A Route to (2α,3β,4α)-(±)-2-(Hydroxymethyl)-3,4-pyrrolidinediol Based on the α-Silyloxyallylation of a Glycolaldehyde-Derived Nitrone

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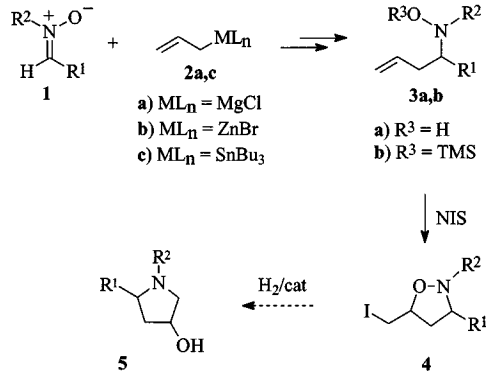
A protected form of title compound **6a**, whose two enantiomers are known to be potent α-glycosidase inhibitors, was obtained through a five-step synthesis based on two thoroughly diastereo-controlled steps. An *anti*-selective α-silyloxyallylation of nitrone **9** afforded hydroxylamine **8a** which, after *O*-silylation, was subjected to iodocyclisation to give 5-iodomethylisoxazolidine **7a** as a single diastereoisomer. Displacement of iodide by mesylate and hydrogenolysis of mesylate **7b** furnished **6b** in 20 % overall yield starting from *tert*-butyldimethylsilyloxyacetaldehyde.

Introduction

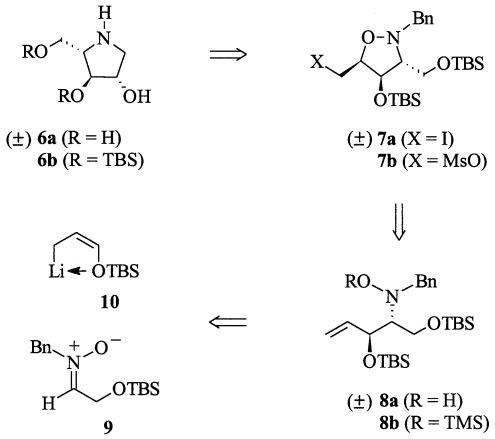
The allylation of nitrones **1** by means of allylic derivatives **2** of magnesium[1][2][3], zinc[4], and tin[5] leads to homoallylic hydroxylamines **3a** which, after silylation to **3b**, are efficiently transformed into 5-iodomethylisoxazolidines **4** by *N*-iodosuccinimide-(NIS-)promoted iodocyclisation. Formally, the final heterocyclic product **4** can be considered a precursor of pyrrolidine **5** since N−O bond hydrogenolysis could be followed by spontaneous intramolecular *N*-alkylation (Scheme 1), as observed in related isoxazolines by Jäger et al.[6].

Scheme 1



Among possible targets, we recognised (2α,3β,4α)-(±)-2-(hydroxymethyl)-3,4-pyrrolidinediol (**6a**) as an attractive candidate for testing our strategy. Both enantiomers of **6a**, naturally occurring 1,4-dideoxy-1,4-imino-D-arabinitol (DAB1) isolated from *Arachniodes standishii* and *Angilocalix boutiqueanus* and synthetic 1,4-dideoxy-1,4-imino-L-arabinitol (LAB1), display powerful activity against α-glycosidases[7]. Our retrosynthetic plan, shown in Scheme 2, involves the isoxazolidine **7a** as key intermediate, and the α-silyloxyallylation of nitrone **9** by means of lithiated allyl ether **10**, as the key step.

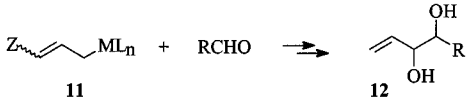
Scheme 2



Results and Discussion

The synthetic usefulness of the diol **12**, which are often embodied into the framework of naturally occurring compounds and which can be easily converted into a variety of polyfunctionalised molecules, has prompted the search for several functionalised allylic metal complexes **11** able to add to aldehydes affording 3-ene-1,2-diol systems **12** (Scheme 3).

