Studies Relating to the Structure of Bruceoside C: Total Synthesis of the Alleged Aglycon of Bruceoside C

James M. VanderRoest and Paul A. Grieco*

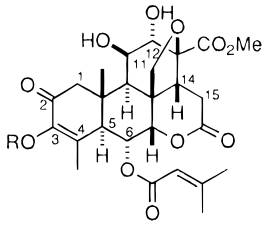
Ernest E. Campaigne and Marvin Carmack Laboratory of Organic Chemistry, Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received March 18, 1996[⊗]

The structures assigned to bruceoside C (**1**) and the derived aglycon (**2**) have been shown to be incorrect. The structural misassignments were made clear by an unambiguous total synthesis of racemic **2** whose structure rests on spectral data and a single-crystal X-ray analysis of intermediate **22**.

Introduction

The most fertile source of quassinoid glycosides has been *Brucea javanica*.[1] In 1992, Okano and co-workers reported the isolation from the fruit of *B. javanica* of a novel quassinoid glycoside, bruceoside C (**1**).[2] The structure proposed for bruceoside C (**1**) and the derived aglycon (**2**) is based exclusively on spectroscopic studies. Careful analysis of the published ^{1}H NMR data for both

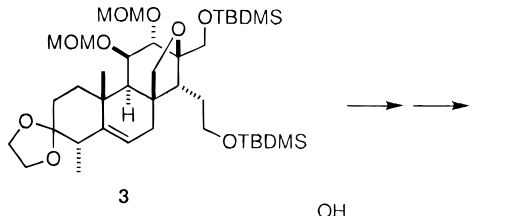


1 R = β-glu
2 R = H

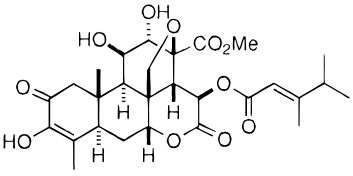
1 and **2** raises questions about the proposed structures. Of particular concern is the multiplicity of the signal for the C(6) hydrogen, which typically appears as a doublet of doublets with coupling constants of approximately 12 Hz and 2 Hz.[3] We were surprised to find upon examination of the ^{1}H NMR data for both **1** and **2** that the C(6) hydrogen has been attributed to a broad singlet at δ 5.18 and δ 5.26, respectively. Furthermore, no signal for the C(5) hydrogen is reported in either ^{1}H NMR spectrum. The inexplicable absence of a signal for the C(5) hydrogen in both **1** and **2** is curious in view of the diagnostic importance of this signal, which generally appears as a broad doublet with a coupling constant of approximately 11−12 Hz.[3] The C(14) and C(15) hydrogen signals which are reported as multiplets in the ^{1}H NMR spectrum of bruceoside C are also inconsistent with the anticipated and previously observed patterns.[3] The C(14) and C(15) hydrogens were not assigned in the ^{1}H NMR spectrum of the aglycon **2**. In order to clarify the issues raised above which raise serious doubt about the proposed structure of bruceoside C (**1**) and the derived aglycon **2**, we undertook an unambiguous total synthesis of racemic **2**.

Results and Discussion

The starting point for our synthetic endeavor was tetracyclic compound **3**, which served as an intermediate in our previously reported total synthesis of bruceantin (**4**).[4] Compound **3** is an attractive starting material for a synthesis of aglycon **2**, since **3** possesses a fully functionalized ring C including an intact epoxy methano bridge. Furthermore, during the course of our synthetic studies toward the total synthesis of bruceantin we had



3



4

converted **3** into tetracyclic olefin **5** with the hope of generating the δ-lactone of bruceantin *via* an iodolactonization−deiodination sequence.[5] Despite our inability to transform **5** into bruceantin, tetracyclic olefin **5** seemed to be a logical starting point for a synthesis of aglycon **2**. It was anticipated, based on our experience with bruceantin, that the methyl group at C(10) and the methylene group attached at C(8) would direct osmylation of the $\Delta^{6,7}$ olefin from the bottom face of the molecule and lead

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) Lee, K.-H.; Imakura, Y.; Huang, H.-C. *J. Chem. Soc., Chem. Commun.* **1977**, 69. Lee, K.-H.; Imakura, Y.; Sumida, Y.; Wu, R. Y.; Hall, I. H.; Huang, H.-C. *J. Org. Chem.* **1979**, *44*, 2180. Sakaki, T.; Yoshimura, S.; Ishibashi, M.; Tsuyuki, T.; Takahashi, T.; Honda, T.; Nakanishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 4702. Yoshimura, S.; Sakaki, T.; Ishibashi, M.; Tsuyuki, T.; Takahashi, T.; Honda, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2673. Sakaki, T.; Yoshimura, S.; Ishibashi, M.; Tsuyuki, T.; Takahashi, T.; Honda, T.; Nakanishi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2680. Sakaki, T.; Yoshimura, S.; Tsuyuki, T.; Takahashi, T.; Honda, T.; Nakanishi, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3541. Sakaki, T.; Yoshimura, S.; Tsuyuki, T.; Takahashi, T.; Honda, T.; Nakanishi, T. *Tetrahedron Lett.* **1986**, *27*, 593. Yoshimura, S.; Ogawa, K.; Tsuyuki, T.; Takahashi, T.; Honda, T. *Chem. Pharm. Bull.* **1988**, *36*, 841.

(2) Fukamiya, N.; Okano, M.; Miyamoto, M.; Tagahara, K.; Lee, K.-H. *J. Nat. Prod.* **1992**, *55*, 468.

(3) Polonsky, J. *Fortschr. Naturst.* **1973**, *30*, 101. Yoshimura, S.; Sakaki, T.; Ishibashi, M.; Tsuyuki, T.; Takahashi, T.; Honda, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2573. Wani, M. C.; Taylor, H. T.; Thompson, J. B.; Wall, M. W. *Lloydia* **1978**, *40*, 578.

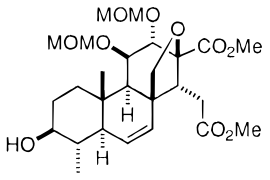
(4) VanderRoest, J. M.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 5841.

(5) Unpublished results of J. M. VanderRoest, Indiana University.

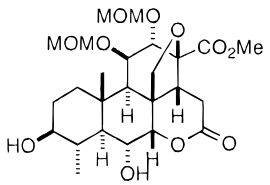
(6) Freeman, D.; Acher, A.; Mazur, Y. *Tetrahedron Lett.* **1975**, 261. Also see, Grieco, P. A.; Inanaga, J.; Sham, H. L.; Sasaki, S.; Kim, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1044. Barton, D. H. R.; Hesse, R. H.; Pecht, M. M.; Rizzardo, E. *J. Am. Chem. Soc.* **1973**, *95*, 2748.

S0022-3263(96)00520-8 CCC: $12.00

directly upon workup to pentacyclic lactone **6**. Selective oxidation at C(3) followed by (a) acylation of the C(6)



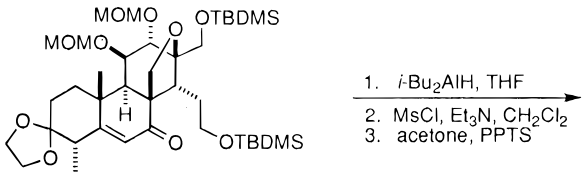
5



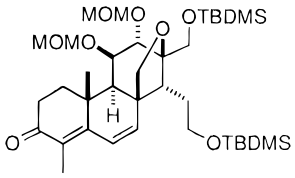
6

hydroxyl, (b) installation of the ring A diosphenol moiety, and (c) cleavage of all protecting groups, would give rise to aglycon **2**.

Transformation of 3 into Tetracyclic Olefin 5. During the course of our synthetic studies on bruceantin it was observed that allylic oxidation (Collins reagent) of olefin **3** gave rise to substantial amounts (ca. 49%) of dienone **8** along with the anticipated enone **7** (39%). Furthermore, enone **7** could be readily transformed in

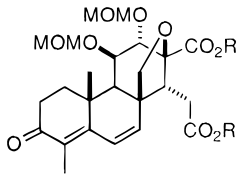


7

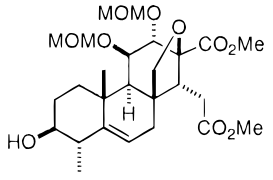


8

ca. 70% overall yield into dienone **8** *via* a three-step sequence: (1) diisobutylaluminum hydride reduction, (2) mesylation of the resultant alcohol, and (3) *trans*-ketalization employing acetone. Prior to submitting **8** to 1,4-reduction, the silyl ethers in **8** were cleaved and the resulting hydroxyl groups were oxidized with 8 M Jones reagent to diacid **9** (R = H). Regioselective 1,4-reduction of **9** using a modification of the Mazur protocol (dissolving metal reduction in the presence of ammonium chloride) provided (90%) after esterification with ethereal diazomethane intermediate **5**, possessing an isolated $\Delta^{6,7}$



9



10

olefin, and the undesired olefin **10** in a ratio of 1.6:1 as an unseparable mixture. This separation problem was readily overcome. Brief exposure of the mixture of **5** and **10** to Jones reagent gave rise to a readily separable mixture of **11** and **12** in isolated yields of 47% and 30%, respectively. Reduction of **11** with sodium borohydride at low temperature regenerated **5** in 86% yield. Not unexpectedly, standard dissolving metal reduction of dienone **9** in the absence of ammonium chloride provided enone **12** exclusively after esterification with diazomethane.

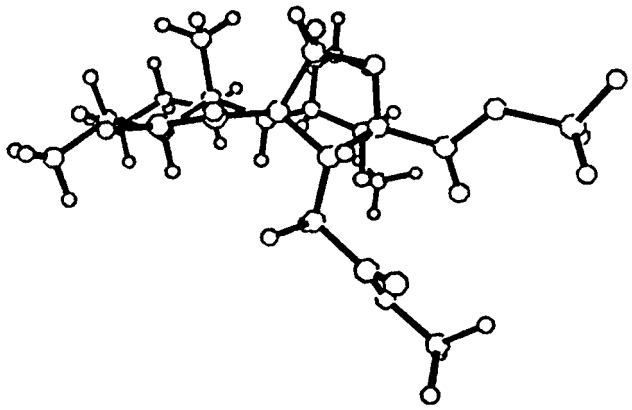
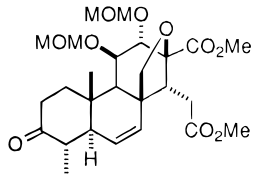
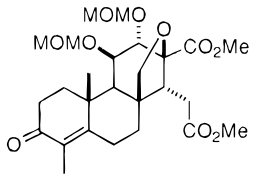


Figure 1. Low energy conformer of **5**.

