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Supplementary Material Available: Experimental and spectral data for compounds **7**, **9**, **17a**, **20-exo**, **20-endo**, **24**, **25c**, **30-exo**, **30-endo**, **34**, **54**, **56**, **60a**, **60b**, **61a** (12 pages). Ordering information is given on any current masthead page.

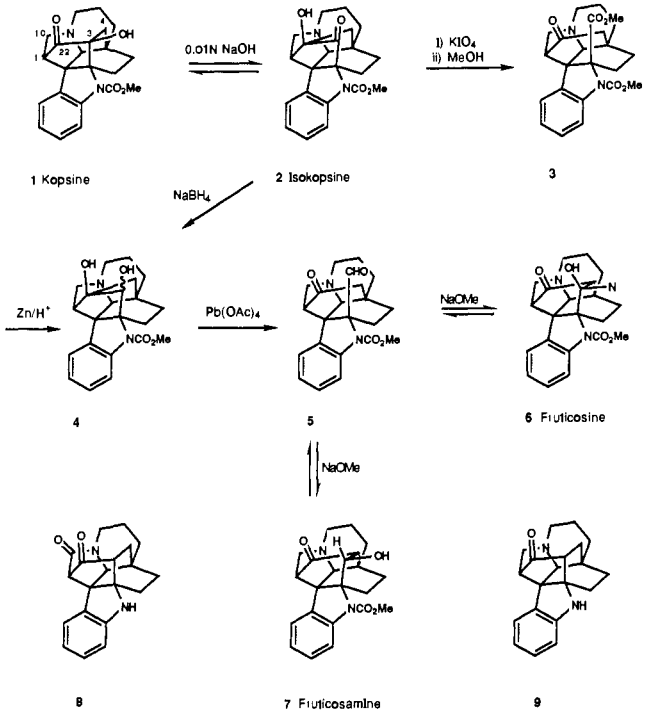
Synthesis of the Heptacyclic Indole Alkaloid (±)-Kopsine and Related Studies

Philip Magnus,*,† Tadashi Katoh,† Ian R. Matthews,† and John C. Huffman‡

Contribution from the Department of Chemistry and the Molecular Structure Center, Indiana University, Bloomington, Indiana 47405. *Received March 17, 1989*

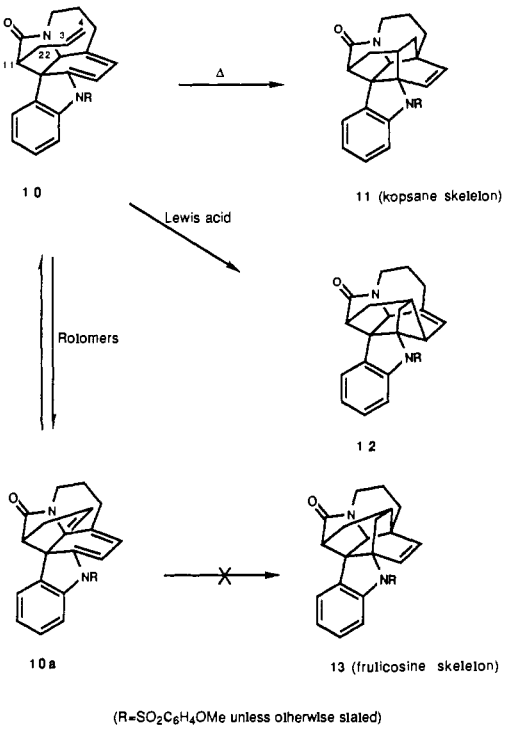
Abstract: The synthesis of the heptacyclic indole alkaloid kopsine (**1**) was achieved by starting with the homoannular diene **14**. Alkylation of the derived anion **15** with allyl bromide gave **16**, which was converted into N^1-[(*p*-methoxyphenyl)-sulfonyl]-10,22-dioxokopsane (**25**) as previously reported. Cleavage of the non-enolizable β-keto amide **25** with sodium hydroxide gave the acid **26**. The (*p*-methoxyphenyl)sulfonyl group was reductively removed and replaced by CO_2Me to give **27**. Reduction of **27** to the primary alcohol **28** followed by conversion to the *o*-nitrophenylselenide and oxidation gave the *exo*-methylene derivative **31**. Osmylation of **31** gave **32**, and Moffatt–Swern oxidation provided the α-hydroxy aldehyde **33**. Treatment of **33** with lithium diisopropylamide in THF at −78 °C gave the aldol product **34**. Diborane reduction of **34** gave the diol **35** after acidic workup. Moffatt–Swern oxidation of **35** gave kopsine (**1**).

Kopsine (**1**) was first isolated in 1890.[1] However, its complex heptacyclic structure was not determined until the early 1960s.[2] For many years, it was thought that **1** was a member of the *Strychnos* family of alkaloids, because of its similar biology.[3] **1** provides a structural correlation and synthetic link with another class of indole alkaloids known as the fruticosanes. In 0.01 N sodium hydroxide, **1** undergoes as α-ketol shift rearrangement to give isokopsine (**2**). Periodate fission of **2** gave **3**, which was



reduced with Zn/H_2SO_4 to give dihydroisokopsine (**4**). Sodium borohydride reduction of isokopsine (**2**) also gave dihydroisokopsine (**4**). Treatment of **4** with lead tetraacetate provided the keto aldehyde **5**, which undergoes aldol condensation leading to fruticosine (**6**) and fruticosamine (**7**) (cf. kopsine ⇌ isokopsine).[4]

Scheme I



(R=$SO_2C_6H_4OMe$ unless otherwise stated)

* Address correspondence to this author at the Department of Chemistry, The University of Texas at Austin, Austin, TX 78712.
† Department of Chemistry.
‡ Molecular Structure Center.

