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Total Synthesis of (-)-Halosaline by a Ruthenium-Catalyzed Ring Rearrangement

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Abstract: The stereoselective synthesis of substituted piperidines by a ruthenium-catalyzed ring rearrangement of cyclopentene derivatives is demonstrated. The influence of different substituents and the effect of ethylene on the metathesis reaction is described. The ring rearrangement can be combined with a molybdenum-catalyzed cross metathesis reaction using allyltrimethyl silane as coupling partner. The first total synthesis of (-)-halosaline was accomplished via domino metathesis reaction utilizing Grubbs' ruthenium catalyst. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *cyclopentenes; metathesis; piperidines; rearrangements*

Introduction:

During the last several years ring closing metathesis (RCM) has become an important synthetic method particularly due to the development of Grubbs' ruthenium catalyst[1] **1** $Cl_2(PCy_3)_2Ru{=}CHPh$ (Cy = cyclohexyl) and Schrock's molybdenum complex[2] **2** $PhMe_2CCH{=}Mo{=}N[2,6\text{-}(i\text{Pr}_2C_6H_3][OCMe(CF_3)_2]_2$. The efficiency of such ring closure reactions has been demonstrated by the synthesis of numerous carbo- and heterocycles[3-6]. It has also been applied as key step in several natural product syntheses[3,7,8]. The formation of a volatile olefin - usually ethylene - is anticipated to be the driving force of the RCM reaction. **1** does also catalyze ring opening metathesis (ROM), which is mainly applied in the ring opening metathesis polymerization (ROMP) of norbornene derivatives[9,10]. We successfully avoided the polymerization of norbornene derivatives in the presence of a terminal olefin and were able to combine the ROM with a highly selective cross metathesis (CRM)[11,12]. ROM can also be combined with RCM[13-15]. The driving force of these reactions is the difference of enthalpy which is mainly due to the loss of ring strain of the reactant cyclic olefin. A particularly attractive aspect of this reaction is the catalytic transfer of stereochemical information from readily available carbocyclic olefins to heterocyclic products.

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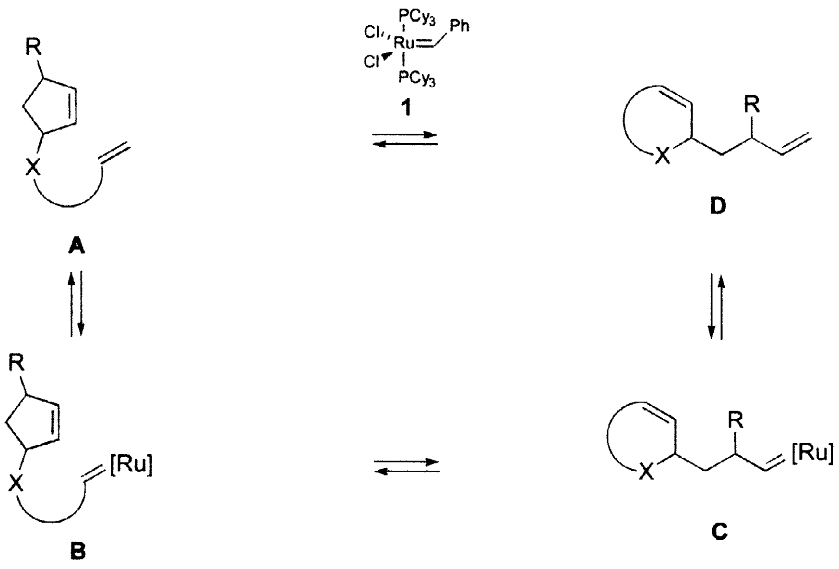
Here we would like to report the ruthenium-catalyzed ring rearrangement of chiral cyclopentene derivatives and the application of this concept to the synthesis of the piperidine alkaloid (-)-halosaline **3**[16].



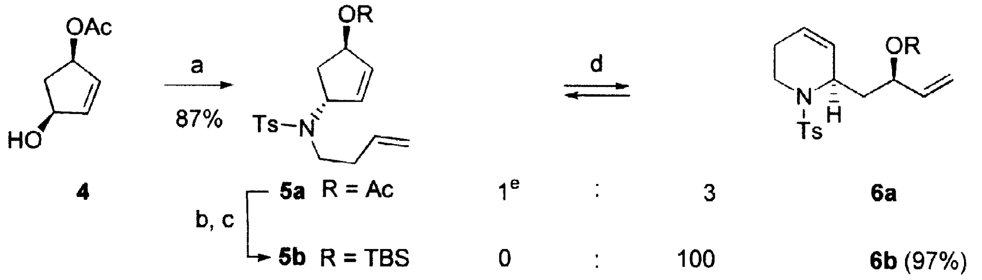
Scheme 1: Ruthenium-catalyzed ring rearrangement.

In a reaction of a cyclopentene derivative **A** with **1** we expect the terminal double bond to be attacked first to form the metal-carbene complex **B** (Scheme 1). A reaction of **B** with **A** could lead to dimerization products. However, if the intramolecular formation of a metallacyclobutane with the endocyclic double bond followed by [2+2]-cycloreversion was faster, carbene complex **C** should be obtained. The catalytic cycle could be closed by a reaction of **C** with another molecule of **A**. Depending on the regioselectivity of the cycloaddition, a cross metathesis or a methylene transfer, which results in formation of product **D**, would occur. In case of X = N, O one would transform cyclopentene derivatives into heterocycles, if cross metathesis can be excluded. The **A** : **D** ratio should depend on thermodynamic effects, e.g. ring strain. As a side reaction cross metathesis may take place, which is strongly effected by steric parameters. Therefor, the yield should depend on the size of the substituent R.

