The relatively complex mutarotation and oxygen exchange of sugars result from a combination of more fundamental reaction processes. Thus, perhaps more appropriate than a comparison of mutarotation and oxygen exchange would be an examination of the relationship between ring-closing and hydration for the open-chain forms of the sugars. By comparing the rates for these two reactions the effective molarity[41] of the relevant backbone hydroxyl group may be estimated (Table IV). The magnitudes of the effective molarities listed in Table IV are in the range previously observed for cyclization reactions involving the hydroxyl group.[41] The values of the effective molarities for the two epimeric aldohexoses glucose and galactose are comparable, as are the values for fructose and its 1,6-diphosphate ester. For ring-closing reactions the effective molarity has generally been interpreted to be a measure of the entropic advantage enjoyed by intramolecular processes compared to intermolecular processes. This principle provides a reasonable explanation for the increased rate of mutarotation over oxygen exchange, thus eliminating the need to introduce novel acyclic intermediates into the tautomerization scheme.

The similarity between the kinetics and mechanism of the mutarotation of glucose and the hydration of acetaldehyde has been noted by several investigators.[18a,18b,42] Oxygen exchange studies can provide a more direct comparison, namely, with the actual hydration of glucose itself. Much of the attention in studies of glucose mutarotation and acetaldehyde hydration/dehydration has been focused on the question of whether proton transfer is coupled to carbon-oxygen bond formation/cleavage.[42] Nielsen and Sorensen have recently proposed that the degree of coupling between these two processes in the general base-catalyzed mutarotation of glucose changes with increasing basicity of the catalyst.[43] A related examination of the general base-catalyzed hydration of glucose might now be indicated.

Acknowledgment. This investigation was supported by U.S. Public Health Service Research Grant GM 27003 from the National Institute of General Medical Sciences and by instrumentation grants from the National Institutes of Health Division of Research Resources (RR 01077 and NSF/BBS-8714258). We appreciate the assistance of Dr. Claude R. Jones with the NMR instrumentation and Dr. John M. Risley for his comments on the manuscript and numerous helpful discussions.

Registry No. ^{18}O, 14797-71-8; ^{16}O, 7782-44-7; D-fructose, 57-48-7; D-mannose, 3458-28-4; α-D-fructopyranose, 10489-81-3; β-D-fructopyranose, 7660-25-5; α-D-fructofuranose, 10489-79-9; β-D-fructofuranose, 470-23-5; α-D-mannopyranose, 7296-15-3; β-D-mannopyranose, 7322-31-8; D-glucose, 50-99-7; α-D-glucopyranose, 492-62-6; β-D-glucopyranose, 492-61-5; α-D-glucofuranose, 36468-84-5; β-D-glucofuranose, 30412-16-9; acetone, 67-64-1; acetaldehyde, 75-07-0; D-fructose 1,6-diphosphate, 488-69-7; D-threose, 95-43-2; D-galactose, 59-23-4; 2,3,4,5-tetra-*O*-methyl-D-glucose, 4261-26-1; 2,3,4,5-tetra-*O*-methyl-D-mannose, 95120-16-4; 2,3,4,5-tetra-*O*-methyl-D-galactose, 69502-91-6.

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Synthesis of (±)-15-Deoxybruceolide and Conversion of (−)-15-Deoxybruceolide into (−)-Bruceantin: Total Synthesis of Bruceantin

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A total synthesis of bruceantin (1) using 15-deoxybruceolides **9** and **43** derived from naturally occurring brusatol as relay compounds was achieved. Previously reported ABCE tetracyclic compound **16** was converted into 11,12-*cis*-diol **30** bearing a suitable oxygen function at C-7. Ring D (δ-lactone) was formed by oxidation of a hydroxyl group at C-16 and selective removal of a C-7 hydroxyl protecting group to give **36**. Inversion of the stereochemistry of the hydroxyl group at C-11 was done by selective oxidation and reduction to give **12**. Enolate oxidation of the C-3 carbonyl group of **40**, which was derived from **12**, followed by bismuth trioxide oxidation yielded (±)-15-deoxybruceolide derivative **42**, which was further converted into acetate (±)-**43** and TBS ether (±)-**9**. Authentic specimens of **9**, **42**, and **43** were derived from naturally occurring brusatol (**3**) by using a radical-mediated deoxygenation of phenyl thiocarbonate **46**. Oxygenation at C-15 was achieved by oxidation of vinyl ethers **52** and **67**. Esterification of the C-15 hydroxyl group followed by acid-catalyzed hydrolysis of protecting groups at C-3, -11, and -12 gave bruceantin (1).

A wide spectrum of biological properties for the quassinoids, bitter principles isolated from the *Simaroubaceae* plants, has enormously increased interest in these highly oxygenated degraded triterpenes in recent years.[1] Among a large number of quassinoids,[1,2] some of those, which have been isolated from the genus *Brucea* and called bruceolides, display marked antileukemic activity. Bruceantin (**1**, Scheme I) and bruceantinol (**2**), isolated from *Brucea antidysenterica* Mill. by Kupchan and co-workers,[3] exhibited remarkably high antitumor activity. The quassinoids have many contiguous chiral centers and highly

