Synthetic Studies on Quassinoids: Total Synthesis of (−)-Chaparrinone, (−)-Glaucarubolone, and (+)-Glaucarubinone

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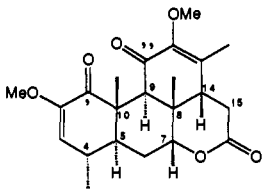
Abstract: The total synthesis of (−)-chaparrinone (**3**), (−)-glaucarubolone (**4**), and (+)-glaucarubinone (**5**) is described. The synthesis features an intermolecular Diels–Alder reaction between dienophile **6** and (*E*)-4-methyl-3,5-hexadienoic acid (**17**) in 5.0 M lithium perchlorate–ethyl acetate. Diels–Alder adduct **16** is converted *via* a two-step process into tetracyclic lactone **10**. Inversion of configuration at C(9) and installation of a $\Delta^{11,12}$ olefin in **10** provide tetracyclic lactone **19**. Incorporation of the ring C functionality into **19** followed by elaboration of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit and removal of the protecting groups on C(1) and C(12) hydroxyl groups affords pre-chaparrinone (**41**). Upon cleavage of the *tert*-butyldiphenylsilyl ether present in **41**, the resultant hydroxymethyl group spontaneously closes to a C(8),C(11) bridged hemiketal giving rise to (−)-chaparrinone (**3**). Tetracyclic alcohol **38**, an intermediate on the pathway to (−)-chaparrinone, serves as a starting point for the preparation of (−)-glaucarubolone (**4**). Incorporation of a C(15) hydroxyl group into **38** *via* tetracyclic dihydropyran **43** followed by introduction of the ring A functionality (cf. **50**) and deprotection affords (−)-glaucarubolone (**4**). The transformation of **50** into (+)-glaucarubinone (**5**) features a novel reagent, (*S*)-(−)-5-ethyl-5-methyl-1,3-dioxolane-2,4-dione (**54**), for direct introduction of a C(15) α-hydroxy-α-methylbutyrate ester unit.

During the intervening years since 1961, when the structures of quassin (**1**) and neoquassin (**2**) were established by Valenta and co-workers,[3] numerous quassinoids have been isolated from the plant family Simaroubaceae and characterized.[4] In 1965, Polonsky published two separate accounts detailing the structures of three novel quassinoids: chaparrinone (**3**),[5] glaucarubolone (**4**),[5] and glaucarubinone (**5**).[6] The major distinction between structures **3–5** and quassin lies in the oxidation state of the C(8) methyl which gives rise to a C(8),C(11) bridged hemiketal, a structural feature common to numerous quassinoids.



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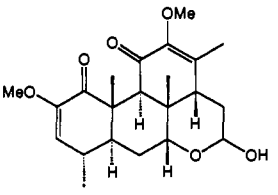
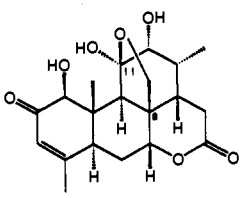


2

All efforts to prepare chaparrinone (**3**) and the closely related natural products glaucarubolone (**4**) and glaucarubinone (**5**), have, to date, met with no success, in part, because of the incompatibility of the methods that have been developed independently for construction of a ring C hemiketal array and a ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit.[7,8] The situation with respect to glaucarubolone (**4**) and glaucarubinone (**5**) is further complicated by the presence of functionality at C(15).



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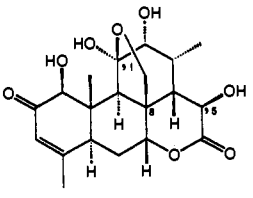

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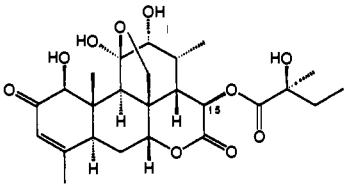

5

Synthetic interest in quassinoids such as glaucarubinone (**5**) was fueled by the early observation that **5** exhibits moderate activity against P-388 lymphocytic leukemia in the mouse (PS).[9] As a consequence, extensive studies have been conducted to determine the structural requirements for biological activity

(1) J. Stewart and Dagmar K. Riley Graduate Fellow, 1991–1992.
(2) Abbott Predoctoral Fellow, 1991–1993.
(3) (a) Valenta, Z.; Papadopoulos, S.; Podesva, C. *Tetrahedron* **1961**, *15*, 100. (b) Valenta, Z.; Gray, A. H.; Orr, D. E.; Papadopoulos, S.; Podesva, C. *Ibid.* **1962**, *18*, 1433. (c) Carman, R. M.; Ward, A. D. *Tetrahedron Lett.* **1961**, 317. (d) *Aust. J. Chem.* **1962**, *15*, 805.
(4) Polonsky, J. *Prog. Chem. Org. Nat. Prod.* **1985**, *47*, 22.
(5) Polonsky, J.; Bourguignon-Zylber, N. *Bull. Soc. Chim. Fr.* **1965**, 2793.
(6) Gaudemer, A.; Polonsky, J. *Phytochemistry* **1965**, *4*, 149. Also, see: Nyburg, S. C.; Walford, G. L.; Yates, P. *Chem. Commun.* **1965**, 203.
(7) For previous reports detailing methods for the elaboration of ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality, see: Spohn, R.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491. McKittrick, B. A.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5897. Grieco, P. A.; Parker, D. T.; Nargund, R. P. *J. Am. Chem. Soc.* **1988**, *110*, 5568. Kim, M.; Applegate, L. A.; Pack, O.; Vasudevar, S.; Watt, D. S. *Synth. Commun.* **1990**, *20*, 989.
(8) For preliminary accounts of this work which culminated in syntheses of (±)-chaparrinone and (±)-glaucarubolone, see: Gross, R. S.; Grieco, P. A.; Collins, J. L. *J. Am. Chem. Soc.* **1990**, *112*, 9436. Fleck, T. J.; Grieco, P. A. *Tetrahedron Lett.* **1992**, *33*, 1813.
(9) Kupchan, S. M.; Lacadie, J. A.; Howie, G. A.; Sickles, B. R. *J. Med. Chem.* **1976**, *19*, 1130.

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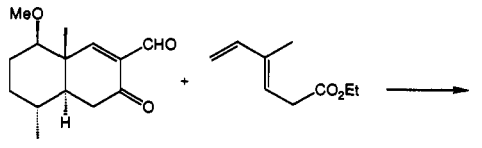
among various esters of glaucarubolone (**4**).[9,10] More recently, it has been established that quassinoids such as chaparrinone (**3**), glaucarubolone (**4**), and glaucarubinone (**5**) possess marked differential solid tumor selectivity.[11]

Our plan for the synthesis of **3–5** involved a modification of an intermolecular Diels–Alder strategy which we had developed over 10 years ago in conjunction with the total synthesis of quassin.[12] It was hoped that conditions could be found wherein cycloaddition of dienophile **6** with ethyl (*E*)-4-methyl-3,5-hexadienoate (**7**) would give rise to Diels–Alder adduct **8**. Note



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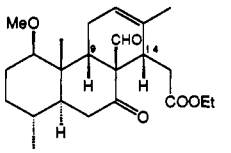
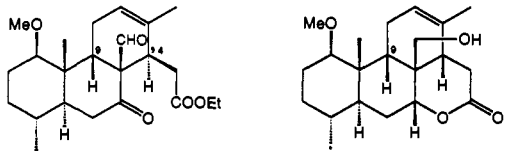


8

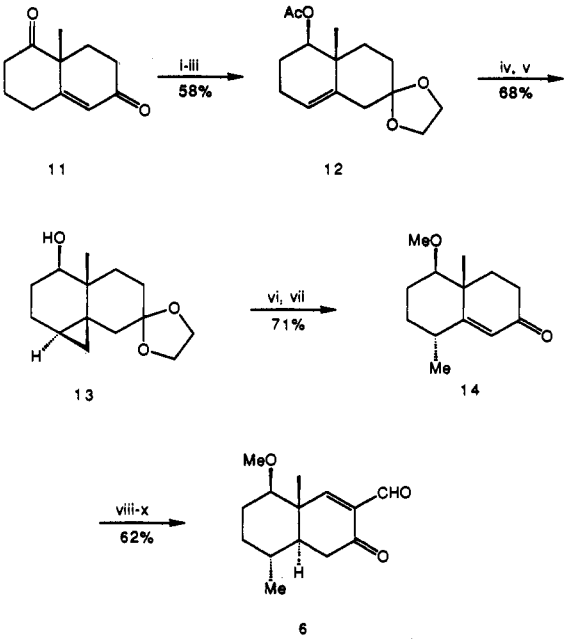
that of the four possible Diels–Alder adducts derived from [4+2] cycloaddition of **6** and **7**, all proceed *via endo* transition states. In reality, only two adducts, **8** and **9**, need be anticipated since the presence of a methyl group at C(10) in dienophile **6** seriously interferes with approach of the diene from the β-face of the molecule. Of particular concern was that in the transition state leading to the formation of the desired cycloadduct **8**, a serious interaction between the diene and the C(5) proton exists. With the realization of **8**, reduction and subsequent lactonization would afford the intact tetracyclic carbon skeleton **10** of chaparrinone and related natural products. The major drawback to such an approach is that eventually one has to deal with the inversion of configuration at C(9).



9 10

A logical starting point for the preparation of dienophile **6** was (*R*)-(−)-8a-methyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenedione (**11**) (Scheme I) which was prepared according to the procedure of Buchschacher and Fürst,[13] employing (*R*)-(+)-proline in place of (*S*)-(−)-proline. The synthesis of **6**, which is outlined in Scheme I, proceeds *via* the intermediacy of octalone **14** which had been prepared previously in racemic form from a Wieland–Miescher ketone in connection with our total synthesis of (±)-quassin.[12] Reduction of **14** ($[\alpha]^{25}_D$ −148.1° (*c* 1.18, $CHCl_3$), mp 39–40 °C) with lithium in liquid ammonia provided the corresponding decalone which, upon formylation and subsequent treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane and acetic acid, afforded **6**, $[\alpha]^{25}_D$ +9.0° (*c* 1.0, $CHCl_3$), mp 130–131 °C.

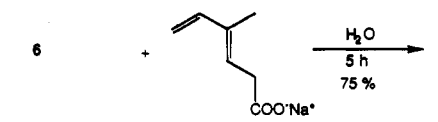
Scheme I. Preparation of Dienophile **6**[a]



[a] (i) $NaBH_4$, MeOH–CH_2Cl_2 (1:1), −78 °C; (ii) Ac_2O, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 0 °C; (iii) $HOCH_2CH_2OH$, *p*-TsOH, PhH, reflux; (iv) $LiAlH_4$, Et_2O; (v) CH_2I_2, Zn/Cu, Et_2O, reflux; (vi) MeI, NaH, THF, reflux; (vii) 70% $HClO_4$, CH_2Cl_2, 0 °C → room temperature; (viii) Li, liquid NH_3, *t*-BuOH, THF, −78 °C; (ix) NaH, HCO_2Et, PhH; (x) DDQ, HOAc, dioxane.

Attempts to carry out a cycloaddition of dienophile **6** with ethyl (*E*)-4-methyl-3,5-hexadienoate (**7**) in conventional hydrocarbon solvents led to disappointing results.[14] For example, treatment of **6** with 10.0 equiv of **7** in benzene at reflux for 72 h gave rise to a 67% yield of tricyclic ketone **9** possessing the wrong configuration at C(14) along with a 23% yield of the desired material **8**. Similar results were obtained with toluene and xylene at 80 °C. The best results were obtained in benzene at ambient temperature; however, the reaction was extremely slow. Workup after 288 h provided 29% of recovered **6** and only a 52% yield of **8** and **9** in a ratio of 1.0:1.15.

The problem of reversing the selectivity in a Diels–Alder reaction between **6** and **7** proved to be a formidable challenge. However, the desired reversal in selectivity could be achieved by (1) conducting the cycloaddition in water and (2) employing the sodium salt of (*E*)-4-methyl-3,5-hexadienoic acid (**15**) (eq 1).[14]



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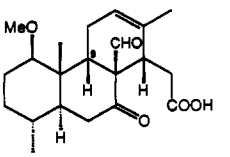


16 (1)

The reaction illustrated in eq 1 is best performed with a 5-fold excess of **15** (2.0 M in water) and is complete within 5 h at ambient temperature, giving rise to a 75% yield of adduct **16**. The

(10) Wall, M. E.; Wani, M. C. *J. Med. Chem.* **1978**, *21*, 1186. Cassady, J. M.; Suffness, M. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; p 201. Polonsky, J. Chemistry and Biological Activity of the Quassinoids. In *The Chemistry and Chemical Taxonomy of the Rutales*; Waterman, P. G., Grandon, M. F., Eds.; Academic Press: New York, 1983; p 247.

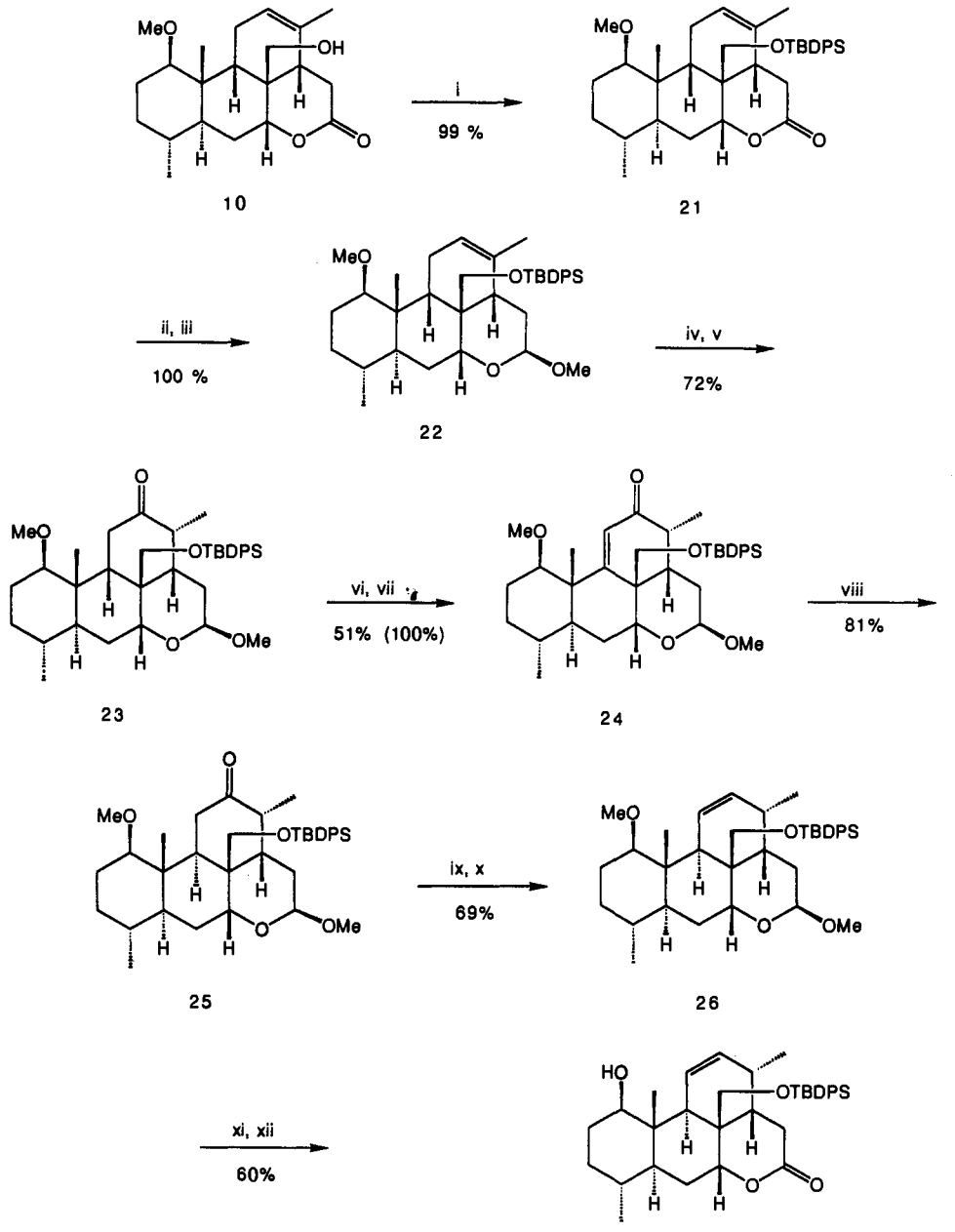
(11) Drs. Thomas H. Corbett and Frederick A. Valeriote, Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI, personal communication.

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

(13) Buchschacher, P.; Fürst, A. *Org. Synth.* **1984**, *63*, 37.

(14) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897. Also, see: Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

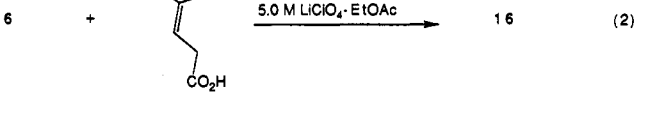
Scheme II. Transformation of **10** into Tetracyclic Olefin **19**[a]



[a] (i) TBDPSCl, imidazole, DMF; (ii) *i*-Bu_2AlH, THF, −78 °C; (iii) MeOH, concentrated HCl, THF; (iv) B_2H_6, THF, 0 °C; 3 N NaOH, 30% H_2O_2; (v) PCC, NaOAc, CH_2Cl_2; (vi) LDA, THF, −78 → 0 °C; TMSCl, −78 °C; (vii) $Pd(OAc)_2$, Na_2CO_3, CH_3CN, 45 °C; (viii) Li, liquid NH_3, *t*-BuOH, THF, −78 °C; (ix) NH_2NHTs, MeOH, THF; (x) *n*-BuLi (excess), THF, −78 → 0 °C; (xi) Jones reagent, acetone, 0 °C → room temperature; (xii) $HSCH_2CH_2SH$, BF_3·Et_2O.

observed rate acceleration and, more importantly, the reversal in selectivity are attributed to the hydrophobic affect (an entropy-driven association of nonpolar species in water that minimizes their exposure to water). When several transition states are possible, the more compact transition state, occupying the smallest volume, should be favored. Examination of the transition state leading to desired C(14) β-H adduct **16** reveals a compact, ball-like structure, whereas the transition state leading to the undesired isomer is bulky and cumbersome.

Despite the above success utilizing water as a solvent for the Diels–Alder reaction, we found that the reaction depicted in eq 1 is best performed on a large scale in 5.0 M lithium perchlorate–ethyl acetate,[15] employing (*E*)-4-methyl-3,5-hexadienoic acid (**17**) (eq 2) as the diene. Thus, treatment of **6** with only 2.0 equiv of **17** in 5.0 M $LiClO_4$–EtOAc gave rise to a 73% isolated yield of **16**, $[\alpha]^{25}_D$ −152.0° (*c* 1.0, $CHCl_3$), mp 161.5–163.0 °C.

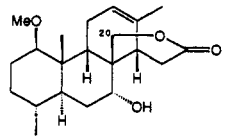


(2)

Treatment of adduct **16** with sodium borohydride in aqueous tetrahydrofuran resulted in reduction of the aldehyde group at C(8) as well as stereoselective reduction of the C(7) ketone exclusively from the convex (β) face. Initial examination of the reaction revealed a mixture of C(7) lactone **10** and C(20) lactone **18**; however, upon acidification to pH 2 with concentrated

(15) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.

hydrochloric acid, equilibration to the more stable C(7) lactone **10** ($[\alpha]^{25}_D$ +44.1° (*c* 1.0, $CHCl_3$), mp 199–200 °C) occurred in quantitative yield.



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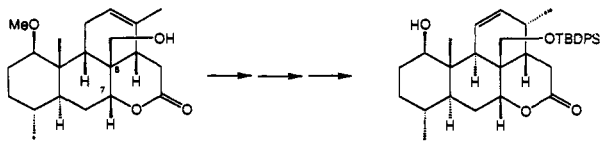
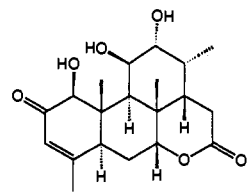
With tetracyclic lactone **10** in hand, we focused our efforts on the transformation of **10** into tetracyclic lactone **19** which would set the stage for elaboration of chaparrinone utilizing protocols for construction of a ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit and elaboration of the *trans* diaxial arrangement of the C(11) and C(12) hydroxyl groups developed previously in conjunction with a total synthesis of klaineanone (**20**).[16] The transformation



10 19



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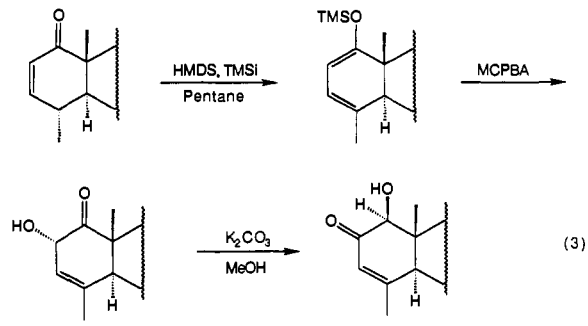
of **10** into **19** necessitated protection of the C(8) hydroxy methyl group and ring D δ-lactone prior to inversion of configuration at C(9). Toward this end, alcohol **10** was protected in near quantitative yield as its *tert*-butyldiphenylsilyl ether **21** by treatment of **10** with *tert*-butylchlorodiphenylsilane and imidazole in *N*,*N*-dimethylformamide (Scheme II). The lactone carbonyl in **21** was reduced with diisobutylaluminum hydride, and the resulting lactol was treated with a catalytic amount of concentrated hydrochloric acid in methanol–tetrahydrofuran, giving rise to **22**. Attention was now focussed on inverting the configuration at C(9). Accordingly, hydroboration of **22** with 1.0 M diborane in tetrahydrofuran and subsequent workup with alkaline hydrogen peroxide afforded, after oxidation with pyridinium chlorochromate, C(12) ketone **23**, mp 182–183 °C. The stereochemical outcome of the hydroboration proceeded as expected with predominate attack from the β-face of **22**; however, minor quantities of the C(13) isomeric ketone were obtained. This is of no consequence since the configuration at C(13) can easily be corrected by exposure to potassium carbonate in methanol–tetrahydrofuran (1:1).