Results and discussion:

Piperidines are found in many natural products. Consequently, we intended to apply our concept to the stereo-controlled synthesis of this class of compounds. As a target, we chose (-)-halosaline **3** which was isolated from *Haloxylon Salicornicum*[16]. It is one representative of the group of natural piperidine alkaloids which differs in the relative and absolute configuration at C2 and C8 as well as the length of the alkyl moiety at C8[17].

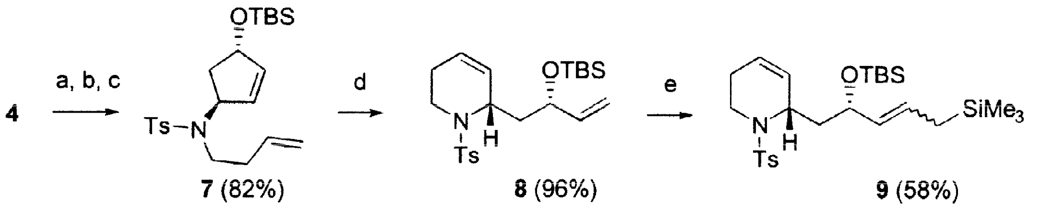
Acetate **4** served as starting material. It can be readily prepared in high enantiomeric purity (> 99 % ee) by enzymatic hydrolysis[18] of the meso diacetate and offers a variety of possibilities for the synthesis of enantiomerically pure diastereomers of type **A**. The trans cyclopentene derivative **5a** was obtained by Mitsunobu reaction[19] of **4** with *N*-tosyl butenylamine (Scheme 2). A 1:3- mixture of starting material and rearranged product **6a** was obtained in the reaction of **5a** with 7 mol % of **1**, as determined by ^{1}H-NMR-analysis of the crude product.



Scheme 2: a) 2.5 eq. ADDP, 3 eq. TBP, 2.5 eq. *N*-tosylbutenylamine, benzene. b) NEt$_3$, MeOH, 18 h. c) TBSCl, imidazole, DMF. d) 7 mol % **1**, CH_2Cl_2, rt., 12 h, Cy = cyclohexyl. [e) Ratio of metathesis is given below the arrow.]

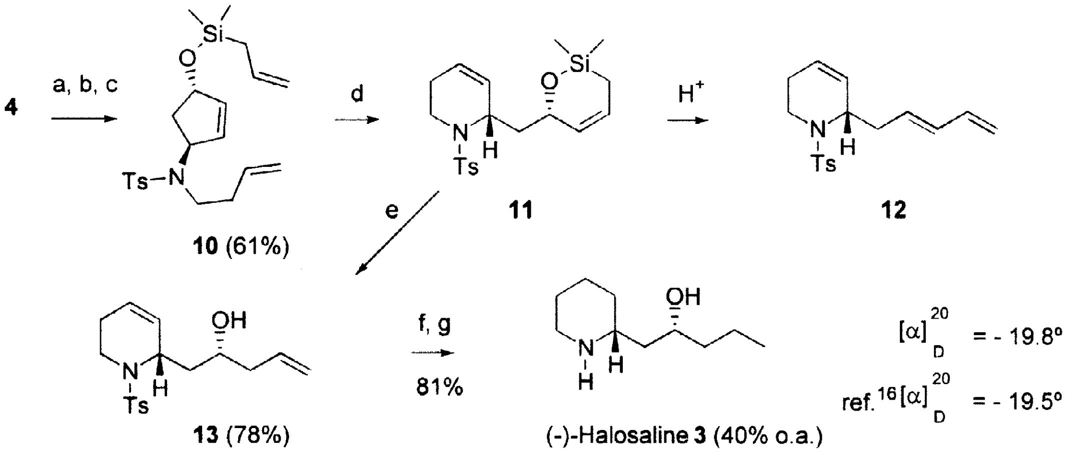
Replacing the acetate by a sterically demanding TBS-ether **5b** complete conversion was observed. With 7 mol % **1** after 12 h in CH_2Cl_2 the heterocycle **6b** was obtained in 80% yield after chromatography. By introducing a large substituent on the oxygen the formation of dimerization of products is suppressed. To accelerate the metathesis reaction and to avoid side product formation we investigated the influence of ethylene. Performing the reaction in 0.05-0.1 M concentration of **5b** in CH_2Cl_2 and excess ethylene, an increase in isolated yield up to 97 % was achieved.

The heterocycle **6b** possesses the correct relative configuration at C2 and C8 (2*R*, 8*R*), which is not the absolute configuration of the naturally occurring (-)-halosaline **3** (Scheme 3). For the synthesis of the naturally product the same starting material **4** can be utilized with only a small variation of the reaction sequence. Silylation of the OH-group, hydrolysis of the acetate, and Mitsunobu reaction with the hydroxyl group at C2 gave the (2*S*, 8*S*)-configured product **8** after the metathesis reaction (7 mol % **1**, CH_2Cl_2, 96 %). Performing the metathesis as an one-pot reaction by adding 3 eq. allyltrimethylsilane, the desired cross metathesis product **9** was only formed with less than 10 % yield and **8** was the main product (react. not shown). We suppose steric effects in the cross metathesis step to be the reason for this low yield. The use of Schrock's much more reactive molybdenum complex **2**, which is known to give higher yields for sterically hindered substrates, only resulted in cross metathesis of the terminal double bond of the cyclopentene derivative **7** with allyltrimethylsilane (react. not shown).



Scheme 3: a) TBSCl, Imidazole, DMF. b) NEt$_3$, MeOH, 18 h. c) 2.5 eq. ADDP, 3 eq. TBP, 2.5 eq. *N*-tosylbutenylamine, benzene. d) 5 mol % **1**, CH_2Cl_2, rt., 5 h. e) 3 eq. allyltrimethylsilane, 10 mol % **2**, CH_2Cl_2.