(1) Greshoff, M. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3537.
(2) Kump, C.; Dugan, J. J.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 1237. Govindachari, T. R.; Nagarajan, K.; Schmid, H. *Ibid.* **1963**, *46*, 433. Kump, C.; Schmid, H. *Ibid.* **1962**, *45*, 1090. Structure of kopsine: Govindachari, T. R.; Rai, B. R.; Rajappa, S.; Viswanathan, N.; Kump, W. G.; Nagarajan, K.; Schmid, H. *Ibid.* **1962**, *45*, 1146; **1963**, *46*, 572. For references to the isolation of kopsane alkaloids, see: Bhattacharya, A.; Chatterjee, A.; Rose, P. K. *J. Am. Chem. Soc.* **1949**, *71*, 3370. Bhattacharya, A. *Ibid.* **1953**, *75*, 381. Crow, W. D.; Michael, M. *Aust. J. Chem.* **1955**, *8*, 129. Bisset, N. G.; Crow, W. D.; Greet, Y. *Ibid.* **1958**, *11*, 388. Crow, W. D.; Michael, M. *Ibid.* **1962**, *15*, 130.

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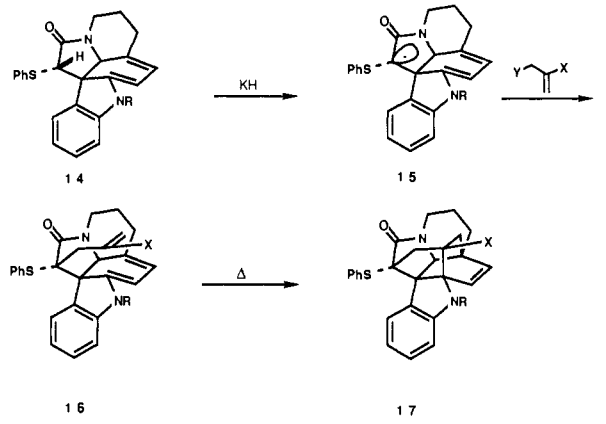
Scheme II



Consequently, kopsine (**1**) occupies a central position in this area of indole alkaloids, since its synthesis would also constitute the total synthesis of isokopsine (**2**), fruticosine (**6**), and fruticosamine (**7**).

While our previous synthetic endeavors in this area have resulted in the total synthesis of (±)-10,22-dioxokopsane (**8**) and (±)-kopsanone (**9**),[5] extension of this work to the more difficult problem of **1** and **6** was not readily apparent. The fruticosane skeletal type cannot be constructed by direct intramolecular Diels–Alder reaction of the homoannular diene **10**, since the preferred (less strained) transition state produces the kopsane system **11**, Scheme I. Attempts to overide the sterically preferred pathway by either substituents placed onto the allyl appendage or Lewis acid catalysis did not produce the fruticosane system **13**, but produced the kopsane skeleton **11** or cyclobutane formation **12**.[6]

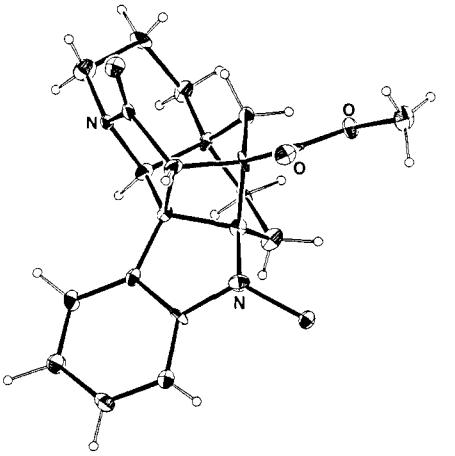
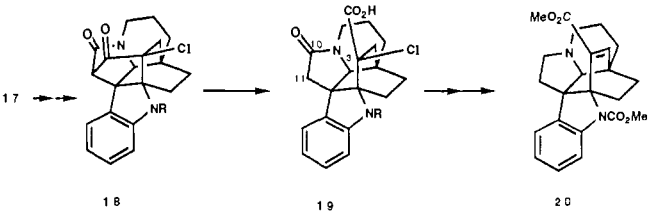


Figure 1. ORTEP representation of **22** (the $SO_2C_6H_4OMe$-*p* group has been deleted for clarity).

Consequently, it was decided to attempt to modify our original strategy to the kopsanes to deal with the problem of compatibility with the C-3 tertiary hydroxy group in **1**. This requires that the key homoannular diene **14** has to be alkylated with a C-2-heterofunctionalized allyl component that can eventually become the crucial C-3 hydroxy group in **1**, Scheme II. The homoannular diene **14** has been made before in the course of our kopsanone synthesis, and its synthesis is briefly outlined in ref 5.

Ideally, X in **16** should be an enol derivative or a synthetic equivalent with the restricting proviso that X in **17** will be a tertiary functional group that cannot undergo S_N1 or S_N2 chemistry. The choices for X are further limited by the fact that alkylation of the anion **15** is severely impeded by the steric bulk of X. For example, treatment of **14** with $KN(SiMe_3)_2$/THF/25 °C followed by addition of $ICH_2C(Br)=CH_2$ resulted in decomposition, whereas addition of $ICH_2C(Cl)=CH_2$ gave **16** (X = Cl) in 92% yield. This is clearly a steric effect of the β-group, albeit situated on a trigonally hybridized carbon, hindering the formation of the pseudopentacoordinate transition state. A number of alkylating agents [X = OMe, $OP(O)(OMe)_2$][7] were tried and were completely unsuccessful. We have recently reported the complete details of the conversion of **17** (X = Cl) into (±)-kopsijasmine (**20**) via the crucial β-keto amide **18** and its seco derivative **19**.[8]

