SiO_2 using a mixture of hexane–ether (95:5) as an eluent to give the (*R*)-olefin **43** (36.8 mg, 42% yield).

Hydrogen gas was bubbled into a mixture of the (*R*)-olefin **43** (151 mg, 536 μmol) and palladium on charcoal (5%, 83.6 mg, 42 μmol) in ethanol (1 mL), and the mixture was stirred for 16 h at room temperature. The solution was passed through Celite and concentrated. The residue was dissolved in acetone (5 mL). A catalytic amount of *p*-toluenesulfonic acid was added to the solution, and the mixture was stirred for 4 h at room temperature. Potassium carbonate was added to the solution, and the mixture was filtered. The filtrate was concentrated, and the residue was chromatographed on SiO_2 using a mixture of hexane–ether (from 98:2 to 95:5) as an eluent to give (*S*)-(−)-**36** (104 mg, 99% yield): $[\alpha]^{24}_D = -0.56°$ (*c* 3.6, EtOH);[34] IR (neat) 2950, 1720, 1465, 1365, 1165, 790 cm^{-1}.

(*Z*)-(5*S*,6*S*)-2,2-(2,2-Dimethylpropylenedioxy)-5,6-epoxy-6,10-dimethyl-7-undecene (44). According to a similar procedure for the preparation of **27**, reaction of **38** with isoamyltriphenylphosphonium iodide in THF gave **44** in 52% yield from **37**: $[\alpha]^{23}_D = +26.5°$ (*c* 5.7, $CHCl_3$); IR (neat) 2960 (s), 2875 (m), 1465 (m), 1370 (m), 1250 (m), 1215 (m), 1100 (s), 865 (m), 730 (w) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.76–5.13 (m, 2 H), 5.56 (d, *J* = 11.6 Hz, 2 H), 3.43 (d, *J* = 11.6 Hz, 2 H), 1.39 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 131.0 (d), 130.7 (d), 98.3 (s), 70.3 (t), 64.2 (d), 59.1 (s), 37.4 (t), 34.9 (t), 29.8 (s), 28.5 (d), 22.9 (q), 22.8 (q), 22.4 (q), 20.2 (q), 18.2 (q).

(*E*)-(5*S*,6*R*)-2,2-(2,2-Dimethylpropylenedioxy)-5-hydroxy-6,10-dimethyl-7-undecene (45). According to the general procedure, hydrogenolysis of **44** gave **45** (89% yield): $[\alpha]^{23}_D = +6.0°$ (*c* 1.5, $CHCl_3$); IR (neat) 3430 (s), 2950 (s), 1720 (m), 1460 (s), 1370 (s), 1090 (s), 970 (m), 850 (m) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.34–5.10 (m, 2 H), 3.34 (b s, 4 H), 1.24 (s, 3 H), 0.96 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 132.9 (d), 130.7 (d), 98.9 (s), 75.1 (d), 70.2 (t), 43.3 (d), 42.0 (t), 34.6 (t), 29.8 (s), 28.4 (d), 27.9 (t), 22.8 (q), 22.5 (q), 22.3 (q), 20.2 (q), 16.9 (q).

(*R*)-(+)-6,10-Dimethylundecan-2-one (36) from 45. To a solution of **45** (290 mg, 0.97 mmol) and Et_3N (202 μL, 1.46 mmol) in CH_2Cl_2 (15 mL) was added methanesulfonyl chloride (82.5 μL, 1.1 mmol) at −20 °C over 15 min. The mixture was stirred for 30 min. The usual workup gave the crude sulfonate, which was used in the next step without purification.

To the solution of the crude sulfonate in ether (5 mL) was added $LiAlH_4$ (18.4 mg, 0.48 mmol) at room temperature over 5 min and the mixture was stirred for 16 h. Dilute hydrochloric acid (3 N) was added to the solution, and the organic layer was extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on SiO_2 using a mixture of hexane–ether (95:5) as an eluent to give the (*S*)-olefin **43** (157 mg, 61% yield): $[\alpha]^{22}_D = +6.85°$ (*c* 2.6, EtOH).

Similar to (*R*)-**43**, hydrogenation of (*S*)-olefin **43** (157 mg), followed by removal of the acetal group, gave (*R*)-(+)-**36** (108 mg, 99% yield): $[\alpha]^{22}_D = +0.59°$ (*c* 3.3, EtOH); ^1H NMR (60 MHz, CCl_4) 2.41 (t, *J* = 6.4 Hz, 2 H), 2.12 (s, 3 H), 0.87 (d, *J* = 5.8 Hz, 6 H); ^{13}C NMR δ 208.4, 44.0, 39.3, 37.1, 36.6, 32.7, 29.7, 28.0, 24.8, 22.7, 22.6, 21.5, 19.6.

General Procedure for the Palladium-Catalyzed Reaction of 10 with Formic Acid Using Various Ligands and Solvents (Tables I and II). A mixture of $Pd_2(dba)_3CHCl_3$ (26 mg, 0.025 mmol) and phosphine or phosphite in solvent (5 mL) was stirred for 5 min. A solution of formic acid (0.19 mL, 5.0 mmol) and Et_3N (0.28 mL, 2.0 mmol) in solvent (2 mL) was added to the mixture, and the mixture was stirred for 5 min. The oxirane **10** (232 mg, 1.0 mmol) in solvent (3 mL) was added, and the mixture was stirred at room temperature. The reaction was monitored by TLC. After the reaction was completed, water (10 mL) was added to the solution, and the aqueous phase was extracted with ether. The organic extract was washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl, and brine, dried over $MgSO_4$, and concentrated. The crude residue was analyzed by gas chromatography. The products **11**, **46**, and **49–51** were separated by column chromatography on SiO_2 using hexane–ether. Physical and analytical data of the products are as follows.

Ethyl (*E*)-5-hydroxy-4-methyl-5-phenyl-3-pentenoate (**46**): TLC R_f 0.42 (hexane–ethyl acetate, 2:1); IR (neat) 3420 (s), 2975 (s), 1720 (s), 1490 (m), 1445 (m), 1370 (s), 1180 (s), 1020 (s), 750 (m), 700 (s) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.18 (s, 5 H), 5.71 (t, *J* = 8.0 Hz, 1 H), 5.03 (s, 1 H), 4.05 (q, *J* = 7.0 Hz, 2 H), 3.22 (s, 1 H), 3.00 (d, *J* = 8.0 Hz, 2 H), 1.42 (s, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 171.9 (s), 141.9 (s), 140.6 (s), 128.1 (d), 127.2 (d), 126.2 (d), 117.8 (d), 78.6 (d), 60.6 (t), 33.3 (t), 14.2 (q), 12.3 (q). High-resolution mass spectrum for $C_{14}H_{18}O_3$, calcd *m/z* 234.1256, found *m/z* 234.1263.

Ethyl (*E*)-5-hydroxy-4-methylene-5-phenyl-2-pentenoate (**49**): TLC R_f 0.44 (hexane–ethyl acetate, 2:1); IR (neat) 3420 (s), 2950 (m), 1700 (s), 1620 (m), 1440 (m), 1355 (m), 1300 (s), 1260 (s), 1165 (s), 1020 (s), 970 (m), 910 (w), 855 (m), 750 (m), 690 (s) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.20 (s, 5 H), 7.15 (d, *J* = 7.0 Hz, 1 H), 5.76 (d, *J* = 7.0 Hz, 1 H), 5.59 (s, 1 H), 5.50 (s, 1 H), 5.28 (s, 1 H), 3.98 (q, *J* = 8.0 Hz, 2 H), 3.46 (s, 1 H), 1.22 (t, *J* = 8.0 Hz, 3 H). High-resolution mass spectrum for $C_{14}H_{16}O_3$, calcd *m/z* 232.1100, found *m/z* 232.1066.

Ethyl (*E*)-4-methyl-5-oxo-5-phenyl-3-pentenoate (**50**): TLC R_f 0.58 (hexane–ethyl acetate, 2:1); IR (neat) 1750 (s), 1665 (s), 1470 (m), 1390 (m), 1290 (s), 1200 (s), 1050 (m), 730 (s) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.70–7.20 (m, 5 H), 6.23 (t, *J* = 7.0 Hz, 1 H), 4.07 (q, *J* = 7.0 Hz, 2 H), 3.16 (d, *J* = 7.0 Hz, 2 H), 1.91 (s, 3 H), 1.23 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 197.8 (s), 170.0 (s), 138.4 (s), 137.7 (s), 135.6 (d), 131.5 (d), 129.3 (d), 127.9 (d), 60.9 (t), 34.3 (t), 14.1 (q), 12.8 (q). High-resolution mass spectrum for $C_{14}H_{16}O_3$, calcd *m/z* 232.1100, found *m/z* 232.1093.

Ethyl (*E*)-4-(formyloxy)-5-hydroxy-4-methyl-5-phenyl-2-pentenoate (**51**): TLC R_f 0.37 (hexane–ethyl acetate, 2:1); IR (neat) 3450 (s), 2975 (m), 1710 (s), 1450 (m), 1370 (m), 1300 (s), 1160 (s), 1030 (m), 990 (m), 870 (w), 760 (w), 700 (m) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.92 (s, 1 H), 7.20 (s, 5 H), 6.88 (d, *J* = 16.0 Hz, 1 H), 5.94 (d, *J* = 16.0 Hz, 1 H), 5.68 (s, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 3.10 (s, 1 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.22 (s, 3 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 166.0 (s), 159.5 (d), 150.5 (d), 135.0 (s), 128.6 (d), 128.1 (d), 79.9 (d), 74.5 (s), 60.5 (t), 24.2 (q), 14.1 (q).