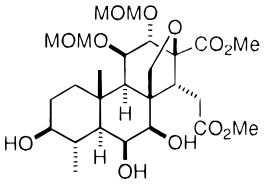


11



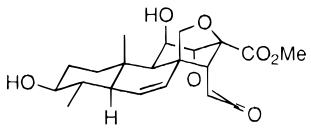
12

Establishment of the C(6), C(7) Vicinal Diol Unit. It was anticipated that glycol formation employing osmium tetraoxide would occur from the bottom face of **5** due to the C(8) methylene unit and the C(10) methyl group, thus leading directly to lactone **6**. Contrary to



13

expectations, only β-diol **13**, mp 184−185 °C, was obtained upon osmylation. Examination of models and the MM2-minimized structure of **5** reveal that the observed facial selectivity can be attributed to the C(14) appendage (Figure 1).[7] Formation of a lactone between the C(12) hydroxyl and the carboxyl group would effectively prevent the offending appendage from hindering approach of the reagent. Toward this end, the C(11), C(12) methoxymethyl esters were cleaved employing Fujita's conditions[8] and the resulting triol upon exposure to *p*-toluenesulfonic acid in benzene gave rise (97%) to crystalline lactone **14**, mp 183−185 °C. Osmylation of



14

14 provided **15** and **16** in a ratio of 3.8:1. Separation of

(7) Calculations were carried out on a Silicon Graphics workstation using the MMX version of Allinger's MM2 program (Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127). Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. *Advances in Molecular Modelling*; JAI Press: New York, 1990; pp 65−92.

(8) Node, M.; Ohta, K.; Kajimoto, T.; Nishide, K.; Fujita, E.; Fuji, K. *Chem. Pharm. Bull.* **1983**, *31*, 4178.

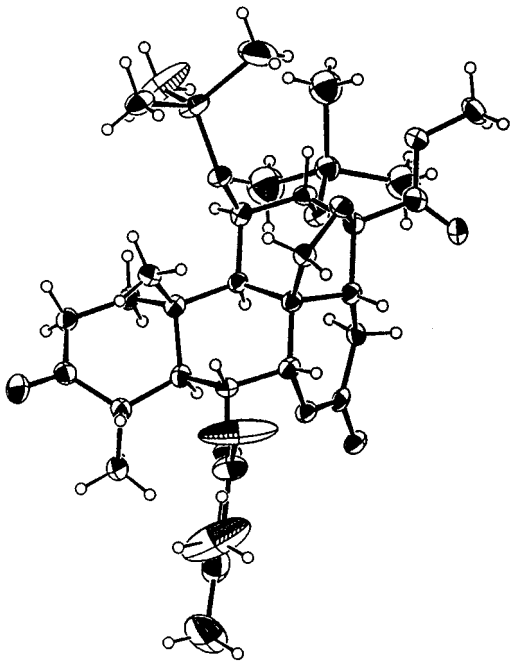
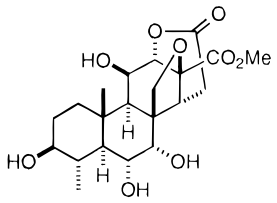
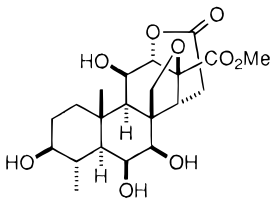


Figure 2. An ORTEP view of **22**.

the highly polar tetraols **15** and **16** proved to be exceedingly difficult. Treatment of **15** and **16** with *p*-toluene-

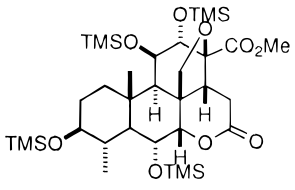


15

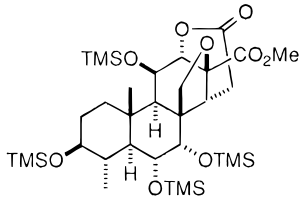


16

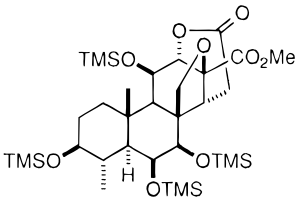
sulfonic acid in methanol in order to transform the C(12) lactone into the C(7) lactone gave rise to three tetrahydroxy lactones which could not be separated by chromatography. Fortunately, persilylation (trimethylsilyl trifluoromethanesulfonate) of this mixture of tetraols led after separation and characterization to desired pentacyclic lactone **17** (28%), unequilibrated lactone **18** (31%), and undesired lactone **19** (18%). The ca. 1:1 thermodynamic mixture of lactones **17** and **18** was unfortunate



17



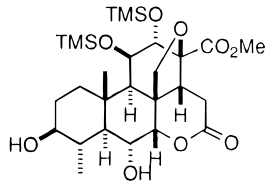
18



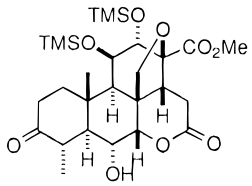
19

but not unanticipated, since MM2 calculations indicate that the C(7) lactone is favored by only 0.7 kcal.[7] Resubmitting either **17** or **18** to the equilibrating conditions regenerates the thermodynamic mixture. By recycling the C(12) lactone **18** *via* the equilibration/persilylation sequence, a 45% yield of pentacyclic lactone **17** was realized.

Completion of the synthesis of **2** necessitated (1) incorporation of the senecioyl side chain, (2) elaboration of the ring A diosphenol unit, and (3) removal of all remaining protecting groups. Toward this end, the less hindered equatorial silyl ethers at C(3) and C(6) were selectively hydrolyzed upon exposure to pyridinium *p*-toluenesulfonate[9] in aqueous tetrahydrofuran giving rise to crystalline diol **20**, mp 251.5−253.0 °C. Regioselective oxidation (Swern)[10] at C(3) proceeded in 75% yield (92%

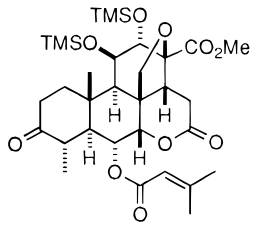


20

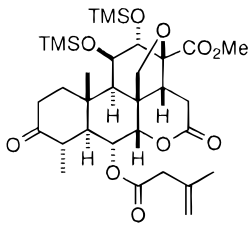


21

based on recovered starting diol) affording ketone **21**, mp 247−249 °C. Acylation of **21** with senecioic acid *via* the agency of dicyclohexylcarbodiimide provided a 65% yield of **22**, mp 207.0−208.5 °C, along with 20% of **23**, mp 212−214 °C, which is presumably derived from a ketene intermediate. In support of this premise, when **22** was



22



23

resubmitted to the reaction conditions (DCC, DMAP, THF) no detectable isomerization of the ester side chain was observed. At this juncture, with all the required carbon atoms and all ten stereocenters in place, the structure of **22** was unambiguously established by single-crystal X-ray analysis (Figure 2).[11]

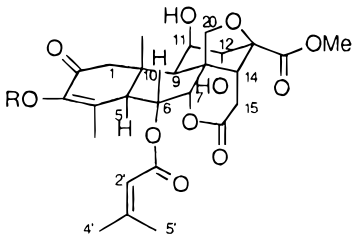
Elaboration of the ring A diosphenol unit was realized using the methodology developed in conjunction with our total synthesis of bruceantin.[4] In straightforward fashion, the thermodynamic $\Delta^{2,3}$ silyl enol ether, generated upon treatment of ketone **22** with trimethylsilyl trifluoromethanesulfonate in the presence of triethylamine, was

(9) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(10) Swern, D.; Mancuso, A. J.; Huang, S.-L. *J. Org. Chem.* **1978**, *43*, 2480.

(11) Ketone **22** crystallized in a triclinic space group *P*1 with cell dimensions (at −171 °C) of a = 14.118 (6) Å, b = 15.198 (7) Å, c = 9.493 (4) Å, α = 104.00 (2) Å, β 91.12 (2) Å, γ = 65.91 (1) Å. Calculated density ρ = 1.203 g/cm^{-3} (for Z = 2). Data were collected using a standard moving crystal, moving detector technique with fixed background counts at each extreme of the scan. Data were corrected for Lorentz and polarization terms and equivalent data averaged. The structure was solved by direct methods (MULTAN78) and Fourier techniques. For more information contact Dr. John C. Huffman, Indiana University Department of Chemistry, Molecular Structure Center, Bloomington, IN, 47405, Report Number 94033. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

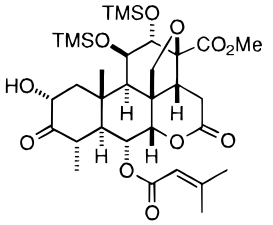
Table 1. Comparison of ^{1}H NMR (CD_3COCD_3) Spectral Data of the Alleged Bruceoside C (1) and Its Aglycon (2) with Synthetic 2



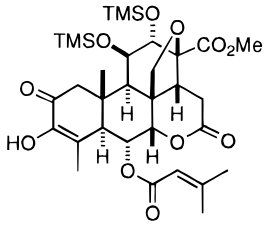
	bruceoside C	aglycon **2** (R = H)	synthetic **2** (R = H)
$C_{1\alpha}$	3.35 (d, J = 16 Hz)	3.39 (d, J = 16 Hz)	3.35 (d, J = 16.7 Hz)
$C_{1\beta}$	2.56 (d, J = 16 Hz)	2.53 (d, J = 16 Hz)	2.75 (d, J = 16.6 Hz)
C_5	*a*	*a*	3.71 (br d, J = 11.9 Hz)
C_6	5.18 (br s)	5.26 (br s)	5.62 (dd, J = 11.9, 2.6 Hz)
C_7	4.98 (br s)	5.10 (br s)	5.22 (d, J = 2.5 Hz)
C_9	3.02 (br s)	3.10 (br s)	2.59 (d, J = 4.4 Hz)
C_{11}	4.92 (br s)	4.88 (br d, J = 5.0 Hz)	4.75 (t, J = 4.4 Hz)
C_{12}	*a*	*a*	*b*
C_{14}	2.50 (m)	*a*	3.28 (dd, J = 13.0, 5.2 Hz)
$C_{15\alpha}$	2.18 (m)	*a*	4.29 (dd, J = 18.8, 13.6 Hz)
$C_{15\beta}$	2.49 (m)	*a*	3.39 (dd, J = 19.1, 6.2 Hz)
$C_{20\alpha}$	3.86 (d, J = 7.5 Hz)	*a*	5.15 (d, J = 7.4 Hz)
$C_{20\beta}$	5.10 (d, J = 7.5 Hz)	*a*	3.93 (d, J = 7.5 Hz)
C_4 methyl	2.52 (s)	2.35 (s)	2.29 (s)
C_{10} methyl	1.80 (s)	1.86 (s)	1.85 (s)
C_{13} CO_2Me	3.65 (s)	3.67 (s)	3.68 (s)
$C_{2'}$	5.68 (s)	5.73 (br s)	5.91 (br s)
$C_{4'}$	2.12 (s)	2.11 (s)	2.25 (s)
$C_{5'}$	1.59 (s)	1.60 (s)	1.72 (s)

[a] Not reported. [b] Obscured by signal due to H_2O.

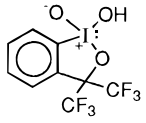
treated sequentially with *m*-chloroperbenzoic acid and tetra-*n*-butylammonium fluoride[12] giving rise to a 50% overall yield of α-hydroxy ketone **24**, mp 212−214 °C, as a single stereoisomer. Oxidation of **24** with bis(trifluoromethyl) iodinane oxide **26** (2.0 equiv)[13,14] provided a



24



25



26

70% yield of diosphenol **25**, 208.5−210.0 °C. Desilylation with hydrofluoric acid in acetonitrile afforded aglycon **2**, mp 293−296 °C, of the alleged bruceoside C in 50% yield. Comparison of the ^{1}H NMR spectrum of synthetically derived **2** with the tabulated ^{1}H NMR data reported by Okano et al.[2] for the aglycon of bruceoside C clearly reveals that the spectra are different (Table 1). Based on the single-crystal X-ray structure which corroborated the structure of ketone **22**, coupled with the ^{1}H NMR data

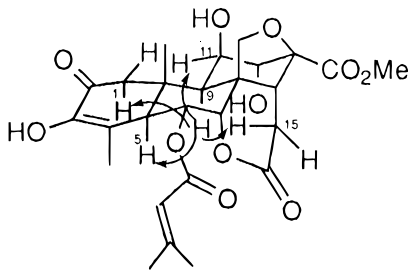


Figure 3.