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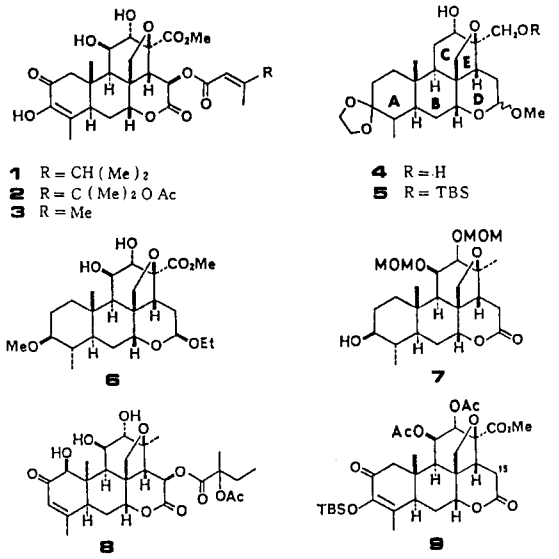
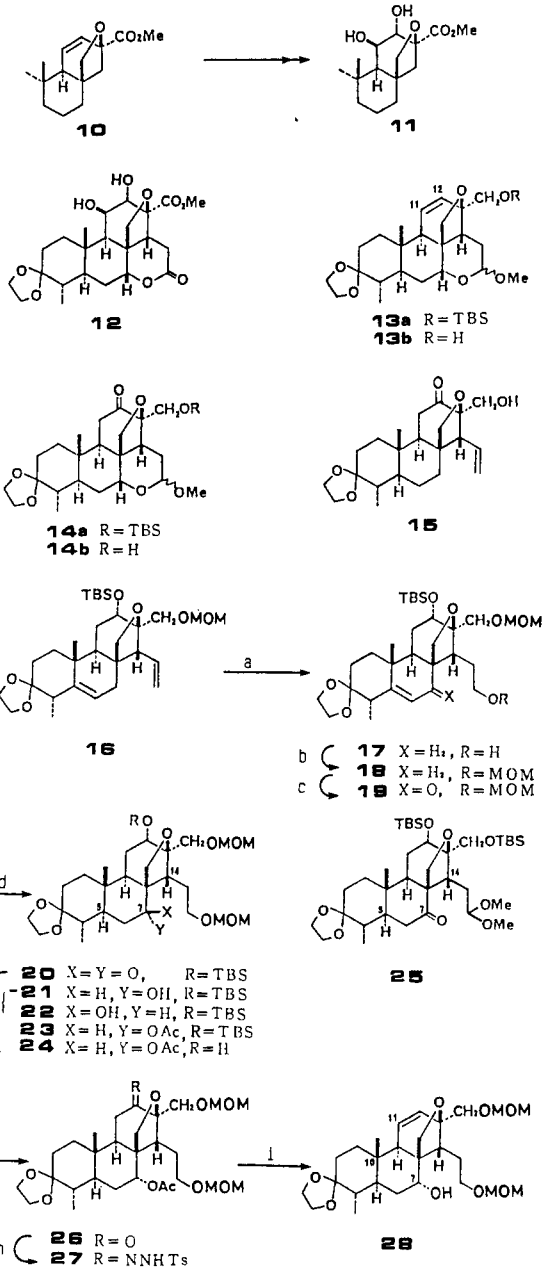
Scheme I



oxygenated carbon frameworks. Therefore, they attracted the attention of synthetic organic chemists as challenging target molecules, and numerous synthetic studies were undertaken.[4] After our report on the synthesis of compound 4[4ee,qq] bearing a complete bruceantin skeleton, two groups have described the preparation of pentacyclic derivatives 6[4hh] and 7,[4jj] as potential intermediates directed toward the total syntheses of bruceantin (1) and quassimarin (8), respectively. However, no report on the synthesis of the antitumor quassinoids has appeared except our preliminary report on the synthesis of (±)-15-deoxybruceolide ((±)-9)[5a] and conversion of (−)-15-deoxybruceolide ((−)-9), which was derived from naturally occurring brusatol (3), into (−)-bruceantin (1).[5b] In this paper we describe the details of the relay total synthesis of bruceantin (1).

Scheme II[a]



[a] (a) Thexylborane, THF, 0 °C; NaOH, H_2O_2; (b) CH_3OCH_2Cl, $(iPr)_2NEt$, CH_2Cl_2, 0 °C to room temperature; (c) CrO_3·2Pyr, CH_2Cl_2; (d) Li, NH_3, *t*-BuOH, THF, −78 then −33 °C; (e) $LiEt_3BH$, LiBr, THF, −78 °C to room temperature; (f) Ac_2O, DMAP, Pyr, CH_2Cl_2; (g) *n*-Bu_4NF, THF, 50 °C; (h) $TsNHNH_2$, TsOH, $MgSO_4$, THF; (i) MeLi, THF, 0 °C then room temperature.

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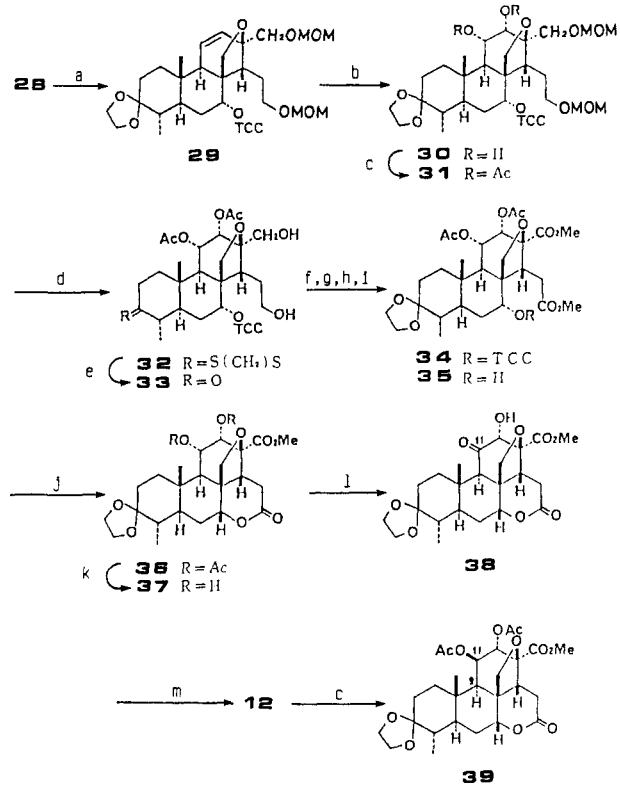
After completion of the synthesis of the skeletal compound 4, the functionalization of rings A, C, and D were required for the synthesis of bruceantin (1). Since functionalization of ring C of 4 required more complicated reactions than those of rings A and D, pentacyclic lactone 12 having complete ring C functionality was selected as the key intermediate from which bruceantin (1) and its congeners would be derived. For the synthesis of 12, we first examined functionalization of ring C of 4.

