Pergamon

Tetrahedron 57 (2001) 6229–6238

TETRAHEDRON

Stereoselective allylic transposition by means of allylic *n*-pentenyl ethers. Part 2: Synthesis of nitrogen heterocycles☆

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Received 25 January 2001; revised 21 May 2001; accepted 29 May 2001

Abstract—Stereospecific synthesis of optically active substituted pyrrolidines, and piperidines was studied via an intramolecular allylic rearrangement by means of allylic *n*-pentenyl ethers as leaving groups when reacting with halonium ions. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

In a previous paper,[1] we reported the stereospecific synthesis of 1,3-diols and of substituted oxygen heterocycles, using a stereoselective intramolecular allylic substitution where *n*-pentenyl ethers served as switch for the generation of an allylic cation on subjection to haloniums ions[2] (Scheme 1, Eq. (1)). The starting material was acyclic, and the success of these reactions required the presence of a *n*-pentenyloxy moiety α to a double bond, the presence of a chiral substituent α′ to the same double bond and the participation of an internal nucleophile [carbonate (Scheme 1, Eq. (2)), benzyl ether (Scheme 1, Eq. (3)). The installation of a removable ligand on the double bond, generating an 1,3 allylic strain[3] between this ligand and the chiral substituent, favoured the nucleophilic attack on the opposite side to the substituent (Scheme 1, Eqs. (2) and (3)). The geometry of the new created halogenated double bond was *Z*, providing an *E* double bond after replacement of the vinylic ligand by hydrogen.[1,4,5] As shown in Scheme 1, the substrates undergoing the nucleophilic attack, were a mixture of epimers, differing for the configuration at the carbon bearing the leaving group. The fact that both epimers led to a *Z* configuration of the newly formed double bond, suggested that leaving group departure preceded nucleophile attack (SN1′ like mechanism).

The products so far obtained were unique,[1,4,5] with satisfactory yields. Therefore the syntheses of five- and six-membered nitrogen heterocycles were performed using this strategy (Scheme 2). In the present paper, our main results were presented.[4,6]

2. Results and discussion

Starting from 1-tosyloxy-2(*R*)-hydroxy-3(*S*)-methyl-6(*RS*)-pentenyloxy-hept-4-yne (**1**), previously described,[1,7] the pyrrolidine **2** and the piperidine **3** were first prepared.

On the one hand, the epoxyde **4** was transformed to the azide **5** by refluxing in EtOH in the presence of NaN_3. Reduction of **5** by $LiAlH_4$ in ether yielded the amine **6** which was regio and stereoselectively stannylated (**7**) using radical conditions,[8] before its transformation into the *p*-toluenesulfonamide **8**. This *N*-substitution was chosen on the basis of the results obtained by Tamaru et al.[9] which showed that sulfonamides were convenient nucleophiles for intramolecular haloamidation. Di-*sym*-collidine iodonium perchlorate was used as iodonium ions source because it was reported to ensure better results and shorter reaction time.[10] Thus, when **8** was reacted with di-*sym*-collidine iodonium perchlorate in $CHCl_3$ at 0°C for 3 h, the pyrrolidine **9**[4] was obtained in 88% yield. 2D NOESY experiment showed nOe interactions between H-3 and CH_3-9 and between H-5 and the same CH_3, thus confirming the expected *trans* relationship between the side chain and the methyl group. This compound was a mixture of conformers due to interaction between the iodine atom and the sulfonamido group as shown by duplication of some signals in the ^1H- and ^{13}C NMR spectra. Synthesis of the (3*R*,4*S*,5*R*)-pyrrolidine **2** was achieved by halogen–metal exchange using *t*-butyllithium

☆ See Ref. 1.

Keywords: *n*-pentenyl ethers; stereoselection; intramolecular allylic substitution; pyrrolidines; piperidines; 1,3-allylic effect.

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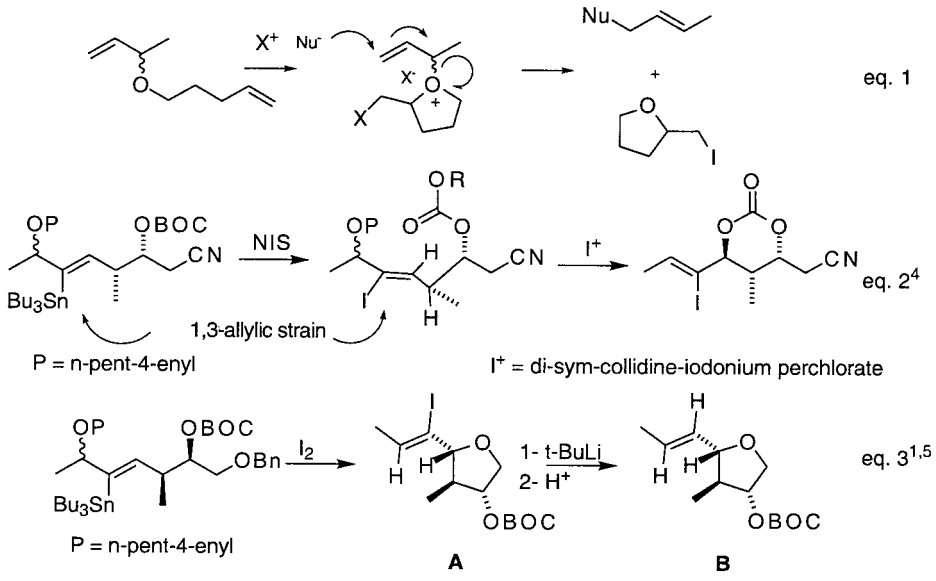
PII: S0040-4020(01)00602-0



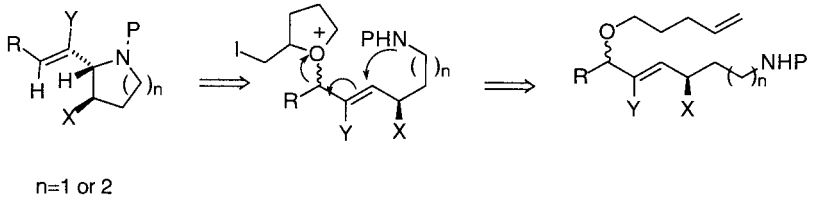
Scheme 1.

followed by acidic work-up.[1,11] Coupling constants of the olefinic protons in the ^{1}H NMR spectrum indicated an *E* geometry for the double bond ($J_{H6,H7}$=16 Hz) (Scheme 3).

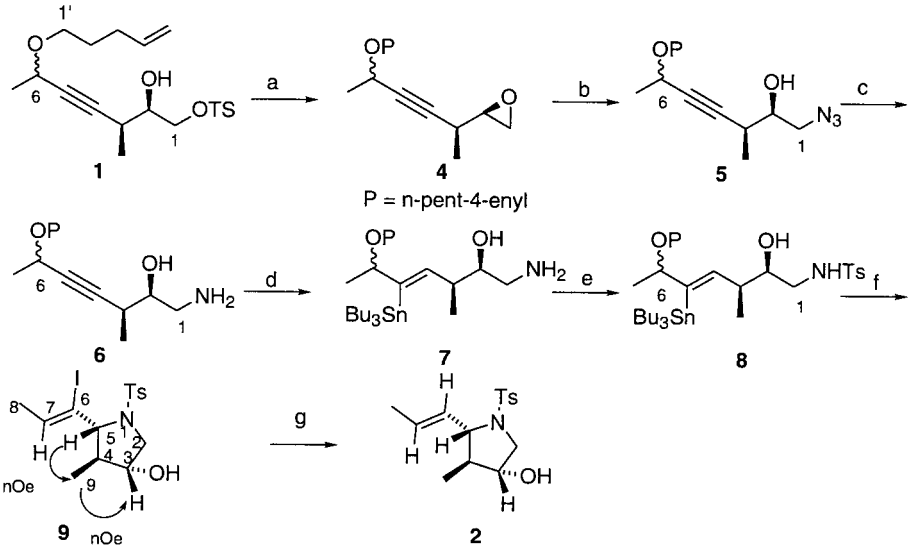
On the other hand, the epoxyde **4** was stannylated under radical conditions[8] to give **10** together with some amounts (6%) of its regioisomer **11**. Opening of epoxyde **10** by KCN in EtOH furnished the nitrile **12** which was further reduced to the amine **13a** with $LiAlH_4$. After transformation into the *p*-toluenesulfonamide **13b**, the allylic substitution reaction was investigated. When treated with 3 equiv. of di-*sym*-collidine iodonium perchlorate in $CHCl_3$, **13b** afforded the expected piperidine **14a** in low yield (12% yield). Suspecting the possible intervention of the free hydroxyl, the secondary alcohol was protected as trimethylsilyl ether (**13d**) after tin/halogen exchange that was performed with 1 equiv. of *N*-iodosuccinimide (**13c**). Reaction of **13d** with di-*sym*-collidine iodonium perchlorate provided the piperidine **14b** in 54% yield. 2D NOESY experiment showed interactions of H-2 with CH_3-10 and H-5$_\beta$ and of H-4 with H-5$_\beta$, demonstrating the *trans* relationship between the side chain and the methyl group. Vinylic iodine removal by reaction with *t*-BuLi and subsequent protonation[4,6] gave the (2*S*,3*S*,4*S*)-piperidine **3** (Scheme 4). In ^{1}H NMR spectrum of **3**, the coupling constants of the olefinic protons confirmed the *E* geometry of the double bond ($J_{H7,H8}$=15.5 Hz). The conformation of the piperidine ring of **3** is a flat chair with *pseudo*-axial substituents at C-2, C-3 and C-4 as shown by coupling constants (J_{H2-H3}=2.5 Hz, J_{H3-H4}=4 Hz) when the conformation of **14a** is also a flat chair but with *pseudo*-equatorial substituents (J_{H2-H3}=7.5 Hz, J_{H3-H4}=7.5 Hz). Molecular modelisation confirmed that these conformations corresponded to the lowest energy ones.

