Chemistry of Natural Compounds and Bioorganic Chemistry

Stereocontrolled synthesis of the alkaloid (−)-actinidine

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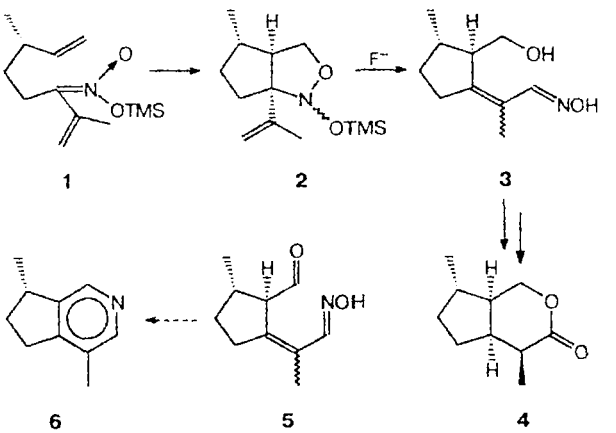
The alkaloid (−)-actinidine of the iridane series was synthesized using intramolecular [3+2] dipolar cycloaddition of silyl nitronates, generated from (3*R*/*S*,6*S*)-2,6-dimethyl-3-nitro-8-phenylthiooct-1,7*E*- and -1,7*Z*-dienes. The key nitro compounds were obtained from (−)-(*S*)-citronellol.

Key words: iridoid, alkaloid, (−)-actinidine, silyl nitronate, intramolecular [3+2] dipolar cycloaddition, (−)-citronellol, (−)-citronellal, vinyl sulfide, *N*-alkyl-*N*-phenylthiohydroxylamine.

Previously we reported[1] on a stereocontrolled synthesis of a natural iridolactone, (+)-iridomyrmecine (**4**). The synthesis was based on intramolecular [3+2]-cycloaddition reaction of silyl nitronate **1**, a (+)-β-citronellene derivative, giving substituted cyclopentanoisoxazolidine **2** and on the stereospecific transformation of the latter into lactone **4** *via* oxime **3** by the route that we developed (Scheme 1).

Scheme 1



It appeared to be an attractive opportunity to use this approach for the synthesis of alkaloid (−)-actinidine (**6**);[2] however, we did not succeed in finding conditions for the selective oxidation of hydroxy oxime **3** to aldehyde **5**, whose cyclization, as expected (*cf.* Ref. 3), would give the *N*-oxide corresponding to pyridine **6**. As an alternative to the scheme discussed, in the present study, we consider a route that includes the formation of a precursor of aldehyde **5** at the step of cleavage of phenylthio derivatives **9** related to isoxazolidine **2** (Scheme 2). We found that thioethers **9** are smoothly formed upon cyclization of silyl nitronates **8a** and **8b** generated *in situ* from the nitro derivatives **7a** and **7b** on treatment with *N*,*O*-bis(trimethylsilyl)acetamide (BSA).

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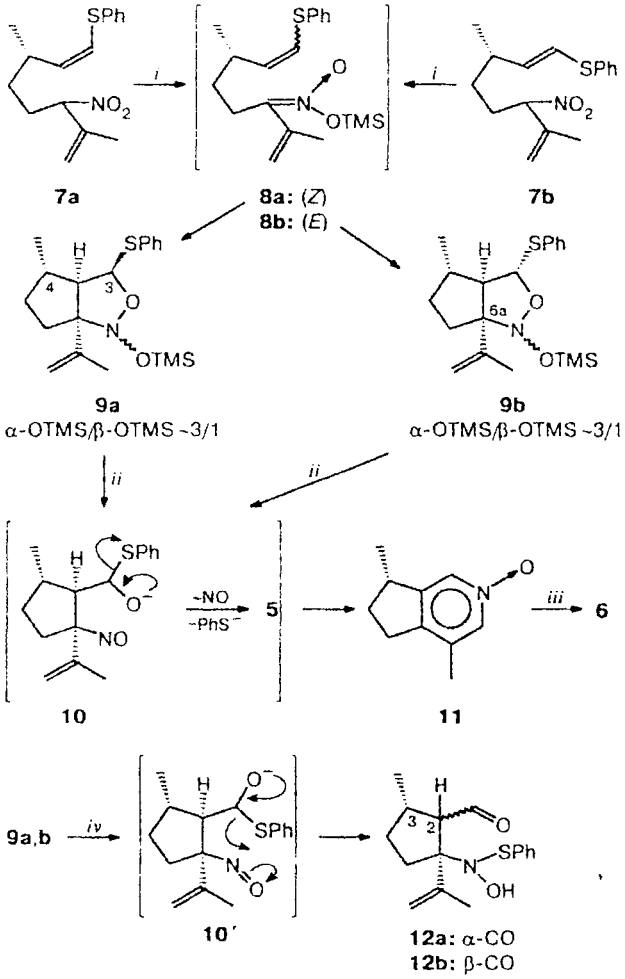
Scheme 2



Reagents and conditions: *i.* BSA/NEt_3/MeCN/PhH, 85 °C; *ii.* $KF \cdot 2H_2O$/MeOH/THF, −40 → 20 °C; *iii.* $LiAlH_4/TiCl_4$/THF, 20 °C; *iv.* $KF \cdot 2H_2O$/THF, −40 → 20 °C.

