Synthesis of a Pentacyclic ABCDE Bruceantin Intermediate[1]

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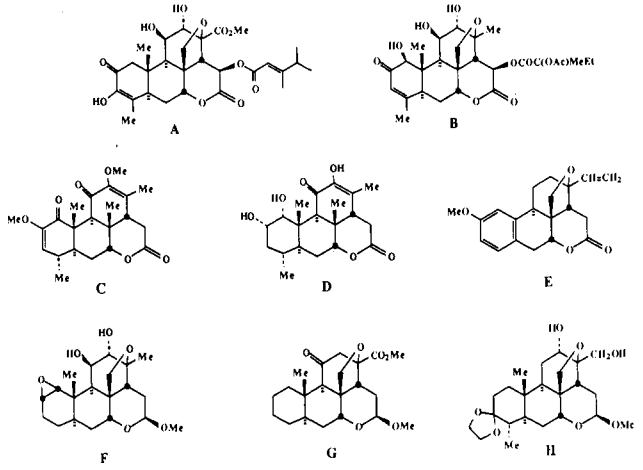
Abstract: The synthesis of pentacyclic diol **34** is described. Key transformations involve the intramolecular alkylation of a ketone enolate by a β-bromo acetal moiety to afford tetracyclic acetal **12**, establishment of pentacyclic tetrahydrofuran **26** by intramolecular oxygen alkylation of a cyanohydrin prepared in situ by cyanide addition to α-selenophenyl ketone **21**, and utilization of tetrahydrofuran lone pair assistance to effect regiospecific monooxidation of 1,2-diol bis(oxosulfonium) ion **32** to prepare monohydroxy ketone **33**.

Bruceantin (A) and quassimarin (B) are members of the quassinoid family of diterpenoids. The architecture, oxidation level, and biological promise of these materials has engendered a massive synthetic effort on the part of many research groups.[2]



Although bruceantin or quassimarin has yet to be synthesized, two tetracyclic quassinoids, quassin (C) and castelanolide (D), have been prepared by the Grieco group at Indiana.[3] In addition, four research groups have reported the preparation of pentacyclic derivatives E,[2b,c] F,[2d] and G,[2e] and H[2f] which sets the stage for the final attack on bruceantin and quassimarin. In this paper, we describe the synthesis of pentacyclic diol **34**, an intermediate which may also prove of value in the total synthesis of bruceantin.

Synthesis of the pentacyclic target began with tricyclic γ-silyloxy enone **1**[4] (Scheme I). Establishment of the C-8 hydroxymethyl functionality was performed by utilization of the Negata hydrocyanation reaction,[4] affording axial nitrile **2**. Protection of the C-13 ketone as the TBDMS enol ether **3** followed by DIBAL reduction of the nitrile moiety produced aldehyde **4** which was converted to neopentyl alcohol **5** by a second DIBAL reaction. Treatment of this alcohol with benzyl bromide and sodium hydride in the presence of tetrabutylammonium iodide smoothly afforded benzyl ether **6**. Deprotection of the silyl enol ether moiety of **6** was best effected by simply treating the crude benzylation product (containing excess benzyl bromide) with dilute aqueous hydrochloric acid. Under these conditions, hydrolysis of the axial C-7 silyloxy group was quite slow; therefore, ketone **7** was isolated and treated in a separate reaction with tetrabutylammonium fluoride to generate hydroxy ketone **8**. Reaction of **8** with 1-ethoxy-1,2-dibromoethane and *N*,*N*-dimethylaniline at room temperature by the method of Schlessinger et al.[5] afforded a 1:1 mixture of bromo acetals **9ax** and **9eq** in 82% yield.

Schlessinger has studied the cyclization of a diastereomeric mixture of bromo acetals **10ax**/**10eq**[5] (Scheme II). In this study, the authors found that only one of the two diastereomers (**10ax**) underwent cyclization to afford cis-fused acetal **11ax**, the remaining diastereomer (**10eq**) being far less reactive.[6] Presumably the diminished reactivity of **10eq** results from the additional energy required to accommodate the unfavorable eclipsing interaction of the leaving group and the alkoxy group which is required to produce **11eq**.[7]

Similar treatment of bromo acetals **9ax**/**9eq** with 2 equiv of potassium *tert*-butoxide in benzene[8] for 3 h at room temperature afforded a 3:2 mixture of cyclized acetals **12ax**/**12eq** in 84% yield along with 6% recovered **9eq**. When the reaction was quenched after 0.5 h, **12ax** was isolated in 39% yield as the only cyclized product along with 56% bromo acetals **9ax**/**9eq** in a ratio of 1:5. Resubjecting this recovered sample to a 4-h, room-temperature reaction afforded a 76% yield of **12ax**/**12eq** in a 1:4 ratio. These results demonstrate that formation of **12ax** is about a factor of 10 faster than formation of **12eq**.

Reaction of either acetal **12ax** or **12eq** with methanesulfonic acid in DMF at 140 °C affords dihydropyran **13** in essentially quantitative yield (Scheme III). Monitoring these reactions by TLC indicates that conversion of the axial isomer to **13** was complete within 0.5 h, but the equatorial isomer was required in excess of 2 h to proceed to completion. Formation of dihydropyran **13** is of significance for two reasons. Firstly, it allows effective utilization of the **12ax**/**12eq** mixture since treatment of **13** with acidic ethanol or methanol affords acetals **12ax** and **14ax**, respectively, thus avoiding the problems associated with carrying a mixture of diastereomers through the subsequent steps of the synthesis. Secondly, efficient access to a D-ring dihydropyran bodes well for ultimate construction of the requisite α-hydroxy lactone since Takashashi has shown that quassin analogue **16**,

(1) Bruceantin Support Studies 12. For paper 11 see: Kuo, F.; Fuchs, P. L. *Synth. Commun.*, in press. For paper 9 see: Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902. For paper 10 see: Hedstrand, D. M.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Org. Chem.*, in press.

(2) For a more information about synthetic efforts in the quassinoid area, see references contained in the following recent papers: (a) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264. (b) Shishido, K.; Saitoh, T.; Fukumoto, K.; Kametani, T. *J. Chem., Soc. Perkin Trans. 1* **1984**, 2139. (c) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1986**, *27*, 1339. (d) Batt, D. B.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353. (e) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730. (f) Murae, T.; Sasaki, M.; Knonsu, T.; Matsuo, H.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 3411.

(3) (a) Grieco, P. A.; Vidari, G.; Ferrino, S. *J. Am. Chem. Soc.* **1984**, *106*, 3539. (b) Grieco, P. A.; Lis, R.; Ferrino, S.; Yan Jaw, J. *J. Org. Chem.* **1984**, *49*, 2342.

(4) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902.

(5) Kieczykowski, G. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 1938; **1980**, *102*, 782.

(6) It should be noted that the structural assignment for cyclization product **11ax** shown in the scheme is as corrected by Grieco (Yoshida, K.; Grieco, P. A. *J. Org. Chem.* **1984**, *49*, 5257); the original assignment of **11eq** resulted in the Rochester group postulating a quite different mechanism for the stereocontrol observed.[5]

(7) Intramolecular alkylation of an cyclohexyl ester bearing a bromo acetal moiety affords a pair of diastereomeric bridged bicyclic acetals (Wakamatsu, T.; Hara, H.; Ban, Y. *J. Org. Chem.* **1985**, *50*, 108.

(8) This reaction is extraordinarily sensitive to the exact choice of base. In model studies conducted with a similar substrate lacking the A ring, it was found that LDA at −40 °C, lithium diethylamide at −40 °C, potassium diethylamide at −78 °C, NaH or KH in ether at room temperature, or DBU at room temperature failed to produce more than trace amounts of **10ax**/**10eq** (Kuo, F. Ph.D. Thesis, Purdue University, 1986).

