Double Addition of Grignard Reagents to *N*-Glycosyl Nitrones: a New Tool for the Construction of Enantiopure Azaheterocycles

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All reactions requiring anhydrous conditions were carried out under nitrogen and solvents were appropriately dried before use. R_f values refer to TLC on 0.25 mm silica gel plates (Merck F₂₅₄) with the same eluent used for the chromatographic purifications. Melting points (mp) were determined on an RCH Kofler apparatus. ¹H and ¹³C NMR spectra were recorded at 200 MHz and 50.3 MHz, respectively, with a Varian Gemini spectrometer recorded or at 400 MHz and 100 MHz, respectively, with a Varian MERCURY plus spectrometer (where specified in brackets) in CDCl₃ solution, unless otherwise stated: the chemical shifts for ¹H and ¹³C NMR spectra are given in ppm from TMS and the coupling constants values are in Hertz. IR spectra were recorded with a Perkin-Elmer 881 spectrophotometer (cm⁻¹ units). Mass spectra (EI, 70 eV) were recorded with a QMD 1000 Carlo Erba instrument by direct inlet. For some hydroxylamines, CI conditions were used (methane as reacting gas). Optical rotation measurements were carried out with a Jasco DIP-370 polarimeter. Elemental analyses were carried out with a Perkin-Elmer 2400 instrument.

Nitrone **3** was prepared according to the published procedure^{S1} by oxidizing the corresponding *N*-benzylhydroxylamine with MnO₂.

Minor isomers are indicated with primes (given in order of product yield) with respect to the corresponding major isomer.

General Procedure for the Synthesis of Double Addition Products. A commercially available solution of Grignard reagent (3 equivalents) is added dropwise to a 0.1 M solution of nitrone **3** (1 mmol) in dry THF at 0 °C under nitrogen atmosphere. The mixture is stirred for 1 h at 0 °C and then quenched with a saturated aqueous solution of sodium bicarbonate (10 mL). The product is extracted with ethyl acetate (3x10 mL). The organic phase is dried over anhydrous Na₂SO₄, then filtered and concentrated. The product is purified by flash column chromatography.

R	Compound
Methyl	4a
Ethyl	4b
Phenyl	4c
Allyl	4d
Vinyl	4e
Ethynyl	4f

1,2-Dideoxy-2-{hydroxy[(1*R*)-1-phenylethyl]amino}-3,4-*O*-(1-methylethylidene)-D-ribose (4a**).**

White solid, 55% yield (eluent ethyl acetate:petroleum benzene=1:4, R_f =0.32); mp = 89-90 °C; ^1H NMR δ 7.89 (bs, 1H), 7.41-7.29 (m, 5H), 4.44-4.35 (m, 2H), 4.03 (q, 1H, J = 6.6 Hz), 3.57 (dd, 1H, J = 11.4, 3.7 Hz), 3.41 (dd, 1H, J = 11.4, 9.5 Hz), 2.84 (dq, 1H, J = 8.8, 6.2 Hz), 1.53 (d, 3H, J = 6.6 Hz), 1.29 (s, 3H), 1.24 (s, 3H), 1.22 (d, 3H, J = 6.2 Hz); ^{13}C NMR δ 140.5 (s, 1C), 128.9 (d, 2C), 128.0 (d, 1C), 127.7 (d, 2C), 107.4 (s, 1C), 79.6 (d, 1C), 77.7 (d, 1C), 64.6 (d, 1C), 60.3 (t, 1C), 57.1 (d, 1C), 27.6 (q, 1C), 24.9 (q, 1C), 21.4 (q, 1C), 8.6 (q, 1C); IR (KBr) 3274 (s), 3040 (w), 2990 (m), 2940 (w), 2915 (w), 2885 (w), 1455 (m), 1378 (m), 1260 (w), 1212 (m), 1166 (m), 1051 (s), 1012 (w), 882 (m) and 709 (s) cm^{-1} ; MS (CI) m/z (rel. int.) 295 (M^+ +1, 2), 281 (1), 237 (3), 222 (2), 164 (7), 133 (8), 105 (100), 84 (95), 77 (12), 60 (23), 59 (23), 51 (67); Anal. calcd. for $\text{C}_{16}\text{H}_{25}\text{NO}_4$: C, 65.06; H, 8.53; N, 4.74 Found: C, 65.20; H, 8.64; N, 4.71; $[\alpha]_{\text{D}}^{27}$ = +39 (c = 0.68, CH_2Cl_2).

(3*S*,4*R*)-1,2-Dideoxy-2-[hydroxy(1-phenylethyl)amino]-3,4-*O*-(1-methylethylidene)-pentitol (4a'**).**

White solid, 14% yield (eluent ethyl acetate:petroleum benzene = 1:4, R_f =0.43); mp = 134-136 °C; ^1H NMR δ 7.35-7.30 (m, 5H), 4.60 (bs, 1H), 4.37-4.24 (m, 2H), 4.02 (q, 1H, J = 6.6 Hz), 3.82 (dd, 1H, J = 11.0, 8.8 Hz), 3.64-3.46 (m, 2H), 1.41 (s, 3H), 1.39 (d, 3H, J = 6.6 Hz), 1.34 (s, 3H), 1.39 (d, 3H, J = 6.2 Hz); ^{13}C NMR δ 142.5 (s, 1C), 128.8 (d, 2C), 127.8 (d, 1C), 127.6 (d, 2C), 107.7 (s, 1C), 79.5 (d, 1C), 78.0 (d, 1C), 64.1 (d, 1C), 61.2 (t, 1C), 56.3 (d, 1C), 28.1 (q, 1C), 25.3 (q, 1C), 19.3 (q, 1C), 8.3 (q, 1C); IR (KBr) 3270 (s), 3077 (w), 2977 (s), 2937 (m), 2889 (m), 1457 (m), 1378 (m), 1366 (m), 1244 (m), 1218 (m), 1058 (s), 1033 (m), 754 (m) and 695 (s) cm^{-1} ; MS (CI) m/z (rel. int.) 295 (M^+ , 2), 281 (3), 237 (8), 222 (2), 164 (6), 149 (9); 133 (8), 105 (100), 84 (48), 77 (16), 60 (51), 59 (20), 51 (39); Anal. calcd. for $\text{C}_{16}\text{H}_{25}\text{NO}_4$: C, 65.06; H, 8.53; N, 4.74 Found: C, 65.46; H, 8.60; N, 4.84; $[\alpha]_{\text{D}}^{28}$ = +6 (c = 0.35, CH_2Cl_2).

(3*S*,4*R*)-1,2-Dideoxy-2-[hydroxy(1-phenylethyl)amino]-3,4-*O*-(1-methylethylidene)-pentitol (4a''). Oil, 10% yield (eluent ethyl acetate:petroleum benzine =1:4, R_f =0.17); ^1H NMR δ 7.41-7.30 (m, 5H), 5.40 (bs), 4.37 (dd, 1H, J = 6.6, 4.2 Hz), 4.18-4.14 (m, 1H), 4.09 (q, 1H, J = 6.6 Hz), 3.68-3.65 (m, 2H), 3.42 (dq, 1H, J = 7.0, 4.2 Hz), 1.54 (s, 3H), 1.40 (d, 3H, J = 7.0 Hz), 1.37 (s, 3H), 1.29 (d, 3H, J = 6.6 Hz); ^{13}C NMR δ 136.1 (s, 1C), 128.8 (d, 2C), 128.5 (d, 1C), 127.8 (d, 2C), 108.8 (s, 1C), 78.3 (d, 1C), 76.8 (d, 1C), 61.4 (d, 1C), 61.0 (t, 1C), 54.6 (d, 1C), 28.0 (q, 1C), 25.4 (q, 1C), 20.8 (q, 1C), 15.4 (q, 1C); IR (CHCl_3) 3430 (s), 3008 (w), 2987 (m), 2917 (m), 1641 (m), 1456 (m), 1380 (m), 1243 (m), 1219 (s), 1161 (m) and 1058 (s) cm^{-1} ; MS (CI) m/z (rel. int.) 295 (M^+ , 1), 281 (3), 237 (5), 222 (2), 164 (7), 149 (8); 133 (7), 105 (100), 84 (44), 77 (21), 60 (50), 59 (20), 51 (35); Anal. calcd. for $\text{C}_{16}\text{H}_{25}\text{NO}_4$: C, 65.06; H, 8.53; N, 4.74 Found: C, 64.98; H, 8.73; N, 4.60; $[\alpha]_{\text{D}}^{28} = +51$ (c = 0.6, CH_2Cl_2).

