1066, 1027 cm^{-1}. LC-ESI-MS room temp. 15.2 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 79.00, H 6.77, N 3.46.

Compound 6a: Yield 84% (346 mg), *dr* 84:16, major isomer, yellow oil; R_f = 0.43. ^{1}H NMR ($CDCl_3$): δ = 0.82 (t, ^1J = 7.5 Hz, 3 H, CH_2CH_3), 1.0–1.2 (m, 2 H, CH_2CH_3), 2.69 (d, ^1J = 2.4 Hz, 1 H, CCHO), 3.34–3.38 (m, 1 H, CH_2CHO), 3.79 (d, ^1J = 15.0 Hz, 1 H, CH_2Ph), 4.66 (s, 1 H, NCHPh), 4.75 (d, ^1J = 15.0 Hz, 1 H, CH_2Ph), 5.33 (s, 1 H, CHOH), 6.34 (d, ^1J = 7.2 Hz, 2 H, Ph), 7.00–7.60 (m, 13 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.5, 24.5, 44.0, 57.3, 57.4, 58.9, 67.5, 72.3, 127.2, 127.4, 127.5, 128.0, 128.1, 128.3, 128.5, 128.6, 128.8, 134.0, 135.0, 139.2, 167.1 ppm. IR (neat): $\tilde{\nu}$ = 3436, 3059, 3025, 2959, 2926, 1733, 1487, 1460, 1408, 1355, 1262 cm^{-1}. LC-ESI-MS room temp. 13.7 min, *m*/*z* 414 [M + 1], 436 [M + Na]. $C_{27}H_{27}NO_3$ (413.51): calcd. C 78.42, H 6.58, N 3.39; found C 78.28, H 6.70, N 3.26.

Compound 6b: Yield 78% (330 mg), *dr* 85:15, major isomer, yellow oil; R_f = 0.22. ^{1}H NMR ($CDCl_3$): δ = 0.83 (t, ^1J = 7.5 Hz, 3 H, CH_2CH_3), 1.18 (t, ^1J = 6.9 Hz, 3 H, OCH_2CH_3), 1.20–1.40 (m, 2 H, CH_2CH_3), 1.59–1.67 (m, 1 H, CH_2CO), 1.79–1.89 (m, 1 H, CH_2CO), 2.63 (d, ^1J = 2.4 Hz, 1 H, CCHO), 2.90–3.00 (m, 1 H, CH_2N), 3.31–3.34 (m. 1 H, CH_2CHO), 3.59–3.68 (m, 1 H, CH_2N), 3.99 (q, ^1J = 6.9 Hz, 2 H, OCH_2CH_3), 4.87 (s, 1 H, NCHPh), 5.29 (s, 1 H, CHOH), 7.25–7.45 (m, 8 H, Ph), 7.63 (d, ^1J = 6.9 Hz, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.4, 14.0, 24.4, 32.0, 35.5, 56.5, 58.4 (2 C), 60.6, 67.3, 72.5, 126.8, 127.2, 127.4, 128.2, 128.5, 128.9, 135.1, 138.5, 164.2, 167.1 ppm. IR (neat): $\tilde{\nu}$ = 3439, 3032, 2973, 2936, 1735, 1495, 1454, 1377, 1195, 1048, 1028 cm^{-1}. LC-ESI-MS room temp. 12.0 min, *m*/*z* 424 [M + 1], 446 [M + Na]. $C_{25}H_{29}NO_5$ (423.5): calcd. C 70.90, H 6.90, N 3.31; found C 70.68, H 7.02, N 3.17.

Compound 6c: Yield 67% (286 mg), *dr* 82:18, major isomer, white solid, m.p. 118–120 °C; R_f = 0.55. [*a*] = –13.6 (*c* = 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, ^1J = 7.5 Hz, 3 H, CH_2CH_3), 0.94–1.06 (m, 2 H, CH_2CH_3), 1.43 (d, ^1J = 7.2 Hz, 3 H, $CHCH_3$), 2.61 (d, ^1J = 1.8 Hz, 1 H, CCHO), 3.30–3.40 (m, 1 H, CH_2CHO), 4.39 (q, ^1J = 7.2 Hz, 1 H, $CHCH_3$), 4.62 (s, 1 H, NCHPh), 5.26 (s, 1 H, CHOH), 6.64 (d, ^1J = 7.0 Hz, 2 H, Ph), 7.00–7.50 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.4, 19.3, 24.4, 53.9, 57.0, 57.7, 58.2, 66.0, 72.6, 126.7, 127.1, 127.3, 127.4, 127.9, 128.1, 128.3, 128.4, 135.0, 138.8, 140.0, 166.9 ppm. IR (neat): $\tilde{\nu}$ = 3412, 3032, 2966, 2927, 1733, 1495, 1378, 1261, 1051, 1027 cm^{-1}. LC-ESI-MS room temp. 14.7 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 78.62, H 6.99, N 3.11.