A synthetic method based on BCE ring model compound 11 was developed by Dailey and Fuchs,[4b] and we planned to adopt this procedure for the functionalization of ring C in 4 provided that we could prepare precursor olefin 13. However, none of the desired olefin 13a was obtained on dehydration of the secondary hydroxyl group of *tert*-butyldimethylsilyl (TBS) ether 5. Although the Shapiro reaction[6] to convert the pentacyclic tosylhydrazone derived from ketone 14 to the olefin 13 was also unsuccessful, examinations using tetracyclic compound 15 dictated the application of the Shapiro reaction to tetracyclic tosylhydrazone 27 (Scheme II). On the basis of this fact and the experience gained during the synthesis of 4[4ee,qq] as well as our retrosynthetic analysis, we considered that compound 16 (Scheme II), which had been prepared in route to 4,[4qq] would be a promising starting material.

Before the modification of ring C, oxygenation at C-7 and C-16 positions of the tetracyclic compound 16 needed for the future formation of ring D was accomplished by using the following reactions. Hydroboration–oxidation of 16 (Scheme II) using thexylborane[7] gave alcohol 17 in 96% yield, which was subsequently protected as the methoxymethyl (MOM) ether 18 quantitatively. Allylic oxidation at the C-7 position was carried out with a complex of 3,5-dimethylpyrazole and chromium trioxide[8] or with Collins' reagent[9] to give enone 19. For large-scale work, the Collins' oxidation was preferable with respect to ease of workup and yield. The enone 19 was subjected to reduction with lithium in ammonia, giving saturated ketone 20 in 37% yield from 18.

We anticipated a highly stereospecific reduction of the C-7 carbonyl group of 20 on the basis of an analogous reduction of ketone 25 during the synthesis of 4.[4ee,qq] However, treatment of 20 with $LiEt_3BH$ in THF at −78 °C gave 74% yield of desired 7_α-alcohol 21 and 23% yield of the undesired 7_β-alcohol 22, reflecting the influence of the less bulky OMOM protecting group in 20. For improvement of selectivity in this reduction of 20, chelation-controlled reduction[10] was examined. If a metal cation chelates between the C-7 carbonyl oxygen and the methoxymethoxyl group at C-16, the α-face of the carbonyl would be effectively blocked by the C-14 appendage, and hydride reduction would afford the desired alcohol 21 predominantly. Indeed, on treatment with $LiEt_3BH$ in the presence of 1 equiv of lithium bromide in THF, 20 yielded the desired 21 in 89% yield along with only a 10% yield of 22. The alcohols 21 and 22 were easily separated by column chromatography on silica gel, and the undesired β-alcohol 22 was oxidized with pyridinium dichromate (PDC)[11] to the starting ketone 20 in 84% yield and recycled. The alcohol 21 was converted to ketone 26 via acetate 23 and alcohol 24 in 96% overall yield of 26 from 21.

Scheme III[a]



[a] (a) CCl_3CH_2OCOCl, DMAP, Pyr, 0 °C then room temperature; (b) OsO_4, Pyr, THF; $NaHSO_3$; (c) Ac_2O, DMAP, CH_2Cl_2; (d) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C then room temperature; (e) NBS, $CaCO_3$, H_2O–CH_3CN; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C then room temperature; (g) CrO_3, H_2SO_4, acetone; (h) $CH_2N_2{\cdot}Et_2O$, AcOEt, 0 °C; (i) $(CH_2OH)_2$, TsOH, PhH, reflux; (j) Zn, AcOH–THF (1:9); Pyr; (k) KOMe, MeOH; (l) $(COCl)_2$, DMSO, $(iPr)_2NEt$, CH_2Cl_2, −78 °C then room temperature; (m) n-Bu_4NBH_4, AcOEt, 0 °C.

Introduction of the C-11 double bond, the initial step in the construction of ring C, was achieved by a Shapiro reaction. Conversion of the ketone 26 into tosylhydrazone 27 required excess reagent relative to the parallel reaction of 15, magnesium sulfate as water scavenger,[12] and longer reaction time (2 days) probably due to steric hindrance by MOM group at C-21. Treatment of 27 with methyllithium (excess) afforded hydroxy olefin 28 in 92% overall yield.

The formation of the undesired 12,16-lactone along with the desired 7,16-lactone on the hydrolysis of a C-7,12 diacetate necessitated different protecting groups at C-7 and C-12. The protecting group at C-7 would have to be sufficiently stable to subsequent reaction conditions (especially acidic conditions) and be selectively removed without disturbing the methoxymethyl and acetyl groups. The (2,2,2-trichloroethoxy)carbonyl (TCC) group[13] was a satisfactory protecting group for this purpose. Thus, trichloroethyl carbonate derivative 29 (Scheme III) was prepared by a treatment of 28 with 2,2,2-trichloroethyl chloroformate in the presence of a catalytic amount of DMAP in pyridine at room temperature in 98% yield. Osmium tetroxide oxidation of 29 gave diol 30 (88%), and acetylation afforded diacetate 31 (97%). The α-orientation of the vicinal diol was expected since the β-face of the