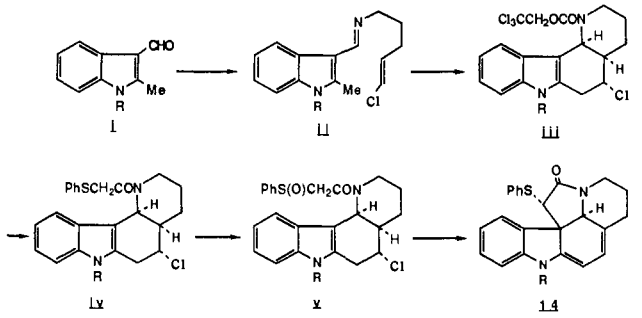


The α-chloro ketone **18** was found to be inert to Ag^1 salts, whereas when **19** was treated with $AgOAc/CH_3NO_2$/20 °C four compounds were isolated; the α,β-unsaturated acid **21** (20%), the cyclobutane adduct **22** (25%) (Figure 1 shows an ORTEP representation), and what we tentatively believe to be the rearranged

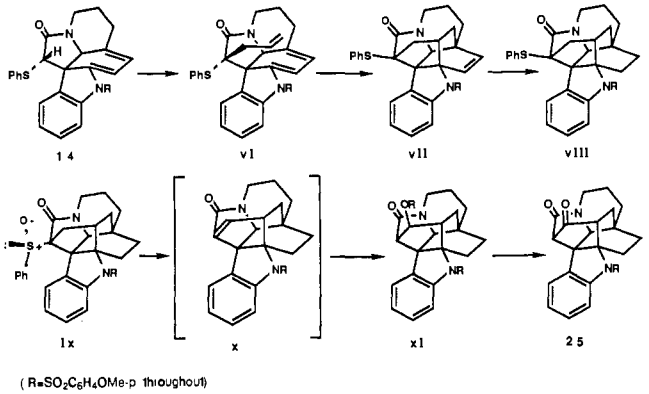
(3) Mukherjee, S. R.; Maiti, A.; Dey, P. K. *Nature (London)* **1957**, *180*, 196. Dey, P. K.; Chatterjee, M.; Chatterjee, A. *Indian J. Physiol. Allied Sci.* **1962**, *16*(3), 99; *Chem. Abstr.* **1962**, *60*, 8515. Bhattacharya, A. *Sci. Cult* **1956**, *22*, 120.

(4) Battersby, A. R.; Byrne, J. C.; Gregory, H.; Popli, S. P. *J. Chem. Soc. C* **1967**, 813. Achenbach, H.; Bieman, K. *J. Am. Chem. Soc.* **1965**, *87*, 4944. Djerassi, C.; Budzikiewicz, H.; Owellen, R. J.; Wilson, J. M.; Kump, W. G.; LeCount, D. J.; Battersby, A. R.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 742. Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Ibid.* **1964**, *47*, 1147. Shumann, D.; Bycroft, B. W.; Schmid, H. *Experientia* **1964**, *20*, 202. Battersby, A. R.; Gregory, H. *J. Chem. Soc.* **1963**, 22. Ferreira, J. M.; Gilbert, B.; Kitagawa, M.; Paes Leme, L. A.; Durham, L. J. *J. Chem. Soc. C* **1966**, 1260. Battersby, A. R.; Byrne, J. C.; Gregory, H.; Popli, S. P. *Chem. Commun.* **1966**, 786. Guggisberg, A.; Hesse, M.; von Philipsborn, W.; Nagarajan, K.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 2321.

(5) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. For parallel studies on kopsane alkaloids, see: Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, *50*, 4790.



The sequence of transformations i through to the homoannular diene **14** is described in detail in the above reference.



(R=$SO_2C_6H_4OMe$-p throughout)

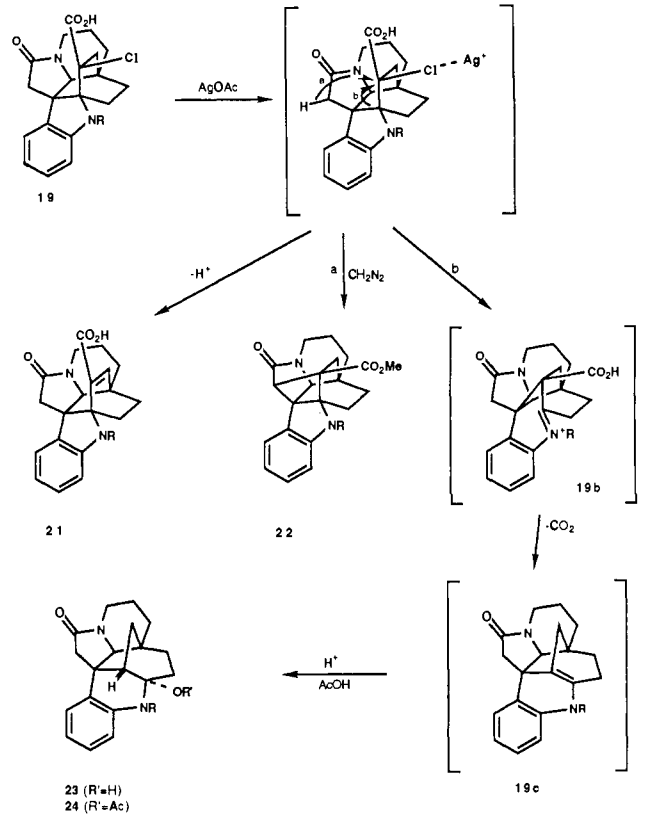
The sequence of **14** through the 10,22-dioxokopsane derivative **25** is described in full detail in the above reference.

(6) Magnus, P.; Schultz, J.; Houk, K. N. *Tetrahedron Lett.* **1986**, *27*, 655.

(7) The anion **15** undergoes slow decomposition at 0–20 °C and as a consequence only reacts efficiently with unhindered allylic halides.