General Procedure for the Intramolecular Ring Opening of Epoxides 2 and 6: $BF_3{\cdot}Et_2O$ (1.1 mmol, 1.1 equiv., 156 mg, 0.139 mL) was added in one portion to a solution of epoxide **2** or **6** (1 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at the temperature of choice for 1 h and was then diluted with CH_2Cl_2 (5 mL). After having been washed twice with water, the organic layer was separated and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The products were purified by flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 50:50).

Yield **3a** + **4a** = 80%, *dr* **3a/4a** = 90:10.

Compound 3a: 297 mg, yellow oil; R_f = 0.27. ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.04–2.09 (m, 1 H, CH_2CH_3), 2.20–2.24 (m, 1 H, CH_2CH_3), 2.83–2.86 (m, 1 H, CHOH), 3.50 (d, ^1J = 11.4 Hz, 1 H, $CHCHO$), 3.59 (d, ^1J = 15.6 Hz, 1 H, CH_2Ph), 4.58 (s, 1 H, NCHPh), 4.63 (d, ^1J = 15.6 Hz, 1 H, CH_2Ph), 5.41 (s, 1 H, OCHPh), 6.84 (d, ^1J = 7.8 Hz, 1 H, Ph), 6.90–6.92 (m, 2 H, Ph), 7.10–7.13 (m, 1 H, Ph), 7.20–7.33 (m, 9 H, Ph), 7.43 (d, ^1J = 6.6 Hz, 2 H, Ph) ppm. ^{13}C NMR: δ = 9.4, 18.2, 42.8, 43.5, 56.4, 65.8, 72.7, 74.0, 126.3, 126.5, 127.4, 128.0, 128.3, 128.5, 128.6, 128.9, 130.0, 134.7, 139.0, 139.6, 169.4 ppm. IR (neat): $\tilde{\nu}$ = 3337, 3018, 2972, 2919, 1719, 1620, 1487, 1461, 1408, 1334, 1261, 1070 cm^{-1}. LC-ESI-MS room temp. 12.4 min, *m*/*z* 414 [M + 1], 436 [M + Na]. $C_{27}H_{27}NO_3$ (413.51): calcd. C 78.42, H 6.58, N 3.39; found C 78.31, H 6.79, N 3.14.

Compound 4a: 33 mg, white oil; R_f = 0.44. ^{1}H NMR ($CDCl_3$): δ = 1.06 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 2.06–2.32 (m, 2 H, CH_2CH_3), 3.53 (d, ^1J = 15.4 Hz, 1 H, CH_2Ph), 3.87 (m, 1 H, CH_2CHO), 4.21 (s, 1 H, NCHPh), 4.33 (br s, 1 H, CHOH), 4.72 (d, ^1J = 15.4 Hz, 1 H, CH_2Ph), 5.27 (s, 1 H, OCHPh), 6.21 (d, ^1J = 7.0 Hz, 2 H, Ph), 6.98–7.60 (m, 13 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.5, 25.1, 43.0, 57.2, 75.1, 76.2, 82.2, 88.4, 127.2, 127.5, 128.2, 128.5, 128.6, 128.7, 129.4, 129.9, 134.3, 135.2, 135.9, 169.3 ppm. IR (neat): $\tilde{\nu}$ = 3398, 3057, 2957, 2922, 1750, 1672, 1655, 1490, 1454, 1407 cm^{-1}. LC-ESI-MS room temp. 13.8 min, *m*/*z* 414 [M + 1], 436 [M + Na]. $C_{27}H_{27}NO_3$ (413.51): calcd. C 78.42, H 6.58, N 3.39; found C 78.55, H 6.51, N 3.48.

Yield **3b** + **4b** = 75%, *dr* **3b/4b** > 99:1.