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Total Synthesis of the Highly Oxygenated Quassinoid (±)-Klaineanone

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Abstract: The total synthesis of klaineanone (**1**), isolated from the seeds of *Hannoa klaineana*, is described in racemic form. The synthesis commences with the tetracyclic ketone **6**, which is transformed into tetracyclic olefinic lactone **23**, which possesses the correct configuration at C(9). Incorporation of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit into tetracyclic olefinic lactone **23**, which features a Rubottom epoxidation of silyloxy diene **35** followed by a base-catalyzed tautomerism of the resultant hydroxy ketone **36**, provides tetracyclic olefin **37**. Epoxidation of the C(11), C(12) olefin in tetracyclic compound **37** and subsequent acid-catalyzed ring opening affords *dl*-klaineanone.

The highly oxygenated carbon skeleton of quassinoids[2] coupled with their complex stereochemical arrangement of carbon atoms continues to present a formidable synthetic challenge to the organic chemist despite the advances made during the past 15 years.[3] One

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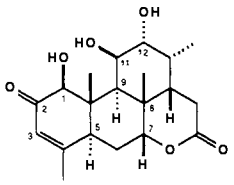
of the characteristic features common to many naturally occurring quassinoids is the presence in ring A of a 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit bearing a methyl group at C(4) [cf. klaineanone (**1**)[4] and quassimarin (**2**)[5]]. This structural fragment appears to be



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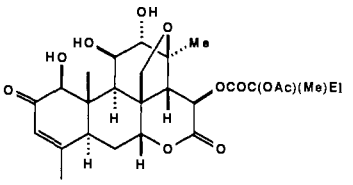

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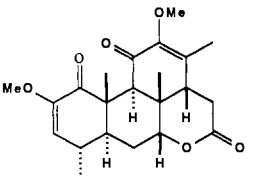
essential for the wide spectrum of pharmacological properties including in vivo antineoplastic, antiviral, antimalarial, antifeedant, amoebicidal, and insecticidal activity associated with quassinoids.[6] Since the report in the literature dealing with the total synthesis of quassin (**3**) in 1980,[7] there has been a plethora of publications[3] dealing with studies directed toward the synthesis of quassinoids. However, success at total synthesis has been recorded in the literature on only two additional occasions [cf. castelanolide (**4**)[8] and amarolide (**5**)[9]]. The lack of significant synthetic progress



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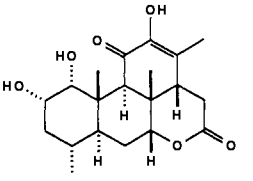

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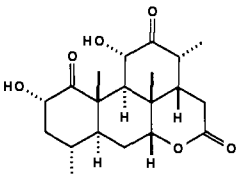

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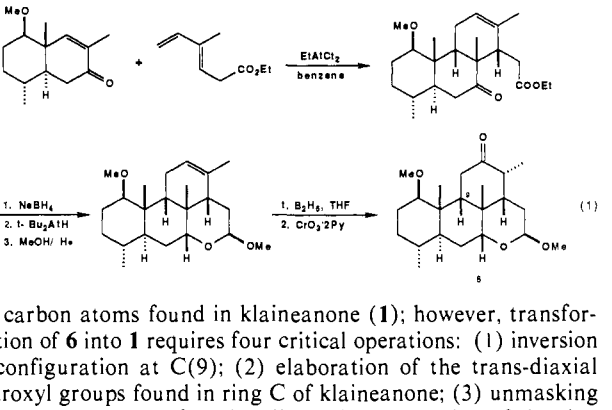
(cf. **1** and **2**) has been in large part due to problems associated with elaboration of the ring A functionality.[10] We detail here the first total synthesis of the highly oxygenated quassinoid (±)-klaineanone (**1**), which possesses the 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality in ring A.[11] The total synthesis of **1** confirms the structural assignment put forth by Polonsky and Bourguignon-Zybler for klaineanone over a quarter of a century ago.[4] Since that time, the structure of **1** has rested on limited spectroscopic data and its conversion into quassin.

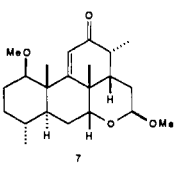
A logical starting point for the synthesis of klaineanone was the picrasane derivative **6**, which was prepared previously in connection with the total synthesis of *dl*-quassin.[7] Ketone **6** had been synthesized via a six-step sequence commencing with a Diels–Alder reaction (eq 1). Tetracyclic ketone **6** possesses all



(1)

the carbon atoms found in klaineanone (**1**); however, transformation of **6** into **1** requires four critical operations: (1) inversion of configuration at C(9); (2) elaboration of the trans-diaxial hydroxyl groups found in ring C of klaineanone; (3) unmasking the ring D δ-lactone functionality; (4) construction of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality.

Our preliminary efforts focused on inverting the configuration at C(9) by transforming tetracyclic ketone **6** into the corresponding tetracyclic enone **7**. While it was anticipated that metal–ammonia



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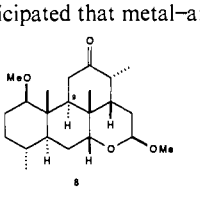

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(1) Procter and Gamble Predoctoral Fellow, 1987–1988.

(2) For an excellent review on quassinoids, see: Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 22.

(3) (a) Stojanac, N.; Sood, A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1975**, *53*, 619. (b) Koch, H. J.; Pfenninger, H.; Graf, W. *Helv. Chim. Acta* **1975**, *58*, 1727. (c) Dias, J. R.; Ramachandra, R. *Tetrahedron Lett.* **1976**, 3685. (d) Dias, J. R.; Ramachandra, R. *J. Org. Chem.* **1977**, *42*, 1613. (e) Dias, J. R.; Ramachandra, R. *Ibid.* **1977**, *7*, 293. (f) Dias, J. R.; Ramachandra, R. *Ibid.* **1977**, *42*, 3584. (g) Snitman, D. L.; Tsai, M.-Y.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 195. (h) Stojanac, N.; Stojanac, Z.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3346. (i) Daily, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (j) Kraus, G. A.; Taschner, M. J. *Ibid.* **1980**, *45*, 1175. (k) Grieco, P. A.; Vidari, G.; Ferrino, S.; Haltiwanger, R. C. *Tetrahedron Lett.* **1980**, 1619. (l) Pfenninger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1562. (m) Okano, M.; Lee, K.-H., *J. Org. Chem.* **1981**, *46*, 1138. (n) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. (o) Kraus, G. A.; Taschner, M.; Shimagaki, M. *J. Org. Chem.* **1982**, *47*, 4271. (p) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J.-Y. *Ibid.* **1981**, *47*, 601. (q) Mandell, L.; Lee, D. E. Courtney, L. F. *Ibid.* **1982**, *47*, 610. (r) Fukumoto, K.; Chihiro, M.; Shiratori, Y.; Ihara, M.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1982**, 2973. (s) Honda, T.; Murae, T.; Ohta, S.; Kurata, Y.; Kawai, H.; Takahashi, T.; Itai, A.; Iitaka, Y. *Chem. Lett.* **1981**, 299. (t) Fuchs, P. L.; Pariza, R. J. *J. Org. Chem.* **1983**, *48*, 2306. (u) Watt, D. S.; Voyle, M.; Dunlap, N. K. *Ibid.* **1983**, *48*, 3242. (v) Weller, D. D.; Stirchak, E. P. *Ibid.* **1983**, *48*, 4873. (w) Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353. (x) Vidari, G.; Ferrino, S.; Grieco, P. A. *Ibid.* **1984**, *106*, 3539. (y) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264. (z) Kanai, K.; Zelle, R. E.; Sham, H. L.; Grieco, P. A.; Callant, P. *Ibid.* **1984**, *49*, 3867. (aa) Grieco, P. A.; Sham, H. L.; Inanaga, J.; Kim, H.; Tuthill, P. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1345. (bb) Schlessinger, R. H.; Wong, J. W.; Poss, M. A.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 3950. (cc) Stevens, R. V.; Vinogradoff, A. P. *Ibid.* **1985**, *50*, 4056. (dd) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730. (ee) Sasaki, S.; Grieco, P. A.; Huffman, J. C.; Callant, P.; Imamura, P. *J. Org. Chem.* **1985**, *50*, 4880. (ff) Inanaga, J.; Sasaki, S.; Grieco, P. A.; Kim, H. *J. Am. Chem. Soc.* **1985**, *107*, 4800. (gg) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1986**, *27*, 1339. (hh) McKittrick, B. A.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5897. (ii) Chandler, M.; Mincione, E.; Parson, P. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1233. (jj) Stevens, R. V.; Angle, S. R.; Kloc, K.; Mak, K. F.; Trueblood, K. N.; Liu, Y.-X. *J. Org. Chem.* **1986**, *51*, 4347. (kk) Murae, T.; Sasaki, M.; Konosu, T.; Matsuo, H.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 3411. (ll) Ziegler, F. E.; Hwang, K.-J.; Kadow, J. F.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Org. Chem.* **1986**, *51*, 4573. (mm) Kametani, T.; Kanaya, N.; Mochizuki, T.; Honda, T. *Tetrahedron Lett.* **1983**, *24*, 1511. (nn) Fukumoto, K.; Chihiro, M.; Ihara, M.; Kametani, T.; Honda, T. *J. Chem. Soc., Perkin Trans 1* **1983**, 2569. (oo) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902. (pp) Kraus, G. A.; Krolski, M. E. *J. Org. Chem.* **1986**, *51*, 3347. (qq) Hedstrand, D. M.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 592. (rr) Kuo, F.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 1122. (ss) Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686. (tt) Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Jaw, J. Y.; Tu, S. *J. Org. Chem.* **1987**, *52*, 3346. (uu) Grieco, P. A.; Inanaga, J.; Sham, H.-L.; Sasaki, S.; Kim, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1044. (vv) Kim, M.; Gross, R. S.; Sevestre, H.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1988**, *53*, 93.

(4) Polonsky, J.; Bourguignon-Zylber, N. *Bull. Soc. Chim. (Fr.)* **1965**, 2793.

(5) Kupchan, S. M.; Streelman, D. R., *J. Org. Chem.* **1976**, *41*, 5481.