The interest for polyhydroxylated piperidines as antiviral and antitumor agents is well known,[12] wherefore, we studied the capacity of our technology to provide such compounds, with a versatile side chain at C-2, starting from a substrate where the alkyl group of the precedent strategy would be replaced by an hydroxyl for generating the 1,3-allylic strain.

Sugars are convenient chiral starting materials to synthesize compounds with vicinal hydroxyls of various stereochemistry. Examination of the literature showed that lactols could be efficiently opened by hydroxylamines to give precursors of primary amines.[13] Thus, 5-*O*-dimethyl-*t*-butylsilyl-2,3-isopropylidene-D-ribonolactone[14] was chosen as chiral starting material and was reduced to **15** with DIBAH. This lactol when treated with hydroxylamine gave **16** as *syn*/*anti* isomers. After reduction of the oximes with $LiBH_4$, the amine **17a** was transformed to the corresponding *p*-toluenesulfonamide **17b**. After desylilation of the primary hydroxyl, periodate oxidation of the *vic*-diol **17c** led to the carbinolamine **18** as single isomer which was stereoselectively opened by 1-lithio-3-pentenyloxy-butyne to give **19**. The stereochemistry of the hydroxyl group at C-4 of **19** was

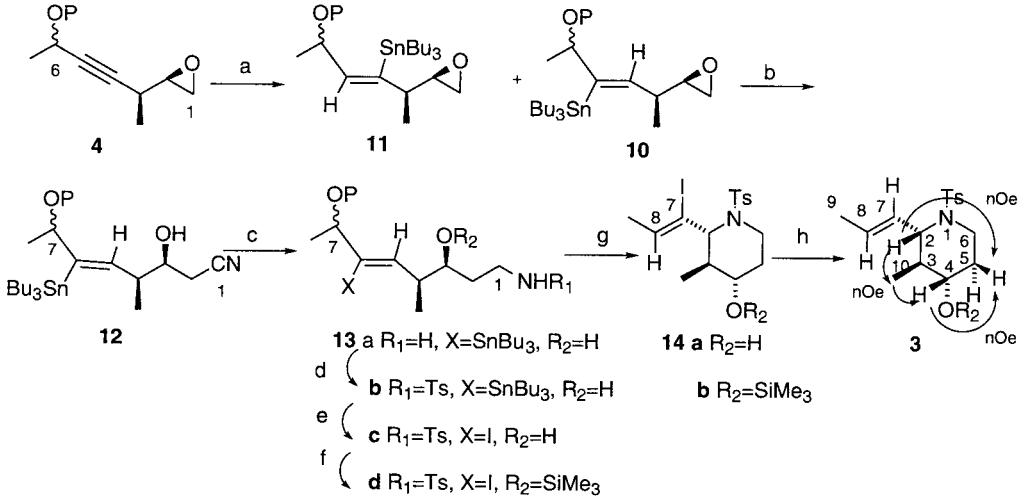


Scheme 2.



Scheme 3. (a) 1% NaOMe in MeOH, rt, 1 h, quantitative; (b) NaN_3, 7 equiv., EtOH, reflux, 5 h, 97%; (c) $LiAlH_4$, 1.2 equiv., ether, rt, 93%; (d) $HsnBu_3$, 1 equiv. AIBN cat., 90°C, 3 h, 78%; (e) ClTs 1 equiv., CH_2Cl_2:pyridine 2/1, rt, overnight, 83%; (f) $[I(B_2)ClO_4$, 3 equiv., $CHCl_3$, 0°C, 3 h, 88%; (g) *t*-BuLi 2 equiv., THF, −78°C, 1 h then 10% aqueous HCl −78°C to rt, 77%.

deduced from a crystallographic study of compound **21c** subsequently obtained. To introduce the removable ligand on the triple bond, regioselective iodation of the triple bond was studied and realized according to Denmark's modification[15] of Corey's procedure[16] using Red Al® as reducing agent. Vinylic iodide **20a** was obtained in 82% yield. After silylation of the free hydroxyl as TBDMS ether, the vinylic iodide **20b** when treated with di-*sym*-collidine–iodonium perchlorate provided the piperidine **21a** in 66% yield. A small amount (13%) of epoxyde **22a** was also formed. Migration of the dimethyl-*t*-butylsilyl group from oxygen to nitrogen, allowed nucleophilic attack to the double bond by the oxygen atom. With **20a**, the compound having a free hydroxyl at C-4, the allylic substitution reaction took place to give the piperidine **21b** and the epoxyde **22b** in 36 and 24% yield, respectively. 2D NOESY spectrum of **21b** showed nOe interaction between H-2 and C(3)–OH indicating a *trans* relationship between the side chain and this hydroxyl, but the configuration of C-3 could not be attributed by this procedure because H-3 did not present any nOe interaction. Therefore, a crystallographic study of ester **21c** was performed and allowed to set the 3*R* configuration at C-3 and to confirm the *Z* configuration of the halogenated double bond (Fig. 1).[17] We tested the reduction of the vinylic iodine under different conditions, starting from piperidines **21a** and **21b**. When lithium/iodine exchange was tested with **21a** by treatment by *t*-butylithium, the major product was the piperidine **23a** resulting from acetone elimination after deprotonation at C-6, followed by lithium/iodine exchange. Steric hindrance of the side chain due to the bulky silyl group allowed the organometallic agent to attack the proton at C-6 before iodine/lithium exchange. Furthermore, the allene **24** (78%), the piperidine **25** (18%) and the dehydropiperidine



Scheme 4. (a) Bu_3SnH, 1 equiv., AIBN catalytic, 90°C, 3 h, 69%; (b) KCN 3 equiv., EtOH, 45°C, 7 h, 97%; (c) $LiAlH_4$, 2 equiv., ether, rt, 2 h, 90%; (d) ClTs, 1 equiv., CH_2Cl_2/ py 2/1, rt, overnight, 95%; (e) NIS, 1 equiv., CH_2Cl_2, rt, 1 h, 73%; (f) $ClSiMe_3$, 1.2 equiv., Et_3N 3 equiv., THF, rt, overnight, 95%; (g) di-*sym*-collidine iodonium perchlorate, 3 equiv., $CHCl_3$, 0°C, 1 h, 54%; (h) *t*-BuLi, 2 equiv., THF, −78°C, 1 h, 60%.

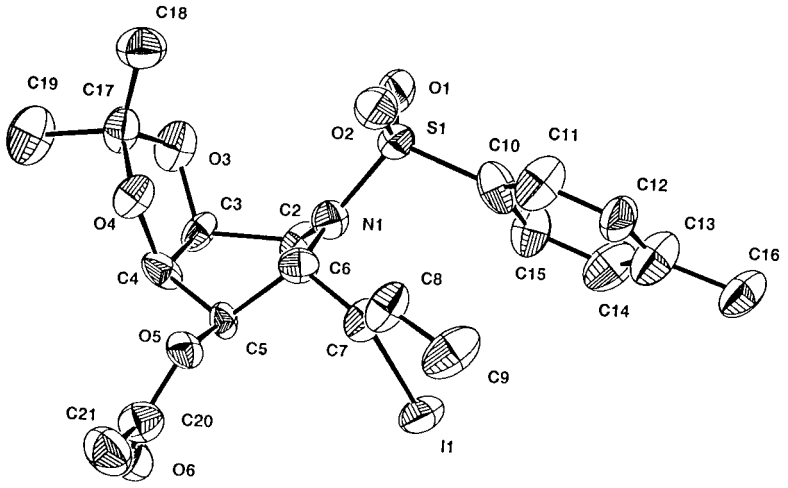
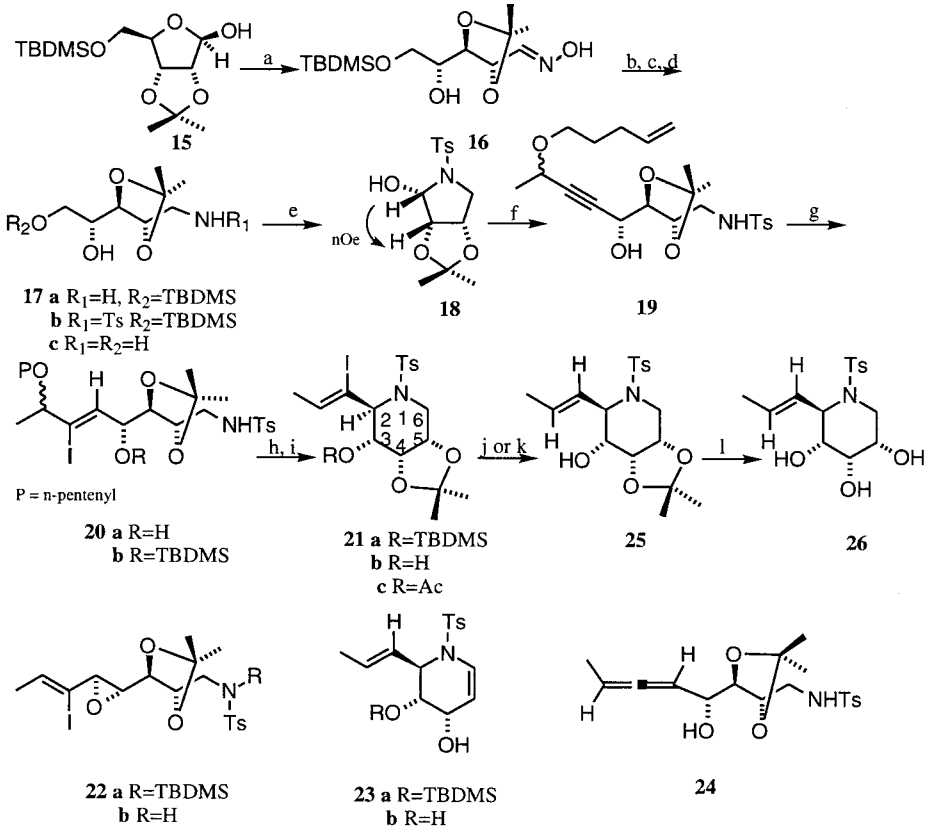


Figure 1. Crystal structure of **21c**.

