A Solid-Phase Synthesis of Functionalized 6-, 7- and 8-Membered Azacycles via Olefin Metathesis

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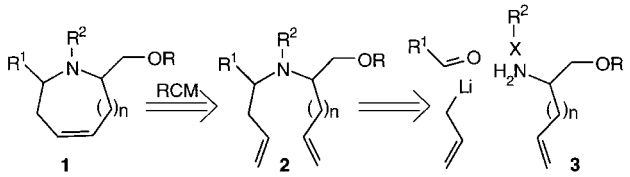
Abstract: A modular solid-phase synthesis of functionalized azacycles is described. The approach is based on a ring-closing metathesis to form heterocycles of different ring sizes. Furthermore, the epoxidation of the primarily formed cyclic double bond has been investigated.

Key words: metathesis, solid-phase synthesis, nitrogen heterocycles, epoxidation

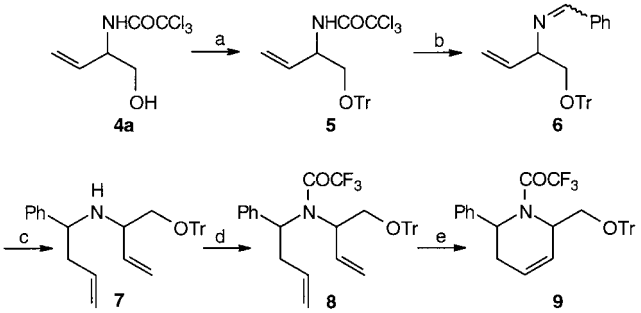
Natural, as well as synthetic, nitrogen heterocycles of different ring sizes represent an important class of bioactive compounds. For example, iminocyclitols are potent inhibitors of glycosidic enzymes, since their protonated forms closely resemble the transition states of the latter.[1] They have also found widespread medical application.[2] Due to their structural diversity iminocyclitols have been the target of considerable synthetic efforts. Recently, efficient syntheses of iminocyclitols[3] and other azacycles[4] employing ring-closing olefin metathesis as the key step have been reported. We wish to present a solid-phase synthesis towards functionalized 6-, 7- and 8[5]-membered azacycles. The modular character of our concept should also enable a combinatorial application.

Olefin metathesis has emerged as a powerful tool in organic synthesis during the last few years, especially because of the development of a new generation of metathesis catalysts which are highly active even in the presence of a wide range of functional groups.[6] A well-established catalyst is Grubbs' ruthenium based $Cl_2(PCy_3)_2Ru{=}CHPh$ (**[Ru]**, Cy = cyclohexyl).[7] Until now only a few authors have described applications of olefin metathesis in combination with solid-phase chemistry.[8] Our retrosynthetic strategy contains a ring-closing olefin metathesis (RCM) as the key step, whereby azacycles **1** are formed from the polymer-supported diolefinic acyclic precursors **2** (Scheme 1). These precursors are readily prepared from olefinic amino alcohols **3**, which are tethered to the solid phase via the alcohol function, an aldehyde R^1-CHO, an allyl anion equivalent and an acyl moiety R^2-X. We decided to use polystyrene/2% divinylbenzene–trityl chloride[9] as the solid support since cleavage conditions are exceptionally mild.



Scheme 1

The viability of the synthetic concept was first confirmed by synthesizing 6-membered compound **9** in solution using trityl chloride as a soluble trityl resin equivalent (Scheme 2). *N*-(Trichloroacetyl)vinylglycinol **4a**, which was easily accessed from (*Z*)-but-2-ene-1,4-diol and trichloroacetonitrile according to established procedures[10] (Scheme 3) was *O*-tritylated to get a solution-phase analog **5** of the corresponding polymer-bound substrate. Cleavage of the trichloroacetamide using KOH/isopropyl alcohol and subsequent formation of the imine **6** with benzaldehyde proceeded quantitatively. Addition of allyllithium to the imine moiety produced the dialkenyl amine **7**.[11] Although olefin metatheses of unprotected amines have been described,[12] we decided to acylate the nitrogen of **7** since metathesis reactions of amides usually proceed more reliably. Moreover, the acylation comprises an additional source for molecular diversity. Consequently, *N*-trifluoroacetylation of **7** gave the olefin metathesis precursor **8**. RCM using 2.5 mol% **[Ru]** proceeded smoothly to give 97% of six-membered **9**. Encouraged by this result, we attempted the synthesis of 6-, 7- and 8-membered azacycles on the solid phase, requiring the synthesis of the homologous *N*-trichloroacetylated amino alcohols **4b** and **4c** (Scheme 3). Reduction of *C*-allylglycine and reaction of the crude amino alcohol with trichloroacetyl chloride yielded **4b** in 62% over two steps. Hex-5-ene-1,2-diol was selectively *O*-monotritylated to give **10**. The secondary hydroxy function was then trans-



(a) TrCl, pyridine, r.t., 12 h (84%); (b) 1. KOH, *i*PrOH, r.t., 1 h; 2. PhCHO, toluene, r.t., 10 min (100%); (c) $CH_2{=}CHCH_2Li$, benzene, r.t., 2 h (91%); (d) TFAA, pyridine, r.t., 5 min (96%); (e) 2.5 mol% [Ru], CH_2Cl_2, reflux (97%)

Scheme 2

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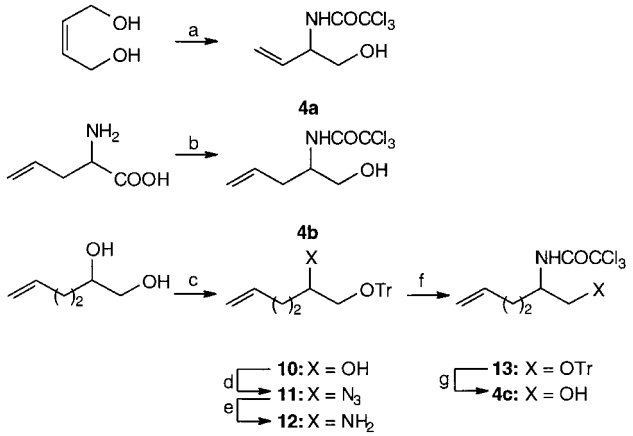


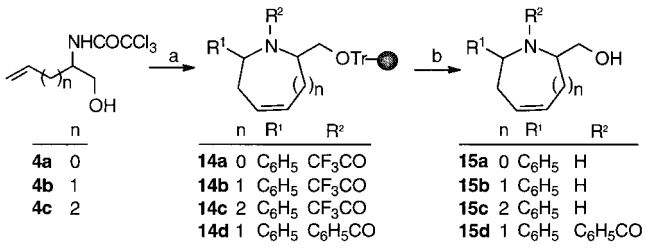
(a) 1. Cl_3CCN, Na (cat,), 70°C, 3 h; 2. tBuPh, reflux, 2 h; (b) 1. $LiAlH_4$, THF, reflux, 4 h; 2. CCl_3COCl, NEt_3, 0°C, 30 min (62%); (c) TrCl, pyridine, 45°C, 12 h (99%); (d) DEAD, PPh_3, $(PhO)_2P(O)N_3$, r.t., 12 h (77%); (e) $LiAlH_4$, THF, reflux, 1 h (73%); (f) CCl_3COCl, tBuOMe, sat. $NaHCO_3$, r.t. (95%); (g) TFA, CH_2Cl_2 (95%)

Scheme 3

formed into azide **11** by a Mitsunobu reaction. Reduction of **11** yielded amine **12**, which was *N*-trichloroacetylated to give **13**. Acidic cleavage of the trityl group afforded **4c** in 51% overall yield starting from hex-5-ene-1,2-diol.