The fairly labile bicyclic products **9a** and **9b** are mixtures of nitrogen invertomers (α-OTMS/β-OTMS ~3 : 1, ^1H NMR data; *cf.* lit.[1,4,5]). In particular, the presence of minor components in the mixtures is indicated by the presence of additional characteristic proton signals, not overlapping with the main signals: δ 5.76 (**9a**) and δ 5.42 (**9b**) for HC(3) and δ 0.32 (**9a**) and δ 0.27 (**9b**) for the β-OTMS group. The orientation of the SPh group in compounds **9** was established by virtue of NOESY spectra, which revealed the spatial proximity of the SPh and H—C(4) groups in **9a** and the SPh and Me—C(4) groups in **9b**. Treatment of cyclopentanoisoxazolidines **9a** or **9b** (without additional purification) with $KF \cdot 2H_2O$ in a MeOH—THF mixture gives in both cases the known *N*-oxide **11**[6] as the major product; the product was isolated by chromatography in 45% yield. Obviously, *N*-oxide **11** is formed *via* highly reactive aldehyde **5**, which arises upon cleavage of the semithioacetal group in the probable intermediate **10** and allylic isomerization of the tertiary nitroso compound to a primary one and then to oxime, which we described previously for related structures.[1,4,5]

At the final step of the synthesis of (−)-actinidine (**6**), *N*-oxide **11** is smoothly reduced by the $TiCl_4/LiAlH_4$ system[7] to give the target product. The overall yield of **6** over the three steps amounts to ~27% and almost does not depend on the configuration of the double bond in the initial vinyl sulfide **7**.

A more detailed investigation of the transformation of isoxazolidines **9** on treatment with $KF \cdot 2H_2O$ resulted in isolation from the reaction mixture of isomeric hydroxylamine derivatives **12** with an unusual type of substitution (yield ~25%). It was found that the yield of these products can be increased to ~60% by conducting this reaction in THF at −40 °C.

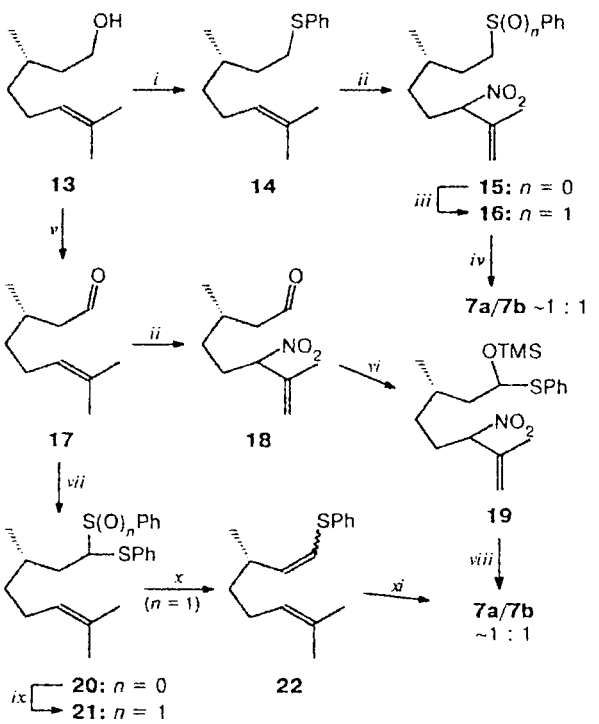
Compounds **12** are apparently the first representatives of the previously unknown *N*-arylthio-*N*-alkylhydroxylamines. The structure of these compounds was established based on the data of elemental analysis and NMR, IR, and mass spectra. To the predominant component of the mixture (**12b**), the structure with β-orientation of the formyl group was ascribed; this follows from examination of the NOESY spectra, which indicate that the HC(2) proton is located close to the protons of the MeC(3) methyl group and the formyl group proton is located close to HC(3).

A possible pathway to *N*-phenylthiohydroxylamines **12** might include intermolecular addition of the thiolateione released upon the formation of the aldehyde group to the N=O group in intermediate **10**. To verify this suggestion, we carried out model experiments using isoxazolidines **2**, prepared previously[1] from citronellene. It was found that cleavage of these compounds in THF on treatment with $KF \cdot 2H_2O$ in the presence of PhSH or PhS^- does not give *N*-phenylthiohydroxylamines **12** but gives instead isomeric oximes **3**, resulting from "normal" transformation of type **2** isoxazolidines, in high yields (*cf.* Ref. 1). In view of the foregoing, it can be suggested that the formation of *N*-phenylthiohydroxylamines **12** in the reaction carried out in THF is due to an intramolecular bond reorganization in intermediate **10'**. This is additionally confirmed by the fact that the introduction of excess PhSH or PhS^- in the reaction medium does not change the ratio of the reaction products **11** and **12**.