Therefore we performed the **7** → **8** ring rearrangement using the ruthenium catalyst **1** and utilized the molybdenum complex **2** for subsequent cross metathesis with allyltrimethyl silane. The reaction of the piperidine derivative **8** with allyltrimethylsilane using **2** gave the desired allylsilane **9** in 58 % yield after chromatography (Scheme 3). This product would be suitable for the synthesis of the natural (-)-halosaline **3**.



Scheme 4: a) 1.5 eq. dimethylallylchlorosilane, pyridine, CH_2Cl_2. b) 3 eq. DiBAH, THF. c) 2.5 eq. ADDP, 3 eq. TBP, 2.5 eq. *N*-tosylbutenylamine, benzene. d) 5 mol % 1, CH_2Cl_2, rt., 4 h. e) 3 eq. TBAF, -78 °C - warm up, CH_2Cl_2. f) H_2, Pd/C. g) Na/Hg, MeOH, K_2HPO_4, refl. 12 h.

However, to increase the overall yield, we replaced the CRM-step by an additional ring closure metathesis using the cheaper and less sensitive ruthenium catalyst **1** (Sheme 4). Therefore the allyldimethylsilylether was used as protective group in the first synthesis step. A domino metathesis of **10** with 5 % **1** gave the cyclic silyl ether **11** in high yield after 5 h in CH_2Cl_2, as determined by ^{1}H-NMR. Desilylation was performed without isolation of the metathesis product. Protic conditions resulted in the formation of diene **12**. Treatment of **11** with tetrabutylammonium fluoride (TBAF) gave **13** in 78 % yield. **13** was quantitatively hydrogenated using Pd/C under atmospheric pressure. Cleavage of the tosyl-group was achieved using Na/Hg in methanolic phosphate buffer[20]. (-)-Halosaline **3** was isolated in 82 % yield as a white solid. Spectroscopical data and optical rotation $[\alpha]_D$ = -19.8 (c = 0.6, in 95% EtOH) accorded to the data of the natural product $[\alpha]_D$ = -19.5 (c = 0.6, in 95% EtOH).

With the first total synthesis of (-)-halosaline **3** we demonstrated the high efficiency of the combined ring opening/ring closing metathesis and its potential for the transfer of chirality between different ring systems. This concept of intramolecular ring opening metathesis reaction could serve as a key step in a variety of stereoselective natural product syntheses. The influence of substituents at the cyclic olefin was also demonstrated. Further studies of these effects as well the application of this reaction to other ring systems of different size and constitution are currently investigated and will be reported in due course.

Experimental:

^{1}H-NMR spectra (400 MHz) and ^{13}C-NMR spectra (100.6 MHz) were recorded on a BRUKER AM 400 spectrometer in $CDCl_3$. NMR chemical shifts are expressed in ppm upfield, relative to the internal solvent peak. Mass spectra were recordet on a FINNIGAN MAT 95 SQ and IR spectra on a NICOLET FT-IR 750 spectrometer. Columm chromatography was performed on MERCK Silica gel 60 (0.040-0.063 mm). Chemicals were purchased from ALDRICH or MERCK and use without further purification. Metathesis reactions were performed in a BRAUN MB 150B-G glove box. Optical rotations were masured on a PERKIN-ELMER 141 polarimeter.

(1*S*, 4*R*)-Acetic acid 4-[but-3-enyl(toluene-4-sulfonyl)amino]cyclopent-2-enyl ester (5a). 4 (100 mg 0.7 mmol), *N*-tosyl butenylamine (400 mg, 1.76 mmol) and tributylphoshine (TBP) (440 mg, 2.11 mmol) were dissolved in dry benzene (10 mL). Azodicarboxylic dipiperidide (ADDP) (440 mg, 1.76 mmol) was then added in portions over 5 min and the solution was stirred for 24 h. The mixture was concentrated under vacuum and the residue was chromatographed on silica gel using 5 % MTBE/hexane (R_f 0.8, 20 % MTBE/hexane) to afford **5a** (211 mg, 86 %). IR (film) 3070 (w), 2978 (w), 2931 (w), 2865 (w), 1735 (s), 1641 (w), 1598 (w), 1494 (w), 1370 (m), 1342 (sb), 1238 (sb), 1161 (sb), 1090 (m), 1020 (s), 915, 816, 776, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.71 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H), 5.86 (dt, J = 6, 2 Hz, 1 H), 5.78 (ddd, J = 6, 2, 1 Hz, 1 H), 5.69 (ddt, J = 17, 10, 7 Hz, 1 H), 5.63 (m, 1 H), 5.25 (m, 1 H), 5.04 (d, J = 17 Hz, 1 H), 5.02 (d, J = 10 Hz, 1 H), 2.99 (ddd, J = 15, 10, 6 Hz, 1 H), 2.71 (ddd, J = 15, 10, 6 Hz, 1 H), 2.44 (s, 3 H), 2.35 (m, 2 H), 2.00 (s, 3 H), 1.94 (ddd, J = 15, 8, 3 Hz, 1 H), 1.86 (ddd, J = 15, 8, 3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 170.83 (Cq), 143.43 (Cq), 137.17 (CH), 134.70 (CH), 133.47 (CH), 129.78 (CH), 127.17 (CH), 117.01 (CH_2), 78.21 (CH), 63.28 (CH), 43.47 (CH_2), 36.03 (CH_2), 34.58 (CH_2), 21.51 (CH_3), 21.06 (CH_3); HRMS calcd. for [M^+-Ac] $C_{16}H_{22}O_3NS$ 308.1320, found 308.1319.