(6) Polonsky, J. Chemistry and Biological Activity of the Quassinoids. In *The Chemistry and Chemical Taxonomy of the Rutales*; Waterman, P. G., Grundon, M. F., Eds.; Academic Press: New York, 1983; p 247. Lidert, Z.; Wing, K.; Polonsky, J.; Imakura, Y.; Okano, M.; Tani, S.; Lin, Y.-M.; Kiyokawa, H.; Lee, K.-H. *J. Nat. Prod.* **1987**, *50*, 442.

(7) Grieco, P. A.; Ferrino, A.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. Vidari, G.; Ferrino, S.; Grieco, P. A. *Ibid.* **1984**, *106*, 3539.

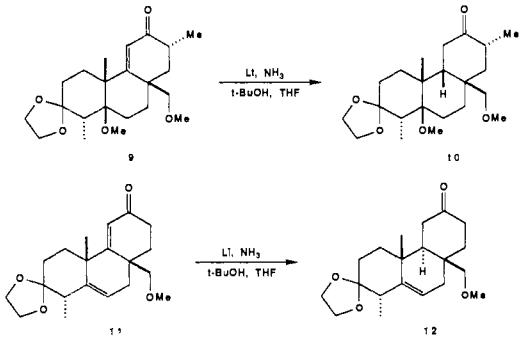
(8) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601. Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *J. Org. Chem.* **1984**, *49*, 2342.

(9) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 435.

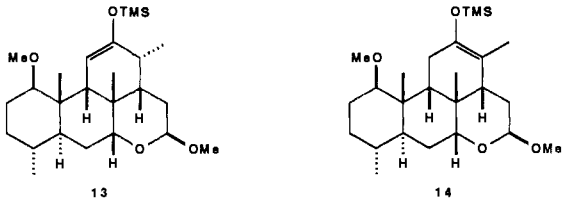
(10) For synthetic methods addressing the problems associated with the construction of the 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality present in ring A of quassinoids see: (a) McKittrick, B. A.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5897. (b) Spohn, R.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491.

(11) For a preliminary account of this work, see: Grieco, P. A.; Parker, D. T.; Nargund, R. P. *J. Am. Chem. Soc.* **1988**, *110*, 5568.

reduction of **7** would give rise to the epimeric tetracyclic ketone **8**, the outcome of this process was by no means assured, since, in conjunction with some earlier quassinoid model studies,[3ee] we had observed that metal–ammonia reduction of tricyclic enone **9** provided an 84% yield of the BC cis-fused tricyclic ketone **10** as the sole product. During the same study it was found that reduction (Li, NH_3, *t*-BuOH, THF) of tricyclic enone **11** afforded in 95% yield the BC trans-fused product **12**.



Preparation of the requisite tetracyclic enone **7** required prior formation of the $\Delta^{11,12}$ silyl enol ether **13**, which proved not to be straightforward. For example, treatment of ketone **6** with

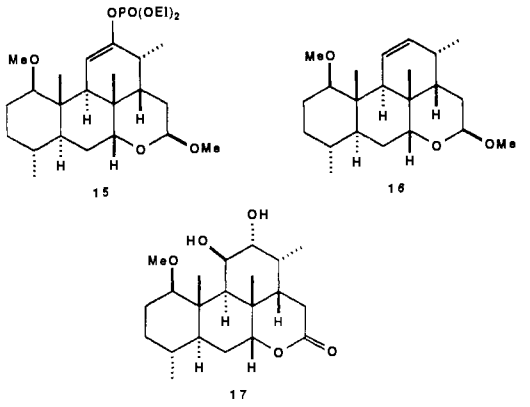


excess lithium diisopropylamide at −30 °C in tetrahydrofuran–hexamethylphosphoramide (2:1) provided, upon quenching with chlorotrimethylsilane, the undesired enol ether **14** exclusively. Addition of ketone **6** to a solution of lithium diisopropylamide (3.0 equiv) in tetrahydrofuran at −78 °C followed by trapping with chlorotrimethylsilane afforded a mixture of **13** and **14** in a disappointing ratio of 1:4. It was eventually found that addition of **6** to 3.0 equiv of lithium diisopropylamide in tetrahydrofuran at −78 °C followed by warming to 0 °C, where the reaction was allowed to stand for 1 h, and subsequent cooling to −78 °C generated in quantitative yield a ~2.0–2.5:1 mixture of the $\Delta^{11,12}$ and $\Delta^{12,13}$ silyl enol ethers **13** and **14**, respectively. The problems encountered above arise from the fact that ring C exists in a boat conformation wherein the C(11) axial proton is located on the concave face of the molecule thereby rendering deprotonation extremely difficult.

The mixture **13** and **14** was not separated but directly exposed to 1.3 equiv of palladium acetate and 4.0 equiv of sodium carbonate in acetonitrile.[12] It was anticipated that the $\Delta^{12,13}$ silyl enol ether would react much more slowly since it has been established that substituents on the silyl enol ether inhibit the formation of the oxo-π-allyl palladium complex. Fortuitously, workup gave rise to a 46% isolated yield of crystalline tetracyclic enone **7**, mp 172.5–174.0 °C, along with ca. 12% of tetracyclic ketone **6** and ca. 30% of unreacted $\Delta^{12,13}$ silyl enol ether **14**. Desilylation of **14** with tetrabutylammonium fluoride gave rise to ketone **6** quantitatively. The yield of enone **7** based on recovered starting ketone was 92%.

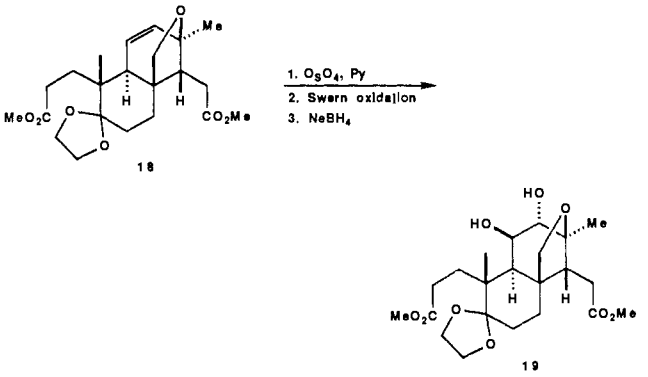
Dissolving metal reduction (Li, NH_3, THF, *t*-BuOH) of tetracyclic enone **7** cleanly provided a single crystalline compound, mp 125.0–125.5 °C, in 88% yield, which was isomeric with **6**. The ^{1}H NMR (300 MHz) spectrum of the product unambiguously confirmed that the new tetracyclic ketone possessed structure **8**.

Having established a protocol for inverting the configuration at C(9), attention was focused on elaborating the trans-diaxial arrangement of the C(11) and C(12) hydroxyl groups (cf. tetracyclic diol **17**). A logical precursor to diol **17** appeared to be

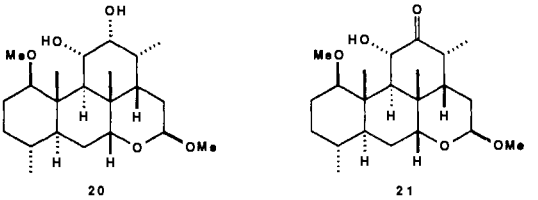


tetracyclic olefin **16**. Toward this end, the regiospecific lithium enolate generated during the metal–ammonia reduction of enone **7** was trapped, via a modification of the original Ireland–Pfister procedure,[13] with diethyl phosphorochloridate in tetrahydrofuran–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (2:1), giving rise to enol phosphate **15**, mp 102.0–102.5 °C, in 80% overall yield. Reductive elimination (Li, $EtNH_2$, *t*-BuOH, THF) of the phosphate group proceeded smoothly, affording tetracyclic olefin **16** in 92% yield.

Introduction of the trans-diaxial arrangement of hydroxyl groups at C(11) and C(12) was attempted using a sequence of reactions that proved quite successful some years ago in conjunction with a synthesis of a quassimarin model system (cf. **18** → **19**).[3aa] Thus exposure of tetracyclic olefin **16** to osmium



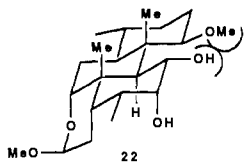
tetraoxide in pyridine followed by workup with sodium bisulfite gave in 80% yield tetracyclic diol **20**, mp 173.5–174.5 °C. The exclusive formation of **20** is not surprising since the C(8) and



C(10) methyl groups severely hinder β-approach of the osmium tetraoxide. Swern oxidation of **20** followed by immediate reduction with sodium borohydride gave rise to only a trace of diol **17**. The major product, obtained in 83% yield, was recovered *cis*-diol **20**. Examination of the ^{1}H NMR (360 MHz) spectrum of the intermediate keto alcohol revealed a one-proton doublet at δ 4.38 with J = 10.8 Hz, which clearly reveals that oxidation had taken place at C(12) and not at C(11) as was anticipated. Reduction of **21** simply regenerated *cis*-diol **20**. In retrospect, the above result is not surprising since the C(11) hydroxyl group is sterically encumbered due to its proximity to the C(1) methyl ether (cf. structure **22**).

(12) Cf.: Ito, Y.; Mirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(13) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1966**, 2145.



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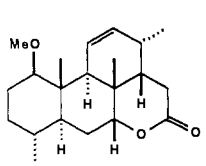
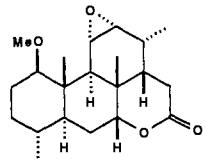
To circumvent the problems encountered above, an alternate method for introduction of the trans-diaxial diol unit was investigated. Toward this end, a model study was undertaken employing olefin **23**, which was obtained from **16** via hydrolysis of



23



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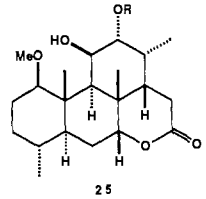
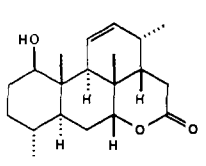


25

the protected lactol and subsequent Jones oxidation. A solution of olefin **23** in methylene chloride containing sodium bicarbonate was treated with *m*-chloroperbenzoic acid (MCPBA) at 0 °C for 1 h. The resulting epoxide **24**, which was obtained in excellent yield, was exposed to 35% perchloric acid in tetrahydrofuran for 22 h. Workup provided an excellent yield of the *trans*-diol **25** (R = H). The diaxial arrangement of the C(11) and C(12) hydroxyl groups was confirmed by examination of the ^{1}H NMR (360 MHz) spectrum of the monoacetate **25** (R = Ac).

