expressed in parts per million downfield from tetramethylsilane as internal standard. Column chromatography was performed on alumina (Merck aluminium oxide 90) with benzene as eluant. 3,5-Di-*tert*-butylaniline was prepared by the reported method.[6]

***N,N'*-Bis(3,5-di-*tert*-butylphenyl)-1,3-benzenedisulfenamide (1a).** 1,3-Benzenedithiol (1.00 g, 7.03 mmol) was dissolved in 14 mL of dry CH_2Cl_2. To the solution was added dropwise at room temperature a solution of 2.35 g (17.4 mmol) of SO_2Cl_2 in 5 mL of dry CH_2Cl_2 with stirring. The resulting mixture was heated at reflux for 1.5 h with stirring, giving a homogeneous orange solution. The solvent and the excess SO_2Cl_2 were removed in vacuo, and the resulting orange oil (benzene-1,3-disulfenyl chloride) was dissolved in 30 mL of dry ether. The ethereal solution was then added dropwise to a stirred solution of 3.18 g (15.5 mmol) of 3,5-di-*tert*-butylaniline and 2.1 g (21 mmol) of Et_3N in 150 mL of dry ether at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was filtered, evaporated, and passed through a short alumina column to remove polar byproducts. Crystallization from hexane yielded 1.89 g (3.44 mmol, 49%) of colorless needles with mp 137–139 °C: IR (KBr) 3380 (NH), 2950–2850 cm^{-1} (*t*-Bu); ^1H NMR ($CDCl_3$) δ 1.27 (s, *t*-Bu, 36 H), 5.07 (s, NH, 2 H), 6.85–7.35 (m, aromatic, 10 H). Anal. Calcd for $C_{34}H_{48}N_2S_2$: C, 74.40; H, 8.81; N, 5.11. Found: C, 74.15; H, 8.82; N, 4.76.

***N,N'*-Bis(3,5-di-*tert*-butylphenyl)-4-chloro-1,3-benzenedisulfenamide (1b).** 1,3-Benzenedithiol (1.00 g, 7.03 mmol) was dissolved in 50 mL of dry CH_2Cl_2, and chlorine gas was bubbled in a steady stream through the solution at −10 °C until the solution became orange and homogeneous (ca. 30 min). Excess chlorine gas and the solvent were removed in vacuo, giving an orange oil of 4-chlorobenzene-1,3-disulfenyl chloride.[7] The disulfenyl chloride was dissolved in 30 mL of dry ether, and the solution was added dropwise to a stirred solution of 3.18 g (15.5 mmol) of 3,5-di-*tert*-butylaniline and 2.1 g (21 mmol) of Et_3N in 150 mL of dry ether at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was filtered, evaporated, and passed through a short alumina column to remove polar byproducts. Crystallization from hexane yielded 1.41 g (2.42 mmol, 34%) of colorless needles with mp 92–96°C: IR (KBr) 3350 (NH), 2950–2850 cm^{-1} (*t*-Bu); ^1H NMR ($CDCl_3$) δ 1.26 and 1.29 (each s, *t*-Bu, 36 H), 4.51 and 4.93 (each s, NH, 2 H), 6.76–7.20 (m, aromatic, 9 H). Anal. Calcd for $C_{34}H_{47}ClN_2S_2$: C, 70.00; H, 8.12; N, 4.80; Cl, 6.08. Found: C, 69.58; H, 8.14; N, 4.68; Cl, 5.93.

***N,N'*-Bis(3,5-di-*tert*-butylphenyl)-1,4-benzenedisulfenamide (1c).** In a manner analogous to the above, 1.00 g (7.03 mmol) of 1,4-benzenedithiol was treated with 2.35 g (17.4 mmol) of SO_2Cl_2, and benzene-1,4-disulfenyl chloride, obtained as orange crystals after removal of the solvent, was allowed to react with 3.18 g (15.5 mmol) of 3,5-di-*tert*-butylaniline in ether in the presence of Et_3N. After column chromatography, the product was crystallized from hexane to give 1.91 g (3.48 mmol, 50%) of light pink prisms with mp 193–195 °C dec: IR (KBr) 3380 (NH), 2950–2850 cm^{-1} (*t*-Bu); ^1H NMR ($CDCl_3$) δ 1.26 (s, *t*-Bu, 36 H), 5.07 (s, NH, 2 H), 6.84–7.18 (m, aromatic, 10 H). Anal. Calcd for $C_{34}H_{48}N_2S_2$: C, 74.40; H, 8.81; N, 5.11. Found: C, 74.16; H, 8.87; N, 5.12.

This compound was also prepared in 58% yield by reaction of 3,5-di-*tert*-butylaniline with benzene-1,4-disulfenyl chloride obtained by bubbling chlorine gas into a solution of 1,4-benzenedithiol in dry CH_2Cl_2 at −10 °C.

General Procedure for Isolation of Cyclic Compounds 5. Compound 1 (500 mg) was dissolved in 20 mL of benzene with stirring. To the solution was added 3.0 g of anhydrous K_2CO_3, and stirring was continued. PbO_2 (4.0–5.0 g) was then added in four portions to the stirred mixture over a period of 3–4 min, and stirring was continued for an additional 1 min. After filtration, the solvent was removed by freeze-drying, and ca. 2 mL mL of hexane was added to the blue microcrystalline residue. Upon cooling of the mixture to −20 °C overnight, light blue microcrystals were given, which were collected by filtration, and again recrystallized from hexane (**5c**) or 1:10 benzene–hexane (**5a** and **5b**).

5a: light blue microprisms; mp 143–145 °C dec; yield 198 mg (40%); IR (KBr) 2950–2850, 1580, 1475, 1455, 1420, 1385, 1360, 1300, 1240, 1200, 980, 855, 765, 705, 680 cm^{-1}. Anal. Calcd for $(C_{34}H_{46}N_2S_2)_n$: C, 74.68; H, 8.48; N, 5.12. Found: C, 74.42; H, 8.70; N, 5.05.