23b (2%) were formed from the reaction of **21b** having a free hydroxyl at C-4 with *t*-butyllithium followed by protonation. In this case, hydrogenolysis of **21b** in the presence of palladium on charcoal[18] was found to be the best method to obtain **25** (80% yield). Finally, hydrolysis of isopropylidene group performed with 1N HCl led to the triol **26** (8.6% from D-ribonolactone) (Scheme 5).[6]

3. Conclusions

The introduction of a 1,3-allylic strain during an intramolecular allylic substitution using a pentenyl ether as leaving group in the presence of haloniums has proved to be an interesting versatile methodology to synthesize polyfunctionalized nitrogen heterocycles. In the examples studied, the overall yields obtained with five- and six-membered rings



Scheme 5. (a) NH_2OH, HOAc, 2 equiv., py, 2 equiv., MeOH, rt, 16 h, 98%; (b) $LiBH_4$, 2 equiv., THF, reflux, 16 h, 84%; (c) ClTs, 1 equiv., Net_3 1.2 equiv., CH_2Cl_2, 0°C, 2 h, 57%; (d) $Bu_4NF.3H_2O$, 1.2 equiv., THF, rt, 1 h, 82%; (e) $NaIO_4$, 2 equiv., pH 5.6 acetate buffer, EtOH, rt, 1 h, 98%; (f) 1-lithio-3-pentenyloxy-propyne, 2.1 equiv., THF, −78°C to rt, 16 h, 95%; (g) Red Al®, 3 equiv., ether, 0°C then rt, 16 h, then EtOAc, 15 min, then −78°C, I_2 2 equiv. in THF, − 78 to −5°C, 2 h, 82%; (h) TBDMSCl, 2.5 equiv., imidazole, 5 equiv., THF, 95%; (i) $I(B_2)ClO_4$, 3 equiv., $CHCl_3$, 0°C, 1 h, 66%; (j) Bu_4NF, 1.2 equiv., THF, rt, 1 h, 85%; (k) H_2, Pd/c, quinoline, MeOH, 80%; (l) 1N HCl, THF, rt, 1 h, 78%.

were satisfying and the cyclisation step was always stereoselective.

4. Experimental

4.1. General experimental procedures

Melting points (mps) were determined in capillary tubes and are uncorrected. Optical rotations, $[\alpha]_D$, were measured at room temperature, in $CHCl_3$ with 0.5% EtOH, on a PERKIN–ELMER 241 polarimeter. IR spectra were determined with a NICOLET FT-IR 205 spectrometer. ^1H NMR spectra were performed in $CDCl_3$, unless otherwise stated, chemical shifts δ were expressed in ppm, coupling constants in Hz, and registered with BRUKER WP-250, WP-300 or WP-400 instruments. ^{13}C NMR spectra were recorded on Bruker WP-300 or WP-250. Mass spectra (MS) were run on AEI MS-50 or AEI MS-9 spectrographs. Column chromatography were performed on Merck Kieselgel 60, flash column chromatography on Merck Kieselgel 60H. Analytical thin layer chromatography was carried out using silica Gel pre-coated foils, visualization using spraying 50% aqueous H_2SO_4 and heating.

Crystallographic data were registered with a Philips PW1100 diffractometer using the Mo Kα radiation (λ=0.707 Å) with a graphite monochromator. The structure was resolved by Patterson methods and the SHELXL program[19] was used for the structure refinements.

Standard work-up means quenching of the reaction by NH_4Cl aqueous solution, extraction by ether or CH_2Cl_2, washing of the organic phase with brine, drying on $MgSO_4$ and evaporation under vacuum.

4.2. General procedure for the cyclization reaction

$[I(B)_2]ClO_4$ (3 equiv.) was added, at 0°C, to a solution of sulfonamide (1 equiv.) in dry $CHCl_3$ under inert atmosphere. The reaction mixture was stirred at 0°C. After completion of the reaction as monitored by TLC, CH_2Cl_2 was added and the resulting solution was washed successively with 10% $Na_2S_2O_7$ and NH_4Cl solutions. The aqueous phases were further extracted twice with CH_2Cl_2. The combined organic phases were dried on $MgSO_4$ and evaporated under reduced pressure to give a crude reaction mixture which was purified by silica gel column chromatography.

4.2.1. (2*R*,3*S*,6*RS*)-4-Methylbenzenesulfonic acid 6-[pent-4-enyloxy]-3-methyl-2-hydroxy-(hept-4-yn)-yl ester (1). *n*-BuLi (33.5 mL of 1.3 M solution in hexane, 43.5 mmol) was added to a solution of 3-(penten-4-yloxy)-but-1-yne (6 g, 43.5 mmol) in ether (120 mL) at −78°C under inert atmosphere. After 15 min, Me_3Al (26.1 mL of 2 M solution in toluene, 46.1 mmol) was added. The mixture was stirred at −40°C for 1 h and then cooled at −78°C. A solution of (2*S*,3*S*)-2-(4-methylbenzenesulfonyloxymethyl)-3-methyloxirane (10.5 g, 43.5 mmol) in toluene (120 mL) and $BF_3{\cdot}OEt_2$ (4.7 mL, 43.5 mmol) were successively added. After 4 h at −78°C, the reaction was quenched with saturated NH_4Cl solution and the organic products were extracted three times with ether. The ethereal solutions washed with brine and dried on $MgSO_4$ were evaporated under reduced pressure to give a residue which was chromatographed on silicagel column to give **1** eluted by heptane/ether 8/2 (11.57 g, 70%), as an oil, HR CI MS: calcd for $C_{20}H_{29}O_5S$ (MH^+) 381.1736, found 381.1770; IR (neat) ν_{max}: 3487, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21 (3H, d, *J*=7 Hz), 1.32 (3H, d, *J*=6.5 Hz), 1.65 (2H, qn, *J*=7 Hz), 2.11 (2H, q, *J*=7 Hz), 2.45 (3H, s), 2.49 (1H, d, *J*=5 Hz, OH), 2.58 (1H, qn, *J*=7 Hz), 3.31 (1H, m, *J*=11.5, 7, 1.5 Hz), 3.61 (1H, m, *J*=11.5, 7, 2 Hz), 3.71 (1H, m), 4.07 (2H, m), 4.30 (1H, dd, *J*=10, 3 Hz), 4.96 (1H, dd, *J*=10.5, 1.5 Hz), 5.02 (1H, dd, *J*=17, 1.5 Hz), 5.81 (1H, ddt, *J*=17, 10.5, 7 Hz), 7.36 (2H, d, *J*=8 Hz), 7.81 (2H, d, *J*=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 17.0, 21.6, 22.2, 28.8, 29.3, 30.3, 65.2, 67.9, 72.4, 72.5, 83.3, 84.7, 114.7, 128.0, 129.9, 132.6, 138.2, 145.1.

4.2.2. (2*R*,3*S*)-2-[4*RS*-(Pent-4-enyloxy)-1-methyl-pent-3H-ynyl]-oxirane (4). A solution of **1** (5.38 g, 14 mmol) in MeOH (40 mL) was added to a 2% methanolic solution of MeONa. After 1 h at room temperature, standard work-up gave **4** (2.85 g, 98%) as an oil, used without further purification, anal. calcd for $C_{13}H_{20}O_3$ %: C 74.75, H 9.68, O 15.37, found: C 74.75, H 9.75, O 15.24; IR (neat) ν_{max}: 2237, 1637, 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.29 (3H, d, *J*=7 Hz), 1.38 (3H, d, *J*=6.5 Hz), 1.67 (2H, qn, *J*=7 Hz), 2.12 (2H, q, *J*=7 Hz), 2.51 (1H, dq, *J*=7, 1 Hz), 2.67 (1H, dd, *J*=5, 2.5 Hz), 2.77 (1H, t, *J*=5 Hz), 2.90 (1H, m), 3.35 (1H, dt, *J*=9, 7 Hz), 3.67 (1H, dt, *J*=9, 7 Hz), 4.11 and 4.12 (1H, 2q, *J*=6.5 Hz), 4.95 (1H, dd, *J*=10.5, 1.5 Hz), 5.02 (1H, dd, *J*=17, 1.5 Hz), 5.81 (1H, ddt, *J*=17, 10.5, 7 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 18.0, 22.5, 29.0, 29.3, 30.4, 46.4, 54.9, 65.4, 68.0, 82.7, 84.1, 114.8, 138.4.

4.2.3. (2*R*,3*S*,6*RS*)-1-Azido-3-methyl-6-(pent-4-enyloxy)-hept-4-yn-2-ol (5). NaN_3 (1.24 g, 12.2 mmol) was added to a solution of **4** (0.40 g, 1.92 mmol) in EtOH (30 mL) and the resulting mixture was refluxed for 5 h. Standard work-up (CH_2Cl_2) led to a residue which was purified by silica gel column chromatography with CH_2Cl_2/MeOH 99/1 as eluent to give **5** (0.47 g, 97% yield) as an oil, CI MS: MH^+ 252; anal. calcd for $C_{13}H_{21}N_3O_2$ %: C 62.10, H 8.42, N 16.73, O 12.73; found %: C 62.11, H 8.42, N 16.63, O 12.95; IR (neat) ν_{max} 3435, 2100, 1642, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ: 1.2 (3H, d, *J*=7 Hz), 1.3 (3H, d, *J*=6.5 Hz), 1.7 (2H, qun, *J*=7.5 Hz), 2.1 (2H, q, *J*=7 Hz), 2.6–2.7 (1H, m, *J*=7, 2 Hz), 3.3 and 3.6 (2H, 2 m), 3.5 and 3.7 (ABX, *J*=13, 7, 5 Hz), 3.6–3.7 (1H, m), 4,1 (1H, qd, *J*=6.5, 2 Hz), 5.0 (2H, 2d, *J*=18, 11 Hz), 5.8 (1H, m);.^{13}C NMR, ($CDCl_3$, 75 MHz) δ: 17.0, 22.4, 28.8, 30.3, 30.6, 55.1, 65.4, 68.0, 73.8, 83.4, 85.1, 114.8, 138.2.