(8) Magnus, P.; Matthews, I. R.; Schultz, J.; Waditschatka, R.; Huffman, J. C. *J. Org. Chem.* **1988**, *53*, 5772.

product **23** (19%) and its derived acetate **24** (10%). The mass

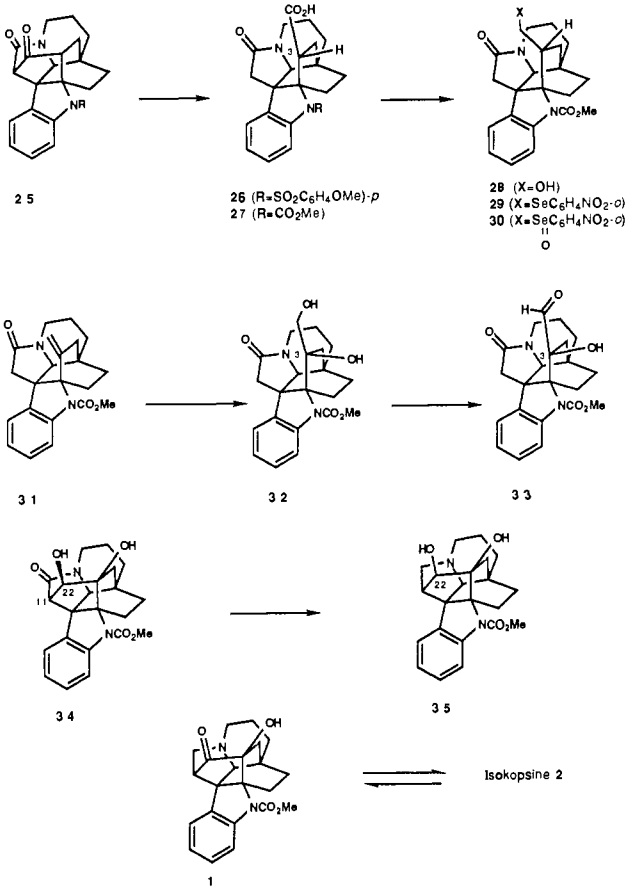


spectrum of **23** indicated that decarboxylation had taken place. The absence of a methine proton in the ^{1}H NMR of **24** in the region δ 5.4 shows that the product is a tertiary acetate. The structural formation **23**/**24** best explains these facts. Decarboxylation of **19b** could give **19c**, which should rapidly protonate to relieve the strain of the bridgehead double bond and hydrate to give **23**/**24**. Unfortunately while **23** was crystalline, the crystals were not suitable for single-crystal X-ray crystallography. Consequently, while we could convert the α-chloro acid **19** into (±)-kopsijasmine (**20**), it was *not* a useful substrate for **1**. We therefore pursued a route to **1** from the 10,22-dioxokopsane derivative **25**. The synthesis of **25** has been described in detail in a previous publication, and this is briefly outlined in ref 5.

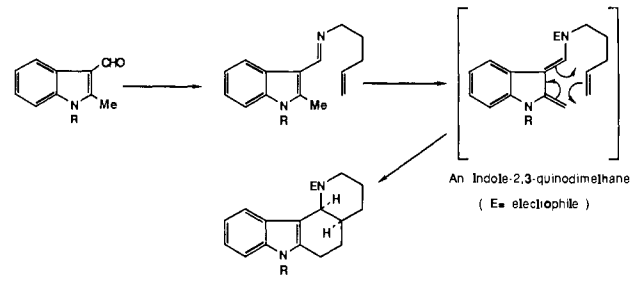
N^1-[(*p*-Methoxyphenyl)sulfonyl]-10,22-dioxokopsane (**25**) was cleaved with aqueous base to give the carboxylic acid **26** (96%). Reductive removal of the $SO_2C_6H_4OMe$-*p* group was achieved by treatment of **26** with sodium naphthalenide followed by workup with $ClCO_2Me$ to give **27** (93%). The carboxylic acid functionality was reduced via the derived mixed anhydride from isobutyryl chloroformate and **27** by treatment with $NaBH_4$ to give the alcohol **28** (87%). Conversion of the alcohol into the *exo*-methylene derivative **31** was best carried out with the Grieco protocol.[9] Treatment of **28** with $NCSeC_6H_4NO_2$-*o*/PBu_3 gave the derived *o*-nitrophenylselenide **29**, which was immediately oxidized with H_2O_2 to give **31** (73%) via the selenoxide **30**. The presence of the *exo*-methylene group was readily revealed from its ^{1}H NMR spectrum, δ 5.14 (1 H, s) and 5.07 (1 H, s).

Osmylation of **31** using the Kelly–Van Rheenen[10] procedure OsO_4 (cat)/*N*-methylmorpholine *N*-oxide (stoichiometric)/*t*-BuOH/THF/H_2O gave the diol **32** (92%). The assignment of its stereochemistry is based upon the reasonable premise that the exo face (less hindered) is the side of the double bond that is preferentially osmylated. Swern–Moffatt oxidation of the diol **32** gave the α-hydroxy aldehyde **33** (95%): ^{1}H NMR δ 9.64 (1 H, s). To confirm the assigned stereochemistry at C-3 and proceed

Scheme III



Scheme IV



toward the synthesis of kopsine (**1**), we treated **33** with LDA/THF at −78 °C to give the diol **34** (91%) as a single stereoisomer. The stereochemistry of the newly formed *sec*-alcohol **34** was readily ascertained from its ^{1}H NMR spectrum. In kopsane derivatives where the C-11 proton and the C-22 proton are trans (dihedral angle ca. 90°) there is no observable vicinal proton–proton coupling. Reduction of the amide carbonyl group in **34** was accomplished by treatment with a large excess of diborane in THF and hydrolytic workup with 5 N HCl in order to decompose the borane hydride complex of **35** to give the diol **35** (37%). Swern–Moffatt oxidation of 35 gave (±)-kopsine (**1**) (78%). Comparison of the synthetic compound **1** with an authentic sample of (−)-kopsine, kindly supplied by Prof. Manfred Hesse (Zurich), confirmed the identity of synthetic (±)-kopsine (Scheme III).