5b: light blue microprisms; mp 155–158 °C dec; yield 79 mg (16%);[9] IR (KBr) 2950–2850, 1580, 1475, 1445, 1420, 1360, 1300, 1245, 1200, 1025, 980, 855, 800, 705 cm^{-1}. Anal. Calcd for $(C_{34}H_{45}ClN_2S_2)_n$: C, 70.25; H, 7.80; N, 4.82. Found: C, 70.47; H, 7.84; N, 4.77.

5c: light blue needles; mp 132–134 °C dec; yield 86 mg (17%); IR (KBr) 2950–2850, 1580, 1470, 1420, 1390, 1360, 1295, 1245, 1200, 980, 860, 810, 708 cm^{-1}. Anal. Calcd for $(C_{34}H_{46}N_2S_2)_n$: C, 74.68; H, 8.48; N, 5.12. Found: C, 74.43; H, 8.30; N, 4.91.

Measurements of ESR Spectra. ESR samples were prepared by the following two methods. (1) A mixture of 20 mg of **1**, 200 mg of anhydrous K_2CO_3, and 200 mg of PbO_2 in 5 mL of benzene was stirred for 2–4 min. After filtration, 0.20 mL of the filtrate was placed in an ESR cell, the solution was degassed by three freeze–pump–thaw cycles with a high vacuum system, and the cell was sealed off. (2) In the same manner as above, 0.5–5.0 mg of **5** and 0.40 mL of benzene were placed in an ESR cell, the solution was degassed, and the cell was sealed off.

ESR spectra were recorded with a JEOL JES-ME-3X spectrometer equipped with an X-band microwave unit and 100 kHz field modulation. Hyperfine splitting constants and *g* values were determined by comparison with Fremy's salt in aqueous K_2CO_3 solution (a_N, 13.09 G; *g*, 2.0057). Estimated accuracy: ±0.1 G for a_N and a_H, ±0.2 G for $a_{^{13}C}$ and $a_{^{33}S}$, and ±0.0002 for *g*. The temperatures of the ESR cavity were controlled with JEOL JES-VT-3 apparatus and determined with a copper-constantan thermocouple. Spin concentrations were determined by weighing the areas of integrated ESR spectra obtained with a JEOL JES-ID-2 integrator.[3] Calibration curves were drawn with 1,3,5-triphenylverdazyl solutions in benzene.

Acknowledgment. We thank Seitetsu Kagaku Co., Ltd., for the gift of 1,4-benzenedithiol.

(6) Allinger, N. L.; Blatter, H. M.; Freiberg, L. A.; Karkowski, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 2999–3011.

(7) In a previous paper[8] it was reported that chlorination of 1,3-benzenedithiol with Cl_2 gave benzene-1,3-disulfenyl chloride. In our case, however, the same reaction gave 4-chlorobenzene-1,3-disulfenyl chloride.

(8) Feher, F.; Malcharek, F.; Glinka, K. *Z. Naturforsch.* **1971**, *26B*, 67–68.

(9) Sufficiently pure crystals of **5b** were given in 70% yield by washing the residue with hexane after the benzene was removed by freeze-drying.

Synthesis of the Hexacyclic Indole Alkaloid (±)-Kopsijasmine

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(−)-Kopsijasmine, **1**, the 16,17-dehydro analogue of pleiocarpine **2**, was recently isolated from *Kopsia Jaminiflora Pitard*, and its structure was determined largely from NMR data.[1] Here we report the total synthesis of (±)-**1** via the 3-chloro heptacyclic kopsane derivative **11**.

The known homoannular diene **3**[2] was treated with KH/THF/0 °C, followed by 1-iodo-2-chloroprop-2-ene to give **4** in 92% yield (Scheme I). It should be noted that the alkylation of the C-11 carbanion derived from **3** always takes place on the endo face, as originally reported in the synthesis of kopsanone.[2] In general, nonplanar amides appear to undergo alkylation on the face opposite the pyramidalized nitrogen lone pair of electrons. Recently,

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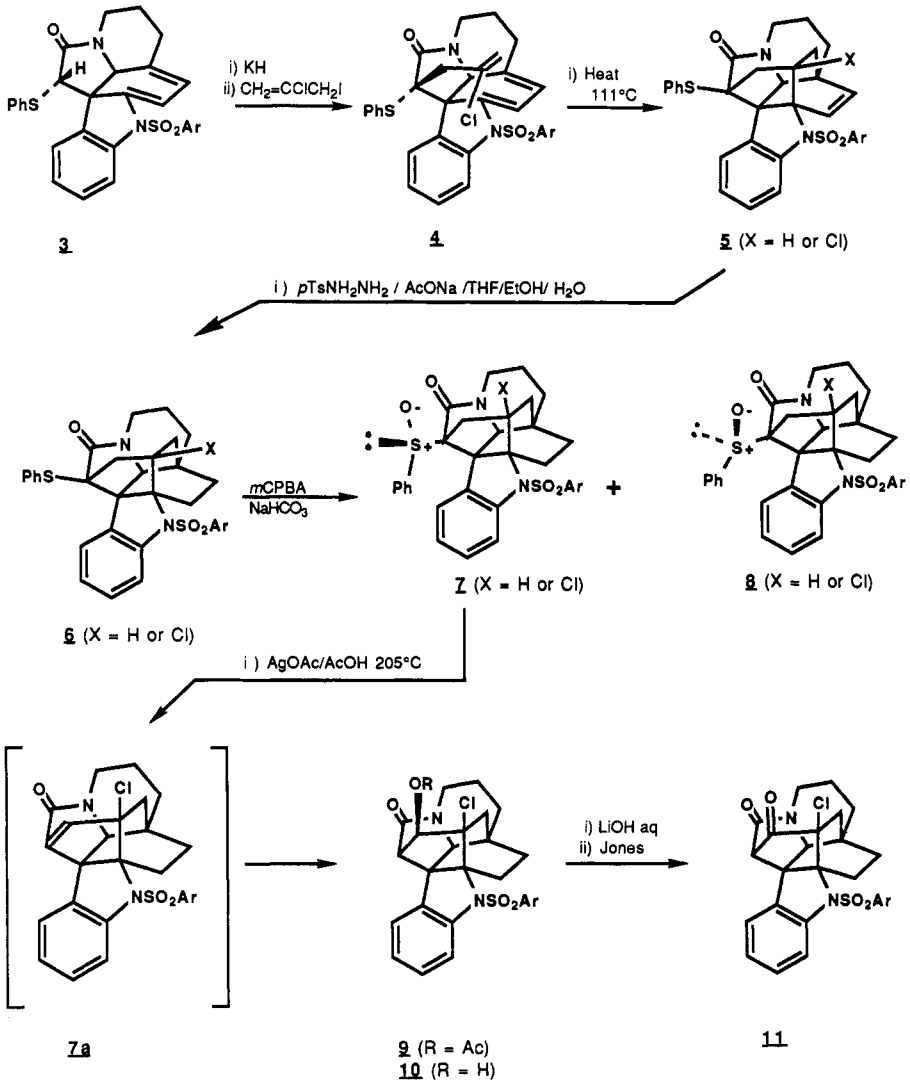
0022-3263/88/1953-5772$01.50/0