Vinyl sulfides **7a,b**, the starting compounds in this synthetic route to (−)-actinidine (**6**), were prepared from (−)-citronellol (**13**), available as a commercial preparation (Fluka, enantiomeric excess *ee* of no less than 95%). In order to optimize the synthesis, three variants of the preparation of compounds **7** were investigation. The basic difference between these variants lies in the method of formation of the vinyl sulfide fragment (Scheme 3). The first route is based on the transformation of sulfoxide **16** according to the Pummerer type

reaction (*cf.* Ref. 8), whereas in the second route, which is the most efficient (the yield is >50% based on the initial **13**), cleavage of semithioacetal **19** on treatment with trimethylsilyl iodide (TMSI) in the presence of Et_3N was used (*cf.* Ref. 9). Yet another method that we found for the synthesis of sulfides **7** (yield ~30%) is based on the use of the sulfenate cleavage of monosulfoxide **21** (*cf.* Ref. 10), the product of partial oxidation of (−)-citronellal thioacetal **20**. All the reactions considered afford mixtures of *Z*/*E*-isomers of **7**, present in approximately equal proportions. The individual components of these mixtures can be isolated by HPLC; however, this is not necessary for the preparation of the target compound **6**. As mentioned above, the geometry of the double bond in vinyl sulfides **7** has virtually no influence on the general efficiency of their transformation into *N*-oxide **11**.

Scheme 3



Reagents and conditions: *i.* Ph_2S_2/Bu_3P, 20 °C; *ii.* $NaNO_2$/AcOH, 15 → 20 °C; *iii.* H_2O_2/AcOH/SeO_2, *iv.* TMSOTf/Pr^i_2NEt/CH_2Cl_2, 20 °C; *v.* PCC/CH_2Cl_2 20 °C; *vi.* PhSH/TMSCl/Py, 25 °C; *vii.* Ph_2S_2/Bu_3P, 20 °C; *viii.* TMSI/Et_3N/CH_2Cl_2, −70 → 20 °C; *ix.* MCPBA/Et_2O, −50 °C; *x.* PhMe, 110 °C; *xi.* $NaNO_2$/AcOH/Et_2O, 5 °C.

The structures of the previously unknown compounds **7**, **12**, **15**, **16**, and **18**—**22** were confirmed by the data of physicochemical and elemental analysis. The ^1H NMR spectrum of the (−)-actinidine **6** sample prepared in this way virtually coincides with the spectrum reported[11] for the racemate. The measured optical rotation $[\alpha]_D$ = −10.1° (*c* 0.37, $CHCl_3$) corresponds to ~93% optical purity of the compound synthesized (Ref. 12: for enantiomerically pure non-natural (+)-actinidine $[\alpha]_D^{17}$ = +10.8° (*c* = 0.36, $CHCl_3$)).

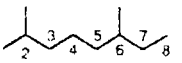
Experimental

IR spectra (ν/cm^{-1}) were recorded on a Specord M-80 instrument, ^1H NMR (δ, *J*/Hz) and ^{13}C NMR (δ) spectra of solutions in $CDCl_3$ were run on a Bruker AC-200 spectrometer (200.13 MHz and 50.32 MHz, respectively). The ^1H and ^{13}C chemical shifts were referred to the residual solvent signal (7.27, ^1H and 77.0, ^{13}C). Mass spectra (EI) were recorded on a Varian MAT 311A instrument at 70 eV. The R_f values are given for a SiO_2 layer (Silufol). The $[\alpha]_D$ values are measured on a Jasco DIP-360 polarimeter. HPLC was performed on a Silasorb 600 column (10 mm, 250×24 mm), using a heptane—AcOEt mixture (95 : 5 v/v, 7 mL min^{-1}) as the eluent and a refractometric detector.

(6*S*)-2,6-Dimethyl-8-phenylthiooct-2-ene (14). A solution of (−)-citronellol (5 g, 32 mmol), Ph_2S_2 (6.79 g, 35 mmol), and Bu_3P (7.07 g, 35 mmol) in 50 mL of MeCN was refluxed (Ar) for 6 h and concentrated *in vacuo*, and the residue was dissolved in 50 mL of hexane. The solution was washed with water (20 mL), 30% NaOH (30 mL), and brine (20 mL), dried with $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on SiO_2 (100 g). Gradient elution (hexane → hexane—AcOEt, 98 : 2) gave 5.9 g (74%) of sulfide **14** [13] as a colorless oil, R_f 0.35 (hexane). ^1H NMR, δ: 0.97 (d, 3 H, MeC(6), *J* = 5.5 Hz); 1.10—2.10 (m, 5 H, CH_2, CH); 1.61 (br. s, 3 H, *E*-MeC(2)); 1.73 (br.s, 3 H, *Z*-MeC(2)); 2.93 (m, 2 H, $H_2C(8)$); 5.10 (m, 1 H, HC(3)); 7.10—7.40 (m, 5 H, C_6H_5).