Scheme 3



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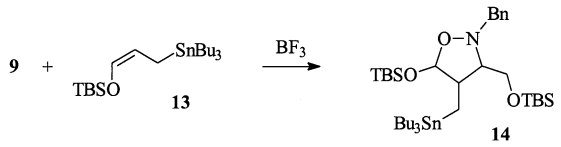
Typical examples of functionalised allylic metal complexes include **11a** (Z = OMe or OTHP, ML_n = Li)[8], **11b** (Z = OTMS, ML_n = $SnBu_3$)[9], **11c** (Z = OMe, ML_n = $SnBu_3$)[10], **11d** (Z = OTHP, ML_n = $SnBu_3$)[11], **11e** (Z = OBn, ML_n = CrCl)[12], **11f** (Z = OMOM, ML_n = $InCl_2$)[13], **11g** [Z = OMOM, ML_n = $B(OR)_2$][14], **11h** (Z = OMOM, ML_n = R_3B^- or Et_3Al^-)[15], **11i** (Z = OMOM, ML_n = $BIpc_2$)[16], **11j** (Z = OMe, ML_n = $AlEt_2$)[17], **11k** [Z =(*i*Pr_2N)Me_2Si, ML_n = ZnCl][18], **11l** [Z = $PhMe_2$Si, ML_n = $B(OR)_2$][19], **11m** [Z = $(RO)_2$B, ML_n = $BIpc_2$][20].

Unfortunately, no record of α-hydroxyallylation reactions of nitrones is available in the literature, so we performed a careful screening for the identification of a good α-hydroxyallylating agent for nitrone **9**. Boranes and boronates did not react, zinc derivatives gave disappointing low and irreproducible yields and [3-(silyloxy)allyl]stannane **13** did react in the presence of $BF_3 \cdot EtO_2$ but as a silyl enol ether[21] affording **14** as a mixture of 2 diastereoisomers in a 1:2 ratio (Scheme 4)[21]. We only obtained acceptable results using the lithiated allyl silyl ether **10**.

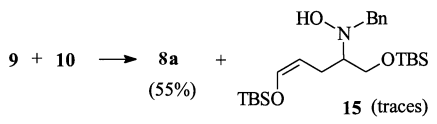
Scheme 4



In the 1970s Still et al. reported that condensation of lithiated allyl trimethylsilyl ether with carbonyl compounds takes place regioselectively in the presence of HMPTA affording α-adducts in excellent yields[22][23]. On the other hand, the observed lack of diastereoselectivity combined with the risk of concurrent sila Wittig/Brook rearrangements[24][25], probably discouraged further studies on the use of this organolithium compound in condensation reactions.

Not biased by the previous points, we carried out the preparation of **10** by metalating allyl *tert*-butyldimethylsilyl ether with *s*BuLi in THF at −40°C for 15 min. Nitrone **9** (0.8 equiv.) was added at − 40°C and the temperature was allowed to raise to −10°C. Analysis of the reaction mixture showed that: i) yields of **8a** in several replicate experiments never exceeded 35% both after 1 and 3 h at −10°C, ii) the α-adduct **8a** was diastereochemically pure, iii) no more than traces of (*Z*)-configurated regioisomeric γ-adduct **15** were obtained, and iv) remarkable but variable amounts of 1-(*tert*-butyldimethylsilyl)-2-propen-1-ol (sila Wittig product) were detected. The only way to increase the yield to 55% was to use 2 equivalents of **10** (Scheme 5).

Scheme 5



Attempts to improve the process by adding HMPTA (5%) as cosolvent or (−)-sparteine (equimolar to **10**) afforded disappointing results; the regioselectivity worsened slightly, the yield of **8a** did not increase and, using the chiral amine, no evidence of asymmetric induction was obtained[26].

Subsequent steps involve formation of **8b** (TMSCl, imidazole, 96%) and NIS-promoted iodocyclisation (82%)[27]. We were delighted to observe that iodocylisation led to a single diastereoisomer **7a**, possessing the 3,4-*trans*-4,5-*cis* stereorelationship. Having in our hands the right relative stereochemistry, we examined the last step, namely the hydrogenolysis of **7**.

Unfortunately, reductive deiodination was the fastest reaction when **7a** was exposed to hydrogen in the presence of $Pd(OH)_2$, thus we were forced to replace iodide with a leaving group stable to hydrogen. To this purpose we converted **7a** into mesylate **7b** (AgOMs, AcCN, 70°C) in 65% yield.