Scheme I



Baldwin[3] and Meyers[4] have reported some exemplary illustrations of this intriguing stereoelectronic effect. Mild thermolysis of **4** ($PhCH_3$/reflux) gave **5** (X = Cl) (83%, mp 268–269 °C).

Reduction of **5** (X = Cl) with in situ generated diimide ($TsNHNH_2$/NaOAc/EtOH) gave the dihydroderivative **6** (X = Cl) (95%, mp 241–244 °C). Oxidation of **6** (X = Cl) with *m*-chloroperoxybenzoic acid gave the expected diastereomeric sulfoxides **7** (X = Cl) and **8** (X = Cl) in the ratio of 1:3.5. Only **7** (X = Cl) can undergo a thermal syn elimination of PhSOH to the α,β-unsaturated anti-Bredt amide **7a** (X = Cl), which undergoes nucleophilic addition of AcOH at C-22 to give **9**. The diastereoisomer ratio should be contrasted with the prototype system **6** (X = H), which on oxidation under identical conditions gave **7** (X = H) and **8** (X = H) in the ratio 3.5:1. A plausible explanation for the change in sulfoxide ratios may involve an interaction between the lone-pair orbitals on sulfur and the σ^*-orbital of the C–Cl bond that is effectively transmitted through the conformationally rigid Cl–C(3)–C(22)–C(11) bonds. The single-crystal X-ray crystallographic structure of **5** (X = H), Figure 1 (partial structure), shows that the *S*-phenyl group is oriented approximately parallel to the indoline ring. If this represents a major conformer in solution, and for these rigid highly fused structures we have in general found good correspondence between crystal structures and solution conformers (as evidenced by ^1H NMR), the most accessible lone pair of electrons on sulfur is on the opposite side of the indoline moiety; oxidation of this lone pair would lead to **7** (X = H) as the major sulfoxide, and this is the case. The situation of **5** (X = Cl) is reversed. The accessible sulfur lone pair orbital is aligned antiperiplanar to the C(3)–Cl σ-bond, leading to a stabilizing n–σ^* orbital interaction. The C(11)–C(22) bond is 1.80% shorter in **5** (X = Cl) compared to **5** (X = H). The change in conformation distribution brought about by the C(3) chlorine atom now exposes the diastereotopic sulfur lone pair of electrons to be more sterically accessible toward oxidation, resulting in **8** (X = Cl) as the major sulfoxide. In summary, the inductive effect of the chlorine atom at C(3) causes a change in the ground-state conformer population of the C(11)–SPh rotamers and, as a result, changes in an adverse way the diastereotopic sulfur lone pair most exposed toward oxidation.

(1) Ruangrungsi, N.; Likhitwitayawuid, K.; Jongbunprasert, V.; Ponglux, D.; Aimi, M.; Ogata, K.; Yasuoka, M.; Haginiwa, J.; Sakai, S. *Tetrahedron Lett.* **1987**, *28*, 3679.

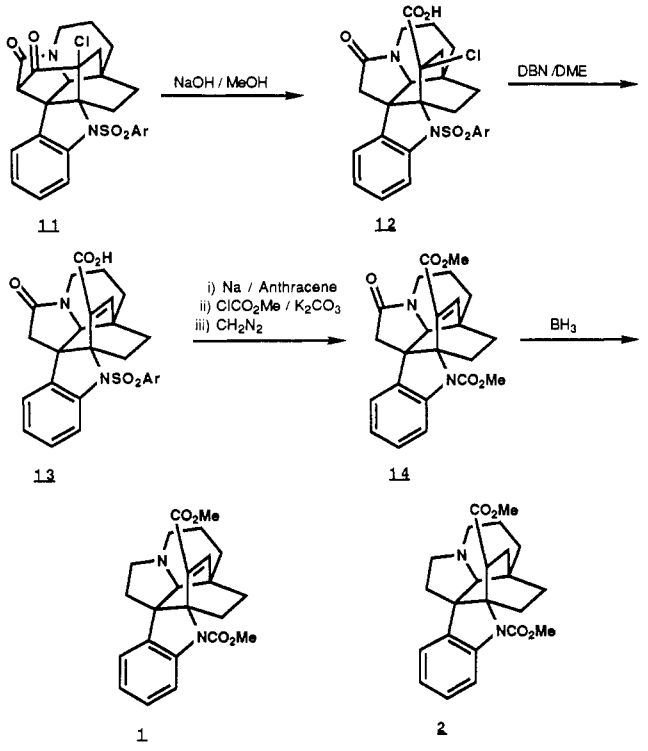
(2) Magnus, P.; Gallagher, R.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. Magnus, P.; Schultz, J.; Houk, K. N. *Tetrahedron Lett.* **1986**, *27*, 655.