(3*R*/*S*,6*S*)-2,6-Dimethyl-3-nitro-8-phenylthiooct-1-ene (15). Sodium nitrite (20.7 g, 0.3 mol) was added in portions over a period of 2 h to a solution of sulfide **14** (5.75 g, 23.2 mmol) in 70 mL of AcOH, stirred at 15 °C. The reaction mixture was kept for 2 h at 20 °C, diluted with 140 mL of water, and extracted with petroleum ether (3×50 mL). The extract was washed with water (3×20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (~6.5 g) was chromatographed on 100 g of SiO_2. Gradient elution (hexane → hexane—AcOEt, 9 : 1) gave 1.1 g of the starting compound **14** and 4.35 g (79%) of nitro derivative **15** as a colorless oil, R_f 0.52 (hexane—ether, 9 : 1). IR (film): 714, 757, 800, 929, 1015, 1100, 1350, 1440, 1530, 2860—3070. ^1H NMR, δ: 0.98 (d, 3 H, MeC(6), *J* = 6 Hz); 1.85 (br.s, 3 H, MeC(2)); 1.00—2.00 (m, 6 H, CH_2); 2.15 (m, 1 H, HC(6)); 2.90 (m, 2 H, HC(8)); 4.82 (m, 1 H, HCN); 5.10—5.20 (m, 2 H, HC(1)); 7.15 and 7.30 (both m, 5 H, C_6H_5). The ^{13}C NMR spectrum is presented in Table 1. MS, *m*/*z*: 293 $[M]^+$, 247 $[M-46]^+$. Found (%): C, 65.76; H, 8.07; N, 4.67; S, 10.73. $C_{16}H_{23}NO_2S$. Calculated (%): C, 65.49; H, 7.90; N, 4.77; S, 10.92.

(3*R*/*S*,6*S*)-2,6-Dimethyl-3-nitro-8-phenylsulfinyloct-1-ene (16). A mixture of sulfide **15** (2.93 g, 10 mmol), H_2O_2 (a 35% solution) (2.82 g, 60 mmol), and SeO_2 (5 mg) was vigorously stirred at 20 °C for 6 h and treated with H_2O and $CHCl_3$. The aqueous layer was separated and extracted with $CHCl_3$. The conventional workup (which included washing of the extracts with water, drying with $MgSO_4$, and concentration *in vacuo*) of the combined organic solution gave 3.1 g of a product, which was chromatographed on SiO_2 (100 g). Elution with

Table 1. ^{13}C NMR spectra (δ) of compounds **7**, **15**, **16**, **18**—**22**: 

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	MeC(2)	MeC(6)	C_{arom}	MeSi
7a	118.5	138.5	92.7	28.8	32.7	37.2	126.3	121.4	20.3	18.1	128.8; 128.9; 135.9; 140.2	
7b	118.6	138.7	92.6	29.0	33.2	33.4	126.3	123.1	20.4	18.2	128.7; 128.8; 136.0; 137.5	
15	113.7	138.6	92.5	28.8	32.4	37.4	32.6	42.6	20.2	19.1	128.3; 129.2; 130.1; 134.4	
16	113.7	138.6	92.5	27.4	33.5	37.4	35.4	64.6	21.2	19.2	128.3; 129.4; 130.1; 145.6	
18*	118.7	138.7	92.8	27.5	32.9	37.3	28.7	200.7	19.9	18.2		
19	118.4	138.6	92.4	27.4	32.2	37.3	43.3	72.7	22.3	18.2	128.3; 129.7; 132.2; 141.5	−0.1
20	25.8	131.1	124.7	25.3	36.8	30.3	43.4	56.8	19.3	17.8	127.6; 128.8; 133.0; 134.5	
21	25.7	131.0	124.3	25.0	33.7	29.7	37.5	72.2	18.7	20.1	124.4; 128.0; 128.6; 130.1; 131.1; 142.5	
22*	25.8	131.1	120.0	25.9	37.3	37.2	128.8	124.5	17.8	20.5	121.9; 125.9; 128.6; 142.4	

* The numbering of C atoms in this compound in the table does not coincide with IUPAC rules.

AcOEt gave 2.75 g (89%) of compound **16** as a colorless oil, R_f 0.45 (AcOEt). IR (film): 715, 755, 930, 1050, 1350, 1440, 1530, 2860—3070, 3460. ^1H NMR, δ: 0.85 (d, 3 H, MeC(6), J = 6.0 Hz); 1.75 (br.s, 3 H, MeC(2)); 1.00—1.85 (m, 6 H, CH_2); 2.05 (m, 1 H, HC(6)); 2.70 (m, 2 H, HC(8)); 4.75 (m, 1 H, HCN); 5.10 (m, 2 H, HC(1)); 7.45 and 7.55 (both m, 5 H, C_6H_5). The ^{13}C NMR spectrum is presented in Table 1. MS, m/z: 309 $[M]^+$, 263 $[M-46]^+$. Found (%): N, 4.56; S, 10.45. $C_{16}H_{23}NO_3S$. Calculated (%): N, 4.53; S, 10.36.