(3*S*,4*R*)-1,2-Dideoxy-2-[hydroxy(1-phenylethyl)amino]-3,4-*O*-(1-methylethylidene)-pentitol (4a''') selected signals (inseparable mixture with 4a, the major isomer). 3% yield from integration of methyl signals (eluent ethyl acetate:petroleum benzine=1:4, R_f =0.28); ^1H NMR δ 7.43-7.29 (m, 5H), 5.84 (bs), 4.17-4.10 (m, 1H), 3.96 (q, 1H, J = 6.6), 3.93-3.88 (m, 1H), 3.58-3.50 (m, 1H), 3.31 (dd, 1H, J = 13.2, 2.2 Hz), 2.87-2.78 (m, 1H), 1.61 (s, 3H), 1.55 (d, 3H, J = 6.2 Hz), 1.34 (s, 3H), 1.29 (d, 3H, J = 6.6 Hz).

1,2,3-Trideoxy-3-{hydroxy[(1*R*)-1-phenylpropyl]amino}-4,5-*O*-(1-methylethylidene)-D-ribo-hexitol (4b) selected signals (inseparable mixture with 4b', one of the two minor isomers). 60% yield (eluent ethyl acetate:petroleum benzine=1:4, R_f =0.19); ^1H NMR (400 MHz) δ 7.43-7.28 (m, 5H), 4.56 (dd, 1H, J = 9.2, 5.8 Hz), 4.44 (dt, 1H, J = 9.0, 5.8 Hz), 3.87 (dd, 1H, J = 10.3, 2.9 Hz), 3.57-3.48 (m, 2H), 2.67 (td, 1H, J = 9.2, 2.9 Hz), 2.38-2.31 (m, 1H), 1.95-1.63 (m, 3H), 1.34 (s, 3H), 1.31 (s, 1H), 0.70 (t, 3H, J = 7.8 Hz), 0.70 (t, 3H, J = 7.5 Hz); ^{13}C NMR δ 138.3 (s, 1C), 128.8 (d, 4C), 128.2 (d, 1C), 107.3 (s, 1C), 79.0 (d, 1C), 77.9 (d, 1C), 71.6 (d, 1C), 61.9 (d, 1C), 60.8 (t, 1C), 27.6 (q, 1C), 26.8 (t, 1C), 24.8 (q, 1C), 19.1 (t, 1C), 11.4 (q, 1C), 10.5 (q, 1C).

(4*S*,5*R*)-1,2,3-Trideoxy-3-[hydroxy(1-phenylpropyl)amino]-4,5-*O*-(1-methylethylidene)-hexitol (4b''). Oil, 16% yield (eluent ethyl acetate:petroleum benzine=1:4, R_f =0.22); ^1H NMR δ 7.45-7.31 (m, 5H), 6.00 (bs, 1H), 4.26 (d, 1H, J = 7.0 Hz), 3.86-3.82 (m, 1H), 3.76 (dd, 1H, J = 10.6, 3.7 Hz), 3.56 (dd, 1H, J = 13.3, 2.6 Hz), 3.56 (d, 1H, J = 13.3 Hz), 2.41 (m, 1H), 2.01-1.71 (m, 4H), 1.63 (s, 3H), 1.34 (s, 1H), 0.81 (t, 3H, J = 7.4 Hz), 0.63 (t, 3H, J = 7.3 Hz).

{{(4*R*,5*S*)-5-[(*S*)-[Benzhydryl(hydroxy)amino](phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (4c). White solid, 55% yield (eluent ethyl acetate:petroleum benzine=1:4, R_f =0.18); mp = 172-174 °C; ^1H NMR δ 7.41-7.17 (m, 15H), 5.13 (bs, 1H), 4.95 (dd, 1H, J = 10.3, 5.8 Hz), 4.53 (s, 1H), 4.56-4.47 (m, 1H), 4.09-3.97 (m, 2H), 3.75 (dd, 1H, J = 11.0, 5.8 Hz), 1.23 (s, 3H), 1.21 (s, 1H); ^{13}C NMR δ 141.4 (s, 1C), 138.9 (s, 1C), 135.7 (s, 1C), 130.6 (d, 2C), 128.9 (d, 2C), 128.7 (d, 2C), 128.5 (d, 2C), 128.0 (d, 1C), 127.9 (d, 1C), 127.8 (d, 2C), 127.4 (d, 1C), 127.3 (d, 2C), 107.7 (s, 1C), 78.9 (d, 1C), 78.3 (d, 1C), 75.2 (d, 1C), 66.4 (d, 1C), 61.5 (t, 1C), 27.9 (q, 1C), 25.2 (q, 1C); IR (KBr) 3399 (s), 3183 (m), 3029 (w), 2985 (m), 2939 (m), 2842 (w), 1494 (m), 1455 (m), 1383 (s), 1250 (m), 1221 (m), 1063 (s), 1028 (s), 882 (w), 802 (w), 776 (m), 751 (w) and 710 (s) cm^{-1} ; MS m/z (rel. int.) 419 (M^+ , 0.1), 361 (3), 272 (5), 182 (3), 169 (23), 167 (100), 165 (57), 152 (25), 103 (14), 91 (30), 77 (28), 59 (44); Anal. calcd. for $\text{C}_{26}\text{H}_{29}\text{NO}_4$: C, 74.44; H, 6.97; N, 3.34 Found: C, 74.43; H, 6.95; N, 3.11; $[\alpha]_{\text{D}}^{27} = +22$ (c = 0.89, CH_2Cl_2).

{{(4*R*,5*S*)-5-[(*R*)-[Benzhydryl(hydroxy)amino](phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (4c'). White solid, 26% yield (eluent eluent ethyl acetate:petroleum benzine=1:3, R_f =0.10); mp = 138-140 °C; ^1H NMR δ 7.52-7.07 (m, 15H), 5.29 (bs, 1H), 5.06 (dd, 1H, J = 9.5, 5.9 Hz), 4.70 (s, 1H), 4.07 (d, 1H, J = 9.5 Hz), 3.93 (ddd, 1H, J = 7.3, 5.9, 3.3 Hz), 3.26 (dd, 1H, J = 11.0, 7.3 Hz), 3.04 (dd, 1H, J = 11.0, 3.3 Hz), 1.64 (s, 3H), 1.48 (s, 1H); ^{13}C NMR δ 142.7 (s, 1C), 141.4 (s, 1C), 134.9 (s, 1C), 130.4 (d, 2C), 128.7 (d, 2C), 128.4 (d, 2C), 128.3 (d, 1C), 128.2 (d, 2C), 128.0 (d, 2C), 127.7 (d, 2C), 127.4 (d, 1C), 126.9 (d, 1C), 108.6 (s, 1C), 77.7 (d, 1C), 76.9 (d, 1C), 73.9 (d, 1C), 63.5 (d, 1C), 61.3 (t, 1C), 28.3 (q, 1C), 25.8 (q, 1C); IR (CH_2Cl_2) 3685 (s), 3599 (m), 3558 (m), 3063 (m), 3030 (m), 2991 (m), 2935 (m), 2875 (w), 1604 (s), 1494 (m), 1454 (s), 1382 (m), 1371 (m), 1219 (m), 1165 (m), 1067 (s) and 1030 (s) cm^{-1} ; MS m/z (rel. int.) 419 (M^+ , 0.1), 361 (1), 288 (5), 272 (13), 197 (6), 180 (6), 169 (26), 167 (100), 165 (91), 152 (35), 133 (14), 103 (25), 91 (42), 77 (37), 59 (48); Anal. calcd. for $\text{C}_{26}\text{H}_{29}\text{NO}_4$: C, 74.44; H, 6.97; N, 3.34 Found: C, 74.41; H, 6.83; N, 3.26; $[\alpha]_{\text{D}}^{27} = +28$ (c = 0.885, CH_2Cl_2).