Conversion of **23** into tetracyclic enone **24** required prior formation of the $\Delta^{11,12}$ silyl enol ether which was realized by trapping the kinetic enolate of **23** generated from lithium diisopropylamide in tetrahydrofuran with chlorotrimethylsilane. Exposure of the corresponding $\Delta^{11,12}$ silyl enol ether to sodium carbonate and palladium(II) acetate[17] in acetonitrile at 45 °C gave rise to enone **24**, mp 171.5–173 °C, in 51% yield (100% based on recovered material) along with recovered silyl enol ether (33%) and ketone **23** (16%). Interestingly, attempts to generate the corresponding $\Delta^{11,12}$ silyl enol ether from **23** employing lithium hexamethyldisilazane in place of lithium diisopropylamide gave rise exclusively, in quantitative yield, to the $\Delta^{12,13}$ silyl enol ether.

Our initial intention was to install the $\Delta^{11,12}$ olefin in **19** from enone **24** *via* a dissolving metal reduction and trapping of the resulting enolate with diethyl phosphorochloridate followed by reductive cleavage of the enol phosphate according to the Ireland protocol.[18] Unfortunately, the yield of the enol phosphate was low (ca. 34%) and subsequent attempts at reductive cleavage were not successful, in part, due to reduction of the phenyl groups on the silicon atom. It thus became obvious that an indirect approach was in order. Dissolving metal reduction of **24** in liquid ammonia at −78 °C with 10 equiv of lithium metal in the presence of 0.95 equiv of *tert*-butyl alcohol provided (81%) tetracyclic ketone **25**, mp 152–153 °C, possessing the desired configuration at C(9). That the reduction had proceeded as anticipated was readily confirmed by comparison of the ^{1}H NMR (500 MHz) of **23** and **25**.

To set the stage for the eventual functionalization of ring C, tetracyclic ketone **25** was transformed into tetracyclic olefin **26**, $[\alpha]^{25}_D$ +63.7° (*c* 1.0, $CHCl_3$), by conversion of **25** into the corresponding tosylhydrazone followed by treatment with excess *n*-butyllithium at −78 °C.[19] Subjection of **26** to Jones reagent at 0 °C followed by warming to ambient temperature led, in 90% yield, to the corresponding lactone which was subsequently demethylated, employing boron trifluoride etherate and 1,2-ethanedithiol,[20] to provide hydroxy lacetone **19** ($[\alpha]^{25}_D$ −10.5° (*c* 1.0, $CHCl_3$), mp 210–211 °C) in 67% yield.

Having successfully prepared **19** possessing a $\Delta^{11,12}$ olefin, we proceeded to complete the synthesis of chaparrinone by first installing the 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit in ring A (Scheme III) followed by elaboration of ring C. Thus, oxidation of alcohol **19** using pyridinium chlorochromate provided ketone **27** in 96% yield. Formation [hexamethyldisilazane (10 equiv), triethylamine (10 equiv), iodotrimethylsilane (7.0 equiv), and 1,2-dichloroethane; −15 → 0 °C][21] of the corresponding $\Delta^{1,2}$ silyl enol ether followed by reaction with 1.2 equiv of benzeneselenenyl chloride in tetrahydrofuran (0 °C, 25 min) and subsequent oxidation (hydrogen peroxide, pyridine, 0 °C) and elimination of benzeneselenenic acid generated tetracyclic enone **28** in 77% overall yield. Our plan featured the transformation of **28** into **29**, employing a protocol developed previously in our laboratory (cf. eq 3).[7] Thus, conversion of enone **28** into the corresponding silyl dienol ether followed by selective epoxidation of the $\Delta^{1,2}$ olefin and subsequent base-catalyzed tautomerism of the intermediate ketol provided **29**.



(3)

At this point, the remaining task of installing the ring C hemiketal array[16,22] appeared to be a straightforward exercise. It was anticipated that expoxidation of the $\Delta^{11,12}$ olefin in **29** would give rise to **30** which upon acid-catalyzed epoxide opening would generate triol **31**. We were not concerned about the ability

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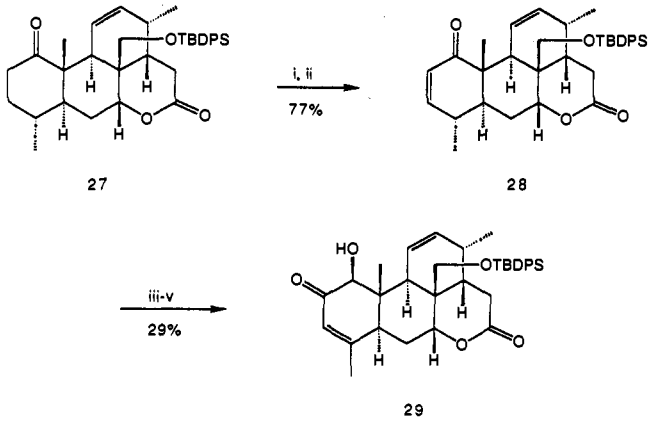
(17) Cf.: Ito, Y.; Mirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(18) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1966**, 2145.
(19) Shapiro, R. H. *Org. React.* (*N.Y.*) **1976**, *23*, 405.
(20) Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2237.
(21) Cf.: Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.
(22) Grieco, P. A.; Parker, D. T.; Garner, P.; Sasaki, S. *Tetrahedron Lett.* **1989**, *30*, 3401.

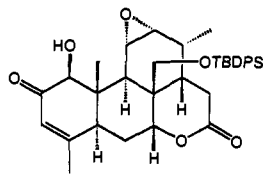
Scheme III. Installation of the Ring A Functionality of Chaparrinone into Tetracyclic Ketone **27**[a]



27 28 29

[a] (i) HMDS, TMSI, Et_3N, $ClCH_2CH_2Cl$, −15 → 0 °C; (ii) PhSeCl, THF, 0 °C; H_2O_2, pyr, 0 °C; (iii) HMDS, TMSI, Et_3N, pentane–$ClCH_2CH_2Cl$ (1:4), −23 °C → room temperature; (iv) MCPBA, $NaHCO_3$, CH_2Cl_2, −23 °C; (v) K_2CO_3, MeOH.

of the ring A functionality in **30** to withstand the strongly acidic conditions required to effect epoxide ring opening because of our prior experience during klaineanone synthesis.[16] Selective protection of the C(1) and C(12) hydroxyl groups in **31** followed by oxidation of the remaining C(11) hydroxyl and subsequent exhaustive deprotection would provide access to chaparrinone (**3**). Treatment of olefin **29** with *m*-chloroperbenzoic acid in methylene chloride afforded epoxide **30** in 65% yield. However, upon treatment of **30** with 23% perchloric acid in tetrahydrofuran, none of the desired *trans* diaxial vicinal diol **31** could be detected. Isolated in 81% yield was deoxychaparrinone (**32**). In retrospect, the formation of **32** is not surprising as it is nicely set up for an acid-catalyzed intramolecular epoxide ring opening followed by desilylation. This type of transformation has recently been utilized for incorporation of the C(8),C(13) epoxymethano bridge of bruceantin.[23] Attempts to prevent C(8),C(11) epoxymethano bridge formation by changing the protecting group on the C(8) hydroxymethyl group were unsuccessful as well as efforts to prepare the β-epoxide of olefin **29**.



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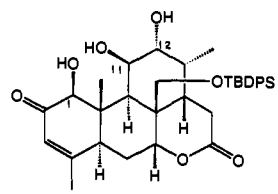

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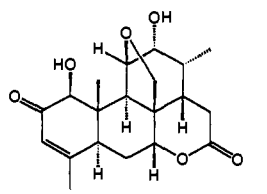
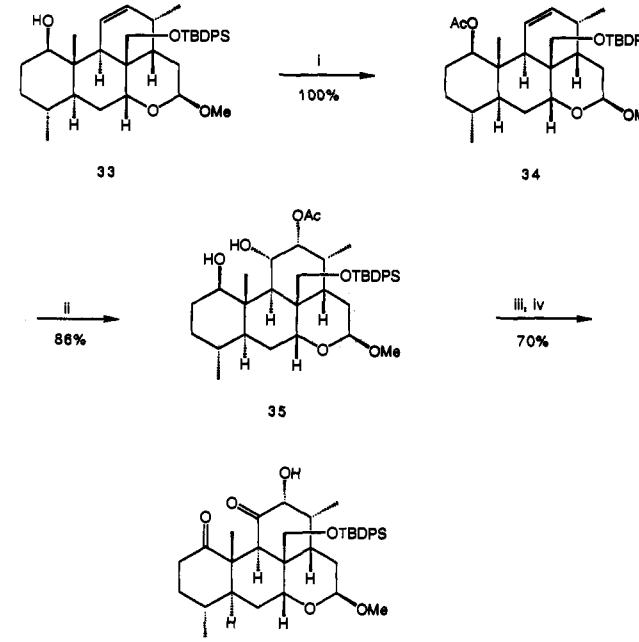


32

(23) Murae, T.; Sasaki, M.; Konosu, T.; Matsuo, H.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 3411.

Scheme IV. Transformation of **33** into Tetracyclic Diketone **36**[a]



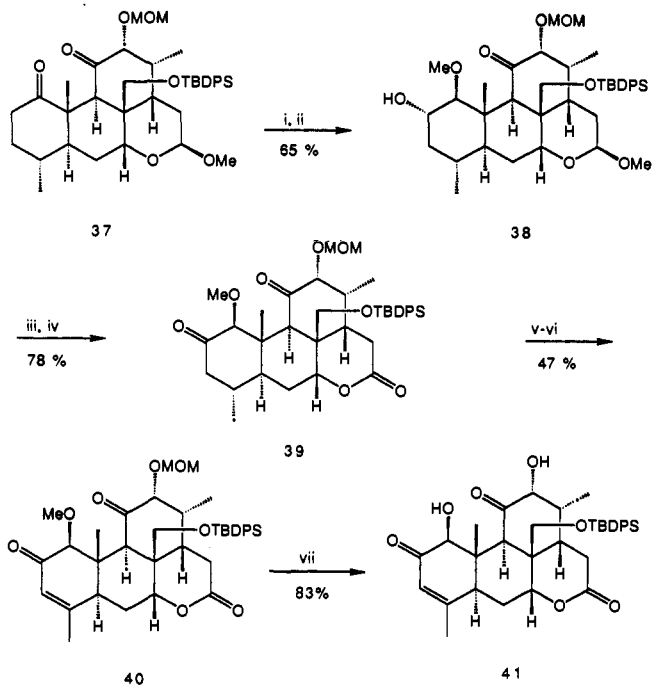
33 34 35 36

[a] (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2 0 °C → room temperature; (ii) OsO_4, pyr, 0 °C → room temperature; $NaHSO_3$, H_2O; (iii) CrO_3·2 pyr, CH_2Cl_2, 0 °C → room temperature; (iv) 1.5 N NaOH, THF–MeOH (1:1), 0 °C → room temperature.

Frustrated by our inability to transform **30** into chaparrinone, we set out to explore the feasibility of elaborating the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit on a substrate possessing a fully functionalized, protected ring C. Toward this end, the preparation of a ring C equivalent (cf. tetracyclic diketone **36**, Scheme IV) was investigated. Reduction of tetracyclic lactone **19** followed by brief exposure of the resultant lactol to methanol containing *p*-toluenesulfonic acid provided protected lactol **33** (Scheme IV) as a 3:1 mixture about the anomeric carbon with the major isomer possessing a β-orientation. Acetylation of **33** afforded **34**, which, upon exposure to osmium tetraoxide in pyridine and subsequent mild reduction with sodium bisulfite, gave rise (86%) to diol **35** wherein the C(1) acetyl group had migrated, presumably intramolecularly, exclusively to the C(12) hydroxyl as evidenced by the presence of a one-proton triplet centered at 5.20 ppm with J = 3.3 Hz in the ^1H NMR spectrum. This serendipitous event set the stage for simultaneous oxidation of the C(1) and C(11) hydroxyl groups and hydrolysis of the C(12) acetate, giving rise to tetracyclic diketone **36**, $[\alpha]^{25}_D$ +30.1° (*c* 1.10, $CHCl_3$), mp 228–230 °C.

With the oxidation state of ring C in place for eventual elaboration of the C(8),C(11) bridged hemiketal moiety, we focussed our attention on construction of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit. Unfortunately all previous protocols for formation of ring A were not compatible with the existing ring C functionality. However, success was finally realized as illustrated in Scheme V. Installation of the ring A functionality of chaparrinone into tetracyclic diketone **36** necessitated prior protection of the C(12) hydroxyl group as its methoxymethyl ether. Thus, treatment of **36** with chloromethyl methyl ether and Hünig's base in 1,2-dichloroethane provided, after 24 h, an 89% yield of **37** (Scheme V). Selective deprotonation at C(2) employing lithium bis(dimethylsilyl)amide followed by treatment with dimethyl sulfate provided the corresponding methyl enol

Scheme V. Conversion of Tetracyclic Diketone **37** into Pre-chaparrinone (**41**)[a]



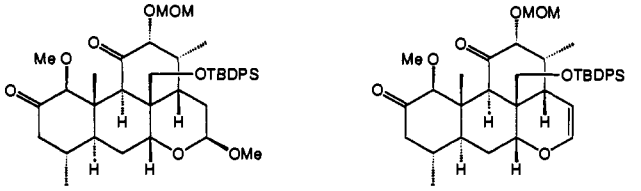
37 38 39 40 41

[a] (i) LiHMDS, THF, HMPA; Me_2SO_4; (ii) B_2H_6, THF; NaOH, H_2O_2; (iii) HCl, H_2O, THF; (iv) PCC, NaOAc, CH_2Cl_2; (v) $PyHBr_3$, CSA, THF; (vi) LiBr, Li_2CO_3, DMF, 120 °C; (vii) BBr_3, CH_2Cl_2, −78 → −23 °C.

ether which, upon subjection to hydroboration,[24] gave rise to tetracyclic alcohol **38**. Hydrolysis of the protected lactol and simultaneous oxidation at C(2) and C(16) generated tetracyclic diketo lactone **39**. Attempts at formation of the $\Delta^{2,3}$ silyl enol ether of **39** for a subsequent Saegusa reaction proved extremely difficult with the ring D lactone in place. However, direct bromination followed by dehydrobromination provided, in ca. 50% overall yield, compound **40** possessing the fully functionalized ring A of chaparrinone. Boron tribromide induced cleavage of the C(1) methyl ether and C(12) methoxymethyl ether afforded pre-chaparrinone (**41**), mp 216–219 °C, in 83% yield. Exposure of **41** to tetra-*n*-butylammonium fluoride in tetrahydrofuran gave rise to (−)-chaparrinone (**3**), whose physical properties (mp, $[\alpha]_D$), as well as spectral data (^{1}H NMR, IR), were in agreement with data in the literature.[5] Unfortunately, we were unable to secure a sample of natural chaparrinone in order to make the standard comparison of spectra. However, our sample of (−)-chaparrinone was identical with a sample of racemic chaparrinone,[8] by comparison of IR and ^{1}H NMR spectra. After completion and publication of our synthesis of racemic chaparrinone,[8] we fully characterized chaparrinone by single-crystal X-ray analysis.

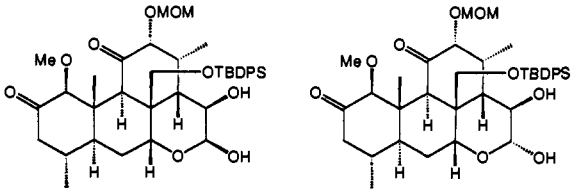
Having secured *via* total synthesis (−)-chaparrinone (**3**), our efforts were directed toward (−)-glaucarubolone (**4**) which differs from **3** by the presence of a hydroxyl group at C(15). Unfortunately, attempts to introduce a hydroxyl group into the C(15) position of chaparrinone or pre-chaparrinone (**41**) met with no success. It was anticipated, however, that a number of intermediates on the pathway to **3** might serve as a starting point for synthesis of **4**. Indeed, tetracyclic alcohol **38** appeared well-suited for transformation into glaucarubolone. The conversion of **38** into **4** necessitated (a) incorporation of a β-hydroxy group at C(15), (b) introduction of a 2-oxo-$\Delta^{3,4}$ olefin unit into ring A, and (c) deprotection of the C(8) hydroxymethyl group with concomitant formation of a C(8),C(11) bridged hemiketal.

To set the stage for hydroxylation at C(15), **38** was transformed into tetracyclic dihydropyran **43**. Oxidation (PCC, NaOAc, CH_2Cl_2) of **38** gave rise to diketone **42** which upon hydrolysis (10% HCl, THF) of the protected lactol and subsequent dehydration, ($POCl_3$, pyr, 80 °C) afforded crystalline dihydropyran **43** ($[\alpha]^{25}_D$ −32.7° (*c* 1.0, $CHCl_3$), mp 106–108 °C) in 95% overall yield.



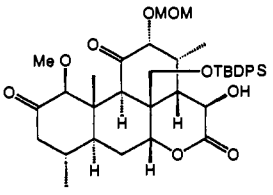
42 43

Osmylation of **43** provided, in near quantitative yield, readily separable C(15) β-hydroxylated lactols **44**, mp 180–182 °C, and **45**, mp 203–205 °C, in a ratio of ca. 6:1. The formation of **45** arises from **44** *via* equilibration at C(16). Exposure of enantiomerically pure **44** to 5% hydrochloric acid in tetrahydrofuran resulted in a 2:3 equilibrium mixture of **44** and **45**. Attempts to



44 45

oxidize the mixture of **44** and **45** under mild conditions (e.g., Fetizon's reagent; manganese oxide–chloroform; silver oxide in acetonitrile; Dess–Martin periodinane reagent (**46**)[25]) led to cleavage products. After extensive experimentation, it was found that known hydroxyiodinane oxide **47**[25] readily oxidized both **44** and **45** into desired tetracyclic lactone **48** in excellent yield. The use of **47** as an oxidizing reagent in organic chemistry has received virtually no attention, in part, because of the tremendous success reported in the literature on the use of **46**.



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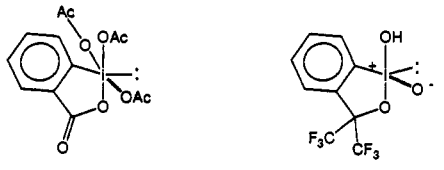


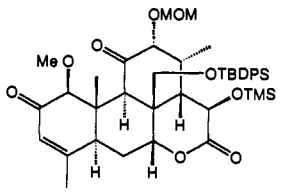
46 47

At this stage, completion of the total synthesis of (−)-glaucarubolone (**4**) appeared all but assured. Indeed, **48** was transformed in a straightforward fashion into **4**. Protection of the C(15) hydroxyl as its trimethylsilyl ether followed by bromination at C(3) and subsequent dehydrobromination generated enone **49**. The final task was removal of all the protecting groups. Brief exposure of **49** to 10% hydrochloric acid in tetrahydrofuran afforded, in quantitative yield, **50** which, in addition to being converted into glaucarubolone, served as a logical precursor to glaucarubinone (**5**). Treatment of **50** with boron tribromide at −78 °C cleaved the C(1) methyl ether and C(12) methoxymethyl ether, giving rise to **51**. Brief treatment of **51**

(24) Kane, V. V.; Singh, V.; Martin, A.; Doyle, D. L. *Tetrahedron* **1983**, *39*, 345. Klein, J.; Levene, R.; Dunkelblum, E. *Tetrahedron Lett.* **1972**, *28*, 2845.

(25) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

with fluoride ion liberated the C(8) hydroxymethyl group which spontaneously gave rise to the C(8),C(11) bridged hemiketal, thus providing crystalline (–)-glaucarubolone (**4**) mp 263–265 °C, $[\alpha]^{25}_D$ –33.6° (*c* 1.06, pyr)) whose physical and spectral properties were found to be identical with those of an authentic sample kindly provided by the National Cancer Institute.