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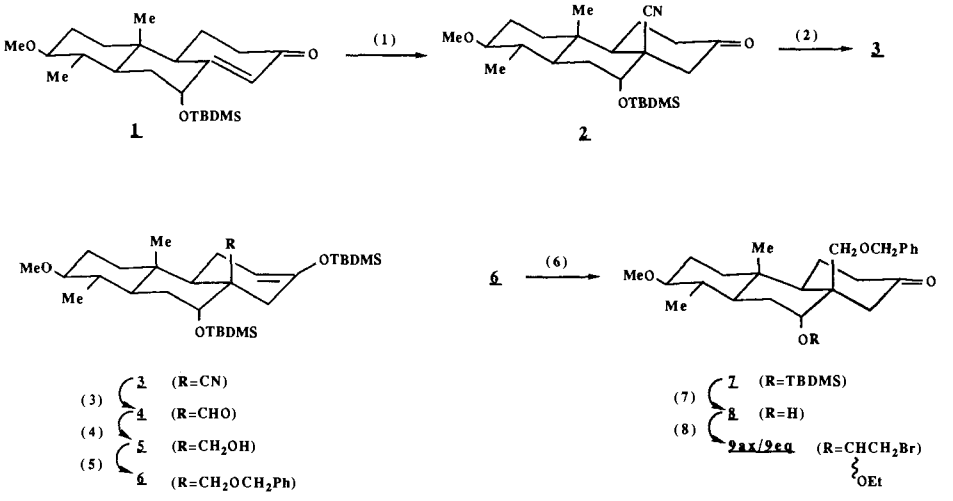
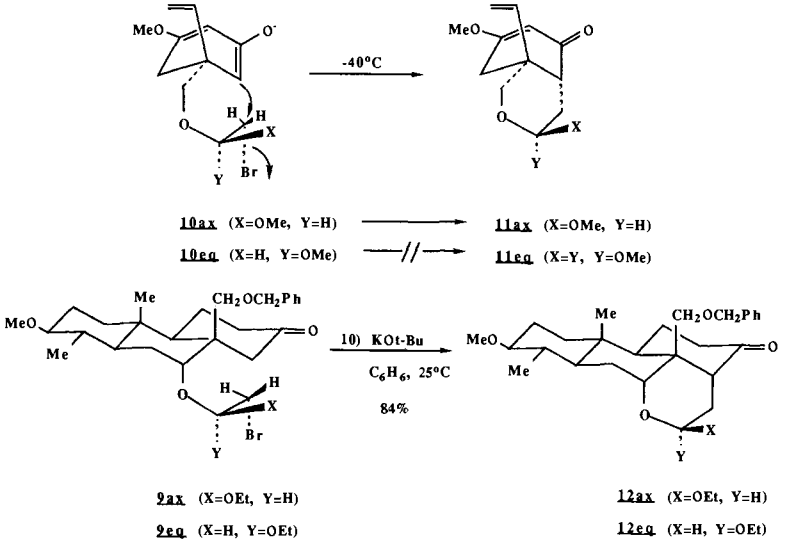
Scheme I

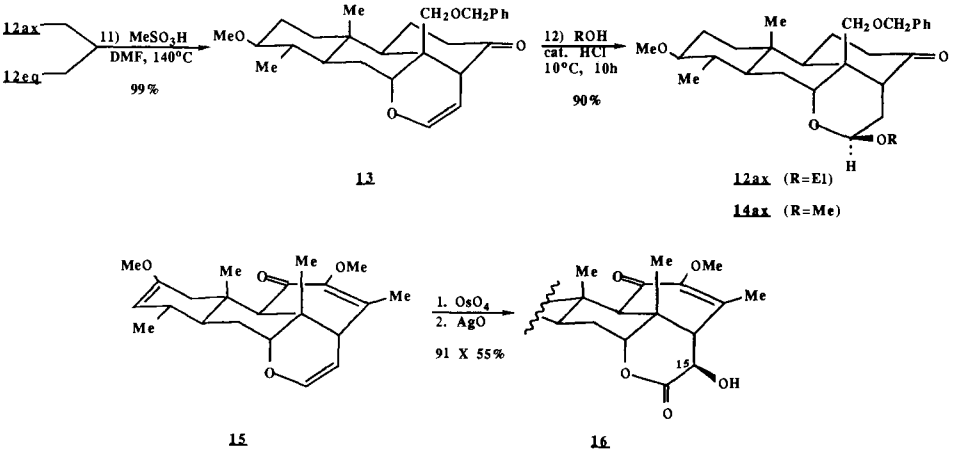


(1) Et_2AlCN, 60%; (2) TBDMS-Tf, 100%; (3) i. DIBAL ii. HOAc, 95%; (4) DIBAL, 90%; (5) BzBr; (6) HCl; (7) n-Bu_4NF, 90% from 5; (8) $BrCH_2CH(Br)OEt$, 82%.

Scheme II



Scheme III



bearing the correct C-15 stereochemistry, can be obtained via osmylation/oxidation of dihydropyran **15**.[9]

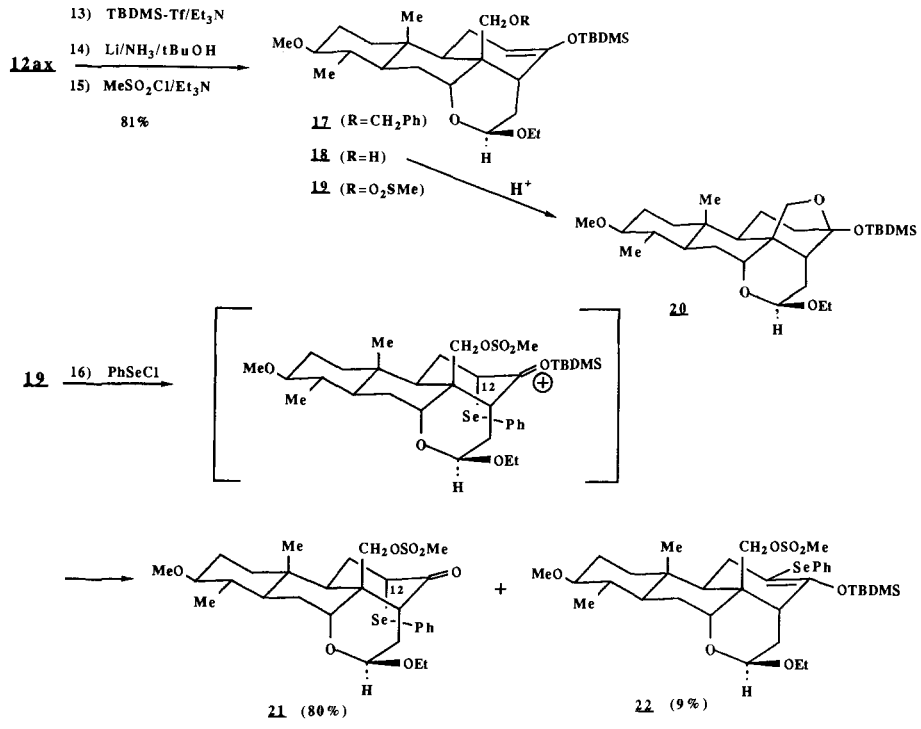
Conversion of **12ax** to appropriate precursors of the E-ring tetrahydrofuran moiety was accomplished as follows (Scheme IV).

Treatment of **12ax** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine at 0 °C affords silyl enol ether **17** which is debenzylated by using lithium in liquid ammonia[10]

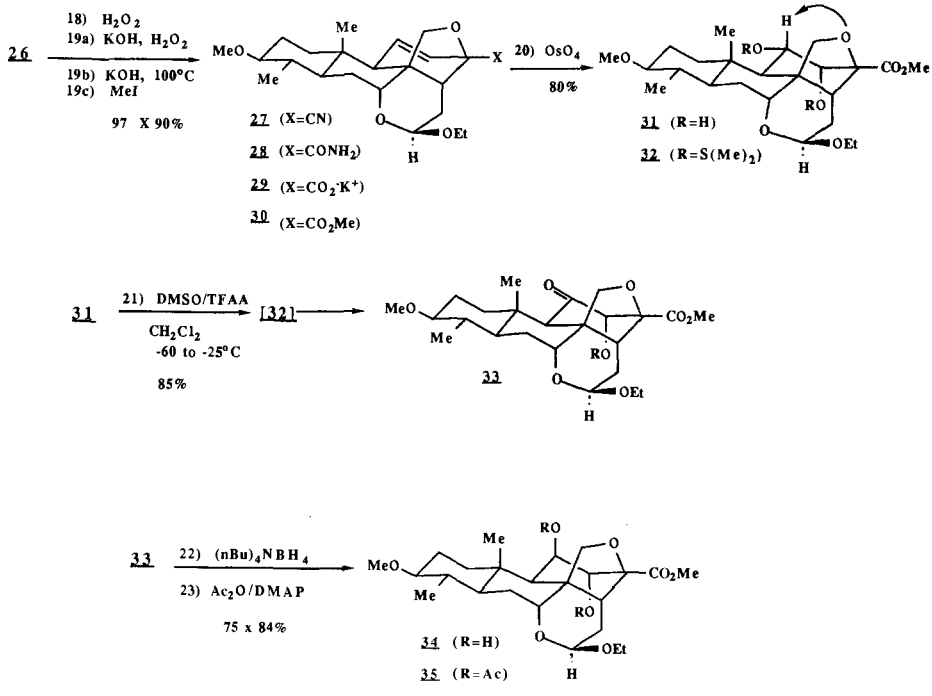
(9) Murae, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 941.

(10) Reist, E. J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 3725.