4.2.4. (2*R*,3*S*,6*RS*)-1-Amino-3-methyl-6-(pent-4-enyloxy)-hept-4-yn-2-ol (6). LAH (28 mg, 0.71 mmol) was added to a solution of **5** (150 mg, 0.59 mmol) in ether (15 mL), under inert atmosphere, at room temperature. The mixture was stirred for 5 h, then saturated Na_2SO_4 solution was added. The precipitate was filtered off, washed with CH_2Cl_2 and the solution evaporated to dryness to give **6** (125 mg, 93%) as an oil used without further purification, $C_{13}H_{23}NO_2$, CI MS: MH^+ 226; ^1H NMR ($CDCl_3$,

300 MHz), δ: 1.2 (3H, d, *J*=7 Hz), 1.3 (3H, d, *J*=6.5 Hz), 1.6 (2H, qun, *J*=7 Hz), 2.1 (2H, q, *J*=7 Hz), 2.5 (3H, m, with NH_2), 2.7 and 3.0 (2H,ABX, *J*=13, 8, 3 Hz), 3.3 (1H, m, C–2H), 3.3 and 3.6 (2H, 2dt, *J*=9, 7 Hz), 4.1 (1H, qd, *J*=6.5, 1.5 Hz) 4.9 (2H, 2d, *J*=18, 11 Hz) 5,8 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.4, 22.4, 28.8, 30.3, 36.9, 44.8, 65.3, 67.8, 74.6, 82.6, 86.2, 114.6, 138.2.

4.2.5. (2*R*,3*S*,6*RS*)-1-Amino-3-methyl-6-(pent-4-enyloxy)-5-tri-*n*-butylstannyl-hept-4*Z*-en-2-ol (7). $HsnBu_3$ (0.3 mL, 0.88 mmol) and catalytic amount AIBN were added to **6** (0.2 g, 0.88 mmol) under inert atmosphere and the mixture was stirred for 3 h at 90°C and then poured on a silica gel column to give **7** (357 mg, 78% yield) by elution with toluene/CH_2Cl_2 8/2, $C_{25}H_{51}O_2NSn$, CI MS: MH^+ 517 with ^{118}Sn and 519 with ^{120}Sn; ^{1}H NMR ($CDCl_3$, 250 MHz), δ: 0.9 (9H, t, *J*=7 Hz), 1.0 (3H, 2d, *J*=7 Hz), 1.1 (3H, d, *J*=6 Hz), 1.3 and 1.4 (18H, 2 m,), 1.6 (2H, m), 2.0 (3H, m), 3.1–3.4 (4H, m), 3.6 (1H, m), 3.8 (1H, q, *J*=6 Hz), 4.9–5.0 (2H, m), 5.7–5.8 (1H, m), 9.0 (1H, d, *J*=10 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz), δ: 11.3, 13.7, 17.7, 22.8, 27.5, 29.3 29.3, 30.6, 43.3, 45.9, 67.6 and 67.7 (C-1′), 76.2, 83.6, 114,5, 138.5, 142.5 and 142.8 (C-4), 148.5.

4.2.6. (2*R*,3*S*,6*RS*)-*N*-[-2-Hydroxy-3-methyl-6-(pent-4-enyloxy)-5-tri-*n*-butylstannyl-hept-4*Z*-enyl]-4-methylbenzenesulfonamide (8). TsCl (36 mg, 0.19 mmol) was added to a solution of **7** (100 mg, 0.19 mmol) in pyridine (3 mL) and CH_2Cl_2 (6 mL) and the solution let overnight at room temperature before standard work-up (CH_2Cl_2). Chromatographic purification on silica gel column of the crude residue gave **8** (107 mg, 83%) as an oil, $C_{32}H_{57}O_4NSSn$, CI MS: MH^+ 672 with ^{120}Sn; IR (neat) ν_{max} 3456, 3289, 1447, 1328, 1152, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.8 (9H, m), 0.9 (3H, d, *J*=7 Hz), 1.1 (3H, d, *J*=6 Hz), 1.2–1.5 (18H, m), 1.6 (2H, m), 2.1 (3H, m), 2.6 and 3.1 (2H, 2 m), 3.3 (2H, m), 3.5 (1H, m), 3.8 (1H, q, *J*=6 Hz), 4.9–5.1 (2H, m), 5.1–5.2 (1H, m, NH), 5.7–5.9 (1H, m), 5.9 (1H, d, *J*=10 Hz), 7.3 (2H, d, *J*=8 Hz), 7.7 (2H, d, *J*=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 11.3, 13.7, 17.6, 21.5, 22.6, 27.5, 29.3, 29.3, 30.5, 43.3, 47.6 and 47.7 (C-1), 67.7 and 67.8 (C-1′), 74.5, 83.4, 114.6, 127.1, 129.8, 136.8, 138.5, 140.8 and 141.1 (C-4), 143.6, 150.6.

4.2.7. (3*R*,4*S*,5*R*)-5-(1-Iodo-prop-1*Z*-enyl)-4-methyl-1-(4-methylbenzenesulfonyl)-pyrrolidin-3-ol (9). A solution of **8** (44 mg, 0.065 mmol) was treated according to the general procedure to give **9**, as an oil, (24 mg, 88 %), $[\alpha]_D$=−45.2 ($CHCl_3$, *c* 1.4); HR CI MS: calcd for $C_{15}H_{20}O_3NSI$ 422.0288 (MH^+), found 422.0315; IR (neat) ν_{max} 3437, 1637, 1349, 1159, 1098, 660 cm^{-1}; ^{1}H NMR, ($CDCl_3$, 250 MHz) δ: mixture of conformers, 0.9 (3H, d, *J*=6.5 Hz), 1.7 and 1.8 (3H, 2d, *J*=6, 7 Hz), 2.1 (1H, m), 2.4 (3H, 2s), 3.2 (1H, ABX, *J*=10, 8 Hz), 3.5 (1H, d, *J*=8 Hz), 3.6 (1H, m), 3.8 (1H, ABX, *J*=10, 6 Hz), 6.0 (maj) and 6.4 (min) (1H, 2q, *J*=6, 7 Hz), 7.3 (2H, 2d, *J*=9 Hz), 7.8 and 7.9 (2H, 2d, *J*=8 Hz); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 14.6, 21.6, 24.1, 47.6, 54.3, 73.9, 74.4, 121.4, 127.7, 129.6, 129.8, 133.2, 143.6, 157.3; 2D NOESY ($CDCl_3$, 400 MHz): nOe H5–H9, H3–H9.

4.2.8. (3*R*,4*S*,5*S*) 5-(Pro-5*E*-enyl)-4-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-3-ol (2). *t*-BuLi (2 M solution in pentane, 33 μL) was added to a solution of **9** (14 mg, 0.033 mmol) in anhydrous THF (5 mL),under inert atmosphere, at −78°C. After 1 h at −78°C, the reaction was quenched at this temperature with a 10% aqueous HCl solution. After standard work-up (ether), the crude reaction mixture was purified on silica gel column (CH_2Cl_2/MeOH 95/5) to give **2** (7 mg, 77%), as an oil, HR EI MS: calcd for $C_{15}H_{21}O_3NS$ 295.1242 (M^+), found 295.1235; IR (neat) ν_{max} 3437, 1637, 1349, 1159, 1098, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.8 (3H, d, *J*=7 Hz), 1.7 (3H, dd, *J*=6, 1.5 Hz), 1.85 (1H, m), 2.4 (3H, s), 3.3 (1H, m), 3.5 (1H, t, *J*=7 Hz), 3.6 (2H, m), 5.4 (1H, dd, *J*=16, 7 Hz), 5.6 (1H, dq, *J*=16, 6 Hz), 7.3 (2H, d, *J*=8 Hz), 7.8 (2H, d, *J*=8 Hz).

4.2.9. (2*R*,3*S*)-2-[4*RS*-(Pen-4-enyloxy)-3-tri-*n*-butylstannyl-1-methyl-pent-2*Z*-enyl]-oxirane (10) and (2*R*,3*S*)-2-[4*RS*-(pen-4-enyloxy)-2-tri-*n*-butylstannyl-1-methyl-pent-2*Z*-enyl]-oxirane (11). Bu_3SnH (1.55 mL, 5.76 mmol) and AIBN (20 mg, catalytic) was added to n (1 g, 4.8 mmol) and the mixture was stirred for 3 h at 90°C under inert atmosphere. After cooling at room temperature, the mixture was poured on a silicagel column. Elution with heptane/CH_2Cl_2 95/5 gave **10** (1.66 g, 69 %) and **11** (0.15 g, 6%).

10: oil, anal. calcd for $C_{25}H_{48}0_2Sn$ %: C 60.12, H 9.61, O 6.41, found %: 60.15, 9.68, O 6.41; IR (neat) ν_{max} 1637, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.89 (9H, t, *J*=7 Hz), 0.94 (6H, t, *J*=7 Hz), 1.04 and 1.08 (3H, 2d, *J*=7 Hz), 1.14 and 1.16 (3H, 2d, *J*=6.5 Hz), 1.32 (6H, tt, *J*=7 Hz), 1.48 (6H, m), 1.62 (2H, qn, *J*=7 Hz), 2.08 (2H, q, *J*=7 Hz), 2.52 (1H, dd, *J*=4.5, 3.5 Hz), 2.69 (1H, dd, *J*=4.5, 4 Hz), 2.80 (1H, m), 3.20 (1H, dt, *J*=9, 7 Hz), 3.35 (1H, dt, *J*=9, 7 Hz), 3.83 (1H, q, *J*=6.5 Hz), 4.93 (1H, dd, *J*=10.5, 1.5 Hz), 5.0 (1H, dd, *J*=17, 1.5 Hz), 5.80 (1H, ddt, *J*=17, 10.5, 7 Hz), 5.99 and 6.01 (1H, 2d, *J*=10 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 11.3, 13.7, 17.6 and 17.7 (C-8), 22.8, 27.5, 29.2, 30.6, 40.6 and 40.7 (C-3), 46.0, 56.0, 67.5 and 67.6 (C-1′), 83.5, 114.5, 138.5, 140.4 and 140.6 (C-4), 149.5.