These homologous *N*-acylated amino alcohols **4a–c** were tethered to chlorotrityl resin (approximately 0.6 mmol g^{-1}) (Scheme 4). Cleavage of the trichloroacetyl moieties proceeded smoothly with KOH in a mixture of isopropyl alcohol/dichloromethane (1:3).[13] The polymer-bound amines were reacted with benzaldehyde to the corresponding imines. Subsequent addition of allyllithium resulted in the formation of the solid-phase-bound dialkenyl amines.[11] *N*-Trifluoroacetylation gave the corresponding metathesis precursors. The RCM using 8–15 mol% of **[Ru]** proceeded well to give **14a–c** in good yields (Table). The cyclic products were cleaved by treating the resins with dichloromethane/2% trifluoroacetic acid. The trifluoroacetyl groups were found to be partially removed during cleavage, but treatment of the crude cleavage products with K_2CO_3/MeOH (or KOH/MeOH in the case of **14c**) afforded the amino alcohols **15a–c** as exclusive products.

When using benzoyl chloride instead of trifluoroacetic anhydride as the acylating agent we obtained an acyl residue



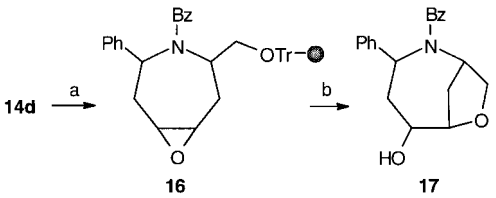
(a) 1. styrene/2% divinylbenzene–TrCl, pyridine, 70°C, 3 h; 2. KOH, iPrOH, CH_2Cl_2, 40 °C, 12 h; 3. R^1-CHO, toluene, r.t., 3 h; 4. CH_2=$CHCH_2Li$, benzene, r.t., 12 h (85–95%); 5. R^2-X (R^2 = acyl), pyridine; 6. **[Ru]**, CH_2Cl_2, reflux; (b) CH_2Cl_2, 2% TFA (85–89%)

Scheme 4

Table Cyclization Reactions on the Solid Phase

Product	[**Ru**][a] mg (mol%)	Yield[b] (%)
14a	30 (15)	85
14b	23 (11)	89
14c	17 (8)	87
14d	30 (15)	88

on the nitrogen, which turned out to be stable to the cleavage procedure as we demonstrated for the 7-membered ring **14d**, thus enabling the solid-phase synthesis of acylated azacycles. The further functionalizability of the polymer-bound metathesis products was exemplarily demonstrated by epoxidation of the double bond of **14d** with Cl_3CCN/H_2O_2[14] to give **16**. For characterization purposes the oxidation product **16** was cleaved using the standard conditions described above. Obviously, acidic cleavage was accompanied by 5-*exo*-*tet*-recyclization of the epoxide, resulting in the formation of bicyclic products **17** in 70% overall yield[15] (Scheme 5). The further functionalization of the solid-phase supported epoxides is currently under investigation in our laboratory.



(a) Cl_3CCN, CH_2Cl_2, H_2O_2, K_2HPO_4, reflux, 3 h; (b) CH_2Cl_2, 2% TFA (70%)

Scheme 5

In summary, we have presented a modular solid-phase synthesis approach towards functionalized azacycles of different ring sizes.

All chemicals were obtained from commercial suppliers, solvents were distilled prior to use. Only if indicated, they were dried as follows. THF: distillation over K; Et_2O: distillation over Na; CH_2Cl_2, pyridine: distillation over CaH_2. The following stationary phases were used for chromatography. TLC: aluminum foils Merck 60 F 254, flash chromatography: 0.0040–0.0063 mm Merck silica. Analytical and semi-preparative HPLC was performed with a Knauer HPLC-64 equipped with a Waters-C18 reverse-phase column (8 mm × 300 mm) using a MeOH/H_2O gradient (50:50 to 95:5 over 25 min, flow rate 2.5 mL min^{-1}) with a mass sensitive Sedere SEDEX-55 Evaporative Light Scattering Detector. The following spectrometers were used to record physical data. NMR: Bruker AM 400 (^{1}H: 400 MHz), Bruker AC 200 (^{13}C: 50 MHz) at 25°C, unless otherwise stated, vs. TMS as external standard. MS and HRMS: Finnigan MAT 95 SQ or Varian MAT 711. MS spectra are EI spectra (70 eV) unless otherwise noted. FAB-MS spectra were recorded using a 3-nitrobenzyl alcohol matrix. IR: Nicolet 750 FT-IR spectrophotometer, resins: in KBr on a Perkin–Elmer IR 881. Mps: Leica Galen III microscope (uncorrected).

2,2,2-Trichloro-*N*-[1-(trityloxymethyl)allyl]acetamide (5)

Alcohol **4a** (3.8 g, 15 mmol) and trityl chloride (4.5 g, 16 mmol) were dissolved in a mixture of CH_2Cl_2 (90 mL) and pyridine

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(3.5 mL). The resulting solution was stirred at r.t. overnight, then washed with 20% aq citric acid (50 mL) and water (25 mL), dried ($MgSO_4$) and evaporated to dryness in vacuo. Recrystallization of the residue from EtOH afforded **5** as colorless crystals (5.8 g, 84%); mp 120 °C.

^{1}H NMR ($CDCl_3$): δ = 3.32 (d, 1H, *J* = 4 Hz, CH_2O), 4.55–4.65 (m, 1H, CH-N), 5.30 (d, 1H, *J* = 10 Hz, C*H*$_2$=CH), 5.32 (d, 1H, *J* = 17 Hz, C*H*$_2$=CH), 5.92 (ddd, 1H, *J* = 17/10/5 Hz, CH_2=C*H*), 7.15 (d, 1H, *J* = 8 Hz, NH), 7.23–7.35 (m, 9H, Ar-*H*), 7.41–7.45 (m, 6H, Ar-*H*).

^{13}C NMR ($CDCl_3$): δ = 53.1 (CH, CH-N), 64.2 (CH_2, CH_2O), 86.5 (C_q, *C*Ph_3), 92.5 (C_q, *C*Cl_3), 116.9 (CH_2, *C*H_2=CH), 127.1 (CH), 127.8 (CH), 128.3 (CH), 134.0 (CH, CH_2=*C*H), 143.1 (C_q), 161.0 (C_q, C=O).

IR (CCl_4): ν = 3430 (N–H), 1725 cm^{-1} (C=O).

Anal. ($C_{25}H_{22}Cl_3NO_2$): calcd: C, 63.24; H, 4.67; N, 2.95. Found: C, 63.70; H, 4.75; N, 2.94.