Gratified with the results of the model study, we turned our attention to completion of the total synthesis of (±)-klaineanone. Accordingly, demethylation[14] of tetracyclic compound **23** using ethanedithiol in the presence of boron trifluoride ethereate and concentrated hydrochloric acid provided in 70% yield crystalline hydroxy lactone **26**, mp 167.5–169.5 °C. Olefinic alcohol **26** was



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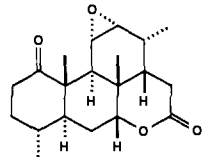

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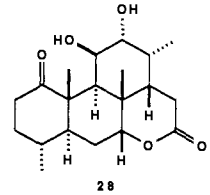
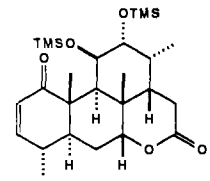


28

transformed via epoxidation (MCPBA, CH_2Cl_2, $NaHCO_3$, 0 °C) and subsequent oxidation (PCC, NaOAc, CH_2Cl_2) of the C(1) hydroxyl group into crystalline keto epoxide **27**, mp 214–217 °C, in 94% overall yield with the expectation that exposure of epoxide **27** to aqueous acid would generate *trans*-diol **28**. Indeed, treatment of **27** with 26% perchloric acid in tetrahydrofuran at ambient temperature for 24 h gave rise to crystalline diol **28**, mp 254–256 °C, in 85% yield. Similar yields were obtained by employing 15% sulfuric acid in place of perchloric acid.

With 9 of the 10 stereocenters of klaineanone embodied in tetracyclic lactone **28**, we set out to transform **28** into enone **29**, which would set the stage for completion of the total synthesis

(14) Cf.: Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkins Trans. 1* **1976**, 2237.



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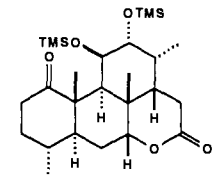

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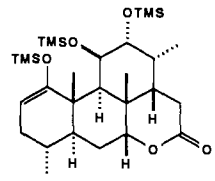

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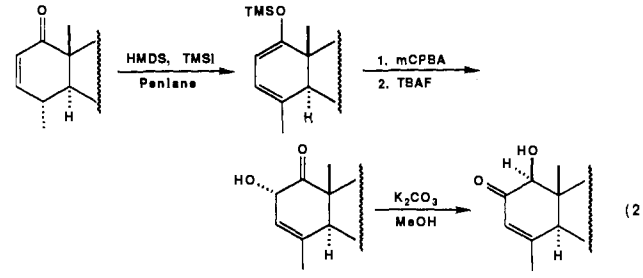
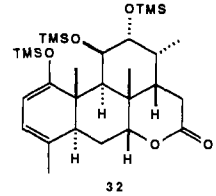
of **1** employing the protocol developed previously in our laboratory[10b] for the elaboration of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality (cf. eq 2). Initial attempts to convert tet-



(2)

racyclic ketone **28** into tetracyclic enone **29** met with no success. For example, treatment of **28** with iodotrimethylsilane and hexamethyldisilazane in methylene chloride–pentane according to the procedure of Miller[15] gave rise exclusively to the bis(silyl ether) **30**. Use of trimethylsilyl triflate in methylene chloride–triethylamine also gave **30** as the sole product. The desired silyl enol ether **31** was finally realized in quantitative yield by treatment of **28** with iodotrimethylsilane and hexamethyldisilazane in 1,2-dichloroethane–triethylamine at ambient temperature for 15 h. Enol ether **31** was smoothly transformed (78% overall yield) into enone **29**, mp 203.0–205.5 °C, by reaction with phenylselenenyl chloride in tetrahydrofuran at 0 °C and subsequent oxidative elimination of benzeneselenenic acid. It is of interest to note that application of the method of Saegusa failed to provide enone **29** even after heating at 55 °C for 48 h.

At this stage in our quest for (±)-klaineanone, the completion of the synthesis appeared to hinge on the transformation of **29** into **32** and its subsequent conversion into the natural product



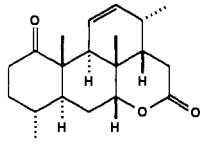
32

utilizing the chemistry depicted in eq 2. Treatment of **29** with iodotrimethylsilane and hexamethyldisilazane in 1,2-dichloroethane–triethylamine gave rise to only recovered enone. Other modifications of the Miller procedure failed to give any silyl dienol ether. Use of trimethylsilyl triflate and either triethylamine or 2,6-di-*tert*-butyl-4-methylpyridine in 1,2-dichloroethane met with no success. In 1984, Kraft and Holton reported[16] that trimethylsilyl dienol ethers could be prepared in good yield from the corresponding enone by a modified version of the Kharasch reaction.[17] Treatment of **29** with activated Fe(0) (prepared in situ from $FeCl_3$ and MeMgBr) in the presence of chlorotri-

(15) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.
(16) Kraft, M. E.; Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 7619.
(17) Kharashch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308; **1945**, *67*, 128.

methylsilane, triethylamine, and hexamethylphosphoramide in ether led once again to only recovery of starting material.

Frustrated by our lack of success in transforming tetracyclic enone **29** into silyl dienol ether **32**, we set out to explore the feasibility of elaborating the ring A functionality prior to assembling the ring C *trans*-diol unit. We were well aware of the potential problems that might arise as a direct consequence of trying to carry the sensitive ring A functionality through the remaining steps of the synthesis. Toward this end, tetracyclic alcohol **26** was transformed into enone **34** via a four-step sequence.



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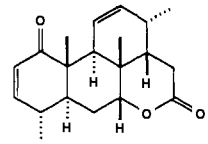

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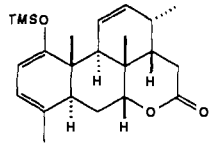

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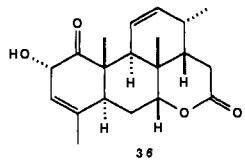
Oxidation (PCC, NaOAc, CH_2Cl_2) of alcohol **26** afforded crystalline ketone **33**, mp 180.5–181.0 °C. Treatment of **33** with iodotrimethylsilane and hexamethyldisilazane in 1,2-dichloroethane–triethylamine provided the corresponding silylenol ether which was exposed directly to phenylselenenyl chloride in tetrahydrofuran at 0 °C. Oxidative elimination of benzeneselenenic acid generated enone **34** in 82% overall yield from **26**. To our surprise, treatment of enone **34** with 15 equiv of hexamethyldisilazane, 15 equiv of triethylamine, and 10 equiv of trimethylsilyl iodide in 1,2-dichloroethane initially at −23 °C and at room temperature for 10 h afforded in near quantitative yield silyl dienol ether **35**.

Peracid oxidation of silyloxydiene **35** with *m*-chloroperbenzoic acid followed by treatment with 3.0 equiv of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran for 1 h at −23 °C gave rise to hydroxy ketone **36** in 50% overall yield.[18] The



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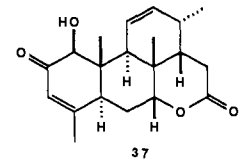
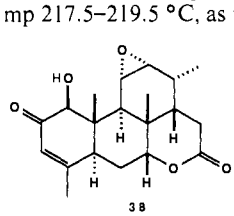


37

conversion of the 1-oxo-2α-hydroxy-$\Delta^{3,4}$ olefin unit in **36** into the desired 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit found in klaineanone was realized by a base-catalyzed tautomerism, which proceeded with remarkable efficiency despite the opportunity for numerous undesired side products. Treatment of a 0.02 M solution of **36** in methanol with 1.2 equiv of potassium carbonate at ambient temperature for 5 h afforded crystalline tetracyclic enone **37**, mp 227–230 °C, in 75% yield.

The remaining task for completion of the total synthesis of racemic klaineanone was elaboration of the C(11),C(12) trans-diaxial arrangement of hydroxyl groups in ring C. Epoxidation of **37** with *m*-chloroperbenzoic acid proceeded smoothly giving rise to epoxide **38**, mp 217.5–219.5 °C, as the sole product in 80%



38

yield. The final step in the conversion of epoxide **8** into (±)-klaineanone required an acid-catalyzed opening. Of particular concern was the ability of the ring A functionality to withstand the strongly acidic conditions required to effect epoxide ring opening. To dampen these concerns, tetracyclic olefin **36**, possessing the ring A functionality, was treated with 26% perchloric acid in tetrahydrofuran (1:1.2). After 35 h at ambient temperature, olefin **36** possessing the 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit in ring A was recovered intact. Fortunately, acid-catalyzed opening of epoxide **38** with 23% perchloric acid in tetrahydrofuran–methylene chloride, 15:1, afforded (76%) after 36 h synthetic (±)-klaineanone, mp 234–239 °C. Our racemic sample of klaineanone was identical with a sample of the natural material by comparison of ^{1}H NMR (500 MHz) and IR spectra and thin-layer mobility in several solvent systems.

The total synthesis of *dl*-klaineanone was accomplished in 17 steps in 6.8% overall yield from tetracyclic ketone **6**. The synthesis of klaineanone confirms the structural assignment made by Polonsky and Bourguignon-Zybler in the early sixties.