Scheme IV



Scheme V

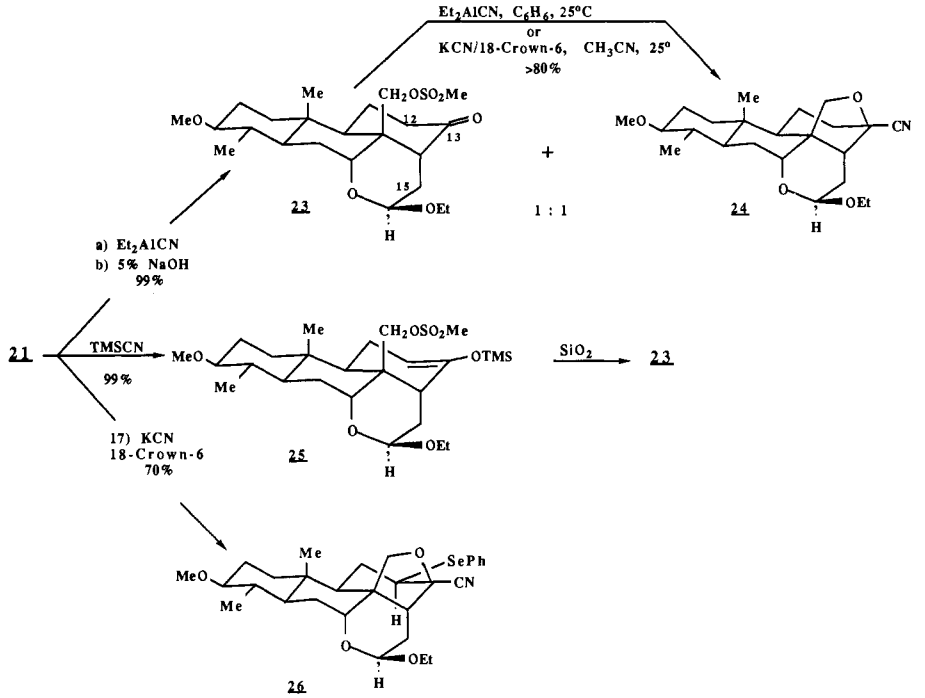


to afford the acid-sensitive neopentyl alcohol **18**. Standing in commercial $CDCl_3$ or chromatography on silica gel results in transformation of **18** to pentacyclic ketal **20**. Fortunately, treatment of crude **18** with methanesulfonyl chloride and triethylamine in methylene chloride[11] smoothly affords the desired mesylate **19** in 81% overall yield for the three-step sequence from **12ax**. Reaction of silyl enol ether **19** with phenylselenyl chloride[12] in THF at 0 °C produces the desired α-selenyl ketone **21** in addition to a small amount of selenylated silyl enol ether **22**.

With **21** in hand, the stage was set to employ an E-ring strategy we had developed in a model study,[13] namely, addition of a carboxylate surrogate to the C-13 carbonyl, followed by intramolecular oxygen alkylation of the incipient alkoxy anion (Scheme V). Earlier studies had demonstrated that highly basic anions such as tris(thiomethyl)methyllithium[13] were inappropriate nucleophiles for this task due to irreversible enolization of the keto moiety.[14] Surprisingly, treatment of **21** with 5 equiv of diethylaluminum cyanide[15] in benzene at room temperature affords a 1:1 mixture of keto mesylate **23** and pentacyclic nitrile **24** in essentially quantitative yield. Control studies demonstrate that either diethylaluminum cyanide or potassium cyanide/18-crown-6 will add to **23** to produce **24** in excellent yield. Monitoring the

(11) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(12) Sharpless, K. B.; Laucr, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 6137.
(13) Dailey, O. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216.
(14) These studies included both α-bromo and α-phenylselenyl ketones. See: Kuo, F. Ph.D. Thesis, Purdue University, 1986.
(15) Nagata, W.; Yoshioka, M.; Hirai, S. *J. Am. Chem. Soc.* **1972**, *94*, 4635, 4672.

Scheme VI



reaction between **21** and diethylaluminum cyanide reveals that **23** (presumably as its aluminum enolate) is the primary reaction product and that **24** is apparently formed during the quench of the reaction mixture. Reaction of **21** with trimethylsilyl cyanide[16] also affords a product of reductive deselenylation, silyl enol ether **25** (99%). Verification of the structure of **25** was aided by conversion to keto mesylate **23** during chromatography. Apparently the axial phenylselenyl group in **21** is rendered unusually labile by virtue of its 1,3-diaxial relationship to the C-15 methylene of the acetal moiety.

A solution to this problem was provided by reaction of **21** with potassium cyanide and 18-crown-6 in acetonitrile at room temperature which afforded pentacyclic nitrile **26** in 70% yield. The structure of **26** was secured by the standard of battery of spectral tools (see Experimental Section) and was further confirmed by single-crystal X-ray analysis (see Figure 1 and supplemental material). As can be seen, this transformation has involved inversion of the center bearing the phenylselenide group. Whether this reaction occurs by simple cyanide-catalyzed epimerization or via nucleophilic deselenylation/reselenylation with phenylselenyl cyanide generated in situ was not experimentally determined.

Treatment of the equatorial selenide **26** with 30% H_2O_2 at 0 °C in THF[17] affords olefin **27** in 97% yield (Scheme VI). Hydrolysis of the nitrile was accomplished by sequential treatment with basic hydrogen peroxide[18] to produce a material which was neither purified nor characterized but was assumed to be the primary amide **28**. Further saponification of this material under more forcing conditions produced the potassium salt **29** which was further subjected to methyl iodide to complete conversion to the requisite methyl ester **30** (90% overall yield from nitrile **27**).

Final functionalization of the C-11,12 olefin was smoothly accomplished by utilizing the method which had been established in the earlier model study.[13,19] Reaction of ester **30** with osmium tetroxide in pyridine at room temperature produced cis-diol **31** in 80% yield. Treatment of **31** with the Swern reagent[20,13] *in the absence of any base*[13] afforded the single α-keto alcohol **33** in 85% yield. Presumably this reaction is proceeding via the intermediacy of bis(oxosulfonium) ion **32** which suffers intramolecular deprotonation of the axial C-11 hydrogen by the tetrahydrofuran lone pair.[13] Tetrabutylammonium borohydride reduction of **33** stereospecifically produces the trans-diol in 75% yield. Acetylation affords diacetate **35** for the purposes of spectral comparison. Thus, diol **34** has been prepared in 22 steps from **1** in an overall yield of 5%.[21]

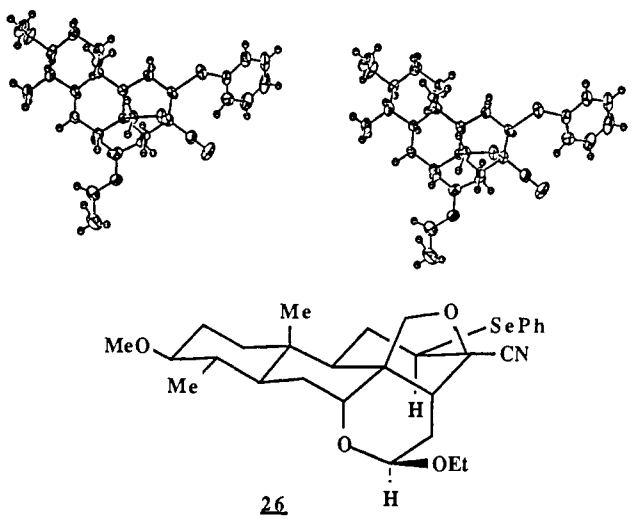


Figure 1. X-ray structure of compound **26**.

Pentacyclic compounds **27**, **30**, **31**, **34**, and **35** were found to be devoid of cytotoxic activity in the KB assay at a concentration of 200–600 μg/mL.[22]

Experimental Section

See supplementary material for general procedures.

1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Tetradecahydro-10α-[(*tert*-butyldimethylsilyl)oxy]-10aβ-cyano-7β-methoxy-4bβ,8α-dimethyl-2-phenanthrenone (2). Diethylaluminum cyanide (275 mL of 1 M solution in toluene, 275 mmol) was added slowly (over a period of 15 min) to an

(16) (a) Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inone, M.; Nozaki, H. *Tetrahedron Lett.* **1980**, 3389. (b) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.

(17) (a) Nicolaou, K. C.; Joullie, M. M. et al. *J. Am. Chem. Soc.* **1980**, *102*, 3784. (b) Sharpless, K. B.; Lauer, R. J. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

(18) Hartley, D. *J. Chem. Soc.* **1962**, 4722.

(19) See ref 2d for another application of this protocol for establishment of a trans-diol in an advanced Bruceantin intermediate.

(20) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.

(21) Lee, K. H.; Imakura, Y.; Sumida, Y.; W, R. Y.; Hall, I. H. *J. Org. Chem.* **1979**, *44*, 2180.