11: oil, $C_{25}H_{48}O_2Sn$, IC MS: MH^+ 501 with ^{120}Sn; IR (neat) ν_{max} 1637, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.90 (9H, t, *J*=7 Hz), 0.94 (6H, t, *J*=7 Hz), 1.14 and 1.16 (3H, 2d, *J*=7 Hz), 1.22 (3H, dd, *J*=6.5, 1.5 Hz), 1.34 (6H, tt, *J*=7 Hz), 1.49 (6H, m), 1.66 (2H, qn, *J*=7 Hz), 2.11 (2H, q, *J*=7 Hz), 2.21 (1H, dq, *J*=7, 2 Hz), 2.44 (1H, dd, *J*=5, 3 Hz), 2.70 (1H, dd, *J*=5, 4 Hz), 2.90 (1H, m), 3.29 (1H, dt, *J*=9.5, 7 Hz), 3.41 (1H, dt, *J*=9.5, 7 Hz), 3.71 (1H, m), 4.94 (1H, dd, *J*=10.5, 1.5 Hz), 5.01 (1H, dd, *J*=17, 1.5 Hz), 5.81 (1H, ddt, *J*=17, 10.5, 7 Hz), 6.01 (1H, dq, *J*=4, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 11.3, 13.7, 18.1, 22.0 and 22.2 (C-7), 27.5, 29.2, 30.4, 44.4, 46.0, 56.3 and 56.4 (C-2), 67.4, 78.1, 114.7, 138.3, 143.6, 146.9.

4.2.10. (3*S*,4*S*,7*RS*)-7(Pent-4-enyloxy)-6-tri-*n*-butylstannyl-4-methyl-3-hydroxy-hept-5*Z*-enyl-1-nitrile 12. A solution of **10** (3.2 g, 6.4 mmol) and KCN (0.6 g, 9 mmol) in EtOH (100 mL) was warmed at 45°C for 16 h. After cooling, a saturated aqueous $NaHCO_3$ solution was added and the organic products were extracted three times with CH_2Cl_2. The organic phases washed with brine and dried on $MgSO_4$ were evaporated under reduced pressure to give a residue which was chromatographed on silica gel column

(heptane/ether 9/1) to give **12** (3.37 g, 97%) as an oil, anal. calcd for $C_{26}H_{49}NO_2Sn$%: C 59.3, H 9.38, found %: C 59.5, H 9.59; IC MS: MH^+ 528 with ^{120}Sn; IR (neat) ν_{max} 3460, 2258, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.89 (9H, t, J=7 Hz), 0.94 (6H, t, J=7 Hz), 1.07 and 1.10 (3H, 2d, J=7 Hz), 1.15 and 1.17 (3H, 2d, J=6.5 Hz), 1.35 (6H, tt, J=7 Hz), 1.49 (6H, m), 1.64 (2H, qn, J=7 Hz), 2.06–2.22 (3H, m), 2.33–2.44 (2H, m), 2.54 (1H, dd, J=10, 4 Hz), 3.22 (1H, dt, J=9, 7 Hz), 3.33 (1H, dt, J=9, 7 Hz), 3.76 (1H, m), 3.84 (1H, dq, J=6.5, 2 Hz), 4.97 (1H, dd, J=10.5, 1.5 Hz), 5.03 (1H, dd, J=17, 1.5 Hz), 5.81 (1H, ddt, J=17, 10.5, 7 Hz), 5.94 (1H, dd, J=4, 2 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 11.4, 13.8, 17.2, 22.7, 24.5 and24.6 (C-2), 27.6, 29.2, 29.4, 30.6, 44.6, 67.8 and 68.0 (C-1′), 72.0, 83.3 and 83.4 (C-7), 114.8, 118.3, 138.5, 140.0 and 140.4 (C-4), 151.7.

4.2.11. (3*S*,4*S*,7*RS*)-1-Amino-4-methyl-7-(pent-4-enyloxy)-6-tri-*n*-butylstannyl-oct-5*Z*-en-3-ol (13a). LAH (480 mg, 2 equiv.) was added to a solution of **12** (3.35 g, 6.35 mmol) in anhydrous ether (350 mL) at room temperature. The suspension was stirred for 2 h before addition of saturated aqueous Na_2SO_4 solution. The precipitate was filtered off, washed with ether and evaporation of the ethereal phase gave **13a** (3.03 g, 90% yield) as an oil, which was used without further purification, $C_{26}H_{53}NO_2Sn$, CI MS: MH^+ 532 with ^{120}Sn; IR (neat) ν_{max} 3410, 1590, 1262, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.89 (9H, t, J=7 Hz), 0.94 (6H, t, J=8 Hz), 1.08 and 1.10 (3H, 2d, J=7 Hz, CH_3-9), 1.17 and 1.19 (3H, 2d, J=6.5 Hz, CH_3-8), 1,35 (6H, m), 1.45 (8H, m), 1.63 (2H, qn, J=7 Hz), 2.0 (4H, m with OH), 2.81 (2H, m, NH_2), 3.22 (2H, m), 3.38 (2H, m), 3.63 (1H, m), 3.84 (1H, dq, J=6.5, 2 Hz), 4.95 (2H, dd, J=10.5, 1.5 Hz), 5.01 (1H, dd, J=17, 1.5 Hz), 5.81 (1H, ddt, J=10.5, 17, 7 Hz), 6,0 (1H, dd, J=10, 2 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 11.3, 13.7, 17.1, 22.8, 27.5, 29.2, 29.3, 30.6, 35.9, 41.2, 45.6, 67.5 and 67.6 (C-1′), 77.1, 83.7, 114.5, 138.5, 143.5 and 143.9 (C-5), 147.8.

4.2.12. (3*S*,4*S*,7*RS*)-*N*-[3-Hydroxy-4-methyl-7-(pent-1′-enyloxy)-6-tri-*n*-butylstannyl-oct-5*Z*-enyl]-4-methyl-benzenesulfonamide 13b. TsCl (1.5 g, 7.9 mmol) was added to a solution of **13a** (3 g, 5.668 mmol) in CH_2Cl_2/pyridine 2/1 (350 mL) at room temperature and let to react overnight. Standard work-up (CH_2Cl_2) led to **13b** (3.68 g, 95% yield) after silica gel chromatography of the crude extract with CH_2Cl_2/MeOH 99/1 as eluent, $C_{33}H_{59}NO_4SSn$; EI MS: M^+ 684, m/z 629; IR (neat) ν_{max} 3483, 3291, 2924, 1639, 1612, 1599, 1454, 1417, 1095, 905, 809 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz), δ: 0.94 (9H, t, J=7 Hz), 0.99 (6H, t, J=7 Hz), 1.03 and 1.07 (3H, 2d, J=7 Hz, CH_3-9), 1.2 (3H, d, J=6 Hz), 1.37 (6H, tt, J=7 Hz), 1.4–1.52 (8H, m), 1.69 (2H, qn, J=7 Hz), 1.99 (1H, d, J=6.5 Hz, OH), 2.15 (3H, m), 2.49 (3H, s), 2.99 (1H, m, J=9, 7 Hz), 3.20 (2H, m), 3.32 (1H, m, J=9, 7, 4 Hz), 3.52 (1H, m), 3.8 (1H, dq, J=6, 1 Hz), 4.95 (1H, dd, J=10.5, 1.5 Hz), 5.01 (1H, dd, J=17, 1.5 Hz), 5.14 (1H, t, J=4 Hz, NH), 5.81 (1H, ddt, J=17, 10.5, 7 Hz), 5.9 (1H, dd, J=10, 1 Hz), 7.31 (2H, d, J=8 Hz) 7.75 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.3, 13.6, 16.9, 21.4, 22.6, 27.4, 29.1, 29.1, 30.4, 33.6, 41.5, 44.8, 67.6 and 67.8 (C-1′), 74.5, 83.4 and 83.7 (C-7), 114.4, 127.1, 129.6, 138.3, 141.1 and 141.6 (C-5), 143.2, 149.9.

4.2.13. (3*S*,4*S*,7*RS*)-*N*-[3-Hydroxy-4-methyl-6-iodo-7-(pent-1′-enyloxy)-oct-5*Z*-enyl]-4-methyl-benzenesulfonamide 13c. NIS (1.07 g, 4.7 mmol) was added to **13b** (2.5 g, 3.65 mmol) in anhydrous THF (80 mL) at 0°C and under inert atmosphere. The solution was stirred for 1 h at 0°C and standard work-up (ether) followed by flash chromatography with CH_2Cl_2/MeOH 99/1 as eluent, gave **13c** as an oil, $C_{21}H_{32}NO_4SI$; CI MS: MH^+ 522, 436; IR (neat) ν_{max} 3476, 3284, 1638, 1594, 1450, 1329, 1156, 1097, 912, 812 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.98 and 1.0 (3H, 2d, J=7 Hz, CH_3-9), 1.18 and 1.19 (3H, 2d, J=6 Hz, CH_3-8), 1.63 (4H, m), 2.09 (2H), 2.41 (3H, s), 2.54 (2H with OH), 2.98 (1H, m, J=9, 7, 4 Hz), 3.14 (2H, m), 3.36 (2H, m), 3.62 (2H, m), 4.91 (1H, dd, J=10.5, 1.5 Hz), 5.0 (1H, dd, J=17, 1.5 Hz), 5.36 (1H, t, J=4 Hz, NH), 5.67 (1H, dd, J=10, 1 Hz), 5.78 (1H, ddt, J=17, 10.5, 7 Hz), 7.29 (2H, d, J=8 Hz), 7.72 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ; 15.0, 21.6, 22.5, 28.9, 30.5, 33.8, 41.0, 46.6, 67.6 and 67.8 (C-1′), 72.9 and 73.2 (C-3), 81.3 and 81.5 (C-7), 114.8, 116.4, 127.2, 129.8, 131.6, 138.4, 138.5, 143.5.

