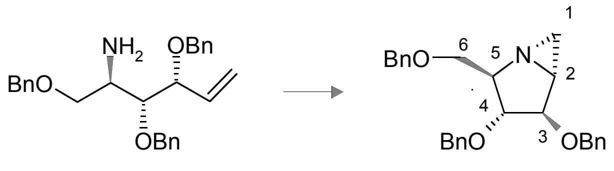
Sugar-derived aziridines : functionalization via lithiation of the aziridine ring

Experimental procedures and spectroscopic data



3 **5**

To a solution of amine **3** (226 mg, 0.54 mmol) in CH_3CN (25 mL), under Ar atmosphere, was added DMAP (289 mg, 2.4 mmol), dissolved in CH_3CN (5 mL). A solution of TfN_3* in CH_2Cl_2 (1.7 mmol) was added and the mixture was heated to 40°C for 3 h. The solvent was removed and the residue was purified on silica gel (eluent: Cyclohexane/AcOEt 8/2 then 1/1) to give **5** as a pale yellow oil (124 mg) 55%.

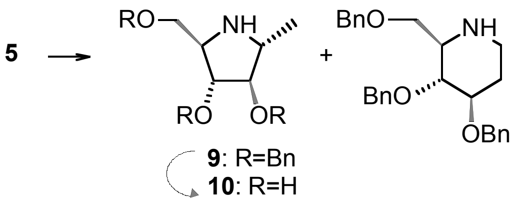
α_D= -18.7 (c=1.7)

^1H NMR(500 MHz, $CDCl_3$): δ 1.80 (dd, 1H, *J*=3.7 *J*=0.8, H_1); 1.83 (dd, 1H, *J*=6.1 *J*=0.8, $H_{1'}$); 2.57 (ddd, 1H, *J*=6.1 *J*=3.7 *J*=0.9, H_2); 3.35 (dd, 1H, *J*=6.1 *J*=9.2, H_5); 3.41 (t, 1H, *J*=9.2, H_6); 3.70 (dd, 1H, *J*=9.2 *J*=6.1, $H_{6'}$); 4.02 (t, 1H, *J*=0.9, H_4); 4.17 (s, 1H, H_3); 4.43 (2d, 2H, *J*=11.0, O-C$\underline{H}_2$-Ph); 4.46 (s, 2H, O-C$\underline{H}_2$-Ph); 4.59 (2d, 2H, *J*=11.4, O-C$\underline{H}_2$-Ph); 7.24-7.34 (m, 15H, Ph).

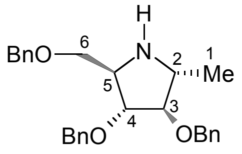
^{13}C NMR (62.5 MHz, $CDCl_3$) : δ 28.7 (C_1), 43.4 (C_2), 69.2 (C_5), 73.1-71.4-71.1-71.0 (4xO-$\underline{C}H_2$), 83.9 (C_3), 86.9 (C_4), 128.4-127.5 (3xPh), 138.2-137.7 (C ipso).

* Preparation of TfN_3.

To a cold (0°C) solution of NaN_3 (1.60 g, 24.6 mmol) in water (4 mL) were successively added CH_2Cl_2 (5 mL) and, under vigorous stirring, Tf_2O (0.82 mL, 5 mmol), freshly distilled over P_2O_5. The mixture was then stirred at 0°C for 2 h.
The organic layer was recovered, the aqueous layer was extracted with CH_2Cl_2 (3x3 mL). The combined organic solutions were washed with saturated $NaHCO_3$ (4 mL), water, then dried over Na_2SO_4.
The 0.18 M solution of TfN_3 thus obtained was kept at 4°C over 4Å molecular sieves.



The aziridine **5** (15 mg, 0.04 mmol), was dissolved in AcOEt (5 mL) and hydrogenated over $Pd(OH)_2$/C, 10%. The reaction mixture was stirred for 12h under pressure (5 bar). The catalyst was filtered-off, the solvent was removed and the residue was purified (silica-gel plate, eluent: Cyclohexane/AcOEt 2/8). The least polar fraction is **9** (7 mg, 55%), the other fraction is a piperidine derivative (4 mg, 25%).

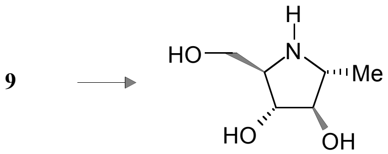


9

R_f= 0.35 (Silicagel plate, AcOEt/MeOH 92/8)

^{1}H NMR(250 MHz, $CDCl_3$): δ 1.22 (d, 3H, *J*=6.6, H_1); 3.22 (dq, 1H, *J*=6.6 *J*=5.6, H_2); 3.53-3.39 (m, 3H, H_5, H_6, $H_{6'}$); 3.63 (dd, 1H, *J*=3.5 *J*=5.6, H_3); 3.88 (dd, 1H, *J*=3.5 *J*=3.7, H_4); 4.53 (m, 6H -C$\underline{H}_2$-Ph); 7.32-7.27 (m, 15H, Ph).

