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Combining the [2,3] Sigmatropic Rearrangement and Ring-Closing Metathesis Strategies for the Synthesis of Spirocyclic Alkaloids. A Short and Efficient Route to (±)-Perhydrohistrionicotoxin.

David Tanner,*[a] Lars Hagberg[a,b] and Anders Poulsen[a]

[a]Department of Organic Chemistry, The Technical University of Denmark, Building 201, DK-2800 Lyngby, Denmark

[b]Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden

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Abstract

This paper describes the use of selenium-based [2,3] sigmatropic rearrangement in combination with ruthenium-catalyzed ring-closing metathesis (RCM) for the synthesis of azaspiro ring systems, as exemplified by the reactions of model substrates **5** and **6**. The methodology has been applied to a short and efficient formal total synthesis of the alkaloid (±)-perhydrohistrionicotoxin (**2**). Thus, (±)-depentylperhydrohistrionicotoxin, **1**, a known key intermediate for the synthesis of **2**, was synthesised from 2,3-epoxycyclohexan-1-one in 10 laboratory operations and *ca.* 20% overall yield. The synthetic route is potentially enantioselective, and key steps were the [2,3] sigmatropic rearrangement of **11** to **12** *via* the corresponding allylic selenide (86% yield) and ruthenium-catalyzed RCM of **13** to **14** (80%).

Keywords: Rearrangements; Metathesis; Spiro compounds; Alkaloids.

The exquisite electronic and stereochemical features which characterize most sigmatropic rearrangement reactions [1] mean that such processes have long been strategically important in the design of organic syntheses. More recently, the development of well-defined transition metal catalysts for the ring-closing metathesis (RCM) reaction of olefins [2] has provided yet another excellent tool for the construction of complex molecules, particularly natural products [3]. We became attracted to the RCM methodology in connection with a project aimed at the total synthesis of biologically active spirocyclic alkaloids, and in this paper we report that the combination of selenium-based [2,3] sigmatropic rearrangement and ruthenium-catalyzed RCM provides rapid and simple access to azaspiro ring systems. Further, we have applied this strategic combination to a short, efficient, and potentially enantioselective route to the important neurotoxic alkaloid perhydrohistrionicotoxin (**2**) *via* the known key intermediate **1**.

Our overall strategy is outlined retrosynthetically in Scheme 1, and our initial targets were simple azaspiro[4.5] and [5.5] systems, the latter being exemplified below. (To our

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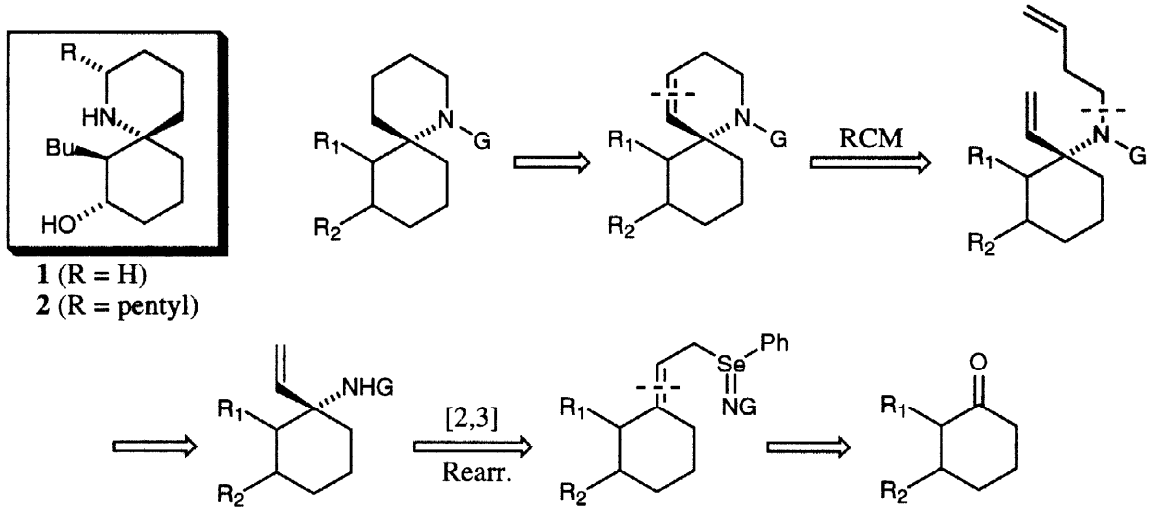
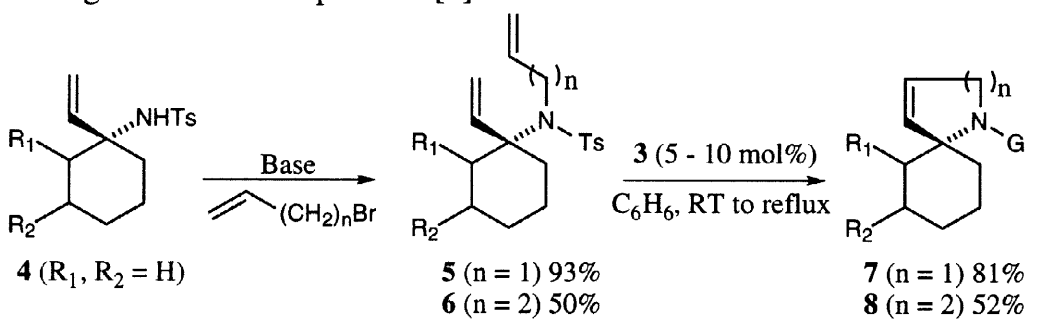
knowledge, little has so far been published on the use of RCM to synthesise spirocyclic structures, with the exception of the recent work [4] of Undheim and coworkers.)



Scheme 1. Retrosynthetic analysis of the azaspiro[5.5]undecane ring system of the histrionicotoxin alkaloids **1** and **2**. (G = protective/anion-stabilising group).

Since the group G in Scheme 1 is required to act as a protective group as well as to facilitate *N*-alkylation, tosyl was regarded as a good choice, since this would allow application of the [2,3] sigmatropic rearrangement of allylic selenide derivatives introduced by Sharpless [5] and developed by Hopkins [6]. (In these reactions, the source of nitrogen is chloramine-T.) For the crucial RCM step, the easily-handled ruthenium-alkylidene catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (**3**) developed by Grubbs [2g] was chosen. The results of our initial experiments using the known compound **4** [6] are shown in Scheme 2.