(*S*)-(−)-Citronellal (17). A solution of (−)-citronellol (**13**) (0.4 g, 2.6 mmol) (Fluka) was added in one portion to a suspension of PCC (1 g, 4.7 mmol) in 20 mL of CH_2Cl_2, vigorously stirred at 20 °C. The reaction mixture was stirred for 2 h, then 50 mL of ether was added, and the mixture was stirred for an additional 10 h, filtered through 20 g of SiO_2, and concentrated *in vacuo*. Vacuum distillation of the residue gave 0.34 g (84%) of compound **17** as a colorless oil, b.p. (bath) 65 °C (2 Torr) (see Ref. 14: b.p. 207 °C), n_D^{20} 1.4470 (see Ref. 15: 1.4473), $[\alpha]_D$ − 14.2° (c = 0.99, CH_2Cl_2) (see Ref. 14: $[\alpha]_D$ −14° (c = 10, EtOH)), R_f 0.52 (hexane—ether, 9 : 1). ^1H NMR, δ: 0.97 (d, 3 H, MeC(3), J = 6.6 Hz); 1.60 (br.s, 3 H, *Z*-MeC(7)); 1.69 (br.s, 3 H, *E*-MeC(7)); 1.00—2.50 (m, 7 H, CH_2, CH); 5.08 (m, 1 H, HC(6)); 9.76 (dd, 1 H, HCO, J = 2.3, 2.5 Hz).

(3*S*,6*R*/*S*)-3,7-Dimethyl-6-nitrooct-7-en-1-al (18). The procedure was similar to that described for compound **15**. The reaction of aldehyde **17** (5 g, 25 mmol) with $NaNO_2$ (22 g, 0.32 mol) in 50 mL of AcOH gave 3.8 g (58%) of nitro derivative **18**, R_f 0.46 (hexane—ether, 8 : 2). IR (film): 760, 800, 950, 1017, 1200, 1350, 1445, 1530, 1720, 2900—3100. ^1H NMR, δ: 0.96 (d, 3 H, MeC(3), J = 6.2 Hz); 1.70 (br.s, 3 H, MeC(7)); 1.00—2.00 (m, 7 H, CH, CH_2); 4.75 (m, 1 H, HCN); 5.10—5.20 (m, 2 H, HC(8)); 9.70 (s, 1 H, HCO). The ^{13}C NMR spectrum is presented in Table 1. MS, m/z: 153 $[M - 46]^+$. Found (%): C, 60.35; H, 8.66; N, 7.37. $C_{10}H_{17}NO_3$. Calculated (%): C, 60.28; H, 8.60; N, 7.03.

(3*R*/*S*,6*S*,8*R*/*S*)-2,6-Dimethyl-3-nitro-8-trimethylsilyloxy-8-phenylthiooct-1-ene (19). A solution of PhSH (1.65 g, 15 mmol) in 10 mL of Py was added dropwise over a period of 2 h to a solution of aldehyde **18** (3 g, 15 mmol) and TMSCl (1.33 g, 17 mmol) in 10 mL of Py, stirred at 5 °C (Ar). The reaction mixture was stirred for 2 h at 20 °C and diluted with 50 mL of petroleum ether, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo*, and the residue (~5 g) was immediately chromatographed on SiO_2 (100 g) cooled to −10 °C. Elution with hexane gave 4.7 g (90%) of labile compound **19** as a colorless oil, R_f 0.80 (hexane). ^1H NMR, δ: 0.12 (s, 9 H, Me_3Si); 0.98 (d, 3 H, MeC(6), J = 6 Hz); 1.75 (br.s, 3 H, MeC(2)); 1.00—2.00 (m, 6 H, CH_2); 2.30 (m, 1 H, HC(6)); 4.30 (m, 1 H, HCOSi); 4.84 (m, 1 H, HCN); 5.10—5.20 (m, 2 H, HC(1)); 7.15 and 7.30 (both m, 5 H, C_6H_5). The ^{13}C NMR spectrum is presented in Table 1. MS, m/z: 349 $[M]^+$.

(6*S*)-2,6-Dimethyl-8,8-di(phenylthio)oct-2-ene (20). Bu_3P (7.2 g, 35.7 mmol) was added dropwise over a period of 0.5 h to a mixture of aldehyde **17** (5 g, 32.5 mmol) and Ph_2S_2 (7.78 g, 35.7 mmol), stirred at 25 °C (Ar). After the reaction mixture had been stirred for 1 h, it was diluted with 50 mL of hexane, washed with water (2×20 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~11 g) was chromatographed on SiO_2 (200 g). Gradient elution (hexane → hexane—AcOEt, 95 : 5) gave 10.5 g (91%) of disulfide **20** as a colorless oil, R_f 0.62 (hexane—AcOEt, 9 : 1). IR (film): 710, 755, 1026, 1070, 1095, 1380, 1445, 1480, 1583, 2800—3100. ^1H NMR, δ: 0.91 (d, 3 H, MeC(6), J = 5.9 Hz); 0.90—2.10 (m, 7 H, CH_2, CH); 1.60 (br.s, 3 H, *E*-MeC(2)); 1.68 (br.s, 3 H, *Z*-MeC(2)); 4.42 (m, 1 H, HC(8)); 5.06 (m, 1 H, HC(3)); 7.15—8.00 (m, 10 H, 2 C_6H_5). The ^{13}C NMR spectrum is presented in Table 1. MS, m/z: 356 $[M]^+$, 247 (100%) $[M-109]^+$. Found (%): C, 74.11; H, 8.21; S, 17.44. $C_{22}H_{28}S_2$. Calculated (%): C, 74.10; H, 7.91; S, 17.98.