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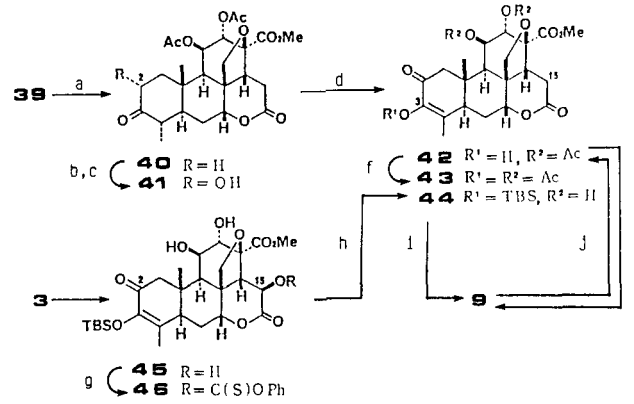
double bond of **29** was sterically hindered by ring E and the angular methyl group at C-10. This was confirmed by the analysis of the ^1H NMR spectrum of **31**: the large coupling constant between C-9 and C-11 protons (J = 12 Hz) indicated a trans-diaxial relationship between these protons. Removal of the methoxymethyl groups of **31** using TMSBr resulted in the formation of diol **33** in low yield, presumably due to the presence of TCC group in the molecule, contrary to literature claims for its stability.[14] When the deprotection was carried out according to the procedure of Fuji et al.[15] (ethanedithiol, $BF_3{\cdot}OEt_2$, dichloromethane, 0 °C), acetal–thioacetal exchange was observed along with cleavage of the methoxymethyl groups to afford thioacetal **32** in 97% yield. Removal of the thioacetal group of **32** was necessary prior to conversion of the primary hydroxyl groups into carbomethoxy groups, because **32** yielded many products on Jones' oxidation. Therefore, **32** was treated with *N*-bromosuccinimide in the presence of calcium carbonate in aqueous acetonitrile to give **33** in 92% yield.

The keto diol **33** was converted to diester **34** by the following sequence: Swern oxidation[16] to the dialdehyde, Jones' oxidation to dicarboxylic acid, diazomethane esterification, and protection of the carbonyl group at C-3 as its acetal under standard conditions. The overall yield of **34** from **33** was 82%. Although the dicarboxylic acid was obtained also by single-step oxidation of **33** using Jones' reagent, the yield in the single-step oxidation was inferior to that of the stepwise one in large-scale experiments.

The TCC group of **34** was selectively removed with zinc powder in acetic acid–THF (1:9) at room temperature. The product was a mixture of the desired pentacyclic lactone **36** and hydroxy diester **35**, which afforded additional **36** on heating in refluxing benzene containing pyridinium *p*-toluenesulfonate (PPTS). More conveniently, the reaction mixture obtained by the treatment with zinc was worked up with pyridine (excess) to effect pyridinium acetate mediated lactonization giving rise to **36** in 94% yield. The presence of the δ-lactone ring in **36** was indicated by the ^1H NMR spectrum; namely, a three-spin system typical of the δ-lactone moiety of quassinoids[17] was observed at δ 2.60 (dd, J = 14 and 5.5 Hz, 14-H), 2.96 (dd, J = 19 and 5.5 Hz, 15β-H), and 3.41 (dd, J = 19 and 14 Hz, 15α-H). Methanolysis of **36** with potassium methoxide in methanol gave **37** in 75% yield.

The remaining step for the synthesis of the key intermediate **12** was selective inversion of the configuration of the hydroxyl group at C-11. Initially, **37** was oxidized by the Fuchs' procedure (trifluoroacetic anhydride, DMSO, dichloromethane, −60 to −20 °C; aqueous sodium dihydrogen phosphate, 0 °C)[4b,hh] to give an unexpectedly low and variable yield (40–50%) of ketol **38**. Oxidation of **37** with pyridinium dichromate (PDC)[41] afforded **38** as sole product but also in disappointingly low yield (13%). After many trials, a satisfactory yield (98%) of **38** was realized by a treatment of **37** with 2 equiv of oxalyl chloride and 4 equiv of DMSO in dichloromethane at −78 °C for 30 min and then with 8 equiv of *N,N*-diisopropylethylamine at −78 °C to room temperature over 30 min. Extremely high

Scheme IV[a]



[a] (a) 2 M HCl, THF; (b) TMSOTf, Et_3N, CH_2Cl_2, −10 °C; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C; 2 M HCl; (d) Bi_2O_3, AcOH, reflux; (e) *t*-Bu(Me)$_2$SiCl, imidazole, DMF; (f) Ac_2O, DMAP, Pyr, CH_2Cl_2; (g) PhOC(S)Cl, DMAP, Pyr, 0 °C to room temperature; (h) *n*-Bu_3SnH, AIBN, toluene, reflux; (i) Ac_2O, DMAP, CH_2Cl_2; (j) *n*-Bu_4NF, THF, 0 °C.

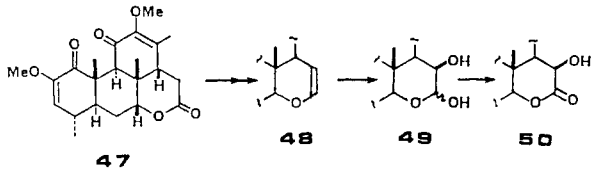
regioselectivity of the oxidation could be attributed to the steric hindrance around the C-12 axial hydroxyl group, which presumably disfavored formation of oxysulfonium salt at this position under the carefully controlled conditions mentioned above. Subsequent reduction of **38** with 4 equiv of *n*-Bu_4NBH_4 in ethyl acetate at 0 °C[4b,18] gave the desired trans-diaxial diol **12** in 60% yield. On acetylation under similar conditions as those used for preparation of previously mentioned acetates, the diol **12** afforded diacetate **39** in 85% yield, whose ^1H NMR spectrum (the coupling constant between C-9 and C-11 protons was J = 5 Hz) established the configuration of the C-11 hydroxyl group as β-axial.