4.2.14. (2*R*,3*S*,4*S*)-3-Methyl-2-(1-iodo-prop-1*Z*-enyl)-1-(toluene-4-sulfonyl)-piperidin-4-ol (14a). TMSCl (0.55 mL, 2.4 mmol), Et_3N (0.65 mL, 2.6 mmol) and catalytic DMAP were successively added to a solution of **13c** (312 mg, 0.6 mmol) in anhydrous THF (10 mL). The mixture was stirred at rt for 1 h and after addition of aqueous saturared $NaHCO_3$, standard work-up (ether) gave **13d** wich was cyclized according to the general procedure to provide **14b** (118 mg, 54%) as an oil, $[\alpha]_D$=+33 ($CHCl_3$, c 1); EI MS: M^+ 507, m/z 380, IR (neat) ν_{max} 3468, 1638, 1598, 1494, 1454, 1343, 1155, 1090, 812 cm^{-1}. $Bu_4NF{\cdot}3H_2O$ (109 mg, 0.29 mmol) was added to a solution of **14b** (150 mg, 0.29 mmol) in THF at rt. The mixture was stirred for 1 h before standard work-up (CH_2Cl_2) which gave **14a** (120 mg, 95%), as an oil, HR CI MS: calcd for $C_{16}H_{23}NO_3Si$ 436.0445 (MH^+), found 436.0481; ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.92 (3H, d, J=7 Hz), 1.50 (1H, m), 1.66 (3H, d, J=6.5 Hz), 1.74 (1H, broad s, OH), 2.15 (1H, m), 2.33 (1H, sex, J=7 Hz), 2.40 (3H, s), 3.60 (3H, m), 3.88 (1H, d, J=7 Hz), 5.78 (1H, q, J=6.5 Hz), 7.28 (2H, d, J=8 Hz), 7.62 (2H, J=8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.8, 21.6, 21.8, 30.8, 39.0, 39.7, 66.9, 69.7, 111.2, 127.4, 129.4, 132.8, 137.8, 143.2; 2D NOESY ($CDCl_3$, 400 MHz): nOe H2–H4, H4–H10.

4.2.15. (2*S*,3*S*,4*S*)-3-Methyl-2-(prop-*E*-enyl)-1-(4-methyl-benzenesulfonyl)-piperidin-4-ol (3). *t*-BuLi (0.5 mL of 1.5 M solution in pentane, 0.75 mmol) was added to a solution of **14a** (115 mg, 0.26 mmol) in THF (15 mL) at −78°C under inert atmosphere. After 1 h at −78°C, AcOH (30 μL) was added and the solution was allowed to warm up to rt, before standard work-up (ether) which provided **3** (48 mg, 60%), as an oil, after silica gel column chromatography (heptane/AcOEt 8/2), $[\alpha]_D$=−9 ($CHCl_3$, c 1.3); EI MS: M^+ 309, m/z 268; IR (neat) ν_{max} 3476, 1665 cm^{-1}; ^1H NMR, ($CDCl_3$, 250 MHz) δ: 1.02 (3H, d, J=7 Hz), 1.18 (1H, s, OH), 1.44 (3H, dd, J=6.5, 2.5 Hz), 1.55 (1H, m), 1.77 (1H, m), 1.93 (1H, m), 2.41 (3H, 2 s), 3.26 (1H, td, J=11.5, 3 Hz), 3.38 (1H, td, J=11.5, 3.5 Hz), 3.64 (1H, qn, J=4 Hz), 3.96 (1H, dd, J=8, 2.5 Hz), 5.26 (1H, dq, J=6.5, 15.5 Hz), 5.60, (1H, ddq, J=15.5, 8, 2.5 Hz), 7.25 (2H, d, J=8 Hz), 7.61 (2H, d, J=8 Hz); ^{13}C NMR, ($CDCl_3$,

62.5 MHz) δ: 16.8, 17.5, 21.5, 28.7, 37.9, 41.6, 61.1, 69.9, 127.6, 128.8), 129.1, 129.7, 137.1, 142.8; 2D NOESY ($CDCl_3$, 400 MHz): nOe H4–H10, H4–H5β, H2–H10, H2–H5β, H7–H9.

4.2.16. 5*S*-[2-(*tert*-Butyldimethylsilanyloxy)-1*R*-hydroxyethyl]-2,2-dimethyl-[1,3]-dioxolane-4*S*-carbaldehyde oxime (16). A solution of hydroxylamine acetate (442 mg, 5.56 mmol), pyridine (0.45 mL, 5.56 mmol) and **15**[16] (845 mg, 2.78 mmol) in MeOH (24 mL) was kept at rt for 16 h. After standard work-up (CH_2Cl_2) **16** (mixture of isomers) (869 mg, 98%) was obtained as crystals, mp 60–64°C, and was used without further purification, anal. calcd for $C_{14}H_{29}NO_5Si$%: C 52.63, H 9.16, N 4.39; found %: C 52.83, H 8.98, N 4.34; IR ($CHCl_3$) ν_{max} 3381, 2952, 2861, 1644, 1462, 1384, 1265, 920, 846; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.10 (6H, s), 0.90 (9H, s), 1.37 (3H, s), 1.48 (3H, s), 3.08 (1H, s, OH), 3.68 (2H, m), 3.83 (1H, t, *J*=7.5 Hz), 4.18 (1H, dd, *J*=6.5, 6 Hz *anti*), 4.3 (1H, t, *J*=6.5 Hz *syn*), 4.89 (1H, dd, *J*=7.5 Hz, *J′*=6.5 Hz *anti*), 5.4 (1H, t, *J*=6.5 Hz *syn*), 6.92 (1H, d, *J*=6.5 Hz *syn*), 7.51 (1H, d, *J*=7.5 Hz *anti*), 8.73 (1H, s, N–OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: −0.5, 18.3, 25.3, 25.8, 27.7, 64.5, 69.3, 75.3 (*anti*), 75.5 (*syn*), 77.1 (*anti*), 77.6 (*syn*), 109.8, 148.3 (*anti*), 150.0 (*syn*).

4.2.17. 5*S*-[2-(*tert*-Butyldimethylsilanyloxy)-1*R*-hydroxyethyl]-4*S*-methylamino-2,2-dimethyl-[1,3]-dioxolane (17a). $LiBH_4$ (28 mg, 1.28 mmol) was added to a solution of **16** (205 mg, 0.64 mmol) in THF (4 mL). The mixture was refluxed for 16 h. After cooling, standard work-up ($CHCl_3$) followed by silica gel column chromatography (CH_2Cl_2/MeOH 9/1) gave **17a** (164 mg, 84%), as an oil, $[\alpha]_D$=+3 ($CHCl_3$, *c* 0.7), HR CI MS calcd for $C_{14}H_{32}NO_4Si$ (MH^+) 306.2100, found 306.2077; IR (neat) ν_{max} 3367, 3297, 2991, 1602, 1470, 1463, 1163, 1055, 1006, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.09 (6H, s), 0.91 (9H, s), 1.33 (3H, s), 1.40 (3H, s), 2.70 (3H, broad s, OH, NH_2), 2.93 (1H, ABX, *J*=12.5, 7.5 Hz), 3.04 (1H, ABX, *J*=12.5, 7.5 Hz), 3.68–3.78 (2H, m), 3.86 (1H, m), 4.11–4.22 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: −5.2, 18.6, 26.1, 26.5, 28.2, 41.7, 65.1, 69.7, 77.4, 78.5, 108.8.

4.2.18. 5*S*-[2-(*tert*-Butyldimethylsilanyloxy)-1*R*-hydroxyethyl]-2,2-dimethyl-[1,3]-dioxolan-4*S*-ylmethyl-(4-methyl)-benzenesulfonamide (17c). Net_3 (0.6 mL, 8.9 mmol) and TsCl (1.42 g, 7.44 mmol) were added to a solution of **17a** (2.27 g, 7.44 mmol) in CH_2Cl_2 (40 mL) at 0°C. The mixture was stirred for 2 h before addition of aqueous $NaHCO_3$ solution. Standard work-up (CH_2Cl_2) led to **17b** (1.94 g, 57%), as crystals, mp 105°C (heptane/ether), after silica gel column chromatography (CH_2Cl_2/heptane 1/1), $[\alpha]_D$=+20 ($CHCl_3$, *c* 1.4), anal. calcd for $C_{21}H_{37}NO_6SSi$%: C 54.88, H 8.12, N 3.05, S 6.96; found %: C 54.75, H 8.01, N 2.98, S 6.88; IR (neat) ν_{max} 3531, 3270 cm^{-1}. A sample of **17b** (1.87 g, 4.07 mmol) in THF was desilylated with $Bu_4NF{\cdot}3H_2O$ (1.54 g, 4.88 mmol) to give **17c** (1.15 g, 82%), after silica gel column chromatography (CH_2Cl_2/MeOH 95/5), as crystals, mp 153–155°C (MeOH/heptane), $[\alpha]_D$=−27 (MeOH, *c* 1.2), anal. calcd for $C_{15}H_{23}NO_6S$ %: C 52.16, H 6.72, N 4.06, S 9.26; found %: C 52.21, H 6.79, N 3.84, S 9.21; HR CI MS calcd for $C_{15}H_{24}NO_6S$ (MH^+) 346.1324, found 346.1355; IR (neat) ν_{max} 3531, 3269, 2906, 1595, 1497, 1474, 1463, 1230, 1150, 897, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.23 (3H, s), 1.27 (3H, s), 2.38 (3H, s), 2.99 (1H, ABX, *J*=13, 7.5 Hz), 3.19 (1H, ABX, *J*=13, 6 Hz) 3.43–3.52 (2H, m), 3.68 (1H, m), 3.92 (1H, dd, *J*=9, 6 Hz), 4.13 (1H, dt, *J*=7.5, 6 Hz), 4.40 (3H, broad s, OH, NH), 7.26 (2H, d, *J*=8 Hz), 7.66 (2H, d, *J*=8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.3, 25.7, 28.3, 44.5, 65.2, 70.8, 77.4, 77.6, 110.0, 128.1, 130.7, 138.9, 144.7.