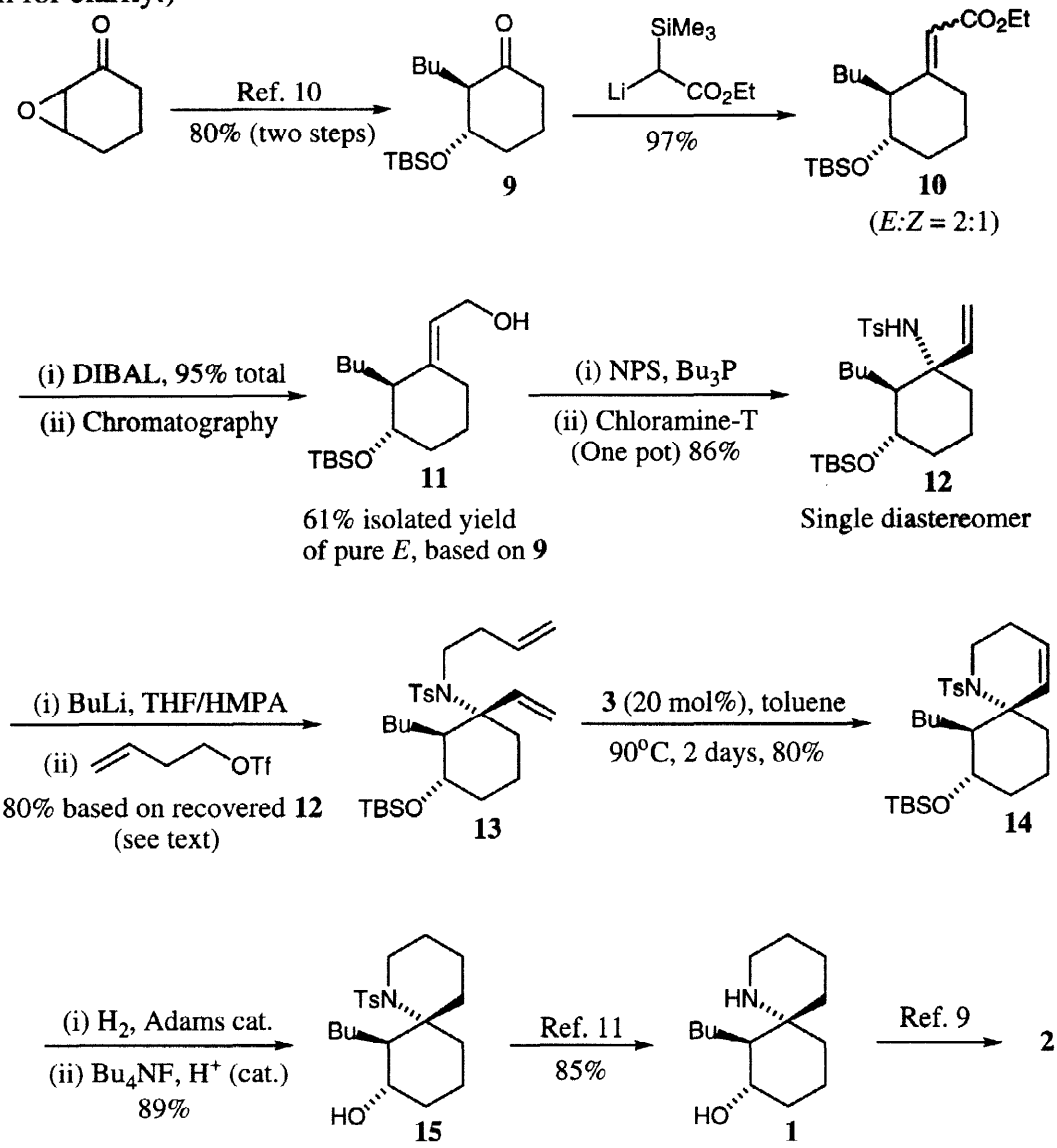


Scheme 2. Model studies for the RCM route to histrionicotoxin alkaloids. (**3** = $RuCl_2(=CHPh)(PCy_3)_2$). Conditions for **5**: NaH, THF/DMF, reflux; for **6**: NaOH, K_2CO_3, $(Bu)_4NHSO_4$, toluene, reflux.

As anticipated, alkylation of the *N*-anion of **4** with allyl bromide proceeded smoothly to yield **5** in 93% yield. Alkylation with 4-bromo-1-butene proved unexpectedly problematic, but conditions [7] were eventually found which allowed preparation of **6** in modest yield. Subjection of **5** and **6** to the RCM reaction catalyzed by **3** gave **7** and **8**, respectively, the yield for ring-closure to the five-membered heterocycle being consistently higher than that for the 6-membered analog.

Having shown that the overall strategy was tenable, we proceeded to apply it to the more complex targets **1** and **2** [8] without attempting to optimize the conditions for the

model reaction sequences shown above. A successful route to **1** (and thereby **2** [9]) is shown in Scheme 3. (All intermediates shown below were racemic, but a single enantiomer is shown for clarity.)



Scheme 3. Total synthesis of histrionicotoxin alkaloids using [2,3] sigmatropic rearrangement and RCM as key steps. (TBS = *tert.*-butyldimethylsilyl; NPS = *N*-(phenylseleno)phthalimide).

The synthesis began with ketone **9** which is easily available in two steps from 2,3-epoxycyclohexan-1-one according to a published procedure [10]. Peterson-type olefination [12] then proceeded in near-quantitative yield to provide **10** as a 2:1 *E:Z* mixture of isomers; these could be separated chromatographically, but only with difficulty, so the mixture was normally carried on to the next step. DIBAL reduction gave a 95% total yield of allylic alcohols, which could be separated easily by flash chromatography. There was isolated 61% (based on **9**) of the pure *E*-isomer of olefin **11**, the stereochemistry of which was assigned unequivocally on the basis of NOE effects involving the vinylic proton and the adjacent methine proton.

For the key transformation of **11** to **12**, involving [2,3] sigmatropic rearrangement, a one-pot process was devised which gave considerably higher overall yield than that involving isolation of the allylic selenide. Thus, treatment of the allylic alcohol with *N*-(phenylseleno)phthalimide (NPS) and tributylphosphine [13] to form the allylic selenide was followed directly by exposure to chloramine-T to induce the rearrangement [5,6]. This convenient procedure delivered **12** as a single diastereomer in 86% yield. (A more detailed discussion of the stereochemical - particularly conformational - features of **11** and **12** is presented below.)