Introduction of the bruceantin-type ring A functionality into the diol **12** would complete a synthesis of (±)-15-deoxybruceolide, a general precursor of bruceolides including bruceantin (**1**). This was achieved by the following reactions. The diacetate **39** (Scheme IV) was hydrolyzed with 2 M hydrochloric acid in THF to afford ketone **40** in 94% yield. The ketone **40** was next transformed into α-hydroxy ketone **41** via a three-step sequence in 39% overall yield: (i) Δ^2-enol silyl ether formation with trimethylsilyl trifluoromethanesulfonate[19] in the presence of triethylamine, (ii) peracid oxidation[20] (MCPBA, $NaHCO_3$), and (iii) acid treatment. Oxidation of the C-2 hydroxyl group of **41** was carried out with bismuth trioxide[21] in refluxing acetic acid to give diosphenol **42** in 72% yield. The UV maximum (274 nm) and bathochromic shift (322 nm) in alkali indicated the presence of the diosphenol moiety. TBS ether (±)-**9** and acetate (±)-**43** were derived from **42** for identification with authentic specimens, whose preparation are described below.

The authentic specimens of 15-deoxybruceolide derivatives **9**, **42**, and **43** were prepared from brusatol (**3**) isolated from *Brucea javanica* (L.) Merr.[22] After many trials, selective removal of the hydroxyl group at C-15 of 3-*O*-

(14) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.
(15) (a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662. (b) Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724.
(16) (a) Mancuso, A.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(17) Niimi, Y.; Tsuyuki, T.; Takahashi, T.; Matsusita, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1638, and references therein.
(18) (a) Brandstrom, A.; Junggren, U.; Lamm, B. *Tetrahedron Lett.* **1972**, 3173. (b) Raber, D. J.; Guida, W. C. *J. Org. Chem.* **1976**, *41*, 690.
(19) (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *23*, 3899, and references therein. (b) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953.
(20) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.
(21) Rigby, W. *J. Chem. Soc.* **1951**, 793.
(22) (a) Polonsky, J.; Baskevitch, Z.; Gaudemer, A.; Das, B. C. *Experientia* **1967**, *23*, 424. (b) Lee, K. H.; Imakura, Y.; Sumida, Y.; Wu, R.-Y.; Hall, I. H. *J. Org. Chem.* **1979**, *44*, 2180. (c) Sakaki, T.; Yoshimura, S.; Ishibashi, M.; Tsuyuki, T.; Takahashi, T.; Honda, T.; Nakanishi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2680.

Scheme V



(*tert*-butyldimethylsilyl)bruceolide (**45**), which was derived from brusatol (**3**) according to the methods described in the literature,[23b,24] was successfully carried out by a radical-mediated deoxygenation[25] of the phenyl thiocarbonate **46** using tributyltin hydride (AIBN, toluene, reflux) to give 15-deoxybruceolide derivative **44** in 65% yield from **45**. The structure of **44** was confirmed by the ^{1}H NMR spectrum; characteristic signals due to the methylene protons at C-15 were observed at δ 2.80 (dd, J = 19 and 6 Hz) and 3.59 (dd, J = 19 and 13.5 Hz).[17] Acetylation (acetic anhydride, DMAP, dichloromethane) of **44** gave the corresponding diacetate (−)-**9** in 73% yield. Desilylation of (−)-**9** using *n*-Bu_4NF was followed by acetylation to afford the triacetate (−)-**43** in 87% yield.

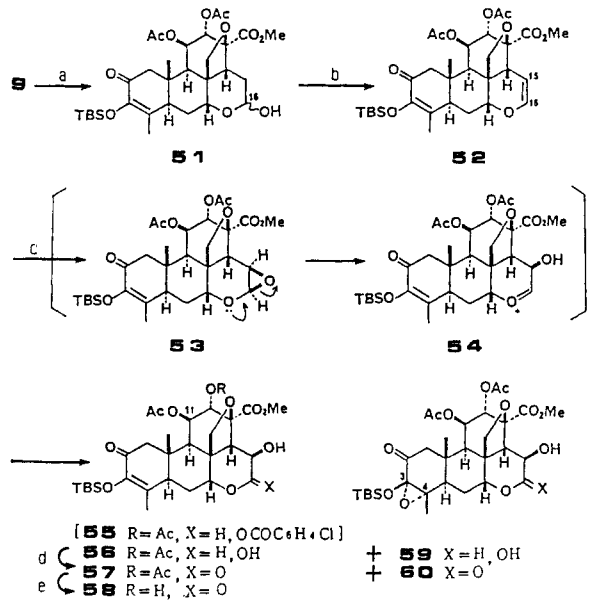
All spectral data for the totally synthesized racemate of 15-deoxybruceolide derivative (±)-**9** were identical with the authentic (−)-**9** excepting optical rotation ((−)-**9**: $[\alpha]_D^{26}$ −22° (*c* 0.44, $CHCl_3$)), thereby completing a total synthesis of a general precursor of bruceolides, (±)-15-deoxybruceolide. Since ample supplies of the 15-deoxybruceolide derivatives **9** and **43** were available through the degradation of brusatol (**3**), investigations of the remaining steps in the synthesis of bruceantin (**1**) were undertaken using (−)-**9** and (−)-**43** as "relay compounds".

The remaining step for the synthesis of bruceantin (**1**) required the functionalization of ring D and removal of protecting groups. In the case of **9** the following reactions were required: (i) regio- and stereoselective oxygenation at C-15, (ii) removal of the acetyl and TBS protecting groups, and (iii) selective esterification of the hydroxyl group at C-15.

We developed a method for oxygenation at C-15 of quassin **47** (Scheme V) to give **50** via vinyl ether **48** and hydroxyhemiacetal **49**.[26] Direct, single-step enolate oxidation reactions were used by Polonsky's[27] and Grieco's[28] groups. Application of the single-step reactions to the oxygenation at C-15 of **9** were unsuccessful.