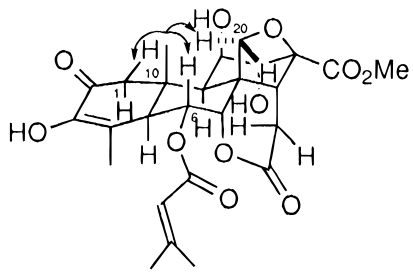


Figure 4.

of synthetic **2**, it was with a great deal of confidence that structure **2** was assigned to our synthetic material. Further support for the stereochemical assignments in structure **2** was provided by extensive NOE experiments. Upon irradiation of the C(9α) hydrogen signal, NOE enhancements are clearly observed with hydrogen atoms at C(1α), C(11α), C(15α), and, most importantly, C(5) (Figure 3). Moreover, irradiation of the C(10) methyl group leads to enhancements of the proton signals at C(6β), C(1β), and C(20α) (Figure 4). Therefore, on the basis of (1) the unambiguous structural proof of intermediate **22**, in which all stereocenters are intact, (2) NOE experiments which confirm the stereochemistry at C(5)

(12) Rubottom, G. M.; Graber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.
(13) For the synthesis of **26** see: Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(14) For the use of **26** as an oxidizing agent in organic chemistry see: Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078. Grieco, P. A.; Piñeiro-Núñez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606. Also see reference 4.

and C(6) in **2**, and (3) extensive decoupling experiments which account for all hydrogen atoms, we conclude that synthetically derived material possesses structure **2** and that the structures proposed for bruceoside C and its aglycon are incorrect.

Characterization of quassinoid glycosides is based primarily on hydrolysis of the glycoside under either acidic or enzymatic conditions followed by comparison of the resulting aglycon with known quassinoids. In the event that the data for the aglycon of bruceoside C was tabulated or reported incorrectly, an authentic sample of bruceoside C was hydrolyzed under the conditions reported in the literature.[2] It was immediately obvious that the aglycon derived from natural material was different from the synthetically derived material, since they exhibited very different R_f values in several solvent systems. Needless to say, the ^{1}H NMR spectrum of the isolated aglycon differs from the ^{1}H NMR spectrum of our synthetic material.

In summary, it is concluded based on the unambiguous synthesis of **2** that the structures proposed for bruceoside C and the derived aglycon are incorrect. Without additional information or natural material no alternative structures for these molecules are obvious at this time.

Experimental Section

^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were recorded in the indicated solvent. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Infrared (IR) spectra were taken as a solution in chloroform. Absorption intensities are indicated as strong (s), medium (m), or weak (w). High resolution and low resolution mass spectra were obtained by EI (70 eV; direct insertion). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and Robertson Microlit Laboratories, Inc., Madison, NJ. Melting points are uncorrected. 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 hotplate. E. Merck silica gel 60 (230−400 mesh) was used for flash chromatography.

All solvents are reagent grade unless otherwise stated. Anhydrous solvents were dried immediately before use. Dichloromethane, triethylamine, pyridine, acetonitrile, and oxalyl chloride were distilled from calcium hydride. Liquid ammonia was distilled from sodium metal. Tetrahydrofuran was freshly distilled from benzophenone ketyl. Trimethylsilyl trifluoromethanesulfonate was distilled immediately before use. Anhydrous dimethyl sulfoxide and 10% silver nitrate-impregnated silica gel (200 mesh) were purchased from Aldrich Chemical Co., Inc. and used as received.

(4a*β*,4bα,5*β*,6α,8α,8a*β*)-8-[2-(*tert*-Butyldiphenylsiloxy)-ethyl]-7α-[(*tert*-butyldiphenylsiloxy)methyl]-2,3,4,4a,-4b,5,6,7,8,8a-decahydro-5,6-bis(methoxymethoxy)-1,4a-dimethyl-7*β*,8a-(epoxymethano)-2-oxophenanthrene (8) and (1′α,4′a*β*,4′bα,5′*β*,6′α,8′α,8′a*β*)-8′-[(2-*tert*-Butyldiphenylsiloxy)methyl]-7′α-[(*tert*-butyldiphenylsiloxy)methyl]-(3′,4′,4′a,4′b,5′,6′,7′,8′a,9′-decahydro-5′,6′-bis(methoxymethoxy)-1′4′a-dimethyl-7′*β*,8′a-(epoxymethano)-9′-oxaspiro-1,3-dioxolane-2,2′(1′*H*)-phenanthrene (7). To a solution of 7.0 mL (86.5 mmol) of dry pyridine in 122 mL of dry methylene chloride at 0 °C under argon were added 4.33 g (43.3 mmol) of chromium trioxide, stirred at room temperature for 30 min followed by addition of 4.92 g of Celite, and stirred for an additional 15 min. To this reaction mixture were added 2.11 g (2.16 mmol) of olefin **3** and allowed to stir for 15 h. The dark heterogeneous reaction mixture was filtered through a short pad of silica gel (ca. 100 g) and was washed repeatedly with ethyl acetate. The filtrate was concentrated *in vacuo* and purified by flash chromatography on 200 g of silica gel. Elution with hexane−ethyl acetate (8:1) provided 1.00 g (49%) of dienone **8** and 0.84 g (39%) of enone **7** both as white foams. **Dienone 8:** R_f 0.17 (hexanes−ethyl acetate, 4:1); IR ($CHCl_3$) 3080 (w), 3060 (w), 3010 (m), 2940 (s), 2870 (s), 1655 (s), 1625 (s), 1595 (w), 1470 (m), 1430 (s), 1380 (m), 1363 (m), 1330 (m), 1110 (s), 1040 (s), 942 (m), 918 (m), 825 (s), 700 (s), 610 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−7.68 (m, 4H), 7.62−7.51 (m, 4H), 7.48−7.20 (m, 12H), 6.42 (d, J = 10.0 Hz, 1H), 5.69 (d, J = 10.0 Hz, 1H), 4.84 and 4.70 (AB quartet, J = 6.8 Hz, 2H), 4.63 and 4.49 (AB quartet, J = 6.6 Hz, 2H), 4.56 (d, J = 7.6 Hz, 1H), 4.08 (br d, J = 4.5 Hz, 1H), 4.04 (br s, 1H), 3.89 and 3.64 (AB quartet, J = 10.9 Hz, 2H), 3.59 (t, J = 7.4 Hz, 2H), 3.51 (br d, J = 7.6 Hz, 1H), 3.42 (s, 3H), 3.22 (s, 3H), 2.68−2.48 (m, 2H), 2.20−2.11 (m, 1H), 2.06 (t, J = 5.9 Hz, 1H), 2.02−1.92 (m, 1H), 1.87 (br d, J = 4.2 Hz, 1H), 1.86−1.78 (m, 1H), 1.78 (s, 3H), 1.56−1.46 (m, 1H), 1.41 (s, 3H), 1.03 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.61, 156.30, 140.25, 135.80, 135.75, 135.48, 135.43, 133.85, 133.82, 133.46, 129.54, 129.51, 127.75, 127.58, 127.54, 126.48, 97.57, 97.20, 83.76, 79.05, 78.40, 71.31, 65.51, 63.27, 56.25, 55.77, 47.87, 47.75, 42.96, 36.71, 33.21, 32.35, 26.90, 26.83, 19.91, 19.31, 19.13, 10.47. High-resolution MS (EI) calcd for $C_{52}H_{63}O_8Si_2$ (M − t-Bu) m/e 871.4063, found 871.4043. **Enone 7:** R_f 0.11 (hexanes−ethyl acetate, 4:1); IR ($CHCl_3$) 3080 (m), 3010 (s), 2945 (s), 2900 (s), 2870 (s), 2838 (m), 1660 (s), 1614 (m), 1598 (m), 1468 (m), 1430 (m), 1394 (m), 1367 (m), 1351 (m), 1289 (m), 1270 (m) 1186 (m), 1150 (s), 1110 (s), 1043 (s), 949 (m), 920 (m), 900 (m), 823 (m), 700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.62 (m, 4H), 7.60−7.51 (m, 4H), 7.41−7.20 (m, 12H), 5.89 (d, J = 2.2 Hz, 1H), 4.82 and 4.73 (AB quartet, J = 6.7 Hz, 2H), 4.66 and 4.52 (AB quartet, J = 6.4 Hz, 2H), 4.46 (d, J = 6.9 Hz, 1H), 4.15 (d, J = 4.7 Hz, 1H), 4.08 (s, 1H), 4.08−3.92 (m, 4H), 3.90 (d, J = 6.0 Hz, 1H), 3.84 and 3.64 (AB quartet, J = 10.9 Hz, 2H), 3.51−3.42 (m, 2H), 3.41 (s, 3H), 3.24 (s, 3H), 2.88−2.79 (m, 1H), 2.54 (dd, J = 6.3, 6.3 Hz, 1H), 2.36 (d, J = 4.3 Hz, 1H), 2.02−1.92 (m, 2H), 1.90−1.74 (m, 3H), 1.68−1.58 (m, 1H), 1.46 (s, 3H), 1.08 (d, J = 6.5 Hz, 3H), 1.02 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.47, 173.51, 135.82, 135.69, 135.49, 135.41, 133.99, 133.96, 133.61, 133.31, 129.44, 129.38, 127.51, 124.72, 110.37, 97.48, 97.11, 83.90, 78.54, 77.79, 72.92, 65.65, 65.68, 64.98, 63.40, 56.38, 55.79, 54.39, 48.74, 43.25, 41.41, 38.71, 32.90, 30.51, 27.68, 26.91, 26.81, 24.44, 19.29, 19.12, 9.10. High-resolution MS (EI) calcd for $C_{52}H_{61}O_8Si_2$ (M − t-Bu, OCH_3 and OCH_3) m/e 869.3906, found 869.3937.

Conversion of Enone 7 into Dienone 8. To a solution of 4.14 g (4.19 mmol) of enone **7** in 84 mL of anhydrous tetrahydrofuran at −23 °C under argon were added 105 mL (10.5 mmol) of a 1.0 M diisobutylaluminum hydride in toluene solution. After stirring for 45 min, the reaction was quenched at −23 °C with 3.4 mL of methanol. The reaction was warmed to room temperature, diluted with 50 mL of a 50% saturated NH_4Cl solution, treated with 2 g of Celite, and stirred for 90 min. The reaction mixture was diluted with ether and filtered through a pad of Celite/sand. The layers were separated, and the organic layer was washed with brine. The combined organic layers were back-extracted with ether. The combined organics were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on ca. 200 g of silica gel. Elution with hexanes−ethyl acetate (4:1) gave 4.45 g (82%) of the corresponding allylic alcohol as a white foam.