The problems encountered in the model studies with the introduction of the requisite four-carbon terminal olefin unit reappeared at this stage, and the seemingly trivial conversion of **12** to the RCM precursor **13** required extensive experimentation. Eventually, it was found that generation of the *N*-anion of **12** in THF-HMPA (9:1) followed by addition at low temperature of a slight excess of the triflate derived from 3-buten-1-ol gave a clean (but usually incomplete) conversion into **13** (typically 57% isolated yield, 80% based on recovered starting material). Following chromatographic separation, recovered **12** was recycled, thus providing satisfactory quantities of **13**.

The crucial RCM step also proved very troublesome initially, and success was realized only by prolonged heating (toluene, 90°C, 2 days) of **13** with 20 mol% of complex **3**. (This reaction will be discussed in more detail later.) Fortunately, this gave a very acceptable 80% isolated yield of the desired azaspirocycle **14** which was subjected to catalytic hydrogenation of the double bond followed by acidic workup to remove the silyl protective group. This efficiently yielded compound **15** which has previously been described by Cvetovich [11] and converted in high yield into depentylperhydrohistrionicotoxin, **2**, a known key intermediate [9] for the total synthesis of perhydrohistrionicotoxin, **1**.

The two key steps of the synthesis deserve some further comment, and we will begin with a discussion of the [2,3] sigmatropic rearrangement. The stereoelectronics [1] of the rearrangement of the selenium species derived from **11** (or its *Z* isomer) suggest that the new carbon-nitrogen bond be formed preferentially on an equatorial face of the cyclohexane ring [11]. The rearrangement was found to be completely stereospecific, and it is therefore instructive to compare and contrast the conformational properties of the double bond isomers of **11**, both of which have been fully characterized, as have their allyl selenide counterparts (see Experimental). Analysis of coupling constants in the ^{1}H NMR spectra of *E*- and *Z*-**11** (and of the corresponding allyl selenides) reveals that both isomers show a strong preference for conformations in which the butyl group and the TBS-ether are *trans*-diaxial (Fig. 1). (For *E*-**11**, the CHOTBS signal has J = 5 and 2.5 Hz, while in the *Z*-isomer this multiplet has $W_{1/2}$ = 5 Hz). For the *Z* isomer this is hardly surprising, in view of the $A^{1,3}$ strain [14] which would be present in the diequatorial conformer. As shown in Fig. 1, the equatorial face in the *Z* isomer is ß which means that sigmatropic rearrangement of the allyl selenide derivative should give **12c** with the undesired relative configuration at the newly formed stereocentre. This has been observed in practice (see Experimental) and the stereochemistry of the rearrangement product has been confirmed by X-ray crystallography

[15]. In **12c** the vinyl, butyl and silyl ether groups are all equatorial, both in the crystal and in solution.

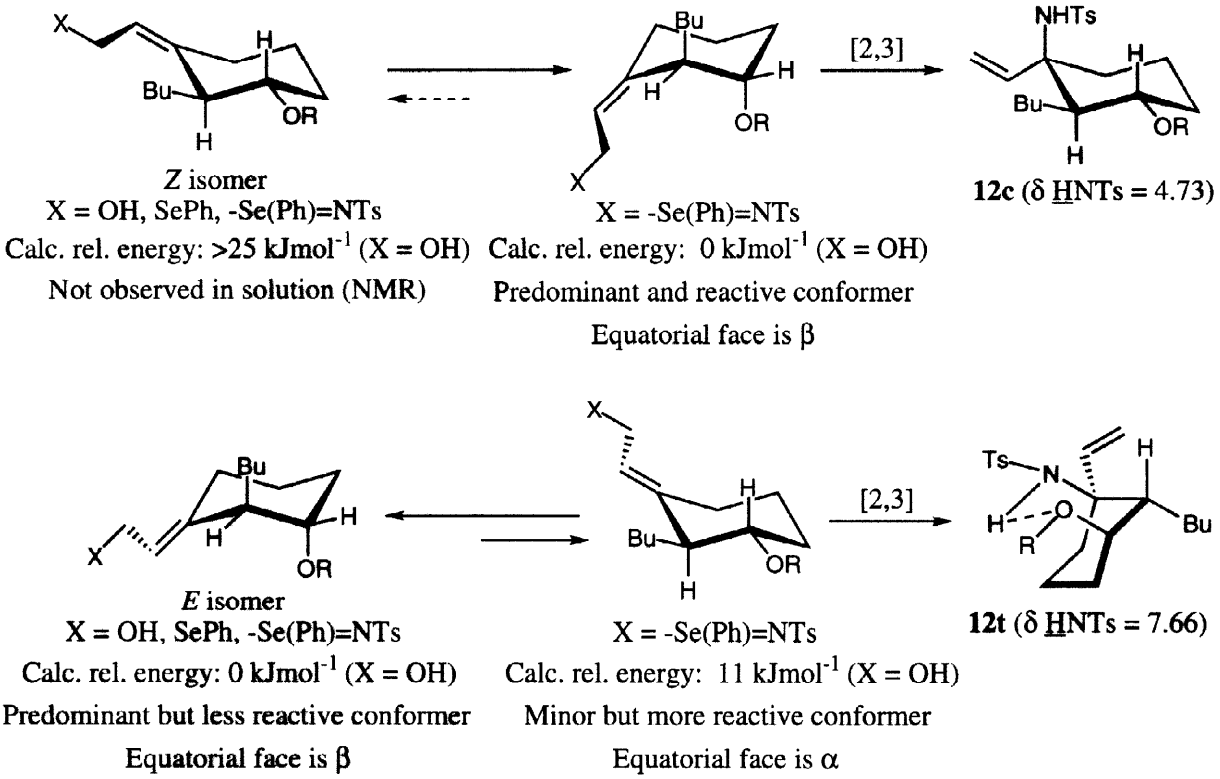


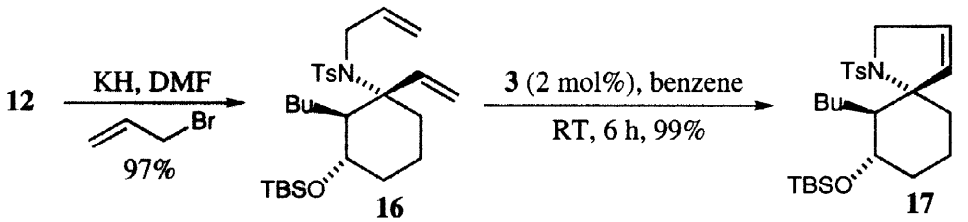
Fig. 1. Conformational preferences of *Z* and *E* isomers of **11** and **12** (R = TBS).