Compound 3b: 318 mg, sticky oil; R_f = 0.10. ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, ^1J = 7.4 Hz, 3 H, CH_2CH_3), 1.26 (t, ^1J = 7.0 Hz, 3 H, OCH_2CH_3), 2.0–2.3 (m, 2 H, CH_2CH_3), 2.3–2.5 (m, 2 H, CH_2CO), 2.83 (m, 1 H, CHOH), 3.02 (m, 1 H, NCH_2), 3.38–3.49 (m, 2 H, $CHCHO$, NCH_2), 4.10 (q, ^1J = 7.0 Hz, 2 H, OCH_2CH_3), 4.75 (s, 1 H, NCHPh), 5.43 (s, 1 H, OCHPh), 7.2–7.5 (m, 10 H, Ph) ppm. ^{13}C NMR: δ = 8.9, 13.7, 17.8, 32.4, 35.1, 42.4, 56.9, 60.4, 65.4, 71.8, 73.0, 126.2, 126.8, 127.9, 128.1, 128.5, 129.6, 131.3, 139.1, 164.1, 170.7 ppm. IR (neat): $\tilde{\nu}$ = 3439, 3056, 3034, 2960, 2924, 1724, 1451, 1377, 1192, 1043 cm^{-1}. LC-ESI-MS room temp. 10.7 min, *m*/*z* 424 [M + 1], 446 [M + Na]. $C_{25}H_{29}NO_5$ (423.5): calcd. C 70.90, H 6.90, N 3.31; found C 71.01, H 6.79, N 3.52.

Yield **3c** + **4c** = 60%, *dr* **3c/4c** = 72:28.

Compound 3c: 185 mg, sticky oil; R_f = 0.36. [*a*] = +25.5 (*c* = 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, ^1J = 7.4 Hz, 3 H, CH_2CH_3), 1.61 (d, ^1J = 7.2 Hz, 3 H, $CHCH_3$), 1.98–2.22 (m, 2 H, CH_2CH_3), 2.84 (m, 1 H, CHOH), 3.43 (d, ^1J = 11.2 Hz, 1 H, $CHCHO$), 3.50 (q, ^1J = 7.2 Hz, 1 H, $CHCH_3$), 4.59 (s, 1 H, NCHPh), 5.40 (s, 1 H, OCHPh), 6.8–7.5 (m, 15 H, Ph) ppm. ^{13}C NMR: δ = 9.5, 18.2, 19.9, 42.9, 53.7, 56.2, 64.6, 72.9, 73.8, 126.0, 126.2, 126.3, 126.6, 127.3, 127.4, 128.2, 128.4, 128.5, 128.7, 129.7, 130.0, 131.8, 139.1, 139.7, 140.6, 169.5 ppm. IR (neat): $\tilde{\nu}$ = 3414, 3062, 2970, 2932, 1724, 1493, 1454, 1348, 1043 cm^{-1}. LC-ESI-MS room temp. 13.1 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 78.81, H 6.68, N 3.11.

Compound 4c: 71 mg, white oil; R_f = 0.60. [*a*] = +21.9 (*c* = 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.06 (t, ^1J = 7.6 Hz, 3 H, CH_2CH_3), 1.50 (d, ^1J = 7.2 Hz, 3 H, $CHCH_3$), 1.83–2.0 (m, 1 H, CH_2CH_3), 2.0–2.23 (m, 1 H, CH_2CH_3), 3.87 (m, 1 H, CH_2CHO), 4.07 (s, 1 H, NCHPh), 4.12 (q, ^1J = 7.2 Hz, 1 H, $CHCH_3$), 4.33 (br s, 1 H, CHOH), 5.26 (s, 1 H, OCHPh), 6.35 (d, ^1J = 7.0 Hz, 2 H, Ph), 7.0–7.6 (m, 13 H, Ph) ppm. ^{13}C NMR: δ = 10.5, 20.3, 25.0, 54.3, 57.1, 73.7, 76.0, 82.2, 88.3, 126.3, 127.2, 128.0, 128.2, 128.4, 128.5, 128.8, 129.2, 129.7, 135.6, 135.9, 140.0, 167.2 ppm. IR (neat): $\tilde{\nu}$ = 3352, 3062, 3023, 2968, 2929, 1743, 1494, 1454, 1377, 1026 cm^{-1}. LC-ESI-MS room temp. 15.1 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 78.59, H 6.90, N 3.34.