1,2,3,4-Tetradeoxy-4-{hydroxy[(1*S*)-1-phenylbut-3-enyl]amino}-5,6-*O*-(1-methylethylidene)-*D*-ribo-hept-1-enitol (4d). White solid, 79% yield (eluent ethyl acetate:petroleum benzine=1:2, R_f =0.46); mp = 117-118 °C; ^1H NMR δ 7.36-7.22 (m, 5H), 6.08 (dddd, 1H, J = 16.9, 9.9, 8.4, 5.9 Hz), 5.34 (ddt, 1H, J = 17.2, 10.2, 6.6 Hz), 5.27-4.85 (m, 4H), 4.37 (dd, 1H, J = 8.5, 5.5 Hz), 4.19 (dt, 1H, J = 8.5, 5.1 Hz), 4.06 (dd, 1H, J = 10.6, 4.4 Hz), 3.68 (dd, 1H, J = 11.4, 8.4 Hz), 3.49 (dd,

1H, $J = 11.4, 4.8$ Hz), 3.40 (dt, 1H, $J = 13.5, 4.8$ Hz), 2.80-2.62 (m, 2H), 2.58-2.38 (m, 2H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR δ 139.7 (s, 1C), 137.0 (d, 1C), 133.8 (d, 1C), 128.7 (d, 2C), 128.6 (d, 2C), 127.9 (d, 1C), 117.5 (t, 1C), 116.2 (t, 1C), 107.9 (s, 1C), 78.2 (d, 1C), 77.7 (d, 1C), 69.2 (d, 1C), 61.1 (t, 1C), 60.7 (d, 1C), 36.8 (t, 1C), 30.7 (t, 1C), 28.0 (q, 1C), 25.3 (q, 1C); IR (KBr) 3282 (s), 3073 (w), 2983 (m), 2934 (w), 2886 (w), 1640 (m), 1456 (m), 1442 (m), 1418 (m), 1379 (m), 1370 (m), 1244(m), 1220 (m), 1071 (m), 1053 (s), 1034 (m) and 910 (m) cm^{-1} ; MS m/z (rel. int.) 248 ($\text{M}^+ + 1$, 5), 212 (9), 131 (100), 128 (21), 116 (9), 106 (14), 91 (50), 87 (10), 84 (40), 77 (18), 72 (15), 59 (21), 51 (16); Anal. calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_4$: C, 69.14; H, 8.41; N, 4.03 Found: C, 69.08; H, 8.40; N, 4.19; $[\alpha]_{\text{D}}^{21} = +43$ ($c = 1.00$, CH_2Cl_2).

1,2,3,4-Tetradeoxy-4-{hydroxy[(1*R*)-1-phenylbut-3-enyl]amino}-5,6-*O*-(1-methylethylidene)-D-ribo-hept-1-enitol (4d'). White solid, 19% yield (eluent ethyl acetate:petroleum benzine=1:2, R_f =0.29); mp = 81-82 °C; ^1H NMR δ 7.36-7.26 (m, 5H), 5.95 (ddt, 1H, $J = 17.2, 9.9, 7.3$ Hz), 5.45 (ddt, 1H, $J = 17.2, 9.9, 7.3$ Hz), 5.11-4.84 (m, 4H), 4.55 (dd, 1H, $J = 9.5, 5.9$ Hz), 4.38 (dt, 1H, $J = 9.5, 5.2$ Hz), 4.05 (dd, 1H, $J = 10.3, 4.0$ Hz), 3.87-3.42 (m, 2H), 3.12-3.01 (m, 1H), 2.88-2.79 (m, 1H), 2.60-2.38 (m, 3H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR δ 137.9 (s, 1C), 136.6 (d, 1C), 134.4 (d, 1C), 128.8 (d, 2C), 128.7 (d, 2C), 128.1 (d, 1C), 117.4 (t, 1C), 116.0 (t, 1C), 107.5 (s, 1C), 78.2 (d, 1C), 77.7 (d, 1C), 69.7 (d, 1C), 60.7 (t, 1C), 60.4 (d, 1C), 39.2 (t, 1C), 30.7 (t, 1C), 27.7 (q, 1C), 24.9 (q, 1C); IR (KBr) 3237 (s), 3077 (w), 2978 (m), 2938 (w), 2908 (w), 2858 (w), 1641 (m), 1494 (m), 1454 (m), 1428 (m), 1385 (m), 1371 (m), 1250 (s), 1221 (s), 1072 (s), 1055 (s), 926 (s) and 874 (s) cm^{-1} ; MS m/z (rel. int.) 248 ($\text{M}^+ + 1$, 16), 199 (6), 131 (100), 115 (17), 105 (9), 92 (19), 90 (33), 86 (11), 77 (15), 71 (14), 69 (12), 60 (25), 57 (11); Anal. calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_4$: C, 69.14; H, 8.41; N, 4.03 Found: C, 69.35; H, 8.42; N, 4.07; $[\alpha]_{\text{D}}^{24} = +45$ ($c = 0.40$, CH_2Cl_2).

1,2,3-Trideoxy-3-{hydroxy[(1*R*)-1-phenylprop-2-enyl]amino}-4,5-*O*-(1-methylethylidene)-D-ribo-hex-1-enitol (4e) and (4*S*,5*R*)-1,2,3-trideoxy-3-[hydroxy(1-phenylprop-2-enyl)amino]-4,5-*O*-(1-methylethylidene)-hex-1-enitol (4e'') (inseparable mixture) 66 % yield (eluent ethyl acetate:petroleum benzine=1:2, R_f =0.25); **selected ^1H NMR signals for 4e** δ 7.45-7.27 (m, 5H), 6.99 (bs, 1H), 6.26 (dt, 1H, $J = 17.6, 9.5$ Hz), 6.23-6.04 (m, 1H), 5.50 (dd, 1H, $J = 9.5, 1.6$ Hz), 5.19 (bd, 1H, $J = 16.1$ Hz), 5.17 (bd, 1H, $J = 10.3$ Hz), 4.99 (dd, 1H, $J = 17.6, 2.2$ Hz), 4.57 (dd, 1H, $J = 9.5, 5.9$ Hz), 4.48-4.37 (m, 2H), 3.62 (dd, 1H, $J = 11.7, 4.4$ Hz), 3.48 (dd, 1H, $J = 11.7, 9.5$ Hz), 3.21 (t, 1H, $J = 9.5$ Hz), 1.29 (s, 3H), 1.25 (s, 3H); **observed ^1H NMR signals for 4e''** (two undetectable proton, hidden by the major isomer signals) δ 7.45-7.27 (m, 5H), 6.22-5.91 (m, 2H),

5.83 (bs, 1H), 5.34 (dd, 1H, $J = 8.1, 1.6$ Hz), 5.27-5.09 (m, 3H), 4.23-3.96 (m, 2H), 3.87 (dd, 1H, $J = 8.8, 3.7$ Hz), 3.77-3.72 (m, 1H), 1.57 (s, 3H), 1.38 (s, 3H).