Hydrogenation of **7b** in the presence of $Pd(OH)_2$ resulted in a cascade process involving N−O cleavage, *N*-debenzylation and, finally, spontaneous cyclisation to **6b** which was isolated in 82% yield, 20% overall yield starting from (*tert*-butyldimethylsilyloxy)acetaldehyde.

Conclusion

In conclusion, this short synthetic route to a protected form of (2α,3β,4α)-(±)-2-(hydroxymethyl)-3,4-pyrrolidinediol (**6a**) is denoted by two thoroughly diastereocontrolled steps, namely the hydroxyallylation of a nitrone by the lithium derivative **10**, and the iodocylisation of **8b** to **7a**. If the *anti* selectivity displayed by **10** was confirmed with other substrates, **10** and related carbanions would enjoy a renewed interest, for example for the synthesis of 2-amino-3-en-1-ol substructures. Finally, it is worth noting the strong steric and electronic effect exerted by the TBSO group in controlling the 5-*exo*-*trig* ring closure reaction which affords a virtually pure 3,4-*trans*-4,5-*cis* isoxazolidine. To make a comparison, when the TBSO group in **8** is replaced by a methyl group, a reversed stereoselectivity is observed, and in particular 3,4-*trans*-4,5-*trans* and 3,4-*trans*-4,5-*cis* isoxazolidines are obtained in a 3:1 ratio[4].

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Experimental Section

General Remarks: All reactions were performed in oven-dried glassware under dry argon. − NMR: Varian Gemini 300 (300 and 75 MHz, for ^1H and ^{13}C, respectively; $CHCl_3$ at δ_H = 7.27 and $CDCl_3$ at δ_C = 77.0 as internal standard). − GC-MS: HP 5890 II instrument connected to HP 5970 quadrupole mass detector. − IR: Nicolet 205. − CC: Merck Kieselgel 60. − TLC: Merck silica gel plates (60F-254). Water content of anhydrous solvents used was determined by Karl-Fisher titrator Mettler DL18. Hydrogenations were performed at 45 p.s.i. on a Parr apparatus. Moist 20%

$Pd(OH)_2$ on carbon (Degussa type E101) was purchased from Aldrich. Melting points are uncorrected.

N-Benzyl-2-(tert-butyldimethylsilyloxy)ethylideneamine N-Oxide (**9**): *tert*-Butyldimethylsilyloxyacetaldehyde (0.87 g, 5.0 mmol) and *N*-benzylhydroxylamine (0.62 g, 5.0 mmol) were allowed to react in CH_2Cl_2 (5 ml) for 12 h in the presence of Na_2SO_4. After filtration (Celite) and solvent evaporation, pure nitrone **9** (1.2 g, 86%) was obtained as a dense oil by flash chromatography on SiO_2 (ethyl acetate/cyclohexane, 3:7). – ^{1}H NMR ($CDCl_3$): δ = 0.06 [s, 6 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $SiC(CH_3)_3$], 4.60 (dt, $J_{2\text{-H,NCH2Ph}}$ = 1.4 Hz, $J_{2\text{-H,1-H}}$ = 4.1 Hz, 2 H, 2-H), 4.88 (br s, 2 H, NCH_2Ph), 6.77 (t, $J_{1\text{-H,2-}H}$ = 4.1 Hz, 1 H, 1-H), 7.42 (s, 5 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = −5.5 [$Si(CH_3)_2$], 18.2 [$SiC(CH_3)_3$], 25.8 [$SiC(CH_3)_3$], 60.0 (NCH_2Ph), 68.8 (C-2), 129.0, 129.1, 129.5, 132.4, 140.4 (C-1). – $C_{15}H_{25}NO_2Si$ (279.2): calcd. C 64.48, H 9.03, N 5.02; found C 64.62, H 8.91, N 5.14.