(3) Baldwin, J. E.; Adlington, R. M.; Jones, R. H.; Schofield, C. J.; Zaracostas, C.; Greengrass, C. W. *Tetrahedron* **1986**, *42*, 4879.

(4) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146. Meyers, A. I.; Wanner, K. Th. *Tetrahedron Lett.* **1985**, *26*, 2047. Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541. Meyers, A. I.; Lefker, B. A.; Wanner, K. Th.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936.

Reduction of 8 (X = Cl) with acetyl bromide/cyclohexene gave 6 (X = Cl) (95%), which provided a recycling protocol that gave reasonable quantities (3–4 g) of the stereochemically correct sulfoxide 7 (X = Cl). Thermolysis of 7 (X = Cl) at 205 °C/AcOH/AgOAc (sealed tube) gave 9 (74%, mp 263–264 °C).[5] The relative stereochemistry of the *sec*-OAc could be readily assigned as shown, since the C-22 proton appears as a singlet at δ 5.4. Hydrolysis of 9 ($LiOH/H_2O/THF$) gave 10 (95%, mp 264 °C), which was oxidized (Jones reagent) to the β-keto amide 11 (89%, mp 180 °C).

The nonenolizable β-keto amide 11 was cleaved with MeOH/NaOH to provide 12, which was treated with DBN in DME heated at reflux for 12 h to give the α,β-unsaturated acid 13. The N-$SO_2C_6H_4OMe$-*p* was selectively removed by reduction with Na/anthracene/DME at −30 °C for 1 h,[6] and the mixture was worked up with $ClCO_2Me/K_2CO_3/Et_3BnNCl$/4 h, diazomethane/THF/$Et_2O$ for 5 min to give 10-oxokopsijasmine (14) (68% yield from 11). Reductive removal of the N-$SO_2C_6H_4OMe$-*p* protecting group with Na/naphthalene also reduced the C(3)–C(4) double bond. To complete the synthesis 14 was treated with BH_3·THF, followed by 6 N HCl under reflux for 0.5 h, to give (±)-kopsijasmine 1 (52%, mp 162–165 °C).[7,8]



(Ar = C_6H_4OMe-*p*, throughout).

Experimental Section

General experimental protocol was the same as for reference 9 except that ^1H NMR spectra were recorded either at 300 MHz on a Varian XL300 spectrometer or at 360 MHz on a Nicolet NT360 spectrometer.

20,21-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-3-chlorokopsan-10-one (5) (X = Cl). An ice-cold solution of 3 was treated with KH (2.11 g of a 35% suspension in oil). The solution was stirred at 0 °C for 40 min, and 1-iodo-2-chloroprop-2-ene (2 mL) was added via a pipette containing basic alumina. The mixture was stirred for 40 min after which time saturated aqueous ammonium chloride (4 mL) and water (70 mL) were added.

The product was extracted with ethyl acetate (3 × 70 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent gave the crude product as a pale yellow foam. This was dissolved in toluene (50 mL) and heated under reflux for 14 h before cooling. The solvent was removed and the residue purified by flash chromatography, eluting with 1% EtOAc in CH_2Cl_2 to give 5 as a colorless foam (0.87 g, 76%). This was recrystallized from MeOH: mp 268–269 °C; IR ($CHCl_3$) 2960, 1695, 1603, 1170 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 8.17 (2 H, d, J = 9 Hz), 7.8 (1 H, d, J = 9 Hz), 7.35 (3 H, m), 7.24 (1 H, d, J = 7 Hz), 7.15 (2 H, t, J = 7 Hz), 7.0 (2 H, d, J = 9 Hz), 6.95 (2 H, m), 6.5 (1 H, d, J = 9 Hz), 6.19 (1 H, d, J = 9 Hz), 4.22 (1 H, dd, J = 15, 4 Hz), 3.9 (3 H, s), 3.44 (1 H, br s), 2.94 (1 H, dt, J = 15, 4 Hz), 2.51 (2 H, s), 2.45 (1 H, d, J = 15 Hz), 1.7–2.0 (5 H, m). Anal. Calcd for $C_{33}H_{29}ClN_2O_4S_2$: C, 64.22; N, 4.74; N, 4.54. Found: C, 64.24; H, 4.70; N, 4.39.

1-[(*p*-Methoxyphenyl)sulfonyl]-11β-(phenylthio)-3-chlorokopsan-10-one (6) (X = Cl). A solution of 5 (X = Cl) (1.96 g, 3.176 mol), *p*-toluenesulfonyl hydrazide (3 g, 16.1 mmol), and sodium acetate trihydrate (2.63 g, 19.3 mmol) in 4:4:1 THF/EtOH/water (225 mL) was heated under reflux for 5.5 h and allowed to cool. Sodium hydroxide (2 N, 50 mL) and brine (50 mL) were added, and the products were extracted into CH_2Cl_2 (4 × 50 mL). The organic layer was separated and dried (Na_2SO_4) before being concentrated to a colorless foam. This was recrystallized from $MeOH/CH_2Cl_2$ to give 6 (X = Cl) as colorless prisms (1.87 g, 95%) (mp 241–244 °C): IR ($CHCl_3$) 2960, 1690, 1600, 1170 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 8.05 (2 H, d, J = 9 Hz), 7.8 (1 H, d, J = 8 Hz), 7.33 (1 H, m), 7.22 (3 H, m), 7.12 (2 H, m), 6.97 (4 H, d, J = 9 Hz), 4.2 (1 H, dd, J = 14, 5 Hz), 3.85 (3 H, s), 3.6 (1 H, s), 3.17 (1 H, m), 2.85 (1 H, m), 2.4 (3 H, m), 2.03 (1 H, d, J = 15 Hz), 1.9–1.25 (7 H, m); MS, m/e (EI) 618 (47), 447 (39), 411 (81), 171 (100). Anal. Calcd for $C_{33}H_{31}ClN_2O_4S_2$: C, 64.01; H, 5.05; N, 4.52. Found: C, 63.88; H, 5.12; N, 4.42.