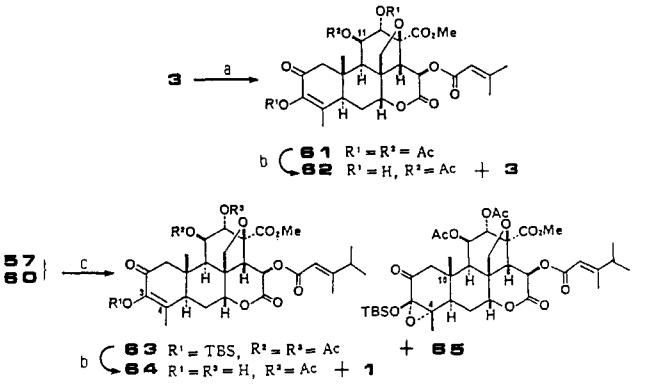
Reduction of the lactone (−)-**9** with 1 equiv of sodium borohydride in a mixture of ethanol and dichloromethane (2:1) at 0 °C gave **51** (Scheme VI) selectively as a mixture of diastereomers at C-16 (α:β = ca. 2:3)[29] in 87% yield. The mixture was subsequently treated with phosphoryl chloride in pyridine at 100 °C to give **52** in 67% yield. The ^{1}H NMR spectrum of **52** showed a characteristic three-spin system at δ 2.93 (m, 14-H), 5.12 (dd, J = 6 and 2 Hz, 15-H), and 6.42 (dd, J = 6 and 3 Hz, 16-H).

Scheme VI[a]



[a] (a) $NaBH_4$, EtOH, CH_2Cl_2, 0 °C; (b) $POCl_3$, Pyr, 100 °C; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, H_2O; (d) Ag_2O, MeCN, reflux; (e) KOMe, MeOH.

Scheme VII[a]



[a] (a) Ac_2O, DMAP, CH_2Cl_2; (b) 3 M H_2SO_4, MeOH, reflux; (c) $(Me)_2CH(Me)C{=}CHCO_2H$, DCC, DMAP, CH_2Cl_2.

Although hydroxyhemiacetal **49** was obtained in high yield on osmium tetroxide oxidation of the vinyl ether **48** in our previous study,[26] the vinyl ether **52** did not afford the desired hydroxyhemiacetal **56**. The isolated product of this reaction retained the D-ring double bond and was presumed to be an adduct of osmium tetroxide at the C-3(4) double bond of **52**. On the other hand, the major product obtained on MCPBA oxidation of **52** was 16-*O*-*m*-chlorobenzoylated hemiacetal **55**, whose structure was deduced on the basis of its ^{1}H NMR spectrum. This result suggested that epoxide **53** was extremely unstable and generated oxonium ion **54** that was attacked by a *m*-chlorobenzoate nucleophile from the β-side. Accordingly, if water was present in the reaction mixture, it should attack competitively at C-16 giving rise to **56**, and in fact, epoxidation in a two-phase solvent system[5b] (1:1 saturated aqueous $NaHCO_3$–dichloromethane) with vigorous stirring furnished **56** in 50–60% yield along with a small amount of **55**. However, the hydroxyhemiacetal **56** was contaminated with barely separable 3,4-epoxy derivative **59**. Therefore, all reactions from **56** to **1** were carried out on

(23) (a) Okano, M.; Lee, K. H. *J. Org. Chem.* **1981**, *46*, 1138. (b) Honda, T.; Imao, K.; Inoue, M.; Nakatsuka, N.; Tateoka, T.; Nakanishi, T. 103rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, Sendai, Apr 1983; Abstr, p 303.

(24) Sakaki, T.; Yoshimura, S.; Tsuyuki, T.; Takahashi, T.; Honda, T.; Nakanishi, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3541.

(25) (a) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932. (b) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

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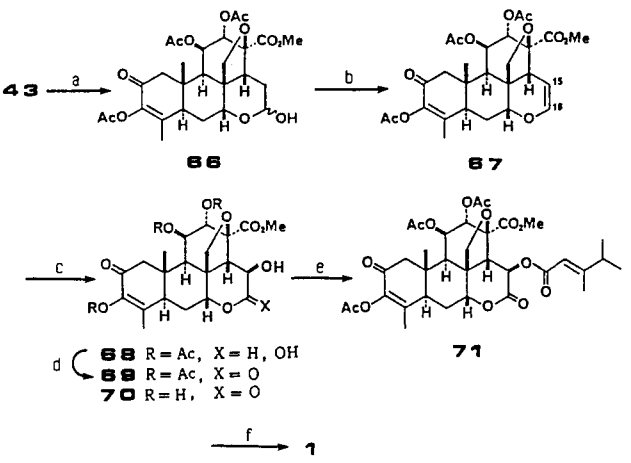
(27) (a) Carusso, A. J.; Polonsky, J. *Tetrahedron Lett.* **1982**, *23*, 2567. (b) Bhatnagar, S. C.; Caruso, A. J.; Polonsky, J. Tetrahedron **1987**, *43*, 3471.

(28) Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Jaw, J. Y.; Tu, S. *J. Org. Chem.* **1987**, *52*, 3346.

(29) The ratio was determined by the ^{1}H NMR spectrum in which the signal of 16-H due to the 16β-OH isomer appeared as a broad doublet (0.6 H, J = 2 Hz) at δ 5.47, while the corresponding signal due to the 16α-OH isomer appeared as a double doublet (0.4 H, J = 9 and 1.5 Hz) at δ 4.71.

Scheme VIII[a]



[a] (a) $NaBH_4$, EtOH, CH_2Cl_2, THF, 0 °C; (b) $POCl_3$, Pyr, 100 °C; (c) OsO_4, Pyr, THF; $NaHSO_3$, H_2O, Pyr; (d) Ag_2O, MeCN, 80 °C; (e) $(Me)_2CH(Me)C{=}CHCO_2H$, DMAP, DCC, CH_2Cl_2; (f) 3 M H_2SO_4, 12 M HCl, MeOH, reflux.

a mixture containing some of the corresponding 3,4-epoxide.