Experimental Section

(1β,16β)-1,16-Dimethoxypicras-9(11)-en-12-one (7). To a solution of 2.9 mL (20 mmol) of diisopropylamine in 120 mL of tetrahydrofuran at 0 °C under argon was added 12.1 mL (19.4 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After stirring for 15 min, the solution of lithium diisopropylamide (LDA) was cooled to −78 °C, and a solution of 2.4 g (6.5 mmol) of ketone **6** in 30 mL of tetrahydrofuran was added in a dropwise fashion. After 15 min at −78 °C, the reaction was warmed to 0 °C, where stirring was continued for an additional 45 min. The enolate solution was cooled to −78 °C, and 2.6 mL (19 mmol) of freshly distilled trimethylsilyl chloride was added dropwise. After 30 min at −78 °C and 30 min at 0 °C, the reaction mixture was quenched by pouring into 100 mL of a saturated sodium bicarbonate solution. The product was extracted with ether (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude yellow product was chromatographed on 250 g of silica gel. Elution with hexanes–ether (1:1) provided 2.8 g (99%) of **13** and **14** as a 2:1 mixture (R_f 0.80, hexanes–ether 1:1), which was used directly in the next reaction.

To 1.7 g (7.7 mmol) of palladium(II) acetate in 25 mL of dry acetonitrile at room temperature under an argon atmosphere was added a solution of 2.6 g (6.0 mmol) of the above mixture of **13** and **14** in 25 mL of acetonitrile and 1.9 g (18 mmol) of sodium carbonate. The reaction was stirred at 45–50 °C. After 24 h, an additional 650 mg (2.9 mmol) of palladium(II) acetate was added. After 12 h, the reaction mixture was cooled to room temperature and was filtered through a pad of Celite. The pad was washed with 250 mL of ethyl acetate. The combined organic layers were concentrated, and the residue was chromatographed on 300 g of silica gel. Elution with hexanes–ether (3:1) → (1:1) gave in order of elution 1.1 g (44%) of **14**, 270 mg (12%) of **6**, and 1.0 g (46%) of tetracyclic enone **7** as a crystalline compound: mp 172.5–174 °C; R_f 0.46 (hexanes–ether 1:1); IR ($CHCl_3$) 2970, 1660, 1598, 1450, 1370, 1375, 1320, 1200, 1180, 1135, 1080, 1048, 1038, 998, 963, 948, 900, 880 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.17 (s, 1 H), 4.62 (d, 1 H, J = 2.9 Hz), 3.59 (br s, 1 H), 3.24 (s, 6 H), 3.19 (dd, 1 H, J = 10.5, 4.7 Hz), 2.85 (dq, 1 H, J = 6.5, 2.2 Hz), 2.06 (t, 1 H, J = 3.6 Hz), 2.02 (t, 1 H, J = 4.0 Hz), 1.6–1.8 (m, 4 H), 1.36 (s, 3 H), 1.1–1.5 (m, 5 H), 1.05 (s, 3 H), 0.94 (d, 3 H, J = 6.9 Hz), 0.78 (d, 3 H, J = 6.1 Hz). An analytical sample was prepared by recrystallization from ether. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.87; H, 9.46. Found: C, 72.82; H, 9.34.

(1β,16β)-1,16-Dimethoxypicrasan-12-one (8). To 20 mL of freshly distilled ammonia at −78 °C was added 28 mg (4.0 mmol) of lithium wire cut into small pieces. After 10 min, 122 mg (0.34 mmol) of tetracyclic enone **7** and 64 μL (0.67 mmol) of *tert*-butyl alcohol in 3 mL of tetrahydrofuran were added. The reaction was quenched after 1 h with 1.5 mL of isoprene and 1.5 mL of methanol. The ammonia was allowed to evaporate overnight. The residue was dissolved in 25 mL of water, and the product was extracted with methylene chloride (3 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was chromatographed on 20 g of silica gel. Elution with hexanes–ether (2:1) afforded 103 mg (84%) of ketone **8** as a white solid: mp 125.0–125.5 °C; R_f 0.33 (hexanes–ether 1:1); IR ($CHCl_3$) 3000, 2990, 2975, 2965, 2550, 2915, 1700, 1460, 1440, 1385, 1375, 1355, 1320, 1310, 1210, 1165, 1130, 1090, 1075, 1048, 1000, 990, 960, 935, 795, 730 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.73 (d, 1 H, J = 3.2 Hz), 3.65 (t, 1 H, J = 2.8 Hz), 3.32 (s, 3 H), 3.26 (s, 3 H), 2.92 (dd, 1 H, J = 14.0, 3.8 Hz), 2.87 (m, 1 H), 2.42 (t, 1 H, J = 14.1 Hz), 2.15 (dd, 1 H, J = 14.0, 4.0 Hz), 2.03 (dt, 1 H, J = 14.0, 5.1 Hz), 1.8–2.0 (m, 1 H), 1.6–1.7 (m,

(18) Cf.: Rubbottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

2 H), 1.52 (dd, 1 H, J = 13.9, 4.2 Hz), 1.1–1.4 (m, 6 H), 1.28 (s, 3 H), 0.9–1.0 (m, 1 H), 0.90 (d, 3 H, J = 6.5 Hz), 0.88 (s, 3 H), 0.81 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from ether. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.48; H, 9.96. Found: C, 72.36; H, 9.75.

(1β,16β)-1,16-Dimethoxypicras-11-en-12-ol Tetramethylphosphoradiamidate (15). To 4 mL of freshly distilled ammonia at −78 °C was added 20 mg (2.8 mmol) of lithium metal. A solution of 200 mg (0.55 mmol) of tetracyclic enone **7** and 48 μL (0.51 mmol) of *tert*-butyl alcohol in 2 mL of tetrahydrofuran was added. After 1 h, the reaction was quenched with 0.25 mL of freshly distilled isoprene. The ammonia was removed at 0 °C under reduced pressure (~30 mmHg). To the cloudy residue was added 1.5 mL of tetrahydrofuran and 1.5 mL of *N,N,Nm,Nm*-tetramethylethylenediamine. Freshly distilled diethyl chlorophosphate (0.26 mL, 1.80 mmol) was added, and the reaction was stirred at 0 °C for 30 min and at room temperature for 3 h. The reaction mixture was poured into 25 mL of a cold saturated sodium bicarbonate solution. The product was extracted with ether (4 × 25 mL). The combined extracts were washed with 25 mL of brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The oily residue was chromatographed on 25 g of silica gel. Elution with ether afforded 13.5 mg (6.7%) of ketone **8** and 240 mg (90%) of enol phosphate **15** as a pale yellow oil that solidified upon standing: mp 102.0–102.5 °C; R_f 0.47 (ether); IR ($CHCl_3$) 2975, 2930, 1668, 1445, 1395, 1360, 1340, 1260, 1123, 1028, 995, 968, 915, 892 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.44 (br s, 1 H), 4.79 (br s, 1 H), 4.1–4.2 (m, 4 H), 3.59 (br s, 1 H), 3.33 (s, 3 H), 3.28 (s, 3 H), 2.95 (dd, 1 H, J = 11.2, 4.7 Hz), 2.78 (m, 1 H), 2.61 (br s, 1 H), 1.7–2.0 (m, 2 H), 1.5–1.7 (m, 4 H), 1.34 (br t, 6 H, J = 7.2 Hz), 1.03 (s, 3 H), 0.97 (d, 3 H, J = 7.2 Hz), 0.87 (s, 3 H), 0.79 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from isooctane. Anal. Calcd for $C_{26}H_{45}O_7P$: C, 62.36; H, 9.07. Found: C, 62.56; H, 9.10.

(1β,16β)-1,16-Dimethoxypicras-11-ene (16). To 5 mL of distilled ethylamine at 0 °C was added 35 mg (5.0 mmol) of lithium metal. After 45 min, a solution of 240 mg (0.48 mmol) of enol phosphate **15** and 78 μL (0.75 mmol) of *tert*-butyl alcohol in 5 mL of dry tetrahydrofuran was added dropwise. Stirring was continued for 2 h at 0 °C. The reaction mixture was quenched with isoprene followed by slow addition of 1.5 mL of methanol. The ethylamine was allowed to evaporate. The residue was taken up in 25 mL of water and the product was extracted with ether (3 × 25 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on 20 g of silica gel. Elution with hexanes–ether (5:1) afforded 150 mg (88%) of tetracyclic olefin **16** as a colorless oil: R_f 0.74 (hexanes–ether 3:1); IR ($CHCl_3$) 3000, 2958, 2935, 2878, 2830, 1460, 1442, 1380, 1357, 1232, 1198, 1142, 1127, 1090, 1075, 1048, 1000, 996, 973, 940, 906, 870, 696 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.43 (d, 1 H, J = 10.5 Hz), 5.32 (d, 1 H, J = 10.5 Hz), 4.79 (d, 1 H, J = 1.8 Hz), 3.56 (br s, 1 H), 3.33 (s, 3 H), 3.27 (s, 3 H), 2.97 (dd, 1 H, J = 10.8, 4.7 Hz), 2.5–2.6 (m, 1 H), 2.50 (br s, 1 H), 1.9–2.0 (m, 1 H), 1.4–1.8 (m, 5 H), 1.1–1.4 (m, 3 H), 1.00 (s, 3 H), 0.86 (s, 3 H), 0.85 (d, 3 H, J = 6.0 Hz), 0.79 (d, 3 H, J = 6.1 Hz); high-resolution MS, calcd for $C_{22}H_{36}O_3 - OCH_3$ 317.2481, found 317.2448.