^{13}C NMR(62.5 MHz, $CDCl_3$): δ 19.2; 57.3; 61.7; 70.4; 71.8; 71.9; 73.2; 86.4; 90.7; 128.3-127.,6 (3xPh); 138.1(C ipso).

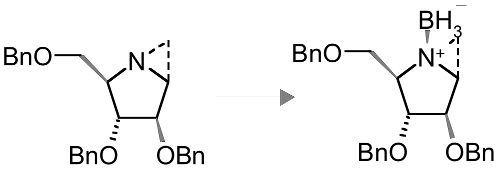


10

9 (7 mg , 0.017 mmol), was dissolved in *i*-PrOH (5mL) and hydrogenated over $Pd(OH)_2$/C, 10% (10 mg). The reaction mixture was stirred for 45 h under pressure (50 bar). The catalyst was filtered-off, the solvent was removed and the residue was purified (silica-gel plate, eluent: $CHCl_3/MeOH/H_2O/NH_4OH$ 5/4/1/0.1) to afford **10** (1mg, 40%).

R_f= 0.20 ($CHCl_3/MeOH/H_2O/NH_4OH$, 5/4/1/0.1)

^{1}H NMR (250 MHz, CD_3OD): δ 1.18 (d, 3H, *J*=6.5, 3xH_1); 2.92 (dq, 1H, *J*=6.5 *J*=8.0, H_2); 2.98 (dt, 1H, *J*=5.0 *J*=6.7, H_5); 3.47 (dd, 1H, *J*=8.0 *J*=6.8, H_3); 3.54 (dd, 1H, *J*=11.2 *J*=6.7, H_6); 3.63 (dd, 1H, *J*=11.2 *J*=5.0, $H_{6'}$); 3.76 (dd, 1H *J*=6.8 *J*=6.7, H_4).
Litt[7] (500 MHz, CD_3OD): δ 1.19 (d, 3H, *J*=6.5, 3xH_1); 2.92 (dq, 1H, *J*=6.5 *J*=7.5, H_2); 2.98 (ddd, 1H, *J*=4.5 *J*=6.5 *J*=6.5, H_5); 3.50 (dd, 1H, *J*=7.5 *J*=6.5, H_3); 3.54 (dd, 1H, *J*=11 *J*=6, H_6); 3.64 (dd, 1H, *J*=11 *J*=4.5, $H_{6'}$); 3.75 (dd, 1H *J*=6.5 *J*=6.5, H_4).



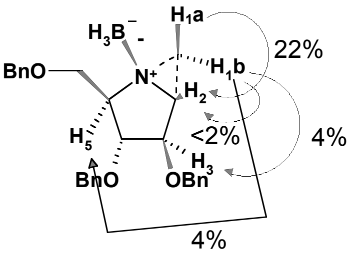
5 **6**

To a cold (0°C) solution of **5** (47 mg, 0.12 mmol) in THF (2 mL), was added BH_3-THF (1M in THF, 0.16 mL, 0.16 mmol) via syringe. After 30 min the solvent was evaporated and the residue was filtered through a pad of silicagel (eluent: Cyclohexane/AcOEt 7/3) to afford pure **6** (46 mg, 90%) as a white gum.

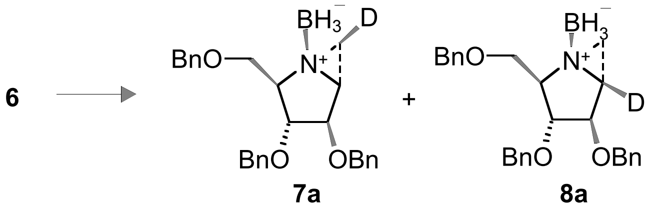
R_f= 0.50 (Cyclohexane/AcOEt 8/2).

^{1}H NMR (250 MHz, $CDCl_3$): δ 0.9-2.1 (very broad signal, 3H, BH_3); 2.41 (dd, 1H, *J*=1.6 *J*=7.2, H_1); 2.68

J=5.0, $H_{6'}$); 4.39 (s, 2H, O-C$\underline{H}_2$-Ph); 4.42 (2d, 2H, *J*=12.5, O-C$\underline{H}_2$-Ph); 4.53 (2d, 2H, *J*=12.5, O-C$\underline{H}_2$-Ph); 7.24-7.34 (m, 15H, Ph).