Oxidation of the mixture of **56** and **59** with silver(I) oxide (excess) in refluxing acetonitrile gave desired bruceolide derivative **57**[30] along with epoxide **60**.[31] The configuration at the C-15 position was confirmed by the coupling constant, J = 12.5 Hz, between 14-H (δ 2.81) and 15-H (δ 5.02) in the ^{1}H NMR spectrum.[30]

The next step in the synthesis toward bruceantin (**1**) required the removal of the acetyl groups of **57**, because the resulting triol **45** had already been converted to bruceantin (**1**).[23b] All results obtained on base-catalyzed hydrolysis of **57** were disappointing. For example, **58** was the only product characterized under mild conditions (potassium methoxide, methanol, room temperature), and decomposition occurred under forcing conditions (potassium hydroxide, methanol, reflux). However, it appeared that acid-catalyzed hydrolysis might work well in this case because 3,11,12-tri-*O*-acetylbrusatol (**61**, Scheme VII), prepared from brusatol (**3**), was hydrolyzed under acidic conditions [3 M H_2SO_4–methanol (1:1), reflux, 30 h] to give brusatol (**3**, 20% yield) along with 11-*O*-acetylbrusatol (**62**, 43% yield). Therefore, the mixture of **57** and **60** was esterified with 3,4-dimethyl-2-pentenoic acid[23a,26] by using *N,N'*-dicyclohexylcarbodiimide (DCC) and DMAP in dichloromethane at room temperature to give a mixture of 11,12-di-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)bruceantin (**63**) and its epoxide **65** in 72% yield. Acid hydrolysis of this mixture under the same conditions as those used for hydrolysis of **61** afforded bruceantin (**1**) and 11-*O*-acetylbruceantin (**64**) in 15% and 47% yields based on **63**, respectively. These products were isolated in the pure form, since the epoxide contaminant **65** decomposed under the hydrolysis conditions. The synthetic bruceantin (**1**) was identical with an authentic sample and thus completed the first total synthesis of bruceantin (**1**).

However, there still remained the problem of the oxidation of the vinyl ether **52** with MCPBA. The high reactivity of the C-3(4) double bond toward electrophiles was attributed to the electron-donating effect of the *tert*-butyldimethylsiloxy (TBS) group.[32] Therefore, if a protecting group having an electron-withdrawing nature such as an acetyl group was used instead of the TBS group, this problem would be overcome. With such a consideration, 3,11,12-tri-*O*-acetyl-15-deoxybruceolide (**43**, Scheme VIII) was converted to vinyl ether **67** via hemiacetal **66** in 53% yield. On MCPBA oxidation under the conditions used for the conversion of **52** to **56**, the vinyl ether **67** gave 15β-hydroxyhemiacetal **68** in 56% yield. As expected, the corresponding 3,4-epoxy derivative was not detected in the ^{1}H NMR spectrum of the oxidation product. The hydroxyhemiacetal **68** was also obtained exclusively in high yield (85%) on oxidation of **67** with osmium tetroxide.

The oxidation of the hydroxyhemiacetal **68** gave hydroxylactone **69** in 73% yield, which was esterified to afford the bruceantin derivative **71** in 81% yield. On acid hydrolysis under conditions similar to those used for the hydrolysis of **63**, the ester **71** afforded bruceantin (**1**) as the sole product in 19% yield.[33] Thus, an effective and selective route for total synthesis of bruceantin (**1**) was established.

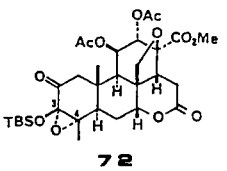
Experimental Section

Melting points are uncorrected. Reactions were run under Ar or N_2. Ether and THF were distilled from $LiAlH_4$, CH_2Cl_2 from P_2O_5, and EtOH and MeOH from Mg or CaH_2 under N_2. Hexane, benzene, toluene, pyridine, amines, DME, MeCN, DMF, DMSO, and dimethyl carbonate were distilled from CaH_2 and NH_3 from Na. CrO_3 was dried over P_2O_5 under reduced pressure. Column chromatography was performed with silica gel (Wakogel C-200). ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz), JEOL FX-90Q (90 MHz), Bruker WH-270 (270 MHz), JEOL GX-270 (270 MHz), or Bruker AM-500 (500 MHz) spectrometer, and ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.5 MHz), JEOL GX-270 (67.5 MHz), or Bruker AM-500 (125 MHz) spectrometer. The following abbreviations are used for peak multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. IR spectra were recorded on a Hitachi Model 260-30 or 270-30 grating infrared spectrophotometer, and UV spectra on a Hitachi 340 instrument. Low- and high-resolution mass spectra were determined on a JEOL JMS-D300 mass spectrometer in electron ionization mode at 70 eV.

1,2,3,4,4a,4b,5,6,8,10-Decahydro-3α-(*tert*-butyldimethylsiloxy)-1α-(2-hydroxyethyl)-4bβ,8α-dimethyl-2α-((methoxymethoxy)methyl)-7*H*-2β,10aβ-(epoxymethano)-phenanthren-7-one 7-(Ethylene acetal) (17). To a cold (0 °C) borane–THF solution (ca. 2 M in THF, 18 mL) in THF (100 mL) was added 2,3-dimethyl-2-butene (11 mL, 92 mmol) dropwise. After the mixture was stirred for 2 h at 0 °C, a solution of **16** (6.22 g, 11.6 mmol) in THF (60 mL) was added. After being stirred at 0 °C for 2 h and then at room temperature for 1 h, the reaction was quenched at 0 °C by the careful addition of water (5 mL) followed by addition of 3 M NaOH solution (30 mL) and 30%

(30) The assignment of the ^{1}H NMR spectrum of **57** was based on that of the authentic sample prepared from **45** through the following reactions: (i) triethylsilylation of the C-15 hydroxyl group, (ii) acetylation of the C-11 and C-12 hydroxyl groups, and (iii) removal of the C-15 hydroxyl protecting group.