N-Benzylidene-1-(trityloxy)but-3-en-2-amine (6)

2,2,2-Trichloro-*N*-[1-(trityloxymethyl)allyl]acetamide **(5)** (1.5 g, 3.1 mmol) was added to a solution of KOH (1 g) in *i*PrOH (10 mL) and stirred for 1 h at r.t. The mixture was evaporated to dryness in vacuo, the residue was dissolved in water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to yield 1-(trityloxy)but-3-en-2-amine (1.0 g, 100%) as pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 3.02 (dd, 1H, *J* = 9/8 Hz, CH_2O), 3.17 (dd, 1H, *J* = 9/4.5 Hz, CH_2O), 3.53–3.61 (m, 1H, CH-N), 5.09 (d, 1H, *J* = 10.5 Hz, C*H*$_2$=CH), 5.20 (d, 1H, *J* = 17 Hz, C*H*$_2$=CH), 5.83 (ddd, 1H, *J* = 17/10.5/6 Hz, CH_2=C*H*), 7.21–7.27 (m, 3H, Ar-*H*), 7.28–7.34 (m, 6H, Ar-*H*), 7.43–7.50 (m, 6H, Ar-*H*).

^{13}C NMR ($CDCl_3$): δ = 54.2 (CH, CH-N), 68.2 (CH_2, CH_2O), 86.4 (C_q, *C*Ph_3), 115.0 (CH_2, *C*H_2=CH), 127.0 (CH), 127.8 (CH), 128.6 (CH), 139.5 (CH, CH_2=*C*H), 144.0 (C_q).

MS (FI): *m/z* (%) = 330 (MH^+, 100), 260 (45), 245 (35), 243 (77).

IR (CCl_4): ν = 3393 (N–H), 988, 925 cm^{-1} (Alkene C–H).

Freshly distilled benzaldehyde (840 mg, 7.9 mmol) was added to a solution of crude 1-(trityloxy)but-3-en-2-amine (2.6 g, 7.9 mmol) in toluene (6 mL). After 10 min the volatiles were evaporated in vacuo. To remove residual water, the residue was dissolved twice in toluene (5–6 mL each) and subsequently evaporated to yield **6** (3.3 g, 100%) as a yellow oil.

^{1}H NMR ($CDCl_3$): δ = 3.21 (dd, 1H, *J* = 9/5 Hz, CH_2O), 3.42 (dd, 1H, *J* = 9/9 Hz, CH_2O), 4.06 (ddd, 1H, *J* = 9/6.5/5 Hz, CH-N), 5.13 (ddd, 1H, *J* = 10.5/1.5/1.5 Hz, C*H*$_2$=CH), 5.22 (ddd, 1H, *J* = 17/1.5/1.5 Hz, C*H*$_2$=CH), 6.00 (ddd, 1H, *J* = 17/10.5/6.5 Hz, CH_2=C*H*), 7.10–7.55 (m, 18H, Ar-*H*), 7.62–7.66 (m, 2H, Ar-*H*), 8.43 (s, 1H, Ph-C*H*).

^{13}C NMR ($CDCl_3$): δ = 66.8 (CH_2, CH_2O), 73.4 (CH, CH-N), 86.5 (C_q, *C*Ph_3), 116.4 (CH_2, *C*H_2=CH), 126.9–128.8 (5 CH), 130.7 (CH), 136.4 (C_q), 137.2 (CH, CH_2=*C*H), 144.1 (C_q), 161.6 (C_q, Ph-*C*H).

HRMS (FAB, $C_{30}H_{28}NO$, MH^+): calcd 418.2171, found 418.2171.

IR (film): ν = 1647 (C=N), 922 cm^{-1} (Alkene C–H).

N-(1-Phenylbut-3-enyl)-1-(trityloxymethyl)allylamine (7)

A solution of allyllithium[16] was prepared by addition of PhLi in hexane (3.8 mmol) to a solution of allyltriphenylstannane (1.5 g, 3.8 mmol) in anhyd Et_2O (20 mL) at r.t. under exclusion of moisture and air. After stirring for 20 min the clear supernatant (10 mL) was collected using a syringe, the residue was washed with Et_2O (2 × 10 mL). The combined clear ethereal solutions were added at r.t. to a solution of **6** (460 mg, 1.1 mmol) in anhyd benzene (100 mL). After stirring for 2 h MeOH (1 mL) was added and the mixture was evaporated to dryness in vacuo. The residue was partitioned between water (25 mL) and hexanes (3 × 25 mL), the combined organic layers were dried ($MgSO_4$), the solvent was removed by distillation and the residue was purified by flash chromatography (silica gel, *t*BuOMe/hexanes 3:97) to yield **7** (460 mg, 91%) as a pale yellow oil (inseparable mixture of two diastereomers; ratio 1:4, as determined by ^{1}H NMR).

^{1}H NMR ($CDCl_3$): δ = 2.33–2.43 (m, 2H, Ph-CHCH_2), 3.01–3.19 (m, 3H, C*H*CH_2O,), 3.60 (dd, 0.8H, *J* = 7/7 Hz, Ph-CH_{major}), 3.73 (dd, 0.2H, *J* = 7/7 Hz, Ph-CH_{minor}), 4.93–5.23 (m, 4H, 2 C*H*$_2$=CH), 5.58–5.78 (m, 2H, 2 CH_2=C*H*), 7.16–7.47 (m, 20H, Ar-*H*).

^{13}C NMR (major isomer, $CDCl_3$): δ = *42.9 (CH$_2$, Ph-CH*CH_2), 58.7 (CH), 59.7 (CH), 65.2 (CH_2, CH_2O), 86.4 (C_q, *C*Ph_3), 115.5 (CH_2), 117.6 (CH_2), 126.6–128.8 (6 CH), 135.4 (CH, CH_2=*C*H), 139.4 (CH, CH_2=*C*H), 144.1 (C_q, Trityl), 144.4 (C_q).

HRMS (FAB, $C_{33}H_{33}NO$, M^+): calcd 459.2562, found 459.2562.

IR (CCl_4): ν = 992, 920 cm^{-1} (Alkene C–H).

2,2,2-Trifluoro-*N*-(1-phenylbut-3-enyl)-*N*-[1-(trityloxymethyl)allyl]acetamide (8)

N-(1-Phenylbut-3-enyl)-1-(trityloxymethyl)allylamine **(7)** (460 mg, 1.0 mmol) was dissolved in a mixture of anhyd CH_2Cl_2 (5 mL) and pyridine (1 mL). TFAA (0.26 mL, 1.8 mmol) was added and the mixture was stirred for 5 min, diluted with CH_2Cl_2 (25 mL), washed with 20% aq citric acid (25 mL) and water (10 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel, *t*BuOMe/hexanes 3:97) to yield **8** (530 mg, 96%) as colorless crystals (inseparable mixture of two diastereomers, NMR indicates the presence of rotamers).

^{1}H NMR (DMSO-d_6, 423 K, major isomer): δ = 2.75–2.84 (m, 1H, Ph-CHCH_2), 2.96 (dd, 1H, *J* = 9/5 Hz, CH_2O), 2.97–3.07 (m, 1H, Ph-CHC*H*$_2$), 3.35 (dd, 1H, *J* = 9/7 Hz, CH_2O), 4.26–4.35 (m, 1H, C*H*CH_2O), 4.80–4.99 (m, 1H, Ph-C*H*), 5.03 (d, 1H, *J* = 10 Hz, C*H*$_2$=CH), 5.08 (d, 1H, *J* = 17 Hz, C*H*$_2$=CH), 5.28 (d, 1H, *J* = 10 Hz, C*H*$_2$=CH), 5.29 (d, 1H, *J* = 17 Hz, C*H*$_2$=CH), 5.53–5.76 (m, 1H, CH_2=C*H*), 6.04–6.12 (m, 1H, CH_2=C*H*), 7.10–7.40 (m, 20H, Ar-*H*).