The indole 2,3-quinodimethane strategy,[11] as depicted in Scheme IV, has provided a convenient route to the kopsia indole alkaloids[12] and resulted in the total synthesis of 10,22-dioxokopsane (**8**), kopsanone (**9**), kopsijasmine (**20**), and kopsine (**1**). Since

(9) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(10) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(11) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.
(12) Complete details of the single crystal X-ray structural determination of **22** may be obtained from Dr. John Huffman. Please ask for structure report 87192.

kopsine has been converted into isokopsine (**2**), fruticosine (**6**), and fruticosamine (**7**), this constitutes the synthesis of all of these alkaloids.

Experimental Section

For general experimental protocol, see ref 5. ^{1}H NMR spectra were recorded at 300 MHz for solutions in $CDCl_3$, unless otherwise stated.

1-[(*p*-Methoxyphenyl)sulfonyl]-10-oxokopsinoic Acid (26). NaOH/MeOH (5 M, 11 mL) was added dropwise to a stirred solution of **25**[5] (330 mg, 0.673 mmol) in THF (70 mL) at 25 °C. After 1 h, 10% aqueous HCl (8 mL) was added slowly at 0 °C and the mixture diluted with EtOAc/$CHCl_3$ (3:1, 200 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), and evaporated to give a white solid. Purification by chromatography over silica gel (8 g) eluting with $CHCl_3$/MeOH (97:3) gave **26** (328 mg, 96%), as an amorphous solid. IR ($CHCl_3$) 1730, 1650, and 1600 cm^{-1}. ^{1}H NMR δ 8.22 (2 H, d, J = 9 Hz), 7.12 (1 H, dd, J = 8.2 and 1.0 Hz), 6.90–7.06 (2 H, m), 6.74 (1 H, dd, J = 8.2 and 1.0 Hz), 6.63 (2 H, d, J = 9 Hz), 4.26–4.38 (1 H, m), 4.30 (1 H, d, J = 19.2 Hz, part of AB system for C-10), 3.85 (1 H, t, J = 10.2 Hz), 3.69 (1 H, s), 3.63 (3 H, s), 2.73–2.87 (1 H, m), 2.37 (1 H, d, J = 19.2 Hz), 2.12–2.30 (2 H, m), 2.20–2.08 (9 H, m). HRMS calcd for $C_{27}H_{28}N_2O_6S$ m/e 508.1668; found m/e 508.1667.

1-Carbomethoxy-10-oxokopsinoic Acid (27). A solution of 0.5 M sodium naphthalenide [prepared from sodium (23 mg) and naphthalene (128 mg) in dry 1,2-dimethoxyethane (2 mL)] was added dropwise to a stirred solution of **26** (140 mg, 0.276 mmol) in dry 1,2-dimethoxyethane (25 mL) at −30 °C under N_2. After 1 h, saturated aqueous potassium carbonate solution (28 mL), benzyltriethylammonium chloride (28 mg, 0.123 mmol), and methyl chloroformate (1.4 mL, 18 mmol) were added, and the mixture was stirred at 20 °C for 4 h. The mixture was cooled to 0 °C, 6 M HCl (8 mL) added, and the solution diluted with EtOAc/$CHCl_3$ (3:1, 100 mL). The organic layer was washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a white solid, which was purified by chromatography over silica gel (6 g), eluting with $CHCl_3$/MeOH (9:1) to give **27** (102 mg, 93%) as an amorphous solid. IR ($CHCl_3$) 3400, 1735, and 1680 cm^{-1}. MS calcd for $C_{22}H_{22}N_2O_4$ ($M^+ - H_2O$) m/e 378.1579; found m/e 378.1586. This material was taken into the next stage without further characterization.

1-Carbomethoxy-3-decarbomethoxy-10-oxokopsininecarbinol (28). Triethylamine (0.07 mL 0.502 mmol) was added to a stirred solution of **27** (100 mg 0.253 mmol) in dry THF (20 mL) at 0 °C. After 20 min, isobutyl chloroformate (0.069 mL 0.532 mmol) was added dropwise at 0 °C and the resulting mixture stirred at 0 °C for 1 h. To the above mixture was added 2% aqueous sodium borohydride solution (5 mL, 2.64 mmol) at 0 °C. After 1 h at 20 °C, the mixture was diluted with EtOAc/$CHCl_3$ (3:1, 100 mL), and the resulting solution was washed with aqueous potassium hydrogen sulfate solution, water, and brine and dried (Na_2SO_4). Evaporation in vacuo of the solvent gave a white residue, which was purified by chromatography over silica gel (5 g), eluting with $CHCl_2$/MeOH (98:2) to give **28** (84 mg, 87%) as an amorphous solid. Recrystallization from EtOAc/CH_2Cl_2 gave **28**. Mp 210.5–212 °C. IR ($CHCl_3$) 3400 and 1675 cm^{-1}. ^{1}H NMR δ 7.55–7.69 (1 H, m), 7.22 (1 H, dt, J = 8.2 and 1.0 Hz), 7.13 (1 H, dd, J = 8.2 and 1.0 Hz), 7.05 (1 H, dt, J = 8.2 and 1.0 Hz) 4.27 (1 H, dd, J = 12.5 and 3 Hz), 4.15 (1 H, dd, J = 11.5 and 2.5 Hz), 3.91 (3 H, s), 3.64 (1 H, s), 3.63 (2 H, br s), 2.82–2.96 (1 H, m), 2.72 (1 H, d, J = 19.2 Hz), 2.63–2.82 (1 H, m), 2.10 (1 H, d, J = 19.2 Hz), 1.23–1.94 (10 H, m). MS calcd for $C_{22}H_{26}N_2O_4$ m/e 382.1892; found m/e 382.1893. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.00; H, 6.85; N, 7.32. Found: C, 68.58; H, 6.80; N, 7.20.