4.2.19. (2*S*,3*S*,4*S*)-3,4-Isopropylidenedioxy-1-(4-methylbenzenesulfonyl)-pyrrolidin-2-ol (18). A solution of $NaIO_4$ (2.63 g, 12.29 mmol) in aqueous pH 5 solution (55 mL) was added to a solution of **17c** (2.12 g, 6.14 mmol) in EtOH (80 mL). The mixture was stirred for 1 h at rt before addition of aqueous $Na_2S_2O_7$ solution followed by standard work-up (CH_2Cl_2) to give **18** (1.88 g, 98%) used without further purification, crystals, mp 101–102°C (MeOH/heptane), $[\alpha]_D$=−21 ($CHCl_3$, *c* 0.5), anal. calcd for $C_{14}H_{19}NO_5S$ %: C 53.66, H 6.12, N 4.41, S 10.21; found %: C 53.83, H 6.34, N 4.43, S 10.31; HR CI MS calcd for $C_{14}H_{20}NO_5S$ (MH^+) 314.1062, found 314.1054; IR (neat) ν_{max} 3226, 3025, 1602, 1459, 1377, 1172, 1163, 1116, 1029 cm^{-1}; ^1H NMR ($CDCl_3$ 250 MHz) δ: 1.10 (3H, s), 1.22 (3H, s), 2.41 (3H, s), 3.25 (1H, broad s, OH), 3.54 (1H, d, *J*=11.5 Hz), 3.77 (1H, dd, *J*=11.5, 4.5 Hz), 4.54 (1H, d, *J*=6 Hz), 4.78 (1H, dd, *J*=6, 4.5 Hz), 5.38 (1H, s), 7.30 (2H, d, *J*=8 Hz), 7.77 (2H, d, *J*=8 Hz); ^{13}C NMR, ($CDCl_3$, 75 MHz) δ: 21.3, 24.3, 25.7, 52.1, 78.2, 85.1, 87.6, 111.6, 127.0, 129.4, 136.5, 143.6. 2D NOESY ($CDCl_3$, 400 MHz): nOe H5β–H4, H3–H4, H2–H3.

4.2.20. 5*S*-[4*RS*-(Pentenyloxy)-1*R*-hydroxybut-2-ynyl]-[2,2-dimethyl-(1,3)-dioxolan-4*S*-ylmethyl]-4-methylbenzenesulfonamide (19). *n*BuLi (7.56 mL of 1.3 M solution in hexane) was added to a solution of 3-pentenyloxy-but-1-yne (1.36 g, 9.8 mmol) in THF (38 mL) at −78°C under inert atmosphere. After 15 min, **18** (1.47 g, 4.68 mmol) in THF solution (16 mL) was slowly added. The solution was warmed up to rt and kept to react at this temperature for 16 h. Quenching with aqueous NH_4Cl solution was followed by standard work-up (ether). The crude reaction mixture was chromatographed on silica gel comumn to give **19** eluted by CH_2Cl_2/MeOH 99/1 (2.0 g, 95%), as an oil, HR CI MS: calcd for $C_{23}H_{34}NO_6S$ 452.2106, found 452.2096; IR (neat) ν_{max} 3455, 3285, 3075, 2986, 1641, 1599, 1451, 1383, 1373, 1161, 1095, 1075, 913, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.29 (3H, s), 1.35 (3H, s), 1.38 (3H, d, *J*=6.5 Hz), 1.65 (2H, qn, *J*=7 Hz), 2.12 (1H, q, *J*=7 Hz), 2.40 (3H, s), 3.28 (2H, q, *J*=6.5 Hz), 3.36 and 3.67 (2H, ABX_2Y, *J*=11.5, 7, 2.5 Hz), 4.06–4.18 (2H, m), 4.26 (1H, q, *J*=6.5 Hz), 4.46 (1H, d, *J*=4 Hz), 4.94 (1H, dd, *J*=10.5, 1.5 Hz), 5.0 (1H, dd, *J*=17, 1.5 Hz), 5.20 (1H, t, *J*=6.5 Hz, NH), 5.81 (1H, ddt, *J*=17, 10.5, 7 Hz), 7.30 (2H, d, *J*=8 Hz), 7.73 (2H, d, *J*=8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.6, 21.9, 25.3, 27.6, 28.8, 30.3, 42.7, 61.3, 65.3, 68.3, 75.9, 78.6, 82.4, 87.3, 109.1, 114.8, 127.1, 129.8, 137.0, 138.3, 143.5.

4.2.21. 5*S*-[4*RS*-(Pentenyloxy)-1*R*-hydroxybut-3-iodo-2-enyl]-[2,2-dimethyl-(1,3)-dioxolan-4*S*-ylmethyl]-4-methyl-benzenesulfonamide (20a). Red Al® (2.46 μL of 65% solution in toluene, 1.26 mmol) was added to a solution of **19** (190 mg, 0.42 mmol) in ether (5 mL) at 0°C under inert

atmosphere. The mixture was stirred for 16 h at rt before addition of EtOAc (40 μL). After 15 min at rt, the mixture was cooled to −78°C and after addition of a solution of I_2 (214 mg, 0.84 mmol) in THF (4 mL) was warmed up to −5°C for 2 h. Quenching successively by aqueous $Na_2S_2O_7$ and NH_4Cl solutions (6 mL of each) was followed by filtration of the mixture upon Celite®. The solution was extracted with CH_2Cl_2. The organic phase washed, dried on $MgSO_4$ and evaporated gave **20a** (234 mg, 96% yield) which was used witout further purification, as an oil HR CI MS: calcd for $C_{23}H_{33}NO_6SI$ 562.1126, found 562.1106; IR (neat) ν_{max} 3364, 3018, 2987, 1641, 1600, 1384, 1373, 1161, 1095, 1074, 767 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.22 (3H, d, J=6.5 Hz), 1.27 (3H, s), 1.32 (3H, s), 1.67 (2H, qn, J=7), 2.15 (1H, q, J=7 Hz), 2.42 (3H, s), 3.15–3.54 (6H, m with OH), 4.09 and 4.12 (1H, 2t, J=5.5 Hz), 4.25 (1H, m), 4.46 (1H, ddd, J=8, 6, 5.5 Hz), 4.97 (1H, dd, J=10.5, 1.5 Hz), 5.02 (1H, dd, J=17, 1.5 Hz), 5.27 (1H, t, J=6.5 Hz, NH), 5.81 (1H, ddt, J=17, 10.5, 7 Hz), 6.06 and 6.09 (1H, 2d, J=8 Hz), 7.32 (2H, d, J=8 Hz), 7.76 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.6, 22.1, 25.5, 27.9, 28.9, 30.5, 42.7, 68.1, 73.1, 75.9, 78.1, 81.3, 108.8, 114.8, 120.6, 127.2, 129.9, 134.5 and 135.1 (C-5), 137.1, 138.4, 143.6.

4.2.22. 5*S*-[4*RS*-(Pentenyloxy)-1*R*-(*tert*-butyl-dimethylsilanyloxy)-but-3-iodo-3*Z*-enyl]-[2,2-dimethyl-(1,3)-dioxolan-4*S*-ylmethyl]-4-methyl-benzenesulfonamide (20b). Imidazole (526 mg, 7.75 mmol) and TBDMSCl (5.82 mg, 3.87 mmol) were added to a solution of **20a** (895 mg, 1.55 mmol) in DMF (3 mL) at rt. The mixture was stirred for 16 h at rt before addition of H_2O standard work-up (ether) which led to **20b** (1.02 g, 95 %) which was used without further putification, EI MS: M^+ 693, m/z 678; IR (neat) ν_{max} 3291, 2935, 1642, 1598, 1380, 1373, 1327, 1332 cm^{-1}.

4.2.23. (2*S*,3*R*,4*S*,5*S*)-2-[1-Iodo-prop-1*Z*-enyl]-3-(*tert*-butylsilanyloxy)-4,5-isopropylidenedioxy-1-(4-methyl-benzenesulfonyl)-piperidine (21a) and (2*S*,3*R*,4*S*,5*S*)-4,5-epoxy-2,3-isopropylidenedioxy-6-iodo-oct-6*Z*-en-1-(4-methyl-benzenesulfonyl)-1-(*tert*-byutyldimethylsilanyl)-1-amine (22). 20b (78 mg, 0.1 mmol) was cyclized according to the general procedure to give **21a** (45 mg, 66%) and **22a** (9 mg, 13%).