(22) These tests were performed by the Cell Culture Laboratory of the Purdue Cancer Center.

ice-cooled solution of γ-silyloxy enone **1**[4] (17.9 g, 45.6 mmol) in 120 mL of benzene and 40 mL of toluene containing a catalytic amount of potassium cyanide (0.5 g) and 18-crown-6 (ca. 0.7 g). The solution was stirred at 0 °C for 5 h and then at room temperature for 43 h. The mixture was then poured into 2500 mL of ice-cooled 5% NaOH, stirred for 0.5 h, and extracted with ether (2 × 500 mL). The combined organic layer was washed with water and brine and dried ($MgSO_4$). Removal of solvent yielded a white solid which upon recrystallization from 25% ether/hexane afforded 7.4 g of **2**. The mother liquid was chromatographed on silica gel. Elution with 10% EtOAc/hexane afforded a faster moving mixture of starting material **1** and product **2** which upon recrystallization from 25% ether in hexane afforded 1.25 g of **2** (combined product 8.6 g, 20.5 mmol, 48%) and 3.53 g (9 mmol, 20%) of starting material. Thus, **2** was obtained in 60% yield based on recovered starting material: mp 172.5–173.5 °C; ^1H NMR ($CDCl_3$) δ 3.91 (br s, 1 H, C-7H), 3.36 (s, 3 H, CH_3O), 2.8 (d, 1 H, J = 15 Hz), 2.65 (m, 1 H, C-3H), 2.55 (m, 3 H), 2.31 (dd, 1 H) 1.07 (s, 3 H, CH_3), 0.93 (s, 9 H, t-Bu), 0.87 (d, 3 H, J = 6 Hz, CH_3), 0.12 (s, 3 H, CH_3), 0.08 (s, 3 H, CH_3), and 1.25–2.20 (m, remaining H); ^{13}C NMR ($CDCl_3$) δ 206.8, 121.3, 84.8, 70.9, 56.3, 49.4, 46.7, 45.2, 42.1, 40.7, 36.7, 35.8, 29.4, 25.7, 25.2, 23.1, 17.9, 15.1, 12.0, −4.5, and −5.1; exact mass calcd for $C_{24}H_{41}NO_3Si$ 419.2845, found, EI, $(M^+ + H)$ 420.2931 (self-protonated).

1,2,3,4aα,4b,5,6,7,8,8aα,9,10,10a-Tetradecahydro-7β-methoxy-4bβ,8α-dimethyl-10aβ-[(benzyloxy)methyl]-2-oxo-10α-phenanthrenol (8). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (5.8 mL, 25.2 mmol) was added to a solution of **2** (8.5 g, 20.3 mmol) and triethylamine (9.4 mL) in 150 mL of methylene chloride at 0 °C. The mixture was stirred for 2 h and then was poured into saturated aqueous sodium bicarbonate (500 mL). The aqueous layer was extracted with methylene chloride (2 × 100 mL), and the combined organic layer was washed with brine (200 mL) and water (200 mL), and dried (Na_2CO_3). Removal of solvent and chromatography (plug column) afforded silyl enol ether **3** (10.8 g, 20.2 mmol, 100%) as a white foam: ^1H NMR ($CDCl_3$, partial) δ 4.90 (br s, 1 H, C-12 vinyl proton) 3.95 (br s, 1 H, C-7H), 3.30 (s, 3 H, CH_3O) 1.00 (s, 3 H, CH_3). The white foam was dissolved in 200 mL of ether, to which diisobutylaluminum hydride (28 mL, 1 M solution in hexane, 1.4 equiv) was added at 0 °C. The mixture was stirred at 0 °C for 40 min. A white precipitate formed during the reaction. One-hundred milliliters of 6% acetic acid (saturated with sodium acetate) was added along with 50 mL of THF to dissolve the white precipitate. The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic layer was washed with 100 mL of saturated sodium bicarbonate. The aqueous layer was then extracted with 50 mL of ether, washed with brine, and dried ($MgSO_4$). Removal of the solvent afforded aldehyde **4** as white solid (10.38 g, 19.36 mmol, crude yield 95%): ^1H NMR ($CDCl_3$, partial) δ 9.90 (s, 1 H, C*H*O), 4.90 (m, 1 H, C-12 vinyl proton), 4.10 (br s, 1 H, C-7H), 3.24 (s, 3 H, CH_3O); exact mass (EI) calcd for $C_{30}H_{36}O_4Si_2$ 536.3702, found 536.3720. The crude aldehyde (10.2 g, 19 mmol) was dissolved in 100 mL of ether which was then cooled to −78 °C. Diisobutylaluminum hydride (29 mL, 1 M solution in hexane, 1.5 equiv) was added to the ether solution at −78 °C, and the mixture was stirred for 1 h. Fifty milliliters of THF and 100 mL of 6% acetic acid were added and the solution was stirred at room temperature for an additional 0.5 h. The aqueous layer was extracted with 50 mL of ethyl acetate, and the combined organic layer was washed with saturated sodium bicarbonate (2 × 100 mL). The latter aqueous layer was then back-extracted with 50 mL of ethyl acetate. The combined organic layer was washed with brine and dried ($MgSO_4$). Removal of solvent afforded alcohol **5** (9.2 g, 17 mmol, 90%) as a white solid, which was used directly in the next step without further purification: mass calcd for $C_{30}H_{58}O_4Si_2$ 538, found, CI, (M + H) 539 as base peak. Sodium hydride (0.7 g, excess, partially prewashed with hexane) was added to a solution of crude alcohol **5** (3.11 g, 5.78 mmol), benzyl bromide (3 mL, 4 equiv), and tetra-*n*-butylammonium iodide (1 eq.) in 60 mL of THF at room temperature. The mixture was stirred at room temperature for 48 h, 60 mL of 10% HCl was added to quench the reaction, and the solution was stirred at room temperature overnight. The resultant red organic solution was washed with aqueous sodium sulfite solution. The light-yellow organic layer was then washed with brine and dried ($MgSO_4$). Removal of the solvent and chromatography (SiO_2, 25% EtOAc/hexane) to remove the excess benzyl bromide resulted in isolation of a mixture of **7** and **8** as a glassy paste which was then stirred with excess tetra-*n*-butylammonium fluoride (4 equiv) in 50 mL of THF at room temperature until the reaction was complete (ca. 48 h). The mixture was diluted with 100 mL of ethyl acetate, washed with saturated sodium bicarbonate and brine and dried ($MgSO_4$). Removal of the solvent and chromatography (SiO_2, 30% EtOAc/hexane) afforded benzyl ether **8** (2.10 g, 5.24 mmol, 90% from **5**) as a white foam **7**: ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H, arom.), 4.43 and 4.39 (AB pattern, 2 H, J = 12 Hz, benzyl protons), 3.67 (br s, 1 H, C-7H), 3.53 and 3.35 (AB pattern, 1 H each, J = 9.5 Hz, CH_2O), 3.35 (s, 3 H, CH_3O), 2.63 (m, 1 H, C-3H), 2.55 (d, 1 H, J = 14 Hz), 2.30 (dd, 1 H, J = 14, 2.3 Hz), 1.05 (td, 1 H), 0.92 (s, 9 H, t-Bu), 0.89 (d, 3 H, J = 5 Hz, CH_3), 0.76 (s, 3 H, CH_3), 0.06 (s, 3 H, CH_3), 0.02 (s, 3 H, CH_3), and 1.00–2.50 (m, remaining H). **8**: ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, arom.), 4.42 and 4.38 (AB pattern, 2 H, J = 12 Hz, benzyl protons), 3.77 (br s, 1 H, C-7H), 3.51 and 3.39 (AB pattern, 1 H each, J = 9.8 Hz), 3.35 (s, 3 H, CH_3O), 2.66 (m, 1 H, C-3H), 2.62 and 2.43 (AB pattern, 1 H each, J = 14 Hz), 1.09 (td, 1 H), 0.92 (d, 3 H, J = 5.9 Hz, CH_3), 0.77 (s, 3 H, CH_3), and 1.40–2.30 (m, reamining H); ^{13}C NMR ($CDCl_3$) δ 212.8, 137.9, 128.0, 127.3, 84.9, 73.4, 72.7, 68.9, 56.3, 48.4, 47.3, 46.9, 42.9, 40.7, 37.0, 36.3, 35.8, 28.7, 25.6, 21.4, 14.9, and 13.4; exact mass calcd for $C_{25}H_{36}O_4$ (**8**) 400.2604, found (M + H) 401.2688.

20-(Benzyloxy)-16β-ethoxy-3β-methoxy-13-oxo-21-norpicrasane (12ax) and the 16α Isomer 12eq. 1-Ethoxy-1,2-dibromoethane (freshly made from 2.5 mL of Br_2 and 5 mL of ethyl vinyl ether at −5 °C) was added to a solution of **8** (1.78 g, 4.44 mmol) and *N*,*N*-dimethylaniline (7 mL) in 40 mL of THF at room temperature. The mixture was stirred at room temperature for 5 h before it was poured into 150 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (100 mL), and the combined organic layer was washed with cold 5% HCl, saturated sodium bicarbonate and brine, and dried ($MgSO_4$). Removal of the solvent and chromatography on SiO_2 (using hexane as the initial eluent to remove fast-moving *N*,*N*-dimethylaniline followed by 5% ether in methylene chloride as eluent) afforded bromo acetal **9** as a mixture of two diastereomers (oil, 2.0 g, 3.64 mmol, 82%) which, without further purification or separation, was used in the next step: mass, CI, (M + 1) 551/553 for $C_{29}H_{43}BrO_5$. The bromo acetal **9** was dissolved in 36 mL of benzene, to which potassium *tert*-butoxide (850 mg, 2 equiv) was added at room temperature. The mixture was stirred for 0.5 h, 50 mL of 5% HCl was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with saturated aqueous sodium bicarbonate and dried ($MgSO_4$). Removal of the solvent and chromatography (5% ether in CH_2Cl_2) afforded tetracyclic acetal **12ax** (white foam, 669 mg, 1.42 mmol, 39%) along with unreacted starting material (oil, 1.12 g, 2.15 mmol).