(1β,11α,12α,16β)-1,16-Dimethoxypicrasane-11,12-diol (20). To 32 mg (0.092 mmol) of tetracyclic olefin **16** in 1.0 mL of pyridine at room temperature was added 28 mg (0.11 mmol) of osmium tetraoxide. After 2 h, the reaction mixture was treated with 1.8 mL of water and 200 mg of sodium bisulfite. The color of the reaction mixture changed from brown–black to orange–red during the next 3 h. The reaction mixture was poured into 5 mL of water. The product was extracted with ethyl acetate (3 × 10 mL). The combined layers were washed with 5% hydrochloric acid and brine (5 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography of the residue on 15 g of silica gel and elution with hexanes–ethyl acetate (1:1) afforded 32 mg (91%) of *cis*-diol **20** as a crystalline compound; mp 173.5–174.5 °C; R_f 0.44 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3540, 3170, 3000, 2945, 2910, 1465, 1453, 1370, 1320, 1295, 1190, 1140, 1050, 1045, 985, 965, 935, 905, 890, 855 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 4.74 (d, 1 H, J = 3.6 Hz), 3.8–3.9 (m, 2 H), 3.45 (t, 1 H, J = 2.9 Hz), 3.35 (s, 3 H), 3.31 (s, 3 H), 3.12 (dd, 1 H, J = 10.5, 5.0 Hz), 2.95 (s, 1 H), 2.26 (td, 1 H, J = 13.9, 3.6 Hz), 2.0–2.2 (m, 3 H), 1.45–1.74 (m, 6 H), 1.3–1.4 (m, 2 H), 1.04 (s, 3 H), 1.03 (d, 3 H, J = 6.5 Hz), 0.99 (s, 3 H), 0.86 (d, 3 H, J = 5.8 Hz). An analytical sample was prepared by recrystallization from ether-hexanes. Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.06; H, 10.01. Found: C, 68.93; H, 9.87.

(1β)-1-Methoxypicras-11-en-16-one (23). To a solution of 160 mg (0.48 mmol) of **16** in 10 mL of tetrahydrofuran at 0 °C was added 5 mL of 5% hydrochloric acid. The reaction mixture was warmed to room temperature, where stirring was continued for 5 h. The reaction mixture was diluted with 5 mL of brine, and the product was extracted with methylene chloride (3 × 15 mL). The combined organic extracts were washed with 10 mL of brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The colorless residue was dissolved in 10 mL of acetone and cooled to 0 °C, and 0.36 mL (0.96 mmol) of a 2.67 M solution of Jones reagent was added dropwise. After 15 min, the reaction was quenched by the addition of 0.10 mL of isopropyl alcohol and diluted with 20 mL of water. The product was isolated by extraction with methylene chloride (3 × 20 mL). The combined organic extracts were washed with 15 mL of saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography of the residue over 20 g of silica gel with hexanes–ether (1:1) as the eluent afforded 126 mg (78%) of tetracyclic lactone **23** as a white solid: R_f 0.36 (hexanes–ether 1:1); IR ($CHCl_3$) 3090, 2960, 2930, 2873, 2820, 1713, 1460, 1390, 1370, 1354, 1341, 1336, 1310, 1273, 1240, 1135, 1090, 1075, 1032, 995, 960, 953, 905, 870, 690 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.44 (d, 1 H, J = 10.5 Hz), 5.33 (d, 1 H, J = 10.5 Hz), 4.17 (s, 1 H), 3.23 (s, 3 H), 2.86 (dd, 1 H, J = 11.0, 4.9 Hz), 2.52 (m, 1 H), 2.45 (dd, 1 H, J = 18.8, 6.1 Hz), 2.19 (dd, 1 H, J = 18.8, 13.0 Hz), 2.03 (br s, 1 H), 1.8–2.0 (m, 3 H), 1.6–1.7 (m, 4 H), 1.42 (qd, 1 H, J = 13.7, 4.7 Hz), 1.2–1.4 (m, 2 H), 1.08 (s, 3 H), 0.9–1.0 (m, 2 H), 0.88 (d, 3 H, J = 7.6), 0.86 (s, 3 H), 0.76 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from ether, mp 174–176 °C. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.85; H, 9.71. Found: C, 75.68; H, 9.88.

(1β)-1-Hydroxypicras-11-en-16-one (26). To a soltuion of 250 mg (0.75 mmol) of tetracyclic lactone **23** in 6.7 mL of 1,2-ethanedithiol cooled to 0 °C was added 4.0 mL of boron trifluoride etherate and 15 μL of concentrated hydrochloric acid. The reaction was warmed to room temperature. After 70.5 h, the reaction mixture was cooled to 0 °C and quenched by careful addition of 10 mL of a saturated sodium bicarbonate solution. The reaction mixture was poured into 20 mL of water and was extracted with methylene chloride (3 × 20 mL). The combined organic extracts were washed with 15 mL of a 2 N sodium hydroxide solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude alcohol was chromatographed on 30 g of silica gel. Elution with hexanes–ether (1:1 → 1:3) afforded 167 mg (70%) of tetracyclic alcohol **26** as a white solid: R_f 0.39 (hexanes–ethyl acetate 1:1); IR ($CHCl_3$) 3600, 3460, 2960, 2925, 2870, 1710, 1460, 1372, 1245, 1135, 1030, 986 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.62 (d, 1 H, J = 10.5 Hz), 5.35 (d, 1 H, J = 10.5 Hz), 4.20 (br s, 1 H), 3.46 (dd 1 H, J = 10.5, 5.0 Hz), 2.56 (m, 1 H), 2.47 (dd, 1 H, J = 18.8, 6.1 Hz), 2.21 (dd, 1 H, J = 18.8, 13.4 Hz), 2.09 (br s, 1 H), 1.91 (dt, 1 H, J = 14.8, 3.1 Hz), 1.5–1.8 (m, 5 H), 1.45 (br s, 1 H), 1.2–1.3 (m, 1 H), 1.11 (s, 3 H), 1.0–1.1 (m, 2 H), 0.90 (d, 3 H, J = 6.5 Hz), 0.89 (s. 3 H), 0.79 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from ether, mp 167.5–169.5 °C. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.41; H, 9.50. Found: C, 75.46; H, 9.51.

(11α,12α)-11,12-Epoxypicrasane-1,16-dione (27). To a solution of 19.4 mg (0.061 mmol) of olefinic alcohol **26** in 2.6 mL of dichloromethane at 0 °C was added 26 mg (0.30 mmol) of sodium bicarbonate and 31 mg (0.18 mmol) of *m*-chloroperbenzoic acid. After 1.5 h, the reaction was quenched by the addition of 2 mL of a saturated sodium sulfite solution and diluted with 2 mL of a saturated sodium bicarbonate solution. The product was extracted with methylene chloride (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate, concentrated in vacuo, and used immediately in the next reaction.

To a solution of the above crude alcohol in 2 mL of methylene chloride cooled to 0 °C was added 12.4 mg (0.15 mmol) of anhydrous sodium acetate, 0.20 g of Celite, and 39 mg (0.18 mmol) of pyridinium chlorochromate. After 30 min the reaction was warmed to room temperature and was stirred for an additional 2 h. Ether (2 mL) was added, and the salts were filtered through a plug of Celite–silica gel and washed well with ether and ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was chromatographed on 10 g of silica gel. Elution with ethyl acetate afforded 19.0 mg (94.0%) of epoxy ketone **27** as colorless crystals; mp 214–217 °C; R_f 0.23 (ether); IR ($CHCl_3$) 2960, 2930, 1710, 1455, 1445, 1375, 1360, 1240, 1210, 1035, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (t, 1 H, J = 2.7 Hz), 3.05–3.12 (m, 2 H), 2.92 (td, 1 H, J = 14.0, 7.0 Hz), 2.76, (dd, 1 H, J = 19.5, 13.1 Hz), 2.43 (dd, 1 H, J = 19.5 Hz, 6.2 Hz), 2.23–2.35 (m, 2 H), 2.22 (br s, 1 H), 1.7–2.1 (m, 4 H), 1.3–1.7 (m, 4 H), 1.33 (s, 3 H), 1.44 (d, 3 H, J = 7.0 Hz), 1.12 (s, 3 H), 0.91 (d, 3 H, 6.0 Hz); high-resolution MS calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.1999.

(11β,12α)-11,12-Dihydroxypicrasane-1,16-dione (28). To 110 mg (0.33 mmol) of epoxy ketone **27** in 10 mL of tetrahydrofuran was added 10 mL of 15% sulfuric acid. The reaction was stirred at room temperature for 8 h and at 50 °C for 4 h. The reaction mixture was cooled to 0 °C and quenched by the careful addition of sodium bicarbonate. The reaction mixture was diluted with 10 mL of water. The product was

extracted with methylene chloride (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The thick oily residue was chromatographed on 15 g of silica gel. Elution with dichloromethane–acetone (4:1) gave 92 mg (79%) of diol **28** as a colorless solid: R_f 0.39 (dichloromethane–acetone 4:1); IR ($CHCl_3$) 3590, 3480, 2960, 2935, 2870, 1710, 1455, 1435, 1375, 1320, 1255, 1210, 1130, 1045, 1025, 995, 980, 955, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (br s, 1 H), 4.00 (t, 1 H, J = 2.7 Hz), 3.66 (t, 1 H, J = 2.6 Hz), 3.54 (dd, 1 H, J = 19.8, 12.3 Hz), 2.8–3.0 (m, 1 H), 2.50 (dd, 1 H, J = 19.5, 7.2 Hz), 2.3–2.4 (m, 2 H), 1.8–2.2 (m, 5 H), 1.6–1.8 (m, 2 H), 1.59 (s, 3 H), 1.48 (s, 3 H), 1.07 (d, 3 H, J = 7.0 Hz), 0.89 (d, 3 H, J = 6.3 Hz). An analytical sample was prepared by recrystallization from chloroform–ether, mp 254–256 °C. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.53; H, 8.63. Found: C, 68.26; H, 8.86.

(11β,12α)-11,12-Bis(trimethylsiloxy)picras-2-ene-1,16-dione (29). To a solution of 32 mg (0.091 mmol) of the keto diol **28** in 5 mL of 1,2-dichloroethane cooled to −23 °C was added 0.12 mL (0.54 mmol) of hexamethyldisilazane, 76 μL (0.54 mmol) of triethylamine, and 74 μL (0.45 mmol) of iodotrimethylsilane. The reaction was gently warmed to room temperature. After 36 h, the reaction mixture was poured into a cold saturated sodium bicarbonate solution (10 mL). The product was extracted with ether (3 × 5 mL), and the combined organic extracts were washed with 5 mL of brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was passed through a pad of silica gel and was washed with hexanes–ether (1:1). Concentration of the filtrate gave **31** as a yellow solid, which was used immediately in the next reaction.