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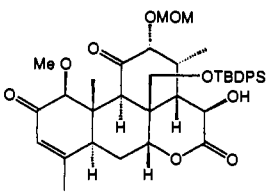

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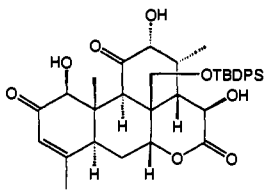

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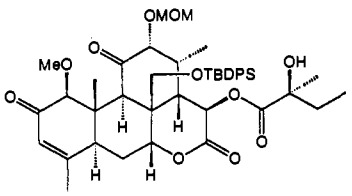
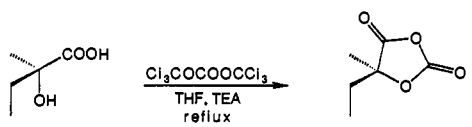
At this point in our synthetic studies, we focussed efforts on the synthesis of glaucarubinone (**5**), which, in principle, requires transformation of **50** into α-hydroxy-α-methylbutyrate ester **52** followed by deprotection. This seemingly simple operation (**50** → **52**) is complicated by the fact that there are no general methods available for the direct preparation of α-hydroxy-α-methylbutyrate esters. We have developed a potential solution, which



52

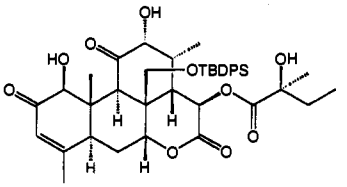
employs (*S*)-(–)-5-ethyl-5-methyl-1,3-dioxolane-2,4-dione (**54**) as a reagent for the direct preparation of the α-hydroxy-α-methylbutyrate ester fragment present in glaucarubinone, to this problem. The synthesis of **54** originates (eq 4) with the known (*S*)-(+)-2-hydroxy-2-methylbutyric acid (**53**)[26] (mp 75–76 °C, $[\alpha]^{25}_D$ +7.8° (*c* 1.72, $CHCl_3$)) which was prepared according to the Terashima protocol[27] employing (*R*)-proline in place of (*S*)-proline. Treatment of enantiomerically pure **53** with 0.67 equiv of triphosgene in tetrahydrofuran containing 1.0 equiv of triethylamine at reflux for 5 h provided **54** in 68% yield after distillation.[28]



(4)

53 54

The remaining task for completion of the total synthesis of glaucarubinone was acylation of the C(15) hydroxyl, employing novel reagent **54**. Toward this end, tetracyclic alcohol **50** was treated with 2.5 equiv of **54** in methylene chloride containing 1.1 equiv of 4-(dimethylamino)pyridine. Workup provided a 92% yield of crystalline **52**, mp 172–173 °C, $[\alpha]^{25}_D$ +30.8° (*c* 1.0, $CHCl_3$). Deprotection of the C(1) and C(12) hydroxyl groups, employing boron tribromide, afforded **55** which, upon exposure to tetra-*n*-butylammonium fluoride, gave rise to (+)-glaucarubinone (**5**) (mp 222–224 °C, $[\alpha]^{25}_D$ +49.0 (*c* 0.10, MeOH)), whose physical and spectral properties were identical in all respects with those of an authentic sample.



55

Experimental Section

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectra were recorded on a Varian XL-300 MHz, Varian VXR-400 MHz, or a Bruker AM-500 MHz spectrometer, as indicated. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Infrared (IR) spectra were taken on a Perkin-Elmer Model 298 spectrophotometer as a solution in chloroform or on a Mattson Galaxy 4020 series FTIR spectrometer as a KBr pellet. Absorption intensities are indicated as strong (s), medium (m), or weak (w). High-resolution mass spectra were obtained on a Kratos MS 80/RFAQ spectrometer. Elemental analyses were performed by Robertson Laboratories, Inc., Madison, NJ, and Galbraith Laboratories, Inc., Knoxville, TN. Melting points were obtained on a Fisher-Johns hot stage or a Thomas Hoover melting point apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter. Reactions were monitored by thin layer chromatography (TLC) using E. Merck precoated silica gel 60 F-254 (0.25-mm thickness) plates. The plates were visualized by immersion in a *p*-anisaldehyde solution and warming on a hot plate. E. Merck silica gel 60 (70–230 mesh) was used for coarse silica gel chromatography whereas E. Merck silica gel 60 (230–400 mesh) was used for flash silica gel chromatography.

All solvents were reagent grade unless otherwise stated. Anhydrous solvents were dried immediately before use. Dichloromethane, 1,2-dichloroethane, hexamethyldisilazane, pyridine, chloromethyl methyl ether, triethylamine, chlorotrimethylsilane, diisopropylamine, diisopropylethylamine, hexamethylphosphoric triamide, phosphorus oxychloride, ethyl acetate, dimethyl sulfate, and ethyl formate were distilled from calcium hydride. Diethyl ether and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl. Benzene and ammonia were distilled from sodium metal. *tert*-Butyl alcohol was distilled from and stored over 4-Å molecular sieves. Solvents were deoxygenated utilizing the freeze–pump–thaw method. Lithium perchlorate was dried under high vacuum at 165 °C for 64 h.

(*R*)-(–)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenedione (11) (mp 49–50 °C; $[\alpha]^{25}_D$ –98.5° (*c* 8.28, toluene)) was prepared according to the procedure of Buchschacher and Fürst,[13] employing (*R*)-(+)-proline in place of (*S*)-(–)-proline.

(–)-1,2,3,4,8,8a-Hexahydro-1β-hydroxy-8aβ-methyl-6(7*H*)-naphthalenone ($[\alpha]^{25}_D$ –196.4° (*c* 1.40, $CHCl_3$)) was prepared according to the procedure of Ward et al.[29]

(–)-1β-Acetoxy-1,2,3,4,8,8a-hexahydro-8aβ-methyl-6(7*H*)-naphthalenone (mp 63–64 °C; $[\alpha]^{25}_D$ –111.7° (*c* 1.54, $CHCl_3$)) was prepared according to the procedure of Heathcock and Ratcliffe.[30]

(+)-1β-Acetoxy-1,2,3,7,8,8a-hexahydro-8aβ-methyl-6(5*H*)-naphthalenone Ethylene Ketal (12) (mp 93–94 °C; $[\alpha]^{25}_D$ +39.7° (*c* 1.10, $CHCl_3$)) was prepared according to the procedure of Heathcock and Ratcliffe.[30]

(+)-1,2,3,7,8,8a-Hexahydro-1β-hydroxy-8aβ-methyl-6(5*H*)-naphthalenone Ethylene Ketal (mp 93–94 °C; $[\alpha]^{25}_D$ +62.9° (*c* 1.0, $CHCl_3$)) was prepared according to the procedure of Heathcock and Ratcliffe.[30]

(+)-*cis*-10β-Methyl-7,7-(ethylenedioxy)-4β,5β-methano-1β-decalol (13). To a solution of 128.6 g of diiodomethane in 500 mL of anhydrous ether was added 62 g of zinc–copper couple (freshly prepared via the LeGoff modification[31]). The heterogeneous mixture was allowed to reflux under nitrogen. After 30 min, 15.9 g (71 mmol) of octalol **8** in 300 mL of

(26) Mattocks, A. R. *J. Chem. Soc.* **1964**, 1918.
(27) Terashima, S.; Jew, S. *Tetrahedron Lett.* **1977**, 1005.
(28) Cf.: Toyooka, K.; Takeuchi, Y.; Kubota, S. *Heterocycles* **1989**, *29*, 975.
(29) Ward, D. E.; Rhee, C. K.; Zoghaib, W. M. *Tetrahedron Lett.* **1988**, *29*, 517.
(30) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
(31) LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048.

anhydrous ether was added dropwise over 30 min with the aid of a dropping funnel. The reaction was refluxed for 2 h. The cooled reaction mixture was filtered, and the filtrate was poured into 200 mL of cold saturated aqueous ammonium chloride solution. The organic layer was separated, washed with saturated sodium bicarbonate solution and saturated brine solution, and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* provided 39 g of crude product. Chromatography on 800 g of silica gel eluting with diethyl ether–hexanes (1:2) gave 12.8 g (78%) of pure **13** as an oil: R_f 0.49 (ethyl acetate–hexanes, 1:1); IR ($CHCl_3$) 3630 (w), 3010 (w), 2950 (s), 1456 (w), 1361 (w), 1225 (w), 1096 (s), 1070 (m), 1026 (m), 977 (m), 946 (m), 899 (w), 826 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96–3.82 (m, 4H), 3.38 (br d, 1H, J = 5.6 Hz), 2.12 (d, 1H, J = 14 Hz), 1.99–1.88 (m, 1H), 1.86–1.62 (m, 5H), 1.43–1.32 (m, 2H), 1.29–1.22 (m, 1H), 1.09 (s, 3H), 0.91–0.84 (m, 1H), 0.63 (dd, 1H, J = 14, 1.6 Hz), 0.58 (t, 1H, J = 4.5 Hz), 0.066 (dd, 1 H, J = 9, 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.33, 7474, 64.15, 63.78, 43.51, 34.56, 33.03, 30.92, 24.70, 22.93, 20.06, 19.66, 19.52, 15.68. An analytical sample was prepared by distillation: bp 143–144 °C (0.2 mmHg); $[\alpha]^{25}_D$ +24.3° (*c* 1.56, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.71; H, 9.46.

(–)-[4a*R*-(4aβ,5β,5β,8aα)]-4,4a,5,6,7,8-Hexahydro-4a,8-dimethyl-5-methoxy-2(3*H*)-naphthalenone (14). A solution of 10.3 g (43.3 mmol) of alcohol **13** in 30 mL of tetrahydrofuran was added to a suspension of 12.4 g (258 mmol) of sodium hydride (50% oil dispersion) in tetrahydrofuran at room temperature under argon. After the suspension was refluxed for 30 min, 14.4 mL (231 mmol) of methyl iodide and 3 g (8 mmol) of tetra-*n*-butylammonium iodide were added at room temperature. The reaction mixture was allowed to reflux for 1 h. The suspension was cooled to room temperature, and the inorganic salts were filtered. The solvent was evaporated, and the residue was diluted with ether and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate *in vacuo* provided a crude residue, which was dissolved in 500 mL of methylene chloride and cooled to 0 °C prior to the dropwise addition of 30 mL of 70% perchloric acid. The reaction mixture was stirred for 1 h at 0 °C and 3 h at room temperature. The excess acid was neutralized by careful addition of solid sodium bicarbonate. The inorganic salts were filtered, and the organic layer was washed with a saturated sodium bicarbonate solution. The aqueous phase was extracted with methylene chloride, and the combined organic extracts were dried over anhydrous magnesium sulfate. After filtration and concentration *in vacuo*, the crude product was chromatographed on 500 g of silica gel. Elution with hexane–ether, 4:1, gave 6.42 g (71%) of octalone **14** as a crystalline solid: mp 39–40 °C; $[\alpha]^{25}_D$ –148.1° (*c* 1.18, $CHCl_3$); R_f 0.34 (hexanes–ether, 2:1); IR ($CHCl_3$) 2950 (s), 2880 (w), 2835 (w), 1665 (s), 1612 (m), 1463 (m), 1365 (w), 1275 (w), 1220 (m), 1145 (m), 1100 (s), 1011 (w), 985 (w), 950 (w), 880 (w), 852 (w) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 5.78 (d, 1H, J = 1.8 Hz), 3.37 (s, 3H), 2.88 (dd, 1H, J = 11.5 Hz), 1.2–2.5 (m, 9H), 1.17 (s, 3H), 1.05 (d, 3H, J = 6.5 Hz). High-resolution MS (EI) calcd for $C_{13}H_{20}O_2$ (M) *m/e* 208.1464, found 208.1456.

(–)-[4a*R*-(4aβ,5β,8aα,8aα)]-3,4,4a,5,6,7,8,8a-Octahydro-4a,8-dimethyl-5-methoxy-2(1*H*)-naphthalenone. To 900 mL of freshly distilled ammonia at –78 °C was added 2.8 g (0.40 mol) of lithium wire cut into small pieces. After the mixture was stirred for 30 min, 13.5 g (64.90 mmol) of enone **14** and 6.1 mL (64.90 mmol) of *tert*-butyl alcohol in 175 mL of anhydrous tetrahydrofuran were added over 20 min. After the solution was stirred at –78 °C for 1.5 h, the blue reaction was quenched by the addition of 91 mL of isoprene followed by 37 g of solid ammonium chloride and the ammonia was allowed to evaporate overnight. The residue was diluted with water, and the product was extracted with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was chromatographed on ca. 800 g of flash silica gel. Elution with hexanes–ethyl acetate (9:1) provided 11.0 g (80%) of (–)-[4a*R*-(4aβ,5β,8aα,8aα)]-3,4,4a,5,6,7,8,8a-octahydro-4a,8-dimethyl-5-methoxy-2(1*H*)-naphthalenone as a crystalline solid: R_f 0.53 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 2990 (s), 2960 (s), 2945 (s), 2880 (m), 2855 (m), 2830 (m), 1705 (s), 1464 (m), 1455 (m), 1415 (w), 1379 (w), 1363 (w), 1342 (w), 1331 (w), 1316 (w), 1300 (w), 1275 (w), 1238 (m), 1221 (m), 1205 (m), 1185 (w), 1173 (w), 1155 (m), 1135 (m), 1094 (s), 1057 (w), 1003 (m), 976 (w), 957 (w), 934 (w), 915 (w), 843 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.32 (s, 3H), 2.72 (dd, 1H, J = 11.6, 4.4 Hz), 2.44–2.34 (m, 2H), 2.32–2.22 (m, 2H), 2.08 (t, 1H, J = 14.3 Hz), 1.90 (dq, 1H, J = 13.0, 2.9 Hz), 1.74 (dq, 1H, J = 13.6, 3.0 Hz), 1.48–1.31 (m, 3H), 1.17–1.07 (m, 1H), 1.06–0.89 (m, 1H), 1.00 (s, 3H), 0.77 (d, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.91, 88.17, 57.29, 50.19, 40.93, 38.36, 37.51, 37.04, 33.68, 31.73, 25.18, 19.14, 10.67. An analytical sample was prepared by recrystallization from hexanes: mp 50–52 °C; $[\alpha]^{25}_D$ –71.8° (*c* 1.06, $CHCl_3$). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.92; H, 10.44.

(–)-[4a*S*-(4aβ,5β,8aα,8aα)]-3,4,4a,5,6,7,8,8a-Octahydro-4a,8-dimethyl-3-formyl-5-methoxy-2(1*H*)-naphthalenone. To a suspension of 7.14 g (0.169 mol) of NaH (56.8% in oil, prewashed with hexanes 3×) in 110 mL of anhydrous benzene at room temperature was added a solution of 11.0 g (56.33 mmol) of (–)-[4a*R*-(4aβ,5β,8aα,8aα)]-3,4,4a,5,6,7,8,8a-octahydro-4a,8-dimethyl-5-methoxy-2(1*H*)-naphthalenone dissolved in 230 mL of anhydrous benzene over 10 min followed by 13.6 mL (0.169 mmol) of ethyl formate. The reaction solution was treated with 2 drops of absolute ethanol and stirred for 1 h. An additional 5 drops of absolute ethanol was added, and stirring was continued for 2 h. After the reaction was quenched by the addition of ice/water, the aqueous layer was separated and the organic layer was extracted with a 0.25 N aqueous sodium hydroxide solution (2 × 200 mL). The combined aqueous layers were acidified with a 10% aqueous hydrochloric acid solution and extracted with diethyl ether. The combined diethyl ether layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give 12.7 g (95%) of (–)-[4a*S*-(4aβ,5β,8aα,8aα)]-3,4,4a,5,6,7,8,8a-octahydro-4a,8-dimethyl-3-formyl-5-methoxy-2(1*H*)-naphthalenone as yellow crystals: R_f 0.62 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 2985 (m), 2940 (s), 2905 (m), 2860 (m), 1640 (s), 1590 (s), 1460 (m), 1410 (m), 1378 (m), 1363 (m), 1345 (m), 1323 (m), 1294 (m), 1253 (m), 1186 (m), 1163 (m), 1133 (m), 1094 (s), 1065 (m), 1005 (w), 989 (w), 969 (w), 957 (w), 937 (w), 905 (w), 868 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 14.35 (br d, 1H, J = 2.4 Hz), 8.62 (d, 1H, J = 2.4 Hz), 3.36 (s, 3H), 2.78 (dd, 1H, J = 11.7, 4.0 Hz), 2.58 (d, 1H, J = 14.7 Hz), 2.47 (dd, 1H, J = 19.2, 5.7 Hz), 2.03 (d, 1H, 14.7 Hz), 2.03–1.94 (m, 1H), 1.92 (dq, 1H, J = 12.8, 4.0 Hz), 1.75 (dq, 1H, J = 13.5, 3.6 Hz), 1.37 (dq, 1H, J = 11.7, 3.7 Hz), 1.33–1.24 (m, 1H), 1.10 (dt, 1H, J = 11.5, 5.8 Hz), 1.01 (dq, 1H, J = 13.4, 3.9 Hz), 0.84 (d, 3H, J = 6.4 Hz), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.88, 183.60, 107.52, 87.92, 57.14, 44.70, 38.01, 36.20, 33.15, 32.66, 32.00, 25.01, 19.31, 10.71. An analytical sample was prepared by recrystallization from hexanes: mp 50–52 °C; $[\alpha]^{25}_D$ –104.9° (*c* 0.80, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.48; H, 9.19.

(+)-[4a*R*-(4aβ,5β,8aα,8aα)]-4a,5,6,7,8,8a-Hexahydro-4a,8-dimethyl-3-formyl-5-methoxy-2(1*H*)-naphthalenone (6). To a solution of 12.7 g (53.50 mmol) of the above formyl ketone in 170 mL of *p*-dioxane at room temperature was added, over 30 min, a solution of 15.8 g (69.55 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 170 mL of *p*-dioxane containing 1.27 mL of acetic acid. After being stirred for 1 h 37 min, the reaction mixture was filtered into 1 L of chloroform. The filtrate was washed with a saturated aqueous sodium bicarbonate solution (3×), and the combined aqueous layers were extracted with chloroform (2×). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified on ca. 500 g of flash silica gel. Elution with hexanes–ethyl acetate (9:1) provided 10.18 g (81%) of 6 as a crystalline solid: R_f 0.41 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 2955 (s), 2915 (m), 2880 (m), 2855 (m), 2835 (m), 2740 (w), 1722 (s), 1700 (s), 1680 (s), 1609 (s), 1464 (m), 1444 (m), 1404 (m), 1375 (m), 1365 (m), 1335 (m), 1297 (w), 1274 (w), 1245 (m), 1235 (m), 1224 (m), 1207 (m), 1174 (m), 1132 (s), 1101 (s), 1066 (m), 995 (m), 985 (m), 960 (m), 945 (w), 926 (w), 885 (m), 856 (m), 835 (w), 812 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.00 (s, 1H), 3.38 (s, 3H), 2.95 (dd, 1H, J = 11.3, 4.4 Hz), 2.59 (dd, 1H, J = 17.9, 4.1 Hz), 2.31 (dd, 1H, J = 17.9, 13.7 Hz), 2.04 (dq, 1H, J = 13.0, 3.3 Hz), 1.81 (dq, 1H, J = 13.7, 3.4 Hz), 1.64–1.40 (m, 3H), 1.15–0.96 (m, 1H), 1.07 (s, 3H), 0.86 (d, 3H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.59, 189.88, 164.81, 132.27, 81.79, 57.05, 46.84, 42.12, 37.57, 33.06, 30.45, 24.71, 18.79, 11.98. An analytical sample was prepared by recrystallization from ether–hexanes: mp 130–131 °C; $[\alpha]^{25}_D$ +9.0° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.54. Found: C, 71.29; H, 8.55.

(*E*)-4-Methyl-3,5-hexadienoic Acid (17). To a solution of 29.1 g (0.189 mol) of ethyl (*E*)-4-methyl-2,4-hexadienoate in 303 mL of methanol at 0 °C was added 303 mL of a 1.0 N aqueous sodium hydroxide solution over 5 min. After the solution was stirred at 0 °C for 5 min and then at room temperature for 24 h, the methanol was removed and the reaction mixture was cooled to 0 °C and acidified with concentrated hydrochloric acid to pH 2. The white solid was collected by filtration and dried on a vacuum pump.

To 100 mL (0.714 mol) of diisopropylamine dissolved in 300 mL of anhydrous tetrahydrofuran at –78 °C under argon was added dropwise 286 mL (0.714 mol) of a 2.5 M solution of *n*-butyllithium in hexanes over 30 min. After the mixture was stirred at –78 °C for 20 min, 45.2 mL

(0.276 mol) of hexamethylphosphoric triamide (HMPA) was added followed by stirring for 1 h 5 min. The solution of lithium diisopropylamide (LDA) was treated with 30.0 g (0.238 mol) of the above conjugated acid dissolved in 300 mL of anhydrous tetrahydrofuran dropwise over 41 min. After being stirred at −78 °C for 2 h, the reaction mixture was rapidly poured into 600 mL of a 10% aqueous hydrochloric acid solution containing ice and diluted with 600 mL of diethyl ether. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with water (1×) and then a saturated aqueous sodium chloride solution (1×). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give 30 g (100%) of **17** as a yellow oil: bp 110 °C (7 mmHg); R_f 0.25 (hexanes–diethyl ether–acetic acid; 1:1:1 dropwise); IR ($CHCl_3$) 3600–2200 (s), 1708 (s), 1647 (m), 1600 (m), 1414 (s), 1297 (s), 1240–1180 (m), 1180–1125 (m), 1084 (w), 1056 (w), 986 (s), 935 (m), 902 (s), 840 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.39 (dd, 1H, J = 17.4, 10.8 Hz), 5.62 (br t, 1H, J = 7.3 Hz), 5.13 (d, 1H, J = 17.4 Hz), 5.01 (d, 1H, J = 10.8 Hz), 3.21 (d, 2H, J = 7.3 Hz), 1.74 (d, 3H, J = 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.90, 140.44, 137.38, 122.37, 112.53, 33.60, 11.92; high-resolution MS (EI) calcd for $C_7H_{10}O_2$ (M) m/e 126.0681, found 126.0679.