(1*R*, 4*S*)-*N*-But-3-enyl-*N*-(4-hydroxycyclopent-2-enyl)-4-methylbenzene sulfonamide. 5a (256 mg, 0.593 mmol) was added to a mixture of NEt_3 (5 mL) and MeOH (5 mL). The solution was stirred for 18 h at room temperature. The solvent was removed under vacuum, the residue was redissolved in two times with MTBE (30 mL) and flushed through silica gel. Removal of the solvent under vacuum gave a clear oil (175 mg, 96 %). IR (film) 3700 - 3200 (b, OH), 3064 (w), 2977 (w), 2943 (w), 1641 (w), 1598 (w), 1494 (w), 1335 (sb), 1158 (s), 1107 (m), 1019 (m), 918, 886, 816, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.69 (d, J = 8 Hz, 2 H), 7.29 (d, J = 8 Hz, 2 H), 5.85 (dt, J = 6, 2 Hz, 1 H), 5.68 (ddt, J = 17, 10, 7 Hz, 1 H), 5.64 (m, 1 H), 5.24 (m, 1 H), 5.03 (d, J = 17 Hz, 1 H), 5.01 (d, J = 10 Hz, 1 H), 4.85 (m, 1 H), 2.98 (ddd, J = 15, 10, 6 Hz, 1 H), 2.67 (ddd, J = 15, 10, 6 Hz, 1 H), 2.41 (s, 3 H), 2.35 (m, 2 H), 1.95 (sb, OH), 1.82 (ddd, J = 15, 8, 3 Hz, 1 H), 1.69 (ddd, J = 15, 8, 3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 143.34 (Cq), 137.48 (CH), 136.90 (Cq), 134.81 (CH), 134.49 (CH), 129.70 (CH), 127.15 (CH), 116.84 (CH_2), 75.68 (CH), 63.54 (CH), 43.40 (CH_2), 37.79 (CH_2), 36.08 (CH_2), (CH), 21.47 (CH_3); HRMS calcd. for [M^+] $C_{16}H_{21}O_3NS$ 307.1242, found 307.1249.

(1*R*, 4*S*)-*N*-But-3-enyl-*N*-[4-(tert-butyldimethylsilanyloxy)cyclopent-2-enyl]-4-methyl benzene sulfonamide (5b). To a solution of (1*S*, 4*S*) *N*-But-3-enyl-*N*-(4-hydroxycyclopent-2-enyl)-4-methyl benzene sulfonamide (190 mg, 0.618 mmol) and tert butyldimethyl chlorosilane (112 mg, 0.743 mmol) in dry DMF (5 mL) imidazole (50 mg, 0.743 mmol) was added over 10 min. The mixture was stirred for 12 h at room temperature. Hexane (30 mL) and saturated $NaHCO_3$ solution (10 mL) was added to the solution and the aqueous layer was extracted two times with hexane (20 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$ and concentrated to give a clear oil (239 mg, 92 %). IR (film) 3065 (w), 2954 (s), 2874 (s), 2856 (s), 1642 (w), 1599 (w), 1472 (w), 1344 (sb), 1252 (m), 1161 (s), 1091 (w), 1074 (s), 905, 835, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.71 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H), 5.85 (dt, J = 6, 2 Hz, 1 H), 5.70 (ddt, J = 17, 10, 7 Hz, 1 H), 5.55 (m, 1 H), 5.19 (m, 1 H), 5.04 (d, J = 17 Hz, 1 H), 5.02 (d, J = 10 Hz, 1 H), 4.86 (m, 1 H), 2.98 (ddd, J = 15, 10, 6 Hz, 1 H), 2.68 (ddd, J = 15, 10, 6 Hz, 1 H), 2.43 (s, 3 H), 2.35 (m, 2 H), 1.85 (ddd, J = 15, 8, 3 Hz, 1 H), 1.70 (ddd, J = 15, 8, 3 Hz, 1 H), 0.85 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 143.20 (Cq), 138.18 (CH), 137.17 (Cq), 134.96 (CH), 133.03 (CH), 129.62 (CH), 127.19 (CH), 116.76 (CH_2), 76.15 (CH), 63.67 (CH), 43.53 (CH_2), 38.39 (CH_2), 36.12 (CH_2), 25.79 (CH), 21.46 (CH_3), 18.12 (Cq), -1.05 (CH_3), -1.10 (CH_3); HRMS calcd. for $[M^+-CH_3]$ $C_{21}H_{32}O_3NSSi$ 406.1872, found 406.1878.

(2*R*, 8*R*)-6-[2-(tert-Butyldimethylsilanyloxy)but-3-enyl]-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine (6b). **5b** (250 mg, 0.594 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and C_2H_4 (20 mL) was bubbled slowly through the solution. **1** (35 mg, 0.042 mmol) was added and the mixture was stirred for 12 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel using 10 % MTBE/hexane (R_f 0.65, 20 % MTBE/hexane) to give **6b** (243 mg, 97 %). IR (film) 3078 (w), 3033 (w), 2954 (m), 2928 (m), 2856 (m), 1644 (w), 1598 (w), 1494 (w), 1472 (w), 1345 (s), 1331 (m), 1251 (m), 1160 (s), 1097 (s), 948 (s), 837, 778, 710, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.68 (d, J = 8 Hz, 2 H), 7.23 (d, J = 8 Hz, 2 H), 5.80 (ddd, J = 18, 10, 7 Hz, 1 H), 5.62 (m, 1 H), 5.53 (m, 1 H), 5.18 (d, J = 18 Hz, 1 H), 5.05 (d, J = 10 Hz, 1 H), 4.50 (m, 1 H), 4.31 (dt, J = 7, 7 Hz, 1 H), 3.87 (dd, J = 15, 6 Hz, 1 H), 2.40 (s, 3 H), 1.85 - 1.65 (m, 4 H), 0.92 (s, 9 H), 0.14 (s, 3 H); 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 142.86 (Cq), 141.49 (CH), 138.55 (Cq), 129.41 (CH), 128.59 (CH), 126.89 (CH), 124.25 (CH), 114.54 (CH_2), 71.68 (CH), 50.88 (CH), 44.03 (CH_2), 38.23 (CH_2), 25.85 (CH_3), 22.81 (CH_2), 21.44 (CH), 18.14 (Cq), -1.02 (CH_3), -1.75 (CH_3); HRMS calcd. for $[M^+-CH_3]$ $C_{21}H_{32}O_3NSSi$ 406.1872, found 406.1872.