(4S,5R)-1,2,3-Trideoxy-3-[hydroxy(1-phenylprop-2-enyl)amino]-4,5-O-(1-methylethylidene)-hex-1-enitol (4e'). White solid, 21% yield (eluent ethyl acetate:petroleum benzene=1:2, $R_f=0.35$); mp = 143-145 °C; ^1H NMR δ 7.36-7.27 (m, 5H), 6.08 (ddd, 1H, $J = 15.4, 10.3, 8.8$ Hz), 5.96 (dt, 1H, $J = 17.5, 10.3$ Hz), 5.56 (dd, 1H, $J = 10.3, 2.2$ Hz), 5.31 (dd, 1H, $J = 17.5, 2.2$ Hz), 5.30 (dd, 1H, $J = 15.4, 1.7$ Hz), 5.22 (dd, 1H, $J = 10.3, 1.7$ Hz), 4.65-4.35 (m, 4H, one of which is an exchanging proton), 3.96-3.68 (m, 3H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 140.4 (d, 2C), 135.8 (s, 1C), 130.8 (d, 1C), 129.1 (d, 2C), 127.7 (d, 2C), 122.2 (t, 1C), 119.3 (t, 1C), 108.3 (s, 1C), 78.0 (d, 1C), 76.4 (d, 1C), 74.0 (d, 1C), 64.9 (d, 1C), 61.2 (t, 1C), 28.0 (q, 1C), 25.4 (q, 1C); IR (KBr) 3247 (s), 3070 (m), 2987 (m), 2936 (m), 2868 (m), 1634 (m), 1454 (m), 1424 (m), 1379 (m), 1243 (m), 1221 (m), 1073 (s), 1035 (s), 922 (s) and 697 (s) cm^{-1} ; MS m/z (rel. int.) 167 (2), 144 (4), 132 (6), 117 (100), 115 (50), 91 (24), 85 (19), 77 (9), 60 (17), 57 (16), 55 (18); Anal. calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_4$: C, 67.69; H, 7.89; N, 4.39 Found: C, 67.30; H, 7.76; N, 4.12; $[\alpha]_{\text{D}}^{25} = +22$ ($c = 0.13$, CH_2Cl_2).

1,2,3-Trideoxy-3-{hydroxy[(1R)-1-phenylprop-2-ynyl]amino}-4,5-O-(1-methylethylidene)-D-ribo-hex-1-ynitol (4f). Pale yellow solid, 75% yield (eluent ethyl acetate:petroleum benzene=1:3, $R_f=0.11$); mp = 99-101 °C; ^1H NMR (400 MHz) δ 7.58-7.56 (m, 2H), 7.41-7.38 (m, 3H), 4.97 (d, 1H, $J = 2.4$ Hz), 4.58 (dd, 1H, $J = 9.7, 5.3$ Hz), 4.31 (dt, 1H, $J = 8.8, 5.3$ Hz), 3.53 (dd, 1H, $J = 12.2, 4.9$ Hz), 3.45 (dd, 1H, $J = 9.7, 2.0$ Hz), 3.17 (dd, 1H, $J = 12.2, 8.8$ Hz), 2.60 (d, 1H, $J = 2.0$ Hz), 2.52 (d, 1H, $J = 2.4$ Hz), 1.32 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz) δ 134.9 (s, 1C), 129.5 (d, 1C), 129.0 (d, 2C), 128.9 (d, 2C), 108.7 (s, 1C), 82.1 (s, 2C), 77.2 (d, 1C), 76.9 (d, 1C), 76.5 (d, 1C), 73.8 (d, 1C), 63.2 (d, 1C), 59.8 (t, 1C), 55.5 (d, 1C), 27.6 (q, 1C), 25.0 (q, 1C); IR (CH_2Cl_2) 3545 (w), 3300 (s), 3065 (w), 3039 (w), 2991 (w), 2938 (w), 2884 (w), 1493 (m), 1456 (m), 1383 (m), 1373 (m), 1221 (s), 1075 (s) and 1057 (s) cm^{-1} ; MS (CI) m/z (rel. int.) 315 (M^+ , 2), 184 (3), 131 (5), 115 (100), 77 (5), 59 (48); Anal. calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}_4$: C, 68.55; H, 6.71; N, 4.44 Found: C, 68.55; H, 6.85; N, 4.40; $[\alpha]_{\text{D}}^{29} = +64$ ($c = 0.92$, CH_2Cl_2).

(4S,5R)-1,2,3-Trideoxy-3-[hydroxy(1-phenylprop-2-ynyl)amino]-4,5-O-(1-methylethylidene)-hex-1-ynitol (4f'). Yellow solid, 19% yield (eluent ethyl acetate:petroleum benzene=1:3, $R_f=0.14$); m.p. = 156-158 °C; ^1H NMR δ 7.43-7.41 (m, 2H), 7.33-7.29 (m, 3H), 5.11 (bs, 1H), 4.76 (bs, 1H),

4.62 (bd, 1H, $J = 9.3$), 4.42 (dd, 1H, $J = 9.3, 5.6$), 4.24 (dt, 1H, $J = 7.7, 5.6$), 3.84 (dd, 1H, $J = 11.9, 7.7$), 3.69 (dd, 1H, $J = 11.9, 5.6$), 2.56 (d, 1H, $J = 2.6$), 2.50 (d, 1H, $J = 2.1$), 1.43 (s, 3H), 1.32 (s, 1H); ^{13}C NMR δ 136.9 (s, 1C), 129.1 (d, 1C), 128.8 (d, 2C), 128.7 (d, 2C), 109.0 (s, 1C), 79.8 (s, 2C), 77.7 (d, 1C), 76.5 (d, 1C), 76.2 (d, 1C), 75.9 (d, 1C), 62.2 (d, 1C), 60.5 (t, 1C), 56.8 (d, 1C), 27.9 (q, 1C), 25.3 (q, 1C); IR (CH_2Cl_2) 3543 (w), 3299 (s), 3056 (w), 2990 (w), 2937 (w), 2884 (w), 1493 (w), 1456 (m), 1383 (m), 1373 (m), 1221 (m), 1075 (s) and 1034 (m) cm^{-1} ; MS (C. I.) m/z (rel. int.) 315 (M^+ , 4), 184 (8), 169 (7), 131 (19), 115 (100), 105 (47), 77 (29), 59 (87), 57 (75); Anal. calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}_4$: C, 68.55; H, 6.71; N, 4.44 Found: C, 68.53; H, 6.60; N, 4.43; $[\alpha]_{\text{D}}^{30} = -0.7$ ($c = 0.73$, CH_2Cl_2).

Effects of variation of reaction conditions on diastereoselectivity. The effects of varying the solvent and reagent concentrations and ratios and reaction temperature have been studied. Ethereal solvents gave the best results with negligible differences between THF and Et_2O , while the reactions were less diastereoselective when carried out in CH_2Cl_2 . Concerning the reaction temperature, we found that operating at rt afforded more complex mixtures containing decomposition products, while at $-78\text{ }^\circ\text{C}$ the reactions were slower; no significant improvement of diastereoselectivity was observed. However, it is also worth noting that use of a lower excess of Grignard reagent did result in less clean reaction mixtures, containing, besides the same bis-adducts, considerable amounts of starting nitron and only traces of mono-addition products. Even when working with a molar equivalent of Grignard reagent we were not able to obtain predominant products of monoaddition, with the exception of the addition of phenylmagnesium bromide which gave the expected monoadduct cleanly. Unreacted nitron and bis-adducts were still the main products under these conditions, even when the reactions were carried out at low temperature.

More interesting results were obtained through changes to the concentration of reagents which, albeit producing relatively small effects, showed a trend to increase the preference of the first attack at the *re* face of nitron on increasing concentration. Particularly, higher concentrations of Grignard reagents seemed to favor the first addition at the *re* face of **3**. Accordingly, the bis-adduct **4f** was effectively obtained almost quantitatively with an 87% d.r. when an inverted addition procedure of nitron **3** to ethynyl magnesium bromide (6 equiv) was followed.

Chemical Correlation of Compounds 4b, 4e and 4f. The diethynyl major diastereoisomer **4f** was reduced by catalytic hydrogenation over Pd-C. From the crude reaction mixture (containing the desired divinyl compound and other reduction products, including debenzylated ones and ethyl

substituted derivatives) compound **4e** was isolated, demonstrating the absolute stereochemistry of **4f** at C1 and C1' (*R* and *S*, respectively, as expected).