^{13}C NMR ($CDCl_3$, not coalesced): δ = 35.6/38.1 (CH_2, Ph-CH*C*H_2), 59.8/60.1/60.3/60.4/61.3 (2 CH, Ph-*C*H, *C*HCH_2O), 63.3/63.5 (CH_2, CH_2O), 86.2/87.1/87.3 (C_q, *C*Ph_3), 116.6 (q, *J* = 287 Hz, *C*F_3), 117.7–120.1 (2 CH_2, *C*H_2=CH*)*, 126.7–129.0 (CH), 132.7–134.8 (2 CH, CH_2=*C*H), 135.7/135.8 (C_q), 139.3 (C_q), 143.3–143.8 (C_q, Trityl), 155.9 (C_q, q, *J* = 35 Hz, C=O).

HRMS (FAB, $C_{33}H_{33}NO$, M^+): calcd 556.24634, found 556.2463.

IR (film): ν = 1692 (C=O), 1215 (C–F), 993, 926 cm^{-1} (Alkenyl C–H).

Anal. ($C_{35}H_{32}F_3NO_2$): calcd: C, 75.57; H, 5.80; N, 2.52. Found: C, 75.47; H, 5.79; N, 2.55.

2-Phenyl-1-(trifluoroacetyl)-6-(trityloxymethyl)-1,2,3,6-tetrahydropyridine (9)

2,2,2-Trifluoro-*N*-(1-phenylbut-3-enyl)-*N*-[1-(trityloxymethyl)allyl]acetamide **(8)** (87 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (2 mL) under argon. **[Ru]** (3.0 mg, 3.6 μmol) was added and the solution was refluxed overnight. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, *t*BuOMe/hexanes 3:97) to yield **9** (80 mg, 97%) as colorless wax (inseparable mixture of two diastereomers, NMR indicates the presence of rotamers).

^{1}H NMR (C_6D_6, 348 K, major isomer): δ = 2.13–2.25 (m, 1H, H-3a), 2.57–2.75 (m, 1H, H-3b), 3.53 (dd, 1H, *J* = 9/4 Hz, CH_2O), 3.75 (dd, 1H, *J* = 9/5 Hz, CH_2O), 4.78–4.90 (m, 1H, H-6), 5.22–5.30 (m, 1H, H-2), 5.40–5.53 (m, 1H, H-4), 5.75 (ddd, 1H, *J* = 10/7/3 Hz, H-5), 6.90–7.41 (m, 14H, Ar-*H*), 7.50–7.60 (m, 6H, Ar-*H*).

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^{13}C NMR ($CDCl_3$, major isomer): δ = 26.8 (CH_2, C-3), 54.3 (CH, C-2 or C-6), 55.6 (CH, C-2 or C-6), 63.0 (CH_2, CH_2O), 86.8 (C_q, CPh_3), 116.1 (C_q, q, J = 288 Hz, CF_3), 125.4 (CH), 126.8–128.7 (5 CH), 143.3 (C_q), 143.7 (C_q, Trityl).

IR (film): ν = 1688 (C=O), 1209, 1190 cm^{-1} (C–F).

Anal. ($C_{33}H_{28}F_3NO_2$): calcd: C, 75.13; H, 5.35; N, 2.66. Found: C, 75.17; H, 5.41; N, 2.75.

2,2,2-Trichloro-*N*-[1-(hydroxymethyl)but-3-enyl]acetamide (4b)

C-Allylglycine (1.5 g, 13 mmol) was added to a suspension of $LiAlH_4$ (1.2 g, 32 mmol) in THF (50 mL). The resulting mixture was heated under reflux for 4 h. After cooling, Et_2O (150 mL) was added, followed by water (10 mL) until the aluminum salts precipitated. The supernatant was collected and the remainder washed with *t*BuOMe (5 × 100 mL). NEt_3 (5 mL) was added to the combined organic extracts. At 0°C trichloroacetic chloride (3.5 g, 20 mmol) was added slowly. After stirring for another 30 min, the mixture was washed with aq K_2CO_3 (50 mL), 1 M HCl (50 mL) and water (50 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (silica gel, *t*BuOMe/hexanes 1:2) to yield **4b** (1.9 g, 62%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.37–2.51 (m, 2H, CH_2=CHCH_2), 3.74–3.81 (m, 2H, CH_2O), 4.02 (dddd, 1H, J = 17/7.5/7.5/4 Hz, CH-N), 5.17 (br d, 1H, J = 10 Hz, CH_2=CH), 5.19 (br d, 1H, J = 17 Hz, CH_2=CH) 5.81 (dddd, 1H, J = 17/10/7/7 Hz, CH_2=CH), 6.84–7.06 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ = 34.9 (CH_2, CH_2=CHCH_2), 52.5 (CH, CH-N), 62.7 (CH_2, CH_2O), 92.4 (CCl_3), 118.6 (CH_2, CH_2=CH), 133.0 (CH, CH_2=CH), 162.0 (C_q, C=O).

HRMS ($C_6H_7Cl_3NO$, M^+ – CH_2OH): calcd 213.9593, found 213.9589.

IR (film): ν = 3410, 3334 (O–H, N–H), 1695 (C=O), 1042, 921 cm^{-1} (Alkenyl C–H).

1-(Trityloxy)hex-5-en-2-ol (10)

Hex-5-ene-1,2-diol (600 mg, 5.2 mmol) was dissolved in pyridine (5 mL), trityl chloride (1.5 g, 5.3 mmol) was added and the mixture was stirred overnight at 45°C. After distillation in vacuo, the residue was dissolved in water (25 mL) and extracted with *t*BuOMe (3 × 25 mL). The combined organic extracts were washed with 20% aq citric acid (25 mL) and water (25 mL), dried ($MgSO_4$), the solvent was removed, and the residue was purified by flash chromatography (silica gel, *t*BuOMe/hexanes 1:9–1:1) to yield **10** (1.8 g, 99%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.42–1.58 (m, 2H, CH_2), 2.00–2.21 (m, 2H, CH_2=CHCH_2), 2.33 (d, 1H, J = 3.5 Hz, OH), 3.05 (dd, 1H, J = 9.5/7.5 Hz, CH_2O), 3.19 (dd, 1H, J = 9.5/3.5 Hz, CH_2O), 3.77–3.85 (m, 1H, CH-OH), 4.91 (ddd, 1H, J = 10.5/3.5/1 Hz, CH_2=CH), 4.99 (ddd, 1H, J = 17/3.5/2 Hz, CH_2=CH), 5.78 (dddd, 1H, J = 17/10.5/7/7 Hz, CH_2=CHCH$_2$), 7.22–7.34 (m, 9H, Ar-H), 7.42–7.48 (m, 6H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 29.6 (CH_2), 32.4 (CH_2), 67.6 (CH_2, CH_2O), 70.3 (CH, CH-OH), 86.7 (C_q, CPh_3), 114.7 (CH_2, CH_2=CH), 127.0 (CH), 127.8 (CH), 128.6 (CH), 138.2 (CH, CH_2=CH), 143.8 (C_q, Trityl).

MS (FAB): *m/z* (%) = 281 (2), 243 (100).

IR (film): ν = 3426 cm^{-1} (O–H).