Turning to the *E* isomer, the preference for the *trans*-diaxial conformation was at first sight more surprising but we attribute this once again to the presence of $A^{1,3}$ strain, in this case between the vinylic hydrogen and the butyl group in the diequatorial conformer, exacerbated by a buttressing effect from the silyl ether. (The conformational consequences of this interaction were unexpected, since $A^{1,3}$ strain is normally associated with vinylic substituents larger than hydrogen [14].) As shown in Fig. 1, the equatorial face of the predominant conformer of the *E* isomer is also ß; reaction *via* this conformer should thus lead once again to the undesired stereoisomer, but this is not observed. We thus conclude that reaction occurs in the desired sense *via* the less-populated *trans*-diequatorial species: carbon-nitrogen bond formation on the equatorial α face of this conformer avoids severe steric interactions between the allyl selenimide moiety and the butyl side-chain. Fig. 1 also summarizes the results of molecular mechanics calculations [16] on the *Z* and *E* isomers of **11** which show a much smaller energy difference between the conformers of the *E* isomer.

The rearrangement product **12t** (Fig. 1) is not crystalline, but the ^{1}H NMR spectrum is consistent with the conformation shown in Fig. 1, with the *N*-tosyl, butyl and silyl ether groups all *axial* ($W_{1/2}$ for the multiplet from the CHOTBS proton is 6 Hz). We attribute this to a rather unusual case of hydrogen bonding between the sulfonamide hydrogen and the oxygen of the TBS ether: this places the vinyl and butyl groups "diequatorial" on the newly

formed six-membered hydrogen-bonded ring, and it is interesting to compare the chemical shifts shown above for the *N*-H protons of **12c** and **12t**, respectively.

As for the RCM reaction, our first experiments with tetrasubstituted cyclohexane systems were actually carried out with substrate **16**, smoothly derived from **12** in 97% yield by *N*-alkylation with allyl bromide (Scheme 4). The subsequent RCM reaction (30 mmolar concentration of substrate) required merely a few hours at room temperature in the presence of only 2 mol% of **3**, and gave spirocycle **17** in essentially quantitative isolated yield.



Scheme 4. RCM reaction yielding an azaspiro[4.5] ring system (TBS =*tert.*-butyldimethylsilyl).

Attempts to apply these conditions to **13** were totally fruitless, with quantitative recovery of starting material. The catalyst loading was increased to 10 and, finally, 20 mol% for a series of experiments in toluene solution at a variety of temperatures, and it was found that reaction at reflux did generate minor amounts of **14**. However, we also observed formation of two other products which, on the basis of their ^{1}H NMR and mass spectroscopic data, were concluded to be isomeric "dimers" of **13** formed by intermolecular reaction. Thus, to promote the desired intramolecular process, the ultimately successful reaction shown in Scheme 3 was run at 0.5 mmolar substrate concentration. We were both surprised and delighted that the catalyst survived these conditions long enough to deliver the desired azaspirocycle in such good yield. The marked difference in reactivity between **13** and **16** is probably due to entropic factors.

In conclusion, we have demonstrated that a strategic combination of [2,3] sigmatropic rearrangement and RCM provides rapid and stereocontrolled access to azaspirocycles. The power of the method is underlined by the fact that the synthesis of the spirocyclic alkaloid depentylperhydrohistrionicotoxin (**1**) outlined above proceeds from 2,3-epoxycyclohexan-1-one in ten laboratory operations and approximately 20% overall yield. Finally, we note that the present synthetic route can easily be made enantioselective, since both antipodes of the starting epoxide are available [17] in a state of high enantiomeric purity.

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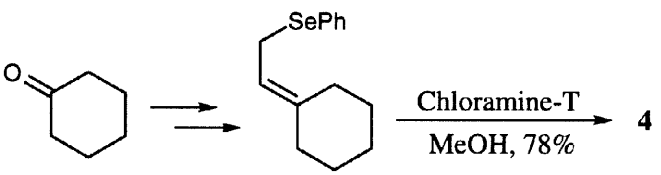
EXPERIMENTAL

General Remarks.

^1H (250 or 500 MHz) and ^{13}C (63 or 126 MHz) NMR spectra were recorded on either a Bruker AC-250 or Bruker AC-500 spectrometer ($CDCl_3$) and shifts are quoted in ppm with residual $CHCl_3$ as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument and only the strongest/structurally most important peaks are listed. Elemental analyses were performed at the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria. Melting points are uncorrected. Ether, tetrahydrofuran (THF) and 1, 2-dimethoxyethane (DME) were distilled under nitrogen from Na/benzophenone. Dichloromethane, benzene, toluene and diisopropylamine were dried over calcium hydride and distilled under nitrogen. Hexamethylphosphoramide (HMPA) was dried over calcium hydride, distilled under argon and stored over activated molecular sieves (3Å). Dimethylformamide (DMF) was dried over activated molecular sieves (3Å). Silica gel for flash chromatography was purchased from Grace-Amicon. Reactions requiring exclusion of air and moisture were performed under argon in glassware that had been flame-dried under vacuum. "Aqueous work up" refers to extraction of the aqueous phase 3 times with ether followed by washing the combined organic phases with brine, drying over $MgSO_4$ and subsequent concentration under reduced pressure. Anhydrous chloramine-T was prepared according to Sharpless [18]. Alkyllithiums were titrated against *N*-pivaloyl-*o*-toluidine [19]. Compound **4** was prepared according to the method of Hopkins [6] as summarised below.



Diene **5**.