(−)-10a-Formyl-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-5-methoxy-2,4b,8-trimethyl-10-oxo-(1α,4aβ,4bβ,5β,8α,8aα,10aβ)-1-phenanthreneacetic Acid (16). To 5.36 g (42.6 mmol) of diene acid **17** in 34 mL of a 5.0 M lithium perchlorate in ethyl acetate solution at room temperature was added 4.0 g (17.02 mmol) of dienophile **6**. The reaction mixture was stirred at room temperature. After 43 h, 100 mL of diethyl ether and 100 mL of water were added. The aqueous layer was extracted with diethyl ether (4 × 50 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on 650 g of flash silica gel. Elution with hexanes–diethyl ether–acetic acid (75:23.5:1.5) gave 4.53 g (73%) of **16** as a white foam: $[\alpha]^{25}_D$ −152.0° (*c* 1.00, $CHCl_3$); R_f 0.17 (hexanes–ether–acetic acid, 1:1:1 dropwise); IR ($CHCl_3$) 3600–2400 (m), 3045 (m), 2940 (s), 2857 (m), 2835 (m), 1712 (s), 1445 (m), 1418 (m), 1384 (m), 1336 (m), 1298 (m), 1275 (m), 1217 (m), 1168 (m), 1133 (m), 1117 (m), 1090 (s), 1057 (w), 997 (w), 965 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 5.38 (br s, 1H), 3.29 (s, 3H), 3.14 (dd, 1H, J = 11.1, 4.6 Hz), 2.95–2.84 (m, 3H), 2.44–2.26 (m, 3H), 2.14 (dt, 1H, J = 17.4, 5.8 Hz), 2.02–1.87 (m, 2H), 1.70 (br s, 3H), 1.77–1.65 (m, 1H), 1.53–1.36 (m, 3H), 1.09 (s, 3H), 0.92 (dq, 1H, J = 14.1, 4.4 Hz), 0.76 (d, 3H, J = 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.30, 200.49, 179.46, 131.61, 120.36, 81.35, 68.77, 55.98, 46.70, 45.54, 42.42, 40.77, 34.67, 33.13, 32.59, 31.36, 23.96, 22.70, 20.99, 19.33, 15.98; high-resolution MS (EI) calcd for $C_{20}H_{27}O_5$ (M − OCH_3) m/e 347.1859, found 347.1892; calcd for $C_{20}H_{29}O_4$ (M − CHO) m/e 333.2067, found 333.2046.

(+)-(1β,9β)-20-Hydroxy-1-methoxypicras-12-en-16-one (10). To a solution of 6.1 g (16.9 mmol) of Diels–Alder adduct **16** in 240 mL of tetrahydrofuran and 12 mL of water cooled to 0 °C was added 1.9 g (50.6 mmol) of solid sodium borohydride in small portions over 30 min. After being stirred at 0 °C for 50 min, the reaction mixture was acidified at 0 °C with concentrated hydrochloric acid to pH 2, whereupon the reaction was stirred overnight while warming to room temperature. The reaction mixture was diluted with 100 mL of water and 100 mL of ether. The aqueous phase was extracted with ether, and the combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate *in vacuo* afforded 5.87 g (100%) of **10** as a white foam: R_f 0.24 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3632 (w), 3455 (w), 2933 (s), 2822 (w), 1733 (s), 1466 (m), 1447 (m), 1377 (m), 1345 (m), 1319 (m), 1272 (m), 1260–1185 (m), 1141 (m), 1091 (s), 1075 (s), 1035 (m), 998 (m), 985 (m), 957 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (m, 1H), 4.42 (br s, 1H), 3.84 and 3.59 (AB quartet, 2H, J = 10.7 Hz), 3.25 (s, 3H), 3.20 (dd, 1H, J = 11.1, 4.6 Hz), 2.85 (AB part of an ABX, 2H, J_{AB} = 7.6 Hz, $\Delta\nu_{AB}$ = 23.5 Hz), 2.49 (X part of an ABX, 1H, J_{AX} = 14.4 Hz, J_{BX} = 0.3 Hz), 2.09–1.93 (m, 4H), 1.83 (br s, 1H), 1.74–1.65 (m, 2H), 1.69 (br s, 3H), 1.60 (ddd, 1H, J = 16.2, 12.8, 3.4 Hz), 1.53–1.42 (m, 1H), 1.34 (dt, 1H, J = 10.7, 3.4 Hz), 1.31–1.21 (m, 1H), 1.01 (s, 3H), 0.95 (dq, 1H, J = 13.4, 4.5 Hz), 0.83 (d, 3H, J = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.34, 133.82, 124.84, 82.85, 77.39, 69.07, 55.42, 43.14, 42.62, 41.21, 40.97, 38.01, 33.09, 33.02, 30.59, 26.39, 24.10, 23.87, 21.54, 19.43, 17.54. An analytical sample was prepared by recrystallization from ethyl acetate: mp 199–200 °C; $[\alpha]^{25}_D$ +44.1° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.57; H, 9.47.

(+)-(1β,9β)-20-(*tert*-Butyldiphenylsiloxy)-1-methoxypicras-12-en-16-one (21). To a solution of 2.5 g (9.0 mmol) of *tert*-butylchlorodiphenylsilane dissolved in 5 mL of *N,N*-dimethylformamide was added 1.23 g (18.0 mmol) of imidazole at room temperature. After being stirred for 15 min, the reaction mixture was treated with a solution of 0.80 g (2.3 mmol) of hydroxy lactone **10** in 10 mL of *N,N*-dimethylformamide dropwise over 5 min followed by stirring at room temperature for 42 h. The reaction mixture was diluted with 50 mL of chloroform, and the organic phase was washed with 30 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on 160 g of flash silica gel. Elution with hexanes–ethyl acetate (4:1) provided 1.34 g (99%) of silyl ether **21** as an oil: $[\alpha]^{25}_D$ +2.5° (*c* 1.00, $CHCl_3$); R_f 0.32 (hexanes–ethyl acetate, 4:1); IR ($CHCl_3$) 3071 (w), 3022 (w), 3000 (m), 2955 (s), 2932 (s), 2882 (m), 2853 (m), 2822 (w), 1734 (s), 1586 (w), 1465 (m), 1442 (m), 1422 (m), 1374 (m), 1360 (w), 1342 (m), 1312 (w), 1304 (w), 1266 (m), 1240–1180 (m), 1163 (w), 1141 (m), 1111 (s), 1100 (s), 1075 (s), 1050 (m), 1033 (s), 1018 (m), 993 (m), 983 (w), 952 (w), 840 (w), 814 (m), 692 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.59 (m, 4H), 7.49–7.36 (m, 6H), 5.65 (d, 1H, J = 5.3 Hz), 4.57 (br s, 1H), 3.97 and 3.41 (AB quartet, 2H, J = 10.3 Hz), 3.20 (s, 3H), 3.13 (dd, 1H, J = 11.0, 4.6 Hz), 3.02 (br d, 1H, J = 7.7 Hz), 2.90 (dd, 1H, J = 14.5, 7.7 Hz), 2.50 (dd, 1H, J = 14.5, 1.3 Hz), 2.00–1.88 (m, 3H), 1.84 (dt, 1H, J = 14.9, 3.0 Hz), 1.67 (br s, 3H), 1.63 (dq, 1H, J = 13.7, 2.7 Hz), 1.51 (dd, 1H, J = 10.6, 6.1 Hz), 1.44–1.33 (m, 1H), 1.28–1.03 (m, 3H), 1.10 (s, 9H), 0.89 (dq, 1H, J = 13.4, 4.5 Hz), 0.76 (d, 3H, J = 6.4 Hz), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.43, 135.69, 135.66, 133.79, 133.07, 132.81, 130.02, 129.96, 127.90, 127.84, 124.87, 82.77, 77.25, 70.41, 55.32, 43.51, 42.92, 42.13, 40.85, 37.89, 33.65, 33.03, 30.44, 27.06, 25.74, 24.21, 23.88, 21.71, 19.34, 17.96; high-resolution MS (EI) calcd for $C_{37}H_{50}O_4Si$ (M) m/e 586.3480, found 586.3468.

(+)-(1β,9β,16β)-20-(*tert*-Butyldiphenylsiloxy)-1,16-dimethoxypicras-12-ene (22). To a solution of 7.4 g (12.6 mmol) of silyl ether **21** in 350 mL of anhydrous tetrahydrofuran at −78 °C under argon was added 16.8 mL of a 1.0 M solution of diisobutylaluminum hydride in toluene. The reaction mixture was stirred at −78 °C for 2 h and quenched by the slow addition of 4 mL of methanol. After being warmed to room temperature, the reaction mixture was diluted with a 5% aqueous hydrochloric acid solution. The aqueous phase was extracted with ether, and the combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate *in vacuo* afforded a crude lactol which was used in the next reaction without further purification.

The above lactol dissolved in 500 mL of methanol and 250 mL of tetrahydrofuran was treated with a catalytic amount of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 16 h, neutralized with solid sodium bicarbonate at room temperature, and concentrated *in vacuo*. The residue was diluted with brine and ether. The aqueous phase was extracted with ether, and the combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* leaving 7.76 g (100%) of **22** as a white foam: $[\alpha]^{25}_D$ +34.6° (*c* 1.09, $CHCl_3$); R_f 0.32 (hexanes–ethyl acetate, 8:1); IR ($CHCl_3$) 3075 (w), 3055 (w), 3000 (m), 2938 (s), 2860 (m), 2830 (w), 1588 (w), 1466 (m), 1427 (m), 1376 (m), 1357 (w), 1243 (w), 1187 (w), 1162 (w), 1110 (s), 1084 (s), 1056 (s), 1039 (s), 1019 (m), 989 (m), 955 (m), 820 (m), 697 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.59 (m, 4H), 7.44–7.33 (m, 6H), 5.55 (br d, 1H, J = 6.9 Hz), 4.43 (dd, 1H, J = 9.1, 5.4 Hz), 3.77 (br s, 1H), 3.54 and 3.47 (AB quartet, 2H, J = 10.3 Hz), 3.32 (s, 3H), 3.26 (s, 3H), 3.23 (dd, 1H, J = 11.1, 4.7 Hz), 2.42 (br s, 1H), 2.21–2.11 (m, 1H), 2.01 (m, 1H), 1.93 (dq, 1H, J = 12.9, 2.7 Hz), 1.88–1.80 (m, 2H), 1.76 (dd, 1H, J = 9.0, 5.8 Hz), 1.74–1.68 (m, 1H), 1.68–1.61 (m, 1H), 1.63 (br s, 3H), 1.51–1.40 (m, 1H), 1.37–1.03 (m, 4H), 1.08 (s, 9H), 0.94 (m, 1H), 0.88 (s, 3H), 0.79 (d, 3H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.89, 135.81, 133.86, 133.57, 129.67, 129.63, 127.63, 127.59, 123.09, 99.12, 83.02, 69.37, 67.13, 55.61, 54.47, 42.82, 41.18, 40.68, 39.79, 38.28, 33.34, 30.77, 27.85, 27.52, 27.03, 24.81, 24.02, 21.82, 19.55, 19.40, 16.79; high-resolution MS (EI) calcd for $C_{34}H_{46}O_4Si$ (M − C_4H_9) m/e 546.3167, found 546.3186.

(−)-(1β,9β,16β)-20-(*tert*-Butyldiphenylsiloxy)-1,16-dimethoxypicrasan-12-one (23). To a rapidly stirring solution of 8.1 g (13.5 mmol) of tetracyclic olefin **22** in 215 mL of anhydrous tetrahydrofuran at 0 °C under argon was added dropwise, over 10 min, 40.5 mL (40.5 mmol) of a 1.0 M solution of diborane in tetrahydrofuran. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 4 h. The intermediate organoborane was oxidized at 0 °C by adding, successively, 29 mL of a 3.0 N aqueous sodium hydroxide solution and 29 mL of 30% hydrogen peroxide. After being stirred at room temperature overnight, the reaction solution was diluted with 100 mL of water. The aqueous phase was extracted with ether, and the combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. Filtration

and concentration of the filtrate *in vacuo* gave 8.3 g of a crude alcohol as a white foam which was used in the next reaction without purification.

To a solution of 8.3 g (13.4 mmol) of the above alcohol in 300 mL of dichloromethane at 0 °C were added 2.74 g (33.4 mmol) of anhydrous sodium acetate, 21.6 g of Celite, and 8.63 g (40.1 mmol) of pyridinium chlorochromate followed by 1.2 g of 4-Å molecular sieves. After being stirred at 0 °C for 30 min and then at room temperature for 1 h 15 min, the reaction mixture was diluted with 200 mL of ether and stirred vigorously for 10 min. The reaction contents were filtered through a pad of Celite–silica gel and washed successively with ether. The filtrate was concentrated *in vacuo* and chromatographed on 700 g of flash silica gel. Elution with hexanes–ethyl acetate (9:1 and then 8:2) gave 1.85 g (22%) of **23** as a mixture of epimers at C(13) and 4.1 g (50%) of pure **23** as a solid: R_f 0.44 (hexanes–ethyl acetate, 7:3); IR ($CHCl_3$) 3070 (w), 3060 (w), 2934 (s), 2890 (s), 2857 (m), 2820 (m), 1701 (s), 1587 (w), 1463 (m), 1445 (m), 1425 (m), 1374 (m), 1342 (w), 1304 (w), 1287 (w), 1230 (m), 1182 (m), 1135 (s), 1107 (s), 1081 (s), 1057 (s), 1036 (s), 1019 (m), 994 (w), 975 (m), 946 (m), 933 (m), 895 (w), 837 (w), 815 (m), 694 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.62 (m, 4H), 7.47–7.35 (m, 6H), 4.68 (dd, 1H, J = 4.6, 2.0 Hz), 4.15 (t, 1H, J = 3.0 Hz), 3.78 and 3.47 (AB quartet, 2H, J = 10.6 Hz), 3.31 (s, 3H), 3.19 (s, 3H), 2.97 (dd, 1H, J = 11.1, 4.5 Hz), 2.88–2.78 (m, 2H), 2.37 (AB part of an ABX, 2H, J_{AB} = 18.0 Hz, $\Delta\nu_{AB}$ = 46.7 Hz), 1.92 (dq, 1H, J = 12.9, 2.8 Hz), 1.87 (X part of an ABX, 1H, J_{AX} = 14.2 Hz, J_{BX} = 4.0 Hz), 1.77 (ddd, 1H, J = 14.5, 7.1, 2.1 Hz), 1.70–1.59 (m, 2H), 1.43–1.05 (m, 5H), 1.10 (s, 9H), 0.99 (d, 3H, J = 6.4 Hz), 0.97–0.86 (m, 1H), 0.82 (d, 3H, J = 5.9 Hz), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.31, 135.69, 135.65, 133.38, 133.12, 129.79, 129.77, 127.75, 127.68, 97.48, 83.05, 68.39, 63.59, 54.97, 54.25, 42.98, 40.71, 40.57, 38.87, 38.58, 34.41, 33.09, 30.49, 29.83, 26.88, 23.79, 19.76, 19.37, 17.69, 10.92. An analytical sample was prepared by recrystallization from diethyl ether: mp 182–183 °C; $[\alpha]^{25}_D$ –38.9° (c 1.05, $CHCl_3$). Anal. Calcd for $C_{38}H_{54}O_5Si$: C, 73.74; H, 8.79. Found: C, 73.95; H, 9.05.

Conversion of 23 as a Mixture of Epimers at C(13) into 23. A solution of 3.8 g (6.14 mmol) of the C(13) epimers of **23** dissolved in 33 mL of methanol and 33 mL of tetrahydrofuran was treated with 850 mg (6.14 mmol) of potassium carbonate. After being stirred at room temperature for 22 h, the reaction mixture was concentrated in vacuo. The reaction contents were dissolved in ethyl acetate and filtered through a pad of flash silica gel. Successive washings with ethyl acetate and concentration of the filtrate *in vacuo* provided 3.8 g (100%) of **23**.

(+)-(1β,16β)-20-(*tert*-Butyldiphenylsiloxy)-1,16-dimethoxypicras-9-(11)-en-12-one (24). To 6.5 mL (46.3 mmol) of diisopropylamine dissolved in 37 mL of anhydrous tetrahydrofuran at 0 °C under argon was added dropwise 28.4 mL (45.4 mmol) of a 1.6 M solution of *n*-butyllithium in hexanes. After being stirred at 0 °C for 1 h followed by cooling to –78 °C, the solution of lithium diisopropylamide (LDA) was treated dropwise over 1 h 25 min with 5.7 g (9.3 mmol) of ketone **23** dissolved in 111 mL of anhydrous tetrahydrofuran. After being stirred at –78 °C for 1 h, the reaction mixture was warmed to 0 °C and stirred for 1 h. Upon recooling to –78 °C, the enolate was treated dropwise with 5.9 mL (46.3 mmol) of chlorotrimethylsilane. After being stirred at –78 °C for 30 min and at 0 °C for 30 min, the reaction mixture was quenched by the addition of 11.5 mL of a saturated aqueous ammonium chloride solution and diluted with water and ether. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give an orange oil. The crude product was chromatographed on 475 g of coarse silica gel. Elution with hexanes–ether (4:1) provided 6.4 g (100%) of the corresponding $\Delta^{11,12}$ silyl enol ether as a light oil.

A total of 24.2 g (35.0 mmol) of $\Delta^{11,12}$ silyl enol ether (obtained from running the above reaction four times) dissolved in 230 mL of anhydrous acetonitrile under argon was treated with 7.4 g (70.0 mmol) of sodium carbonate followed by 11.8 g (53.0 mmol) of palladium(II) acetate. The heterogeneous mixture was placed in a 45 °C oil bath and stirred for 26.5 h. The reaction mixture was treated with an additional 3.7 g (35.0 mmol) of sodium carbonate followed by 5.9 g (26.5 mmol) of palladium(II) acetate and stirred at 45 °C for 40 h. Filtration through silica gel and sand followed by successive washings with ether provided, after concentration *in vacuo*, a crude, red oil. The residue was chromatographed on ca. 1500 g of flash silica gel. Elution with hexanes–ether (4:1, then 3:1, then 2:1, and then 1:1) gave, in order of elution, 8.0 g (33%) of recovered silyl enol ether, 3.45 g (16%) of 9β-ketone **23**, and 11.0 g (51%) of tetracyclic enone **24** as a white solid: R_f 0.30 (hexanes–ethyl acetate, 4:1); IR ($CHCl_3$) 3070 (w), 2925 (s), 2894 (m), 2858 (w), 2830 (w), 1664 (s), 1595 (m), 1463 (m), 1447 (m), 1426 (m), 1378 (m), 1357 (m), 1314 (w), 1227 (m), 1183 (w), 1167 (w), 1130 (s), 1110 (s), 1074 (s), 1053 (s), 1027 (m), 991 (m), 965 (m), 941 (m), 905 (s), 873 (w), 819 (m), 694 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.59 (m, 4H), 7.49–7.35 (m, 6H), 4.69 (d, 1H, J = 2.6 Hz), 4.14 (t, 1H, J = 2.7 Hz), 3.89 and 3.76 (AB quartet, 2H, J = 10.9 Hz), 3.35 (s, 3H), 3.28 (s, 3H), 3.25–3.18 (m, 2H), 2.84 (dq, 1H, J = 6.7, 4.3 Hz), 2.08 (dq, 1H, J = 13.4, 3.1 Hz), 1.67–1.58 (m, 2H), 1.56 (dt, 1H, J = 14.3, 3.0 Hz), 1.45–0.90 (m, 7H), 1.11 (s, 9H), 1.02 (d, 3H, J = 6.7 Hz), 0.79 (d, 3H, J = 6.5 Hz), 0.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.69, 165.23, 135.75, 135.55, 133.12, 133.03, 129.94, 128.21, 127.85, 127.80, 97.58, 83.73, 66.13, 64.58, 54.61, 54.17, 46.56, 45.26, 42.56, 39.47, 34.48, 33.20, 30.08, 26.89, 26.11, 25.89, 19.85, 19.43, 15.36, 11.34. An analytical sample was prepared by recrystallization from diethyl ether: mp 171.5–173 °C; $[\alpha]^{25}_D$ +90.5° (c 1.00, $CHCl_3$). Anal. Calcd for $C_{38}H_{52}O_5Si$: C, 73.98; H, 8.50. Found: C, 74.27; H, 8.58.

(+)-(1β,16β)-20-(*tert*-Butyldiphenylsiloxy)-1,16-dimethoxypicrasan-12-one (25). To 50 mL of freshly distilled ammonia at –78 °C was added 180 mg (25.9 mmol) of lithium wire cut into small pieces. After the mixture was stirred for 30 min, 1.6 g (2.6 mmol) of enone **24** and 232 μL (2.5 mmol) of *tert*-butyl alcohol in 11 mL of anhydrous tetrahydrofuran were added. After the solution was stirred at –78 °C for 1.5 h, the blue reaction was quenched by addition of 4 mL of isoprene followed by solid ammonium chloride until the orange solution turned white. The reaction mixture was diluted with ether, and the ammonia was allowed to evaporate overnight. The residue was diluted with water, and the product was extracted with ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was chromatographed on 200 g of flash silica gel. Elution with hexanes–ethyl acetate (4:1) provided 1.3 g (81%) of **25** as a white solid: R_f 0.29 (hexanes–ethyl acetate, 4:1); IR ($CHCl_3$) 3050 (w), 2935 (s), 1708 (s), 1462 (m), 1446 (m), 1429 (m), 1360 (m), 1225 (m), 1185 (m), 1109 (s), 1080 (s), 1058 (s), 1007 (m), 983 (m), 939 (m), 910 (s), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.61 (m, 4H), 7.49–7.36 (m, 6H), 4.72 (d, 1H, J = 2.9 Hz), 4.09 (br s, 1H), 4.06 and 3.86 (AB quartet, 2H, J = 11.1 Hz), 3.35 (s, 3H), 3.26–3.18 (m, 1H), 3.20 (s, 3H), 2.84–2.76 (m, 2H), 2.72 (m, 1H), 2.28–2.18 (m, 2H), 1.94–1.86 (m, 1H), 1.62 (dd, 1H, J = 13.8, 4.6 Hz), 1.62–1.55 (m, 1H), 1.43 (dd, 1H, J = 12.4, 2.4 Hz), 1.34–1.19 (m, 3H), 1.11 (s, 9H), 1.17–0.87 (m, 3H), 0.92 (d, 3H, J = 6.6 Hz), 0.73 (d, 3H, J = 5.8 Hz), 0.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.26, 135.82, 135.58, 133.35, 133.27, 129.88, 127.79, 97.75, 88.63, 65.61, 62.15, 55.28, 54.00, 44.68, 44.26, 42.92, 42.88, 42.60, 40.87, 35.53, 33.78, 29.61, 26.93, 26.22, 26.12, 25.77, 19.78, 19.43, 11.17, 10.52. An analytical sample was prepared by recrystallization from diethyl ether–hexanes: mp 152–153 °C; $[\alpha]^{25}_D$ +22.3° (c 1.18, $CHCl_3$). Anal. Calcd for $C_{38}H_{54}O_5Si$: C, 73.74; H, 8.79. Found: C, 74.01; H, 8.79.