exo-Methylene Adduct 31. Tri-*n*-butylphosphine (0.329 mL 1.34 mmol) was added to a stirred solution of **28** (63 mg, 0.165 mmol) and *o*-nitrophenyl selenocyanate (229 mg, 1.32 mmol) in dry THF (6 mL) at 20 °C. After 2 h, 50% H_2O_2 (0.168 mL, 2.47 mmol) was added and the resulting solution stirred at 20 °C for 1 h. The mixture was quenched with water (20 mL), extracted with EtOAc (20 mL), washed with aqueous sodium hydrogen carbonate solution, aqueous potassium hydrogen sulfate solution, and brine, and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a pale-yellow solid, which was purified by chromatography over silica gel (5 g), eluting with hexane/EtOAc (4:1) to give **31** (44 mg, 73%). IR ($CHCl_3$) 1710 and 1675 cm^{-1}. ^{1}H NMR δ 7.76 (1 H, dd, J = 8.2 and 1.0 Hz), 7.23 (1 H, dt, J = 8.2 and 1.0 Hz), 7.19 (1 H, dd, J = 8.2 and 1.0 Hz), 7.06 (1 H, dt, J = 8.2 and 1.0 Hz), 5.14 (1 H, s), 5.07 (1 H, s), 4.16–4.29 (2 H, m), 3.87 (3 H, s), 3.72 (1 H, s), 3.12 (1 H, d, J = 19.2 Hz), 2.78 (1 H, br t, J = 19.8 Hz), 2.57 (1 H, br d, J = 17.9 Hz), 2.30–2.43 (1 H, m), 2.02 (1 H, br d, J = 17.9 Hz), 2.01 (1 H, d, J = 19.2 Hz), 1.22–1.76 (6 H, m). MS calcd for $C_{22}H_{24}N_2O_3$ m/e 364.1787; found m/e 346.1758.

1-Carbomethoxy-3-decarbomethoxy-10-oxo-3-hydroxykopsininecarbinol (32). Osmium tetraoxide (2.8 mg, 0.011 mmol) in THF (0.5 mL) was added to a stirred solution of **31** (40 mg, 0.11 mmol) in *tert*-butyl alcohol/THF/water (10:8:1, 2.7 mL) containing *N*-methylmorpholine *N*-oxide (64 mg, 0.546 mmol) at 25 °C. After the mixture was stirred for 10 h, saturated aqueous sodium hydrogen sulfide solution (1.5 mL) was added and the mixture stirred for 20 min and diluted with ethyl acetate (50 mL). The organic layer was washed with water and brine and dried (Na_2SO_4). Evaporation under reduced pressure gave a white solid, which was purified by chromatography over silica gel (3.0 g), eluting with chloroform containing 1% MeOH to give **32** (40 mg, 92%). Mp 239–241 °C (from EtOAc/hexane). IR ($CHCl_3$) 3350 and 1680 cm^{-1}. ^{1}H NMR δ 7.54 (1 H, d, J = 8.2 Hz), 7.22 (1 H, t, J = 8.2 Hz), 7.17 (1 H, d, J = 8.2 Hz), 7.09 (1 H, t, J = 8.2 Hz), 5.88 (1 H, s), 4.28 (1 H, dd, J = 12.4 and 3.8 Hz), 3.96 (3 H, s), 3.91 (1 H, s), 3.67 (1 H, s), 3.21 (1 H, d, J = 19.3 Hz), 2.78 (1 H, dt, J = 12.4 and 3.8 Hz), 2.50–2.60 (1 H, m), 2.13 (1 H, d, J = 19.3 Hz), 1.97–2.27 (3 H, m), 1.18–1.82 (8 H, m). MS calcd for $C_{22}H_{26}N_2O_5$ m/e 398.1842; found m/e 398.1836. Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.21; H, 6.50; N, 6.96.

1-Carbomethoxy-10-oxo-3-hydroxykopsinine Carboxaldehyde (33). Dimethyl sulfoxide (0.13 mL, 1.83 mmol) in dry dichloromethane (0.7 mL) was added dropwise to a stirred solution of oxalyl chloride (0.08 mL, 0.917 mmol) in dry dichloromethane (1 mL) at −60 °C. After 10 min, a solution of **32** (36 mg, 0.09 mmol) in dry dichloromethane (1 mL) was added slowly, and the resulting mixture was kept at −60 °C for 15 min. Triethylamine (0.7 mL, 5.02 mmol) was added to the above mixture, and after 5 min, water (1 mL) was added and the solution warmed to room temperature and diluted with ethyl acetate (50 mL). The solution was washed with aqueous potassium hydrogen sulfate solution, aqueous sodium hydrogen carbonate solution, and brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a white solid, which was purified by chromatography over silica gel (3 g), eluting with chloroform/1% methanol to give **33** (34 mg, 95%). Mp 245.5–247 °C (from MeOH). IR ($CHCl_3$) 3350, 1730, and 1675 cm^{-1}. ^{1}H NMR δ 9.64 (1 H, s), 7.55 (1 H, d, J = 8.2 Hz), 7.23 (1 H, t, J = 8.2 Hz), 7.17 (1 H, d, J = 8.2 Hz), 7.09 (1 H, t, J = 8.2 Hz), 6.61 (1 H, s), 4.28 (1 H, dd, J = 12.4 and 3.8 Hz), 3.97 (3 H, s), 3.64 (1 H, d, J = 1 Hz), 3.06 (1 H, d, J = 19.3 Hz), 2.78 (1 H, dt, J = 12.4 and 3.8 Hz), 2.90 (1 H, d, J = 15.3 Hz), 2.00–2.26 (2 H, m), 1.98 (1 H, d, J = 19.3 Hz), 1.2–1.84 (7 H, m). MS calcd for $C_{22}H_{24}N_2O_5$ m/e 396.1685; found m/e 396.1676. Anal. Calcd for $C_{22}H_{24}N_2O_5$; C, 66.65; H, 6.10; N, 7.07. Found: C, 66.47; H, 5.91; N, 6.96.