The inseparable mixture of the major diastereoisomer **4e** of the vinyl adducts and one of the two minor products **4e''** was converted to the corresponding diacetyl derivatives in order to separate them. The major diacetyl derivative **6** was then isolated and further reduced by hydrogenation over Pd-C to the diethyl compound **7**. The mixture of the major diethyl adduct **4b** and one of the minor isomers **4b'** was transformed into their diacetyl derivatives (which even in this form resulted inseparable by chromatography). However, ¹H NMR of the crude mixture proved the identity of the major isomer with compound **7** (see scheme below).

Synthesis of 4e: Partial Hydrogenation of Diethynyl Derivative 4f. Pd-C 5% (15 mg) is added to a stirred solution of compound **4f** (29 mg, 0.09 mmol) in methanol (1 mL) and stirred at rt under hydrogen atmosphere. After 15 min the mixture is filtered over Celite and concentrated. A short pad filtration over silica gel affords the pure desired product **4e** (13 mg, 0.04 mmol) in 44% yield.

Synthesis of 6: Complete Acetylation of Divinyl Derivative 4e. Acetic anhydride (190 μ L, 2 mmol), pyridine (32 μ L, 0.4 mmol) and DMAP (5 mg, 0.04 mmol) are added to a stirred solution of hydroxylamine **4e** (64 mg, 0.2 mmol) in THF (5 mL). The mixture is stirred for 1 h at rt and then added with a saturated aqueous solution of sodium carbonate (10 mL). The product is extracted with ethyl acetate (3x10 mL). The organic phase is dried over anhydrous Na₂SO₄, then filtered and concentrated. A short pad filtration over silica gel affords the pure desired product **6** (77 mg, 0.19 mmol) in 95% yield.

6-*O*-Acetyl-3-[(acetyloxy)[(1*R*)-1-phenylprop-2-enyl]amino]-1,2,3-trideoxy-4,5-*O*-(1-methylethylidene)-D-ribo-hex-1-enitol (6). White solid, 95% yield (eluent ethyl acetate:petroleum benzine=1:5, R_f =0.40); mp = 99-101 °C; ^1H NMR (400 MHz) δ 7.41-7.28 (m, 5H), 6.08 (ddd, 1H, J = 17.2, 14.7, 9.2 Hz), 5.96 (ddd, 1H, J = 15.4, 10.6, 8.8 Hz), 5.53 (dd, 1H, 10.6, 2.0 Hz), 5.19 (dd, 1H, J = 17.2, 2.0 Hz), 5.05 (dd, 1H, J = 15.4, 2.0 Hz), 5.01 (dd, 1H, J = 14.7, 2.0 Hz), 4.66 (dd, 1H, J = 11.7, 2.9 Hz), 4.47 (d, 1H, J = 9.2 Hz), 4.35 (td, 1H, J = 6.2, 2.9 Hz), 4.12 (dd, 1H, J = 8.8, 6.2 Hz), 3.89 (dd, 1H, J = 11.7, 6.2 Hz), 3.26 (t, 1H, J = 8.8 Hz), 2.01 (s, 3H), 1.95 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H); ^{13}C NMR δ 170.7 (s, 1C), 169.8 (s, 1C), 138.5 (d, 1C), 138.1 (s, 1C), 131.2 (d, 1C), 129.1 (d, 2C), 128.7 (d, 2C), 128.3 (d, 1C), 122.5 (t, 1C), 117.1 (t, 1C), 108.5 (s, 1C), 76.2 (d, 1C), 75.8 (d, 1C), 73.3 (d, 1C), 64.3 (d, 1C and t, 1C), 27.5 (q, 1C), 25.2 (q, 1C), 20.9 (q, 1C), 19.2 (q, 1C); IR (KBr) 3450-3350 (m), 3075 (w), 3033 (w), 2988 (m), 2891 (w), 1755 (s), 1738 (s), 1634 (w), 1456 (m), 1386 (m), 1252 (s), 1203 (s), 1087 (s), 1051 (s) cm^{-1} ; MS m/z (rel. int.) 403 (0.5), 346 (1), 286 (1), 230 (9), 149 (2), 117 (100), 91 (6); Anal. calcd. for $\text{C}_{22}\text{H}_{29}\text{NO}_6$: C, 65.49; H, 7.24; N, 3.47 Found: C, 65.14; H, 7.27; N, 3.22; $[\alpha]_{\text{D}}^{23} = -129$ (c = 0.93, CH_2Cl_2).

Synthesis of 7:

a) Reduction of Divinyl Derivative 6. 5% Pd-C (20 mg) is added to a stirred solution of compound **6** (44 mg, 0.11 mmol) in methanol (1.5 mL) and stirred at rt under hydrogen atmosphere. After 30 min the mixture is filtered over Celite and concentrated. A short pad filtration over silica gel affords the pure desired product **7** (34 mg, 0.08 mmol) in 76% yield.

b) Acetylation of the Mixture of Diethyl Derivatives 4b and 4b'. Acetic anhydride (95 μL , 1 mmol), pyridine (16 μL , 0.2 mmol) and DMAP (2.5 mg, 0.02 mmol) are added to a stirred solution of hydroxylamines **4b** and **4b'** (31 mg, 0.1 mmol) in THF (2.5 mL). The mixture is stirred for 1 h at rt and then added with a saturated aqueous solution of sodium carbonate (10 mL). The products are extracted with ethyl acetate (3x10 mL). The organic phase is dried over anhydrous Na_2SO_4 , then filtered and concentrated. A short pad filtration over silica gel affords the pure desired product **7** (33 mg, 0.08 mmol) in mixture with the minor derivative with a 80% yield.

6-*O*-Acetyl-3-[(acetyloxy)[(1*R*)-1-phenylpropyl]amino]-1,2,3-trideoxy-4,5-*O*-(1-methylethylidene)-D-ribo-hexitol (7). Oil (eluent ethyl acetate:petroleum benzine=1:6, R_f =0.47); ^1H NMR (400 MHz) δ 7.37-7.29 (m, 5H), 4.45 (bd, 1H, J = 11.6 Hz), 4.35 (bt, 1H, J = 8.0 Hz),

4.06 (dd, 1H, $J = 8.7, 6.3$ Hz), 3.92 (t, 1H, $J = 7.3$ Hz), 3.72 (dd, 1H, $J = 11.6, 8.0$ Hz), 2.60 (m, 1H), 2.08 (s, 3H), 1.97 (s, 3H), 1.94-1.64 (m, 4H), 1.30 (s, 3H), 1.27 (s, 3H), 0.97 (t, 3H, $J = 7.5$ Hz), 0.59 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR δ 170.8 (s, 1C), 169.9 (s, 1C), 138.1 (s, 1C), 129.1 (d, 2C), 128.7 (d, 2C), 128.2 (d, 1C), 107.7 (s, 1C), 77.4 (d, 1C), 75.8 (d, 1C), 70.4 (d, 1C), 64.4 (t, 1C), 61.3 (d, 1C), 27.5 (q, 1C), 26.2 (t, 1C), 25.1 (q, 1C), 20.9 (q, 1C), 19.6 (t, 1C), 19.2 (q, 1C), 11.8 (t, 1C), 10.5 (q, 1C); IR (KBr) 3500-3300 (m), 3065 (w), 3030 (w), 2962 (m), 2916 (s), 2848 (s), 1767 (s), 1740 (s), 1462 (m), 1369 (m), 1245 (s), 1199 (s), 1080 (m), 1048 (m), 706 (m) cm^{-1} ; MS m/z (rel. int.) 408 (0.2), 392 (1), 278 (2), 234 (13), 116 (100), 91 (97), 77 (5); Anal. calcd. for $\text{C}_{22}\text{H}_{33}\text{NO}_6$: C, 64.84; H, 8.16; N, 3.44 Found: C, 65.08; H, 8.12; N, 3.38; $[\alpha]_{\text{D}}^{23} = -16$ ($c = 1.10$, CH_2Cl_2).

Synthetic Application of Diallyl Derivative 4d: Synthesis of Pyrroloazepine 12.