N-Benzyl-1,3-bis(tert-butyldimethylsilyloxy)-N-hydroxy-4-penten-2-amine (**8a**): *tert*-Butyldimethyl(2-propenyloxy)silane (0.85 ml, 4 mmol) was added to a solution of *s*BuLi (1.3 M in cyclohexane, 3.10 ml, 4 mmol) in THF (8 ml) at −40°C and the solution was stirred for 15 min at −40°C. Nitrone **9** (0.56 g, 2 mmol) was added and after an additional 15 min at −40°C the solution was warmed to −10°C. The reaction mixture was then stirred for 3 h allowing to reach room temperature. The solution was quenched with water, filtered (Celite), and the aqueous layer was extracted with diethyl ether (3 × 10 ml). The combined organic layers were dried (Na_2SO_4) and, after solvent evaporation, the crude reaction mixture was purified by flash chromatography on SiO_2 (ethyl acetate/cylohexane, 1:9) affording hydroxylamine **8a** (0.5 g, 55%) as a white solid and a trace of silyl enol ether **15** (0.004 g, 0.5%).

8a: M.p. 93−95°C. – IR (nujol): $\tilde{\nu}$ = 3202 cm^{-1} (br., OH). – ^{1}H NMR ($CDCl_3$): δ = 0.04 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.10 [s, 6 H, $Si(CH_3)_2$], 0.91 [s, 9 H, $SiC(CH_3)_3$], 0.93 [s, 9 H, $SiC(CH_3)_3$], 2.96 (br. q, $J \approx$ 6.0 Hz, 1 H, 2-H), 3.90 (dd, $J_{1\text{-Ha,2-H}}$ = 5.0 Hz, $J_{1\text{-Ha,1-Hb}}$ = 10.8 Hz, 1 H, 1-Ha), 4.09 (dd, $J_{1\text{-Hb,2-H}}$ = 6.3 Hz, $J_{1\text{-Hb,1-H}}$ = 10.8 Hz, 1 H, 1-Hb), 4.11 (s, 2 H, NCH_2Ph), 4.49 (br. t, $J \approx$ 5.5 Hz, 1 H, 3-H), 5.01 (s, 1 H, NOH), 5.15−5.30 (m, 2 H, 5-H), 6.05 (ddd, $J_{4\text{-H,3-H}}$ = 5.8 Hz, $J_{4\text{-H,5-HZ}}$ = 10.3 Hz, $J_{4\text{-H,5-HE}}$ = 16.5 Hz, 1 H, 4-H), 7.20−7.42 (m, 5 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = −5.4 [$Si(CH_3)_2$], −4.8 ($SiCH_3$), −4.2 ($SiCH_3$), 18.1 [$SiC(CH_3)_3$], 25.9 [$SiC(CH_3)_3$], 60.5, 62.3, 72.2, 73.1, 115.0 (C-4), 126.9, 128.2, 128.9, 139.1, 139.3 (C-5). – $C_{24}H_{45}NO_3Si_2$ (451.3): calcd. C 63.82, H 10.05, N 3.10; found C 63.97, H 10.12, N 3.02.

15: ^{1}H NMR ($CDCl_3$): δ = 0.09 [s, 6 H, $Si(CH_3)_2$], 0.13 [s, 6 H, $Si(CH_3)_2$], 0.92 [s, 18 H, $SiC(CH_3)_3$], 2.34−2.48 (m, 2 H, 3-H), 2.92 (br. quint, $J \approx$ 6.0 Hz, 1 H, 2-H), 3.78 (dd, $J_{1\text{-Ha,2-H}}$ = 4.4 Hz, $J_{1\text{-Ha,1-Hb}}$ = 10.7 Hz, 1 H, 1-Ha), 3.95 (dd, $J_{1\text{-Hb,2-H}}$ = 6.1 Hz, $J_{1\text{-Hb,1-Ha}}$ = 10.7 Hz, 1 H, 1-Hb), 3.98 (d, J = 14.0 Hz, 1 H, NCH_2Ph), 4.06 (d, J = 14.0 Hz, 1 H, NCH_2Ph), 4.57 (dt, $J_{4\text{-H,5-H}}$ = 6.0 Hz, $J_{4\text{-H,3-Ha}}$ = $J_{4\text{-H,3-Hb}}$ = 7.5 Hz, 1 H, 4-H), 5.32 (br. s, 1 H, NOH), 6.28 (d, $J_{5\text{-H,4-H}}$ = 6.0 Hz, 1 H, 5-H), 7.18−7.38 (m, 5 H, aromatic H).