5-Azido-6-(trityloxy)hex-1-ene (11)

1-(Trityloxy)hex-5-en-2-ol **(10)** (380 mg, 1.1 mmol) was dissolved in THF (5 mL) and PPh_3 (320 mg, 1.2 mmol) was added. After cooling in an ice bath, DEAD (200 mg, 1.2 mmol) and subsequently diphenylphosphoryl azide (320 mg, 1.2 mmol) were added slowly. This mixture was stirred overnight at r.t. in the darkness. The solvent was removed, and the residue was purified by flash chromatography (silica gel, hexanes/*t*BuOMe 98:2) to yield **11** (310 mg, 77%) as yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.46–1.55 (m, 2H, CH_2, CH_2CH_2CHOH), 1.98–2.16 (m, 2H, CH_2=CHCH_2), 3.15 (dd, 1H, J = 10/7 Hz, CH_2O), 3.21 (dd, 1H, J = 10/4 Hz, CH_2O), 3.39–3.48 (m, 1H, CH-N_3), 4.97 (ddd, 1H, J = 10.5/3.5/2 Hz, CH_2=CH), 4.98 (ddd, 1H, J = 17/3.5/1.5 Hz, CH_2=CH), 5.71 (dddd, 1H, J = 17/10.5/7/6.5 Hz, CH_2=CH), 7.19–7.34 (m, 9H, Ar-H), 7.42–7.49 (m, 6H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 29.9 (CH_2), 30.0 (CH_2), 61.7 (CH, CH-N_3), 66.2 (CH_2, CH_2O), 87.0 (C_q, CPh_3), 115.5 (CH_2, CH_2=CH), 127.0 (CH), 127.8 (CH), 128.6 (CH), 137.1 (CH, CH_2=CH), 143.6 (C_q, Trityl).

IR (film): ν = 2099 cm^{-1} (N_3).

Anal. ($C_{25}H_{25}N_3O$•0.5 H_2O): calcd: C, 76.50; H, 6.68; N, 10.70. Found: C, 76.42; H, 6.75; N, 10.38.

1-(Trityloxy)hex-5-en-2-amine (12)

5-Azido-6-(trityloxy)hex-1-ene **(11)** (3.7 g, 9.6 mmol) was dissolved in anhyd THF (10 mL) and added to a refluxing suspension of $LiAlH_4$ (1.8 g, 48 mmol) in THF (20 mL). After 1 h, the mixture was cooled, and after addition of Et_2O (100 mL), water was added slowly until the white aluminum salts precipitated. The supernatant was collected, the precipitate was extracted with *t*BuOMe (5 × 100 mL). The combined organic layers were evaporated to dryness, and the residue was purified by flash chromatography (silica gel, MeOH/*t*BuOMe/NEt_3 0:99:1–2:97:1) to yield **12** (2.5 g, 73%) as yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.40 (m, 1H, CH_2, CH_2CH_2CHOH), 1.44–1.59 (m, 1H, CH_2, CH_2CH_2CHOH), 1.94–2.14 (m, 2H, CH_2=CHCH_2), 2.90 (dd, 1H, J = 8.5/7 Hz, CH_2O), 2.92–3.00 (m, 1H, CH-N), 3.13 (dd, 1H, J = 8.5/4 Hz, CH_2O), 4.93 (dm, 1H, J = 10 Hz, CH_2=CH), 4.97 (dm, 1H, J = 18 Hz, CH_2=CH), 5.76 (dddd, 1H, J = 18/10/13/3 Hz, CH_2=CH), 7.21–7.33 (m, 9H, Ar-H), 7.41–7.43 (m, 6H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 30.2 (CH_2), 33.4 (CH_2), 50.9 (CH, CH-N), 68.5 (CH_2, CH_2O), 86.3 (C_q, CPh_3), 114.6 (CH_2, CH_2=CH), 126.9 (CH), 127.7 (CH), 128.6 (CH), 138.3(CH, CH_2=CH), 144.1 (C_q, Trityl).

IR (film): ν = 995 cm^{-1} (Alkenyl C–H).

2,2,2-Trichloro-*N*-[1-(trityloxymethyl)pent-4-enyl]acetamide (13)

1-(Trityloxy)hex-5-en-2-amine **(12)** (90 mg, 0.25 mmol) was dissolved at r.t. in a mixture of *t*BuOMe (2 mL) and aq $NaHCO_3$ (5 mL). Trichloroacetyl chloride (70 mg, 0.38 mmol) was added slowly under vigorous stirring. After no starting material was detectable by TLC, the mixture was extracted with *t*BuOMe (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$), the solvent was removed in vacuo and the residue was purified by flash chromatography (silica gel, *t*BuOMe/hexanes 1:1) to yield **13** (120 mg, 95%) as colorless crystals; mp 88–91°C (hexanes).

^{1}H NMR ($CDCl_3$): δ = 1.72–1.89 (m, 2H, CH_2, CH_2CH_2CHOH), 1.98–2.08 (m, 2H, CH_2=CHCH_2), 3.18 (dd, 1H, J = 10/4 Hz, CH_2O), 3.29 (dd, 1H, J = 10/4 Hz, CH_2O), 3.98–4.09 (m, 1H, CH-N), 4.97 (br d, 1H, J = 11 Hz, CH_2=CH), 4.98 (br d, 1H, J = 17 Hz, CH_2=CH), 5.77 (dddd, 1H, J = 17/11/7/6 Hz, CH_2=CH), 7.19–7.34 (m, 9H, Ar-H), 7.36–7.43 (m, 6H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 30.0 (CH_2), 30.9 (CH_2), 51.2 (CH, CH-N), 63.7 (CH_2, CH_2O), 86.6 (C_q, CPh_3), 92.8 (C_q, CCl_3), 115.6 (CH_2, CH_2=CH), 127.2 (CH), 127.9 (CH), 128.5 (CH), 137.1 (CH, CH_2=CH), 143.4 (C_q, Trityl), 161,2 (C_q, C=O).

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MS (FAB): *m/z* (%) = 501 (M^+, 1 isotope, 100).

IR (film): ν = 3343 (N–H), 1705 cm^{-1} (C=O).

2,2,2-Trichloro-*N*-[1-(hydroxymethyl)pent-4-enyl]acetamide (4c)

TFA (3.6 g, 32 mmol) was added to a solution of **13** (3.2 g, 6.4 mmol) in CH_2Cl_2 (15 mL). After 10 min MeOH (3 mL) and water (20 mL) were added and the mixture was stirred for another 30 min. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ (25 mL). The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated and the residue was purified by flash chromatography (silica gel, *t*BuOMe/hexanes 1:1–1:0) to yield **4c** (1.6 g, 95%) as colorless crystals, mp 46–50 °C (hexanes).

^1H NMR ($CDCl_3$): δ = 1.72–1.79 (m, 2H, CH_2, CH_2CH_2CHOH), 1.98 (br s, 1H, OH), 2.12–2.19 (m, 2H, CH_2=$CHCH_2$), 3.73 (dd, 1H, *J* = 11/4 Hz, CH_2O), 3.79 (dd, 1H, *J* = 11/4 Hz, CH_2O), 3.94–4.03 (m, 1H, CH-N), 5.02 (ddd, 1H, *J* = 10/3/1.5 Hz, CH_2=CH), 5.07 (ddd, 1H, *J* = 17/3/1.5 Hz, CH_2=CH), 5.81 (dddd, 1H, *J* = 17/10/7.5/7.5 Hz, CH_2=CH), 6.92 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.8 (2 CH_2), 52.8 (CH, CH-N), 63.4 (CH_2, CH_2O), 92.5 (C_q, CCl_3), 115.6 (CH_2, CH_2=CH), 137.0 (CH, CH_2=CH), 162.1 (C_q, C=O).