To a stirred solution of 3.56 g (3.60 mmol) of the above alcohol in 72 mL of dry methylene chloride at 0 °C under argon were added 10.0 mL (71.9 mmol) of triethylamine followed by 1.39 mL (18.0 mmol) of methanesulfonyl chloride. The reaction mixture was stirred at 0 °C for 5 min, at room temperature for 15 min, and then diluted with ether and water. The layers were separated, and the organic layer was washed with 1 M HCl and saturated sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was taken up in 100 mL of acetone and treated with 45 mg (0.18 mmol) of pyridinium *p*-toluenesulfonate. After stirring at room temperature for 90 min, the reaction mixture was quenched with solid sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatog-

raphy on 200 g of silica gel. Elution with hexanes−ethyl acetate (2:1) gave 3.36 g (82%) of dienone **8** as a white foam which was identical in all aspects with the sample prepared above.

Methyl (4a*β*,4bα,5*β*,6α,8α,8a*β*)-7α-Carbomethoxy-2,3,4,-4a,4b,5,6,7,8,8a-decahydro-5,6-bis(methoxymethoxy)-1,-4a-dimethyl-7*β*,8a-(epoxymethano)-2-oxophenanthrene-8-acetate (9) (R = Me). To a solution of 5.79 g (6.13 mmol) of bis-silyl ether **8** in 61 mL of tetrahydrofuran at 0 °C were added 18.4 mL (18.4 mmol) of a 1.0 M tetrabutylammonium fluoride solution in tetrahydrofuran. The reaction mixture was warmed to room temperature, stirred for 3 h, and then diluted with ethyl acetate and 50% saturated brine. The layers were separated, and the organic layer was washed with water and brine. The combined aqueous layers were back-extracted with ethyl acetate (3×). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on 100 g of silica gel. Elution with ethyl acetate (100%) to ethyl acetate−methanol (95:5) gave 2.52 g (91%) of the corresponding diol as a white solid: R_f 0.15 (ethyl acetate); IR ($CHCl_3$) 3450 (br m), 3010 (s), 2955 (s), 2895 (s), 2830 (m), 1650 (s), 1622 (s), 1570 (m), 1445 (m), 1408 (m), 1380 (m), 1358 (m), 1330 (s), 1235 (m), 1195 (m), 1150 (s), 1128 (s), 1100 (s), 1205 (s), 980 (m), 910 (s), 870 (w), 840 (w), 645 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.57 (d, J = 10.0 Hz, 1H), 5.82 (d, J = 10.0 Hz, 1H), 4.80 and 4.69 (AB quartet, J = 6.8 Hz, 2H), 4.65 and 4.55 (AB quartet, J = 6.7 Hz, 2H), 4.59 (d, J = 7.7 Hz, 1H), 4.05 (br d, J = 4.5 Hz, 1H), 3.87 and 3.76 (AB quartet, J = 12.2 Hz, 2H), 3.80 (br s, 1H), 3.73−3.58 (m, 3H), 3.42 (s, 3H), 3.36 (s, 3H), 2.64−2.40 (m, 4H), 2.21 (dd, J = 8.4, 3.7 Hz, 1H), 2.17 (ddd, J = 12.9, 5.0, 2.4 Hz, 1H) 2.03−1.93 (m, 1H), 1.92 (br d, J = 4 Hz, 1H), 1.86−1.76 (m, 1H), 1.81 (s, 3H), 1.50−1.41 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.52, 155.88, 139.36, 128.15, 127.10, 97.22, 97.07, 83.65, 79.48, 77.90, 71.62, 64.17, 61.84, 56.17, 56.13, 48.15, 46.81, 43.00, 36.69, 33.13, 32.36, 26.21, 19.78, 10.48. An analytical sample was prepared by recrystallization from ethyl acetate−hexanes: mp 127−129 °C. Anal. Calcd for $C_{24}H_{36}O_8$: C, 63.70; H, 8.02. Found: C, 63.70; H, 8.20. High-resolution MS (CI) calcd for $C_{24}H_{37}O_8$ (M + 1) m/e 453.2489, found 453.2470.

To a solution of 680 mg (1.50 mmol) of the above diol in 30 mL of acetone at 0 °C were added 2.26 mL of 8 M Jones reagent. After stirring at 0 °C for 4 h, the reaction mixture was quenched with 2.8 mL (36.3 mmol) of 2-propanol and diluted with 25 mL of ethyl acetate and 25 mL of water. The layers were separated, and the aqueous layer was saturated with sodium chloride and washed with ethyl acetate (3×). The combined organic layers were cooled to 0 °C and treated with excess ethereal diazomethane. The yellow solution was allowed to stir for 10 min before quenching with glacial acetic acid. The reaction mixture was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on 75 g of silica gel. Elution with ether−hexanes (4:1 to 20:1) gave 543 mg (71%) of the bis-ester **9** (R = Me) as a white solid: R_f 0.50 (ethyl acetate−hexanes, 2:1); IR ($CHCl_3$) 3110 (m), 2960 (s), 2900 (m), 1740 (s), 1653 (s), 1623 (s), 1588 (w), 1440 (s), 1378 (m), 1325 (s), 1270 (s), 1150 (s), 1103 (s), 1035 (s), 967 (m), 910 (s), 650 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.53 (d, J = 10.1 Hz, 1H), 5.83 (d, J = 10.1 Hz, 1H), 4.84 and 4.69 (AB quartet, J = 6.8 Hz, 2H), 4.64 and 4.57 (AB quartet, J = 6.8 Hz, 2H), 4.64 (d, J = 7.8 Hz, 1H), 4.29 (br s, 1H), 4.08 (br d, J = 4.4 Hz, 1H), 3.78 (s, 3H), 3.73 (dd, J = 7.8, 1.4 Hz, 1H), 3.64 (s, 3H), 3.45 (s, 3H), 3.31 (s, 3H), 3.04 (ddd, J = 7.4, 5.4, 1.2 Hz, 1H), 2.96 (dd, J = 16.6, 5.4 Hz, 1H), 2.64−2.48 (m, 2H), 2.33 (dd, J = 16.6, 7.4 Hz, 1H), 2.18 (ddd, J = 12.8, 4.9, 2.4 Hz, 1H), 1.09−1.79 (m, 2H), 1.79 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.29, 172.96, 170.44, 155.15, 137.44, 128.54, 127.33, 97.71, 97.21, 82.96, 79.39, 78.05, 72.05, 56.28, 56.07, 52.46, 51.55, 48.79, 47.33, 42.11, 36.58, 33.09, 32.22, 28.72, 19.59. An analytical sample was prepared by recrystallization from ethyl acetate−hexanes: mp 124−125 °C. Anal. Calcd for $C_{26}H_{36}O_{10}$; C, 61.41; H, 7.14. Found: C, 61.43; H, 6.98. High-resolution MS (EI) calcd for $C_{26}H_{36}O_{10}$ (M^+) m/e 508.2308, found 508.2292.

Methyl (1α,4a*β*,4bα,5*β*,6α,8α,8a*β*,10aα)-7α-Carbomethoxy-5,6-bis((methoxymethoxy)-1,4a-dimethyl-1,2,3,4,4a,-4b,5,6,7,8,8a,10a-dodecahydro-7*β*,8a-(epoxymethano)-2-oxophenanthrene-8-acetate (11) and Methyl (4a*β*,-4bα,5*β*,6α,8α,8a*β*)-7α-Carbomethoxy-5,6-dimethoxy-1,4a-dimethyl-2,3,4,4a,4b,5,6,7,8,8a-dodecahydro-7*β*,8a-(epoxymethano)-2-oxophenanthrene-8-acetate (12). To a solution of 1.58 g (3.11 mmol) of the bis-methyl ester **9** (R = Me) in 46 mL of tetrahydrofuran and 18 mL of methanol were added 9.32 mL (9.32 mmol) of a 1.0 M sodium hydroxide solution and allowed to stir for 13 h. The reaction mixture was acidified to pH 1 with 1 M hydrochloric acid and diluted with ethyl acetate and water. The layers were separated. The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (3×). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude reaction mixture was used directly in the next reaction.

To 500 mL of dry ammonia at −78 °C under argon was added 18.3 g (341.8 mmol) of solid ammonium chloride and allowed to stir until the reaction became homogeneous. To this solution was added the above acid **9** (R = H) (ca. 3.11 mmol) in 100 mL of anhydrous tetrahydrofuran. The reaction mixture was warmed to −33 °C and treated with small pieces of lithium (ca. 2.4 g) until the mixture remained blue. The reaction mixture was quenched with additional solid ammonium chloride, and the solvent was removed by evaporation. The residue was dissolved in ethyl acetate and water. Upon cooling to 0 °C, the reaction mixture was acidified to pH 1 with 1 M hydrochloric acid. The aqueous layer was saturated with sodium chloride, and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (3×). The combined organic extracts were cooled to 0 °C and treated with excess ethereal diazomethane. After quenching the yellow solution with glacial acetic acid, the solution was dried over magnesium sulfate, filtered, concentrated *in vacuo*, and used directly in the next reaction.

To a solution of the above crude alcohols (**5** and **10**) in 63 mL of acetone at 0 °C were added 2.0 mL of 8 M Jones reagent and stirred for 10 min before quenching with excess 2-propanol. The reaction mixture was diluted with ether and water. The layers were separated and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on 175 g of silica gel. Elution with hexanes−ethyl acetate (2:1) gave 0.75 g (47%) of ketone **11** as a white foam and ca. 0.47 g (30%) of enone **12** as a white solid. **Ketone 11:** R_f 0.31 (ethyl acetate-hexanes, 2:1); IR ($CHCl_3$) 2960 (s), 2940 (s), 1740 (s), 1445 (m), 1385 (m), 1290 (m), 1272 (m), 1148 (s), 1105 (s), 1030 (s), 965 (m), 910 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (dd, J = 10.1, 1.2 Hz, 1H), 5.38 (dd, J = 10.1, 2.8 Hz, 1H), 4.81 and 4.68 (AB quartet, J = 6.9 Hz, 2H), 4.63 and 4.57 (AB quartet, J = 6.7 Hz, 2H), 4.69 (d, J = 8.7 Hz, 1H), 4.22 (br s, 1H), 4.02 (br d, J = 4.2 Hz, 1H), 3.76 (s, 3H), 3.60 (s, 3H), 3.57 (br d, J = 8.5 Hz, 1H), 3.43 (s, 3H), 3.31 (s, 3H), 3.00−2.88 (m, 2H), 2.56 (dt, J = 14.0, 6.7 Hz, 1H), 2.50−2.40 (m, 2H), 2.36−2.24 (m, 1H), 2.17 (ddd, J = 12.9, 6.5, 1.9 Hz, 1H), 1.98 (br d, J = 13.0 Hz, 1H), 1.85 (br d, J = 4.2 Hz, 1H), 1.57 (dt, J = 13.2, 5.3 Hz, 1H), 1.31 (s, 3H), 1.07 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.98, 173.01, 170.65, 130.62, 130.56, 97.61, 97.01, 82.93, 79.43, 78.36, 73.08, 56.25, 56.01, 53.28, 52.37, 51.30, 48.69, 47.26, 44.29, 36.96, 35.33, 34.97, 29.63, 29.28, 13.47, 11.36. High-resolution MS (CI) calcd for $C_{24}H_{33}O_9$ (M − C_2H_5O) m/e 465.2125, found 465.2144. **Enone 12:** R_f 0.22 (ethyl acetate−hexanes, 2:1) IR ($CHCl_3$) 2990 (m), 2942, (s), 2880 (m), 1735 (s), 1653 (s), 1610 (m), 1435 (m), 1372 (m), 1358 (m), 1308 (m), 1265 (m), 1140 (s), 1100 (s), 1030 (s), 950 (m), 910 (m), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 and 4.69 (AB quartet, J = 6.8 Hz, 2H), 4.62 and 4.55 (AB quartet, J = 6.7 Hz, 2H), 4.61 (d, J = 7.4 Hz, 1H), 4.26 (br s, 1H), 4.00 (br d, J = 4.1 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.56 (d, J = 7.4 Hz, 1H), 3.42 (s, 3H), 3.30 (s, 3H), 3.09 (dd, J = 17.4, 4.3 Hz, 1H), 2.90 (br dd, J = 7.3, 4.4 Hz, 1H), 2.64 (ddd, J = 18.3, 14.3, 5.3 Hz, 1H), 2.57 (dd, J = 17.5, 8.3 Hz, 1H), 2.58−2.50 (m, 1H), 2.44 (ddd, J = 18.1, 5.0, 2.2 Hz, 1H), 2.30−2.18 (m, 1H), 2.09 (ddd, J = 12.7, 4.9,

2.0 Hz, 1H), 1.80 (d, J = 4.2 Hz, 1H), 1.94−1.74 (m, 3H), 1.66 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.55, 173.24, 170.77, 163.68, 128.22, 97.65, 97.21, 83.83, 79.01, 78.96, 75.37, 56.15, 56.03, 52.35, 51.75, 49.79, 42.10, 41.23, 38.52, 33.95, 32.91, 29.60, 26.16, 25.70, 20.82, 10.57. An analytical sample was prepared by recrystallization from ether−hexanes: mp 106−108 °C. Anal. Calcd for $C_{26}H_{38}O_{10}$; C, 76.01; H, 8.03. Found: C, 75.96; H, 7.97. High-resolution MS (CI) calcd for $C_{26}H_{39}O_{10}$ (M + 1) m/e 511.2545, found 511.2521.