In another experiment, potassium *tert*-butoxide (816 mg, 2.2 equiv) was added to a solution of bromo acetal **9ax/9eq** (1.82 g, 3.3 mmol) in 33 mL of benzene at room temperature. The mixture was stirred for 3 h. Usual workup procedure afforded a white foam (1.3 g, 2.77 mmol, 84%) which was a mixture of **12ax/12eq**, which could only be partially separated by chromatography, along with 100 mg of **9eq** (0.18 mmol, 6%) as a single isomer **9eq**: ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H, arom.), 4.59 (t, 1 H, J = 5.1 Hz, O*CH*OEt), 4.45 and 4.38 (AB pattern, 2 H, J = 12 Hz, benzyl protons), 3.57 and 3.70 (m, 1 H each, CH_3CH_2O), 3.58 (br s, 1 H, C-7H), 3.43 (s, 2 H, CH_2O), 3.35 (s, 3 H, CH_3O), 3.34 (m, 2 H, CH_2Br), 2.74 (d, 1 H, J = 14 Hz), 2.44 (dd, 1 H, J = 14, 2 Hz), 2.67 (m, 1 H, C-3H), 1.24 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.09 (td, 1 H), 0.92 (d, 3 H, J = 6.2 Hz, CH_3), 0.75 (s, 3 H, CH_3), and 1.30–2.40 (m, remaining protons); ^{13}C NMR ($CDCl_3$) δ 211.8, 137.9, 128.2, 127.4, 102.8, 84.9, 76.8, 73.5, 71.4, 62.2, 56.4, 48.2, 48.0, 47.3, 43.3, 40.7, 37.0, 36.3, 36.0, 31.7, 26.1, 25.7, 21.4, 15.0, 14.7, and 13.8; MS for $C_{29}H_{43}BrO_5$ 550, found, CI, (M + H) 551/553. **12ax**: ^1H NMR ($CDCl_3$) δ 7.35–7.26 (m, 5 H, arom.), 4.87 (d, 1 H, J = 3 Hz, C-16H), 4.46–4.35 (AB pattern, 2 H, J = 12 Hz, benzyl protons), 3.77 and 3.20 (AB pattern, 2 H, J = 9.7 Hz, CH_2O), 3.71 (br s, 1 H, C-7H), 3.68 and 3.41 (m, 1 H each, CH_3CH_2O), 3.35 (s, 3 H, CH_3O), 2.93 (dd, 1 H, J = 4.7, 13.5 Hz, C-14H), 2.68 (m, 1 H, C-3H), 1.19 (t, 3 H, J = 7 Hz, CH_3CH_2O), 0.92 (d, 3 H, J = 5.7 Hz, CH_3), and 0.80 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 212.7, 137.9, 128.1, 127.5, 127.2, 95.4, 84.9, 66.2, 62.1, 56.4, 48.8, 43.6, 41.6, 41.1, 37.3, 37.2, 36.4, 36.3, 36.0, 29.9, 26.8, 25.7, 21.1, 15.1, 14.9, 14.7, 13.8, and 13.6; MS for $C_{29}H_{42}O_5$ 470, found, CI, (M + H) 471, base peak (M + H − C_2H_5OH) 425. **12eq**: ^1H NMR ($CDCl_3$) δ 7.36–7.26 (m, 5 H, arom.), 4.42 (br s, 1 H, C-16H), 4.40 (s, 2 H, benzyl protons), 4.41 and 3.52 (m, 1 H each, CH_3CH_2O), 3.64 and 3.27 (AB pattern, 2 H, J = 9.7 Hz, CH_2O), 3.53 (br s, 1 H, C-7H), 3.35 (s, 3 H, CH_3O), 2.73 (dd, 1 H, J = 4.7, 13 Hz), 2.69 (m, 1 H, C-3H), 1.23 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.14 (dt, 1 H), 0.91 (d, 3 H, J = 6.2 Hz, CH_3), and 0.79 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 212.1, 137.8, 128.3, 127.6, 101.4, 84.8, 74.6, 73.7, 64.3, 56.6, 53.7, 43.3, 42.4, 41.8, 37.6, 37.1, 36.5, 36.1, 31.7, 27.0, 25.8, 21.2, 15.2, 14.8, and 13.9; MS for $C_{24}H_{42}O_5$ (**12eq**) 470, found, CI (M + H − C_2H_5OH) 425 as base peak.

20-(Benzyloxy)-3β-methoxy-13-oxo-21-norpicrasene (13). Methanesulfonic acid (1 drop, catalytic amount) was added to a solution of **12eq** (47 mg, 0.1 mmol) in 0.5 mL of DMF under a stream of nitrogen at room temperature. The mixture was then stirred at 140 °C for 2 h and cooled to room temperature, and 10 mL of saturated aqueous sodium bicarbonate was added. The solution was extracted with ether (2 × 10 mL), and the combined organic layer was washed with brine and dried

(K_2CO_3). Removal of the solvent and chromatography afforded **13** (oil, 41 mg, 99%). The same product was obtained when **12ax** was subjected to the same reaction conditions except the reaction was complete in 0.5 h: ^1H NMR ($CDCl_3$) δ 7.35–7.25 (m, 5 H, arom.), 6.40 (m, 1 H, C-16 vinyl proton), 4.42 (m, 1 H, C-15 vinyl proton), 4.41 (br s, 2 H, benzyl protons), 3.85 (br s, 1 H, C-7H), 3.74 and 3.30 (d, 1 H each, J = 9.5 Hz, CH_2O), 3.35 (s, 3 H, CH_3O), 3.20 (br s, 1 H, C-14 allylic proton), 2.67 (m, 1 H, C-3H), 2.41 (m, 2 H, C-12H), 1.06 (td, 1 H), 0.93 (d, 3 H, J = 11.5 Hz, CH_3), 0.84 (s, 3 H, CH_3), and 1.20–2.10 (m, remaining H); ^{13}C NMR ($CDCl_3$) δ 212.0, 142.8, 137.6, 128.2, 127.5, 97.5, 84.9, 74.1, 73.8, 73.7, 56.5, 51.3, 43.4, 40.8, 38.5, 37.3, 36.2, 35.8, 26.4, 25.8, 21.2, 14.8, and 14.2; MS for $C_{27}H_{36}O_4$ 424, found, CI, (M + 1) 425 as base peak.

Conversion of Dihydropyran 13 to Tetracyclic Acetal 12ax and 14ax. One drop of concentrated hydrochloric acid was added to a solution of dihydropyran **13** (21 mg, 0.05 mmol) in 5 mL of anhydrous ethanol (or methanol) at 0 °C. The mixture was stirred for 10 h while the temperature was allowed to warm to 10 °C. Solid sodium bicarbonate was added to neutralize the acid, the mixture was filtered, and the solvent was removed and chromatographed (SiO_2, 10% ether in methylene chloride) to afford 21 mg of **12ax** (20 mg for **14ax**) as a white foam **14ax**: ^1H NMR ($CDCl_3$) δ 7.35–7.25 (m, 5 H, arom.), 4.76 (d, 1 H, J = 3.2 Hz, C-16H), 4.43 and 4.36 (AB pattern, 1 H each, J = 12.2 Hz, benzyl protons), 3.77 and 3.17 (AB pattern, 1 H each, J = 9.7 Hz, CH_2O), 3.35 (s, 3 H, CH_3O), 3.31 (s, 3 H, CH_3O), 2.85 (dd, 1 H, J = 4.8, 13.6 Hz, C-14H), 2.68 (m, 1 H, C-3H), 2.35 (m, 2 H, C-12H), 1.10 (m, 1 H), 0.92 (d, 3 H, J = 5.9 Hz, CH_3), 0.82 (s, 3 H, CH_3), and 1.26–2.10 (m, remaining H); ^{13}C NMR ($CDCl_3$) δ 212.5, 137.8, 128.2, 127.4, 96.9, 84.5, 75.3, 73.6, 66.3, 56.4, 54.4, 48.8, 43.7, 41.7, 41.4, 37.4, 37.2, 36.4, 36.1, 29.6, 26.9, 25.8, 21.1, 14.7, and 13.6; MS for $C_{28}H_{40}O_5$ (**14ax**) 456, found, CI, (M + H) 457, (M + H – CH_3OH) 425 as base peak.