(+)-(1β,16β)-20-(*tert*-Butyldiphenylsiloxy)-1,16-dimethoxypicras-11-ene (26). To a solution of 1.3 g (2.1 mmol) of **25** in 7 mL of methanol and tetrahydrofuran (1:1) was added 1.2 g (6.3 mmol) of (*p*-tolylsulfonyl)-hydrazine in one portion. The reaction mixture was stirred at room temperature. After 12.5 h, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed on 150 g of flash silica gel. Elution with hexanes–ethyl acetate (2:1 and then 1:1) provided 1.7 g (100%) of the tosylhydrazone as a white solid.

To 1.7 g (2.1 mmol) of the above tosylhydrazone dissolved in 81 mL of anhydrous tetrahydrofuran at –78 °C under argon was added 9.5 mL (21.0 mmol) of a 2.2 M solution of *n*-butyllithium in hexanes over 7 min. After the solution was stirred at –78 °C for 45 min and at 0 °C for 3 h 10 min, the reaction was quenched by addition of a saturated aqueous ammonium chloride solution until the red color dissipated. The aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give a green oil. The residue was chromatographed on 150 g of flash silica gel. Elution with hexanes–ether (4:1) provided 874 mg (69%) of **26** as a white foam: $[\alpha]^{25}_D$ +63.7° (c 1.00, $CHCl_3$); R_f 0.59 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3070 (w), 2967 (s), 2938 (s), 2855 (m), 2830 (m), 1588 (w), 1462 (m), 1445 (m), 1425 (m), 1390 (w), 1375 (m), 1358 (m), 1288 (w), 1180 (w), 1165 (m), 1123 (s), 1112 (s), 1083 (s), 1072 (s), 1047 (s), 1023 (m), 996 (m), 971 (m), 963 (m), 938 (m), 904 (m), 865 (w), 827 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.46–7.34 (m, 6H), 6.31 (d, 1H, J = 10.7 Hz), 5.36 (d, 1H, J = 10.7 Hz), 4.79 (d, 1H, J = 2.2 Hz), 3.98 (br s, 1H), 3.83 and 3.68 (AB quartet, 2H, J = 10.7 Hz), 3.36 (s, 3H), 3.22 (s, 3H), 2.94–2.86 (m, 2H), 2.64–2.55 (m, 2H), 1.90–1.83 (m, 1H), 1.69–1.53 (m, 3H), 1.40–0.71 (m, 6H), 1.10 (s, 9H), 0.89 (d, 3H, J = 7.1 Hz), 0.67 (d, 3H, J = 5.7 Hz), 0.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.97, 135.69, 134.06, 133.91, 132.65, 129.63, 129.56, 127.64,

127.58, 127.27, 98.31, 90.65, 66.67, 62.99, 56.09, 53.93, 44.32, 43.04, 42.61, 41.13, 34.12, 30.20, 29.60, 29.56, 27.01, 26.62, 25.48, 19.61, 19.50, 17.27, 12.10; high-resolution MS (EI) calcd for $C_{38}H_{54}O_4Si$ (M) *m/e* 602.3793, found 602.3818.

(−)-(1β)-20-(*tert*-Butyldiphenylsiloxy)-1-hydroxypicras-11-en-16-one (19). To a solution of 1.9 g (3.2 mmol) of **26** in 34 mL of acetone at 0 °C was added 6.3 mL (12.7 mmol) of a 2.0 M solution of Jones reagent. After the solution was stirred at 0 °C for 5 min and then at room temperature for 4 h 10 min, the reaction was quenched with 1 mL of isopropyl alcohol and diluted with 30 mL of water and 30 mL of ether. The organic layer was separated, and the aqueous layer was extracted with ether (4 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was chromatographed on 250 g of flash silica gel. Elution with hexanes–ether (4:1) provided 1.7 g (90%) of (−)-(1β)-20-(*tert*-butyldiphenylsiloxy)-1-methoxypicras-11-en-16-one as a white solid: R_f 0.40 (hexanes–ethyl acetate, 4:1); IR ($CHCl_3$) 3075 (w), 3010 (m), 2970 (s), 2945 (s), 2868 (s), 2830 (m), 1711 (s), 1590 (w), 1462 (m), 1434 (m), 1391 (m), 1373 (m), 1350 (w), 1334 (w), 1310 (w), 1272 (m), 1241 (s), 1206 (m), 1180 (m), 1171 (m), 1122 (s), 1072 (s), 1029 (s), 1003 (m), 998 (m), 972 (w), 961 (m), 904 (w), 850 (w), 823 (m), 697 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.56 (m, 4H), 7.48–7.36 (m, 6H), 6.33 (br d, 1H, *J* = 10.6 Hz), 5.34 (br d, 1H, *J* = 10.6 Hz), 4.54 (br s, 1H), 3.88 and 3.72 (AB quartet, 2H, *J* = 11.0 Hz), 3.20 (s, 3H), 2.81 (dd, 1H, *J* = 10.9, 4.8 Hz), 2.69 (dt, 1H, *J* = 13.3, 5.9 Hz), 2.60 (dd, 1H, *J* = 18.6, 6.2 Hz), 2.65–2.57 (m, 1H), 2.27 (dd, 1H, *J* = 18.6, 13.3 Hz), 2.12 (br s, 1H), 1.92–1.84 (m, 1H), 1.62–1.53 (m, 2H), 1.38–1.27 (m, 1H), 1.16–0.75 (m, 4H), 1.08 (s, 9H), 0.93 (d, 3H, *J* = 7.4 Hz), 0.67 (d, 3H, *J* = 6.5 Hz), 0.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.93, 135.75, 135.59, 133.12, 133.09, 132.17, 129.98, 129.89, 127.87, 127.78, 126.67, 90.10, 80.54, 62.16, 55.93, 44.04, 43.28, 41.19, 40.75, 33.91, 33.81, 29.67, 29.48, 28.82, 27.07, 26.25, 25.58, 19.40, 19.36, 16.39, 11.84. An analytical sample was prepared by recrystallization from hexanes: mp 179.5–180 °C; $[\alpha]^{25}_D$ −10.6° (*c* 1.04, $CHCl_3$). Anal. Calcd for $C_{37}H_{50}O_4Si$: C, 75.72; H, 8.59. Found: C, 75.74; H, 8.76.

To a solution of 2.3 g (3.9 mmol) of the above methyl ether dissolved in 50 mL of 1,2-ethanedithiol at room temperature was added 17.2 mL of boron trifluoride etherate. After being stirred for 36 h, the reaction mixture was cooled to 0 °C and neutralized with 30 mL of a saturated aqueous sodium bicarbonate solution followed by solid sodium bicarbonate. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on 800 g of flash silica gel. Elution with hexanes–ethyl acetate (10:1, then 7:3, and then 1:1) provided 1.5 g (67%) of alcohol **19** as a white solid: R_f 0.35 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3605 (w), 3430 (w), 3070 (w), 3005 (w), 2963 (s), 2933 (s), 2865 (m), 1711 (s), 1589 (w), 1462 (m), 1426 (m), 1372 (m), 1348 (w), 1333 (w), 1317 (m), 1270 (m), 1241 (m), 1215 (m), 1168 (w), 1150 (w), 1109 (s), 1069 (s), 1027 (m), 1001 (w), 973 (w), 952 (w), 930 (w), 902 (m), 815 (m), 750 (m), 722 (m), 693 (s), 684 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64–7.55 (m, 4H), 7.48–7.36 (m, 6H), 6.49 (dt, 1H, *J* = 10.6, 2.1 Hz), 5.37 (br d, 1H, *J* = 10.6 Hz), 4.55 (t, 1H, *J* = 2.7 Hz), 3.89 and 3.72 (AB quartet, 2H, *J* = 10.9 Hz), 3.43–3.36 (m, 1H), 2.69 (dt, 1H, *J* = 13.3, 6.2 Hz), 2.65–2.58 (m, 1H), 2.60 (dd, 1H, *J* = 18.6, 6.2 Hz), 2.27 (dd, 1H, *J* = 18.6, 13.3 Hz), 2.16 (br s, 1 H), 1.72–1.51 (m, 3H), 1.51–1.40 (m, 1H), 1.08 (s, 9H), 1.15–0.75 (m, 5H), 0.92 (d, 3H, *J* = 7.4 Hz), 0.67 (d, 3H, *J* = 6.2 Hz), 0.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.85, 135.77, 135.60, 133.11, 132.06, 129.99, 129.90, 127.88, 127.78, 126.99, 80.47, 80.32, 62.13, 43.65, 43.26, 41.10, 40.94, 33.94, 32.63, 29.64, 29.30, 28.78, 27.07, 25.69, 19.36, 19.32, 16.39, 11.16. An analytical sample was prepared by recrystallization from diethyl ether–ethyl acetate: mp 210–211 °C; $[\alpha]^{25}_D$ −10.5° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{36}H_{48}O_4Si$: C, 75.48; H, 8.45. Found: C, 75.53; H, 8.41.

(+)-(1β,16β)-20-(*tert*-Butyldiphenylsiloxy)-16-methoxypicras-11-en-1-ol (33). To a solution of 2.25 g (3.9 mmol) of lactone **19** dissolved in 100 mL of anhydrous tetrahydrofuran at −78 °C under argon was added dropwise, over 5 min, 9.8 mL (9.8 mmol) of a 1.0 M solution of diisobutylaluminum hydride in toluene. After being stirred for 2 h 15 min, the reaction mixture was quenched at −78 °C with 4.5 mL of methanol followed by warming to room temperature. The reaction mixture was diluted with 50 mL of a 5% aqueous hydrochloric acid solution and extracted with ether (4 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*.

To the above crude lactol dissolved in 100 mL of methanol and 5 mL of tetrahydrofuran was added 400 mg (0.16 mmol) of pyridinium *p*-toluenesulfonate. After being stirred for 12 h, the reaction mixture was concentrated *in vacuo* and the residue was chromatographed on 200 g of flash silica gel. Elution with hexanes–diethyl ether (3:1, then 1:1, and then 0:1) provided 2.3 g (100%) of a 5/1 mixture of C(16) β-OCH_3/α-OCH_3 epimers, respectively, as a white foam. A fraction containing pure C(16) β-OCH_3 epimer was concentrated *in vacuo* giving rise to **33** as a white foam: $[\alpha]^{25}_D$ +65.6° (*c* 1.00, $CHCl_3$); R_f 0.44 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3605 (w), 3460 (w), 3070 (w), 3000 (m), 2955 (s), 2932 (s), 2858 (s), 1590 (w), 1462 (m), 1428 (m), 1376 (m), 1359 (m), 1326 (w), 1310 (w), 1290 (w), 1166 (w), 1110 (s), 1072 (s), 1061 (s), 1046 (s), 1028 (m), 1000 (m), 969 (m), 960 (m), 947 (m), 937 (m), 901 (w), 823 (m), 817 (m), 697 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.58 (m, 4H), 7.46–7.35 (m, 6H), 6.44 (br d, 1H, *J* = 10.6 Hz), 5.38 (br d, 1H, *J* = 10.6 Hz), 4.79 (br s, 1H), 4.00 (br s, 1H), 3.84 and 3.68 (AB quartet, 2H, *J* = 10.7 Hz), 3.51–3.45 (m, 1H), 3.37 (s, 3H), 2.91 (dt, 1H, *J* = 12.9, 5.5 Hz), 2.62 (br s, 1H), 2.65–2.54 (m, 1H), 1.69–1.38 (m, 6H), 1.26 (dt, 1H, *J* = 14.5, 3.3 Hz), 1.10 (s, 9H), 1.15–0.95 (m, 3H), 0.89 (d, 3H, *J* = 7.3 Hz), 0.82–0.71 (m, 1H), 0.67 (d, 3H, *J* = 5.3 Hz), 0.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.98, 135.69, 134.04, 133.89, 132.77, 129.64, 129.57, 127.65, 127.58, 127.43, 98.31, 80.80, 66.61, 62.95, 53.94, 43.90, 42.97, 42.50, 41.27, 34.25, 32.84, 30.19, 29.61, 29.38, 27.04, 27.00, 25.57, 19.53, 19.49, 17.22, 11.35; high-resolution MS (EI) calcd for $C_{37}H_{52}O_4Si$ (M) *m/e* 588.4728, found 588.3650.

(+)-(1β,16β)-20-(*tert*-Butyldiphenylsiloxy)-1-(acetyloxy)-16-methoxypicras-11-ene (34). A solution of 400 mg (0.679 mmol) of alcohol **33** in 13.9 mL of anhydrous dichloromethane at 0 °C was treated with 83 mg (0.679 mmol) of 4-(dimethylamino)pyridine, 473 μL (3.40 mmol) of triethylamine, and 320 μL (3.40 mmol) of acetic anhydride. After the solution was stirred at 0 °C for 1 h and at room temperature for 45 min, the solvent was removed *in vacuo* without heat. The crude product was chromatographed on ca. 80 g of flash silica gel. Elution with hexanes–ethyl acetate (2:1) provided 428 mg (100%) of **34** as a white foam: R_f 0.67 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3073 (w), 3042 (w), 3010 (w), 2965 (s), 2940 (s), 2919 (m), 2882 (m), 2862 (m), 1720 (s), 1589 (w), 1481 (w), 1463 (m), 1453 (m), 1442 (m), 1424 (m), 1390 (w), 1370 (m), 1357 (m), 1310 (w), 1290 (w), 1254 (s), 1201 (m), 1168 (m), 1124 (s), 1110 (s), 1081 (m), 1070 (s), 1057 (s), 1046 (s), 1023 (m), 1000 (m), 971 (m), 965 (m), 934 (m), 904 (w), 897 (w), 820 (m), 810 (m), 691 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.64 (m, 2H), 7.62–7.57 (m, 2H), 7.47–7.34 (m, 6H), 5.76 and 5.35 (AB quartet, 2H, *J* = 10.8 Hz), 4.75 (s, 1H), 4.65 (dd, 1H, *J* = 10.9, 5.0 Hz), 3.98 (s, 1H), 3.80 and 3.66 (AB quartet, 2H, *J* = 10.6 Hz), 3.35 (s, 3H), 2.93–2.85 (m, 1H), 2.60 (br s, 1H), 2.61–2.50 (m, 1H), 1.98 (s, 3H), 1.77–1.68 (m, 1H), 1.64–0.65 (unresolved, 9H), 1.09 (s, 9H), 0.87 (d, 3H, *J* = 7.2 Hz), 0.68 (d, 3H, *J* = 5.2 Hz), 0.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.38, 135.97, 135.68, 133.80, 129.69, 129.59, 127.68, 127.60, 125.60, 98.19, 83.22, 66.24, 62.81, 53.94, 43.82, 43.02, 41.58, 40.06, 33.77, 30.12, 29.85, 29.31, 27.84, 27.05, 26.98, 25.27, 21.85, 19.47, 19.44, 17.03, 12.26. An analytical sample was prepared by recrystallization from hexanes: mp 179–180 °C; $[\alpha]^{25}_D$ +74.9° (*c* 0.80, $CHCl_3$). Anal. Calcd for $C_{39}H_{54}O_5Si$: C, 74.24; H, 8.63. Found: C, 74.18; H, 8.43.

(+)-(1β,11α,12α,16β)-20-(*tert*-Butyldiphenylsiloxy)-12-(acetyloxy)-16-methoxypicrasane-1,11-diol (35). To a solution of 428 mg (0.679 mmol) of olefin **34** dissolved in 6.8 mL of pyridine at 0 °C was added 190 mg (0.747 mmol) of solid osmium tetraoxide. After the solution was stirred for 10 min at 0 °C and for 25.5 h at room temperature, 4.0 mL of a 5% aqueous sodium bisulfite solution was added followed by ca. 700 mg of solid sodium bisulfite. After being stirred for 24 h, the reaction mixture was diluted with water and diethyl ether. The aqueous layer was extracted with diethyl ether (5×), and the combined ether layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was chromatographed on 75 g of flash silica gel. Elution with hexanes–ethyl acetate (1:1 and then 0:1) provided 389 mg (86%) of **35** as a white foam: R_f 0.24 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3320 (m), 3075 (w), 2938 (s), 2912 (m), 2962 (m), 1728 (s), 1590 (w), 1482 (w), 1461 (m), 1443 (m), 1367 (m), 1320 (w), 1250 (s), 1268 (s), 1204 (s), 1176 (m), 1162 (m), 1130 (s), 1110 (s), 1097 (s), 1070 (s), 1045 (s), 1022 (m), 1002 (m), 985 (m), 977 (m), 966 (w), 950 (w), 930 (w), 904 (s), 880 (m), 818 (m), 692 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.62 (m, 2H), 7.61–7.57 (m, 2H), 7.49–7.37 (m, 6H), 5.20 (t, 1H, *J* = 3.3 Hz), 4.75 (d, 1H, *J* = 2.8 Hz), 4.03 (br s, 1H), 3.87 (dd, 1H, *J* = 11.4, 3.8 Hz), 3.73 and 3.67 (AB quartet, 2H, *J* = 11.2 Hz), 3.44 (dd, 1H, *J* = 9.8, 5.5 Hz), 3.35 (s, 3H), 2.74 (dt, 1H, *J* = 13.6, 4.5 Hz), 2.11 (s, 3H), 2.15–1.98 (m, 3H), 1.80–1.71 (m, 1H), 1.63 (dd,

1H, J = 13.6, 3.5 Hz), 1.59–1.51 (m, 1H), 1.50–1.39 (m, 2H), 1.27–1.19 (m, 1H), 1.09 (s, 9H), 1.15–0.95 (m, 3H), 0.86 (d, 3H, J = 7.0 Hz), 0.77 (d, 3H, J = 6.2 Hz), 0.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.10, 135.81, 135.57, 133.28, 133.19, 129.88, 127.79, 127.75, 98.15, 77.63, 76.26, 67.97, 65.26, 62.29, 53.97, 44.75, 44.65, 44.31, 43.34, 33.15, 31.31, 31.18, 30.29, 29.98, 27.17, 26.90, 26.00, 21.14, 20.39, 19.37, 14.27, 11.23. An analytical sample was prepared by recrystallization from diethyl ether giving fine needles: mp 120–121 °C; $[\alpha]^{25}_D$ +39.7° (c 0.42, $CHCl_3$). Anal. Calcd for $C_{39}H_{56}O_7Si \cdot H_2O$: C, 68.58; H, 8.56. Found: C, 68.72; H, 8.81.

(+)-(12α,16β)-20-(*tert*-Butyldiphenylsiloxy)-12-hydroxy-16-methoxypicrasane-1,11-dione (36). To a solution of 922 μL (11.4 mmol) of anhydrous pyridine in 9.5 mL of anhydrous dichloromethane at 0 °C was added 570 mg (5.7 mmol) of chromium trioxide in one portion. After being stirred for 5 min and at room temperature for 30 min, the reaction mixture was cooled to 0 °C and treated with 765 mg of Celite followed by 379 mg (0.57 mmol) of diol **35** dissolved in 4.8 mL of anhydrous dichloromethane. The reaction mixture was stirred for 10 min and warmed to room temperature. After 5 h, the reaction mixture was diluted with diethyl ether followed by stirring for 30 min. The reaction contents were filtered through silica gel/sand and washed successively with ethyl acetate. The filtrate was concentrated *in vacuo*, and the residue was chromatographed on 75 g of flash silica gel. Elution with hexanes–ethyl acetate (2:1) provided 362 mg (96%) of a white, amorphous solid: $[\alpha]^{25}_D$ +53.4° (c 1.15, $CHCl_3$); R_f 0.27 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3030 (w), 3025 (w), 3021 (w), 3009 (w), 2957 (m), 2933 (m), 2895 (m), 2860 (m), 1748 (s), 1723 (m), 1701 (m), 1470 (w), 1464 (w), 1449 (w), 1428 (m), 1379 (m), 1369 (m), 1232 (s), 1218 (m), 1212 (m), 1207 (w), 1188 (w), 1137 (m), 1113 (s), 1106 (m), 1084 (m), 1064 (m), 1050 (m), 1024 (m), 1009 (m), 982 (m), 941 (m), 901 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.50 (m, 4H), 7.50–7.30 (m, 6H), 4.87 (d, 1H, J = 3.3 Hz), 4.78 (d, 1H, J = 1.8 Hz), 4.04 (t, 1H, J = 2.7 Hz), 3.67 and 3.44 (AB quartet, 2H, J = 11.4 Hz), 3.58 (s, 1H), 3.36 (s, 3H), 2.94 (dt, 1H, J = 14.1, 4.7 Hz), 2.84 (dt, 1H, J = 13.4, 7.4 Hz), 2.42–2.24 (m, 2H), 2.19 (s, 3H), 2.07 (ddd, 1H, J = 14.1, 6.0, 1.4 Hz), 2.00–1.87 (m, 1H), 1.82 (dd, 1H, J = 14.0, 4.7 Hz), 1.77–1.60 (m, 1H), 1.52–0.90 (m, 4H), 1.21 (s, 3H), 1.09 (s, 9H), 0.98 (d, 3H, J = 7.0 Hz), 0.81 (d, 3H, J = 6.9 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 213.21, 206.38, 169.60, 135.80, 135.51, 133.12, 133.02, 129.91, 127.79, 98.03, 80.74, 64.63, 62.69, 54.24, 49.43, 47.02, 46.82, 43.80, 36.58, 36.05, 33.95, 30.97, 28.46, 26.90, 26.14, 21.01, 19.37, 18.57, 15.58, 13.73; high-resolution MS (EI) calcd for $C_{39}H_{52}O_7Si$ (M) m/e 660.3484, found 660.3468.