(1*R*, 4*S*)-Acetic acid 4-(tert-butyldimethysilanyloxy)cyclopent-2-enyl ester.This compound was prepared in 97 % yield from **4** by a procedure similar to that employed for the synthesis of **5b**. IR (film) 3067 (w), 2955 (s), 2930 (s), 2887 (m), 2858 (s), 1738 (s), 1473 (m), 1368 (s), 1238 (sb), 1105 (m), 1064 (s), 1021 (s), 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.97 (dt, J = 6, 2 Hz, 1 H), 5.88 (m, 1 H), 5.45 (m, 1 H), 4.71 (m, 1 H), 2.80 (ddd, J = 14, 7, 7 Hz, 1 H), 2.04 (s, 3 H), 1.60 (ddd, J = 14, 5, 5 Hz, 1 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 170. 90 (Cq), 138.89 (CH), 131.13 (CH), 76.93 (CH), 74.84

(CH), 41.14 (CH_2), 25.85 (CH_3), 21.17 (CH_3), 18.16 (Cq), -1.04 (CH_3), -1.09 (CH_3); HRMS calcd. for [M^+-H] $C_{13}H_{23}O_3Si$ 255.1416, found 255.1416.

(1*R*, 4*S*)-4-(tert-Butyldimethysilanyloxy)cyclopent-2-enol. This compound was prepared in 100 % yield from (1*R*, 4*S*)-Acetic acid 4-(tert-butyldimethylsilanyloxy)cyclopent-2-enyl ester by a procedure similar to that employed for the synthesis of **5b**. IR (film) 3700 - 3200 (b, OH), 3061 (w), 2956 (s), 2929 (s), 2885 (m), 2857 (s), 1676 (w), 1472 (m), 1366 (s), 1252 (s), 1128 (m), 1071 (s), 1021 (sb), 905, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.95 (m, 1 H), 5.89 (m, 1 H), 5.66 (m, 1 H), 5.58 (m, 1 H), 2.69 (ddd, J = 14, 7, 7 Hz, 1 H), 1.74 (b, OH), 1.51 (ddd, J = 14, 5, 5 Hz, 1 H), 0.90 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 137.00 (CH), 135.57 (CH), 75.21 (CH), 75.07 (CH), 44.70 (CH_2), 25.86 (CH_3), 18.25 (Cq), -1.03 (CH_3); HRMS calcd. for [M^+-H] $C_{11}H_{21}O_2Si$ 213.1308, found 213.1313.

(1*S*, 4*S*)-*N*-But-3-enyl-N-[4-(tert-butyldimethylsilanyloxy)cyclopent-2-enyl]-4-methyl benzene sulfonamide (7). This compound was prepared in 87 % yield from (1*R*, 4*S*)-4-(tert-butyldimethylsilanyloxy) cyclopent-2-enol by a procedure similar to that employed for the synthesis of **5b**. Spectroscopical data accorded to the data of **5b**.

(2*S*, 8*S*)-6-[2-(tert-Butyldimethylsilanyloxy)-but-3-enyl]-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine (8). This compound was prepared in 96 % yield from **7** by a procedure similar to that employed for the synthesis of **6b**. Spectroscopical data accorded to the data of **6b**.

(2*S*, 8*S*)-6-[2-(tert-Butyldimethylsilanyloxy)-5-trimethylsilanylpent-3-enyl]-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridine (9). **8** (90 mg, 0.214 mmol) and allyltrimethylsilane (37 mg, 0.321 mmol) were dissolved in dry CH_2Cl_2 (1.5 mL). **2** (8 mg, 0.011 mmol) was added and the mixture was refluxed for 12 h. An additional amount of allyltrimethylsilane (37 mg, 0.321 mmol) and **2** (8 mg, 0.011 mmol) was added and the mixture was refluxed for another 12 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel using 10 % MTBE/hexane (R_f 0.6, 20 % MTBE/hexane) to give **9** (63 mg, 58 %, *E*/*Z*-ratio: 1.5/1). IR (film) 3030 (w), 2954 (m), 2928 (m), 2856 (m), 1657 (w), 1599 (w), 1495 (w), 1472 (w), 1346 (s), 1331 (m), 1248 (m), 1161 (s), 1094 (m), 1075 (m), 966 (s), 852 (s), 837 (s), 777, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.67 (d, J = 8 Hz, 2 H), 7.22 (d, J = 8 Hz, 2 H), 5.56 (m, 3 H), 5.25 (dd, J = 15, 8 Hz, 1 H), 4.37 (m, 1 H), 3.23 (dt, J = 7, 7 Hz, 1 H), 3.87 (dd, J = 15, 6 Hz, 1 H), 3.11 (ddd, J = 15, 12, 5 Hz, 1 H), 2.39 (s, 3 H), 1.9 - 1.60 (m, 4 H), 1.45 (d, J = 8 Hz, 2 H-*Z*), 1.27 (d, J = 8 Hz, 2 H-*E*), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$, 76.6 MHz) δ_C 142.77 (Cq), 138.55 (Cq), 131.92 (CH_2), 129.39 (CH_2), 128.57 (CH_2), 127.79 (CH_2), 126.90 (CH_2), 124.21 (CH-*E*), 122.71 (CH-*Z*), 71.63 (CH), 51.00 (CH), 44.68 (CH_2), 38.38 (CH_2), 25.98 (CH_3), 23.00 (CH_2-*Z*), 22.50 (CH_2-*E*), 21.44 (CH), 18.14 (Cq), -1.81 (CH_3), -3.90 (CH_3) -4.69 (CH_3); HRMS calcd. for [M^+-CH_3] $C_{25}H_{42}O_3NSSi_2$ 492.2423, found 492.2431.