Synthesis of 8: Partial Acetylation of Diallyl Derivative 4d. Acetic anhydride (390 μL , 4.1 mmol) is added to a stirred solution of hydroxylamine 4d (478 mg, 1.4 mmol) in THF (14 mL) and the mixture is heated under reflux for 1.5 h. After cooling, a saturated aqueous solution of sodium carbonate (20 mL) is added. The product is extracted with ethyl acetate (3x12 mL). The organic phase is dried over anhydrous Na_2SO_4 , then filtered and concentrated. After purification by flash column chromatography the pure desired product 8 (506 mg, 1.3 mmol) is recovered.

1,2,3,4-Tetradecoxy-4-{acetyl[(1*S*)-1-phenylbut-3-enyl]amino}-5,6-*O*-(1-methylethylidene)-D-ribo-hept-1-enitol (8). Oil, 93% yield (eluent ethyl acetate:petroleum benzene=1:5, R_f =0.25); ^1H NMR δ 7.28-7.21 (m, 5H), 6.02 (ddt, 1H, J = 16.8, 10.3, 6.6 Hz), 5.35 (ddt, 1H, J = 16.8, 10.3, 6.6 Hz), 5.12 (dd, 1H, J = 16.8, 2.1 Hz), 5.05 (dd, 1H, J = 10.3, 2.1 Hz), 4.96 (dd, 1H, J = 16.8, 2.1 Hz), 4.89 (dd, 1H, J = 10.3, 2.1 Hz), 4.58 (bm, 1H), 4.42 (dt, 1H, J = 8.8, 5.2 Hz), 4.24 (dd, 1H, J = 11.0, 5.2 Hz), 4.00 (dd, 1H, J = 9.5, 5.9 Hz), 3.89 (bd, 1H, J = 11.0 Hz), 3.62 (m, 1H), 2.80-2.41 (m, 4H), 1.60 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 170.1 (s, 1C), 138.5 (s, 1C), 137.1 (d, 1C), 133.5 (d, 1C), 129.0 (d, 2C), 128.0 (d, 2C), 127.9 (d, 1C), 117.7 (t, 1C), 116.2 (t, 1C), 107.4 (s, 1C), 78.1 (d, 1C), 76.7 (d, 1C), 69.7 (d, 1C), 61.0 (d, 1C), 60.5 (t, 1C), 36.9 (t, 1C), 30.4 (t, 1C), 27.8 (q, 1C), 25.1 (q, 1C), 18.4 (q, 1C); IR (CDCl_3) 3424 (m), 3079 (w), 3033 (w), 2988 (m), 2937 (m), 2891 (w), 1759 (s), 1639 (m), 1456 (m), 1370 (m), 1213 (s), 1064(s) cm^{-1} ; MS (CI) m/z (rel. int.) 404 (M^+ +15, 17), 389 (M^+ , 100), 338 (9), 324 (15), 246 (21), 233 (22), 213 (26), 200 (34), 65 (13), 51 (10); Anal. calcd. for $\text{C}_{22}\text{H}_{31}\text{NO}_5$: C, 67.84; H, 8.02; N, 3.60 Found: C, 67.71; H, 8.22; N, 3.82; $[\alpha]_{\text{D}}^{24} = +18$ (c = 1.00, CH_2Cl_2).

Synthesis of 9: RCM with [(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (2nd Generation Grubbs' Catalyst). *O*-Protected hydroxylamine **8** (501 mg, 1.30 mmol) is dissolved in CH_2Cl_2 (20 mL) and 5% of Grubbs' Catalyst 2nd Generation (55 mg, 0.065 mmol) is added. The mixture is heated under reflux and after 5.5 h it is cooled and concentrated. The crude is purified by flash column chromatography to get the pure product **9** (460 mg, 1.27 mmol). Proton spectrum shows some broad signals (probably due to slowly equilibrating conformers) which cannot be resolved even recording spectra at different temperatures.

{(4*R*,5*S*)-5-[(2*S*,7*S*)-1-(Acetyloxy)-7-phenyl-2,3,6,7-tetrahydro-1*H*-azepin-2-yl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (9). Oil, 98% yield (eluent ethyl acetate:petroleum benzene=1:3, R_f =0.18); ^1H NMR δ 7.31-7.25 (m, 5H), 5.86-5.81 (m, 2H), 4.35-4.22 (m, 2H), 4.17-4.01 (bm, 1H), 3.95-3.81 (m, 2H), 3.79-3.64 (bm, 1H), 3.05-2.83 (bm, 1H), 2.76-2.47 (m, 2H), 2.35 (dd, 1H, J = 17.1, 6.3 Hz), 1.83 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR δ 168.9 (s, 1C), 140.9 (s, 1C), 130.8 (d, 1C), 129.3 (d, 1C), 128.2 (d, 2C), 127.7 (d, 2C), 127.6 (d, 1C), 107.5 (s, 1C), 78.3 (d, 1C), 75.6 (d, 1C), 70.6 (d, 1C), 62.2 (d, 1C), 60.7 (t, 1C), 32.2 (t, 1C), 27.8 (q, 1C), 25.3 (q, 1C), 24.8 (t, 1C), 18.8 (q, 1C); IR (CDCl_3) 3423 (m), 3031 (w), 3008 (w), 2985 (w), 2930 (w), 2896 (w), 1759 (s), 1660 (w), 1451 (w), 1368 (m), 1228 (s), 1200 (m), 1060 (m), 1038 (m) cm^{-1} ; MS (CI)

m/z (rel. int.) 361 (M^+ , 22), 131 (11), 85 (30), 71 (60), 57 (100), 55 (74); Anal. calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88 Found: C, 66.43; H, 7.58; N, 3.78; $[\alpha]_D^{25} = +38$ ($c = 1.1$, $CHCl_3$).

Synthesis of 10:

a) Deprotection of Hydroxylamine 9 to Free Hydroxylamine 9a. *N*-protected hydroxylamine **9** (168 mg, 0.46 mmol) is dissolved in MeOH saturated with $KHCO_3$ (20 mL). The solution is stirred at room temperature. After 12 h the mixture is concentrated, H_2O (10 mL) is added and the product is extracted with ethyl acetate (3x10 mL). The organic phase is dried over anhydrous Na_2SO_4 , then filtered and concentrated. The crude is analytically pure and quantitatively recovered and is used directly for the following step.

(2*S*,7*S*)-2-[(4*S*,5*R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-7-phenyl-2,3,6,7-tetrahydro-1*H*-azepin-1-ol (9a). White solid, 100% yield (eluent ethyl acetate:petroleum benzene=1:2, $R_f=0.47$); mp = 170-172 °C; 1H NMR (400 MHz) δ 7.37-7.29 (m, 5H), 6.27 (bs, 1H, exchanging proton), 5.87 (bm, 2H), 5.78 (bm, 1H, exchanging proton), 4.34 (bs, 1H), 4.17 (bs, 1H), 3.97 (bs, 1H), 3.74 (bs, 1H), 3.09 (bd, 1H), 3.01-2.75 (m, 2H), 2.48-2.28 (m, 1H), 2.21 (bm, 1H), 2.15 (bdd, 1H), 1.37 (s, 3H), 1.33 (s, 1H); ^{13}C NMR δ 142.5 (s, 1C), 130.3 (bd, 2C), 128.4 (d, 2C), 127.6 (d, 3C), 107.1 (s, 1C), 77.1 (d, 2C), 72.2 (bd, 1C), 63.3 (bd, 1C), 60.7 (t, 1C), 32.2 (bt, 1C), 28.1 (q, 1C), 25.4 (q, 1C), 24.9 (bt, 1C); IR (KBr) 3270 (m), 3064 (w), 3027 (w), 2990 (w), 2934 (w), 2897 (w), 1651 (w), 1456 (m), 1441 (m), 1379 (m), 1369 (m), 1242 (m), 1223 (m), 1076 (m), 1056 (m), 1036 (s), 875 (m), 752 (m) 699 (m) cm^{-1} ; MS (CI) m/z (rel. int.) 319 (M^+ , 27), 111 (21), 85 (41), 71 (90), 69 (100), 59 (90), 57 (82), 55 (69); Anal. calcd. for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39 Found: C, 67.42; H, 7.83; N, 4.50; $[\alpha]_D^{22} = +76$ ($c = 0.44$, $CHCl_3$).

b) Reduction to Azepine 10. The crude **9a** (147 mg, 0.46 mmol) is dissolved in 90% AcOH (8 mL). Zinc powder (150 mg, 2.3 mmol) is added and the mixture is stirred at rt for 2 h. Then the acid is removed and a saturated aqueous solution of sodium bicarbonate (15 mL) is carefully added. The product is extracted with ethyl acetate (3x15 mL). The organic phase is dried over anhydrous Na_2SO_4 , then filtered and concentrated. The crude reaction mixture is purified by flash column chromatography to afford product **10** (126 mg, 0.41 mmol).