(6*S*,8*R*/*S*)-2,6-Dimethyl-8-phenylsulfinyl-8-phenylthiooct-2-ene (21). A solution of 80% *m*-chloroperbenzoic acid (2.8 g, 13 mmol) in 15 mL of ether was added dropwise over a period of 1 h to a solution of disulfide **20** (4.65 g, 13 mmol) in 20 mL of ether, stirred at −50 °C (Ar). The reaction mixture was heated to ~20 °C and washed with water (20 mL), 20% NaOH, and water (20 mL). The ethereal solution was dried with $MgSO_4$ and concentrated *in vacuo*. The residue (~4.5 g) was chromatographed on SiO_2 (100 g). Gradient elution (hexane → hexane—AcOEt, 85 : 15) gave 4.02 g (86%) of a mixture of diastereomers of **21** as a colorless oil, R_f 0.48 (hexane—AcOEt, 8 : 2). IR ($CHCl_3$): 1045, 1090 1382, 1445, 1476, 2900—3000. ^1H NMR, δ: 0.77 (d, 3 H, MeC(6), J = 6 Hz); 0.90—2.00 (m, 7 H, CH_2, CH); 1.55 (br.s, 3 H, *E*-MeC(2)); 1.63 (br.s, 3 H, *Z*-MeC(2)); 3.70—4.20 (m, 1 H, HC(8)); 5.0 (m, 1 H, HC(3)); 7.15—8.00 (m, 10 H, 2 C_6H_5). The ^{13}C NMR spectrum is presented in Table 1. MS, m/z: 247

$[M-125]^+$. Found (%): C, 71.08; H, 7.42. $C_{22}H_{28}OS_2$. Calculated (%): C, 70.92; H, 7.57.

(3*S*)-3,7-Dimethyl-1-phenylthiocta-1*E*-, and -1*Z*,6-dienes (22). A solution of a mixture of isomeric **21** (4.5 g, 12 mmol) and triethylamine (2 g, 20 mmol) in 10 mL of toluene was heated for 2 h at 110 °C, the solvent was evaporated *in vacuo*, and the residue (4.2 g) was chromatographed on SiO_2 (100 g). Gradient elution (hexane → hexane—AcOEt, 95 : 5) gave 2.7 g (92%) of a mixture of vinyl sulfides **22** (~1 : 1, ^1H NMR data) as a colorless oil, R_f 0.77 (hexane—AcOEt, 9 : 1). Almost the same yield was obtained by heating the reaction mixture for 6 h without addition of a base. IR (film): 695, 745, 956, 1030, 1075, 1093, 1380, 1440, 1481, 1590, 1720, 1280—3200. ^1H NMR, δ: 1.05 and 1.10 (both d, 3 H, MeC(3), J = 6.3 Hz); 1.30—2.70 (m, 5 H, CH_2, CH); 1.63 (br.s, 3 H, *E*-MeC(7)); 1.72 (br.s, 3 H, *Z*-MeC(7)); 5.09 (m, 1 H, HC(6)); 5.60—6.20 (m, 2 H, HC(1), HC(2)); 7.15—7.50 (m, 5 H, C_6H_5). The ^{13}C NMR spectrum is presented in Table 1. MS, m/z: 246 $[M]^+$, 231 $[M-15]^+$. Found (%): C, 78.37; H, 9.06. $C_{16}H_{22}S$. Calculated (%): C, 77.99; H, 9.00.

(3*R*/*S*,6*S*)-2,6-Dimethyl-3-nitro-8-phenylthiocta-1,7*E*-diene (7a) and (3*R*/*S*,6*S*)-2,6-dimethyl-3-nitro-8-phenylthiocta-1,7*Z*-diene (7b). *A.* At 0 °C, TMSOTf (3.20 g, 14.4 mmol) was added to a stirred (Ar) solution of sulfoxide **16** (2.22 g, 7.2 mmol) and Pr^i_2NEt (2.04 g, 15.8 mmol) in 30 mL of CH_2Cl_2. The reaction mixture was heated to 20 °C, kept for 2 h, diluted with $CHCl_3$, and washed successively with 2 *N* H_2SO_4 and a 5% solution of $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*, and the residue (2.2 g) was chromatographed on SiO_2 (200 g). Gradient elution (hexane → hexane—Et_2O, 9 : 1) gave 1.07 g (51%) of a mixture of sulfides **7a/7b** (1 : 1, ^1H NMR data) as a colorless oil, R_f 0.58 (hexane—AcOEt, 9 : 1).