A suspension of NaH (55%, 0.22 g) in mineral oil was washed three times with hexane. The last traces of hexane were removed *in vacuo* and the remaining solid was placed under an atmosphere of nitrogen. A solution of **4** (1.17 g, 4.2 mmol) in THF (20 mL) was added and a white solid precipitated. Dry DMF (10 mL) was added and the precipitate dissolved completely. Allyl bromide (1.76 mL, 20 mmol) was added and the mixture was stirred overnight before being brought to reflux for 2 h. The reaction mixture was evaporated to dryness and the residue was taken up in ether (50 mL). The ethereal phase was washed with water (3 x 10 mL) and the solvent was removed to yield the product as an oil (1.24 g, 93%) which was sufficiently pure to be used in the next step. ^1H NMR: ∂ 7.71 and 7.25 (4H, AA'BB', J = 8 Hz), 5.98 (1 H, ddt, J = 16, 11, 7), 5.67 (1 H, dd, J = 17, 11), 5.30 - 5.04 (4H, m), 3.98 (2 H, d, J = 7), 2.43 (3 H, s), 2.30 - 1.85 (4 H, m), 1.71 - 1.06 (6 H, m). ^{13}C NMR: 142.42, 141.16, 140.02, 137.55, 129.20, 127.07, 116.97, 116.44, 65.97, 48.29, 34.94, 25.24, 22.99, 21.37. For analysis, a small sample was purified by flash chromatography (5% EtOAc in hexane). Anal. Calcd. for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.88%. Found: C, 67.60; H, 7.84.

Diene **6**.

Compound **4** (0.92 g, 3.3 mmol) was dissolved in toluene (10 mL). Freshly powdered sodium hydroxide (1 g), potassium carbonate (1 g) and tetrabutylammonium hydrogen

sulfate (0.112g, 0.33 mmol) were added, followed by dropwise addition of a solution of 4-bromo-1-butene (1.0 mL, 9.9 mmol) in toluene (5 mL). The mixture was refluxed for 4 h, cooled, filtered, and the filter cake was washed with fresh toluene (10 mL). The combined organics were washed with water until the washings were neutral, and the organic phase was dried over sodium sulfate. After removal of the solvent, the residue was purified by flash chromatography (5% EtOAc in hexane) to yield the product as an oil (0.55 g, 50%). ^{1}H NMR: 7.71 and 7.27 (4 H, AA'BB', J = 8.5), 5.68 (1 H, m), 5.62 (1 H, dd, J = 18, 11), 5.26 (1 H, dd, J = 11, 1), 5.13 (1 H, dd J = 18, 1), 5.12 - 4.97 (2 H, m), 3.40 - 3.26 (2 H, m), 2.60 -1.07 (12H, m), 2.40 (3 H, s). ^{13}C NMR: 142.39, 141.20, 139.89, 135.20, 129.27, 127.01, 117.11, 116.42, 66.12, 45.52, 36.82, 34.69, 25.27, 23.02, 21.27. Anal. Calcd. for $C_{19}H_{27}NO_2S$: C, 68.43; H, 8.16. Found: C, 68.32; H, 7.98.

Azaspirocycle **7**.

Diene **5** (0.665 g, 2.1 mmol) was dissolved in degassed benzene (50 mL). A solution of **3** (0.086 g, 0.105 mmol) in benzene (5 mL) was added and the reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (10% EtOAc in hexane) to yield the product (0.495 g, 81%) as a crystalline solid (m.p. 80 - 81°C). ^{1}H NMR: 7.76 and 7.27 (4 H, AA'BB', J = 8.5), 6.12 (1 H, dt, J = 6.5, 2.5), 5.66 (1 H, dt, J = 6.5, 2.5), 4.12 (2 H, t, J = 2.5), 2.56 - 1.20 (10 H, m), 2.40 (3 H, s). ^{13}C NMR: 142.57, 138.56, 132.71, 129.25, 127.11, 122.18, 55.01, 37.15, 37.14, 25.10, 24.46, 21.36. IR: 3000, 2924, 2863, 1597, 1453, 1330, 1162. Anal. Calcd. for $C_{16}H_{21}NO_2S$: C, 65.97; H, 7.27; N, 4.81; S, 11.01. Found: C, 65.87; H, 7.28; N, 4.83; S, 10.82.

Azaspirocycle **8**.

Diene **6** (0.299 g, 0.89 mmol) was dissolved in degassed benzene (30 mL). A solution of **3** (0.044 g, 0.05 mmol) in benzene (5 mL) was added and the reaction mixture was stirred at room temperature overnight. TLC analysis indicated incomplete reaction, so the reaction mixture was refluxed for 2.5 h, cooled, and the solvent removed *in vacuo*. The residue was purified by flash chromatography (10% EtOAc in hexane) to yield the product (0.141 g, 52%) as a crystalline solid (m.p. 99 - 100°C). ^{1}H NMR: 7.70 and 7.24 (4 H, AA'BB', J = 8), 6.15 (1 H, dt, J = 10.5, 2), 5.77 (1 H, dt, J = 10.5, 4), 3.60 (2 H, m), 2.44 (2 H, m), 2.53 - 1.20 (10 H, m), 2.40 (3 H, s). ^{13}C NMR: 142.41, 140.94, 131.07, 129.27, 126.65, 123.34, 62.12, 41.22, 35.18, 25.88, 25.18, 22.96, 21.38. IR: 3033, 2930, 2865, 1596, 1458, 1315, 1152. Anal. Calcd. for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.59; S, 10.50. Found: C, 66.61; H, 7.79; N, 4.61; S, 10.12.

Enoates **10**.

A solution of LDA was prepared by dropwise addition of n-butyllithium (0.92 mL, 1.5 mmol, 1.6 M in hexane) over 15 minutes to diisopropylamine (0.195 mL, 1.5 mmol) in THF (3 mL) at -78°C under argon. The mixture was stirred for 15 minutes at -78°C followed by dropwise addition of ethyl (trimethylsilyl)acetate (0.28 mL, 1.5 mmol) over 10 minutes. After an additional 15 minutes, a solution of **9** [10] (0.201 g, 0,706 mmol) in THF (3 mL) was added dropwise over 30 minutes and the reaction mixture was allowed to reach room temperature over night. Aqueous work up and flash chromatographic purification (EtOAc:hexane/5:95) afforded a mixture of the *E* and *Z* isomers of **10** as a colourless oil

(0.242 g, 97%). The *E:Z* ratio was 2:1, as determined by integration of the vinylic resonances in the ^{1}H NMR spectrum. ^{1}H NMR: 5.72 (d, J = 1.5, vinylic *Z*), 5.56 (s, vinylic *E*), 4.21 - 4.00 (m), 3.93 - 3.82 (m), 3.79 - 3.71 (m), 3.40 - 3.28 (m), 2.40 - 1.09 (m), 0.92 - 0.80 (m). 0.02 (2xs, $SiMe_2$, *E*), 0.01 (2xs, $SiMe_2$, *Z*). Anal. Calcd. for $C_{20}H_{38}O_3Si$: C, 67.74; H, 10.80. Found: C, 67.61; H, 10.90. This material was not further characterised.