A solution of 268 mg (0.405 mmol) of the above acetate dissolved in 8 mL of tetrahydrofuran and 8 mL of methanol at 0 °C was treated with 4 mL of a 1.5 N aqueous sodium hydroxide solution. After being stirred for 1 h at 0 °C and at room temperature for 2 h, the reaction mixture was diluted with brine and the aqueous layer was extracted with chloroform (3×) followed by diethyl ether (3×). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography. Elution with hexanes–diethyl ether (2:1) provided 241 mg (95%) of **36** as a white solid: R_f 0.34 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3620–3400 (w), 3050 (w), 2960 (s), 2930 (s), 2895 (s), 2855 (m), 1700 (s), 1468 (m), 1427 (m), 1400–1350 (m), 1319 (m), 1300 (w), 1276 (m), 1138 (m), 1112 (s), 1075 (s), 1050 (s), 1006 (m), 978 (m), 940 (w), 898 (m), 864 (w), 821 (m), 697 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.50 (m, 4H), 7.50–7.30 (m, 6H), 4.74 (d, 1H, J = 2.4 Hz), 4.02 (t, 1H, J = 2.9 Hz), 3.82 (s, 1H), 3.77 (t, 1H, J = 2.7 Hz), 3.65 and 3.43 (AB quartet, 2H, J = 10.5 Hz), 3.35 (s, 3H), 2.96–2.79 (m, 2H), 2.71–2.55 (m, 1H), 2.53 (dt, 1H, J = 14.0, 3.2 Hz), 2.24–2.08 (m, 1H), 2.09 (dd, 1H, J = 14.1, 3.9 Hz), 2.02–1.87 (m, 1H), 1.82 (dd, 1H, J = 14.4, 4.2 Hz), 1.76–1.60 (m, 1H), 1.57–1.25 (m, 3H), 1.15–0.95 (m, 1H), 1.19 (s, 3H), 1.09 (s, 12H), 0.81 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.88, 212.13, 135.83, 135.54, 133.24, 129.83, 127.76, 98.28, 81.14, 64.57, 62.93, 54.14, 49.40, 47.11, 46.71, 42.49, 36.56, 36.24, 34.79, 31.10, 28.49, 27.26, 26.91, 26.23, 19.39, 18.55, 15.75, 13.76. An analytical sample was prepared by recrystallization from diethyl ether–dichloromethane: mp 228–230 °C; $[\alpha]^{25}_D$ +30.1° (c 1.10, $CHCl_3$). Anal. Calcd for $C_{37}H_{50}O_6Si$: C, 71.81; H, 8.14. Found: C, 71.51; H, 8.51.

(+)-(12α,16β)-20-(*tert*-Butyldiphenylsiloxy)-16-methoxy-12-(methoxymethoxy)picrasane-1,11-dione (37). To 165 mg (0.267 mmol) of **36** in 3.6 mL of anhydrous 1,2-dichloroethane at room temperature were added 558 μL (3.20 mmol) of anhydrous *N*,*N*-diisopropylethylamine and 203 μL (2.67 mmol) of chloromethyl methyl ether. After being stirred for 24 h, the reaction mixture was applied directly to a chromatography column containing flash silica gel. Elution with hexanes–diethyl ether (2:1) provided 158 mg (89%) of **37** as a white, amorphous solid: $[\alpha]^{25}_D$ +71.0° (c 1.05, $CHCl_3$); R_f 0.51 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3080–3030 (w), 2955 (s), 2935 (s), 2893 (m), 2855 (m), 1700 (s), 1462 (m), 1446 (m), 1426 (m), 1390–1340 (m), 1318 (w), 1273 (w), 1152 (m), 1136 (m), 1112 (s), 1083 (s), 1050 (s), 1021 (s), 972 (m), 933 (m), 912 (w), 898 (m), 866 (w), 821 (m), 697 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.50 (m, 4H), 7.50–7.30 (m, 6H), 4.82 and 4.71 (AB quartet, 2H, J = 6.6 Hz), 4.74 (d, 1H, J = 2.4 Hz), 4.00 (t, 1H, J = 3.0 Hz), 3.72 (s, 1H), 3.71 (d, 1H, J = 2.7 Hz), 3.66 and 3.44 (AB quartet, 2H, J = 11.7 Hz), 3.39 (s, 3H), 3.35 (s, 3H), 2.96–2.80 (m, 2H), 2.46 (dt, 1H, J = 14.0, 3.6 Hz), 2.32–2.16 (m, 1H), 2.07 (dd, 1H, J = 13.8, 4.1 Hz), 1.98–1.85 (m, 1H), 1.79 (dd, 1H, J = 14.0, 4.7 Hz), 1.76–1.58 (m, 1H), 1.53–1.20 (m, 3H), 1.18 (s, 3H), 1.09 (s, 12H), 1.20–0.95 (m, 1H), 0.79 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.44, 210.63, 135.80, 135.50, 133.16, 129.83, 127.73, 98.22, 94.99, 83.48, 64.59, 62.97, 55.77, 54.12, 49.35, 47.03, 46.80, 43.08, 36.60, 36.28, 34.35, 31.10, 28.54, 27.06, 26.88, 26.18, 19.35, 18.55, 15.70, 14.05; high-resolution MS (CI) calcd for $C_{39}H_{55}O_7Si$ (M + 1) m/e 663.3719, found 663.3737; calcd for $C_{39}H_{54}O_7Si$ (M) m/e 662.3640, found 662.3633.

(+)-(1β,2α,12α,16β)-20-(*tert*-Butyldiphenylsiloxy)-1,16-dimethoxy-2-hydroxy-12-(methoxymethoxy)picrasan-11-one (38). All reagents in this experiment with the exception of *n*-butyllithium were deoxygenated utilizing the freeze–pump–thaw method. To 136 mg (0.205 mmol) of **37** in 2.05 mL of anhydrous tetrahydrofuran and 1.02 mL of anhydrous hexamethylphosphoramide at –78 °C was added dropwise 547 μL (0.41 mmol) of a 0.75 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran. After being stirred at –78 °C for 30 min and at 0 °C for 30 min, the reaction mixture was cooled to –78 °C and treated dropwise with 58 μL (0.615 mmol) of dimethyl sulfate. After the solution was stirred an additional 5 min at –78 °C and at 0 °C for 45 min, the reaction was quenched by addition of 350 μL of a saturated aqueous ammonium chloride solution. After the solution was diluted with water and diethyl ether, the aqueous layer was extracted with diethyl ether (3×) and the combined ether layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude foam was rapidly chromatographed on flash silica gel. Elution with hexanes–diethyl ether (1:1) provided 121 mg (87%) of a white foam which was used immediately in the next reaction. Approximately 13 mg (9%) of **37** was recovered.

A solution of 121 mg (0.179 mmol) of the above methyl enol ether in 3.6 mL of anhydrous tetrahydrofuran at –23 °C under argon was treated with 179 μL (0.179 mmol) of a 1.0 M solution of diborane in tetrahydrofuran. After the solution was stirred at –23 °C for 15 min and at 0 °C for 30 min, an additional 179 μL (0.179 mmol) of a 1.0 M solution of diborane in tetrahydrofuran was added. The reaction was stirred an additional 15 min at 0 °C. The intermediate organoborane was oxidized by dropwise addition of 800 μL of a 3 N aqueous sodium hydroxide solution followed by 800 μL of a 30% aqueous hydrogen peroxide solution. Upon being warmed to room temperature, the reaction mixture was stirred for 1.5 h and diluted with brine. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude foam was chromatographed on flash silica gel. Elution with hexanes–ethyl acetate (2:1) provided 93 mg (75%) of **38** as a white foam: $[\alpha]^{25}_D$ +34.0° (c 1.00, $CHCl_3$); R_f 0.27 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3605 (w), 3470 (w), 3080 (w), 3060 (w), 2965 (s), 2940 (s), 2915 (s), 2870 (m), 1713 (m), 1590 (w), 1465 (m), 1448 (m), 1427 (m), 1390 (w), 1375 (m), 1358 (m), 1319 (w), 1235 (w), 1211 (w), 1184 (w), 1162 (s), 1134 (s), 1113 (s), 1085 (s), 1065 (s), 1051 (s), 1022 (s), 968 (m), 952 (m), 926 (m), 905 (w), 887 (w), 848 (w), 822 (m), 696 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 2H, J = 6.4 Hz), 7.55 (d, 2H, J = 6.4 Hz), 7.50–7.30 (m, 6H), 4.79 (d, 1H, J = 2.8 Hz), 4.59 and 4.55 (AB quartet, 2H, J = 6.6 Hz), 4.11 (br s, 1H), 3.92–3.82 (m, 1H), 3.68 and 3.46 (AB quartet, 2H, J = 11.2 Hz), 3.65 (d, 1H, J = 3.2 Hz), 3.44 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H), 3.32 (s, 3H), 2.82 (dt, 1H, J = 13.6, 5.0 Hz), 2.68 (d, 1H, J = 8.8 Hz), 2.38 (dt, 1H, J = 13.6, 3.4 Hz), 2.18–2.06 (m, 1H), 2.00–2.88 (m, 2H), 1.76 (dd, 1H, J = 14.0, 4.4 Hz), 1.69 (br s, 1H), 1.38–1.17 (m, 3H), 1.08 (s, 9H), 1.01 (d, 3H, J = 7.2 Hz), 0.99 (s, 3H), 0.94–0.83 (m, 1H), 0.79 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.39, 135.79, 135.55, 133.27, 129.79, 127.73, 127.70, 98.09, 96.79, 94.18, 88.59, 69.22, 64.76, 62.08, 58.09, 56.12, 54.10, 48.12, 47.69, 43.99, 42.63, 42.23, 35.93, 31.16, 27.77, 27.03, 26.90, 24.79, 19.36, 14.34, 12.63; high-resolution MS (CI) calcd for $C_{40}H_{59}O_8Si$ (M + 1) m/e 695.3980, found 695.3979.

(–)-(1β,12α)-20-(*tert*-Butyldiphenylsiloxy)-1-methoxy-12-(methoxymethoxy)picrasane-2,11,16-trione (39). To 90 mg (0.129 mmol) of alcohol **38** in 1.3 mL of tetrahydrofuran at room temperature was added 1.3 mL of a 10% aqueous hydrochloric acid solution. After being stirred

for 14 h, the reaction mixture was neutralized by pouring into a cooled (0 °C), saturated aqueous sodium bicarbonate solution followed by the addition of solid sodium bicarbonate until gas evolution ceased. The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give a mixture of lactols.

The crude lactols from above were dissolved in 2.6 mL of dichloromethane at room temperature and treated with 111 mg (0.516 mmol) of pyridinium chlorochromate. After the solution was stirred for 2 h, an additional 30 mg (0.139 mmol) of pyridinium chlorochromate was added and stirring was continued for 1 h. The reaction contents were diluted with diethyl ether and filtered through a pad of flash silica gel, washing successively with diethyl ether. Chromatography of the crude residue on flash silica gel, eluting with hexanes–ethyl acetate (2:1), provided 68 mg (78%) of **39** as a white solid: R_f 0.47 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3037 (w), 2972 (m), 2947 (m), 2912 (m), 2872 (w), 2840 (w), 1721 (s), 1591 (w), 1464 (w), 1442 (w), 1428 (w), 1374 (m), 1340 (w), 1324 (w), 1287 (m), 1276 (m), 1261 (m), 1237 (m), 1209 (m), 1159 (m), 1138 (m), 1113 (s), 1106 (s), 1074 (s), 1021 (s), 970 (w), 941 (w), 925 (w), 907 (m), 854 (w), 820 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.49 (m, 4H), 7.48–7.35 (m, 6H), 4.72 (t, 1H, J = 2.6 Hz), 4.49 (s, 2H), 3.72 (d, 1H, J = 3.6 Hz), 3.71 and 3.48 (AB quartet, 2H, J = 11.5 Hz), 3.52–3.40 (m, 1H), 3.39 (s, 1H), 3.36 (s, 3H), 3.33 (s, 1H), 3.23 (s, 3H), 2.79–2.64 (m, 2H), 2.36 (dd, 1H, J = 14.0, 4.5 Hz), 2.10–2.01 (m, 1H), 1.95 (t, 1H, J = 12.8 Hz), 1.75 (dt, 1H, J = 14.9, 3.0 Hz), 1.73–1.60 (m, 2H), 1.10–0.96 (m, 1H), 1.06 (d, 3H, J = 6.7 Hz), 1.05 (s, 9H), 0.96 (s, 3H), 0.91 (d, 3H, J = 5.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.67, 206.55, 171.06, 135.64, 135.45, 132.30, 132.20, 130.23, 128.02, 127.96, 95.33, 94.95, 86.20, 78.31, 61.05, 58.62, 56.12, 48.80, 45.76, 45.42, 44.36, 43.27, 34.93, 34.47, 31.32, 28.04, 27.00, 25.17, 19.44, 19.21, 13.73, 11.61. An analytical sample was prepared by recrystallization from diethyl ether: mp 188–190 °C; $[\alpha]^{25}_D$ –15.8° (c 1.20, $CHCl_3$). Anal. Calcd for $C_{39}H_{52}O_8Si$: C, 69.20; H, 7.74. Found: C, 69.33; H, 7.99.

(+)-(1β,12α)-20-(*tert*-Butyldiphenylsiloxy)-1-methoxy-12-(methoxymethoxy)picras-3-ene-2,11,16-trione (40). A solution of 43 mg (0.064 mmol) of ketone **39** in 1.2 mL of anhydrous tetrahydrofuran at 0 °C was treated with a catalytic amount of camphorsulfonic acid followed by a solution of 22 mg (0.07 mmol) of pyridinium bromide perbromide in 430 μL of anhydrous tetrahydrofuran. After the solution was warmed to room temperature and stirred for 1 h, the reaction was quenched by addition of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with diethyl ether, and the combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give 33 mg of crude bromo ketone which was used directly in the next reaction.

A heterogeneous solution of 33 mg (0.044 mmol) of the above bromo ketone, 19 mg (0.218 mmol) of lithium bromide, and 32 mg (0.437 mmol) of lithium carbonate in 900 μL of *N,N*-dimethylformamide were heated at 120 °C under argon. After being stirred for 1 h, the reaction contents were filtered through a pad of flash silica gel, washing successively with hexanes–ethyl acetate (1:1). The crude product was chromatographed on two silica gel preparative thin layer chromatography plates (0.25 mm). Elution with hexanes–ethyl acetate (2:1) provided 20 mg (47% over two steps) of **40** as a white solid: R_f 0.35 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3075 (w), 3033 (w), 3003 (m), 2959 (m), 2938 (m), 2900 (m), 2860 (m), 2825 (w), 1723 (s), 1676 (s), 1624 (w), 1588 (w), 1482 (w), 1464 (w), 1438 (m), 1426 (m), 1376 (m), 1363 (m), 1339 (w), 1330 (w), 1283 (m), 1263 (m), 1229 (m), 1193 (m), 1156 (m), 1112 (s), 1102 (s), 1084 (s), 1064 (s), 1020 (s), 966 (w), 928 (w), 913 (w), 896 (w), 849 (m), 819 (m), 800 (w), 760 (w), 730 (w), 694 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.55 (m, 2H), 7.53–7.49 (m, 2H), 7.49–7.36 (m, 6H), 5.85 (br s, 1H), 4.70 (br s, 1H), 4.54 (s, 2H), 3.77 (d, 1H, J = 3.4 Hz), 3.73 and 3.54 (AB quartet, 2H, J = 11.8 Hz), 3.51–3.43 (m, 1H), 3.42 (s, 3H), 3.38 (s, 4H), 3.37 (s, 1H), 2.83–2.67 (m, 3H), 2.20–2.11 (m, 1H), 1.83–1.74 (unresolved, 1H), 1.76 (br s, 3H), 1.12–1.03 (m, 1H), 1.09 (d, 3H, J = 7.0 Hz), 1.07 (s, 9H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.82, 197.33, 170.73, 159.24, 135.72, 135.45, 132.28, 132.09, 130.29, 128.08, 128.01, 127.15, 95.45, 93.96, 85.87, 78.19, 61.15, 59.79, 56.17, 45.84, 45.08, 45.01, 43.28, 34.65, 34.47, 28.03, 27.03, 24.37, 21.75, 19.22, 13.70, 11.03. An analytical sample was prepared by recrystallization from diethyl ether: mp 154–155 °C; $[\alpha]^{25}_D$ +1.8° (c 0.84, $CHCl_3$). Anal. Calcd for $C_{39}H_{50}O_8Si$: C, 69.41; H, 7.47. Found: C, 69.22; H, 7.50.

(+)-(1β,12α)-20-(*tert*-Butyldiphenylsiloxy)-1,12-dihydroxypicras-3-ene-2,11,16-trione (41). A solution of 14.5 mg (0.022 mmol) of methyl ether **40** in 450 μL of dichloromethane at –78 °C was treated dropwise with 172 μL (0.172 mmol) of a 1.0 M solution of boron tribromide in dichloromethane. After the solution was stirred for 20 min, an additional 172 μL (0.172 mmol) of a 1.0 M solution of boron tribromide in dichloromethane was added. After the solution was stirred at –78 °C for 40 min and at –23 °C for 15 min, the reaction was quenched by addition of 400 μL of a saturated aqueous sodium bicarbonate solution. After being warmed to 0 °C and stirred for 15 min, the reaction mixture was diluted with a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, and the combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Chromatography of the residue on a silica gel preparative thin layer chromatography plate (0.25 mm), eluting with hexanes–ethyl acetate (1:1), provided 11.0 mg (83%) of **41** as a white solid: R_f 0.21 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3420 (m), 3075 (w), 3010 (m), 2970 (m), 2940 (m), 2913 (m), 2868 (m), 1725 (s), 1675 (s), 1618 (w), 1591 (w), 1484 (w), 1470 (m), 1464 (m), 1427 (m), 1394 (m), 1378 (m), 1364 (m), 1334 (m), 1279 (m), 1265 (m), 1257 (m), 1237 (m), 1228 (m), 1217 (m), 1205 (m), 1169 (m), 1151 (m), 1110 (s), 1105 (s), 1058 (s), 1035 (m), 1024 (m), 985 (m), 945 (w), 935 (m), 899 (w), 887 (w), 847 (m), 819 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.56 (m, 2H), 7.54–7.50 (m, 2H), 7.49–7.37 (m, 6H), 5.96 (br s, 1H), 4.68 (br s, 1H), 4.29 (br s, 1H, OH), 3.98 (br s, 1H, OH), 3.88 (br s, 1H), 3.79 (br s, 1H), 3.72 and 3.52 (AB quartet, 2H, J = 11.8 Hz), 3.67 (s, 1H), 3.60 (dd, 1H, J = 18.2, 11.8 Hz), 2.82–2.69 (m, 3H), 2.13–2.04 (m, 1H), 1.87–1.75 (unresolved, 1H), 1.11 (d, 3H, J = 7.1 Hz), 1.06 (s, 9H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.03, 196.93, 170.74, 162.78, 135.74, 135.48, 132.36, 132.16, 130.27, 128.08, 128.02, 124.87, 84.58, 81.83, 78.05, 61.17, 45.74, 45.42, 45.13, 42.04, 34.72, 34.62, 28.28, 27.03, 24.46, 22.24, 19.23, 13.38, 10.18. An analytical sample was prepared by recrystallization from diethyl ether: mp 216–219 °C; $[\alpha]^{25}_D$ +0.7° (c 0.87, $CHCl_3$). Anal. Calcd for $C_{36}H_{44}O_7Si \cdot {}^1/_2H_2O$: C, 69.09; H, 7.25. Found: C, 69.16; H, 7.23.

(–)-Chaparrinone (3). To 8.5 mg (0.014 mmol) of pre-chaparrinone (**41**) in 275 μL of tetrahydrofuran at room temperature was added 138 μL (0.138 mmol) of a 1.0 M tetrabutylammonium fluoride in tetrahydrofuran solution. After being stirred for 30 min, the reaction mixture was directly chromatographed on flash silica gel. Elution with ethyl acetate–acetone (85:15) provided 3.5 mg (67%) of (–)-chaparrinone (**3**) as a white solid. Recrystallization from acetone gave rise to fine needles: mp 241–244 °C (lit.[5] mp 238–242 °C); $[\alpha]^{25}_D$ –38.0° (c 0.54, pyridine) (lit.[5] $[\alpha]^{25}_D$ –47° (pyridine)); R_f 0.20 (ethyl acetate–methanol, 98:2); IR (KBr) 3439 (s), 2984 (w), 2963 (w), 2928 (w), 2901 (w), 2880 (w), 1707 (s), 1661 (s), 1628 (m), 1464 (m), 1443 (m), 1397 (m), 1262 (m), 1236 (m), 1202 (m), 1188 (m), 1163 (m), 1117 (m), 1082 (m), 1042 (m), 997 (m), 959 (w), 916 (w), 804 (w), 741 (w), 700 (w) cm^{-1}; ^1H NMR (500 MHz, C_5D_5N) δ 6.08 (br s, 1H), 4.54 (br s, 1H), 4.35 (s, 1H), 4.11 (d, 1H, J = 8.5 Hz), 3.96 (d, 1H, J = 4.2 Hz), 3.73 (d, 1H, J = 8.5 Hz), 3.35 (dd, 1H, J = 18.8, 14.1 Hz), 3.29 (s, 1H), 2.99 (br d, 1H, J = 12.3 Hz), 2.86 (dd, 1H, J = 18.8, 5.2 Hz), 2.46–2.38 (m, 1H), 2.16 (dt, 1H, J = 14.6, 2.6 Hz), 2.03–1.90 (m, 2H), 1.71 (br s, 3H), 1.52 (s, 3H), 1.09 (d, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, C_5D_5N) δ 197.61, 170.40, 162.44, 126.15, 110.56, 84.47, 79.54, 78.58, 71.45, 46.18, 45.42, 44.57, 42.72, 42.48, 31.64, 30.55, 26.18, 22.37, 12.23, 10.30. High-resolution MS (EI) calcd for $C_{20}H_{26}O_7$ (M) m/e 378.1679, found 378.1661.