2-Benzyl-4-(tert-butyldimethylsilyloxy)-3-(tert-butyldimethylsilyloxymethyl)-5-(iodomethyl)isoxazolidine (**7a**): Imidazole (0.11 g, 1.6 mmol) and TMSCl (0.20 ml, 1.6 mmol) were added to a solution of **8a** (0.58 g, 1.3 mmol) in CH_2Cl_2 (10 ml) and the reaction was stirred at room temperature for about 12 h. Hexane was added (5 ml), the solution was filtered (Celite) and concentrated at reduced pressure to afford silylated hydroxylamine **8b** (0.65 g, 96%) as a dense oil that was used without further purification. – GC-MS (70 eV); *m/z* (%): 508 (3) [$M^+ - CH_3$], 352 (53) [$M^+ - CH_2$=CHCHOTBS], 233 (5), 171 (5), 147 (18), 91 (100), 73 (51). **8b** was dissolved in $CHCl_3$ (10 ml), the solution was cooled to 0°C and NIS (0.36 g, 1.6 mmol) was added. After stirring in the dark for 4 h at 0°C, the reaction was quenched with aqueous $Na_2S_2O_3$ and the aqueous layer was extracted with $CHCl_3$ (3 × 10 ml). Pure isoxazolidine **7a** (0.59 g, 82%) was obtained as an oil by flash chromatography on SiO_2 (ethyl acetate/cyclohexane, 5:95). – ^{1}H NMR ($CDCl_3$): δ = 0.00 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.98 [s, 9 H, $SiC(CH_3)_3$], 3.22 (ddd, $J_{3\text{-H,4-H}}$ = 0.9 Hz, $J_{3\text{-H,CHbOSi}}$ = 5.9 Hz, $J_{3\text{-H,CHaOSi}}$ = 8.6 Hz, 1 H, 3-H), 3.26 (dd, $J_{CHaI,5\text{-H}}$ = 5.0 Hz, $J_{CHaI,CHbI}$ = 9.2 Hz, 1 H, CHaI), 3.38 (t, $J_{CHbI,5\text{-H}}$ = $J_{CHbI,CHaI}$ = 9.2 Hz, 1 H, CHbI), 3.43 (dd, $J_{CHaOSi,3\text{-H}}$ = 8.6 Hz, $J_{CHaOSi,CHbOSi}$ = 10.5 Hz, 1 H, CHaOSi), 3.50 (dd, $J_{CHbOSi,3\text{-H}}$ = 5.9 Hz, $J_{CHbOSi,CHaOSi}$ = 10.5 Hz, 1 H, CHbOSi), 4.11 (d, J = 12.9 Hz, 1 H, NCH_2Ph), 4.25 (ddd, $J_{5\text{-H,4-H}}$ = 4.0 Hz, $J_{5\text{-H,CHaI}}$ = 5.0 Hz, $J_{5\text{-H,CHbI}}$ = 9.2 Hz, 1 H, 5-H), 4.32 (d, J = 12.9 Hz, 1 H, NCH_2Ph), 4.58 (dd, $J_{4\text{-H,3-H}}$ = 0.9 Hz, $J_{4\text{-H,5-H}}$ = 4.0 Hz, 1 H, 4-H), 7.28−7.40 (m, 5 H, aromatic H). The 4-H/5-H *cis* and 3-H/4-H *trans* stereorelationships were determined by NOE experiments: upon irradiation of 4-H, a strong enhancement of 5-H (11%) and a weaker response of 3-H (4%) were observed. – ^{13}C NMR ($CDCl_3$): δ = −5.6 ($SiCH_3$), −5.5 ($SiCH_3$), −4.9 ($SiCH_3$), −4.1 ($SiCH_3$), −0.4 (CH_2I), 18.1 [$SiC(CH_3)_3$], 18.3 [$SiC(CH_3)_3$], 25.9 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 63.5, 64.0, 74.8, 77.3, 82.5, 127.4, 128.3, 129.2, 137.4. – GC-MS (70 eV); *m/z* (%): 518 (24) [$M^+ - C(CH_3)_3$], 392 (6) [$M^+ - I$], 281 (13), 220 (35), 207 (42), 171 (34), 147 (16), 105 (98), 73 (100). – $C_{24}H_{44}INO_3Si_2$ (577.2): calcd. C 49.90, H 7.68, N 2.43; found C 49.83, H 7.75, N 2.36.