MS, m/z: 309 $[M]^+$, 263 $[M-46]^+$. Found (%): C, 65.83; H, 7.39; S, 10.88. $C_{16}H_{21}NO_2S$. Calculated (%): C, 65.95; H, 4.81; S, 11.00.

Individual sulfides **7a** and **7b** were isolated by HPLC under the conditions described above.

Vinyl sulfide 7a. IR (film): 690, 745, 790, 920, 1030, 1090, 1250, 1380, 1440, 1540, 2860—3060. ^1H NMR, δ: 1.07 (d, 3 H, MeC(6), J = 6 Hz); 1.25—2.45 (m, 5 H, CH_2, CH); 1.82 (br.s, 3 H, MeC(2)); 4.90 (m, 1 H, HCN); 5.20 (m, 2 H, HC(1)); 5.76 (ddd, 1 H, HC(7), J = 2.5, 8.2 and 15 Hz); 6.16 (br.d, 1 H, HC(8), J = 15 Hz); 7.15—7.40 (m, 5 H, C_6H_5). The ^{13}C NMR spectrum is presented in Table 1.

Vinyl sulfide 7b. IR (film): 690, 745, 845, 920, 1030, 1090, 1250, 1380, 1440, 1540, 2860—3060. ^1H NMR, δ: 1.06 (d, 3 H, Me—C(6), J = 6 Hz); 1.4 (m, 2 H, CH_2); 1.85 (br.s, 3 H, MeC(2)); 1.9, 2.25 and 2.7 (all m, 3 H, CH_2, CH); 4.95 (m, 1 H, HCN); 5.20 (m, 2 H, HC(1)); 5.55 (ddd, 1 H, HC(7), J = 1.3, 1.3 and 9.3 Hz); 6.23 (br.d, 1 H, HC(8), J = 9.2 Hz); 7.15—7.40 (m, 5 H, C_6H_5). The ^{13}C NMR spectrum is presented in Table 1.

B. Sodium nitrite (2 g, 29 mmol) was added at 5 °C over a period of 1 h to a solution of vinyl sulfide **22** (1.2 g, 4.9 mmol) in 10 mL of ether and 10 mL of AcOH. The usual workup of the reaction mixture (see above) gave 0.68 g (45%) of mixture **7a/7b**, which was virtually identical (R_f, ^1H NMR) to that described previously.

C. Me_3SiI (1.2 g, 6 mmol) was added in one portion to a solution of TMS ether **19** (2.1 g, 6 mmol) in 20 mL of CH_2Cl_2, stirred at −80 °C (Ar). The reaction mixture was stirred for 1 h, treated with Et_3N (1.2 g, 12 mmol), and kept for an additional 1 h. The usual workup (see above) gave 1.32 g (71%) of mixture **7a/7b**, which was virtually identical (R_f, ^1H NMR) to that described above.

(3*R*,3a*R*,4*S*,6a*S*)-6a-Isopropenyl-4-methyl-3-phenylthio-1-trimethylsilyloxyperhydrocyclopenta[*c*]isoxazole (9a) and (3*S*,3a*R*,4*S*,6a*S*)-6a-isopropenyl-4-methyl-3-phenylthio-1-trimethylsilyloxyperhydrocyclopenta[*c*]isoxazole (9b). A solution of vinyl sulfide **7a** (0.36 g, 1.2 mmol), BSA (0.49 g, 2.4 mmol), and Et_3N (0.06 g, 0.6 mmol) in 0.8 mL of toluene and 0.08 mL of MeCN was heated for 5 h at 120 °C (Ar) and treated with petroleum ether and water. The aqueous layer was separated and extracted with petroleum ether. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on a cooled (−10 °C) column with SiO_2 (30 g) using petroleum ether as the eluent to give 0.31 g (69%) of isoxazole **9a** as a colorless oil, R_f 0.65 (hexane—ether, 2 : 0.1). ^1H NMR, δ: 0.28 (s, 9 H, Me—Si); 1.2 (d, 3H, MeC(4), J = 6.4 Hz); 1.20—3.10 (m, 6 H, CH, CH_2); 1.82 (br.s, 3 H, MeC=); 5.71 (d, 1 H, HC(3), J = 8.8 Hz); 4.82 and 4.93 (both m, 2 H, H_2C=); 7.20—7.60 (m, 5 H, C_6H_5).

A similar procedure starting from 0.25 g of vinyl sulfide **7b** gave 0.21 g (68%) of isoxazolidine **9b** as a colorless oil, R_f 0.65 (hexane—ether, 2 : 0.1). ^1H NMR, δ: 0.19 (s, 9 H, Me—Si); 1.14 (d, 3 H, MeC(4), J = 7.0 Hz); 1.00—3.10 (m, 6 H, CH, CH_2); 1.87 (br.s, 3 H, MeC=); 5.93 (d, 1 H, HC(3), J = 6.2 Hz); 4.90 (br.s, 2 H, H_2C=); 7.20—7.60 (m, 5H, C_6H_5).