(1*R*, 4*S*)-Acetic acid 4-(allyldimethylsilanyloxy)cyclopent-2-enyl ester. To a solution of **4** (550 mg, 3.87 mmol) and NEt_3 (1.17 g, 11.6 mmol) in dry CH_2Cl_2 (20 mL) allyldimethylchlorosilane (1.3 g, 9.68 mmol) was added over 10 min. The mixture was stirred for 3 h at room temperature. Hexane (20 mL) was added to the solution and the formation of a white solid was observed. The suspension was flushed through silica gel. Removal of solvent under vacuum gave a clear oil (905 mg, 97 %). IR (film) 3077 (w), 2958 (w), 2882 (w), 1737 (s, C=O), 1631 (w), 1368 (s), 1239 (sb), 1102, 1047, 1021, 904, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.96 (m, 1 H), 5.89 (m, 1 H), 5.87 (ddt, J = 16, 10, 7 Hz, 1 H), 5.44 (m, 1 H), 4.88 (d, J = 16 Hz, 1 H), 4.85 (d, J = 10 Hz, 1 H), 4.70 (m, 1 H), 2.78 (ddd, J = 14, 7, 7 Hz, 1 H), 2.02 (s, 3 H), 1.62 (d J = 7 Hz, 2 H), 1.59 (m, 1 H), 0.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 170.77 (Cq), 138.42 (CH), 133.69 (CH), 131.51 (CH), 113.80 (CH_2), 76.8 (CH), 74.60 (CH), 40.80 (CH_2), 24.64 (CH_2), 21.07 (CH_3), -1.99 (CH_3); HRMS calcd. for $[M^+\text{-}C_2H_5]$ $C_9H_{15}O_3Si$ 199.0790, found 199.0794.

(1*R*, 4*S*)-4-(Allyldimethylsilanyloxy)cyclopent-2-enol. (1*R*, 4*S*)-Acetic acid 4-(allyl dimethylsilanyloxy)cyclopent-2-enyl ester (600 mg, 2.5 mmol) was dissolved in dry THF (30 mL). DiBAH (5 mL, 1.5 M in toluol) was slowly added to the solution and the mixture was stirred for 30 min. For work-up, a saturated Na_2SO_4 solution (2 mL) was added followed by $MgSO_4$ and a quick filtration through silica gel. Removal of the solvent under vacuum yielded a clear oil (362 mg, 73 %). IR (film) 3700 - 3200 (b, OH), 3077 (w), 3061 (w), 2971 (m), 2959 (m), 2879 (wb), 1631 (m), 1391 (m), 1253 (s), 1127(m), 1070 (s), 1021 (sb), 905, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.94 (m, 1 H), 5.85 (m, 1 H), 5.78 (ddt, J = 16, 10, 8 Hz, 1 H), 4.87 (d, J = 16 Hz, 1 H), 4.86 (d, J = 10 Hz, 1 H), 4.64 (m, 1 H), 4.56 (m, 1 H), 2.68 (ddd, J = 16, 7, 7 Hz, 1 H), 2.36 (s, OH), 1.63 (d, J = 8 Hz, 2 H), 1.50 (ddd, J = 16, 4, 4 Hz, 1 H), 0.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 136.31 (CH), 136.00 (CH), 133.73 (CH), 113.85 (CH_2), 74.95 (CH), 74.90 (CH), 44.30 (CH_2), 24.66 (CH_2), -1.98 (CH_3); HRMS calcd. for $[M^+\text{-}H]$ $C_{10}H_{17}O_2Si$ 197.0998, found 197.0992.

(1*S*, 4*S*)-*N*-[4-(Allyldimethylsilanyloxy)cyclopent-2-enyl]-*N*-but-3-enyl-4-methylbenzene sulfonamide (10). This compound was prepared in 86 % yield from (1*R*, 4S)-4-(Allyldimethylsilanyloxy)cyclopent-2-enol by a procedure similar to that employed for the synthesis of **5a**. IR (film) 3076 (w), 2956 (m), 2874 (wb), 1641 (s), 1630 (m), 1599 (m), 1451 (w), 1370 (m), 1344 (sb), 1253 (s), 1160 (s), 1091 (s), 1072 (s), 1039 (s), 906, 836, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.69 (d, J = 8 Hz, 2 H), 7.28 (d, J = 8 Hz, 2 H), 5.84 (m, 1 H), 5.70 (m, 2 H), 5.57 (m, 1 H), 5.18 (m, 1 H), 5.02 (d, J = 17 Hz, 1 H), 5.01 (d, J = 10 Hz, 1 H), 4.85 (d, J = 17 Hz, 1 H), 4.83 (d, J = 10 Hz, 1 H), 2.98 (ddd, J = 14, 10, 6 Hz, 1 H), 2.69 (ddd, J = 14, 10, 6 Hz, 1 H), 2.41 (s, 3 H), 2.35 (m, 2 H), 1.83 (ddd, J = 14, 7, 3 Hz, 1 H), 1.66 (ddd, J = 14, 7, 4 Hz, 1 H), 1.57 (d, J = 8 Hz, 2 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 143.18 (Cq), 137.68 (CH), 137.07 (Cq), 136.00 (CH), 133.55 (CH), 129.58 (CH), 127.15 (CH), 116.73 (CH_2), 113.79 (CH_2), 75.89 (CH), 63.57 (CH), 43.49 (CH_2), 38.11 (CH_2), 36.07 (CH_2), 26.87 (CH), 24.59 (CH_2), 21.40 (CH_3), -2.04 (CH_3), -2.06 (CH_3); HRMS calcd. for $[M^+]$ $C_{21}H_{31}O_3NSSi$ 405.1794, found 405.1796.