10-Oxo-22-dihydrokopsine (34). A solution of **33** (32 mg, 80.8 μmol) in dry THF (1.2 mL) was added dropwise to a stirred solution of lithium diisopropylamide (0.828 μmol) in dry THF (2.3 mL) at −78 °C under N_2, and the mixture was stirred for 1 h at −78 °C. The above mixture was quenched with 30% aqueous acetic acid (1 mL) at −23 °C and the solution extracted with ethyl acetate (20 mL). The extract was washed with aqueous sodium hydrogen carbonate solution and brine and dried (Na_2SO_4). Evaporation gave a pale-yellow solid, which was purified by chromatography over silica gel (2 g), eluting with chloroform/2% methanol to give **34** (29 mg, 91%). Mp 236–238 °C (from EtOAc/hexane). IR ($CHCl_3$) 3300 and 1675 cm^{-1}. ^{1}H NMR δ 7.62 (1 H, d, J = 8.2 Hz), 7.17–7.27 (2 H, m), 7.12 (1 H, t, J = 8.2 Hz), 4.47 (1 H, t, J = 10.7 Hz), 4.12 (1 H, dd, J = 12.4 and 3.8 Hz), 3.96 (3 H, s), 3.57 (1 H, d, J = 1 Hz), 3.17 (1 H, br s), 2.85 (1 H, dt, J = 12.4 and 3.8 Hz), 2.61 (1 H, d, J = 10.7 Hz), 2.52–2.78 (2 H, m), 1.20–2.00 (9 H, m). MS calcd for $C_{22}H_{24}N_2O_5$ m/e 396.1685; found m/e 396.1687. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.62; H, 6.06; N, 6.95.

22-Dihydrokopsine (35). BH_3·THF complex (1.0 M, 0.625 mL, 0.625 mmol) was added dropwise to a stirred solution of **34** (5 mg, 12.5 μmol) in dry THF (0.38 mL) at 25 °C under N_2. After 40 min at 25 °C, the mixture was diluted with THF (2 mL)/5 M HCl (1 mL) and the solution warmed to 60 °C for 30 min. After cooling, the mixture was diluted with ethyl acetate (30 mL) and the organic layer washed with aqueous sodium hydrogen carbonate solution and brine and dried (Na_2SO_4). Evaporation of the solvent gave a white solid, which was purified by chromatography over silica gel (1 g), eluting with chloroform/10% methanol to give **35** (1.8 mg, 37%) as a colorless amorphous powder. IR ($CHCl_3$) 3300 and 1675 cm^{-1}. ^{1}H NMR δ 7.55 (1 H, d, J = 8.2 Hz), 7.32–7.47 (1 H, m), 7.18 (1 H, t, J = 8.2 Hz), 7.08 (1 H, t, J = 8.2 Hz), 4.22 (1 H, d, J = 10 Hz), 3.94 (3 H, s), 3.66 (1 H, d, J = 4.7 Hz), 3.48 (1 H, dd, J = 11.3 and 4.7 Hz), 3.10 (1 H, s), 3.92–3.08 (2 H, m), 2.87 (1 H, dd, J = 16.7 and 4 Hz), 2.40–2.60 (2 H, m), 1.10–2.20 (10 H, m). MS calcd for $C_{22}H_{26}N_2O_4$ m/e 382.1893; found: m/e 382.1898.

(±)-Kopsine (1). The same procedure as for **32** was applied to **35** (1.8 mg, 1.8 μmol) to give **1** (1.4 mg, 78%) as colorless prisms. Mp 192–195 °C (dec) (MeOH). IR ($CHCl_3$) 3250, 1755, and 1675 cm^{-1}. ^{1}H NMR δ 7.56 (1 H, d, J = 8.2 Hz), 7.41 (1 H, d, J = 8.2 Hz), 7.25 (1 H, t, J = 8.2 Hz), 7.10 (1 H, d, J = 8.2 Hz), 3.93 (3 H, s), 3.51 (1 H, t, J =

9.4 Hz), 3.33 (1 H, s), 3.15 (1 H, dd, J = 9.4 and 4.4 Hz), 2.94-3.12 (2 H, m), 3.33-2.67 (3 H, m), 1.70-1.92 (1 H, m), 1.10-1.72 (8 H, m). MS calcd for $C_{22}H_{24}N_2O_4$ m/e 380.1736; found m/e 380.1737. It was identical in all respects except rotation and melting point with a sample of (-)-kopsine, which was kindly supplied by Prof. Manfred Hesse (Zurich).