{(4*R*,5*S*)-2,2-Dimethyl-5-[(2*S*,7*S*)-7-phenyl-2,3,6,7-tetrahydro-1*H*-azepin-2-yl]-1,3-dioxolan-4-yl}methanol (10). White hygroscopic solid, 90% yield (eluent ethyl acetate:petroleum benzene=1:2,

$R_f=0.30$); mp = 139-140 °C; ^1H NMR (400 MHz) δ 7.37-7.22 (m, 5H), 5.89-5.73 (m, 2H), 4.39 (d, 1H, J = 10.6 Hz), 4.26 (ddd, 1H, J = 9.4, 5.5, 3.3 Hz), 4.12 (dd, 1H, J = 9.2, 5.5 Hz), 3.81 (dd, 1H, J = 11.4, 9.4 Hz), 3.69 (td, 1H, J = 9.2, 2.6 Hz), 3.55 (dd, 1H, J = 11.4, 3.3 Hz), 2.83-2.71 (m, 1H), 2.61 (dd, 1H, J = 17.2, 6.6 Hz), 2.56-2.44 (m, 1H), 2.37 (dd, 1H, J = 17.2, 6.6 Hz), 1.39 (s, 3H), 1.33 (s, 1H); ^{13}C NMR δ 138.8 (s, 1C), 129.0 (d, 1C), 128.9 (d, 1C), 128.8 (d, 2C), 128.7 (d, 1C), 126.9 (d, 2C), 108.4 (s, 1C), 76.6 (d, 1C), 76.2 (d, 1C), 60.8 (t, 1C), 59.9 (d, 1C), 55.0 (d, 1C), 33.4 (t, 1C), 29.0 (t, 1C), 28.0 (q, 1C), 25.5 (q, 1C); IR (conc. CHCl_3 solution) 3250-3100 (m), 3026 (w), 2988 (w), 2934 (m), 2861 (w), 1653 (w), 1602 (w), 1494 (m), 1454 (m), 1434 (m), 1381 (s), 1372 (m), 1220 (s), 1044 (s); IR (dil. CHCl_3 solution) 3452 (w), 3230-3180 (w), 3053 (m), 3029 (w), 2988 (w), 2935 (w), 2856 (w), 1649 (w), 1493 (w), 1455 (w), 1435 (w), 1382 (m), 1372 (m), 1220 (m), 1040 (m) cm^{-1} ; MS (CI) m/z (rel. int.) 303 (M^+ , 100), 285 (91), 276 (22), 219 (38), 109 (23), 71 (42), 57 (70), 55 (45); Anal. calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_3 \cdot 1/3 \text{H}_2\text{O}$: C, 69.87; H, 8.36; N, 4.53 Found: C, 70.06; H, 8.49; N, 4.51; $[\alpha]_{\text{D}}^{21} = +60$ (c = 1, CHCl_3).

Synthesis of 11: Cyclization of Compound 10. Hydroxylamine **10** (21 mg, 0.07 mmol) is dissolved in dry pyridine (0.5 mL). Triflic anhydride (17 μL , 0.1 mmol) is then added and the mixture is stirred at rt for 2 h. Then ethyl acetate (10 mL) is added and washed with water (2x10 mL). The organic phase is dried over anhydrous Na_2SO_4 , then filtered and concentrated. The crude is purified by flash column chromatography to get product **11** (18 mg, 0.06 mmol).

(3a*R*,6*S*,10a*S*,10b*S*)-2,2-Dimethyl-6-phenyl-3a,6,7,10,10a,10b-hexahydro-4*H*-

[1,3]dioxolo[3,4]pyrrolo[1,2-*a*]azepine (11). White solid, 90% yield (eluent ethyl acetate:petroleum benzene=1:20, $R_f=0.48$); mp = 79-81 °C; ^1H NMR (400 MHz) δ 7.42-7.40 (m, 2H), 7.30-7.26 (m, 2H), 7.22-7.18 (m, 1H), 5.77-5.67 (m, 2H), 4.65 (dd, 1H, J = 6.4, 4.9 Hz), 4.34 (d, 1H, J = 6.4 Hz), 3.97 (d, 1H, J = 11.7 Hz), 3.70 (d, 1H, J = 11.1 Hz), 2.85 (d, 1H, J = 11.5 Hz), 2.76 (m, 1H), 2.52-2.43 (m, 1H), 2.48 (dd, 1H, J = 11.5, 4.9 Hz), 2.12 (dd, 1H, J = 17.5, 7.5 Hz), 1.84 (dd, 1H, J = 17.2, 6.5 Hz), 1.60 (s, 3H), 1.32 (s, 1H); ^{13}C NMR (100 MHz) δ 145.8 (s, 1C), 130.0 (d, 1C), 129.0 (d, 1C), 128.3 (d, 2C), 126.7 (d, 3C), 111.1 (s, 1C), 86.7 (d, 1C), 79.3 (d, 1C), 66.6 (d, 1C), 66.3 (d, 1C), 57.0 (t, 1C), 37.1 (t, 1C), 26.8 (q, 1C and t, 1C), 25.4 (q, 1C); IR (CDCl_3) 3023 (w), 2992 (w), 2930 (m), 2793 (w), 1653 (w), 1488 (w), 1452 (m), 1380 (m), 1371 (s), 1206 (m), 1147 (s), 1060 (s) cm^{-1} ; MS m/z (rel. int.) 285 (M^+ , 51), 270 (16), 231 (100), 216 (82), 185 (22), 173 (28), 156 (31), 143 (28), 129 (59), 117 (50), 104 (30), 91 (41), 57 (28); Anal.

calcd. for C₁₈H₂₃NO₂: C, 75.76; H, 8.12; N, 4.91 Found: C, 75.57; H, 8.12; N, 5.09; [α]_D²⁸ = -13 (c = 0.72, CH₂Cl₂).

1D NOESY experiments on **11** were carried out with a Varian MERCURY plus spectrometer (H-400 MHz) using the automatic pulse sequence NOESY 1D (main parameters used: sw=3998, at=2.664, ss=-2, d1=1, nt=64, spin off; lb=0.38 for the processing). The sample (10 mM in CDCl₃) was carefully degassed by bubbling argon through the solution and the experiments were run at 24 °C varying the mixing times (150 ms, 350 ms, 500 ms, 800 ms and 1000 ms).

Synthesis of 12: Acid Hydrolysis of Compound 11. 37% HCl (50 μ L) is diluted with methanol (2 mL) and compound **11** (18 mg, 0.06 mmol) is dissolved in that solution. The mixture is stirred at rt for 2 h and then concentrated to give analytically pure **12** (13.5 mg, 0.048 mmol).