Methyl (1α,2β,4aβ,4bα,5β,6α,8aβ,10aα)-7α-Carbomethoxy-5,6-bis(methoxymethoxy)-1,4a-dimethyl-1,2,3,4,4a,-4b,5,6,7,8,8a,10a-dodecahydro-7β,8a-(epoxymethano)-2-hydroxyphenanthrene-8-acetate (5). To a stirred solution of 332 mg (0.65 mmol) of ketone **11** in 6.5 mL of methanol and 6.5 mL of tetrahydrofuran at −78 °C was added 50 mg (1.3 mmol) of sodium borohydride. The reaction mixture was stirred at −78 °C for 10 min and then at 0 °C for 10 min. Upon quenching with acetone, and reaction mixture was diluted with brine and ether. The layers were separated, and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on 50 g of silica gel. Elution with ethyl acetate−hexanes (2:1) gave 286 mg (86%) of alcohol **5** as a white foam. R_f 0.20 (ethyl acetate−hexanes, 2:1); IR ($CHCl_3$) 3620 (w), 3495 (br w), 2940 (s), 2860 (m), 1738 (s), 1442 (m), 1360 (m), 1288 (s), 1270 (s), 1145 (s), 1100 (s), 1040 (s), 968 (m), 910 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (br d, J = 10.1 Hz, 1H), 5.28 (dd, J = 10.1, 2.8 Hz, 1H), 4.81 and 4.65 (AB quartet, J = 6.9 Hz, 2H), 4.64 and 4.58 (AB quartet, J = 6.6 Hz, 2H), 4.56 (d, J = 7.6 Hz, 1H), 4.20 (br s, 1H), 4.00 (br d, J = 4.3 Hz, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.52 (d, J = 7.6 Hz, 1H), 3.42 (s, 3H), 3.32 (s, 3H), 3.20−3.10 (m, 1H), 2.97 (dd, J = 15.9, 5.8 Hz, 1H), 2.87 (br dd, J = 7.6, 5.8 Hz, 1H), 2.46 (dd, J = 15.9, 7.6 Hz, 1H), 1.92−1.82 (m, 2H), 1.78 (d, J = 4.2 Hz, 1H), 1.72−1.58 (m, 2H), 1.56 (br d, J = 11.8 Hz, 1H), 1.45−1.35 (m, 1H), 1.30−1.20 (m, 1H), 1.09 (s, 3H), 1.04 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.19, 170.87, 130.94, 129.63, 97.53, 97.13, 82.99, 79.55, 78.55, 76.58, 73.22, 56.20, 56.00, 52.32, 51.64, 51.33, 48.72, 47.23, 44.80, 37.11, 35.33, 33.53, 29.95, 29.40, 14.91, 13.98. High-resolution MS (CI) calcd for $C_{26}H_{41}O_{10}$ (M + 1) m/e 513.2702, found 513.2695.

Methyl (1α,2β,4aβ,4bα,5β,6α,8aβ,9β,10β,10aα)-7α-Carbomethoxy-5,6-bis(methoxymethoxy)-1,4a-dimethyl-7β,-8a-(epoxymethano)-1,2,3,4,4a,4b,5,6,7,8,8a,9,10,10a-tetradecahydro-2,9,10-trihydroxyphenanthrene-8-acetate (13). To a stirred solution of 29.0 mg (0.058 mmol) of olefin **5** in 575 μL of pyridine was added 20.5 mg (0.081 mmol) of osmium tetraoxide in one portion. After stirring for 16 h, the dark brown reaction was treated with a solution of 88 mg of sodium bisulfite in 229 μL of water and 40 μL of pyridine and allowed to stir an additional 24 h. The crude reaction mixture was filtered through a plug of silica gel, washed with ethyl acetate, concentrated *in vacuo*, and purified by preparative thin layer chromatography. Elution with ethyl acetate−hexanes (8:1) provided 18.7 mg of β-diol **13** (60%) and 4.5 (16%) of recovered olefin **5**. **β-Diol 13:** R_f 0.18 (ethyl acetate−hexanes, 8:1); IR ($CHCl_3$) 3600 (m), 3520, (m), 3010 (m), 2950 (s), 1745 (s), 1443 (m), 1325 (m), 1272 (s), 1152 (s), 1105 (s), 1078 (s), 1049 (s), 965 (m), 911 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 and 4.69 (AB quartet, J = 6.8 Hz, 2H), 4.61 and 4.58 (AB quartet, J = 6.6 Hz, 2H), 4.58 (d, J = 7.2 Hz, 1H), 4.26 (br s, 1H), 4.13 (br s, 1H), 4.06 (d, J = 7.7 Hz, 1H), 4.00 (d, J = 5.1 Hz, 1H), 3.98 (br s, 1H, OH), 3.78 (s, 3H), 3.75 (s, 3H), 3.43 (s, 3H), 3.30 (s, 3H), 3.20−3.00 (m, 4H), 2.38 (dd, J = 19.4, 9.2 Hz, 1H), 2.02−1.92 (m, 1H), 1.88−1.80 (m, 2H), 1.70−1.52 (m, 3H), 1.43 (s, 3H), 1.24 (d, J = 4.5 Hz, 1H), 1.14−1.04 (m, 2H), 1.06 (d, J = 6.3 Hz, 3H), 0.69 (br d, J = 10.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.08, 171.39, 97.63, 97.10, 80.11, 79.60, 77.96, 76.45, 71.65, 69.18, 56.18, 55.94, 52.45, 52.43, 52.02, 47.46, 45.80, 42.62, 39.03, 37.05, 35.22, 30.02, 28.25, 19.04, 14.79. An analytical sample was prepared by recrystallization from ethyl acetate: mp 184−185 °C. High-resolution MS (CI) calcd for $C_{26}H_{43}O_{12}$ (M + 1) m/e 547.2755, found 547.2734.

(1β,2β,6β,6aβ,8aα,9α,10β,12aβ,12bα,15α)-15-Carbomethoxy-1,4,5,8a,9,10,11,12,12a,12b-decahydro-1′10-dihydroxy-9,12a-dimethyl-4-oxo-2*H*-6a,2,6-(methanoxymetheno)naphth[1,2-*d*]oxocin (14). To a solution of 41.2 mL of dry acetonitrile at 0 °C under argon was added 3.71 g (27.8 mmol) of aluminum trichloride followed by addition of 4.17 g (27.8 mmol of sodium iodide. After stirring the faint yellow solution at 0 °C for 15 min, a solution of 951 mg (1.86 mmol) of the bis-MOM ether **5** in 20.6 mL of dry methylene chloride was added. The reaction was warmed to room temperature and was stirred for 50 min in the dark. The heterogeneous reaction mixture was cooled to 0 °C and was quenched by addition of 40 mL of water. The reaction mixture was acidified with 1 M hydrochloric acid and was diluted with ethyl acetate. The layers were separated. The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (6×). The combined organic extracts were cooled to 0 °C and treated with excess ethereal diazomethane. After 10 min, the yellow solution was quenched with glacial acetic acid, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on ca. 75 g of silica gel. Elution with ethyl acetate−hexanes (4:1) gave 617.8 mg (73%) of the corresponding triol as a white solid: R_f 0.27 (ethyl acetate−hexanes, 4:1); IR ($CHCl_3$) 3550 (br m), 2965 (s), 2940 (s), 1730 (s), 1720 (s), 1442 (s), 1368 (s), 1315 (s), 1215 (s), 1150 (s), 1110 (m), 1055 (s), 1002 (s), 973 (m), 950 (m), 908 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (br d, J = 10.2 Hz, 1H), 5.23 (dd, J = 10.2, 2.9 Hz, 1H), 4.59 (d, J = 8.1 Hz, 1H), 4.14 (dd, J = 8.0, 3.8 Hz, 1H), 4.00 (br s, 1H), 3.83 (s, 3H), 3.67 (d, J = 8.1 Hz, 1H), 3.63 (d, J = 1.7 Hz, 1H, C_{12} OH), 3.61 (s, 3H), 3.20−3.09 (m, 1H), 3.14 (dd, J = 16.8, 9.3 Hz, 1H), 2.69 (br dd, J = 9.3, 4.8 Hz, 1H), 2.46 (dd, J = 16.7, 4.8 Hz, 1H), 2.19 (d, J = 8.2 Hz, 1H, C_{11} OH), 1.98 (dt, J = 12.9, 3.3 Hz, 1H), 1.92−1.86 (m, 1H), 1.74−1.64 (m, 1H), 1.67 (d, J = 3.2 Hz, 1H), 1.63 (d, J = 5.1 Hz, 1H, C_3 OH), 1.56 (br d, J = 11.8 Hz, 1H), 1.48−1.38 (m, 1H), 1.33 (dt, J = 13.3, 4.0 Hz, 1H), 1.16 (s, 3H), 1.05 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.41, 172.92, 132.77, 127.94, 82.92, 77.41, 76.64, 73.64, 71.81, 52.95, 51.84, 51.68, 49.98, 48.12, 44.97, 36.97, 35.54, 33.77, 30.02, 29.00, 14.87, 14.24. An analytical sample was prepared by recrystallization from ethyl acetate−hexanes: mp 200.5−202.0 °C. Anal. Calcd for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60. Found: C, 62.32; H, 7.81. High-resolution MS (M) calcd for $C_{22}H_{32}O_8$ (M^+) m/e 424.2098, found 424.2084.