To a solution of silyl enol ether **31** in 3 mL of dry tetrahydrofuran cooled to 0 °C was added 21 mg (0.11 mmol) of phenylselenenyl chloride in one portion. After 30 min, the reaction mixture was cooled to 0 °C, and 0.10 mL of pyridine and 50 μL of 30% hydrogen peroxide were added. After 1 h, the reaction was quenched with 10 mL of a saturated sodium bicarbonate solution. The product was extracted with ether (3 × 10 mL). The combined organic extracts were washed with 10 mL of brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The yellow residue was chromatographed on 15 g of silica gel. Elution with hexanes–ether (1:1) gave 30 mg (78%) of enone **29** as a pale yellow solid: R_f 0.37 (ether–hexanes 2;1); IR ($CHCl_3$) 2960, 2880, 1715, 1675, 1455, 1372, 1340, 1320, 1250, 1150, 1125, 1110, 1078, 1035, 990, 975, 962, 938, 888, 838 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.46 (dd, 1 H, J = 10.1, 1.8 Hz), 5.74 (dd, 1 H, J = 10.1, 2.9 Hz), 5.28 (br s, 1 H), 3.95 (br s, 1 H), 3.58 (br s, 1 H), 3.55 (dd, 1 H, J = 19.4, 11.6 Hz), 2.42 (dd, 1 H, J = 19.5, 7.4 Hz), 2.27–2.37 (m, 2 H), 2.26 (d, 1 H, J = 1.1 Hz), 1.8–2.0 (m, 3 H), 1.6–1.7 (m, 2 H), 1.45 (s, 3 H), 1.43 (s, 3 H), 1.10 (d, 3 H, J = 6.5 Hz), 0.93 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from isooctane, mp 203.0–205.5 °C. Anal. Calcd for $C_{26}H_{44}O_5Si_2$: C, 63.35; H, 9.00. Found: C, 62.98; H, 8.90.

Picras-11-ene-1,16-dione (33). To a solution of 29 mg (0.092 mmol) of alcohol **26** in 2 mL of methylene chloride cooled to 0 °C were added 18 mg (0.22 mmol) of anhydrous sodium acetate and 170 mg of dry Celite followed by 56 mg (0.26 mmol) of pyridinium chlorochromate. The reaction mixture was stirred at 0 °C for 30 min and at ambient temperature for 30 min. The mixture was diluted with 5 mL of ether and was chromatographed directly on 15 g of silica gel. Elution with ether afforded 29 mg (100%) of tetracyclic ketone **33** as a white solid: R_f 0.30 (ether–hexanes 3:1); IR ($CHCl_3$) 3030, 2965, 2875, 1712, 1457, 1440, 1383, 1372, 1357, 1338, 1320, 1267, 1243, 1217, 1152, 1139, 1093, 1034, 990, 960, 900, 675 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.62 (d, 1 H, J = 10.4 Hz), 5.41 (d, 1 H, J = 10.4 Hz), 4.21 (t, 1 H, J = 2.7 Hz), 2.94 (td, 1 H, J = 13.7, 7.2 Hz), 2.60 (br s, 2 H), 2.51 (dd, 1 H, J = 18.7, 6.1 Hz), 2.35 (dd, 1 H, J = 18.7, 13.0 Hz), 2.19 (ddd, 1 H, J = 13.7, 5.8, 1.8 Hz), 1.9–2.6 (m, 2 H), 1.8–1.9 (m, 2 H), 1.75 (dt, 1 H, J = 13.0, 5.8 Hz), 1.3–1.5 (m, 2 H), 1.24 (s, 3 H), 1.12 (s, 3 H), 0.95 (d, 3 H, J = 7.5 Hz), 0.89 (d, 3 H, J = 6.5 Hz). Recrystallization from ether provided analytically pure **23** as white needles, mp 180.5–181.0 °C. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.75; H, 8.68.

Picras-2,11-diene-1,16-dione (34). To a solution of 29 mg (0.087 mmol) of ketone **33** in 4 mL of 1,2-dichloroethane at room temperature was added 151 μL (1.08 mmol) of triethylamine and 230 μL (1.09 mmol) of hexamethyldisilazane. The mixture was cooled to −23 °C, and 125 μL (0.878 mmol) of iodotrimethylsilane was added dropwise. The reaction mixture was stirred at −23 °C for 5 min and slowly warmed to room temperature. After 3.5 h, the mixture was cooled to −23 °C, and 350 μL of methanol was added. The mixture was warmed to room temperature, and the contents were directly subjected to column chromatography on silica gel. Elution with ether–hexanes (1:1) afforded 38 mg (100%) of the corresponding silyl enol ether, R_f 0.31 (ether–hexanes 1:1), which was used directly in the next reaction.

To a solution of 38 mg of the above silyl enol ether in 2 mL of dry tetrahydrofuran at 0 °C was added 34 mg (0.18 mmol) of phenylselenenyl chloride. After 15 min, 150 μL of pyridine and 20 μL of 30% hydrogen peroxide were added. After stirring for 1.5 h at 0 °C, 2 mL of a saturated sodium bicarbonate solution was added followed by 20 mL of water. The product was isolated by extraction with methylene chloride (3 × 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified on 13 g of silica gel. Elution with ether–hexanes (7:3) afforded 24 mg (82%) of enone **34** as a white solid: R_f 0.37 (ether); IR ($CHCl_3$) 3025, 3000, 2965, 2940, 2915, 2875, 1720, 1680, 1465, 1453, 1440, 1382, 1371, 1355, 1337, 1318, 1245, 1215, 1147, 1130, 1095, 1048, 1033, 1000, 987, 963, 940, 900, 842, 813, 690 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.53 (dd, 1 H, J = 10.1, 2.2 Hz), 6.03 (dt, 1 H, J = 10.4, 2.2 Hz), 5.76 (dd, 1 H, J = 10.1, 2.9 Hz), 5.44 (dt, 1 H, J = 10.4, 2.2 Hz), 4.24 (m, 1 H), 2.61 (m, 1 H), 2.5–2.6 (m, 1 H), 2.3–2.4 (m, 1 H), 2.0–2.1 (m, 1 H), 1.9–2.0 (m, 2 H), 1.76 (dt, 1 H, J = 13.0, 5.9 Hz), 1.20 (s, 3 H), 1.15 (s, 3 H), 1.07 (d, 3 H, J = 7.2 Hz), 0.95 (d, 3 H, J = 7.2 Hz). Recrystallization from ether provided analytically pure **34** as white crystals, mp 206.5–207.5 °C. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.46; H, 8.26.

(1β)-1-Hydroxypicras-3,11-diene-2,16-dione (37). To a solution of 21 mg (0.064 mmol) of enone **34** in 3.5 mL of 1,2-dichloroethane at room temperature was added 135 μL (0.968 mmol) of triethylamine and 204 μL (0.968 mmol) of hexamethyldisilazane. The mixture was cooled to −23 °C, and 92 μL (0.645 mmol) of iodotrimethylsilane was added dropwise. The reaction mixture was stirred at −23 °C for 5 min and slowly warmed to room temperature. After 9.5 h, the mixture was cooled to 0 °C, and 100 μL of methanol was added. The mixture was warmed to room temperature, and the reaction contents were directly subjected to column chromatography on 30 g of silica gel. Elution with ether–hexanes (1:1) afforded 27 mg (100%) of silyl dienol ether **35** [R_f 0.65 (ether)], which was used directly in the next reaction.

To a solution of 26 mg (0.064 mmol) of the above silyl dienol ether **35** in 2.5 mL of methylene chloride containing 8.0 mg of sodium bicarbonate at −23 °C was added 13 mg (0.076 mmol) of *m*-chloroperbenzoic acid. After 45 min, the reaction mixture was treated at −23 °C for 1 h with 190 μL (3 equiv) of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran. The reaction was quenched by the addition of 150 μL of a saturated solution of sodium sulfite and diluted with 10 mL of water. The product was extracted with methylene chloride (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified on 30 g of silica gel. Elution with ether afforded 11 mg (50%) of hydroxy ketone **36** as a semisolid, which was used directly in the next reaction.

To a solution of 4.1 mg (0.021 mmol) of hydroxy ketone **36** in 600 μL of methanol was added 2.1 mg (0.015 mmol) of finely powdered potassium carbonate. After 5 h, the yellowish solution was diluted with methylene chloride (3 mL) and directly purified on 5 g of silica gel. Elution with methylene chloride afforded 3.1 mg (75%) of hydroxy ketone **37** as a white solid: R_f 0.55 (acetone–methylene chloride 1:9); IR ($CHCl_3$) 3450, 3025, 2960, 2923, 2877, 2855, 1720, 1668, 1455, 1435, 1396, 1375, 1355, 1347, 1303, 1260–1190, 1143, 1127, 1079, 1046, 1032, 993, 918, 900, 845, 833, 610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.55 (br d, 1 H, J = 10.4 Hz), 6.08 (q, 1 H, J = 1.4 Hz), 5.45 (br d, 1 H, J = 10.4 Hz), 4.35 (t, 1 H, 2.7 Hz), 4.19 (br s, 1 H), 4.02 (s, 1 H), 2.91 (br d, 1 H, J = 13.2 Hz), 2.62 (m, 1 H), 2.51 (dd, 1 H, J = 19.0, 6.2 Hz), 2.53 (m, 1 H), 2.31 (dd, 1 H, J = 19.0, 13.2 Hz), 2.23 (dt, 1 H, J = 14.5, 3.5 Hz), 2.0–2.1 (m, 1 H), 1.98 (s, 3 H), 1.79 (dt, 1 H, J = 13.2, 6.0 Hz), 1.16 (s, 3 H), 0.95 (d, 3 H, J = 7.4 Hz), 0.83 (s, 3 H). Recrystallization from ether–methylene chloride (3:1) provided analytically pure **37** as white crystals, mp 227–230 °C. High-resolution MS (CI) calcd for $C_{20}H_{27}O_4$ (M + 1) m/e 331.1909, found 331.1907; calcd for $C_{20}H_{26}O_4$ (M) m/e 330.1831, found 330.1826.