Yield **3d** + **4d** = 57%, *dr* **3c/4c** = 90:10.

Compound 3d: 219 mg, yellow oil; R_f = 0.38. [*a*] = –10.9 (*c* = 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, ^1J = 7.5 Hz, 3 H, CH_2CH_3), 1.15 (d, ^1J = 7.2 Hz, 3 H, $CHCH_3$), 2.0–2.2 (m, 1 H,

CH_2CH_3), 2.2–2.4 (m, 1 H, CH_2CH_3), 2.90 (m, 1 H, *CH*OH), 3.47 (d, ^1J = 9.3 Hz, 1 H, CH*CH*O), 4.48 (s, 1 H, N*CH*Ph), 4.91 (q, ^1J = 7.2 Hz, 1 H, CHCH_3), 5.36 (s, 1 H, O*CH*Ph), 6.70 (d, ^1J = 8.6 Hz, 1 H, Ph), 6.95–7.45 (m, 14 H, Ph) ppm. ^{13}C NMR: δ = 9.4, 18.0, 18.1, 42.8, 51.1, 56.4, 64.6, 73.2, 74.4, 126.3, 127.3, 127.4, 128.3, 128.5, 128.6, 128.8, 129.8, 132.8, 138.5, 139.6, 161.3 ppm. IR (neat): $\tilde{\nu}$ = 3418, 3064, 3027, 2968, 2930, 1724, 1492, 1452, 1381, 1045 cm^{-1}. LC-ESI-MS room temp. 13.3 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 78.79, H 6.73, N 3.16.

Compound 4d: 26 mg, yellow oil; R_f = 0.59. [*a*] = –21.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.06 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.12 (d, ^1J = 7.2 Hz, 3 H, CHCH_3), 1.8–2.0 (m, 1 H, CH_2CH_3), 2.0–2.2 (m, 1 H, CH_2CH_3), 3.87 (t, ^1J = 7.5 Hz, 1 H, CH_2CHO), 4.18 (s, 1 H, N*CH*Ph), 4.34 (br s, 1 H, *CH*OH), 4.48 (q, ^1J = 7.2 Hz, 1 H, *CH*CH_3), 5.26 (s, 1 H, O*CH*Ph), 6.57 (d, ^1J = 8.4 Hz, 2 H, Ph), 7.0–7.6 (m, 13 H, Ph) ppm. ^{13}C NMR: δ = 10.6, 19.5, 25.2, 52.7, 58.0, 73.5, 76.1, 82.2, 88.5, 127.1, 127.5, 128.2, 128.4, 128.5, 128.7, 128.8, 129.4, 129.7, 135.9, 137.0, 139.1, 167.0 ppm. IR (neat): $\tilde{\nu}$ = 3420, 3065, 3022, 2967, 2931, 1744, 1494, 1454, 1377, 1026 cm^{-1}. LC-ESI-MS room temp. 15.0 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 78.48, H 7.00, N 3.09.

Yield **7a** + **8a** = 85%, *dr* **7a/8a** = 34:66.

Compound 7a: 119 mg, white oil; R_f = 0.51. ^{1}H NMR ($CDCl_3$): δ = 0.99 (t, ^1J = 7.2 Hz, 3 H, CH_2CH_3), 1.71–1.78 (m, 1 H, CH_2CH_3), 1.89–1.96 (m, 1 H, CH_2CH_3), 3.80 (d, ^1J = 15.0 Hz, 1 H, CH_2Ph), 3.96 (m, 1 H, CH_2CHO), 3.97 (s, 1 H, N*CH*Ph), 4.45 (d, ^1J = 3.3 Hz, 1 H, *CH*OH), 4.85 (d, ^1J = 15.0 Hz, 1 H, CH_2Ph), 5.27 (s, 1 H, O*CH*Ph), 6.95 (d, ^1J = 6.0 Hz, 2 H, Ph), 7.08 (d, ^1J = 6.0 Hz, 2 H, Ph), 7.22–7.38 (m, 11 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.1, 24.2, 44.5, 59.7, 73.7, 77.1, 81.8, 87.3, 127.0, 127.7, 128.1, 128.3, 128.4, 128.5, 128.7, 129.0 129.5, 134.9, 135.1, 139.5, 169.2 ppm. IR (neat): $\tilde{\nu}$ = 3421, 3030, 2963, 2923, 1750, 1653, 1496, 1456, 1242 cm^{-1}. LC-ESI-MS room temp. 14.4 min, *m*/*z* 414 [M + 1], 436 [M + Na]. $C_{27}H_{27}NO_3$ (413.51): calcd. C 78.42, H 6.58, N 3.39; found C 78.60, H 6.39, N 3.52.