(+)-(1β,12α,16β)-20-(*tert*-Butyldiphenylsiloxy)-1,16-dimethoxy-12-(methoxymethoxy)picrasane-2,11-dione (42). To a solution of 11.1 g (16.0 mmol) of alcohol **38** in 266 mL of methylene chloride at 0 °C containing 26.1 g of Celite and 3.28 g (39.9 mmol) of sodium acetate was added 10.3 g (47.9 mmol) of pyridinium chlorochromate in small portions over 10 min. After being stirred at 0 °C for 20 min and at room temperature for 2 h 15 min, the reaction contents were diluted with diethyl ether (110 mL), stirred for 15 min, and then filtered through a pad of flash silica gel, washing with ethyl acetate. The filtrate was concentrated *in vacuo*, and the crude residue was chromatographed on 1000 g of flash silica gel. Elution with diethyl ether–hexanes (2:1 and then 1:0) provided 10.4 g (94%) of ketone **42** as a white foam: $[\alpha]^{25}_D$ +18.3° (c 1.16, $CHCl_3$); R_f 0.68 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3075 (w), 3010 (m), 2970 (s), 2940 (s), 2910 (m), 2865 (m), 2830 (w), 1721 (s), 1461 (w), 1451 (w), 1423 (w), 1372 (w), 1359 (w), 1320 (w), 1269 (w), 1210 (w), 1151 (s), 1133 (s), 1109 (s), 1077 (s), 1041 (s), 1020 (s), 991 (w), 966 (w), 951 (w), 930 (w), 903 (m), 884 (w), 819 (w), 693 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.60 (m, 2H), 7.56–7.52 (m, 2H), 7.45–7.33 (m, 6H), 4.81 (d, 1H, J = 2.8 Hz), 4.54 and 4.52 (AB quartet, 2H, J = 6.4 Hz), 4.20 (br s, 1H), 3.68 (d, 1H, J = 3.2 Hz), 3.65 and 3.46 (AB quartet, 2H, J = 12.0 Hz), 3.64 (s, 1H), 3.47 (s, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.25 (s, 3H), 2.78 (dt, 1H, J = 10.8, 4.8 Hz), 2.44–2.30 (m, 2H), 2.15–2.05 (m, 1H), 1.96 (t, 1H, J = 13.6 Hz), 1.82–

1.74 (m, 2H), 1.65 (dq, 1H, J = 6.4, 3.0 Hz), 1.43 (dt, 1H, J = 12.0, 3.2 Hz), 1.15–0.85 (m, 1H), 1.08 (s, 9H), 1.01 (d, 3H, J = 7.2 Hz), 0.94 (s, 3H), 0.91 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.56, 207.49, 135.79, 135.54, 133.20, 133.13, 129.82, 127.76, 127.72, 98.15, 95.57, 95.47, 87.19, 64.39, 61.58, 58.65, 55.92, 54.20, 49.20, 48.10, 45.88, 44.83, 43.80, 35.88, 31.55, 31.20, 27.20, 27.09, 25.13, 19.65, 19.36, 14.30, 11.77; high-resolution MS (EI) calcd for $C_{40}H_{56}O_8Si$ (M) m/e 692.3746, found 692.3728.

(–)-(1β,12α)-20-(*tert*-Butyldiphenylsiloxy)-1-methoxy-12-(methoxymethoxy)picras-15-ene-2,11-dione (43). A solution of 230 mg (0.33 mmol) of **42** in 20 mL of tetrahydrofuran at 0 °C was treated dropwise with 16 mL of a 10% aqueous hydrochloric acid solution. After being warmed to room temperature and stirred for 24 h, the reaction mixture was cooled to 0 °C and neutralized by slow addition of solid sodium bicarbonate. The reaction mixture was diluted with water (1 × 20 mL), and the aqueous phase was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude residue on 60 g of flash silica gel, employing hexanes–ethyl acetate (3:1 and then 2:1) as eluent, provided 210 mg (91%) of a mixture of hemiacetals which were used directly in the next reaction. Approximately 20 mg (9%) of **42** was recovered.

To a solution of the above mixture of lactols in 20 mL of anhydrous pyridine at room temperature was added 60 μL (0.65 mmol) of freshly distilled phosphorus oxychloride in a dropwise fashion. The resulting solution was heated to 80 °C and stirred for 1 h. After being cooled to room temperature, the solution was filtered through 20 g of flash silica gel, eluting with hexanes–ethyl acetate (3:1), which provided 205 mg (96%) of **43**: R_f 0.67 (hexane–ethyl acetate, 1:1); IR ($CHCl_3$) 3080 (w), 2970 (s), 2935 (s), 2860 (m), 2830 (m), 1722 (s), 1664 (m), 1592 (w), 1465 (m), 1425 (m), 1392 (m), 1374 (m), 1364 (m), 1324 (w), 1271 (m), 1244 (m), 1215 (m), 1150 (s), 1110 (s), 1076 (s), 1024 (s), 981 (m), 955 (w), 934 (w), 906 (m), 874 (w), 818 (m), 694 (m), 649 (w), 607 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2H), 7.52–7.49 (m, 2H), 7.44–7.32 (m, 6H), 6.36 (dd, 1H, J = 6.2, 3.0 Hz), 4.93 (dd, 1H, J = 6.2, 1.8 Hz), 4.51 and 4.46 (AB quartet, 2H, J = 6.0 Hz), 4.28 (br d, 1H, J = 2.4 Hz), 3.80 and 3.46 (AB quartet, 2H, J = 11.6 Hz), 3.62 (d, 1H, J = 2.4 Hz), 3.52 (s, 1H), 3.39 (s, 1H), 3.36 (s, 3H), 3.22 (s, 3H), 2.94 (m, 1H), 2.34 (dd, 1H, J = 13.6, 4.6 Hz), 2.04–1.98 (m, 1H), 1.93 (dt, 1H, J = 13.6, 0.8 Hz), 1.82 (dt, 1H, J = 12.0, 3.0 Hz), 1.72–1.62 (m, 2H), 1.20–0.88 (m, 1H), 1.10 (d, 3H, J = 6.4 Hz), 1.03 (s, 9H), 0.94 (s, 3H), 0.89 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.96, 207.39, 139.66, 135.70, 135.49, 132.81, 132.75, 129.96, 127.84, 127.79, 100.10, 95.32, 86.35, 72.18, 61.31, 58.56, 55.80, 49.22, 45.95, 44.44, 43.65, 36.44, 33.87, 31.22, 27.00, 25.21, 19.58, 19.26, 14.51, 12.19. An analytical sample was prepared by recrystallization from hexanes: mp 106–108 °C; $[\alpha]^{25}_D$ –32.7° (c 1.00, $CHCl_3$). Anal. Calcd for $C_{39}H_{52}O_7Si$: C, 70.87; H, 7.93. Found: C, 70.93; H, 7.94.

(+)-(1β,12α,15β,16β)-20-(*tert*-Butyldiphenylsiloxy)-15,16-dihydroxy-1-methoxy-12-(methoxymethoxy)picrasane-2,11-dione (44) and (–)-(1β,12α,15β,16α)-20-(*tert*-Butyldiphenylsiloxy)-15,16-dihydroxy-1-methoxy-12-(methoxymethoxy)picrasane-2,11-dione (45). To a solution of 197 mg (0.298 mmol) of **43** dissolved in 10 mL of pyridine at 0 °C was added 90 mg (0.36 mmol) of osmium tetraoxide. After being stirred for 1 h, the dark black solution was treated with a 5% aqueous sodium bisulfite solution (1 × 15 mL) followed by addition of solid sodium bisulfite until the saturation point was reached. After being stirred for an additional 2 h, the solution was diluted with water and ethyl acetate and the aqueous layer was extracted with ethyl acetate (4 × 40 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product on 100 g of flash silica gel, eluting with hexanes–ethyl acetate–methanol (40:10:1), afforded 175 mg (85%) of **44** as a white foam: R_f 0.23 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3620 (w), 3590 (w), 3440 (w), 3010 (m), 2970 (s), 2945 (s), 2870 (m), 2840 (m), 1730 (s), 1598 (w), 1461 (m), 1426 (m), 1390 (m), 1378 (m), 1354 (m), 1324 (w), 1269 (m), 1153 (s), 1107 (s), 1085 (s), 1066 (s), 1027 (s), 990 (m), 967 (m), 915 (m), 907 (m), 859 (w), 819 (m), 697 (m), 638 (w), 607 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.60 (m, 2H), 7.56–7.52 (m, 2H), 7.45–7.34 (m, 6H), 5.23 (d, 1H, J = 4.0 Hz), 4.71 (dd, 1H, J = 11.2, 4.0 Hz), 4.60 and 4.58 (AB quartet, 2H, J = 6.8 Hz), 4.52 (br s, 1H), 3.80 (d, 1H, J = 1.6 Hz), 3.60 and 3.43 (AB quartet, 2H, J = 12.0 Hz), 3.58 (s, 1H), 3.45 (s, 1H), 3.42 (s, 3H), 3.25 (s, 3H), 2.61 (dd, 1H, J = 11.2, 4.8 Hz), 2.34 (dd, 1H, J = 13.6, 4.8 Hz), 2.22–2.14 (m, 1H), 1.95 (t, 1H, J = 13.6 Hz), 1.78 (dt, 1H, J = 13.3, 2.0 Hz), 1.68–1.58 (m, 1H), 1.47 (dt, 1H, J = 13.3, 2.8 Hz), 1.33 (d, 3H, J = 7.2 Hz), 1.08 (s, 9H), 0.99–0.85 (m, 1H), 0.92 (s, 3H), 0.88 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.19, 207.28, 135.76, 135.49, 132.94, 132.83, 129.92, 127.78, 95.43, 95.38, 92.40, 87.72, 68.11, 64.62, 61.60, 58.61, 56.01, 50.03, 49.06, 47.37, 44.99, 43.55, 38.56, 36.75, 31.43, 26.98, 24.98, 19.64, 19.33, 18.21, 11.80. An analytical sample was prepared by recrystallization from diethyl ether–hexanes: mp 180–182 °C; $[\alpha]^{25}_D$ +10.5° (c 1.11, $CHCl_3$). Anal. Calcd for $C_{39}H_{54}O_9Si$: C, 67.40; H, 7.84. Found: C, 67.11; H, 7.77.

Continued elution provided 26 mg (13%) of **45** as a white foam: R_f 0.15 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3595 (w), 2965 (m), 2935 (m), 2865 (m), 1723 (s), 1455 (w), 1425 (w), 1374 (w), 1303 (w), 1270 (w), 1242 (w), 1154 (m), 1108 (s), 1085 (s), 1067 (s), 1025 (s), 906 (s), 817 (w), 695 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.54–7.51 (m, 2H), 7.46–7.34 (m, 6H), 4.58 and 4.56 (AB quartet, 2H, J = 5.8 Hz), 4.53 (br d, 1H, J = 10.4 Hz), 4.45 (t, 1H, J = 10.4 Hz), 4.05 (dd, 1H, J = 2.8, 2.0 Hz), 3.78 (d, 1H, J = 2.4 Hz), 3.64 (s, 1H), 3.63 and 3.42 (AB quartet, 2H, J = 11.6 Hz), 3.46 (s, 1H), 3.41 (s, 3H), 3.40–3.38 (br s, 1H, OH), 3.24 (s, 3H), 2.43 (dd, 1H, J = 10.4, 4.8 Hz), 2.33 (dd, 1H, J = 13.6, 4.8 Hz), 2.22–2.10 (m, 2H), 1.94 (t, 1H, J = 13.6 Hz), 1.87 (dt, 1H, J = 11.2, 2.4 Hz), 1.65–1.56 (m, 2H), 1.32 (d, 3H, J = 6.4 Hz), 1.07 (s, 9H), 0.98–0.85 (m, 1H), 0.92 (s, 3H), 0.88 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.17, 207.22, 135.74, 135.49, 132.79, 132.60, 130.03, 127.91, 127.86, 99.61, 95.47, 95.25, 87.54, 72.83, 71.77, 61.48, 58.63, 55.99, 50.71, 49.01, 47.81, 44.96, 43.49, 42.59, 37.03, 31.40, 27.08, 25.17, 19.50, 19.31, 17.97, 11.90. An analytical sample was prepared by recrystallization from diethyl ether–hexanes: mp 203–205 °C; $[\alpha]^{25}_D$ –12.5° (c 1.00, $CHCl_3$). Anal. Calcd for $C_{39}H_{54}O_9Si$: C, 67.40; H, 7.84. Found: C, 67.46; H, 7.99.

Equilibration of 44. A solution of 100 mg (0.144 mmol) of **44** in 8.0 mL of tetrahydrofuran at 0 °C was treated with 4.0 mL of a 5% aqueous hydrochloric acid solution and stirred at room temperature for 24 h. After being cooled to 0 °C and neutralized slowly with solid sodium bicarbonate, the reaction mixture was diluted with water (1 × 5 mL) and the aqueous layer was extracted with ethyl acetate (4 × 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product on 30 g of flash silica gel eluting with hexanes–ethyl acetate–methanol (20:20:1) afforded 40 mg (40%) of recovered **44** and 60 mg (60%) of **45**.

(+)-(1β,12α,15β)-20-(*tert*-Butyldiphenylsiloxy)-15-hydroxy-1-methoxy-12-(methoxymethoxy)picrasane-2,11,16-trione (48). A solution of 21.6 mg (0.031 mmol) of **45** in 3.1 mL of dichloromethane at room temperature was treated with 24.2 mg (0.062 mmol) of 1-hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole 1-oxide (**47**) and stirred for 1 h. The reaction contents were filtered through a pad of flash silica gel, washing with diethyl ether, and the filtrate was concentrated *in vacuo*. The crude product was purified on 12 g of flash silica gel, eluting with hexanes–ethyl acetate (2:1), to give 18.8 mg (87%) of **48** as a white, amorphous solid: $[\alpha]^{25}_D$ +3.4° (c 0.97, $CHCl_3$); R_f 0.52 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3560 (w), 2960 (s), 2935 (s), 2860 (m), 1724 (s), 1460 (w), 1424 (w), 1374 (w), 1300–1185 (m, broad), 1156 (m), 1113 (s), 1174 (s), 1021 (s), 969 (w), 930 (w), 818 (m), 700 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.56 (m, 2H), 7.54–7.50 (m, 2H), 7.48–7.36 (m, 6H), 5.21 (d, 1H, J = 10.1 Hz), 4.78 (br s, 1H), 4.54 and 4.53 (AB quartet, 2H, J = 6.4 Hz), 3.80 (d, 1H, J = 2.4 Hz), 3.68 and 3.46 (AB quartet, 2H, J = 12.0 Hz), 3.40 (s, 3H), 3.36 (s, 1H), 3.32 (s, 1H), 3.24 (s, 3H), 2.70 (dd, 1H, J = 10.1, 4.8 Hz), 2.37 (dd, 1H, J = 13.6, 4.0 Hz), 2.19–2.09 (m, 1H), 1.95 (t, 1H, J = 13.6 Hz), 1.80–1.65 (m, 3H), 1.28 (d, 3H, J = 7.2 Hz), 1.10–0.85 (m, 1H), 1.07 (s, 9H), 0.95 (s, 3H), 0.91 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.91, 206.35, 174.64, 135.67, 135.49, 132.34, 132.11, 130.25, 128.05, 127.99, 95.42, 94.99, 86.79, 78.73, 67.33, 61.30, 58.67, 56.18, 48.84, 48.13, 47.30, 44.52, 43.22, 42.36, 35.96, 31.23, 27.02, 24.99, 19.46, 19.24, 16.31, 11.92; high-resolution MS (EI) calcd for $C_{39}H_{52}O_9Si$ (M) m/e 692.3380, found 692.3397.

(–)-(1β,12α,15β)-20-(*tert*-Butyldiphenylsiloxy)-1-methoxy-12-(methoxymethoxy)-15-(trimethylsiloxy)picrasane-2,11,16-trione. A solution of 44 mg (0.063 mmol) of **48**, 15 mg (0.12 mmol) of 4-(dimethylamino)-pyridine, 128 mg (1.27 mmol) of triethylamine, and 81 μL (0.63 mmol) of chlorotrimethylsilane in 4.5 mL of anhydrous dichloromethane was allowed to stir at ambient temperature. After 20 min, the solvent was removed *in vacuo* and the crude residue was purified on 12 g of flash silica gel, eluting with hexanes–ethyl acetate (3:1), giving rise to 39 mg (82%) of silyl ether: $[\alpha]^{25}_D$ –1.7° (c 1.00, $CHCl_3$); R_f 0.62 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3075 (w), 2970 (s), 2940 (m), 2865 (m), 2835 (w), 1727 (s), 1464 (m), 1425 (m), 1373 (m), 1355 (w), 1324 (w), 1306 (w), 1287 (m), 1250 (s), 1210 (m), 1157 (m), 1115 (s), 1078 (s), 1026 (s), 967 (w), 940 (w), 907 (w), 863 (m), 843 (s), 823 (m), 698 (m), 645 (w), 607 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.55–7.51 (m, 2H), 7.48–7.36 (m, 6H), 4.94 (d, 1H, J = 6.4 Hz), 4.91

(br d, 1H, J = 2.4 Hz), 4.53 and 4.49 (AB quartet, 2H, J = 6.2 Hz), 3.78 and 3.40 (AB quartet, 2H, J = 11.6 Hz), 3.73 (d, 1H, J = 2.0 Hz), 3.40 (s, 3H), 3.38 (s, 1H), 3.26 (s, 1H), 3.23 (s, 3H), 2.79 (t, 1H, J = 6.0 Hz), 2.34 (dd, 1H, J = 13.6, 4.6 Hz), 2.14–2.06 (m, 1H), 1.95 (t, 1H, J = 13.6 Hz), 1.86–1.58 (m, 3H), 1.16 (d, 3H, J = 7.2 Hz), 1.08 (s, 9H), 1.00–0.80 (m, 1H), 0.94 (s, 3H), 0.89 (d, 3H, J = 6.4 Hz), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.42, 206.75, 171.20, 135.69, 135.51, 132.56, 132.35, 130.15, 127.97, 127.92, 95.28, 95.07, 85.87, 76.87, 67.73, 61.05, 58.55, 56.19, 49.12, 49.03, 46.21, 44.95, 44.28, 43.21, 36.69, 31.06, 27.01, 24.75, 19.30, 19.27, 15.75, 12.44, 0.45; high-resolution MS (EI) calcd for $C_{42}H_{60}O_9Si_2$ (M) m/e 764.3777, found 764.3747.

(+)-(1β,12α,15β)-20-(*tert*-Butyldiphenylsiloxy)-1-methoxy-12-(methoxymethoxy)-15-(trimethylsiloxy)picras-3-ene-2,11,16-trione (49). A solution of 46 mg (0.06 mmol) of the above ketone ((–)-(1β,12α,15β)-20-(*tert*-butyldiphenylsiloxy)-1-methoxy-12-(methoxymethoxy)-15-(trimethylsiloxy)picrasane-2,11,16-trione) in 2.5 mL of anhydrous tetrahydrofuran cooled to –78 °C was treated with 0.40 mL (0.30 mmol) of a 0.75 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran in a dropwise fashion. After the solution was stirred for 45 min, 53 μL (0.42 mmol) of chlorotrimethylsilane was added and stirring was continued for an additional 15 min at –78 °C and for 5 min at 0 °C. The resulting silyl enol ether was treated with 60 mg (0.30 mmol) of *N*-bromosuccinimide, and the solution was stirred for 10 min. The reaction mixture was purified directly on 12 g of flash silica gel, eluting with hexanes–ethyl acetate (4:1), giving rise to 47 mg (92%) of an α-bromo ketone. Recrystallization from hexanes–ethyl acetate provided white needles: mp 169–171 °C; $[\alpha]^{25}_D$ +59.0° (c 1.00, $CHCl_3$); R_f 0.43 (hexanes–ethyl acetate, 3:1); IR ($CHCl_3$) 2960 (m), 2935 (m), 2900 (m), 2860 (m), 1728 (s), 1463 (m), 1427 (m), 1366 (m), 1287 (m), 1250 (s), 1210 (m), 1158 (s), 1103 (s), 1083 (s), 1026 (s), 918 (m), 908 (m), 869 (m), 844 (m), 700 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.54–7.50 (m, 2H), 7.48–7.36 (m, 6H), 4.96 (d, 1H, J = 6.0 Hz), 4.87 (br d, 1H, J = 2.4 Hz), 4.59 and 4.51 (AB quartet, 2H, J = 6.6 Hz), 4.19 (d, 1H, J = 4.4 Hz), 4.18 (s, 1H), 3.74 (d, 1H, J = 2.4 Hz), 3.73 and 3.40 (AB quartet, 2H, J = 12.4 Hz), 3.41 (s, 3H), 3.26 (s, 1H), 3.23 (s, 3H), 2.81 (t, 1H, J = 6.0 Hz), 2.28–2.04 (m, 2H), 1.80–1.66 (m, 1H), 1.58 (dt, 1H, J = 14.8, 3.6 Hz), 1.17 (d, 3H, J = 7.2 Hz), 1.08 (s, 9H), 0.96 (d, 3H, J = 6.4 Hz), 0.93 (s, 3H), 1.00–0.80 (m, 1H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.20, 200.79, 171.02, 135.74, 135.53, 132.57, 132.30, 130.19, 128.00, 127.97, 95.44, 90.15, 86.10, 76.55, 67.73, 61.00, 59.75, 58.17, 56.26, 49.08, 46.10, 44.86, 44.22, 37.29, 36.65, 33.18, 27.02, 24.25, 19.28, 17.02, 15.82, 12.28, 0.49; high-resolution MS (CI) calcd for $C_{38}H_{50}O_9Si_2Br$ (M – C_4H_9) m/e 785.2177, found 785.2199.