(1β,11α,12α)-11,12-Epoxy-1-hydroxypicras-3-ene-2,16-dione (38). To a solution of 10 mg (0.032 mmol) of tetracyclic olefin **37** in 1.5 mL of methylene chloride cooled to 0 °C was added 20 mg (0.095 mmol) of *m*-chloroperbenzoic acid. The reaction mixture was stirred at 0 °C for 35 min and at room temperature for 2.5 h. The reaction mixture was directly applied to a column containing 25 g of silica gel. Elution with acetone–methylene chloride (1:9) provided 9.0 mg (80%) of epoxide **38** as white crystals; mp 217.5–219.5 °C; R_f 0.28 (acetone–methylene chloride 1:9); IR ($CHCl_3$) 3470, 3030, 3005, 2979, 2930, 2885, 1729, 1675, 1630, 1461, 1438, 1399, 1383, 1369, 1352, 1263, 1260–1190, 1178, 1149, 1133, 1098, 1070, 1043, 1010, 1002, 929, 917, 909, 887, 834, 818 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (q, 1 H, J = 1.4 Hz), 4.31 (t, 1 H, J = 2.8 Hz), 4.15 (s, 1 H), 4.10 (br s, 1 H), 3.93 (dd, 1 H, J = 4.0, 1.4 Hz), 3.06 (t, 1 H, J = 3.3 Hz), 2.91 (br d, 1 H, J = 13.3 Hz), 2.76 (dd, 1 H, J = 19.2, 13.3 Hz), 2.50 (dd, 1 H, J = 19.2, 6.3 Hz), 2.34 (d quintets, 1 H, J = 7.1, 2.9 Hz), 2.17–2.25 (m, 2 H), 2.04 (m, 1 H),

1.97 (s, 3 H), 1.69 (dt, 1 H, J = 13.0, 6.5 Hz), 1.16 (s, 3 H), 1.15 (d, 3 H, J = 7.3 Hz), 0.96 (s, 3 H). High-resolution MS (CI) calcd for $C_{20}H_{27}O_5$ (M + 1) m/e 347.1859, found 347.1881; calcd for $C_{20}H_{26}O_5$ (M) m/e 346.1780, found 346.1777.

(±)-**Klaineanone (1).** To a solution of 7 mg (0.02 mmol) of epoxide **38** in 1.6 mL of tetrahydrofuran–methylene chloride (15:1) cooled to 0 °C was added 1.1 mL of 23% perchloric acid. The reaction mixture was warmed to room temperature. After 36 h, the reaction mixture was cooled to 0 °C, quenched with sodium bicarbonate, and diluted with 4 mL of water. The product was extracted with chloroform (4 × 7 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified on 5 g of silica gel. Elution with methylene chloride–acetone (4:1) provided 6.0 mg (76%) of (±)-klaineanone (**1**) as a white solid. Recrystallization from ethyl acetate afforded white crystals, mp 234–239 °C: R_f 0.30 (methylene chloride–acetone 7:3); IR (KBr) 3555, 3415, 2950, 2920, 2865, 1724, 1661, 1430, 1390, 1370, 1353, 1257, 1233, 1219, 1193, 1175, 1160, 1110, 1050, 1030, 1010, 990, 975, 950, 910, 890, 836, 689, 661, 618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (q, 1 H, J = 1.4 Hz), 4.90 (m, 1 H), 4.43 (d, 1 H, J = 1.6 Hz, hydroxyl), 4.16 (t, 1 H, J = 2.9 Hz), 4.05 (s, 1 H), 3.81 (br s, 1 H), 3.51 (dd, 1 H, J = 19.3, 12.0 Hz), 2.95 (br d, 1 H, J = 12.0 Hz), 2.55 (dd, 1 H, J = 19.3, 7.1 Hz), 2.3–2.4 (m, 1 H), 2.25 (dt, 1 H, J = 14.4, 3.2 Hz), 2.20 (br d, 1 H, J = 5.8 Hz, hydroxyl), 2.12 (ddd, 1 H, J = 14.5, 12.9, 2.4 Hz), 2.07 (d, 1 H, 3.2 Hz), 1.97 (br s, 3 H), 1.75 (ddd, 1 H, J = 11.5, 6.9, 4.5 Hz), 1.64 (br s, 1 H, hydroxyl), 1.49 (s, 3 H), 1.09 (s, 3 H), 1.08 (d, 3 H, J = 7.2 Hz). High-resolution MS (CI) calcd for $C_{20}H_{29}O_6$ (M + 1) m/e 365.1964, found 365.1961; calcd for $C_{20}H_{26}O_5$ ($M - H_2O$) m/e 347.1858, found 347.1857.

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Macrocycles Containing Tin. Solid Complexes of Anions Encrypted in Macrobicyclic Lewis Acidic Hosts†

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Abstract: Crystalline complexes of 1,10-dichloro-1,10-distannabicyclo[8.8.8]hexacosane and benzyltriphenylphosphonium chloride (complex **3**) and of 1,8-dichloro-1,8-distannabicyclo[6.6.6]eicosane and tetrabutylammonium fluoride (complex **4**) have been studied by X-ray crystallography and solid-state ^{119}Sn NMR spectroscopy. The halide ions are encrypted within the cavities of the bicyclic hosts in both complexes. Complex **3** is a stannate–stannane species wherein one of the Lewis acidic tins binds the chloride strongly, and the other interacts with the chloride only weakly. Complex **4** is a bis-hemistannate species wherein the Lewis acidic tin atoms bind the guest fluoride simultaneously. Low-temperature solution ^{119}Sn NMR spectra of the two complexes in halogenated solvents were studied. A "chloride jump" from one tin to the other was observed in complex **3**; the dynamic process has an activation energy of 5.3 kcal/mol. Line broadening of the tin signals in complex **4** was consistent with a similar "fluoride jump" with an activation energy of 2.9 kcal/mol. The crystalline complexes were reasonable models for the solution complexes in both cases, and the structural features in the solid state can be used to rationalize the binding energies in solution.

The host–guest chemistry of cation complexation has become a sophisticated field of study, but the corresponding area of guest anion complexation is in a more preliminary state. Studies have shown that charged ammonium ion containing macrocyclic hosts can bind anions in aqueous solution,[1,2] and complex Lewis acidic hosts that employ mercury,[3] boron,[4] and silicon[5] are known that can bind anions in organic solvents. Our group has explored the use of macrocyclic hosts containing Lewis acidic tin atoms for anion complexation in organic media. Macrocycles of various ring sizes containing two or four tin atoms have been described.[6] However, although anion complexation by hosts like **1** with macrocyclic skeletons was possible, poor selectivity in binding was observed.[6b] On the other hand, when a third chain was incorporated into the ditin species to give the more organized macrobicycles **2**, size selective complexation of halides occurred.[7] On the basis of the size selective nature of anion binding by hosts **2**, the stoichiometry of the complexes, and the greatly reduced rates of complexation and decomplexation by hosts **2** in comparison to simple acyclic and monocyclic analogues, we concluded that the anion was bound within the cavity of the hosts and that the Lewis acidic centers acted in a through-space, cooperative manner dictated by the host structure.[7] This was the predicted behavior of the macrobicycles **2** because it is well-known that in simple stannates of structure $R_3SnX_2^-$ the two electron-withdrawing

† Dedicated to Professor D. J. Cram on the occasion of his 70th birthday.

(1) Simmons, H. E.; Park, C. H. *J. Am. Chem. Soc.* **1968**, *90*, 2428–2429; 2429–2431; 2431–2432. Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 720–721. Pierre, J.-L.; Baret, P. *Bull. Soc. Chim. Fr.* **1983**, *II*, 367–380. Schmidtchen, F. P. *Nachr. Chem., Tech. Lab.* **1988**, *36*, 8, 10–17.

(2) Jazwinski, J.; Blacker, A. J.; Lehn, J.-M.; Cesario, M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* **1987**, *28*, 6057–6060. Jazwinski, J.; Lehn, J.-M.; Mric, R.; Vigneron, J.-P.; Cesario, M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* **1987**, *28*, 3489–3492. Graf, E.; Lehn, J.-M. *J. Am. Chem. Soc.* **1976**, *98*, 6403–6405. Dietrich, B.; Guilhem, J.; Lehn, J.-M.; Pascard, C.; Sonveaux, E. *Helv. Chim. Acta* **1984**, *67*, 91–104. Hosseini, M. W.; Lehn, J.-M. *Helv. Chim. Acta* **1986**, *69*, 587–603.

(3) Wuest, J. D.; Zacharie, B. *J. Am. Chem. Soc.* **1987**, *109*, 4714–4715. Beauchamp, A. L.; Olivier, M. J.; Wuest, J. D.; Zacharie, B. *Organometallics* **1987**, *6*, 153–156. Beauchamp, A. L.; Olivier, M. J.; Wuest, J. D.; Zacharie, B. *J. Am. Chem. Soc.* **1986**, *108*, 73–77. Wuest, J. D.; Zacharie, B. *Organometallics* **1985**, *4*, 410–411.

(4) Katz, H. E. *Organometallics* **1987**, *6*, 1134–1136. Katz, H. E. *J. Am. Chem. Soc.* **1986**, *108*, 7640–7645. Katz, H. E. *J. Org. Chem.* **1985**, *50*, 5027–5032.

(5) Jung, M. E. *Tetrahedron Lett.* **1988**, *29*, 297–300.

(6) (a) Azuma, Y.; Newcomb, M. *Organometallics* **1984**, *3*, 9–14. (b) Newcomb, M.; Madonik, A. M.; Blanda, M. T.; Judice, J. K. *Organometallics* **1987**, *6*, 145–150.

(7) (a) Newcomb, M.; Horner, J. H.; Blanda, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 7878–7879. (b) Newcomb, M.; Blanda, M. T. *Tetrahedron Lett.* **1988**, *29*, 4261–4264.

0002-7863/89/1511-6294$01.50/0