E-Allylic alcohol **11**.

DIBAL (6.7 mL, 6.7 mmol, 1.0 M in hexanes) was added dropwise to a solution of **10** (1.09 g, 3.07 mmol) in toluene (13 mL) at -40°C under argon. The reaction mixture was stirred for 2 hours and quenched by addition of 1 mL of methanol. Diethyl ether (100 mL) was added to precipitate the aluminate salts. The mixture was filtered through a pad of celite and the filter cake was washed thoroughly with hot EtOAc. The combined organics were evaporated to dryness and after flash chromatographic purification of the residue (EtOAc:hexane/1:9) the two allylic alcohols **11** (*E*: 0.604 g and *Z*: 0.309 g, total yield 95%), were obtained separately as colourless oils. Data for *E*-**11**: ^{1}H NMR: 5.35 (1 H, t, J = 7), 4.15 (2 H, m), 3.65 (1 H, dt, J = 2.5, 5), 2.25 - 2.19 (1 H, m), 2.05 - 1.95 (2 H, m), 1.79 - 1.67 (2 H, m), 1.53 - 1.10 (8 H, m), 0.86 (12 H, m + s) 0.02 (6 H, 2xs). ^{13}C NMR: 143.20, 122.85, 73.43, 58.67, 53.03, 30.98, 29.78, 29.46, 25.79, 25.55, 22.81, 22.43, 18.05, 13.98, -4.65, -4.71. IR: 3332, 2933, 1666, 1471, 1254 cm^{-1}. Anal. Calcd. for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61%. Found: C, 69.19; H, 11.46.

Data for *Z*-**11**: ^{1}H NMR: 5.68 (1 H, dt J = 1.5, 7.5), 4.16 (1 H, ddd J = 1, 7.5, 11.5), 3.91 (1 H, ddd J =1, 7.5, 11.5), 3.89 (1 H, m), 2.61 (1 H, m), 2.21 - 2.13 (1 H, m), 2.00 - 1.95 (1 H, m), 1.79 - 1.65 (2 H, m), 1.57 - 1.51 (2 H, m), 1.47 - 1.11 (6 H, m) 0.85 (12 H, m + s), 0.05 (6 H, 2xs). ^{13}C NMR: 144.15, 124.39, 72.75, 57.76, 44.80, 32.04, 30.48, 29.76, 28.78, 25.83, 22.81, 22.34, 18.08, 13.93, -4.62, -4.76. IR: 3354, 2930, 1666, 1462, 1253. Anal. Calcd. for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61. Found: C, 69.04; H, 11.40.

Allylic sulfonamide **12**.

To a pre-cooled solution of *E*-**11** (1.03 g, 3.30 mmol) in CH_2Cl_2 (4 mL) under argon at -20°C was added freshly distilled tributylphosphine (1.28 mL, 5.14 mmol) followed by *N*-phenylselenophthalimide (1.45 g, 4.80 mmol). After 20 minutes of stirring, TLC indicated full conversion and methanol (30 mL) was added followed by anhydrous chloramine-T (2.55 g, 11.2 mmol). The reaction mixture was allowed to reach room temperature and was stirred for one hour, before being partitioned between ether and water, followed by extraction of the aqueous phase with ether. The combined organic phases were washed with brine, dried with $MgSO_4$ and evaporated to dryness. Flash chromatographic purification of the residue (EtOAc:hexane/1:9) yielded the rearranged product **12** (1.32 g, 86%) as a viscous colourless oil. ^{1}H NMR: 7.67 and 7.20 (4 H, AA´BB´ J = 8), 7.66 (1 H, s, NH), 5.39 (1 H, dd J = 11, 18), 5.07 (1 H, d J = 11), 5.04 (1 H, d J = 18), 4.00 (1 H, m), 2.40 (3 H, s), 2.21 - 2.15 (1 H, m), 2.04 - 1.94 (1 H, m), 1.62 - 1.51 (2 H, m), 1.49 - 1.32 (2 H, m), 1.30 - 1.05 (7 H, m), 0.98 (9 H, s), 0.82 (3 H, t, J = 7), 0.13 (6 H, 2xs). ^{13}C NMR: 141.99, 141.31, 140.99, 128.95, 127.29, 115.75, 71.91, 62.70, 48.46, 31.36, 27.99, 27.75, 27.41, 25.75, 22.68, 21.45, 17.97, 15.52, 13.89, -4.24, -4.63. IR: 3264, 2950, 2858, 1717, 1600. Anal. Calcd. For $C_{25}H_{43}NO_3SSi$: C, 64.47; H, 9.31; N, 3.01. Found: C, 64.35; H, 9.20; N, 3.12.

The *E*-allylic selenide intermediate could be isolated and fully characterized: ^{1}H NMR: 7.60 - 7.50 (2 H, m), 7.33 - 7.22 (3 H, m) 5.36 (1 H, t, J = 8.5), 3.76 - 3.56 (3 H, m), 2.19 - 2.08 (1 H, m), 2.02 - 1.85 (2 H, m), 1.82 - 1.63 (2 H, m), 1.56 - 1.04 (8 H, m), 0.94 (12H, s + m), 0.01 (6H, 2xs). ^{13}C NMR: 142.65, 133.19, 130.98, 128.79, 126.74, 119.07, 73.50, 53.04, 31.18, 29.70, 29.46, 25.85, 25.37, 25.28, 22.84, 22.27, 18.10, 14.02, -4.61, -4.74. IR: 3057, 2929, 1655, 1579, 1472, 1253. Anal. Calcd. for $C_{24}H_{40}OSeSi$: C, 63.83; H, 8.93. Found: C, 63.78; H, 8.67.