2-Benzyl-4-(tert-butyldimethylsilyloxy)-3-(tert-butyldimethylsilyloxymethyl)-5-(mesyloxymethyl)isoxazolidine (**7b**): Isoxazolidine **7a** (0.29 g, 0.5 mmol) was dissolved in CH_3CN (3 ml), freshly prepared silver mesylate (0.15 g, 0.75 mmol) was added and the solution was refluxed for 5 h. The reaction mixture was filtered (Celite), the organic layer was washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4), and concentrated at reduced pressure. Mesylated isoxazolidine **7b** (0.18 g, 65%) was obtained as an oil by flash chromatography on SiO_2 (ethyl acetate/cyclohexane, 1:9). – ^{1}H NMR ($CDCl_3$): δ = 0.03 [s, 6 H, $Si(CH_3)_2$], 0.12 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.88 [s, 9 H, $SiC(CH_3)_3$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 2.88 (s, 3 H, SCH_3), 3.15 (ddd, $J_{3\text{-H,4-H}}$ = 2.1 Hz, $J_{3\text{-H,CHbOSi}}$ = 6.0 Hz, $J_{3\text{-H,CHaOSi}}$ = 7.9 Hz, 1 H, 3-H), 3.51 (dd, $J_{CHaOSi,3\text{-H}}$ = 7.9 Hz, $J_{CHaOSi,CHbOSi}$ = 10.7 Hz, 1 H, CHaOSi), 3.60 (dd, $J_{CHbOSi,3\text{-H}}$ = 6.0 Hz, $J_{CHbOSi,CHaOSi}$ = 10.7 Hz, 1 H, CHbOSi), 4.18−4.22 (m, 1 H, 5-H), 4.21 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 4.27 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 4.44 (dd, $J_{CHaOS,H\text{-}5}$ = 3.8 Hz, $J_{CHaOS,CHbOS}$ = 11.6 Hz, 1 H, C*H*aOSO$_2$CH$_3$), 4.51 (dd, $J_{CHbOS,5\text{-H}}$ = 7.7 Hz, $J_{CHbOS,CHaOS}$ = 11.6 Hz, 1 H, C*H*bOSO$_2$CH$_3$), 4.62 (dd, $J_{4\text{-H,3-H}}$ = 2.1 Hz, $J_{4\text{-H,5-H}}$ = 4.9 Hz, 1 H, 4-H), 7.28−7.40 (m, 5 H, aromatic H). The 4-H/5-H *cis* and 3-H/4-H *trans* stereorelationships were confirmed by NOE measurements: irradiation of 4-H caused a strong enhancement of 5-H (12%) and a weaker response of 3-H (3%). – ^{13}C NMR ($CDCl_3$): δ = −5.52 ($SiCH_3$), −5.47 ($SiCH_3$), −5.1 ($SiCH_3$), −4.5 ($SiCH_3$), 18.0 [$SiC(CH_3)_3$], 18.3 [$SiC(CH_3)_3$], 25.7 [$SiC(CH_3)_3$], 25.9 [$SiC(CH_3)_3$], 37.7 (CH_3SO_2), 62.9, 63.3, 69.2, 74.9, 78.1, 78.9, 127.4, 128.3, 129.0, 137.4. – $C_{25}H_{47}NO_6SSi_2$ (545.3): calcd. C 55.02, H 8.69, N 2.57; found C 55.13, H 8.76, N 2.49.