13-[(*tert*-Butyldimethylsilyl)oxy]-16β-ethoxy-20-(methanesulfonato)-3β-methoxy-21-norpicras-12-ene (19). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.2 mL, 1.2 equiv) was added to a solution of **12ax** (333 mg, 0.71 mmol) and triethylamine (0.5 mL) in 10 mL of methylene chloride at 0 °C. The mixture was stirred at 0 °C for 0.5 h, 40 mL of saturated sodium bicarbonate was added, and the solution was extracted with methylene chloride (2 × 15 mL). The combined organic layer was washed with brine and dried (K_2CO_3). Removal of the solvent afforded **17** (oil, 0.415 g) quantitatively which exhibited a characteristic vinyl proton ^1H NMR at 4.85 ppm. The crude product was then dissolved in 10 mL of THF and added to a blue solution of lithium (10 equiv) in 40 mL of liquid ammonia at –78 °C. The mixture was stirred for 1 h, water was added dropwise to quench the reaction, and the ammonia was evaporated at room temperature. The residue was treated with saturated sodium bicarbonate (20 mL), and the solution was extracted with ether (2 × 20 mL). The combined organic layer was washed with water and brine and dried (K_2CO_3). Removal of the solvent afforded **18** (340 mg) as white foam, which was unstable to silica gel and $CDCl_3$. The crude **18**, without further purification, was added to 10 mL of methylene chloride containing 0.8 mL of triethylamine at 0 °C. Methanesulfonyl chloride (0.2 mL) was added to the above solution. The mixture was stirred for 16 h and allowed to warm to room temperature. Thirty milliliters of saturated sodium bicarbonate was added, and the aqueous layer was extracted with methylene chloride (2 × 20 mL). The combined organic layer was washed with water and brine and dried (K_2CO_3). Removal of the solvent and chromatography (30% ether in hexane, neutral Al_2O_3) afforded mesylate **19** (328 mg, 0.57 mmol, 81% from **12ax**) as a white foam: ^1H NMR ($CDCl_3$) δ 4.82 (br s, 1 H, C-16H), 4.73 (m, 1 H, C-12 vinyl proton), 4.48 and 4.16 (AB pattern, 1 H each, J = 10 Hz, CH_2O), 4.03 (br s, 1 H, C-7H), 3.66 and 3.43 (m, 1 H each, CH_3CH_2O), 3.34 (s, 3 H, CH_3O), 2.99 (s, 3 H, CH_3SO_3), 2.66 (dd, 1 H, J = 4.8, 12.4 Hz, C-14 allylic proton), 1.20 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.05 (dt, 1 H), 0.94 (d, 3 H, CH_3), 0.84 (s, 3 H, CH_3), 0.15 (s, 3 H, CH_3), 0.12 (s, 3 H, CH_3), 0.91 (s, 9 H, *t*-Bu), and 1.30–2.20 (m, remaining H); ^{13}C NMR ($CDCl_3$) δ 152.1, 128.0, 100.9, 96.3, 85.0, 68.7, 64.5, 62.3, 56.2, 43.7, 40.5, 39.1, 37.5, 36.8, 36.5, 36.0, 34.8, 32.5, 26.5, 26.1, 25.9, 20.8, 18.2, 15.3, 14.0, –4.1, and –4.4; exact mass calcd for $C_{29}H_{52}O_7SSi$ 572.3189, found, EI, (M + H) 573.3281 (self-protonated).

16β-Ethoxy-20-(methanesulfonato)-3β-methoxy-13-oxo-12α-(phenylseleno)-21-norpicrasane (21). Phenylselenyl chloride[12] (90 mg, 0.47 mmol) in 10 mL of THF was added dropwise to a solution of silyl enol ether **19** (239 mg, 0.41 mmol) in 15 mL of THF at 0 °C. The mixture was stirred at 0 °C for 1.5 h, 50 mL of saturated sodium bicarbonate was added, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent and chromatography (30% EtOAc in hexane) afforded **21** (200 mg, 0.33 mmol, 80%) as a white solid along with a less polar product (27 mg) which was identified as **22** (CI, M + H 729). **21**: mp 143–145 °C; ^1H NMR ($CDCl_3$) δ 7.57–7.30 (m, 5 H, arom.), 4.90 (d, 1 H, J = 1.5 Hz, C-16H), 4.38 and 4.12 (AB pattern, 1 H each, J = 10.4 Hz, CH_2O), 3.99 (br s, 1 H, C-7H), 3.77 (br s, 1 H, C-12H), 3.66 and 3.44 (m, 1 H each, CH_3CH_2O), 3.37 (s, 3 H, CH_3O), 2.94 (s, 3 H, CH_3SO_3), 2.72 (m, 1 H), 2.67 (m, 1 H), 1.20 (t, 3 H, J = 7 Hz, CH_3CH_2O), 0.96 (d, 3 H, J = 6.1 Hz, CH_3), 0.89 (s, 3 H, CH_3), and 1.35–2.40 (m, remaining H); ^{13}C NMR ($CDCl_3$) δ 207.6, 135.1, 129.2, 128.9, 128.4, 95.4, 84.7, 71.7, 65.2, 62.4, 56.5, 47.0, 43.2, 40.4, 38.4, 37.3, 37.0, 36.0, 32.4, 27.1, 26.5, 25.6, 15.0, 14.8, and 14.0; exact mass calcd for $C_{29}H_{42}O_7SSe$ 614.1805, found, EI, 614.1812. **22**: ^1H NMR ($CDCl_3$) δ 7.41–7.23 (m, 5 H, arom.), 4.84 (d, 1 H, J = 1.7 Hz, C-16H), 4.56 and 4.13 (AB pattern, 1 H each, J = 10 Hz, CH_2O), 4.02 (br s, 1 H, C-7H), 3.67 and 3.41 (m, 1 H, CH_3CH_2O), 3.31 (s, 3 H, CH_3O), 3.03 (s, 3 H, CH_3SO_3), 3.01 (m, 1 H, C-14 allylic proton), 2.61 (m, 1 H, C-3H), 1.19 (t, 3 H, J = 7 Hz, CH_3CH_2), 0.92 (d, 3 H, J = 5.4 Hz, CH_3), 0.96 (s, 9 H, *t*-Bu), 0.73 (s, 3 H, CH_3), 0.25 (s, 3 H, CH_3), 0.24 (s, 3 H, CH_3), and 1.30–2.35 (m, remaining H); mass calcd for $C_{35}H_{56}O_7SSeSi$ 728, found, CI, (M + H) 729 as base peak.

16β-Ethoxy-20-(methanesulfonato)-3β-methoxy-13-oxo-21-norpicrasane (23) and 13,20-Epoxy-16β-ethoxy-3β-methoxy-21-nitrilopicrasane (24). Diethylaluminum cyanide (0.1 mL, 1 M solution in toluene) was added to a solution of **21** (12 mg, 0.02 mmol) in 1.5 mL of benzene at room temperature. The mixture was stirred at room temperature for 5 h, 5 mL of 5% sodium hydroxide was added, and the solution was stirred for an additional 0.5 h. The solution was then extracted with ether (2 × 10 mL), and the combined organic layer was washed with brine (20 mL) and dried ($MgSO_4$). Removal of the solvent and chromatography (30% ether in hexane) afforded 4.5 mg of **23** (white foam) and 3.5 mg of **24**. Treatment of 2 mg of **23** with potassium cyanide in the presence of 18-crown-6 in 1 mL of acetonitrile at room temperature afforded **24** as confirmed by ^1H NMR. **23**: IR (film, $CHCl_3$) 3.42, 5.85 (C=O), 6.95, 7.39, 8.51, and 10.49 μm; ^1H NMR ($CDCl_3$) δ 4.89 (d, 1 H, J = 3.2 Hz, C-16H), 4.26 (s, 2 H, CH_2O), 3.83 (br s, 1 H, C-7H), 3.67 and 3.43 (m, 1 H each, CH_3CH_2O), 3.36 (s, 3 H, CH_3O), 3.01 (s, 3 H, CH_3SO_5), 2.97 (dd, 1 H, J = 4.7, 13.4 Hz, C-14H), 2.69 (m, 1 H, C-3H), 2.50 and 2.38 (m, 1 H each, C-12H), 1.20 (t, 3 H, J = 7 Hz, CH_3CH_2O), 0.94 (d, 3 H, J = 6 Hz, CH_3), 0.89 (s, 3 H, CH_3), and 1.10–2.20 (m, remaining H). **24**: IR (film, $CHCl_3$) 3.41, 4.46 (w, CN), 6.90, 7.59, 8.25, and 9.20 μm; ^1H NMR ($CDCl_3$) δ 5.01 (br s, 1 H, C-16H), 4.38 and 3.50 (AB pattern, 1 H each, J = 8 Hz, C-20H, CH_2O, bridged ether), 3.76 (br s, 1 H, C-7H), 3.68 and 3.46 (m, 1 H each, CH_3CH_2O), 3.34 (s, 3 H, CH_3O), 2.64 (m, 1 H, C-3H), 2.53 (dd, 1 H, J = 4.8, 11.8 Hz, C-14H), 1.21 (t, 3 H, J = 7 Hz, CH_3CH_2O), 0.91 (d, 3 H, J = 4.8 Hz, CH_3), 0.88 (s, 3 H, CH_3), and 0.95–2.05 (m, remaining H); MS for $C_{23}H_{35}NO_4$ (**24**) 389, found, CI, (M + H) 390.