To a heterogeneous solution of 868.5 mg (2.04 mmol) of the above triol in 68 mL of benzene was added 38.8 mg (0.20 mmol) of *p*-toluenesulfonic acid. The solution was warmed to 78 °C and stirred for 75 min. The reaction was cooled to room temperature and diluted with ethyl acetate and water. The layers were separated and the aqueous layers back-extracted with ethyl acetate (2×). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on 75 g of silica gel. Elution with ethyl acetate−hexanes (4:1) gave 737 mg (92%) of lactone **14** as a highly crystalline white solid and 52.1 mg (6%) of recovered triol. **Lactone 14:** R_f 0.38 (ethyl acetate−hexanes, 4:1); IR ($CHCl_3$) 3660 (br m), 2995, (m), 2950 (m), 2885 (m), 1740 (s), 1443 (m), 1410 (m), 1368 (m), 1329 (m), 1248 (br s), 1148 (m), 1115 (s), 1065 (s), 1005 (m), 972 (m), 950 (m), 910 (w), 870 (w), 850 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (br d, J = 10.2 Hz, 1H), 5.23 (dd, J = 10.2, 3.0 Hz, 1H), 4.66 (t, J = 2.2 Hz, 1H), 4.62 (d, J = 8.9 Hz, 1H), 4.26 (ddd, J = 8.2, 3.7, 2.2 Hz, 1H), 3.85 (s, 3H), 3.71 (br d, J = 8.9, 1H), 3.20−3.10 (m, 1H), 2.89 (dd, J = 19.8, 8.2 Hz, 1H), 2.82 (d, J = 8.2 Hz, 1 H, C_{11} OH), 2.61 (dd, J = 8.1, 2.1 Hz, 1H), 2.56 (d, J = 19.8 Hz, 1H), 1.97 (dt, J = 12.7, 3.9 Hz, 1H), 1.97−1.89 (m, 1H), 1.76−1.66 (m, 2H, $C_{2\beta}$ & C_3 OH), 1.61 (br d, J = 11.8 Hz, 1H), 1.50−1.41 (m, 1H), 1.38 (d, J = 3.7 Hz, 1H), 1.27 (dt, J = 13.2, 4.3 Hz, 1H), 1.19 (s, 3H), 1.07 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.47, 167.54, 134.04, 126.38, 79.22, 76.36, 73.69, 70.90, 53.29, 53.25, 52.20, 49.05, 45.61, 44.77, 36.68, 35.35, 33.39, 29.80, 27.20, 14.73, 14.34. An analytical sample was prepared by recrystallization from ethyl acetate−hexanes: mp 183−185

°C. High-resolution MS (CI) calcd for $C_{21}H_{29}O_7$ ($M + 1$) *m/e* 393.1914, found 393.1923.

(3*β*,6α,11*β*,12α)-13,20-Epoxy-16-oxo-3,6,11,12-tetrakis(trimethylsilyloxy)picrasan-21-oic Acid Methyl Ester (17) and (1*β*,2*β*,6*β*,6a*β*,7α,8α,8aα,9α,10*β*,12a*β*,12bα,15α)-15-Carbomethoxy-9,12a-dimethyl-1,4,5,7,8,8a,9,10,11,12,12a,12b-dodecahydro-4-oxo-1,7,8,10-tetrakis(trimethylsilyloxy)-2*H*-6a,2,6-(methanoxymetheno)naphth[1,2-*d*]oxocin (18) and (1*β*,2*β*,6*β*,6a*β*,7*β*,8*β*,8aα,9α,10*β*,12a*β*,12bα,15α)-15-Carbomethoxy-1,12a-dimethyl-1,4,5,7,8,8a,9,10,11,12,12a,12b-dodecahydro-8-hydroxy-4-oxo-1,7,10-tris(trimethylsilyloxy)-2*H*-6a,2,6-(methanoxymetheno)naphth[1,2-*d*]oxocin (19). To a solution of 105.4 mg (0.269 mmol) of olefin **14** in 2.7 mL of pyridine was added 0.565 mL (0.282 mmol) of a 0.5 M osmium tetraoxide in pyridine solution. The reaction was stirred in the dark for 5 h and then quenched upon addition of a solution of 411 mg of sodium bisulfite in 2 mL water and 0.184 mL of pyridine. After stirring for 1 h the reaction mixture was passed through a plug of silica gel (ca. 20 g), washing the plug with ethyl acetate−methanol (9:1), and concentrated *in vacuo*. The crude tetraols **15** and **16** were used directly in the next reaction.

The above crude mixture of tetraols was dissolved in 13.4 mL of methanol and was treated with 153 mg (0.81 mmol) of *p*-toluenesulfonic acid. The heterogeneous solution was warmed to 45 °C until the reaction became homogeneous (ca. 15 min) and then stirred at room temperature for 40 h. The methanol was concentrated *in vacuo* to ca. 1/4 its total volume, diluted with methylene chloride, and applied to a plug of silica gel. The plug was washed with ethyl acetate−methanol (9:1), and the filtrate and washings were concentrated *in vacuo* and used directly in the following reaction.

To a solution of the above tetraols (ca. 0.269) in 5.4 mL of dry pyridine at 0 °C under argon were added 898 μL (6.45 mmol) of triethylamine followed by dropwise addition of 623.6 μL (3.23 mmol) of trimethylsilyl trifluoromethanesulfonate. The reaction was immediately warmed to room temperature and stirred for 30 min. The reaction mixture was quenched upon addition of 650 μL of a saturated sodium bicarbonate solution, filtered through a plug of silica gel, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on ca. 30 g of silica gel. Elution with hexanes−diethyl ether (4:1) provided 48 mg (25%) of the C(7) lactone **17**, 58.8 mg (31%) of C(12) lactone **18**, and 14 mg (18%) of the alcohol **19**. **Lactone 17:** R_f 0.11 (hexanes−ether, 4:1, run up plate 2×); IR ($CHCl_3$) 3005 (m), 2980 (s), 2905 (m), 1740 (s), 1735 (s), 1475 (m), 1362 (m), 1255 (s), 1160 (m), 1060 (s), 969 (m), 890 (s), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (d, $J = 7.1$ Hz, 1H), 4.28 (d, $J = 2.0$ Hz, 1H), 4.19 (s, 1H), 4.11 (br d, $J = 2.8$ Hz, 1H), 3.86 (dd, $J = 10.4$, 2.1 Hz, 1H), 3.77 (s, 3H), 3.54−3.40 (m, 2H), 3.14−3.04 (m, 1H), 2.92 (dd, $J = 19.3$, 5.9 Hz, 1H), 2.56 (br dd, $J = 13.7$, 6.0 Hz, 1H), 1.77 (br d, $J = 12.7$ Hz, 1H), 1.72−1.64 (m, 1H), 1.62−1.54 (m, 2H), 1.50 (br d, $J = 2.8$ Hz, 1H), 1.48 (t, $J = 10.7$ Hz, 1H), 1.22 (s, 3H), 1.18 (d, $J = 6.0$ Hz, 3H), 1.13 (dt, $J = 12.8$, 3.1 Hz, 1H), 0.19 (s, 9H), 0.13 (s, 9H), 0.12 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.11, 169.92, 88.27, 82.66, 77.55, 76.20, 73.67, 73.49, 72.19, 52.45, 48.92, 42.79, 42.79, 41.42, 38.50, 36.98 (2C), 29.34, 28.54, 18.70 (2C), 0.86, 0.47, 0.19, 0.18. An analytical sample was prepared by recrystallization from ether−hexanes: mp 230−231.5 °C. High-resolution MS (CI) calcd for $C_{33}H_{63}O_9Si_4$ ($M + 1$) *m/e* 715.3550, found 715.3530. **Lactone 18:** R_f 0.30 (hexanes−ether, 4:1, run up plate 2×); IR ($CHCl_3$) 2968 (s), 2910 (m), 1740 (s), 1442 (w), 1380 (m), 1330 (w), 1255 (s), 1157 (s), 1131 (s), 1075 (s), 990 (m), 972 (s), 942 (m), 895 (s), 855 (s), 842 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.72 (d, $J = 7.5$ Hz, 1H), 4.50 (t, $J = 2.1$ Hz, 1H), 4.37 (dd, $J = 4.2$, 1.9 Hz, 1H), 3.82 (s, 3H), 3.61 (dd, $J = 10.3$, 1.8 Hz, 1H), 3.57 (d, $J = 2.0$ Hz, 1H), 3.56 (br d, $J = 7.5$ Hz, 1H), 3.50 (d, $J = 20.3$ Hz, 1H), 3.12−3.02 (m, 1H), 2.84 (dd, $J = 20.3$, 8.4 Hz, 1H), 2.52 (dd, $J = 8.2$, 2.3 Hz, 1H), 1.76 (br d, $J = 12.7$ Hz, 1H), 1.70 (t, $J = 10.9$ Hz, 1H), 1.66−1.48 (m, 3H), 1.43 (br d, $J = 4.0$ Hz, 1H), 1.22 (s, 3H), 1.20−1.12 (m, 1H), 1.13 (d, $J = 6.0$ Hz, 1H), 0.16 (s, 9H), 0.15 (s, 9H), 0.11 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.84, 168.91, 81.62, 79.20, 78.97, 77.93, 75.09, 73.22, 71.66, 53.07, 50.51, 47.31, 45.08, 43.41, 39.35, 37.93, 36.79, 29.43, 29.22, 19.66, 19.09, 1.19, 0.53, .048, −0.30. An analytical sample was prepared by recrystallization from ether: mp 211−212 °C. Anal. Calcd for $C_{33}H_{62}O_9Si_4$: C, 55.42; H, 8.74. Found: C, 55.27; H, 8.94. High-resolution MS (CI) calcd for $C_{33}H_{63}O_9Si_4$ ($M + 1$) *m/e* 715.3551, found 715.3561. **Lactone 19:** R_f 0.17 (hexanes−ether, 4:1, run up plate 2×); IR ($CHCl_3$) 3600 (m), 2980 (s), 2880 (m), 1742 (s), 1440 (m), 1376 (m), 1320 (m), 1255 (s), 1142 (s), 1080 (s), 1020 (s), 989 (s), 963 (s), 900 (s), 870 (s), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.67 (d, $J = 7.8$ Hz, 1H), 4.56 (t, $J = 2.2$ Hz, 1H), 4.37 (dd, $J = 4.4$, 2.0 Hz, 1H), 4.03 (br d, $J = 7.8$ Hz, 1H), 3.95 (br s, 1 H), 3.85 (s, 3H), 3.41 (d, $J = 3.4$ Hz, 1H), 3.08 (dt, $J = 10.0$, 5.6 Hz, 1H), 2.95 (dd, $J = 19.7$, 8.4 Hz, 1H), 2.67 (dd, $J = 8.3$, 2.3 Hz, 1H), 2.51 (d, $J = 19.7$ Hz, 1H), 2.06−1.92 (m, 1H), 1.89 (s, C_6 OH, 1H), 1.76−1.61 (m, 3H), 1.41 (s, 3H), 1.00 (dt, $J = 12.1$, 4.8 Hz, 1H), 0.96 (d, $J = 6.5$ Hz, 3H), 0.68 (br d, $J = 11.0$ Hz, 1H), 0.18 (s, 9H), 0.14 (s, 9H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.36, 167.86, 79.79, 77.10, 73.40, 71.22, 70.02, 69.49, 53.08, 51.85, 49.00, 46.27, 41.01, 39.16, 36.49, 34.89, 30.20, 27.26, 18.83, 14.91, 0.54, 0.40, 0.17. An analytical sample was prepared by recrystallization from hexanes: mp 198−199.5 °C. Anal. Calcd for $C_{30}H_{54}O_9Si_3$: C, 56.04; H, 8.46. Found: C, 55.95; H, 8.56. High-resolution MS (CI) calcd for $C_{30}H_{54}O_9Si_3$ ($M + 1$) *m/e* 642.3076, found 642.3079.