(2*S*, 8*S*)-1-[1-(Toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridin-2-yl]pent-4-en-2-ol (13). **10** (280 mg, 0.691 mmol) and **1** (29 mg, 0.035 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and stirred for 5 h. The solution was then cooled to -78 °C and dry tetrabutylammonium fluoride solution (2.1 mL, 1 M in THF) was added. The reaction mixture was allowed to warm to room temperature while stirring for 15 min. The solvent was removed under vacuum and the residue was chromatographed on silica gel using 10 % MTBE/hexane (R_f 0.3, 50 % MTBE/hexane) to give **13** (172 mg, 78 %) and 21 mg **12** (10 %). **13**: IR (film) 3700 - 3200 (b, OH), 3071 (w), 3031 (w), 2976 (w), 2928 (wb), 2849 (w), 1640 (w), 1598 (w), 1494 (w), 1380 (m), 1341 (s), 1326 (s), 1156 (s), 1099 (s), 917 (s), 815, 712, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.68 (d, J = 8 Hz, 2 H), 7.23 (d, J = 8 Hz, 2 H), 5.88 (ddt, J = 17, 10, 7 Hz, 1 H), 5.51 (s, 2 H), 5.09 (db, J = 17 Hz, 1 H), 5.05 (db, J = 10 Hz, 1 H), 4.50 (dd, J = 12, 3 Hz, 1 H), 3.98 (m, 1 H), 3.89 (ddd, J = 15, 4, 4 Hz, 1 H), 3.52 (OH), 3.08 (ddd, J = 15, 7, 7 Hz, 1 H), 2.39 (s, 3 H), 2.26 (m, 2 H), 1.70 - 1.55 (m, 4 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 143.37 (Cq), 137.85 (Cq), 135.15 (CH), 129.60 (CH), 128.00 (CH), 126.81 (CH), 126.76 (CH), 124.72 (CH), 116.92 (CH_2), 66.18 (CH), 66.13 (CH), 63.09 (CH), 50.72 (CH), 50.61 (CH), 41.10 (CH_2), 40.87 (CH_2), 37.99 (CH_2), 22.23 (CH_2), 22.13 (CH_2), 21.46 (CH_3); HRMS calcd. for [M^+] $C_{17}H_{23}O_3NS$ 321.1399, found 321.1389; Anal. calcd. for $C_{17}H_{23}O_3NS$: C, 63.52; H, 7.21; N, 4.36. Found: C, 62.98; H, 7.31; N, 4.33.

12: IR (film) 3518 (wb), 3083 (w), 3064 (w), 3034 (w), 2927 (w), 2854 (w), 1923 (w), 1806 (w), 1727 (w), 1690 (w), 1653(w), 1598 (w), 1495 (w), 1455(w), 1433 (w), 1378 (m), 1342 (s), 1330 (s), 1159 (s), 1097 (s), 1005 (m), 953 (s), 815 713, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.69 (d, J = 8 Hz, 2 H), 7.29 (d, J = 8 Hz, 2 H), 6.27 (ddd, J = 17, 10, 10 Hz, 1 H), 6.03 (dd, J = 15, 10 Hz, 1 H), 5.65 (m, 3 H), 5.09 (d, J = 17 Hz, 1 H), 5.00 (d, J = 10 Hz, 1 H), 4.35 (m, 1 H), 3.82 (dd, J = 15, 7 Hz, 1 H), 3.11 (ddd, J = 17, 13, 5 Hz, 1 H), 2.40 (s, 3 H), 1.90 (m, 1 H), 1.77 (ddd, J = 19, 5, 5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 142.97 (Cq), 138.53 (Cq), 136.81 (CH), 133.79 (CH), 129.93 (CH), 129.52 (CH), 127.39 (CH), 126.99 (CH), 125.47 (CH), 115.89 (CH_2), 53.34 (CH), 38.63 (CH_2), 23.27 (CH_2), 21.45 (CH_3); HRMS calcd. for [M^+] $C_{17}H_{21}O_2NS$ 303.1293, found 303.1296.