Compound 8a: 231 mg, white oil; R_f = 0.30. ^{1}H NMR ($CDCl_3$): δ = 1.09 (t, ^1J = 7.2 Hz, 3 H, CH_2CH_3), 2.19–2.26 (m, 1 H, CH_2CH_3), 2.27–2.38 (m, 1 H, CH_2CH_3), 2.90 (m, 1 H, *CH*OH), 3.26 (d, ^1J = 15.6 Hz, 1 H, CH_2Ph), 4.10 (d, ^1J = 11.4 Hz, 1 H, CH*CH*O), 4.37 (s, 1 H, N*CH*Ph), 4.50 (d, ^1J = 15.6 Hz, 1 H, CH_2Ph), 5.71 (s, 1 H, O*CH*Ph), 6.35 (d, ^1J = 6.9 Hz, 2 H, Ph), 6.86 (d, ^1J = 6.9 Hz, 1 H, Ph), 7.09–7.59 (m, 12 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.2, 18.6, 42.7, 55.7, 66.8, 70.4, 70.6, 86.0, 126.3, 126.7, 126.9, 127.2, 127.5, 128.2, 128.5, 128.6, 128.9, 131.4, 139.9, 169.1 ppm. IR (neat): $\tilde{\nu}$ = 3427, 3061, 3020, 2958, 2917, 1730, 1495, 1452, 1043 cm^{-1}. LC-ESI-MS room temp. 12.6 min, *m*/*z* 414 [M + 1], 436 [M + Na]. $C_{27}H_{27}NO_3$ (413.51): calcd. C 78.42, H 6.58, N 3.39; found C 78.71, H 6.39, N 3.46.

Yield **7b** + **8b** = 65%, *dr* **7b/8b** = 37:63.

Compound 7b: 101 mg, sticky oil; R_f = 0.31. ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, ^1J = 7.5 Hz, 3 H, CH_2CH_3), 1.21 (t, ^1J = 7.5 Hz, 3 H, OCH_2CH_3), 1.71–1.80 (m, 1 H, CH_2CH_3), 1.85–1.98 (m, 1 H, CH_2CH_3), 2.41 (m, 2 H, CH_2CO), 3.09–3.19 (m, 1 H, NCH_2), 3.75–3.84 (m, 1 H, NCH_2), 3.97 (m, 1 H, CH_2CHO), 4.04 (q, ^1J = 7.5 Hz, 2 H, OCH_2CH_3), 4.19 (s, 1 H, N*CH*Ph), 4.43 (br s, 1 H, *CH*OH), 5.32 (s, 1 H, O*CH*Ph), 7.1–7.5 (m, 10 H, Ph) ppm. ^{13}C NMR: δ = 10.1, 21.0, 24.4, 32.6, 36.1, 60.4, 60.8, 70.1, 73.6, 87.2, 126.6, 127.0, 127.1, 127.4, 128.1, 128.3, 128.6, 128.9, 129.1, 129.5, 130.5, 139.6, 169.2, 171.1 ppm. IR (neat): $\tilde{\nu}$ = 3396, 2962, 2923, 1729, 1655, 1451, 1372, 1188 cm^{-1}. LC-ESI-MS room temp. 12.7 min, *m*/*z* 424 [M + 1], 446 [M + Na]. $C_{25}H_{29}NO_5$ (423.5): calcd. C 70.90, H 6.90, N 3.31; found C 70.84, H 7.02, N 3.08.