To a solution of 60 mg (0.08 mmol) of the above bromo ketone in 2.0 mL of *N*,*N*-dimethylformamide were added 60 mg (0.8 mmol) of lithium carbonate and 35 mg (0.40 mmol) of lithium bromide. The resulting suspension was heated at 120 °C for 45 min. Purification of the product directly on 12 g of flash silica gel, eluting with hexanes–ethyl acetate (4:1), afforded 57 mg (93%) of **49**: $[\alpha]^{25}_D$ +12.6° (c 1.00, $CHCl_3$); R_f 0.32 (hexanes–ethyl acetate, 2:1); IR ($CHCl_3$) 3000 (w), 2960 (m), 2935 (m), 2900 (m), 2860 (w), 2825 (w), 1726 (s), 1680 (s), 1623 (w), 1463 (w), 1437 (w), 1425 (m), 1376 (w), 1360 (w), 1340 (w), 1280 (m), 1243 (m), 1211 (m), 1154 (m), 1111 (s), 1081 (s), 1022 (s), 967 (w), 931 (w), 915 (w), 858 (m), 842 (s), 822 (m), 700 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.59 (m, 2H), 7.54–7.50 (m, 2H), 7.48–7.36 (m, 6H), 5.83 (br s, 1H), 5.03 (d, 1H, J = 6.3 Hz), 4.86 (br d, 1H, J = 2.0 Hz), 4.57 and 4.55 (AB quartet, 2H, J = 6.8 Hz), 3.79 (d, 1H, J = 2.4 Hz), 3.77 and 3.46 (AB quartet, 2H, J = 13.2 Hz), 3.43 (s, 3H), 3.41 (s, 3H), 3.38 (s, 1H), 3.29 (s, 1H), 2.92–2.82 (m, 1H), 2.85 (t, 1H, J = 6.3 Hz), 2.24–2.14 (m, 1H), 1.74 (br s, 3H), 1.70–1.80 (m, 1H), 1.21 (d, 3H, J = 6.4 Hz), 1.12–1.02 (m, 1H), 1.09 (s, 9H), 0.96 (s, 3H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.37, 197.57, 171.09, 159.56, 135.75, 135.50, 132.49, 132.23, 130.23, 128.02, 127.97, 127.08, 95.39, 94.16, 85.76, 76.81, 67.86, 61.19, 59.71, 56.23, 48.47, 46.55, 45.31, 44.60, 43.04, 36.19, 27.03, 24.09, 21.65, 19.28, 15.89, 11.85, 0.49; high-resolution MS (EI) calcd for $C_{38}H_{49}O_9Si_2$ (M – C_4H_9) m/e 705.2915, found 705.2945.

(+)-(1β,12α,15β)-20-(*tert*-Butyldiphenylsiloxy)-15-hydroxy-1-methoxy-12-(methoxymethoxy)picras-3-ene-2,11,16-trione (50). A solution of 25 mg (0.32 mmol) of **49** in 1.5 mL of tetrahydrofuran at 0 °C was treated with 700 μL of a 10% aqueous hydrochloric acid solution. After 30 min, the reaction mixture was neutralized with solid sodium bicarbonate and diluted with water (1 × 5 mL). The aqueous layer was extracted with ethyl acetate (4 × 5 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product on 12 g of flash silica gel, eluting with hexanes–ethyl acetate–methanol (25:10:1), gave 24 mg (100%) of crystalline **50**: R_f 0.32 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3560 (w), 3080 (w), 3005 (m), 2965 (s), 2934 (s), 2860 (m), 1726 (s), 1676 (s), 1626 (w), 1592 (w), 1462 (m), 1439 (m), 1426 (m), 1375 (m), 1340 (m), 1281 (m), 1240 (m), 1220 (m), 1157 (m), 1114 (s), 1091 (s), 1063 (m), 1023 (s), 965 (m), 934 (m), 915 (w), 862 (m), 844 (m), 822 (m), 699 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.58 (m, 2H), 7.53–7.50 (m, 2H), 7.49–7.37 (m, 6H), 5.85 (br s, 1H), 5.25 (d, 1H, J = 10.4 Hz), 4.74 (br s, 1H), 4.58 (s, 2H), 3.86 (d, 1H, J = 2.4 Hz), 3.69 and 3.52 (AB quartet, 2H, J = 11.6 Hz), 3.43 (s, 3H), 3.42 (s, 3H), 3.37 (s, 1H), 3.34 (s, 1H), 3.10–2.90 (br s, 1H, OH), 2.80–2.70 (m, 2H), 2.28–2.20 (m, 1H), 1.80 (dt, 1H, J = 14.7, 3.4 Hz), 1.76 (br s, 3H), 1.32 (d, 3H, J = 7.6 Hz), 1.08 (s, 9H), 1.10–1.00 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.05, 197.21, 174.41, 158.99, 135.75, 135.48, 132.31, 132.00, 130.31, 128.11, 128.04, 127.21, 95.51, 94.02, 86.49, 78.59, 67.40, 61.35, 59.83, 56.22, 47.65, 47.42, 45.27, 43.12, 42.18, 35.68, 27.04, 24.20, 21.72, 19.25, 16.35, 11.35. An analytical sample was prepared by recrystallization from hexanes–ethyl acetate providing white needles: mp 227–228.5 °C; $[\alpha]^{25}_D$ +21.5° (c 1.03, $CHCl_3$). Anal. Calcd for $C_{39}H_{50}O_9Si$: C, 67.79; H, 7.30. Found: C, 67.97; H, 7.53.

(+)-(1β,12α,15β)-20-(*tert*-Butyldiphenylsiloxy)-1,12,15-trihydroxypicras-3-ene-2,11,16-trione (51). A solution of 101 mg (0.146 mmol) of **50** in 3.0 mL of anhydrous dichloromethane cooled to –78 °C was treated dropwise with 1.17 mL (1.17 mmol) of a 1.0 M solution of boron tribromide. After being stirred for 20 min, the reaction mixture was treated dropwise with an additional 1.17 mL (1.17 mmol) of a 1.0 M solution of boron tribromide. After the solution was stirred for 40 min at –78 °C and for 30 min at –23 °C, the reaction was quenched by the addition of a cold (0 °C), saturated aqueous sodium bicarbonate solution and warmed to 0 °C. After being stirred for 5 min, the solution was diluted with ethyl acetate and the aqueous layer was extracted with ethyl acetate (4×). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product on 40 g of flash silica gel, eluting with hexanes–ethyl acetate (1:2), gave 77.4 mg (84%); of **51**: R_f 0.20 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3430 (m), 3080 (w), 3010 (w), 2970 (m), 2940 (m), 2910 (m), 2860 (m), 1724 (s), 1677 (s), 1621 (w), 1590 (w), 1460 (m), 1423 (m), 1391 (m), 1373 (m), 1341 (m), 1330 (m), 1273 (m), 1225 (m), 1024 (m), 1012 (m), 983 (m), 954 (w), 934 (w), 891 (w), 858 (w), 839 (w), 819 (m), 802 (m), 696 (m), 608 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.54–7.50 (m, 2H), 7.49–7.38 (m, 6H), 5.97 (br s, 1H), 5.37 (dd, 1H, J = 10.2, 1.6 Hz), 4.73 (br s, 1H), 4.19 (br d, 1H, OH, J = 2.8 Hz), 4.01 (br s, 1H, OH), 3.86 (br d, 1H, J = 3.2 Hz), 3.86 and 3.50 (AB quartet, 2H, J = 12.4 Hz), 3.85 (br s, 1H), 3.66 (s, 1H), 3.15 (d, 1H, OH, J = 1.6 Hz), 2.79–2.72 (m, 2H), 2.22–2.13 (m, 1H), 1.84–1.78 (m, 1H), 1.79 (br s, 3H), 1.32 (d, 3H, J = 7.6 Hz), 1.15–1.01 (m, 1H), 1.08 (s, 9H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.15, 196.93, 174.28, 162.74, 135.66, 135.48, 132.38, 132.09, 130.26, 128.09, 128.02, 124.88, 84.70, 82.36, 78.29, 67.43, 61.36, 47.77, 47.21, 45.53, 42.18, 41.86, 35.73, 27.03, 24.28, 22.19, 19.26, 16.01, 10.50. An analytical sample was prepared by recrystallization from hexanes–ethyl acetate providing a white solid: mp 208–209 °C; $[\alpha]^{25}_D$ +22.5° (c 1.05, $CHCl_3$). Anal. Calcd for $C_{36}H_{44}O_8Si$: C, 68.33; H, 7.01. Found: C, 68.07; H, 7.01.

(–)-Glaucarubolone (4). To a solution of 37 mg (0.059 mmol) of **51** in 2.0 mL of tetrahydrofuran was added 0.35 mL (0.35 mmol) of a 1.0 M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran. After 10 min, the reaction mixture was diluted with water. The aqueous layer was saturated with sodium chloride, and the product was extracted exhaustively with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude residue on 1 g of flash silica gel, eluting with hexanes–ethyl acetate–methanol (10:20:1), provided 21.5 mg (92%) of **4** as a white solid. Recrystallization from acetone–methanol provided white needles: mp 263–265 °C (lit.[5] mp 255–258 °C); $[\alpha]^{25}_D$ –33.6° (c 1.06, pyridine) (lit.[5] $[\alpha]_D$ –34° (c 1.45, pyridine)); R_f 0.26 (ethyl acetate–methanol, 10:1); IR (KBr) 3518 (s), 2945 (m), 2895 (m), 1728 (s), 1678 (s), 1632 (w), 1499 (w), 1439 (m), 1485 (m), 1334 (w), 1317 (w), 1236 (s), 1196 (s), 1117 (s), 1057 (s), 1018 (s), 992 (m), 960 (m), 916 (m), 810 (w), 698 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (br s, 1H), 4.67 (d, 1H, J = 11.4 Hz), 4.56 (t, 1H, J = 2.8 Hz), 4.03 (s, 1H), 3.92 (d, 1H, J = 8.7 Hz), 3.71 (d, 1H, J = 8.7 Hz), 3.60 (br d, 1H, J = 3.9 Hz), 2.88 (br d, 1H, J = 12.6 Hz), 2.70 (s, 1H), 2.46–2.38 (m, 1H), 2.31 (dt, 1H, J = 14.6, 2.8 Hz), 2.07–1.97 (m, 1H), 2.02 (br s, 3H), 1.98 (dd, 1H, J = 11.4, 6.4 Hz), 1.28 (d, 3H, J = 6.9 Hz), 1.20 (s, 3H); ^{1}H NMR (500 MHz, C_5D_5N) δ 6.07 (br s, 1H), 5.47 (d, 1H, J = 11.4 Hz), 4.67 (br s, 1H), 4.31 (s, 1H), 4.12 and 3.85 (AB quartet, 2H, J = 8.7 Hz), 4.11 (br s, 1H), 3.32 (s, 1H), 3.12 (br d, 1H, J = 12.6 Hz), 2.76–2.65

(m, 1H), 2.34 (dd, 1H, J = 11.4, 6.4 Hz), 2.15 (dt, 1H, J = 14.6, 2.8 Hz), 2.00 (dt, 1H, J = 14.6, 2.4 Hz), 1.73 (d, 3H, J = 6.9 Hz), 1.71 (br s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, C_5D_5N) δ 197.45, 174.16, 162.48, 126.09, 110.85, 84.49, 80.44, 78.19, 71.50, 68.57, 49.62, 47.45, 45.79, 45.55, 42.32, 32.98, 26.21, 22.32, 16.33, 10.64; high-resolution MS (EI) calcd for $C_{20}H_{26}O_8$ (M) m/e 394.1628, found 394.1610.

(+)-[1β,12α,15β(S)]-20-(*tert*-Butyldiphenylsiloxy)-15-(2-hydroxy-2-methyl-1-oxobutoxy)-1-methoxy-12-(methoxymethoxy)picras-3-ene-2,11,16-trione (52). A solution of 83 mg (0.120 mmol) of alcohol **50** in 2.0 mL of methylene chloride containing 16.1 mg (0.132 mmol) of 4-(dimethylamino)pyridine at room temperature was treated with 39.2 μL (0.300 mmol) of **54**. After being stirred at room temperature for 8 h, the reaction mixture was diluted with 5 mL of water and washed with methylene chloride (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resultant yellow oil was chromatographed on 20 g of flash silica gel. Elution with hexanes–ethyl acetate (1:1) provided 87 mg (92%) of **52** as a white foam: R_f 0.51 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3560 (w), 2970 (m), 2870 (w), 1731 (s), 1685 (s), 1630 (w), 1450 (w), 1375 (w), 1344 (w), 1290 (m), 1146 (m), 1114 (s), 1084 (m), 1016 (m), 934 (w), 907 (w), 847 (w), 700 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.52–7.36 (m, 8H), 5.85–5.81 (m, 2H), 5.08 (d, 1H, J = 2.0 Hz), 4.58 and 4.56 (AB quartet, 2H, J = 6.6 Hz), 3.86 (d, 1H, J = 2.8 Hz), 3.79 and 3.47 (AB quartet, 2H, J = 11.8 Hz), 3.43 (s, 3H), 3.42 (s, 3H), 3.38 (s, 1H), 3.35 (s, 1H), 3.02–2.96 (m, 2H), 2.90 (br d, 1H, J = 12.8 Hz), 2.18–2.09 (m, 1H), 1.96–1.70 (m, 3H), 1.75 (s, 3H), 1.45 (s, 3H), 1.18 (d, 3H, J = 7.2 Hz), 1.12–1.03 (m, 1H), 1.06 (s, 9H), 1.02–0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.17, 197.3, 176.61, 167.48, 159.38, 135.78, 135.44, 132.16, 131.97, 130.36, 130.30, 128.10, 128.03, 127.09, 95.42, 93.98, 85.94, 77.35, 74.69, 70.89, 61.21, 59.76, 56.31, 48.32, 46.47, 45.33, 43.07, 40.43, 35.28, 33.19, 26.92, 25.20, 23.93, 21.66, 19.21, 15.97, 11.69, 7.52. An analytical sample was prepared by recrystallization from diethyl ether–hexanes: mp 172–173 °C; $[\alpha]^{25}_D$ +30.8° (c 1.00, $CHCl_3$); high-resolution MS (EI) calcd for $C_{44}H_{58}O_{11}Si$ (M) m/e 790.3749, found 790.3714. Anal. Calcd for $C_{44}H_{58}O_{11}Si$: C, 66.81; H, 7.39. Found: C, 67.13; H, 7.55.

(+)-[1β,12α,15β(S)]-20-(*tert*-Butyldiphenylsiloxy)-1,12-dihydroxy-15-(2-hydroxy-2-methyl-1-oxobutoxy)picras-3-ene-2,11,16-trione (55). A solution of 20.3 mg (0.0257 mmol) of **52** in 529 μL of methylene chloride at –78 °C was treated dropwise, over 3 min, with 205 μL (0.205 mmol) of a 1.0 M boron tribromide solution in methylene chloride. After the solution was stirred at –78 °C for 20 min, another 205 μL (0.205 mmol) of boron tribromide solution was added. The reaction was allowed to stir at –78 °C for an additional 45 min and warmed to –23 °C. After 40 min, it was poured into 2 mL of an aqueous saturated sodium bicarbonate solution cooled to 0 °C. The mixture was diluted with 2 mL of water and washed with methylene chloride (3 × 3 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to a brown oil that was purified by preparative TLC (0.5 mm). Elution with hexanes–ethyl acetate (1:1) afforded 11.4 mg (61%) of **55** as a white, crystalline solid: mp 210–212 °C; $[\alpha]^{25}_D$ +29.0° (c 0.50, $CHCl_3$); R_f 0.23 (hexanes–ethyl acetate, 1:1); IR ($CHCl_3$) 3400 (w), 2955 (m), 1727 (s), 1684 (m), 1390 (m), 1117 (s), 1030 (m), 910 (w), 700 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.58 (m, 2H), 7.51–7.35 (m, 8H), 6.21 (d, 1H, J = 9.6 Hz), 5.94 (br d, 1H, J = 1.2 Hz), 5.02–4.87 (m, 2H), 4.42 (br s, 1H), 4.23 (m, 2H), 4.02 (s, 1H), 3.92 (s, 1H), 3.73 and 3.50 (AB quartet, 2H, J = 11.8 Hz), 3.10 (br d, 1H, J = 12 Hz), 3.01 (dd, 1H, J = 9.6, 4.8 Hz), 2.20–2.10 (m, 1H), 1.82–1.71 (m, 3H), 1.77 (s, 3H), 1.36 (s, 3H), 1.28 (d, 3H, J = 7.2 Hz), 1.09–1.01 (m, 1H), 1.04 (s, 9H), 0.90 (t, 3H, J = 7.6 Hz), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.26, 197.30, 175.41, 167.97, 164.12, 135.91, 135.46, 132.35, 132.21, 130.26, 130.18, 128.07, 127.98, 124.44, 83.57, 82.01, 77.25, 75.35, 71.15, 61.30, 48.34, 45.97, 45.56, 41.42, 40.17, 35.38, 32.54, 26.90, 24.01, 23.42, 22.33, 19.19, 15.74, 10.85, 7.90; high-resolution MS (CI) calcd for $C_{37}H_{43}O_{10}Si$ (M – C_4H_9) m/e 675.2626, found 675.2633.

(+)-Glaucarubinone (5). A solution of 24.7 mg (0.0337 mmol) of silyl ether **55** in 1.2 mL of tetrahydrofuran cooled to 0 °C was treated dropwise with 202 μL (0.202 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran. Upon being warmed to room temperature, the reaction mixture was stirred for 30 min, after which time it was filtered through a pad of flash silica gel, washing with 95:5 ethyl acetate–methanol. The combined filtrate and washings were concentrated *in vacuo* to a yellow oil that was purified by preparative TLC (2 plates, 0.5 mm). Elution with ethyl acetate–hexanes (4:1) containing 1% methanol provided 9.4 mg (56%) of (+)-glaucarubinone as a white, crystalline solid: mp 222–224 °C (lit.[6] mp 228–230 °C); $[\alpha]^{25}_D$ +49.0° (c 0.10, MeOH) (lit.[6] $[\alpha]^{20}_D$ +50° (c 0.27, MeOH)); R_f 0.15 (ethyl acetate–hexanes, 4:1); FTIR (KBr) 3443 (br, s), 2973 (m), 2944 (m), 2888 (m), 1738 (s), 1674 (s), 1628 (w), 1458 (m), 1385 (m), 1229 (s), 1184 (s), 1138 (s), 1117 (s), 1082 (s), 1047 (s), 961 (w), 916 (w), 808 (w), 733 (w), 698 (w) cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6 with 1 drop of D_2O) δ 6.03–6.08 (m, 1H), 5.71 (d, 1H, J = 11.9 Hz), 4.73 (t, 1H, J = 2.6 Hz), 4.40 (s, 1H), 3.99 and 3.70 (AB quartet, 2H, J = 9.2 Hz), 3.39 (br d, 1H, J = 3.2 Hz), 3.16–3.10 (m, 1H), 2.90 (s, 1H), 2.42 (br dd, 1H, J = 11.9, 6.2 Hz), 2.36–2.27 (m, 1H), 2.23–2.17 (m, 2H), 2.02 (br s, 3H), 1.83–1.73 (m, 1H), 1.72–1.61 (m, 1H), 1.34 (s, 3H), 1.19 (s, 3H), 1.06 (d, 3H, J = 7.2 Hz), 0.92 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 197.55, 175.81, 167.68, 165.03, 125.14, 109.98, 83.64, 79.92, 78.54, 75.21, 71.37, 48.18, 46.11, 45.90, 45.09, 42.18, 33.64, 32.55, 26.06, 25.22, 22.79, 15.42, 10.28, 7.96; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.02, 166.80, 164.54, 124.29, 108.86, 82.90, 79.08, 77.49, 74.97, 71.09, 70.91, 47.41, 45.46, 45.19, 44.38, 41.59, 32.87, 31.31, 25.42, 24.79, 22.99, 14.67, 10.03, 7.47; high-resolution MS (CI) calcd for $C_{25}H_{35}O_{10}$ (M + 1) m/e 495.2231, found 495.2252.

(S)-(–)-5-Ethyl-5-methyl-1,3-dioxolane-2,4-dione (54). A solution of 1.06 g (8.97 mmol) of (*S*)-(+)-2-hydroxy-2-methylbutyric acid (**53**) in 20.5 mL of tetrahydrofuran containing 1.25 mL (8.97 mmol) of triethylamine at room temperature was treated dropwise *via* cannula over a 10-min period with a solution of triphosgene (1.78 g, 5.98 mmol) in 4.5 mL of tetrahydrofuran. The resulting heterogeneous reaction mixture was allowed to reflux for 5 h and concentrated *in vacuo*, providing a residue that was triturated with diethyl ether and filtered through a plug of glass wool. The combined filtrate and washings were concentrated *in vacuo* to a yellow oil that was distilled under reduced pressure affording 872 mg (69%) of **54** as a colorless liquid: bp 60–62 °C (1 mmHg); $[\alpha]^{25}_D$ –26.6° (c 2.38, $CHCl_3$); IR ($CHCl_3$) 3015 (w), 2990 (m), 2950 (w), 2895 (w), 1900 (s), 1880 (s), 1810 (s), 1450 (m), 1380 (m), 1273 (s), 1220 (m), 1150 (s), 1035 (m), 981 (s), 905 (m), 850 (m), 640 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (dq, 2H, J = 7.4, 3.4 Hz), 1.68 (s, 3H), 1.03 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.89, 147.77, 88.04, 30.31, 21.98, 7.32; high-resolution MS (CI) calcd for $C_6H_9O_4$ (M + 1) m/e 145.0501, found 145.0505.

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