IR (film): ν = 3410, 3329 (O–H, N–H), 1693 cm^{-1} (C=O).

Anal. ($C_8H_{12}Cl_3NO_2$): calcd: C, 36.88; H, 4.64; N, 5.38. Found: C, 37.15; H, 4.69; N, 5.39.

Attachment of 4a–c to Chlorotrityl Resin; General Procedure

Chlorotrityl resin (1 g) was swollen in a solution of benzene (4 mL) and pyridine (1 mL). After addition of **4a**, **4b** or **4c** (0.6 mmol) the mixture was shaken at 70 °C for 3 h. MeOH (0.5 mL) was added and shaking was continued at 70 °C for 2 h. The mixture was filtered off, washed with MeOH, CH_2Cl_2 and Et_2O (3 × 10 mL each) and dried in vacuo. For all of **4a–c** the loading was found to be approximately 0.5 mmol g^{-1} by quantitative GC analysis of the product isolated from a sample of resin. The IR of the polymers as pellets in KBr showed a characteristic C=O absorption at 1720 cm^{-1}.

Cleavage of Products and Intermediates from the Solid Phase; General Procedure

The resin (200 mg) was placed into a porous glass filter frit and treated with CH_2Cl_2/TFA (4 mL/0.1 mL) in three portions. The combined eluents were evaporated to dryness in vacuo.

Hydrolysis of the Trichloroacetamides; General Procedure

N-Trichloroacetamide resin (1 g) was swollen in CH_2Cl_2 (25 mL). After addition of a solution of KOH (0.8 g) in *i*PrOH (8 mL) the resulting mixture was shaken at 40 °C overnight. The mixture was filtered, repeatedly washed with MeOH, water, MeOH, CH_2Cl_2 and Et_2O (3 × 10 mL each) and dried in vacuo. The IR showed no C=O absorption at 1720 cm^{-1}.

Formation of the Imines; General Procedure

Amine resin (1 g) was swollen in CH_2Cl_2 (10 mL). After addition of benzaldehyde (1.0 g) and $HC(OMe)_3$ (0.2 mL) the mixture was shaken at r.t. for 4 h. The mixture was filtered, repeatedly washed with CH_2Cl_2 and Et_2O (3 × 10 mL each) and dried in vacuo. The IR showed a characteristic C=N absorption at 1645 cm^{-1}.

Allylation; General Procedure

Allyllithium (0.45 mmol) in Et_2O (35 ml) was prepared[16] by the procedure described above. This ethereal solution was added at r.t. to a suspension of the imine resins (1 g each) in anhyd benzene (80 mL) under exclusion of moisture and air. This mixture was shaken at r.t. overnight. MeOH (1 mL) was added, the polymer was filtered, repeatedly washed with MeOH, CH_2Cl_2, and Et_2O (3 × 10 mL each) and dried in vacuo. The IR showed no C=N absorption at 1645 cm^{-1}.

***N*-Acylation; General Procedure**

Dialkenylamine resin (1 g, about 0.5 mmol) was swollen in anhyd CH_2Cl_2 (9 mL) and pyridine (1 mL). After addition of TFAA (0.29 mL, 2.0 mmol) (for **14a–c**) or benzoyl chloride (0.23 mL, 2.0 mmol) (for **14d**) the mixture was shaken at r.t. (for **14a–c**) or at 50 °C (for **14d**) for 4 h. The polymer was filtered, repeatedly washed with CH_2Cl_2 and Et_2O (3 × 10 mL each) and dried in vacuo. The IR showed a characteristic C=O absorption at 1685–1690 cm^{-1}.

Olefin Metathesis; General Procedure

Dialkenylamide resin (0.5 g) was swollen in CH_2Cl_2 (5 mL) in an argon atmosphere. **[Ru]** was added in two equivalent portions (for amounts, see the Table) and the suspension was refluxed intermediately for 4 h. After refluxing overnight the mixture was filtered, repeatedly washed with CH_2Cl_2 and Et_2O (3 × 0.5 mL each) and dried in vacuo.

Isolation of 15a–d from the Solid Phase

14a–d (200 mg each) were treated according to the general cleavage procedure.

(6-Phenyl-1,2,5,6-tetrahydropyridin-2-yl)methanol (15a)

The crude cleavage product was dissolved in MeOH (0.3 mL), some K_2CO_3 was added, after 2 min the mixture was dissolved in water (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (MeOH/*t*BuOMe/NEt_3 0:99:1–1:98:1) to obtain **15a** (14 mg, 85%) (mixture of 2 diastereomers, *cis*/*trans* 2:3).

cis-**15a**: R_f 0.26 (*t*BuOMe/NEt_3 99:1).

^1H NMR ($CDCl_3$): δ = 2.15–2.31 (m, 2H, H-5), 3.60 (dd, 1H, *J* = 11/5 Hz, CH_2O), 3.69 (dd, 1H, *J* = 11/3.5 Hz, CH_2O), 3.76–3.82 (m, 1H, H-2), 3.97 (dd, 1H, *J* = 9.5/4.5 Hz, H-6), 5.64 (ddd, 1H, *J* = 10/4.5/1.5 Hz, H-3), 5.98 (dddd, 1H, *J* = 10/5/2.5/2.5 Hz, H-4), 7.28 (m, 1H, Ar-*H*), 7.31–7.43 (m, 4H, Ar-*H*). NOE (400 MHz, $CDCl_3$): δ = 3.76–3.82 (H-2) ↔ 3.97 (H-6) (1.5%).

^{13}C NMR ($CDCl_3$): δ = 34.5 (CH_2, C-5), 57.1 (CH, C-2 or C-6), 57.4 (CH, C-2 or C-6), 65.8 (CH_2, CH_2O), 126.7 (CH), 127.0 (CH), 127.4 (CH), 128.0 (CH), 128.5 (CH), 144.5 (C_q, Ar-*C*).

HRMS ($C_{12}H_{14}NO$, $M^+ - H$): calcd 188.1075, found 188.1075.

IR (CCl_4): ν = 3400, 3247 cm^{-1} (O–H, N–H).

trans-**15a**: R_f 0.15 (*t*BuOMe/NEt_3 99:1).

^1H NMR ($CDCl_3$): δ = 2.19–2.38 (m, 2H, H-5), 3.49–3.60 (m, 3H, H-1, H-2), 3.97 (dd, 1H, *J* = 9.5/4.5 Hz, H-6), 5.70 (ddd, 1H, *J* = 10/4/2.5 Hz, H-3), 5.97–6.05 (m, 1H, H-4), 7.24–7.42 (m, 5H, Ar-*H*).

^{13}C NMR ($CDCl_3$): δ = 32.9 (CH_2, C-5), 50.9 (CH, C-2 or C-6), 55.1 (CH, C-2 or C-6), 62.9 (CH_2, CH_2O), 126.1 (CH), 126.6 (CH), 127.2 (CH), 127.9 (CH), 128.5 (CH), 143.7 (C_q, Ar-*C*).

HRMS ($C_{12}H_{14}NO$, $M^+ - H$): calcd 188.1075, found 188.1075.