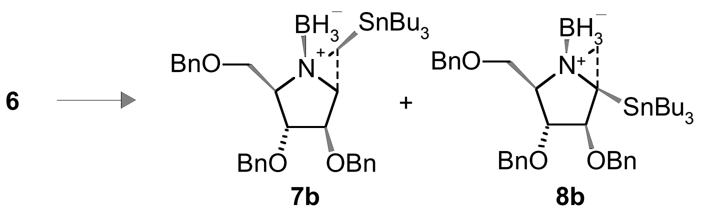


^{13}C NMR (62.5 MHz, $CDCl_3$) : δ 39.2 (C_1), 52.2 (C_2), 69.3 (C_5), 73.3-71.5-71.3-67.8 (4xO-$\underline{C}H_2$), 81.9 (C_3 or C_4), 84.7 (C_4 or C_3), 127.6-128.5 (3xPh), 136.9-137.9 (C ipso).



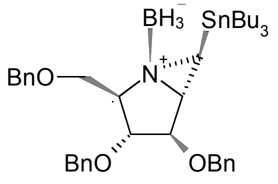
The complex **6** (30 mg, 0.07 mmol), was placed in a 10 mL, round-bottomed flask, under Ar atmosphere. Cumene (1mL), was added, then *(-)*-sparteine (64 µL, 0.28 mmol). The mixture was cooled to –78°C, and *sec*-BuLi (215 µL, 0.28 mmol) was added. After stirring for 6 h, D_2O (10 eq.) was added. The mixture was extracted three times with *t*-butyl methyl ether (3x1.5 mL), the solvent was removed under vacuum and the residue was purified by chromatography (silicagel plate, eluent: Cyclohexane/AcOEt 7/3) to give a 1:1 mixture of **7a** and **8a** (24 mg, 80%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 0.9-2.1 (very broad signal, 3H, BH_3); 2.41 (d, 0.5H, *J*=1.6, H_1 (**8a**)); 2.68 (m, 1H, $H_{1'}$ (**7a** + **8a**)); 2.97 (d, 0.5H, *J*=4.6, H_2(**7a**)); 3.49 (ddd, 1H, *J*=12.5 *J*=5.0 *J*=1.0, H_5); 3.56 (dd, 1H, *J*=10.0 *J*=12.5, H_6); 4.03 (s, 1H, H_3); 4.28 (s, 1H, H_4); 4.32 (dd, 1H, *J*=10.0 *J*=5.0, $H_{6'}$); 4.39 (s, 2H, O-C$\underline{H}_2$-Ph); 4.42 (2d, 2H, *J*=12.5, O-C$\underline{H}_2$-Ph); 4.53 (2d, 2H, *J*=12.5, O-C$\underline{H}_2$-Ph); 7.24-7.34 (m, 15H, Ph).



The complex **6** (19 mg, 0.044 mmol), was placed in a 2 mL, round-bottomed flask, under Ar atmosphere ; cumene (1 mL) was added then *(-)*-sparteine (42 µL, 0.18 mmol). The mixture was cooled to -78°C and *sec*-BuLi (136 µL, 0.18 mmol) was added. The mixture was stirred at -78°C for 5h and Bu_3SnCl (60 µL, 0.22 mmol) was added. The bath was removed and the mixture was stirred for 30 min at which time $NaHCO_3$ (saturated, 0.2 mL) was added.

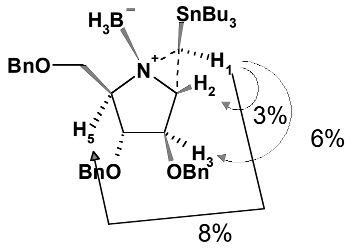
The mixture was extracted twice with CH_2Cl_2 (2x1.5 mL), the solvent was removed under reduced pressure and the residue was purified on a thick silicagel plate (eluent: Cyclohexane/AcOEt 97/3, 2 migrations) to



7b

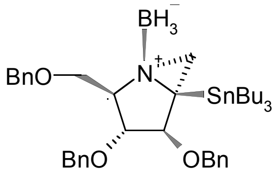
R_f=0.5 (Cyclohexane/AcOEt 9/1).

^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, 9H, *J*=7.2, CH_3); 1.03 (m, 6H); 1.32 (m, 6H); 1.49 (m, 6H); 2.17 (d, 1H; *J*=6,7, H_1); 2.82 (d, 1H, *J*=6.7, H_2); 3,38 (dd, 1H, *J*=4.6 *J*=11.6, H_5); 3.58 (dd, 1H, *J*=9.1 *J*=4.6, H_6); 4.03 (s, 1H, H_3); 4.26 (s, 1H, H_4); 4.28 (d, 1H, *J*=11.6 *J*=9.1, $H_{6'}$); 4.39 (s, 2H, O-C$\underline{H}_2$-Ph); 4.43 (2d, 2H, *J*=12.1, O-C$\underline{H}_2$-Ph); 4.53 (2d, 2H, *J*=11.8, O-C$\underline{H}_2$-Ph); 7.34-7.21 (m, 15H, Ph).