(2*R*, 8*S*)-1-[1-(Toluene-4-sulfonyl)piperidin-2-yl]pentan-2-ol. 30 mg of Pd/C (10 %) was added to a solution of **13** (170 mg, 0.53 mmol) in MTBE (20 mL) under H_2-atmosphere. The suspension was stirred for 8 h. The catalyst was filtered off and the solvent was removed under vacuum to give white solid (170 mg, 99 %,). IR (film) 3700 - 3200 (b, OH), 2936 (s), 2870 (m), 2746 (w), 1598 (w), 1495 (w), 1330 (s), 1304 (m), 1155 (s), 1143 (s), 931 (s), 815, 714, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.72 (d, J = 8 Hz, 2 H), 7.27 (d, J = 8 Hz, 2 H), 4.20 (m, 1 H), 3.88 (ddd, J = 15, 4, 4 Hz, 1 H), 3.74 (m, 1 H), 3.42 (OH), 2.97 (ddd, J = 15, 14, 3 Hz, 1 H), 2.39 (s, 3 H), 1.98 (ddd, J = 15, 14, 2 Hz, 1 H), 1.55 - 0.95 (m, 11 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 143.06 (Cq), 137.57 (Cq), 129.73 (CH), 126.59 (CH), 66.66 (CH), 49.44 (CH), 40.72 (CH_2), 38.96 (CH_2), 37.46 (CH_2), 27.67 (CH_2), 23.76 (CH_2), 21.40 (CH_3), 19.07 (CH_2), 18.55 (CH_2), 14.09 (CH_3); HRMS calcd. for [M^+] $C_{17}H_{27}O_3NS$ 325.1712, found 325.1717. Anal. calcd. for $C_{17}H_{27}O_3NS$: C, 62.74; H, 8.36; N, 4.30. Found: C, 62.54; H, 8.32; N, 4.43.

(2*R*, 8*S*)-1-Piperidin-2-yl-pentan-2-ol (-)-halosaline (3). (2*R*, 8*R*) 1-[1-(Toluene-4-sulfonyl) piperidin-2-yl]pentan-2-ol (100 mg, 0.31 mmol) and $K_2HPO_4 \cdot 3H_2O$ (425 mg, 1.86 mmol) dissolved in dry MeOH (7 mL). Na/Hg (5.87 g, freshly prepared from 170 mg of Na and 5.7 g of Hg) was added and the mixture was refluxed for 12 h. 25 mL of H_2O was then added and the aqueous layer was extracted four times with 30 mL of CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (R_f 0.35, 30 % MeOH/CH_2Cl_2 5 % $NH_3 \cdot H_2O$) to give 42 mg (82 %) (-)-halosaline **3**. $[\alpha]_D = -19.8$ (c = 0.6, in 95% EtOH); IR (film) 3700 - 3200 (b, OH), 2954 (s), 2929 (s), 2856 (m), 1568 (w), 1452 (m), 1330 (m), 1070 (m), 1053 (m), 1027 (m), 935 (w), 886, 780, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 3.88 (m, 1 H), 3.45 (NH, OH), 3.05 (dd, J = 12, 3 Hz, 1 H), 2.88 (m, 1 H), 2.56 (ddt, J = 14, 12, 3 Hz, 1 H), 1.98 (m, 1 H), 1.65 - 1.25 (m, 11 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 106.4 MHz) δ_C 68.62 (CH), 54.77 (CH), 46.77 (CH_2), 41.83 (CH_2), 31.23 (CH_2), 25.84 (CH_2), 24.59 (CH_2), 18.99 (CH_2), 14.15 (CH_3); HRMS calcd. for $[M^+]$ $C_{10}H_{21}ON$ 171.1623, found 171.1642. Anal. calcd. for $C_{10}H_{21}ON$: C, 70.12; H, 12.36; N, 8.18. Found: C, 68.22; H, 12.10; N, 7.74.

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References:

[1] Schwab P, France MB, Ziller JW, Grubbs RH. Angew. Chem. 1995;107:2179; Angew. Chem., Int. Ed. Engl. 1995;34:2039.

[2] Schrock RR, Murdzek JS, Bazan GC, Robbins J, DiMare M, O'Regan M. J. Am. Chem. Soc. 1990;112:3875.

[3] Blechert S, Schuster M. Angew. Chem. 1997;109:2124; Angew. Chem. Int. Ed. Engl. 1997;36:2036.

[4] Hashmi ASK. J. Prakt. Chem. 1997;339:195.

[5] Schmalz HG. Angew. Chem. 1995;107:1981; Angew. Chem. Int. Ed. Engl. 1995;34:1833.

[6] Grubbs RH, Miller SJ, Fu GC. Acc. Chem. Res. 1995;28:446.

[7] Yang Z, He Y, Vourloumis D, Vallberg H, Nicolaou KC. Angew. Chem. 1997;109:170; Angew. Chem. Int. Ed. Engl. 1997;36:166.

[8] Houri AF, Xu ZM, Cogan DA, Hoveyda AH. J. Am. Chem. Soc. 1995;117:2943-2944.

[9] Grubbs RH. J. Macromol. Sci. Chem. 1994;A31(11):1829.

[10] Schrock RR. Pure Appl. Chem. 1994;66:1447.

[11] Schneider MF, Lucas N, Velder J, Blechert S. Angew. Chem. 1997;109: 257; Angew. Chem. Int. Ed. Engl. 1997;36:257.

[12] Schneider MF, Blechert S. Angew. Chem. 1996;108:479; Angew. Chem. Int. Ed. Engl. 1996;35:410.

[13] Zuercher WJ, Hashimoto M, Grubbs RH. J. Am. Chem. Soc. 1996;118:6634.

[14] Harrity JPA, Visser MS, Gleason JD, Hoveyda AH. J. Am. Chem. Soc. 1997;119:1488.

[15] Stragies R, Blechert S. Synlett. 1998:169-170.

[16] Michel KH, Sandberg F, Haglid F, Norin T. Acta Pharm. Suecica 1967;4:97.

[17] Craig JC, Lee C S-Y, Pereira Jr. WE. Tetrahedron 1978;34:510-504.

[18] Johnson CR, Bis SJ. Tetrahedron Lett. 1992;33 (48):7287-7290.

[19] Tsunoda T, Yamamiya Y, Itô S. Tetrahedron Lett. 1993;34 (10):1639-1642.

[20] Chavez F, Sherry AD. J. Org. Chem. 1989;54 (12):2990.