The diastereomer of **12** (from *Z*-**11**) was prepared in the same way as described above. The product was obtained in 89% yield as colourless crystals, m.p. 145 - 146.5 °C (from EtOAc). ^{1}H NMR: 7.74 and 7.26 (4 H, AA´BB´ J = 8.5), 5.75 (1 H, dd, J = 11, 17.5), 5.08 (1 H, d, J = 17.5), 4.97 (1 H, d, J = 11 Hz) 4.73 (1 H, s, NH), 3.49 (1 H, dt, J = 4.5, 10), 2.42 (3 H, s), 2.25 - 2.17 (1 H, m), 1.86 - 1.74 (1 H, m), 1.53 - 1.03 (11 H, m), 0.84 (9 H, s), 0.80 (3 H, t, J = 7 Hz), 0.00 (6 H, 2xs). ^{13}C NMR: d 142.98, 141.62, 140.14, 129.30, 127.19, 144.28, 73.07, 64.80, 54.71, 35.73, 33.93, 32.90, 27.81, 25.76, 23.09, 21.50, 19.15, 17.88, 13.92, -4.10, -4.74. IR: 3300, 2955, 2857, 1328, 1158, 1094. Anal. Calcd. For $C_{25}H_{43}NO_3SSi$: C, 64.47; H, 9.31; N, 3.01. Found: C, 64.34; H, 9.06; N, 3.04.

Data for the *Z*-allylic selenide intermediate: ^{1}H NMR: 7.54 - 7.46 (2 H, m), 7.3 - 7.17 (3 H, m), 5.50 (1 H, t J = 8), 3.86 (1 H, m), 3.70 (1 H, ddd J = 1, 9, 11.5), 3.51 (1 H, ddd, J = 1, 7, 11.5), 2.61 - 2.51 (1 H, m), 2.23 - 2.07 (1 H, m), 2.01 - 1.90 (1 H, m), 1.85 - 1.59 (2 H, m), 1.59 - 1.10 (8 H, m), 0.81 - 0.94 (12 H, m + s), -0.04 (6 H, 2xs). ^{13}C NMR: 142.96, 132.42, 131.61, 128.90, 126.52, 120.17, 71.89, 44.60, 32.50, 30.95, 30.11, 29.05, 25.87, 25.18, 23.02, 21.98, 18.10, 14.01, -4.65, -4.73. IR: 3057, 2932, 1656, 1580, 1472, 1437, 1253. Anal. Calcd. for $C_{24}H_{40}OSeSi$: C, 63.83; H, 8.93. Found C, 64.08; H, 8.89.

Diene **13**.

n-Butyllithium (0.078 mL, 0.117 mmol, 1.5 M in hexane) was added dropwise to a solution of **12** (0.0520 g, 0.112 mmol) in THF:HMPA (5 mL, 9:1) under argon at -78°C and the reaction mixture was stirred for 20 minutes. A solution of freshly distilled 4-butenyl trifluoromethanesulfonate [20] (0.0300 g, 0.147 mmol) in THF (1 mL) was added dropwise to the reaction mixture and after one hour the reaction was quenched at low temperature by addition of water. After aqueous work-up and chromatographic purification (EtOAc:hexane/5:95) the product **13** (0.0331 g, 80%, based on 29% recovered **12**) was obtained as a colourless oil. ^{1}H NMR: 7.68 and 7.23 (4 H, AA´BB´ J = 8), 5.73 - 5.52 (2 H, m), 5.32 (1 H, d, J = 11), 5.14 (1 H, d, J = 18), 5.02 (1 H, m), 4.96 (1 H, m), 3.31 (3 H, m), 2.50 (3 H, s), 2.40 - 1.08 (15 H, m), 0.95 - 0.81 (12 H, m +s), 0.01 (6 H, s). ^{13}C NMR: 142.80, 141.02, 135.15, 134.57, 129.33, 127.97, 121.21, 116.87, 75.40, 70.93, 52.12, 45.61, 36.80, 35.92, 33.75, 32.20, 29.30, 26.16, 24.08, 21.73, 21.03, 18.25, 14.39, -4.02, -4.26. IR: 3000, 2956, 1640, §599, 1327, 1156, 1088. Anal. Calcd. for $C_{29}H_{49}NO_3SSi$: C, 67.00; H, 9.50; N, 2.69. Found C, 67.24; H, 9.48; N, 2.55.

Azaspirocycle **14**.

A mixture of **13** (0.0168 g, 0,0323 mmol) and **3** (0,0053 g, 0.0064 mmol) in degassed toluene (65 mL) was heated to 90°C under argon for 2 days. Concentration of the reaction mixture followed by flash chromatographic purification (EtOAc:hexane/5:95) afforded the

product as a colourless oil (0.0127 g, 80%). ^{1}H NMR: 7.77 and 7.27 (4 H, AA'BB' J = 8.5), 5.85 (1 H, ddd, J = 3.5, 5, 10.5), 5.76 (1 H, dt J = 10.5, 1.5 Hz), 3.60 (1 H, dt, J = 4, 10.5), 3.29 (1 H, dt, J = 5, 12.5), 3.15 (1 H, ddd, J = 3.5, 9, 12.5), 2.84 (1 H, m), 2.51 (1 H, dt , J = 4, 12.5 Hz), 2.41 (3 H, s), 2.10 - 2.01 (1 H, m), 1.93 - 1.85 (2 H, m), 1.80 - 1.14 (10 H, m), 0.89 (12 H, m + s), 0.06 (6 H, 2xs). ^{13}C NMR: 142.90, 139.05, 129.74, 129.34, 127.36, 125.08, 75.15, 68.19, 50.58, 42.91, 35.90, 32.47, 30.01, 25.90, 25.75, 24.92, 23.97, 21.45, 20.37, 18.00, 14.16, -3.95, -4.56. IR: 2950, 1456, 1310, 1160. Anal. Calcd. for $C_{27}H_{45}NO_3SSi$: C, 65.94; H, 9.22; N, 2.85. Found C, 65.90; H, 9.23; N, 2.79.

Azaspirocycle **15**.

PtO_2 (0.010 g) was added to a solution of **14** (0.0122 g, 0,0248 mmol) in hexane (5 mL) and the mixture was stirred under 1 atm. of H_2 at room temperature for two days. The reaction mixture was filtered through celite and to the filtrate was added a 1 M solution of tetrabutylammonium fluoride in THF (0.20 mL, 0.2 mmol) followed by one drop of conc. HCl. The reaction mixture was heated at reflux for 2 days, cooled and neutralised by addition of $NaHCO_3$. The mixture was filtered, the filtrate was evaporated to dryness, and the crude product was purified by flash chromatography (EtOAc:hexane/1:1) to yield the desired compound as a colourless oil (0.0084 g, 89%) with spectral and physical data in accord with those reported by Cvetovich [11]. ^{1}H NMR: 7.74 and 7.25 (4 H, AA'BB' J = 8), 3.53 (1 H, m), 3.27 (1 H, dt, J = 5, 12), 3.23 (1 H, m), 2.71 (1 H, m), 2.50 (1 H, m), 2.40 (3 H, s), 2.11 - 2.03 (1 H, m), 1.92 - 1.86 (2 H, m), 1.82 - 1.10 (15 H, m), 0.89 (3 H, distorted t, J = 7). IR: 3440, 1590, 1320, 1160, 1090. Anal. Calcd. for $C_{21}H_{33}NO_3S$: C, 66.45; H, 8.76; N, 3.69. Found C, 66.39; H, 8.80; N, 3.64.