21a. Oil $[\alpha]_D$=+31 ($CHCl_3$, c 0.9), HR CI MS: calcd for $C_{24}H_{39}NO_5SSiI$ (MH^+) 608.1365, found 608.1375; IR (neat) ν_{max} 3379, 3018, 1640, 1598, 1384, 1258, 1158, 1120, 1061, 933 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.02 (3H, s), 0.10 (3H, s), 0.85 (9H, s), 1.35 (3H, s), 1.57 (3H, d, J=6.5 Hz), 1.66 (3H, s), 2.39 (3H, s), 3.35 (1H, ABX, J=14.5, 2 Hz), 3.88 (1H, dd, J=8.5, 2 Hz), 4.03 (1H, d, J=14.5 Hz), 4.27 (1H, d, J=8.5 Hz), 4.32 (1H, dd, J=8.5, 2.5 Hz), 4.40 (1H, dd, J=8.5 Hz, J'=2.5 Hz), 6.03 (1H, q, J=6.5 Hz), 7.19 (2H, d, J=8 Hz), 7.55 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: −4.1, 18.1, 21.3, 21.6, 24.4, 25.7, 25.8, 45.3, 63.4, 70.1, 73.6, 74.3, 109.9, 111.6, 127.8, 128.9, 136.0, 139.4, 142.5.

22. Oil $[\alpha]_D$=+18 ($CHCl_3$, c 1.7), HR CI MS: calcd for $C_{24}H_{39}NO_5SSiI$ (MH^+) 608.1365, found 608.1375; IR (neat) ν_{max} 1642, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.07 (3H, s), 0.16 (3H, s), 0.85 (9H, s), 1.32 (3H), 1.47 (3H, s,), 1.63 (3H, d, J=6.5 Hz), 2.41 (3H, s), 3.15 (1H, ABX, J=14.0, 10.5 Hz), 3.84 (2H, m), 4.05 (2H, m), 4.47 (1H, m), 5.97 (1H, q, J=6.5 Hz), 7.25 (2H, d, J=8 Hz), 7.61 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: −7.2, 19.0, 20.6, 21.4, 24.6, 25.9, 27.0, 44.7, 65.6, 72.3, 74.2, 78.5, 108.0, 111.6, 127.7, 129.4, 135.8, 138.5, 144.9.

4.2.24. X-Ray crystallographic data of 21c. 21a was acetylated (Ac_2O, pyridine, DMAP) to provide **21c**, as a crystalline material (MeOH). Orthorombic, space group $P2_12_12_1$, Z=4, a=19.470(5), b=14.960(4), c=7.957(3) Å, V=2317.6 $Å^3$, d_C=2.03 g cm^{-3}, λ(Mo Kα)=0.707 Å, 6402 intensities measured of which 1935 were unique. Refinments of 293 variables converged to $R_1(F)$=0.0740 for 1846 $F_0 \geq 4d(F_0)$ $wR_2(F_2)$=0.0780 for all data. The residual electron density in the last Fourier map was found between −0.54 and 0.56 e^-.

4.2.25. (4*S*,5*R*,6*R*)-1-*p*-Toluenesulfonylamido-5-(*tert*-butyldimethylsilylanyloxy)-6-[prop-*E*-enyl]-2,3-dehydropiperidin-4-ol (23). *t*-BuLi (0.1 mL of 1.5 M solution in pentane was added to a solution of **21a** (48 mg, 0.08 mmol) in ether at −78°C, under inert atmosphere. The mixture was stirred for 1 h at −78°C before addition of AcOH, warming up to rt, standard work-up (ether) and silica gel column chromatography (CH_2Cl_2/MeOH 99/1) to give **23** (16 mg, 42%) as an oil, $[\alpha]_D$=+30 ($CHCl_3$, c 0.6), HR CI MS: calcd for $C_{21}H_{32}NO_3SSi$ (MH^+) 406.1872, found 406.1905; IR (neat) ν_{max} 3453, 2930, 1650, 1598, 1354, 1167, 1089, 1037, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.13 (6H, s), 0.88 (9H, s), 1.61 (3H, dd, J=6.5, 1.5 Hz), 2.07 (1H, d, J=10.5 Hz, OH), 2.41 (3H, s), 3.82 (1H, dd, J=4.0, 2.0 Hz), 4.12 (1H, m), 4.55 (1H, m), 4.74 (1H, dd, J=8.5, 2 Hz), 5.01 (1H, ddq, J=15.5, 7.5, 1.5 Hz), 5.60 (1H, ddq, J=15.5, 6.5, 1 Hz), 6.61 (1H, d, J=8.5 Hz), 7.27 (2H, d, J=8 Hz), 7.66 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: −0.5, 17.7, 18.3, 21.6, 26.0, 61.8, 63.1, 79.5, 106.7, 124.4, 127.5, 129.6, 130.1, 137.8, 143.1.

4.2.26. 5*S*-[1*R*-Hydroxybut-3-allenyl]-[2,2-dimethyl-(1,3)-dioxolan-4*S*-ylmethyl]-4-methyl-benzenesulfonamide (24). 21a (114 mg, 0.19 mmol) was desilylated ($Bu_4NF{\cdot}6H_2O$, THF) to provide **21b** (81 mg, 85%) as crystals, mp 205°C MeOH/heptane), $[\alpha]_D$=+31 ($CHCl_3$, c 1.5); CI MS: 494 (MH^+), 476, 366; anal. calcd for $C_{18}H_{24}NO_5SI$ %: C 43.81, H 4.91, N 2.84, S 6.48, found C 44.01, H 5.05, N 2.83, S 6.71; IR (neat) ν_{max} 3469, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.38 (3H, s), 1.62 (3H, d, J=6.5 Hz), 1.64 (3H, s), 2.0 (1H, d, J=3 Hz, OH), 2.41 (3H, s), 3.31 (1H, ABX, J=15, 2 Hz), 3.88 (1H, d, J=8 Hz), 4.13 (1H, dd, J=15, 2 Hz), 4.17 (1H, d, J=8.5 Hz), 4.41 (1H, dt, J=8.5, 2 Hz), 4.59 (1H, dd, J=8, 3 Hz), 6.12 (1H, q, J=6.5 Hz), 7.21 (2H, d, J=8 Hz), 7.55 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 21.5, 21.6, 24.4, 25.7, 44.8, 63.3, 69.0, 73.0, 73.2, 110.5, 110.9, 127.7, 129.0, 136.9, 137.0, 142.7. **21b** (81 mg, 0.16 mmol) was treated with *t*-BuLi as described above to give to give **23b** (1 mg, 2%) **24** (38 mg, 78%), and 25 (9 mg, 18%) after silica gel column chromatography (heptane/AcOEt 3/7).

24. Oil $[\alpha]_D$=−3 ($CHCl_3$, c 1.6), HR CI MS: calcd for $C_{18}H_{26}NO_5S$ (MH^+) 368.1531, found 368.1516; IR (neat)

ν_{max} 3470, 3283, 1967, 1598, 1383, 1218, 1151, 1094, 1071, 866 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.30 (3H, s), 1.34 (3H, s), 1.71 (3H, dd, J=6.5, 3.5 Hz), 2.13 (1H, broad s, OH), 2.44 (3H, s), 3.22 (2H, m), 3.89 (1H, dd, J=9, 6 Hz), 4.07 (1H, m), 4.25 (1H, q, J=6 Hz), 5.38 (3H, m), 7.31 (2H, d, J=8 Hz), 7.75 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 14.2, 21.5, 25.4, 27.8, 42.6, 67.0, 76.1, 79.6, 91.1, 92.7, 108.7, 127.0, 129.7, 137.0, 143.4, 202.7.

25. Oil $[\alpha]_D$=+22 ($CHCl_3$, c 0.5), HR CI MS: calcd for $C_{18}H_{26}NO_5S$ (MH^+) 368.1531, found 368.1516; IR (neat) ν_{max} 3470, 1599, 1383, 1378 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.36 (3H, s), 1.48 (3H, s), 1.65 (3H, dd, J=6.5, 1.5 Hz), 2.25 (1H, d, J=4 Hz, OH), 2.41 (3H, s), 3.48 (2H, d, J=5 Hz), 3.81 (1H, dt, J=4, 3.5 Hz), 4.35 (3H, m), 5.20 (1H, ddq, J=15.0, 7.0, 1.5 Hz), 5.81 (1H, ddq, J=15.0, 6.5, 1 Hz), 7.27 (2H, d, J=8 Hz), 7.66 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ:17.4, 21.6, 24.8, 26.3, 44.3, 58.4, 69.2, 72.1, 110.0, 127.3, 127.8, 129.4, 130.5, 135.9, 143.1.

4.2.27. Hydrogenolysis of 21b. A solution of **21b** (49.4 mg, 0.1 mmol), AcONa (50 mg) and quinoline (I drop) in MeOH (10 mL) was stirred under H_2 atmosphere in the presence of 10% palladium on charcoal (10 mg). After absorption of 1 equiv. of H_2, the catalysor was filtered off and the filtrate diluted with H_2O was extracted by CH_2Cl_2. Vacuum evaporation of the organic layer led to a residue which was purified by flash chromatography (CH_2Cl_2/MeOH 95/5) to give **25** (30 mg, 80 %).

4.2.28. (2*R*,3*R*,4*S*,5*S*)-1-(4-Methylbenzenesulfonyl)-2-[prop-*E*-enyl]-piperidine-3,4,5-triol (26). 1N HCl (0.2 mL) was added to a solution of **25** (8 mg, 0.02 mmol) in THF (0.2 mL). After 1 h at rt, alcalinisation by $NaHCO_3$ and standard work-up (CH_2Cl_2) **26** was obtained (5 mg, 78%) as an oil $[\alpha]_D$=+9 ($CHCl_3$, c 0.2), EI MS: m/z 312 (M−15); IR (neat) ν_{max} 3402 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz), δ: 1.65 (3H, dd, J=6.5, 1.5 Hz), 2.42 (3H, s), 2.93 (2H, m, OH), 3.19 (1H, d, J=13 Hz), 3.56 (2H, m), 3.91 (3H, m), 4.77 (1H, broad s, OH), 5.20 (1H, ddq, J=15.0, 6.0, 1.5 Hz), 5.68 (1H, ddq, J=15.0, 6.5, 1 Hz), 7.28 (2H, d, J=8 Hz), 7.73 (2H, d, J=8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ:17.5, 21.6, 46.2, 58.7, 66.5, 69.0, 73.3, 127.7, 129.6, 131.1, 135.9, 143.1.

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