(3*β*,6α,11*β*,12α)-3,6-Dihydroxy-11,12-bis(trimethylsilyloxy)-13,20-epoxy-16-oxopicrasan-21-oic Acid Methyl Ester (20). To a solution of 23.1 mg (0.032 mmol) of the pentacyclic lactone **17** in 711 μL of a tetrahydrofuran−water (10:1) solution cooled to 0 °C was added a catalytic amount of pyridinium *p*-toluenesulfonate (ca. 1 mg), and the mixture was stirred for 2 h. The reaction was filtered through a plug of silica gel and concentrated *in vacuo*. The crude product was purified by flash chromatography on ca. 10 g of silica gel. Elution with ethyl acetate−hexanes (2:1) provided 14.9 mg (81%) of diol **20** as a white solid: R_f 0.12 (ethyl acetate−hexanes, 2:1); IR ($CHCl_3$) 3558 (m), 3450 (br m), 3010 (m), 2965 (s), 2910 (m), 1735 (s), 1440 (m), 1360 (m), 1328 (m), 1255 (s), 1160 (s), 1110 (s), 1078 (s), 1028 (s), 995 (m) 965 (m), 890 (s), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (d, $J = 7.3$ Hz, 1H), 4.51 (d, $J = 2.5$ Hz, 1H), 4.21 (s, 1 H), 4.11 (d, $J = 2.8$ Hz, 1H), 3.84−3.72 (m, 1H), 3.78 (s, 3H), 3.55 (br d, $J = 6.6$ Hz, 1H), 3.48 (dd, $J = 19.3$, 13.8 Hz, 1H), 3.16−3.04 (m, 1H), 2.94 (dd, $J = 19.3$, 5.8 Hz, 1H), 2.62 (br dd, $J = 13.9$, 4.6 Hz, 1H), 2.37 (d, $J = 12.3$ Hz, 1H, C_6 OH), 1.90−1.78 (m, 2H), 1.76−1.64 (m, 2H, C_3 OH), 1.62−1.52 (m, 1H), 1.51 (d, $J = 3.5$ Hz, 1H), 1.31 (d, $J = 6.1$ Hz, 1H), 1.25 (t, $J = 10.9$ Hz, 1H), 1.21 (s, 3H), 1.22−1.12 (m, 1H), 0.19 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.03, 169.08, 88.10, 82.55, 76.25, 75.70, 73.73, 73.57, 72.15, 52.51, 50.25, 46.30, 42.52, 41.36, 38.49, 37.66, 36.28, 29.03, 28.55, 18.22, 17.26, 0.88, 0.19. An analytical sample was prepared by recrystallization from ethyl acetate−hexanes: mp 251.5−253.0 °C. Anal. Calcd for $C_{27}H_{46}O_9Si_2$; C, 56.81; H, 8.12. Found C, 57.20; H, 7.98. High-resolution MS (CI) calcd for $C_{27}H_{47}O_9Si_2$ (M + 1) *m/e* 571.2759, found 571.2750.

(6α,11*β*,12α)-3,16-Dioxo-11,12-bis(trimethylsiloxy)-13,20-epoxy-6-hydroxypicrasan-21-oic Acid Methyl Ester (21). To a solution of 30.1 μL (0.345 mmol) of oxalyl chloride in 2.5 mL of dry methylene chloride at −78 °C under argon was added a solution of 49.0 μL (0.69 mmol) of dimethyl sulfoxide in 50 μL of dry methylene chloride, and the mixture was stirred for 10 min. To the reaction mixture was added a solution of 140.7 mg (0.247 mmol) of diol **20** in 2.5 mL of dry methylene chloride. After stirring at −78 °C for 40 min, the reaction was treated with 240 μL (1.73 mmol) of triethylamine, stirred at −78 °C for 15 min, warmed to room temperature, and stirred for 20 min. The reaction was quenched by the addition of 200 μL of a saturated sodium bicarbonate solution and was diluted with ethyl acetate and water. The layers were separated, and the organic layer was washed with brine. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on 50 g of silica gel. Elution with ethyl acetate−hexanes (2:1) gave 95.3 mg (68%) of ketone **21** as a white solid and 32.4 mg (23%) of recovered diol **20**.

Ketone 21: R_f 0.32 (ethyl acetate−hexanes, 2:1); IR ($CHCl_3$) 3590 (m), 3500 (br w), 3010 (m), 2965 (m), 2910 (m), 1740 (s), 1710 (s), 1440 (m), 1365 (m), 1255 (s), 1163 (s), 1128 (s), 1080 (s), 1000 (m), 970 (m), 890 (s), 842 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.75 (d, J = 7.4 Hz, 1H), 4.55 (d, J = 2.6 Hz, 1H), 4.23 (br s, 1H), 4.14 (br d, J = 2.7 Hz, 1H), 3.79 (s, 3H), 3.71 (dt, J = 11.6, 2.5 Hz, 1H), 3.57 (br d, J = 6.5 Hz, 1H), 3.51 (dd, J = 19.3, 13.8 Hz, 1H), 2.97 (dd, J = 19.3, 5.8 Hz, 1H), 2.66 (br dd, J = 13.8, 5.8 Hz, 1H), 2.60−2.48 (m, 2H), 2.48−2.36 (m, 1H), 2.34 (d, J = 11.9 Hz, 1H, C_6 OH), 2.04 (ddd, J = 11.4, 8.2, 2.8 Hz, 1H), 1.74 (dd, J = 11.0, 9.1 Hz, 1H), 1.72−1.66 (m, 1H), 1.64 (d, J = 3.6 Hz, 1H), 1.31 (d, J = 7.0 Hz, 3H), 1.24 (s, 3H), 0.20 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.36, 169.87, 168.58, 86.68, 82.53, 76.22, 73.44, 73.36, 71.62, 52.57, 51.68, 46.43, 43.96, 42.55, 40.79, 37.72, 35.51, 33.88, 28.55, 19.56, 16.69, 0.83, 0.18. An analytical sample was prepared by recrystallization from ethyl acetate−hexanes: mp 247−249 °C. High-resolution MS (CI) calcd for $C_{27}H_{45}O_9Si_2$ (M + 1) m/e 569.2602, found 569.2618.

(6α,11*β*,12α)-6-[(3-methyl-1-oxo-2-butenyl)oxy]-11,12-bis(trimethylsiloxy)-13,20-epoxy-3,16-dioxopicrasan-21-oic Acid Methyl Ester (22) and (6α,11*β*,12α)-6-(3-methyl-1-oxo-3-butenyl)oxy]-11,12-bis(trimethylsiloxy)-13,20-epoxy-3,16-dioxopicrasan-21-oic Acid Methyl Ester (23). To a solution of 97.9 mg (0.17 mmol) of the alcohol **21**, 88.9 (0.43 mmol) of 1,3-dicyclohexylcarbodiimide, and 42.1 mg (0.34 mmol) of 4-(dimethylamino)pyridine in 1.43 mL of tetrahydrofuran was added 34.5 mg (0.34 mmol) of 3,3-dimethylacrylic acid. The reaction was stirred for 15 h at room temperature, at which time an additional 88.9 mg (0.43 mmol) of 1,3-dicyclohexylcarbodiimide, 42.1 mg (0.34 mmol) of 4-(dimethylamino)pyridine, and 34.5 mg (0.34 mmol) of 3,3-dimethylacrylic acid were added. After 24 h at room temperature, the heterogeneous reaction mixture was filtered through a plug of silica gel and concentrated *in vacuo*, and the crude residue was purified by flash chromatography on 50 g of silica gel (elution with hexanes−ethyl acetate, 4:1). The product was repurified by chromatography with 45 g of 10% silver nitrate-impregnated silica gel. Elution with hexanes−ethyl acetate (4:1 to 1:1) provided separation of isomeric side chains. The respective compounds were repurified by preparative thin layer chromatography. Elution with hexanes−ethyl acetate (4:1) provided 73 mg (65%) of the desired α,*β* unsaturated ester **22** and 22 mg (20%) of the isomeric compound **23**. **α,*β*-Unsaturated ester 22:** R_f 0.20 (hexanes−ethyl acetate 4:1); IR ($CHCl_3$) 3020 (m), 2995 (s), 2870 (m), 1740 (s), 1720 (s), 1655 (m), 1445 (m), 1260 (s), 1148 (s), 1082 (s), 1025 (m), 1007 (m), 980 (m), 895 (s), 847 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (br s, 1H), 5.02 (dd, J = 11.5, 2.3 Hz, 1H), 4.79 (d, J = 7.5 Hz, 1H), 4.60 (d, J = 2.3 Hz, 1H), 4.23 (s, 1H), 4.16 (d, J = 2.8 Hz, 1H), 3.79 (s, 3H), 3.63 (d, J = 7.5 Hz, 1H), 3.52 (dd, J = 19.3, 13.7 Hz, 1H), 2.96 (dd, J = 19.2, 5.9 Hz, 1H), 2.61 (br dd, J = 13.7, 5.9 Hz, 1H), 2.60−2.50 (m, 1H), 2.47−2.36 (m, 1H), 2.30−2.20 (m, 1H), 2.17 (d, J = 0.8 Hz, 3H), 2.15 (dd, J = 11.4, 8.8 Hz, 1H), 2.07 (ddd, J = 11.4, 10.2, 3.0 Hz, 1H), 1.91 (s, 3H), 1.80−1.68 (m, 2H), 1.29 (s, 3H), 1.26 (d, J = 7.0 Hz, 3H), 0.21 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.15, 169.89, 169.21, 166.10, 159.40, 115.34, 83.60, 82.52, 76.25, 73.35, 73.20, 71.14, 52.55, 48.47, 46.46, 43.27, 42.62, 40.72, 37.98, 35.32, 33.40, 28.43, 27.54, 20.36, 19.49, 17.20, 0.81, 0.18. An analytical sample was prepared by recrystallization from ethyl acetate−hexanes: mp 207.0−208.5 °C. High-resolution MS (CI) calcd for $C_{32}H_{51}O_{10}Si_2$ (M + 1) m/e 651.3021, found 651.3003. **Compound 23:** R_f 0.20 (hexanes−ethyl acetate, 4:1); IR ($CHCl_3$) 3020 (m), 2975 (m), 2920 (m), 1740 (s), 1710 (s), 1445 (m), 1340 (m), 1260 (s), 1160 (s), 1126 (s), 1085 (s), 1025 (m), 1005 (m), 980 (m), 912 (s), 898 (s), 845 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.92 (dd, J = 11.4, 2.2 Hz, 1H), 4.86 (s, 1H), 4.78 (d, J = 7.5 Hz, 1H), 4.64 (d, J = 2.2 Hz, 1H), 4.24 (br s, 1H), 4.16 (br d, J = 3.0 Hz, 1H), 3.79 (s, 3H), 3.61 (d, J = 7.5 Hz, 1H), 3.52 (dd, J = 19.3, 13.7 Hz, 1H), 3.11 and 3.09 (AB quartet, J = 15.4 Hz, 2H), 2.96 (dd, J = 19.3, 5.9 Hz, 1H), 2.62 (br dd, J = 13.6, 5.8 Hz, 1H), 2.56 (ddd, J = 17.9, 9.0, 2.5 Hz, 1H), 2.48−2.36 (m, 1H), 2.24−2.12 (m, 2H), 2.07 (ddd, J = 12.7, 8.7, 2.5 Hz, 1H), 1.82 (s, 3H), 1.78−1.72 (m, 1H), 1.71 (br d, J = 3.8 Hz, 1H), 1.27 (s, 3H), 1.26 (d, J = 6.6 Hz, 3H), 0.21 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.05, 171.38, 169.80, 168.99, 137.71, 115.37, 82.96, 82.49, 76.20, 73.30, 73.10, 72.82, 52.55, 48.25, 46.42, 43.37, 43.33, 42.55, 40.63, 37.91, 35.11, 33.14, 28.41, 22.42, 19.77, 17.14, 0.79, 0.17. An analytical sample was prepared by recrystallization from ether−hexanes: mp 164−165 °C. High resolution MS (CI) calcd for $C_{32}H_{51}O_{10}Si_2$ (M + 1) m/e 651.3023, found 651.3032.