IR (CCl_4): ν = 3400, 3299 cm^{-1} (O–H, N–H).

(7-Phenyl-2,3,6,7-tetrahydro-1*H*-azepin-2-yl)methanol (15b)

The crude cleavage product was dissolved in MeOH (0.3 mL), some K_2CO_3 was added, after 2 min the mixture was dissolved in water (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. This crude material was purified by flash chromatography (MeOH/*t*BuOMe/hexanes/NEt_3 0:66:33:1–1:98:0:1) to obtain **15b** (20 mg, 89%) (mixture of 2 diastereomers, *cis*/*trans* 1:1).

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cis-**15b**: R_f 0.35 (*t*BuOMe/NEt_3 99:1).

^{1}H NMR ($CDCl_3$): δ = 2.06–2.25 (m, 2H, H-3), 2.38–2.59 (m, 2H, H-6), 2.84 (dddd, 1H, *J* = 10/9/4/2.5 Hz, H-2), 3.33 (dd, 1H, *J* = 10/10 Hz, CH_2O), 3.61 (dd, 1H, *J* = 10/4 Hz, CH_2O), 3.71 (dd, 1H, *J* = 10/2.5 Hz, H-7), 5.81–5.91 (m, 2H, H-4, H-5), 7.20–7.48 (m, 5H, Ar-*H*).

NOE (400 MHz, $CDCl_3$): δ = 2.84 (H-2) ↔ 3.71 (H-7) (4%).

^{13}C NMR ($CDCl_3$): δ = 34.1 (CH_2, C-6), 39.8 (CH_2, C-3), 59.5 (CH, C-2 or C-7), 62.8 (CH, C-2 or C-7), 66.2 (CH_2, CH_2O), 126.4 (CH), 127.1 (CH), 128.5 (CH), 129.7 (CH), 130.3 (CH), 145.8 (C_q, Ar-*C*).

HRMS ($C_{13}H_{17}NO$, M^+): calcd 203.1310, found 203.1313.

IR (film): ν = 3400, 3281 cm^{-1} (O–H, N–H).

trans-**15b**: R_f 0.17 (*t*BuOMe/NEt_3 99:1).

^{1}H NMR ($CDCl_3$): δ = 2.19–2.27 (m, 1H, H-3), 2.29–2.39 (m, 1H, H-3), 2.43–2.51 (m, 1H, H-6), 2.76–2.85 (m, 1H, H-6), 3.36–3.45 (m, 2H, CH_2O, H-2), 3.52 (dd, 1H, *J* = 15/9 Hz, CH_2O), 4.33 (dd, 1H, *J* = 11/3 Hz, H-7), 5.70–5.79 (m, 2H, H-4, H-5), 7.20–7.48 (m, 5H, Ar-*H*).

^{13}C NMR ($CDCl_3$): δ = 31.9 (CH_2, Ph-CH*C*H_2), 37.3 (CH_2, *C*H_2CHCH_2O), 55.5 (CH), 56.4 (CH), 65.4 (CH_2, CH_2O), 126.5 (CH), 126.9 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 145.4 (C_q, Ar-*C*).

HRMS ($C_{13}H_{17}NO$, M^+): calcd 203.1310, found 203.1322.

IR (film): ν = 3400, 3276 cm^{-1} (O–H, N–H).

(8-Phenyl-1,2,3,4,7,8-hexahydroazocin-2-yl)methanol (15c)

The crude cleavage product was dissolved in MeOH (0.3 mL), some KOH was added, after 2 min the mixture was dissolved in water (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. This crude product was purified by flash chromatography (EtOAc/*t*BuOMe 1:1) to obtain **15c** (20 mg, 87%) (mixture of 2 diastereomers, *cis*/*trans* 1:2).

cis-**15c**: R_f 0.45 (*t*BuOMe/NEt_3 99:1).

^{1}H NMR ($CDCl_3$): δ = 1.32 (dddd, 1H, *J* = 14.5/10.5/9/4 Hz, H-3a), 1.69 (dddd, 1H, *J* = 14.5/6/6/3 Hz, H-3b), 2.19–2.29 (m, 1H, H-4a), 2.35–2.44 (m, 1H, H-4b), 2.48 (ddd, 1H, *J* = 13.5/10/5 Hz, H-7a), 2.68 (ddd, 1H, *J* = 13.5/9.5/5 Hz, H-7b), 2.86 (dddd, 1H, *J* = 10.5/10/5/3 Hz, H-2), 3.03 (dd, 1H, *J* = 10/10 Hz, CH_2O), 3.48 (dd, 1H, *J* = 10/5 Hz, CH_2O), 3.85 (dd, 1H, *J* = 5/5 Hz, H-8), 5.66 (ddd, 1H, *J* = 10/9.5/8 Hz, H-6), 5.94 (ddd, 1H, *J* = 10/8/8 Hz, H-5), 7.21–7.39 (m, 5H, Ar-*H*).

NOE (400 MHz, $CDCl_3$): δ = 2.86 (H-2) ↔ 3.85 (H-8) (3%).

^{13}C NMR ($CDCl_3$): δ = 24.4 (CH_2, C-3), 33.8 (CH_2, C-4 or C-7), 34.9 (CH_2, C-4 or C-7), 59.0 (CH, C-2 or C-8), 62.6 (CH, C-2 or C-8), 66.3 (CH_2, CH_2O), 126.2 (CH), 126.8 (CH), 127.0 (CH), 128.4 (CH), 132.9 (CH), 144.7 (C_q, Ar-C).

HRMS ($C_{14}H_{19}NO$, M^+): calcd 217.1466, found 217.1460.

IR (film): ν = 3400, 3330 cm^{-1} (O–H, N–H).

trans-**15c**, R_f 0.35 (*t*BuOMe/NEt_3 99:1).

^{1}H NMR ($CDCl_3$): δ = 1.13 (dddd, 1H, *J* = 14/12.5/11/2.5 Hz, H-3a), 1.68 (dddd, 1H, *J* = 14/6/2.5/2 Hz, H-3b), 2.17–2.27 (m, 1H, H-4a), 2.29–2.38 (m, 2H, H-4b, H-7), 2.61–2.69 (m, 1H, H-2), 2.86 (dd, 1H, *J* = 10/9 Hz, CH_2O), 2.87 (dddd, 1H, *J* = 13/12/10/1 Hz, H-7), 3.14 (dd, 1H, *J* = 10/5 Hz, CH_2O), 3.89 (dd, 1H, *J* = 12.5/3.5 Hz, H-8), 5.76 (dddd, 1H, *J* = 11/7/7/2 Hz, H-6), 6.05 (dddd, 1H, *J* = 11/7.5/7.5/1 Hz, H-5), 7.23–7.29 (m, 1H, Ar-*H*), 7.33–7.39 (m, 2H, Ar-*H*), 7.42–7.47 (m, 2H, Ar-*H*).

^{13}C NMR ($CDCl_3$): δ = 25.4 (CH_2, C-3), 29.9 (CH_2, C-4 or C-7), 33.8 (CH_2, C-4 or C-7), 54.0 (CH, C-2 or C-8), 58.1 (CH, C-2 or C-8), 66.3 (CH_2, CH_2O), 127.3 (CH), 127.9 (CH), 128.5 (CH), 128.8 (CH), 133.0 (CH), 143.3 (C_q, Ar-*C*).