^{13}C NMR (62.5MHz, $CDCl_3$): δ 11.6; 14.3; 27.2; 28.3; 41.7 (C_1); 55.8 (C_2); 68.7 (C_5); 73.3-71.5-71.3-71.0 (OCH_2); 83.4 (C_3 or C_4); 86.0 (C_4 or C_3); 128.5-127.6 (3xPh); 138.1-137.8-137.3 (C ipso).

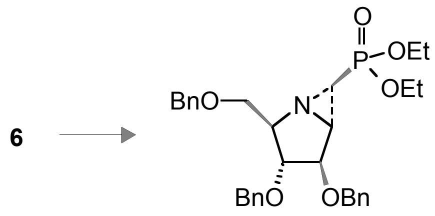
HRMS (ESI, CH3CN) calcd for for $C_{39}H_{58}BNO_3Sn$ ($-BH_3$ +H) 706.3291, found 706.3294



8b

R_f=0.55 (Cyclohexane/AcOEt 9/1).

^{1}H NMR (250 MHz, $CDCl_3$): δ 0.86 (m, 9H); 0.95 (m, 6H); 1.23 (m, 6H); 1.45 (m, 6H); 2.23 (s, 1H, H_1); 2.78 (s, 1H, $H_{1'}$); 3.41 (dd, 1H, *J*=9,7 *J*=11,5, H_6); 3.61(dd, 1H, *J*=5,7 *J*=9,7, H_5); 3.93 (s, 1H, H_3); 4.24 (s, 1H, H_4); 4.30 (m, 6H, O-C$\underline{H}_2$-Ph); 4.58 (dd, 1H, *J*=11,5 *J*=5.7 $H_{6'}$); 7.30-7.26 (m, 15H, Ph).



7c

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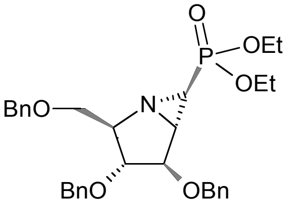
1. *Using ClP(OEt)$_2$*

The complex **6** (17 mg, 0.04 mmol), was placed in a 2 mL, round-bottomed flask, under Ar atmosphere, mmol) was added. The bath was replaced by a cool (-30°C) bath and the mixture was stirred for 2 h at which time $NaHCO_3$ (saturated, 0.2 mL) was added.

The mixture was extracted twice with CH_2Cl_2 (2x1,5 mL), the solvent was removed under reduced pressure and the residue was purified on a thick silicagel plate (eluent : Cyclohexane/AcOEt 1/9) to afford **7c** (3.4 mg, 20%).

2. Using $ClP(O)(OEt)_2$

Same procedure as above except $ClP(O)(OEt)_2$ was used and the mixture was stirred for 15 min at –30°C (instead of 2h). The yield was 15%.



7c

R_f=0.3 (Cyclohexane/AcOEt 1/9).

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (m, 6H); 2.24 (dd, 1H; J=3.4 $J^2{}_{P,C}$=16.6, H_1); 2.89 (dd, 1H, J=3.4 $J^3{}_{P,C}$=9.8, H_2); 3.37 (dd, 1H, J=10.6 J=8.0, H_6); 3.44 (dd, 1H, J=10.6 J=4.1, H_5); 3.80 (dd, 1H, J=8.0 J=4.1, $H_{6'}$); 4.07 (s, 1H, H_4); 4.21-4.01 (m, 4H); 4.22 (s, 1H, H_3); 4.42 (s, 2H, O-C$\underline{H_2}$-Ph); 4.42 (2d, 2H, J=12.0, O-C$\underline{H_2}$-Ph); 4.47 (2d, 2H, J=6.0, O-C$\underline{H_2}$-Ph); 7.37-7.22 (m, 15H, Ph).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ16.4 (2C); 32.5 (d, $J_{C,P}$=208 C_1); 47.4 (d, $J_{C,P}$=5 C_2); 62.5 (2xCH_2) 70.1 (C_5); 73.1-71.6-71.3-70.6 (OCH_2); 83.6 (C_3 or C_4); 86.1 (C_4 or C_3); 128.6-127.6 (3xPh); 138.2-137.5-137.4 (C ipso).

^{31}P NMR (101.5 MHz): 22.37.

HRMS (ESI, MeOH) calcd for $C_{31}H_{38}NO_6P$ (+Na) 574.2334, found 574.2342