(2α,6α,11*β*,12α)-6-[(3-Methyl-1-oxo-2-butenyl)oxy]-11,-12-bis(trimethylsiloxy)-13,20-epoxy-2-hydroxy-3,16-dioxopicrasan-21-oic Acid Methyl Ester (24). To a solution of 17.8 mg (0.0274 mmol) of the ketone **22** in 913 μL of dry methylene chloride at −10 °C under argon was added 30.5 μL (0.219 mmol) of triethylamine followed by 26.5 μL (0.137 mmol) of trimethylsilyl trifluoromethanesulfonate. After 20 min, the reaction was quenched by the addition of 30 μL of a saturated sodium bicarbonate solution. The reaction was applied directly to 10 g of silica gel and purified by rapid flash chromatography. Elution with hexanes−ethyl acetate (2:1) provided 17.4 mg of the crude silyl enol ether.

To a solution of the above crude silyl enol ether (ca. 0.0274 mmol) in 913 μL of dry methylene chloride was added 17.8 mg of solid sodium bicarbonate. The reaction was cooled to −23 °C and was treated with 9.5 mg (0.0548 mmol) of purified *m*-chloroperoxybenzoic acid. The reaction was stirred at −23 °C for 40 min. To the reaction mixture was added 1.0 M tetrabutylammonium fluoride in small portions [ca. 27 μL (0.027 mmol)] until the reaction was complete by TLC. The reaction was quenched upon addition of 150 μL of saturated sodium thiosulfate solution, filtered through a plug of silica gel, concentrated *in vacuo*, and purified by preparative thin layer chromatography. Elution with hexanes−ethyl acetate (4:1) gave 9.6 mg (52%) of **α-hydroxy ketone 24:** R_f 0.12 (hexanes−ethyl acetate, 4:1); IR ($CHCl_3$) 3510 (br w), 2980 (m), 2920 (m), 1740 (s), 1715 (s), 1650 (m), 1445 (m), 1385 (m), 1370 (m), 1358 (m), 1335 (m), 1260 (s), 1145 (s), 1110 (s), 1080 (s), 1020 (m), 995 (m), 970 (m), 890 (s), 840 (s), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5.76 (br s, 1H), 5.29 (dd, J = 11.3, 2.2 Hz, 1H), 4.87 (d, J = 7.5 Hz, 1H), 4.56 (d, J = 2.1 Hz, 1H), 4.38−4.30 (m, 1H), 4.26 (s, 1H), 4.17 (d, J = 2.5 Hz, 1H), 3.79 (s, 3H), 3.70 (d, J = 3.6 Hz, 1H, C_2 OH), 3.64 (d, J = 7.2 Hz, 1H), 3.46 (dd, J = 19.3, 13.8 Hz, 1H), 2.94 (dd, J = 19.3, 5.9 Hz, 1H), 2.76−2.66 (m, 1H), 2.61 (br dd, J = 13.0, 5.1 Hz, 1H), 2.53 (dd, J = 12.3, 6.7 Hz, 1H), 2.18 (d, J = 0.5 Hz, 3H), 2.08 (t, J = 11.5 Hz, 1H), 1.93 (s, 3H), 1.68 (d, J = 3.4 Hz, 1H), 1.65 (s, 3H), 1.38 (t, J = 12.5 Hz, 1H), 1.26 (d, J = 6.3 Hz, 3H), 0.25 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.18, 169.81, 168.89, 166.00, 159.82, 115.53, 84.29, 82.54, 76.04, 73.79, 73.50, 70.84, 70.72, 52.59, 50.54, 47.02, 46.31, 42.41, 41.08, 40.99, 39.46, 28.35, 27.63, 20.43, 18.79, 13.69, 0.96, 0.18. An analytical sample was prepared by recrystallization from ethyl acetate−hexanes: mp 212−214 °C. High-resolution MS (CI) calcd for $C_{32}H_{51}O_{11}Si_2$ (M + 1) m/e 667.2972, found 667.2959.

(6α,11*β*,12α)-6-[(3-Methyl-1-oxo-2-butenyl)oxy]-11,12-bis(trimethylsiloxy)-13,20-epoxy-3-hydroxy-2,16-dioxopicras-3-en-21-oic Acid Methyl Ester (25). To a solution of 1.7 mg (0.0026 mmol) of α-hydroxy ketone **24** in 255 μL of methylene chloride was added 2.0 mg (0.0051 mmol) of bis(trifluoromethyl)iodinane oxide. The reaction was stirred at room temperature for 2.5 h. The reaction mixture was treated with 3.5 μL (0.026 mmol) of triethylamine, filtered through a plug of silica gel, and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography. Elution with hexanes−ethyl acetate (8:1) gave 1.2 mg (70%) of diosphenol **25** as a white solid: R_f 0.12 (hexanes−ethyl acetate, 4:1); IR ($CDCl_3$) 3464 (br m), 3028 (m), 2957 (m), 2897 (m), 1740 (s), 1667 (s), 1641 (s), 1441 (m), 1400 (m), 1364 (m), 1254 (s), 1223 (s), 1144 (s), 1113 (s), 1080 (s), 1042 (m), 891 (s), 845 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (s, 1H, C(3) OH), 5.82 (br s, 1H), 5.16 (dd, J = 11.8, 2.5 Hz, 1H), 4.77 (d, J = 7.6 Hz, 1H), 4.68 (d, J = 2.4 Hz, 1H), 4.26 (br s, 1H), 4.10 (br d, J = 3.3 Hz, 1H), 3.80 (s, 3H), 3.66 (d, J = 7.5 Hz, 1H), 3.56 (dd, J = 19.4, 13.6 Hz, 1H), 3.29 (br d, J = 10.7 Hz, 1H), 2.96 (dd, J = 19.4, 6.1 Hz, 1H), 2.74 (d, J = 16.6 Hz, 1H), 2.64 (dd, J = 13.1, 6.3 Hz, 1H), 2.38 (d, J = 16.6 Hz, 1H),

2.20 (s, 3H), 1.94 (s, 3H), 1.96−1.92 (m, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.42 (s, 3H), 0.22 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.00, 169.78, 168.98, 165.69, 159.92, 144.98, 129.18, 115.51, 83.45, 82.32, 76.37, 73.38, 72.74, 69.10, 52.61, 49.30, 46.47, 44.75, 42.72, 42.10, 39.86, 28.23, 27.65, 20.46, 17.10, 15.71, 0.87, 0.22. An analytical sample was prepared by recrystallization from ether−hexanes: mp 108.5−110 °C. High-resolution MS (EI) calcd for $C_{32}H_{48}O_{11}Si_2$ (M^+) *m/e* 664.2735, found 664.2738.

Synthetic 2. To a solution of 1.5 mg (0.023 mmol) of the silyl ether **25** in 100 μL of tetrahydrofuran were added 225 μL of a stock solution of $HF/CH_3CN/H_2O$ [stock solution is comprised of 17.2 mL of acetonitrile, 1.8 mL of water, and 1 mL of concd hydrofluoric acid (50%)]. The reaction was allowed to stir at room temperature for 6 h and was filtered through a small plug of silica gel. The filtrate was concentrated *in vacuo* and purified by preparative thin layer chromatography (methylene chloride/methanol were used to apply compound to prep TLC). Elution with ethyl acetate−hexanes (4:1) provided 0.8 mg (66%) of pentacyclic **2**: R_f 0.27 (ethyl acetate−hexanes, 4:1); IR ($CHCl_3$) 3439 (br m), 3018 (m), 2928 (m), 2856 (w), 1732 (s), 1705 (s), 1662 (s), 1636 (s), 1454 (w), 1387 (w), 1215 (s), 1141 (s), 1109 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_5D_4N) δ 10.11 (s, 1H, C_3 OH), 8.05 (d, J = 5.8 Hz, 1H, C_{12} OH), 6.75 (br s, 1H, C_{11} OH), 5.91 (br s, 1H), 5.62 (dd, J = 11.9, 2.6 Hz, 1H), 5.22 (d, J = 2.5 Hz, 1H), 5.15 (d, J = 7.4 Hz, 1H), 4.75 (t, J = 4.4 Hz, 1H), 4.29 (dd, J = 18.8 13.6 Hz, 1H), 3.93 (d, J = 7.5 Hz, 1H), 3.71 (br d, J = 11.9 Hz, 1H), 3.39 (dd, J = 19.1, 6.2 Hz, 1H), 3.35 (d, J = 16.7 Hz, 1H), 3.28 (dd, J = 13.0, 5.2 Hz, 1H), 3.35 (d, J = 16.7 Hz, 1H), 2.59 (d, J = 4.4 Hz, 1H), 2.29 (s, 3H), 2.25 (s, 3H), 1.85 (s, 3H), 1.72 (s, 3H); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 6.96 (s, 1H, C_3 OH), 5.81 (br s, 1H, $C_{2'}$), 5.20 (dd, J = 11.9, 2.8 Hz, 1H, C_6), 5.00 (br s, 1H, C_{12} OH), 4.79 (d, J = 2.5 Hz, 1H, C_7), 4.77 (d, J = 7.7 Hz, 1H, $C_{20\alpha}$), 4.26 (br s, 1H, C_{12}), 4.23 (br t, J = 5.0 Hz, 1H, C_{11}), 3.74 (s, 3H, CO_2Me), 3.70 (br d, J = 7.5 Hz, 1H, $C_{20\beta}$), 3.52 (dd, J = 18.7, 13.6 Hz, 1H, $C_{15\alpha}$), 3.40 (br d, J = 11.7 Hz, 1H, C_5), 2.94−2.72 (m, 3H, C_{14}, $C_{1\alpha}$, & $C_{1\beta}$), 2.70 (dd, J = 18.8, 6.0 Hz, 1H, $C_{15\beta}$), 2.26 (br d, J = 4.1 Hz, 1H, C_9), 2.20 (s, 3H), 1.95 (s, 3H), 1.86 (d, J = 1.6 Hz, 3H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, C_5D_4N) δ 192.45, 171.38, 169.20, 165.95, 159.12, 147.23, 128.57, 116.38, 83.66, 83.49, 77.91, 73.30, 72.80, 70.53, 52.24, 50.55, 46.70, 45.42, 43.57, 42.92, 40.13, 29.11, 27.22, 20.32, 17.09, 15.75. An analytical sample was prepared by recrystallization from ethyl acetate, mp 296−298 °C. Anal. Calcd for $C_{26}H_{32}O_{11}$: C, 59.99; H, 6.20. Found: C, 59.85; H, 6.15.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant CA28865 from the National Cancer Institute. We are grateful to Professor Okano for providing a sample of natural bruceoside C.

JO9605206