1-[(*p*-Methoxyphenyl)sulfonyl]-11β-[phenyl-(*R*-*rel*)-sulfinyl]-3-chlorokopsan-10-one (7) (X = Cl) and Its Sulfinyl Epimer (8) (X = Cl). A solution of 6 (X = Cl) (1.799 g, 2.91 mmol) in CH_2Cl_2 (180 mL) and sodium bicarbonate (saturated aqueous solution, 180 mL) was cooled to 0 °C, and a solution of 3-chloroperoxybenzoic acid (0.555 g, 80–90% pure) in CH_2Cl_2 (60 mL) was added over 1 h. The phases were separated, and the organic layer was dried ($NaSO_4$) and concentrated to give a mixture of epimers. These were separated by flash chromatography (10% EtOAc in CH_2Cl_2 then EtOAc) to give 7 (X = Cl) (0.388 g, 21%) and 8 (X = Cl) (1.31 g, 71%).

7 (X = Cl): recrystallized from $CHCl_2$/hexane to give colorless plates (mp 253–255 °C); IR ($CHCl_3$) 3000, 2950, 1690, 1600, 1160 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 8.23 (2 H, d, J = 9 Hz), 7.62 (1 H, d, J = 8 Hz), 7.25–7.48 (6 H, m), 7.08–7.18 (2 H, m), 7.03 (2 H, d, J = 9 Hz), 4.04 (1 H, m), 3.88 (3 H, s), 3.69 (1 H, s), 3.33 (1 H, m), 3.17 (1 H, dd, J = 13, 1 Hz), 2.82 (1 H, m), 2.28 (1 H, dd, J = 16, 4 Hz), 1.96–2.08 (3 H, m), 1.35–1.73 (6 H, m); MS, m/e (EI) 618 (37, M^+ − O), 556 (40), 526 (100), 355 (67). Anal. Calcd for $C_{33}H_{31}ClN_2O_5S_2$: C, 62.40; H, 4.92; N, 4.41. Found: C, 62.62; H, 4.87; N, 4.55.

8 (X = Cl): recrystallized from CH_2Cl_2/hexane to give colorless plates (mp 269–271 °C); IR ($CHCl_3$) 3000, 2950, 1695, 1600, 1170

(5) Thermolysis of the "wrong" sulfoxide 8 under the same conditions that were used to convert 7 into 9 did not give 9, and the starting sulfoxide 8 was recovered in high yield.

(6) Closson, W. D.; Sungchul, J.; Schulenberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650. Quaal, K. S.; Sungchul, J.; Kim, Y. M.; Closson, W. D.; Zubieta, J. A. *J. Org. Chem.* **1978**, *43*, 1311. Sungchul, J.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

(7) (−)-Kopsijasmine has mp 199–202 °C. The IR, ^1H NMR, UV, and MS were identical with spectra supplied by Dr. Sakai. Complete details of the single crystal X-ray structural determinations of 5 (X = H) and 5 (x = Cl) may be obtained from Dr. John Huffman. Please ask for structure report numbers 82053 and 85078, respectively.

(8) Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, *50*, 4790.

(9) Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739.

(10) Crucial bond length changes [(H − Cl), Δ_{H-Cl}]: C_{11b}–S_{11a} (1.786 − 1.796), +0.010 (0.56%); C_{11a}–C_{11} (1.812 − 1.801), −0.011 (0.61%); C_{11}–C_{22} (1.554 − 1.526), −0.028 (1.80%); C_{22}–C_3 (1.531 − 1.517), −0.014 (0.91%). Crucial bond angle changes: $\angle_{11b/11a/11}$ (110°.0′–103°.7′); $\angle_{11a/11/22}$ (103°.4′–111°.4′); $\angle_{11/22/3}$ (105°.5′–103°.7′).

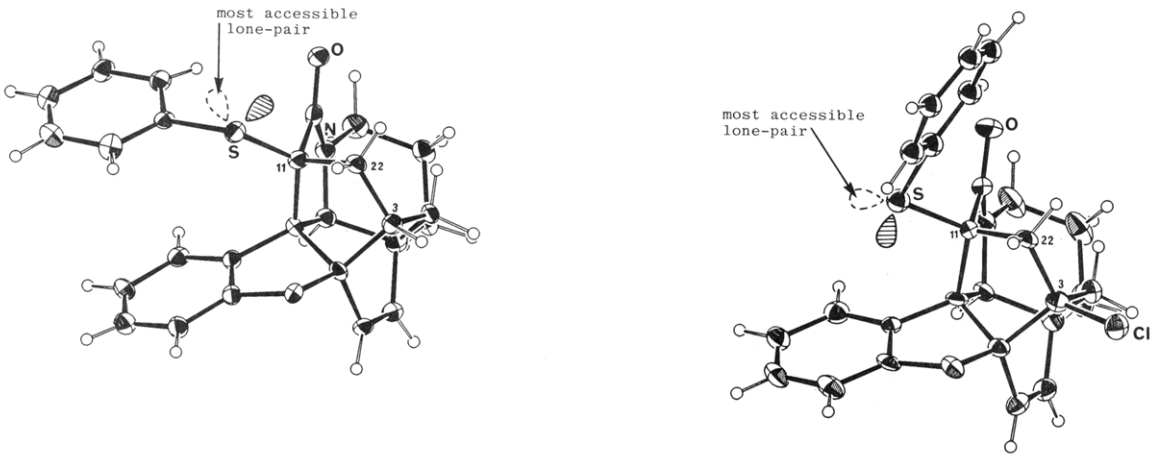


Figure 1. ORTEP drawings of **5** (X = H) (left) and **5** (X = Cl) (right). The $SO_2C_6H_4OMe$-*p* group was omitted for clarity.

cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 8.11 (2 H, d, J = 9 Hz), 7.86 (1 H, d, J = 8 Hz), 7.24–7.46 (7 H, m), 7.18 (1 H, m), 7.07 (2 H, d, J = 8 Hz), 4.22 (1 H, m), 3.94 (3 H, s), 3.67 (1 H, s), 3.07 (1 H, m), 2.87 (1 H, m), 2.33 (1 H, dd, J = 16, 3 Hz), 2.15 (1 H, d, J = 14 Hz), 1.35–2.01 (9 H, m); MS, m/e (EI) 618 (1.3, M^+ – O), 448 (17), 446 (22), 108 (100).