Similarly, a mixture of vinyl sulfides **7a/7b** (1 : 1) gave a mixture of isoxazoles **9a/9b**. MS, m/z: 347 $[M]^+$.

(7*S*)-4,7-Dimethyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-2-oxide (11), *N*-[(1*S*,2*S*,3*S*)-2-formyl-1-isopropenyl-3-methylcyclopent-1-yl]-*N*-phenylthiohydroxylamine (12a) and *N*-[(1*S*,2*R*,3*S*)-2-formyl-1-isopropenyl-3-methylcyclopent-1-yl]-*N*-phenylthiohydroxylamine (12b). A solution of mixture **9a/9b** (0.182 g, 0.5 mmol) in 0.5 mL of THF was added in one portion to a suspension of $KF \cdot 2H_2O$ (188 mg, 2 mmol) in 1 mL of MeOH and 1 mL of THF, vigorously stirred at −50 °C. The reaction mixture was heated to 25 °C for 1 h and diluted with ether, and the precipitate was filtered off and washed with ether. The combined filtrate was concentrated *in vacuo*, and the residue (120 mg) was chromatographed on SiO_2 (15 g). Successive elution with hexane—ether (1 : 4) and ether—MeOH (1 : 1) mixtures gave 38 mg (25%) of mixture **12a/12b** (1 : 4, ^1H NMR data) and 37 mg (45%) of *N*-oxide **11**. Mixture **12a/12b** is amorphous (m.p. 72—82 °C). Found (%): C, 65.89; H, 7.20; N, 4.61; S, 10.38. $C_{16}H_{21}NO_2S$. Calculated (%): C, 65.95; H, 7.26; N, 4.81; S, 11.00.

Chromatographic separation of mixture **12a/12b** on SiO_2 (15 g) gave samples enriched (up to 80%) in stereoisomers **12a** and **12b**.

Hydroxylamine 12b, IR ($CHCl_3$): 690, 920, 1030, 1060, 1090, 1210, 1380, 1445, 1640, 1710, 2730, 2800—3050, 3300. ^1H NMR, δ: 1.23 (d, 3 H, MeC(3), J = 6 Hz); 1.50 (m, 1 H, HC(3)); 1.97 (br.s, 3 H, MeC=); 2.10—2.80 (m, 5 H, CH_2, CH); 4.50 (br.s, 1 H, OH); 5.05 and 5.25 (both br.s, 2 H, H_2C=); 7.5 and 7.7 (both m, 5 H, C_6H_5); 9.8 (s, 1 H, HCO).

Hydroxylamine 12a, IR ($CHCl_3$): 690, 920, 1030, 1060, 1090, 1210, 1380, 1445, 1640, 1710, 2730, 2800—3050, 3300. ^1H NMR, δ: 1.12 (d, 3 H, MeC(3), J = 6 Hz); 1.40 (m, 1 H, HC(3)); 1.95 (br.s, 3 H, MeC=); 2.10—2.80 (m, 5 H, CH_2, CH); 4.35 (br.s, 1 H, OH); 5.12 and 5.28 (br.s, 2 H, H_2C=); 7.50 and 7.65 (both m, 5 H, C_6H_5); 9.91 (s, 1 H, HCO).

***N*-Oxide 11**, m.p. 126 °C (ether) (*cf.* Ref. 15), ^1H NMR, δ: 1.28 (d, 3 H, MeC(7), J = 6 Hz); 1.70 and 2.40 (both m, 2 H, HC(6)); 2.20 (br.s, 3 H, MeC(4)); 2.80 (m, 2 H, HC(5)); 3.25 (m, 1 H, HC(7)); 7.9 (m, 2 H, HCN). The ^{13}C NMR spectrum is presented in Table 1. MS, m/z (I (%)): 164 (16) $[M+1]^+$, 163 (100) $[M]^+$, 148 (23), 131 (15), 121 (22), 93 (24).

(−)-Actinidine (6). $LiAlH_4$ (5 mg, 0.13 mmol) was added to a solution of $TiCl_4$ (35 mg, 0.18 mmol) in 0.5 mL of THF, vigorously stirred at 0 °C (Ar). The mixture was heated to 25 °C and stirred at this temperature for 15 min. A solution of *N*-oxide **11** (33 mg, 0.2 mmol) in 0.1 mL of THF was added at 0 °C to the resulting black suspension. The reaction mixture was stirred for 30 min at 25 °C, treated with 0.5 mL of H_2O and 0.5 mL of 25% NH_4OH, and extracted with ether. The extract was dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was chromatographed on Al_2O_3 (5 g). Elution with ether gave 24 mg (80%) of compound **6** as a light yellow oil, R_f 0.20 (hexane—AcOEt, 1 : 4). ^1H NMR, δ: 1.35 (d, 3 H, MeC(7), J = 6.0 Hz); 1.65 and 2.35 (both m, 2 H, HC(6)); 2.20 (br.s, 3 H, MeC(4)); 2.80 (m, 2 H, CH_2); 3.30 (m, 1 H, HC(7)); 8.20 and 8.30 (both br.s, 2 H, HCN).

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