HRMS ($C_{14}H_{19}NO$, M^+): calcd 217.1466, found 217.1478.

IR (film): ν = 3351 cm^{-1} (br, O–H, N–H).

(1-Benzoyl-7-phenyl-2,3,6,7-tetrahydro-1*H*-azepine-2-yl)methanol (15d)

The crude cleavage product was purified by flash chromatography (CH_2Cl_2/*t*BuOMe 9:1) to obtain **15d** (28 mg, 88%) as a separable mixture of two diastereomeric products. To assign the stereochemistry of the diastereomers, about 0.5 mg each were dissolved in MeOH (0.1 mL), KOH (10 mg) was added, the mixture was heated to 50 °C for 15 min, diluted with water and extracted with *t*BuOMe. The TLC of the two extracts were compared with authentic samples of **15b**.

cis-**15d**: R_f 0.42 (CH_2Cl_2/*t*BuOMe 3:1).

trans-**15d**: R_f 0.48 (CH_2Cl_2/*t*BuOMe 3:1).

^{1}H NMR ($CDCl_3$, 55 °C): δ = 2.06–2.16 (m, $1H_{cis}$, H-3a), 2.26 (ddd, $1H_{cis}$, *J* = 16/7/6 Hz, H-3b), 2.34–2.45 (m, $1H_{trans}$, H-3a), 2.54 (ddd, $1H_{trans}$, *J* =15/8/6 Hz, H-6a), 2.72–2.81 (m, $1H_{cis}$, H-6a; m, $1H_{trans}$, H-6b), 2.92 (ddd, $1H_{cis}$, *J* = 17/6/6 Hz, H-6b), 3.18–3.27 (m, $1H_{cis}$, CH_2O; $1H_{trans}$, H-3b), 3.43 (dd, $1H_{cis}$, *J* = 11/8 Hz, CH_2O), 3.99 (dd, $1H_{trans}$, *J* = 12.5/6 Hz, CH_2O), 4.06–4.16 (m, $1H_{trans}$, H-2), 4.21 (d, $1H_{trans}$, *J* = 12.5 Hz, CH_2O), 4.45–4.60 (m, $2H_{cis}$, H-7, H-2), 5.04 (dd, $1H_{trans}$, *J* = 11/6 Hz, H-7), 5.64–5.74 (m, $1H_{trans}$, =C*H*), 5.76–5.83 (m, $1H_{trans}$, =C*H*), 5.79–5.86 (m, $1H_{cis}$, =C*H*), 5.95–6.03 (m, $1H_{cis}$, =C*H*), 7.21–7.53 (m, 10H, Ar-*H*)

^{13}C NMR ($CDCl_3$, not coalesced, mixture of stereoisomers): δ = 28.9 (CH_2), 32.3 (CH_2), 56.7 (CH), 59.1 (CH), 63.8 (CH), 64.6 (CH_2), 123.7–130.8 (8 CH), 136.9 (C_q), 137.5 (C_q), 141.4 (C_q), 174.9 (C_q).

HRMS ($C_{20}H_{21}NO_2$, M^+): calcd 307.15723, found 307.1577.

IR (film): ν = 3402 (O–H), 1615 cm^{-1} (C=O).

Epoxidation

14d (200 mg) was suspended in CH_2Cl_2 (4 mL) and Cl_3CCN (1.7 g, 12 mmol). A solution of K_2HPO_4 (0.5 g) in 30% aq H_2O_2 (1 mL) was added and the resulting mixture was shaken under reflux for 3 h. The polymer was filtered, washed with water, MeOH, CH_2Cl_2, and Et_2O (2 mL each) and dried in vacuo.

2-Benzoyl-5-hydroxy-3-phenyl-7-oxa-2-azabicyclo[4.2.1]nonane (17)

Isolation from the solid phase: resin **16** (100 mg) was treated according to the general cleavage procedure. The crude product was purified by flash chromatography (*t*BuOMe/MeOH 100:0–98:2) to yield **17** (12 mg, 70%) as mixture of two diastereomeric products.

Diastereomer A: R_f 0.42 (*t*BuOMe).

^{1}H NMR ($CDCl_3$): δ = 2.01 (ddd, 1H, *J* = 15/8/7 Hz, H-9a), 2.27–2.31 (m, 1H, H-4a), 2.45 (d, 1H, *J* = 15 Hz, H-9b), 2.81 (br d, 1H, *J* = 16 Hz, H-4b), 4.07 (dd, 1H, *J* = 7/5 Hz, H-5), 4.14 (d, 1H, *J* = 10 Hz, H-8a), 4.19–4.24 (m, 1H, H-8b), 4.28 (dd, 1H, *J* = 8/5 Hz, H-6), 5.07–5.22 (m, 1H, H-1), 5.36–5.60 (m, 1H, H-3), 7.19–7.42 (m, 10H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.0 (CH_2, C-4 or C-9), 34.0 (CH_2, C-4 or C-9), 56.2 (CH, C-1), 71.2 (CH, C-5), 77.2 (CH_2, C-8), 80.7 (CH, C-6), 125.6 (CH), 125.8 (CH), 127.1 (CH), 128.5 (CH), 128.8 (CH), 129.5. (CH), 136.8 (C_q, Ar-*C*), 141.2 (C_q, Ar-C).

MS (EI): *m/z* (%) = 323 (M^+, 24), 252 (16, $M^+ - C_4H_7O$), 105 (100), 77 (44).

HRMS ($C_{20}H_{21}NO_3$, M^+): calcd 323.15215, found 323.15214.

IR (film): ν = 3423 (O–H), 1614 cm^{-1} (C=O).

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Diastereomer B: R_f 0.32 (*t*BuOMe).
^{1}H NMR ($CDCl_3$): δ = 1.95 (ddd, 1H, *J* = 16/6/3 Hz, H-4a), 2.01 (dd, 1H, *J* = 14/7.5 Hz, H-9a), 2.39 (d, 1H, *J* = 14 Hz, H-9b), 2.44 (ddd, 1H, *J* = 16/11/4 Hz, H-4b), 4.07 (dd, 1H, *J* = 10/7 Hz, H-8a), 4.16 (d, 1H, *J* = 10 Hz, H-8b), 4.18–4.23 (m, 1H, H-5), 4.32 (dd, 1H, *J* = 7.5/4.5 Hz, H-6), 4.97 –5.07 (m, 1H, H-1), 5.42 (dd, 1H, *J* = 11/3 Hz, H-3), 7.12–7.43 (m, 10H, Ar-*H*).

^{13}C NMR ($CDCl_3$): δ = 31.8 (CH_2, C-4 or C-9), 38.9 (CH_2, C-4 or C-9), 55.4 (CH, C-1), 58.5 (CH, C-3), 69.3 (CH, C-5), 73.6 (CH_2, C-8), 80.3 (CH, C-6), 125.5 (CH), 126.4 (CH), 127.5 (CH), 128.4 (CH), 128.6 (CH), 130.0. (CH), 137.0 (C_q, Ar-*C*), 144.6 (C_q, Ar-*C*), 173.6 (C_q, C=O).

MS (EI): *m/z* (%) = 323 (M^+, 24), 252 (26, $M^+ - C_4H_7O$), 105 (100), 77 (28).

HRMS ($C_{20}H_{21}NO_3$, M^+): calcd 323.15215, found 323.15214.

IR (film): ν = 3398 (O–H), 1625 cm^{-1} (C=O).

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