1-[(*p*-Methoxyphenyl)sulfonyl]-22β-hydroxy-3-chlorokopsan-10-one (10). A solution of **7** (X = Cl) (0.3 g, 0.472 mmol) and a suspension of silver acetate (0.856 g, 5.13 mmol) in acetic acid (26 mL) was heated to 205 °C in a sealed tube for 5 h. The reaction mixture was poured into water (70 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with sodium bicarbonate (saturated aqueous solution, 2 × 70 mL), dried ($NaSO_4$), and concentrated to give the crude product. Flash chromatography (20% EtOAc in CH_2Cl_2) gave **9** (0.199 g, 74%) as a colorless foam. This was recrystallized from CH_2Cl_2/hexane: mp 263–264 °C; IR ($CHCl_3$) 2950, 1740, 1690, 1600, 1160 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 8.13 (2 H, d, J = 9 Hz), 6.98–7.24 (6 H, m), 5.40 (1 H, s), 4.21 (1 H, m), 3.87 (3 H, s), 3.60 (1 H, s), 3.25 (1 H, m), 2.84 (1 H, m), 2.57 (1 H, s), 2.49 (1 H, dd, J = 15, 3 Hz), 2.17 (1 H, d, J = 15 Hz), 1.35–2.00 (7 H, m), 1.93 (3 H, s); MS, m/e (EI) 398 (60, M^+ – SO_2Ar), 108 (100). Anal. Calcd for $C_{29}H_{29}ClN_2O_6S$: C, 61.21; H, 5.14; N, 4.92. Found: C, 60.94; H, 5.28; N, 4.92.

A solution of **9** (0.199 g, 0.35 mmol) in THF (35 mL) containing aqueous lithium hydroxide (15 mL, 2.5 M) was heated under reflux for 2.5 h. Upon cooling, the reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried ($NaSO_4$) and concentrated to give **10** as a white foam. This was recrystallized from CH_2Cl_2/MeOH: mp 263–264 °C; IR ($CHCl_3$) 2950, 1685, 1600, 1160 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 8.14 (2 H, d, J = 9 Hz), 7.32 (1 H, d, J = 8 Hz), 7.14–7.22 (2 H, m), 7.06–6.97 (3 H, m), 4.18 (1 H, m), 4.00 (1 H, m), 3.86 (3 H, s), 3.61 (1 H, s), 3.26 (1 H, m), 2.84 (1 H, m), 2.65 (1 H, s), 2.20 (1 H, dd, J = 15, 3 Hz), 2.06 (1 H, d, J = 15 Hz), 1.35–2.02 (8 H, m); MS, m/e (CI, NH_3), 527 (38, M^+ + H), 356 (100). Anal. Calcd for $C_{27}H_{27}ClN_2O_5S$: C, 61.53; H, 5.16; N, 5.32. Found: C, 61.65; H, 5.18; N, 5.50.

1-[(*p*-Methoxyphenyl)sulfonyl]-3-chloro-10,22-dioxokopsane (11). Jones reagent [9.68 g of $Na_2Cr_2O_7 \cdot 2H_2O$ in water (75 mL) and sulfuric acid (25 mL)] (20 mL, 9.3 mmol) was added to a solution of **10** (0.98 g, 1.86 mmol) in acetone (60 mL) and stirred for 2 h. The products were partitioned between water (100 mL) and CH_2Cl_2 (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product. Flash chromatography (20% EtOAc in CH_2Cl_2) gave the ketone as a foam (0.87 g, 89%). This was recrystallized from CH_2Cl_2/hexane: mp 178–180 °C; IR ($CHCl_3$) 2950, 1770, 1690, 1600, 1160 cm^{-1}; NMR ($CDCl_3$, 300 MHz), δ 7.89 (2 H, d, J = 9 Hz), 7.36 (1 H, d, J = 8 Hz), 7.19–7.27 (2 H, m), 7.08 (1 H, m), 6.98 (2 H, d, J = 9 Hz), 4.25 (1 H, m), 3.88 (3 H, s), 3.85 (1 H, d, J = 1.3 Hz), 3.31 (1 H, m), 2.89–3.02 (1 H, m), 2.82 (1 H, s), 2.47 (1 H, dd, J = 16, 3 Hz), 2.17 (1 H, m), 2.06 (1 H, d, J = 16 Hz), 1.25–2.00 (6 H, m); MS, m/e (EI) 524 (38, M^+), 354 (60), 171 (100). Anal. Calcd for $C_{27}H_{25}ClN_2O_5S$: C, 61.76; H, 4.80; N, 5.34. Found: C, 61.54; H, 4.85; N, 5.64.

10-Oxokopsijasmine (14). Sodium hydroxide in MeOH (1.5 M, 10 mL) was added to a stirred solution of **11** (0.5 g, 0.952 mmol) in THF (50 mL) at 0 °C. After 2 h the reaction was acidified with hydrochloric acid (2 M) and partitioned between brine (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), dried (Na_2SO_4), and concentrated to give crude acid **12** (0.5 g).