Reaction of 21 with Trimethylsilyl Cyanide. Isolation of 23. One drop of trimethylsilyl cyanide was added to a solution of 5 mg of **21** in 1 mL of THF in the presence of catalyst (ZnI_2) at room temperature. The solution was stirred for 0.5 h, and TLC (Et_2O) showed a less polar product formed quantitatively. Five milliliters of saturated sodium bicarbonate was added, and the solution was extracted with ethyl acetate (2 × 5 mL). The combined organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent afforded a crude oil whose ^1H NMR showed a vinyl proton peak at 4.79 ppm and a mesylate at 2.88 ppm. The spectrum showed that the new product had retained the trimethylsilyl group but no phenyl selenide group. This labile product was assigned to be enol ether **25**. Chromatography afforded a new product which had the same ^1H NMR spectrum as **23**. **25**: ^1H NMR ($CDCl_3$) δ 4.81 (br s, 1 H, C-16H), 4.79 (br s, 1 H, C-12 vinyl proton), 4.50 and 4.23 (AB pattern, 1 H each, J = 10.2 Hz, CH_2O), 4.08 (br s, 1 H, C-7H), 3.66 and 3.40 (m, 1 H each, CH_3CH_2O), 3.30 (s, 3 H, CH_3O), 2.88 (s, 3 H, CH_3SO_3), 2.74 (dd, 1 H, C-14 allylic proton), 2.65 (m, 1 H, C-3H), 1.18 (t, 3 H, J = 7.2 Hz, CH_3CH_2O), 0.91 (d, 3 H, J = 6.4 Hz, CH_3), 0.88 (s, 3 H, CH_3), 0.19 (s, 9 H, Me_4Si), and 1.30–2.20 (m, remaining H).

13,20-Epoxy-16β-ethoxy-3β-methoxy-21-nitrilo-12β-(phenylseleno)-picrasane (26). A mixture of selenyl ketone **21** (70 mg, 0.114 mmol), potassium cyanide (10 mg, 0.15 mmol), and 18-crown-6 (33 mg, 1.1 equiv) in 5 mL of acetonitrile was stirred at room temperature for 16 h, followed by treatment with 10 mL of 5% NaOH and extraction with ether (2 × 10 mL). The combined organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent and chromatography (SiO_2, 25% EtOAc in hexane) afforded **26** (43.5 mg, 0.08 mmol, 70%) as a white solid. Recrystallization from 50% ether/hexane afforded crystals which were suitable for X-ray analysis (Figure 1): mp 198–200 °C. IR (film, $CHCl_3$) 3.40, 4.45 (w, CN), 6.32 (w), 6.93, 8.21, and 9.2 μm; ^1H NMR ($CDCl_3$) δ 7.69–7.27 (m, 5 H, arom.), 4.97 (d, 1 H, J = 3 Hz, C-16H), 4.34 and 3.55 (AB pattern, 1 H each, J = 8 Hz, C-20H, CH_2O bridged ether), 3.55 (br s, 1 H, C-7H), 3.66 and 3.44 (m, 1 H each, CH_3CH_2O), 3.33 (s, 3 H, CH_3O), 3.06 (d, 1 H, J = 11 Hz, C-12H), 2.68 (dd, 1 H, C-14H), 2.62 (m, 1 H, C-3H), 2.17 (m, 1 H), 1.19 (t, 3 H,

J = 7.2 Hz, CH_3CH_2O), 0.90 (s, 3 H, CH_3), 0.85 (s, 3 H, CH_3), and 1.00–2.10 (m, remaining H); ^{13}C NMR ($CDCl_3$) δ 135.5, 129.0, 128.7, 128.2, 119.0, 84.9, 81.0, 74.5, 69.9, 62.6, 56.5, 48.2, 45.4, 43.2, 42.2, 40.3, 36.7, 36.1, 35.9, 28.8, 28.7, 25.3, 25.2, 15.1, 14.9, and 12.7; exact mass calcd for $C_{29}H_{37}NO_4Se$ 545.2034, found, EI, 545.2035.

13,20-Epoxy-16β-ethoxy-3β-methoxy-21-nitrilopicras-11-ene (27). Hydrogen peroxide (30%, 0.1 mL) was added to a solution of 33 mg (0.06 mmol) of **26** in 5 mL of THF at 0 °C. The solution was stirred overnight while the temperature was allowed to warm to room temperature. Five milliliters of saturated sodium bicarbonate and 100 mg of sodium sulfite were added sequentially at 0 °C. The mixture was stirried for an additional 0.5 h, diluted with 5 mL of water, and extracted with ether (3 × 10 mL). The combined organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent and chromatography (SiO_2, 30% ether in hexane) afforded **27** (22.8 mg, 0.059 mmol, 97%): mp 174–175 °C; IR (film, $CHCl_3$) 3.40, 4.43 (w, CN), 6.12 (w), 6.94, 7.25, 9.10, 9.50, and 10.10 μm; ^1H NMR ($CDCl_3$) δ 5.89 (br s, 2 H, C-12,11 olefin protons), 5.03 (d, 1 H, J = 3.3 Hz, C-16H), 4.53 and 3.59 (AB pattern, 1 H each, d at 4.53, J = 8.6 Hz, and dd at 3.59, J = 8.6, 2 Hz, C-20H, CH_2O bridged ether), 3.80 (br s, 1 H, C-7H), 3.72 and 3.47 (m, 1 H each, CH_3CH_2O), 3.46 (s, 3 H, CH_3O), 2.66 (m, 1 H, C-3H), 2.62 (br s, 1 H, C-9H), 2.61 (dd, 1 H, C-14H), 1.22 (t, 3 H, J = 7 Hz, CH_3CH_2O), 0.92 (d, 3 H, CH_3), 0.90 (s, 3 H, CH_3), and 1.05–2.10 (m, remaining M); ^{13}C NMR ($CDCl_3$) δ 130.3, 125.5, 118.7, 96.0, 84.9, 72.6, 72.5, 71.2, 62.8, 56.6, 46.3, 45.3, 44.1, 43.6, 36.4, 36.1, 35.8, 28.2, 25.9, 25.3, 15.4, 15.1, and 14.6; exact mass calcd for $C_{23}H_{33}NO_4$ 387.2401, found, EI, 387.2391.

13,20-Epoxy-16β-ethoxy-3β-methoxypicrasan-21-oic Acid Methyl Ester (30). To a solution of **27** (20 mg, 0.052 mmol) in 5 mL of THF was sequentially added 0.3 mL of 10% KOH and 0.1 mL of 30% H_2O_2 at room temperature. The mixture was stirred at 40 °C overnight, an additional 5 mL of 10% KOH was then added, and the solution was heated to reflux for an additional 5 h. After cooling to room temperature, the solution was acidified to pH 5–6 by adding aqueous NaH_2PO_4 and extracted with chloroform (3 × 10 mL). The combined organic layer was dried ($MgSO_4$). Removal of the solvent afforded 20 mg of solid which, without further purification, was dissolved in 1.5 mL of acetonitrile and 0.1 mL of methyl iodide, and 50 mg of potassium carbonate and 18-crown-6 was added at room temperature. The mixture was stirred overnight. Chromatography (plug column, SiO_2, ether) of the crude reaction mixture afforded 19.5 mg (0.046 mmol, 90%) of **30**: mp 167–168.5 °C; IR (film, $CHCl_3$) 3.42, 5.75 (C=O), 6.95, 7.65, 9.15, and 9.66 μm; ^1H NMR ($CDCl_3$) δ 5.92 and 5.87 (AB pattern, 1 H each, dd at 5.92, J = 2.5, 10.5 Hz; d at 5.78, J = 10.5 Hz, C-11,12 olefine protons), 4.99 (br s, 1 H, C-16H), 4.53 and 3.63 (AB pattern, 1 H each, d at 4.53, J = 8.7 Hz; dd at 3.63, J = 1.9, 8.7 Hz, C-20H, CH_2O bridged ether), 3.81 (br s, 1 H, C-7H), 3.80 (s, 3 H, CO_2CH_3), 3.72 and 3.47 (m, 1 H each, CH_3CH_2O), 3.35 (s, 3 H, CH_3O), 2.68 (m, 1 H, C-3H), 2.66 (br s, 1 H, C-9 allylic proton), 2.47 (m, 1 H, C-14H), 1.19 (t, 3 H, J = 7 Hz, CH_3CH_2O), 0.93 (s, 3 H, CH_3), and 0.92 (d, 3 H, J = 5.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.8, 128.6, 126.9, 85.0, 80.8, 72.1, 31.5, 62.4, 56.6, 52.4, 45.4, 44.9, 44.8, 43.6, 36.4, 36.1, 35.9, 28.3, 26.7, 25.3, 15.4, 15.1, and 14.7; exact mass calcd for $C_{24}H_{36}O_6$ 420.2502, found, EI, 420.2516.