Treatment of the α-Chloro Acid 19 with AgOAc. A suspension of **19**[8] (49 mg, 0.09 mmol) and AgOAc (50 mg, 0.3 mmol) in nitromethane (4 mL) was stirred at 25 °C in the dark for 24 h. The mixture was partitioned between dichloromethane (10 mL)/water (10 mL), and the organic layer was separated and dried (Na_2SO_4). The products were separated by PLC, eluting with EtOAc/CH_2Cl_2 (3:1) to give **23** (9.1 mg, 19%) and **24** (5 mg, 10%). The base-line material was treated with diazomethane in ether/THF (3 mL, 1:1) to give two compounds, which were separated by PLC, eluting with EtOAc/CH_2Cl_2 (1:3) to give the cyclobutane derivative **22** (11.4 mg, 25%) and the α,β-unsaturated ester **21** (9.1 mg, 20%). **22** was recrystallized from $CHCl_3$/pentane to give colorless cubes, mp 250-252 °C (dec) suitable for single-crystal X-ray structure determination. IR (CH_2Cl_2) 2920, 1730, 1694, 1599, and 1150 cm^{-1}. ^1H NMR δ 8.10 (2 H, d, J = 9 Hz), 6.82-7.16 (4 H, m), 6.99 (2 H, d, J = 9 Hz), 4.12-4.22 (1 H, m), 3.86 (3 H, s), 3.78 (1 H, s), 3.75 (3 H, s), 3.55 (1 H, s), 2.97 (1 H, dt, J = 13 and 4 Hz), 2.66-2.82 (1 H, m), 2.35 (1 H, d, J = 13.9 Hz), 2.17 (1 H, dd, J = 13.9 and 3 Hz), 1.83-2.02 (1 H, m), 1.1-1.8 (6 H, m). **23**: IR (CH_2Cl_2) 3540, 2940, 1680, and 1600 cm^{-1}. ^1H NMR δ 7.9 (2 H, d, J = 9 Hz), 7.1-7.2 (2 H, m), 6.94-7.02 (1 H, m), 6.92 (2 H, d, J = 9 Hz), 4.33 (1 H, s), 4.18-4.26 (1 H, m), 3.83 (3 H, s), 3.59 (1 H, s), 3.15 (1 H, d, J = 17 Hz), 2.88-2.98 (1 H, m), 2.60-2.76 (1 H, m), 2.28 (1 H, m), 1.85 (1 H, d, J = 17 Hz), 1.0-2.0 (10 H, m). MS calcd for $C_{26}H_{28}N_2O_5S$ m/e 480.1719; found m/e (EI) 480.1706. **24** IR (CH_2Cl_2) 2940 (m), 1750 (m), 1680 (s), and 1594 (m) cm^{-1}. ^1H NMR 7.84 (2 H, d, J = 9 Hz), 7.49 (1 H, d, J = 8 Hz), 6.96-7.21 (3 H, m), 6.86 (2 H, d, J = 9 Hz), 4.10-4.20 (1 H, m), 3.83 (3 H, s), 3.59-3.63 (1 H, m), 3.55 (1 H, s), 3.22 (1 H, d, J = 17.8 Hz), 2.61-2.78 (1 H, m), 1.98-2.12 (2 H, m), 1.77 (3 H, s), 1.67 (3 H, s), 1.1-1.9 (4 H, m). MS (EI m/e 463 (67), 292 (98), 171 (100).

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Supplementary Material Available: Crystal data, fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond distances, and bond angles for **22** (10 pages). Ordering information is given on any current masthead page.

Solution Homolytic Bond Dissociation Energies of Organotransition-Metal Hydrides

Mats Tilset*,[1a] and Vernon D. Parker*,[1b]

Contribution from the Department of Chemistry, University of Oslo, P.O. Box 1033 Blindern, N-0315 Oslo 3, Norway, and the Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300. *Received August 4, 1988. Revised Manuscript Received April 8, 1989*

Abstract: The homolytic bond dissocation energies (BDEs) of the mononuclear metal carbonyl hydride complexes (η^5-C_5H_5)$M(CO)_3H$ (M = Cr, Mo, W), (η^5-C_5Me_5)$Mo(CO)_3H$, (η^5-C_5H_5)$W(CO)_2(PMe_3)H$, (η^5-C_5H_5)$M(CO)_2H$ (M = Fe, Ru), $H_2Fe(CO)_4$, $Mn(CO)_4PPh_3H$, $Mn(CO)_5H$, $Re(CO)_5H$, and $Co(CO)_3LH$ (L = CO, PPh_3, $P(OPh)_3$) have been estimated in acetonitrile solution by the use of a thermochemical cycle that requires knowledge of the metal hydride pK_a and the oxidation potential of its conjugate base (anion). The BDE values obtained by this method fall in the range 50-67 kcal/mol. In most cases, these results agree well with literature data. Our data provide strong support for the common assumption that the M-H bond energies are greater for third-row and for second-row metals than for first-row metals, the difference being 5-11 kcal/mol. Effects of neither phosphine or phosphite substitution nor permethylation of the cyclopentadienyl ring on the M-H bond energies could be detected within the error limits of the method. The results are discussed in relation to previous M-H BDE estimates and metal hydride reactivity patterns.

Organotransition-metal hydride (M-H) complexes constitute an important class of compounds and have received considerable attention particularly because of their involvement in many stoichiometric and catalytic processes.[2] It is clear that the M-H bond strengths exert a major influence on the properties of metal hydride compounds, and a detailed knowledge of the factors that determine the M-H bond strengths would greatly aid in understanding reactivity patterns in many processes.[3] For example, the activation of alkane carbon-hydrogen bonds by coordinatively unsaturated transition-metal complexes is a process that is being vigorously pursued.[4] The formation of M-H and M-C bonds

Scheme I

	energy change	
$L_nM-H \rightarrow L_nM^{\bullet} + H^{\bullet}$	BDE	(1)
$L_nM-H \rightarrow L_nM^{-} + H^{+}$	BDE - EA($L_nM^{\bullet}$) + IP($H^{\bullet}$)	(2)
$L_nM-H \rightarrow L_nM^{+} + H^{-}$	BDE + IP($L_nM^{\bullet}$) - EA($H^{\bullet}$)	(3)

provides the driving force for such reactions, and the sum of the M-H and M-C bond dissociation energies must be on the order of 110 kcal/mol for the reaction to be thermodynamically feasible.[5]

Three modes of cleavage of M-H bonds have been envisaged, as shown in Scheme I.[2a] The first reaction is a homolytic cleavage reaction for which the energy change is given by the homolytic bond dissociation energy (BDE) of the M-H bond. In reaction

(1) (a) University of Oslo. (b) Utah State University.

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