The crude acid **12** (63 mg, 0.116 mmol) was suspended in DME (10 mL), and DBN (55 μL, 0.44 mmol) was added. The reaction was heated under reflux for 15 h and allowed to cool. The products were partitioned between hydrochloric acid (2 M, 5 mL) and ethyl acetate (7 mL), and the organic phase was dried (Na_2SO_4) and concentrated to give the crude unsaturated acid **13** (60 mg).

Acid **13** (50 mg, 98.9 μmol, used directly from above) was suspended in DME (12 mL) and cooled to –30 °C. Sodium anthracenide (0.5 M in DME) was added dropwise to the reaction mixture until the deep blue color persisted. After the mixture was stirred for 1 h, potassium carbonate (saturated aqueous solution, 10 ml) was added, and the reaction mixture was allowed to warm to ambient temperature. Benzyltriethylammonium chloride (10 mg) was added followed by methyl chloroformate (0.5 mL, excess), and the reaction mixture was stirred vigorously for 4 h. The products were acidified by the addition of hydrochloric acid (2 M) and extracted into EtOAc (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude acid. This was suspended in THF at 0 °C, and CH_2N_2 in diethyl ether was added until the yellow color persisted. Excess CH_2N_2 was destroyed by the addition of acetic acid, and the solvent was removed under reduced pressure. The crude ester was purified by PLC, eluting with 25% EtOAc in CH_2Cl_2 to give the pure ester as a glass (27 mg, 68% from **11**): IR (CH_2Cl_2) 2950, 1720, 1680, 1610 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.40–7.94 (1 H, m), 7.00–7.30 (3 H, m), 3.59 (1 H, s), 4.22 (1 H, m), 3.67–3.94 (2 H, m), 3.79 (3 H, s), 3.77 (3 H, s), 3.63 (1 H, s), 3.10 (1 H, d, J = 19 Hz), 2.79 (1 H, m), 1.98–2.20 (1 H, m), 2.04 (1 H, d, J = 19 Hz), 1.30–1.90 (5 H, m); MS, m/e (CI, NH_3) calcd for $C_{23}H_{24}N_2O_5$ 408.1685, found 408.1672 (59), 38 (100).

Kopsijasmine (1). A solution of BH_3·THF (50 μL, 1 M, excess) was added to **14** (5 mg, 12.2 μmol) in THF (0.2 mL) at ambient temperature. After the mixture was stirred for 16 h, THF (2 ml) and hydrochloric acid (6 M, 1 mL) were added, and the reaction mixture was heated under reflux for 30 min before being cooled. The products were partitioned between EtOAc (5 mL) and sodium hydroxide solution (2 M, 5 mL). The organic layer was dried ($NaSO_4$) and concentrated to give the crude product. This was purified by PLC, eluting with 5% triethylamine in EtOAc to give **1** as a solid (2.5 mg, 52%). This was found to be spectroscopically identical with natural kopsijasmine: mp 162–165 °C; UV (EtOH) λ_{max} (nm) 204 (ϵ 16 700), 239 (7400), 277 (1600), 286 (1300); IR (KBr) 2930, 1710, 1601, 1362 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.4–8.0 (1 H, m), 7.15–7.37 (2 H, m), 7.0–7.1 (1 H, m), 6.85 (1 H, s), 3.68–3.96 (1 H, m), 3.79 (6 H, s), 3.35 (1 H, s), 3.07 (2 H, m), 2.42–2.75 (3 H, m), 2.0–2.14 (1 H, m), 1.2–1.96 (7 H, m); MS, m/e

calcd for $C_{23}H_{26}N_2O_4$ 394.1893, found 394.1904 (100), 379 (35), 335 (73).

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Registry No. (±)-1, 116949-72-5; (±)-3, 84960-68-9; (±)-5 (X = H), 84960-69-0; (±)-5 (X = Cl), 116926-89-7; (±)-6 (X = Cl), 116912-01-7; (±)-7 (X = Cl), 116912-02-8; (±)-8 (X = Cl), 116912-03-9; (±)-9, 116912-04-0; (±)-10, 116912-05-1; (±)-11, 116912-06-2; (±)-12, 116926-90-0; (±)-13, 116912-07-3; (±)-14, 116912-08-4; CH_2=$CClCH_2I$, 39557-31-8.

Supplementary Material Available: Crystal data, fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond distances, and bond angles for 5 (X = H) and 5 (X = Cl) (27 pages). Ordering information is given on any current masthead page.

Conjugate Addition of *N,N*-Dialkylhydroxylamines: Mechanism of O-Alkylation by 1*H*-Pyrrole-2,5-diones

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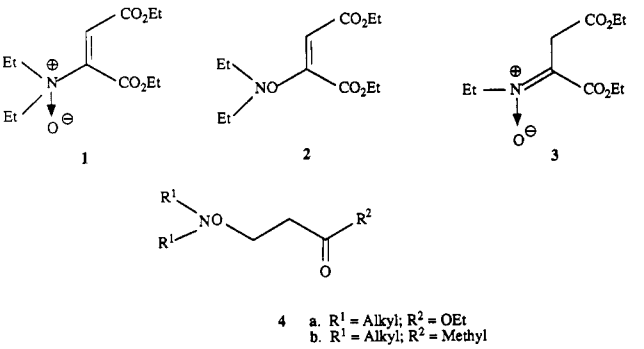
The addition of hydroxylamine to various activated C–C double bonds has been reported in the literature.[1-4] Quite recently, the conjugate addition of *N*-monoalkyl-substituted hydroxylamines to α,β-unsaturated esters was utilized by Baldwin in an elegant synthesis of isoxazolidin-5-ones,[5] which are of pharmacological interest.[6] The conjugate addition of the nitrogen atom of *N*-monoalkylhydroxylamines to the double bonds of pyrroles[7] and pyridones[8] is known.