13,20-Epoxy-16β-ethoxy-11α,12α-dihydroxy-3β-methoxypicrasan-21-oic Acid Methyl Ester (31). A solution of 25 mg (0.06 mmol) of **30** in 2 mL of pyridine was treated with 2 mL (0.078 mmol) of 0.039 M osmium tetroxide in THF at room temperature. The dark-brown mixture was stirred at room temperature for 3 h, and 2 mL of saturated aqueous sodium bisulfite and 2 mL of THF were added. After stirring for an additional 1.5 h, the resulting dark-orange solution was extracted with ethyl acetate (2 × 5 mL). The combined organic layer was washed with saturated aqueous cupric sulfate (3 × 10 mL), water, and brine and dried ($MgSO_4$). Removal of the solvent and chromatography afforded 22 mg (0.048, 80%) of **31** as a white foam: IR (film, $CHCl_3$) 2.90 (br, OH), 3.41, 5.75 (C=O), 6.95, 7.30, 9.16, 9.62, and 10.3 μm; ^1H NMR ($CDCl_3$) δ 4.91 (d, 1 H, J = 3.2 Hz, C-16H), 4.26 and 3.45 (AB pattern, 1 H each, J = 8.5 Hz, C-20H, CH_2O bridged ether), 4.08 (m, 1 H, C-11H), 4.04 (br s, 1 H, C-12H), 3.83 (s, 3 H, CO_2CH_3), 3.73 (br s, C-7H), 3.64 and 3.44 (m, 1 H each, CH_3CH_2O), 3.33 (s, 3 H, CH_3O), 2.64 (m, 2 H, C-3 and C-14H), 1.18 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.05 (s, 3 H, CH_3), 0.92 (d, 3 H, J = 6.1 Hz, CH_3), and 1.30–2.55 (m, remaining H); ^{13}C NMR ($CDCl_3$) δ 173.4, 84.8, 83.0, 73.6, 72.8, 70.4, 68.1, 62.3, 56.4, 52.8, 44.6, 43.8, 43.7, 43.3, 38.3, 37.6, 36.4, 28.7, 26.9, 25.8, 15.2, 15.1, and 13.3; exact mass calcd for $C_{24}H_{38}O_8$ 454.2566; found, EI, 454.2559.

13,20-Epoxy-16β-ethoxy-12α-hydroxy-3β-methoxy-11-oxopicrasan-21-oic Acid Methyl Ester (33). Trifluoroacetic anhydride (0.1 mL) was added to a solution of 0.2 mL of Me_2SO in 1 mL of methylene chloride at −60 °C.[2d,13] After the mixture stirred for 10 min, a solution of 5 mg of **31** in 1 mL of methylene chloride was added. The mixture was stirred at −60 °C for 0.5 h and then warmed rapidly to −20 °C. The solution was stirred for an additional 1 h and then quenched by adding 1 mL of aqueous NaH_2PO_4 solution at −15 °C. The cold mixture was stirred at 0 °C for 0.5 h before 5 mL of water was added. The mixture was extracted with ether (3 × 5 mL), and the combined organic layer was washed with saturated sodium bicarbonate and dried ($MgSO_4$). Removal of the solvent and chromatography afforded 4 mg of **33** as a white foam in 85% yield: IR (film, $CHCl_3$) 2.95 (br OH), 3.41, 5.72 (C=O), 5.90 (C=O), 6.92, 7.30, and 7.94 μm; ^1H NMR ($CDCl_3$) δ 5.0 (br s, 1 H, C-16H), 4.24 and 3.56 (AB pattern, 1 H each, J = 8 Hz, C-20H, CH_2O bridged ether), 4.01 (br s, 1 H, C-12H), 3.91 (br s, 1 H, C-7H), 3.85 (s, 3 H, CO_2CH_3), 3.35 (s, 3 H, CH_3O), 3.12 (br s, 1 H, C-12OH), 2.86 (br s, 1 H, C-9H), 2.64 (m, 2 H, C-3H and C-14H), 1.22 (t, 3 H, J = 7.1 Hz, CH_3CH_2O), 1.12 (s, 3 H, CH_3), 0.92 (d, 3 H, J = 5.5 Hz, CH_3), 1.07 (dt, 1 H), and 1.40–2.00 (m, remaining H); exact mass calcd for $C_{24}H_{36}O_8$ 452.2400, found, EI, 452.2406.

13,20-Epoxy-16β-ethoxy-11β,12α-dihydroxy-3β-methoxypicrasan-21-oic Acid Methyl Ester (34). Tetra-*n*-butylammonium borohydride (25 mg, 10 eq) was added to a solution of **33** (4 mg, 0.01 mmol) in 1 mL of ethyl acetate at 0 °C. The reaction was completed after 100 min at 0 °C. Thereupon, 5 mL of NaH_2PO_4 solution was added, and the mixture was extracted with ethyl acetate (2 × 5 mL). The combined organic layer was washed with saturated sodium bicarbonate and water and dried ($MgSO_4$). Removal of the solvent and chromatography afforded 3 mg of **34**: mp 190–191 °C; IR (film, $CHCl_3$) 2.89 (br OH), 3.42, 5.76 (C=O), 6.96, 7.30, 7.66, 7.95, 8.08, 9.20, 9.60, 10.3, and 10.6 μm; ^1H NMR ($CDCl_3$) δ 4.88 (br s, 1 H, C-16H), 4.57 and 3.61 (AB pattern, 1 H each, d at 4.57, J = 8 Hz; dd at 3.61, J = 8, 1 Hz, C-20H, CH_2O bridged ether), 4.12 (dd, 1 H, J = 4.4, 10 Hz, C-11H), 3.99 (br s, 1 H, C-12H), 3.85 (s, 3 H, CO_2CH_3), 3.79 (br s, 1 H, C-7H), 3.66 and 3.46 (m, 1 H each, CH_3CH_2O), 3.35 (s, 3 H, CH_3O), 3.18 (br s, 1 H, C-12OH), 2.65 (m, 1 H, C-3H), 1.82 (d, 1 H, J = 4.1 Hz, C-9H), 1.32 (s, 3 H, CH_3), 1.19 (t, 3 H, J = 7 Hz, CH_3CH_2O), 0.94 (d, 3 H, J = 5.5 Hz, CH_3), and 1.22–2.55 (m, remaining H); exact mass calcd for $C_{24}H_{38}O_8$ 454.2566, found, EI, 454.2559.

11β,12α-Diacetoxy-13,20-epoxy-16β-ethoxy-3β-methoxypicrasan-21-oic Acid Methyl Ester (35). Two drops of acetic anhydride was added to a solution of 1 mg of **34** and 1 mg of *N*,*N*-(dimethylamino)pyridine in 1 mL of methylene chloride at room temperature. The mixture was stirred for ca. 12 h until TLC (Et_2O) showed the reaction to be complete. The solution was diluted with 10 mL of ethyl acetate, washed with 5% HCl, saturated sodium bicarbonate, and brine, and dried ($MgSO_4$). Removal of the solvent and chromatography (50% ether in hexane) afforded ca. 1 mg of **35**: mp 183.5–185 °C; IR (film, $CHCl_3$) 3.42, 5.69, and 5.75 (br s, C=O), 6.96, 7.32, 8.13, 9.05, and 9.60 μm; ^1H NMR ($CDCl_3$) δ 5.16 (d, 1 H, J = 5.5 Hz, C-11H), 5.02 (s, 1 H, C-12H), 4.93 (d, 1 H, J = 3 Hz, C-16H), 4.63 and 3.57 (AB pattern, 1 H each, d at 4.63, J = 7.5 Hz; dd at 3.57, J = 7.5, 1 Hz, C-20H, CH_2O bridged ether), 3.85 (br s, 1 H, C-7H), 3.72 (s, 3 H, CO_2CH_3), 3.67 and 3.47 (m, 1 H each, CH_3CH_2O), 3.34 (s, 3 H, CH_3O), 2.64 (m, 1 H, C-3H), 2.57 (m, 1 H, C-14H), 2.12 (s, 3 H, CH_3CO_2), 2.03 (s, 3 H, CH_3CO_2), 1.20 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.12 (s, 3 H, CH_3), 0.94 (d, 3 H, J = 5.9 Hz, CH_3), and 1.20–2.30 (m, remaining H); MS for $C_{28}H_{42}O_{10}$ 538, found, EI (M + H) 539 (self-protonated).

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Registry No. (±)-**1**, 105431-11-6; (±)-**2**, 105431-12-7; (±)-**3**, 105431-13-8; (±)-**4**, 105431-14-9; (±)-**5**, 105456-25-5; (±)-**7**, 105431-16-1; (±)-**8**, 105431-15-0; (±)-**9** (isomer 1), 105456-26-6; (±)-**9** (isomer 2), 105431-17-2; (±)-**12ax**, 105498-93-9; (±)-**12eq**, 105431-18-3; (±)-**13**, 105431-19-4; (±)-**14ax**, 105431-20-7; (±)-**17**, 105431-21-8; (±)-**18**, 105431-22-9; (±)-**19**, 105431-23-0; (±)-**21**, 105431-24-1; (±)-**22**, 105431-25-2; (±)-**23**, 105431-26-3; (±)-**24**, 105431-27-4; (±)-**25**, 105431-28-5; (±)-**26**, 105431-29-6; (±)-**27**, 105431-30-9; (±)-**29**, 105431-31-0; (±)-**30**, 105431-32-1; (±)-**31**, 105498-94-0; (±)-**33**, 105431-33-2; (±)-**34**, 105431-34-3; (±)-**35**, 105431-35-4; (±)-1-ethoxy-1,2-dibromoethane, 105431-36-5; ethyl vinyl ether, 109-92-2.

Supplementary Material Available: Experimental procedure, bond angles, bond lengths, and complete listing of the X-ray parameters for compound **26** (17 pages). Ordering information is given on any current masthead page.