(3a*R*,6*S*,10a*S*,10b*S*)-2,2-Dimethyl-6-phenyl-3a,6,7,10,10a,10b-hexahydro-4*H*-

[1,3]dioxolo[3,4]pyrrolo[1,2-*a*]azepin-5-ium chloride (12**).** Very hygroscopic solid, decomposes without melting over 280 °C, 80% yield. ¹H NMR (400 MHz, D₂O) δ 7.33 (m, 5H), 5.70 (bt, 1H, *J* = 9.7 Hz), 5.57-5.52 (m, 1H), 4.83 (bd, 1H, *J* = 11.7 Hz), 4.09-4.05 (m, 1H), 4.02 (dd, 1H, *J* = 6.2, 4.0 Hz), 3.94 (bdd, 1H, *J* = 10.2, 6.2 Hz), 3.15 (dd, 1H, *J* = 12.5, 2.7 Hz), 3.08-2.88 (m, 2H), 2.75 (bd, 1H, *J* = 12.5 Hz), 2.43 (bdd, 1H, *J* = 17.3, 5.7 Hz), 2.35 (bdd, 1H, *J* = 15.0, 9.7 Hz); ¹³C NMR δ 135.7 (s, 1C), 129.8 (d, 1C), 129.5 (d, 2C), 128.1 (d, 1C), 127.6 (d, 2C), 125.7 (d, 1C), 76.3 (d, 1C), 69.8 (d, 1C), 67.8 (d, 1C), 64.6 (d, 1C), 58.0 (t, 1C), 34.8 (t, 1C), 26.3 (t, 1C) cm⁻¹; MS (CI) *m/z* (rel. int.) 173 (13), 123 (14), 111 (17), 85 (33), 71 (79), 69 (78), 57 (100), 55 (77); Anal. calcd.

for $\text{C}_{15}\text{H}_{20}\text{NO}_2 \cdot 9/10 \text{ H}_2\text{O}$: C, 60.46; H, 7.37; N, 4.70 Found: C, 60.59; H, 7.24; N, 4.73; $[\alpha]_{\text{D}}^{26} = +24$ ($c = 0.97$, CH_3OH).

Synthesis of 13 for Structural Determination of Compound 4e by X-ray Analysis: Partial Acetylation of Vinyl Derivative 4e. Acetic anhydride (283 μ L, 3 mmol) is added to a stirred solution of hydroxylamine **4e** (319 mg, 1 mmol) in THF (10 mL) and the mixture is heated under reflux for 1.5 h. A saturated aqueous solution of sodium carbonate (15 mL) is then added. The product is extracted with ethyl acetate (3x10 mL). The organic phase is dried over anhydrous Na₂SO₄, then filtered and concentrated. After purification by flash column chromatography the pure desired product **13** (343 mg, 0.95 mmol) is recovered.

[(1*S*,2*R*)-2-((1*S*)-1-{(Acetyloxy)[(1*R*)-1-phenylprop-2-enyl]amino}prop-2-enyl)-4,4-

dimethylcyclopentyl]methanol (13). White solid, 95% yield (eluent ethyl acetate:petroleum benzene=1:3, R_f =0.28); mp = 94-96 °C; ^1H NMR (400 MHz) δ 7.44-7.31 (m, 5H), 6.07 (dt, 1H, J = 16.8, 9.8 Hz), 5.97 (dt, 1H, J = 17.3, 9.9 Hz), 5.59 (dd, 1H, J = 9.9, 1.5 Hz), 5.17 (bd, 1H, J = 16.8 Hz), 5.11 (dd, 1H, J = 17.3, 1.5 Hz), 5.05 (bd, 1H, J = 9.8 Hz), 4.73 (bs, 1H, exchanging proton), 4.53 (d, 1H, J = 9.8 Hz), 4.36 (dt, 1H, J = 9.8, 5.2 Hz), 4.07 (dd, 1H, J = 9.9, 5.2 Hz), 3.65-3.56 (m, 1H), 3.46 (bdd, 1H, J = 11.4, 9.8 Hz), 3.37 (t, 1H, J = 9.9 Hz), 2.06 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H); ^{13}C NMR δ 170.9 (s, 1C), 137.6 (d, 1C), 137.1 (s, 1C), 130.9 (d, 1C), 128.9 (d, 2C), 128.5 (d, 3C), 122.7 (t, 1C), 117.6 (t, 1C), 108.0 (s, 1C), 78.1 (d, 1C), 75.4 (d, 1C), 73.9 (d, 1C), 64.8 (d, 1C), 59.3 (t, 1C), 27.2 (q, 1C), 25.1 (q, 1C), 18.9 (q, 1C); IR (KBr) 3433 (s), 3088 (w), 3025 (w), 2982 (m), 2948 (m), 2901 (w), 2865 (m), 1755 (s), 1642 (m), 1494 (m), 1455 (m), 1405 (m), 1383 (s), 1372 (s), 1219 (s), 1067(s) cm^{-1} ; MS m/z (rel. int.) 361 (M^+ , 3), 299 (1), 288 (1), 258 (2), 230 (10), 117 (100), 91 (12), 59 (22); Anal. calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_5$: C, 66.46; H, 7.53; N, 3.88 Found: C, 66.45; H, 7.44; N, 3.48; $[\alpha]_{\text{D}}^{28} = -145$ (c = 0.91, CH_2Cl_2).

X-Ray Structural Analyses

Analyses on single crystals were carried out with a Siemens P4 X-Ray diffractometer at room temperature. Graphite-monochromated Cu K α radiation was used for cell parameter determination and data collection. The intensities of three standard reflections were monitored during data collection to check the stability of the crystal and no loss of intensity was recognized. The integrated intensities, measured using the $\theta/2\theta$ scan mode, were corrected for Lorentz and polarization effects.^{S2} The non-hydrogen atoms were refined anisotropically; aromatic, methyl and some methylene hydrogens were assigned in calculated positions, the others were found in the Fourier difference synthesis; all of them were refined as isotropic. These structures were solved by direct methods of SIR97^{S3} and refined using the full-matrix least squares on F² provided by SHELXL97.^{S4}

The X-ray CIF files for these structures have been deposited at the Cambridge Crystallographic Data Center and allocated with the deposition numbers **CCDC 255050** for compound **4d'**, **CCDC 255051** for compound **13**, **CCDC 255052** for compound **10** and **CCDC 255053** for compound **4a**.

Compound 4a

C₃₂H₅₀N₂O₈, M=590.74, Orthorhombic, space group C 2221, $a=11.541(1)$, $b=11.657(1)$, $c=25.231(4)\text{\AA}$, $V=3394.4(7)\text{\AA}^3$, $Z=4$ $D_c=1.156$, $\mu=0.670\text{ mm}^{-1}$, $F(000)=1280$.

1976 reflections were collected with a $3.50<\theta<64.21$ range; 1863 were independent and the final R index was 0.0451 for reflections having $I>2\sigma I$, and 0.0464 for all data.

Compound 4d'

C₂₀H₂₉NO₄, M=347.44, Tetragonal, space group P 41 21 2, $a=9.582(2)$, $b=9.602(2)$, $c=43.305(4)\text{\AA}$, $V=3984.3(12)\text{\AA}^3$, $Z=8$ $D_c=1.158$, $\mu=0.644\text{ mm}^{-1}$, $F(000)=1504$.

3727 reflections were collected with a $4.08<\theta<55.01$ range; 2492 were independent and the final R index was 0.0745 for reflections having $I>2\sigma I$, and 0.0830 for all data.

Compound 10

C₁₈H₂₅NO₃, M=303.39, Monoclinic, space group P 21, $a=10.293(2)$, $b=8.086(3)$, $c=10.357(3)\text{\AA}$, $\beta=103.34(2)$, $V=838.7(4)\text{\AA}^3$, $Z=2$ $D_c=1.201$, $\mu=0.648\text{ mm}^{-1}$, $F(000)=328$.

1959 reflections were collected with a $4.39<\theta<64.06$ range; 1679 were independent and the final R index was 0.0525 for reflections having $I>2\sigma I$, and 0.0539 for all data.

Compound 13

C₂₀H₂₇NO₅, M=361.43, Orthorhombic, space group P 21 21 21, $a=7.689(1)$, $b=15.008(1)$, $c=17.888(2)\text{\AA}$, $V=2064.2(4)\text{\AA}^3$, $Z=4$ $D_c=1.163$, $\mu=0.680\text{ mm}^{-1}$, $F(000)=776$.

2315 reflections were collected with a $3.84<\theta<59.98$ range; 2143 were independent and the final R index was 0.0409 for reflections having $I>2\sigma I$, and 0.0427 for all data.

References and Notes

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