The addition of *N,N*-dialkylhydroxylamines to acetylenedicarboxylate esters was reported by Winterfeldt and Krohn[9] to give initially the *N*-oxide adduct 1. The *N*-oxide 1, which was isolated in 84% yield, upon standing rearranged to a mixture of the O-alkylation product 2 and the nitrone 3 that were suggested to arise by a Meisenheimer rearrangement[10] and by a Cope elimination reaction[11] followed by hydrogen atom rearrangement, respectively. The suggestion that the conversion of 1 to 2 proceeds by a Meisenheimer rearrangement is surprising because the Meisenheimer rearrangement is facile only when the migrating group is allyl[12] or benzyl,[13] although the migration of neopentyl,[14] homoadamantyl,[15] and aryl[16] have been reported.[17] In contrast, Zinner and co-workers[18] reported that the products of direct O-alkylation 4a–b were obtained in the reaction of *N,N*-dialkylhydroxylamines with the activated C–C double bonds of acrylate esters and vinyl ketones, respectively. As recognized by Zinner,[18b] a mechanism involving the Meisenheimer rearrangement of a *N*-oxide adduct is highly unlikely in these cases because a Cope reaction due to the presence of a β-hydrogen atom is expected.[17] Zinner suggested that the observed products were the result of direct O-alkylation.

In view of both our interest in the addition of nucleophiles to 1*H*-pyrrole-2,5-diones,[19,20] commonly known as maleimides, and the apparent dichotomy reported in the literature, we report in this paper an investigation of the reaction of *N,N*-dialkylhydroxylamines with maleimides.



1 2 3

4 a. R^1 = Alkyl; R^2 = OEt
b. R^1 = Alkyl; R^2 = Methyl

Results and Discussion

The reaction of **5a** with the *N,N*-dialkyl-substituted hydroxylamine **6a** in a tetrahydrofuran (THF) reaction medium with potassium *tert*-butoxide as a basic catalyst led to a complex mixture of products. This result is no doubt attributable to the propensity of **5a** toward base-catalyzed oligomerization.[20-22] The uncatalyzed reaction of **5a** and **6a** in THF at reflux temperature gave **7a** as white crystalline solid (56% recrystallized).

The structure of **7a** rests on the following observations. In the IR spectrum of **7a**, two absorptions were observed at 1790 cm^{-1} (weak) and 1725 cm^{-1} (strong), which result from the asymmetrical and symmetrical C=O stretching modes. In the ^1H NMR spectrum of **7a**, a distinct ABX coupling pattern was observed with $^3J_{AX}$ = 5 Hz, $^3J_{BX}$ =

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(1) (a) Belly, A.; Jacquier, R.; Petrus, F.; Verducci, J. *Bull. Soc. Chim. Fr.* **1972**, 330–336. (b) Belly, A.; Petrus, F.; Verducci, J. *Bull. Soc. Chim. Fr.* **1973**, 1396–1398.
(2) Rice, K. C.; Weiss, U. *Tetrahedron Lett.* **1973**, 1615–1618.
(3) Foutain, K. R.; Erwin, R.; Early, T.; Kehl, H. *Tetrahedron Lett.* **1975**, 3027–3030.
(4) For a review, see: *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1971; pp 1117, 1182–1183, 1240–1241.
(5) Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363–4370.
(6) (a) Stammer, C. H.; Wilson, A. N.; Spencer, C. F.; Bachelor, F. W.; Holly, F. W.; Folkers, K. *J. Am. Chem. Soc.* **1957**, *79*, 3236–3240. (b) Wierenga, W.; Harrison, A. W.; Evans, B. R.; Chidester, C. G. *J. Org. Chem.* **1984**, *49*, 438–442.
(7) Jolles, E. *Gazz. Chim. Ital.* **1938**, *68*, 488–496.
(8) Brown, D. M.; Hewlins, M. J. E. *J. Chem. Soc. C* **1968**, 1922–1924.
(9) Winterfeldt, E.; Krohn, W. *Chem. Ber.* **1969**, *102*, 2336–2345.
(10) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 994.
(11) Reference 10, p 909.
(12) Kleinschmidt, R. F.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 1929–1933.
(13) (a) Schöllkopf, U.; Patsch, M.; Schäfer, H. *Tetrahedron Lett.* **1964**, 2515–2520. (b) Schulman, G. P.; Ellgen, P.; Connor, M. *Can. J. Chem.* **1965**, *43*, 3459–3461. (c) Schöllkopf, U.; Ute, L.; Patsch, M.; Franken, W. *Justus Liebigs Ann. Chem.* **1967**, *703*, 77–89. (d) Lorand, J. P.; Grant, R. W.; Samuel, P. A.; O'Connell, E. M.; Zaro, J.; Pilotte, J.; Wallace, R. W. *J. Org. Chem.* **1973**, *38*, 1813–1821.
(14) Brauman, J. I.; Sanderson, W. A. *Tetrahedron* **1967**, *23*, 37–44.
(15) Adams, B. L.; Kovacic, P. *J. Am. Chem. Soc.* **1974**, *96*, 7014–7018.
(16) For a Meisenheimer-type rearrangement of an aryl group by a polar mechanism, see: Khuthier, A. H.; Ahmed, T. Y.; Jallo, L. I. *J. Chem. Soc., Chem. Commun.* **1976**, 1001–1002.
(17) Reference 10, p 994.
(18) (a) Zinner, G. *Angew. Chem.* **1959**, *71*, 311. (b) Zinner, G.; Ritter, W.; Kliegel, W. *Pharmazie* **1965**, *20*, 291–296.
(19) Pastor, S. D.; Hessell, E. T.; Odorisio, P. A.; Spivack, J. D. *J. Heterocycl. Chem.* **1985**, *22*, 1195–1197.
(20) Pastor, S. D.; Hessell, E. T. *J. Heterocycl. Chem.* **1988**, *25*, 807–811.
(21) Renner, A.; Forgo, I.; Hofmann, W.; Ramsteiner, K. *Helv. Chim. Acta* **1978**, *61*, 1443–1453.
(22) Bryce-Smith, D.; Gilbert, A.; McColl, I. S.; Yianni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 951–952.

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