(±)-Depentylperhydrohistrionicotoxin, **1**.

Conversion of **15** to **1** was carried out as described by Cvetovich [11]. Freshly recrystallised naphthalene (0.205 g, 1.6 mmol) was dissolved with stirring under argon in dry DME (5 mL). Sodium metal (0.038 g, 1.6 mmol) was added and the resultant mixture was stirred for 1 h at RT to give a dark blue-green solution. A solution of **15** (0.020 g, 0.052 mmol) in DME (0.5 mL) was added and the mixture was stirred for 2 h before addition of water (5 drops) to quench the reaction. The mixture was partitioned between 5% aqueous HCl solution (5 mL) and hexane (5 mL). The aqueous layer was washed with ether (5 mL) and hexane (5 mL) and finally treated carefully with 6M NaOH solution (5 mL). The resultant aqueous phase was extracted with ether (3 x 5 mL) and the combined organic phases were dried over sodium sulfate. Evaporation of the solvents gave a residue which was purified by filtration through a short plug of silica gel, eluting with ether - triethylamine (20 : 1). There was obtained 0.010 g (85%) of **1** as a colourless oil. ^{1}H NMR: 3.85 (1 H, m, $W_{1/2}$ = 4 Hz), 2.92 (1 H, m), 2.25 (1 H, m), 2.21 (1 H, m), 2.00 - 1.85 (6 H, m), 1.80 - 1.60 (8 H, m), 1.45 - 1.00 (6 H, m), 0.89 (3 H, distorted t, J = 7). ^{13}C NMR: 69.91, 54.70, 41.91, 40.25, 37.16, 33.30, 30.51, 28.09, 27.21, 27.17, 23.00, 19.51, 15.19, 14.00. IR: 3650, 3200, 2940, 1450, 1130, 1080, 965. Anal. Calcd. for $C_{14}H_{27}NO$: C, 74.61; H, 12.07; N, 6.22. Found C, 74.59.39; H, 12.24; N, 6.18.

The spectral and physical data were also in accord with those of an authentic sample of **1** kindly provided (as the hydrochloric acid salt) by Dr. A. Brossi of the NIH.

Diene **16.**

A solution of **12** (0.0515 g, 0.111 mmol) and allylbromide (0.10 mL, 1.2 mmol) in DMF was added to hexane-rinsed KH (0.025 g, 0.22 mmol, 35 % dispersion in mineral oil) under argon. The reaction was stirred at room temperature for 2 hours and quenched by addition of water. Aqueous work-up and flash chromatographic purification (EtOAc:hexane/5:95) yielded the product as a colourless oil (0.0542 g, 97 %). ^{1}H NMR: 7.66 and 7.21 (4 H, AA´BB´ J = 8), 5.89 (1 H, m), 5.55 (1 H, dd, J = 11, 18), 5.20 (1 H, dd, J = 1, 11), 5.16 - 5.02 (3 H, m), 4.02 (2 H, m), 3.30 (1 H, dt, J = 4, 10.5), 2.40 (3 H, s), 2.27 - 2-15 (1 H, m), 2.15 - 1.96 (2 H, m), 1.90 - 1.04 (10 H), 0.91 (3 H, t, J = 7), 0.87 (9 H, s), 0.00 (6 H, s). ^{13}C NMR: 142.38, 140.83, 137.31, 134.54, 128.96, 127.60, 120.77, 116.77, 74.97, 70.77, 51.73, 48.62, 36.50, 33.38, 32.39, 28.69, 25.85, 23.72, 21.39, 20.75, 17.93, 14.01, -4.31, -4.58. IR: 2953, 1461, 1157. Anal. Calcd. for $C_{28}H_{47}NO_3SSi$: C, 66.49; H, 9.37; N, 2.77. Found C, 66.52; H, 9.33; N, 2.69.

Azaspirocycle **17.**

A mixture of **16** (0.0542 g, 0.107 mmol) and **3** (0.0018 g, 0.0022 mmol) in degassed benzene (3.6 mL) was stirred under argon for 6 hours. Concentration and purification by flash chromatography (EtOAc:hexane/1:9) yielded the product (0.0508 g, 99 %) as colourless crystals, m.p. 108-110 °C. ^{1}H NMR: 7.75 and 7.26 (4 H, AA´BB´ J = 8), 5.73 (2 H, s), 4.16 - 3.98 (2 H, m), 3.35 (1 H, dt, J = 4.5, 10.5), 2.52 - 2.28 (5 H, m), 1.95 - 1.83 (1 H, m), 1.76 - 1.05 (10 H, m), 0.91 - 0.83 (12 H, s + m), 0.04 (6 H, 2xs). ^{13}C NMR: 142.68, 138.37, 130.76, 129.31, 127.27, 123.77, 80.00, 75.49, 55.82, 52.90, 36.73, 35.93, 32.62, 29.27, 25.84, 23.73, 21.42, 20.91, 17.84, 14.08, -3.98, -4.66. IR: 2953, 1342, 1160. Anal. Calcd. for $C_{26}H_{43}NO_3SSi$: C, 65.36; H, 9.07; N, 2.93. Found C, 65.36; H, 9.06; N, 2.92.

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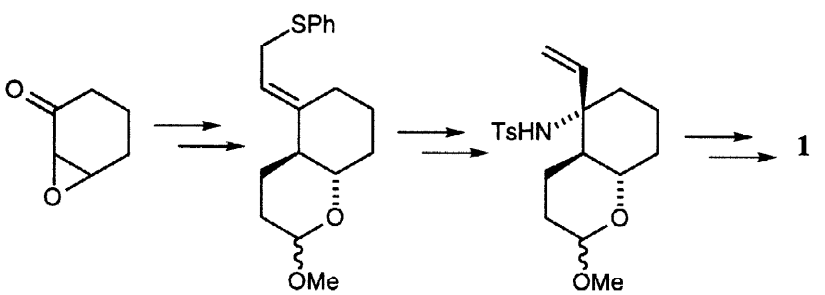

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