Compound 8b: 172 mg, sticky oil; R_f = 0.09. ^{1}H NMR ($CDCl_3$): δ = 1.06 (t, ^1J = 7.2 Hz, 3 H, CH_2CH_3), 1.21 (t, ^1J = 7.0 Hz, 3 H, OCH_2CH_3), 1.70–1.90 (m, 2 H, CH_2CH_3), 1.95 (m, 2 H, CH_2CO), 2.61–2.76 (m, 1 H, NCH_2), 2.85 (m, 1 H, *CH*OH), 3.14–3.32 (m, 1 H, NCH_2), 3.90–4.20 (m, 3 H, CH*CH*O, OCH_2CH_3), 4.51 (s, 1 H, N*CH*Ph), 5.63 (s, 1 H, O*CH*Ph), 7.0–7.6 (m, 10 H, Ph) ppm. ^{13}C NMR: δ = 9.1, 14.1, 18.5, 32.6, 34.6, 57.1, 60.6, 66.4, 70.1, 71.3, 86.2, 126.2, 126.5, 126.6, 126.7, 127.4, 127.9, 128.2, 128.7, 128.9, 130.5, 138.8, 139.7, 169.5, 170.9 ppm. IR (neat): $\tilde{\nu}$ = 3423, 3051, 3031, 2969, 2928, 1735, 1454, 1376, 1190, 1044 cm^{-1}. LC-ESI-MS room temp. 10.9 min, *m*/*z* 424 [M + 1], 446 [M + Na]. $C_{25}H_{29}NO_5$ (423.5): calcd. C 70.90, H 6.90, N 3.31; found C 70.76, H 6.99, N 3.16.

Yield **7c** + **8c** = 65%, *dr* **7c/8c** = 80:20.

Compound 7c: 222 mg, pale yellow oil; R_f = 0.69. [*a*] = –17.8 (*c* = 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, ^1J = 7.5 Hz, 3 H, CH_2CH_3), 1.93 (d, ^1J = 7.2 Hz, 3 H, CHCH_3), 1.7–2.0 (m, 2 H, CH_2CH_3), 3.91 (s, 1 H, N*CH*Ph), 3.98 (m, 1 H, CH_2CHO), 4.43 (q, ^1J = 7.2 Hz, 1 H, *CH*CH_3), 4.67 (d, ^1J = 5.7 Hz, 1 H, *CH*OH), 5.29 (s, 1 H, O*CH*Ph), 7.0–7.5 (m, 15 H, Ph) ppm. ^{13}C NMR: δ = 10.2, 19.7, 24.0, 54.6, 59.8, 72.8, 82.2, 82.4, 87.7, 126.8, 127.2, 127.7, 128.1, 128.4, 128.5, 128.7, 128.9, 129.4, 135.5, 139.7, 140.8, 169.5 ppm. IR (neat): $\tilde{\nu}$ = 3379, 3065, 3024, 2969, 2922, 1745, 1494, 1450, 1371, 1072 cm^{-1}. LC-ESI-MS room temp. 15.8 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 78.83, H 6.67, N 3.09.

Compound 8c: 55 mg, yellow oil; R_f = 0.38. [*a*] = +25.0 (*c* = 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.08 (t, ^1J = 7.2 Hz, 3 H, CH_2CH_3), 1.40 (d, ^1J = 7.2 Hz, 3 H, CHCH_3), 2.10–2.25 (m, 1 H, CH_2CH_3), 2.25–2.40 (m, 1 H, CH_2CH_3), 2.93 (m, 1 H, *CH*OH), 3.95 (q, ^1J = 7.2 Hz, 1 H, *CH*CH_3), 4.04 (d, ^1J = 11.1 Hz, 1 H, CH*CH*O), 4.31 (s, 1 H, N*CH*Ph), 5.69 (s, 1 H, O*CH*Ph), 6.45 (d, ^1J = 6.9 Hz, 2 H, Ph), 6.74 (d, ^1J = 6.9 Hz, 1 H, Ph), 7.0–7.6 (m, 12 H, Ph) ppm. ^{13}C NMR: δ = 9.2, 18.5, 20.3, 42.8, 53.8, 55.6, 60.4, 65.3, 70.6, 126.1, 126.2, 126.8, 126.9, 127.0, 128.0, 128.3, 128.4, 128.7, 138.9, 139.9, 140.3, 169.1 ppm. IR (neat): $\tilde{\nu}$ = 3420, 3065, 3024, 2962, 2928, 1721, 1494, 1449, 1385, 1042 cm^{-1}. LC-ESI-MS room temp. 13.3 min, *m*/*z* 428 [M + 1], 450 [M + Na]. $C_{28}H_{29}NO_3$ (427.53): calcd. C 78.66, H 6.84, N 3.28; found C 78.49, H 6.71, N 3.45.

Supporting Information (see also the footnote on the first page of this article): Chemical shifts of epoxides **2** and **6** and products **3**, **4**, **7** and **8**.

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