3-(tert-Butyldimethylsilyloxy)-2-(tert-butyldimethylsilyloxymethyl)-4-hydroxypyrrolidine (**6b**): Hydrogenation of **7b** (0.11 g, 0.2 mmol) in MeOH (10 ml) in the presence of $Pd(OH)_2$/C (0.025

g) was carried out at 45 p.s.i. for about 12 h. The reaction mixture was quenched with aqueous $NaHCO_3$, filtered (Celite) and methanol was removed at reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml), the combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Pyrrolidine **6b** (0.06 g, 82%) was obtained as a dense oil by flash chromatography on SiO_2 (ethyl acetate). − IR (neat): $\tilde{\nu}$ = 3265 cm^{-1} (sharp, NH), 3200 (br., OH). − ^1H NMR ($CDCl_3$): δ = 0.08 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.12 [s, 6 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $SiC(CH_3)_3$], 0.92 [s, 9 H, $SiC(CH_3)_3$], 2.95 (br. d, $J \approx 12.0$ Hz, 1 H, 5-H), 3.05−3.11 (m, 2 H, 2-H + 5-H), 3.74 (dd, $J_{CHaOSi,2\text{-}H}$ = 3.0 Hz, $J_{CHaOSi,CHbOSi}$ = 10.4 Hz, 1 H, CHaOSi), 3.79 (dd, $J_{CHbOSi,2\text{-}H}$ = 2.8 Hz, $J_{CHbOSi,CHaOSi}$ = 10.4 Hz, 1 H, CHbOSi), 3.83−3.86 (m, 1 H, 4-H), 3.87−3.91 (m, 1 H, 3-H). − ^{13}C NMR ($CDCl_3$): δ = −5.6 [$Si(CH_3)_2$], −4.8 ($SiCH_3$), −4.6 ($SiCH_3$), 18.0 [Si*C*$(CH_3)_3$], 18.4 [Si*C*$(CH_3)_3$], 25.7 [SiC(*C*$H_3)_3$], 25.9 [SiC(*C*$H_3)_3$], 54.1 (C-5), 63.3 (CH_2OSi), 68.5 (C-2), 78.1, 80.9. − GC-MS (70 eV); *m/z* (%): 361 (1) [M^+], 346 (1) [$M^+ - CH_3$], 304 (21) [$M^+ - C(CH_3)_3$], 216 (100) [$M^+ - TBSOCH_2$], 171 (16), 115 (16), 84 (20), 73 (88), 55 (36). − $C_{17}H_{39}NO_3Si_2$ (361.2): C 56.47, H 10.88, N 3.88; found: C 56.33, H 10.82, N 3.96.

N-Benzyl-5-(tert-butyldimethylsilyoxy)-3-(tert-butyldimethylsilyloxymethyl)-4-(tributylstannylmethyl)isoxazolidine (**14**): $BF_3 \cdot Et_2O$ (0.13 ml, 1 mmol) was added at 0°C to a solution of nitrone **9** (0.28 g, 1 mmol) in CH_2Cl_2 (5 ml) and stirred for 15 min. (*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-propene-1-tributylstannane (**13**) (0.55 g, 1.2 mmol), prepared according to Keck et al.,[9] was added and the reaction was stirred for 24 h allowing to reach room temperature. The reaction mixture was quenched with aqueous $NaHCO_3$, filtered (Celite), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic layers were dried (Na_2SO_4) and after solvent evaporation, isoxazolidine **14** (0.29 g, 40%) was obtained as an unseparable mixture of diastereoisomers in a 1:2 ratio by flash chromatography on SiO_2 (ethyl acetate/cyclohexane, 2:98). − ^1H NMR ($CDCl_3$): δ = 0.16−0.20 (m, 12 H, $SiCH_3$), 0.80−0.96 [m, 27 H, $SiC(CH_3)_3 + CH_3$], 1.22−1.55 (m, 18 H, $SnCH_2CH_2CH_2$), 2.59−2.67 (major isomer, m, 1 H, 4-H), 2.98−3.10 (major isomer, m, 1 H, 3-H), 3.68 (minor isomer, d, J = 7.0 Hz, 2 H, CH_2OSi), 3.78 (major isomer, d, J = 6.7 Hz, 2 H, CH_2OSi), 4.05 (s, 2 H, NCH_2Ph), 4.13 (minor isomer, d, J = 14.0 Hz, 1 H, NCH_2Ph), 4.31 (minor isomer, d, J = 14.0 Hz, 1 H, NCH_2Ph), 5.14 (minor isomer, d, J = 3.7 Hz, 1 H, 5-H), 5.22 (major isomer, d, J = 4.3 Hz, 1 H, 5-H), 7.20−7.40 (m, 5 H, aromatic H).

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