(31) The structure of **60** was deduced by the comparison of the spectral data of the mixture of **60** and **57** with those of **72** obtained by epoxidation of (−)-**9** (94% yield). The chemical shift and the coupling constant of the C-4 methyl of **60** (δ 1.39, s) and of **57** (δ 1.85, d, J = 1.8 Hz) were almost the same as those of **72** (δ 1.40, s), and (−)-**9** (δ 1.86, d, J = 1.5 Hz), respectively. The downfield shift (ca. 0.25 ppm) of the 1-α proton observed on the epoxidation indicated α configuration of the epoxide ring.



(32) Negishi, E. *Organometallics in Organic Synthesis*; Willey: New York, 1980; Vol. 1, p 431.

(33) The low recovery of the reaction products was attributed to the formation of highly water-soluble compounds such as bruceolide **70** by intensive hydrolysis.

H_2O_2 solution (30 mL). After being stirred at 50 °C for 1 h, the mixture was cooled to room temperature and saturated with NaCl, extracted with ether (200 mL × 4), washed with brine (200 mL), and dried over $MgSO_4$. After filtration and concentration in vacuo, the residual material was purified by SiO_2 column chromatography (1:3–2:3 EtOAc/hexane) to afford alcohol **17** (6.17 g, 96%) as colorless crystals. An analytical sample was obtained by recrystallization from ether–hexane as colorless prisms: mp 129–130 °C; IR (neat) 3480 cm^{-1}; ^1H NMR (90 MHz) δ 0.89 (s, 9 H), 0.99 (d, J = 7 Hz, 3 H), 1.11 (s, 3 H), 3.37 (s, 3 H), 3.91 (m, 4 H), 4.25 (d, J = 8 Hz, 1 H), 4.67 (s, 2 H), 5.38 (m, 1 H); MS, m/z (rel intensity) 552 (M^+, 0.4), 521 (1), 463 (6), 433 (7), 99 (100); exact mass calcd for $C_{30}H_{52}O_7Si$ 552.3482, found 552.3472. Anal. Calcd for $C_{30}H_{52}O_7Si$: C, 65.47; H, 9.28. Found: C, 65.18; H, 9.48.

1,2,3,4,4a,4b,5,6,8,10-Decahydro-3α-(*tert*-butyldimethylsiloxy)-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (18). To a cold (0 °C) solution of **17** (5.94 g, 10.7 mmol) and *N,N*-diisopropylethylamine (6.4 mL, 37 mmol) in CH_2Cl_2 (150 mL) was added chloromethyl methyl ether (2.6 mL, 34 mmol). After being stirred at 0 °C for 10 min, the mixture was allowed to warm to room temperature (TLC monitoring) and subsequently poured into saturated aqueous $NaHCO_3$ (60 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 column chromatography (100 g, 1:3 EtOAc/hexane) to give bis(methoxymethyl) ether **18** (6.41 g, quantitative) as a colorless oil, which crystallized upon standing in a refrigerator. An analytical sample was obtained by recrystallization from hexane as colorless prisms: mp 109–110 °C; IR (neat) no absorption due to hydroxyl group; ^1H NMR (90 MHz) δ 0.89 (s, 9 H), 0.98 (d, J = 7 Hz, 3 H), 1.09 (s, 3 H), 3.34 (s, 3 H), 3.36 (s, 3 H), 3.90 (m, 4 H), 4.25 (1H, d, J = 8 Hz, 1 H), 4.56 (s, 2 H), 4.64 (s, 2 H), 5.37 (m, 1 H); MS, m/z (rel intensity) 596 (M^+, 4), 564 (10), 539 (4), 507 (11), 463 (19), 432 (19), 387 (35), 99 (over), 73 (100); exact mass calcd for $C_{32}H_{56}O_8Si$ 596.3746, found 596.3749.

1,2,3,4,4a,4b,5,6-Octahydro-3α-(*tert*-butyldimethylsiloxy)-4bβ,8α-dimethyl-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-7*H*-2β,10aβ-(epoxymethano)phenanthrene-7,10(8*H*)-dione 7-(Ethylene acetal) (19). To a flask containing pyridine (28 mL, 0.35 mol) and CH_2Cl_2 (500 mL) cooled to 0 °C was added portionwise chromium trioxide (17.5 g, 0.175 mol). After 80 min, 20 g of Celite was added, and the mixture was stirred at room temperature for 15 min. To the mixture was added a solution of **18** (5.16 g, 8.66 mmol) in CH_2Cl_2 (60 mL). After being stirred at room temperature for 16 h, the mixture was treated with 6.5 g (62 mmol) of $NaHSO_3$, diluted with ether (200 mL), and filtered through a florisil column (150 g) that was washed with EtOAc. The combined organic phases were concentrated in vacuo, and the residual oil was purified by SiO_2 column chromatography (100 g, 1:4–1:2 EtOAc/hexane) to afford essentially pure enone **19** (3.495 g) as a pale yellow oil, which was used in the next reaction without further purification. An analytical sample was obtained by recrystallization from ether–hexane as colorless prisms: mp 124–125.5 °C; IR (neat) 1655 cm^{-1}; ^1H NMR (90 MHz) δ 0.91 (s, 9 H), 1.06 (d, J = 6 Hz, 3 H), 1.23 (s, 3 H), 3.31 (s, 3 H), 3.37 (s, 3 H), 3.94 (m, 4 H), 4.12 (d, J = 8 Hz, 1 H), 4.50 (s, 2 H), 4.64 (s, 2 H), 5.94 (d, J = 2 Hz, 1 H); MS, m/z (rel intensity) 610 (M^+, 0.1), 579 (0.7), 553 (0.2), 477 (17), 446 (16), 99 (100). Anal. Calcd for $C_{32}H_{54}O_9Si$: C, 62.79; H, 8.73. Found: C, 62.92; H, 8.91.

1,2,3,4,4a,4b,5,6,8,8a-Decahydro-3α-(*tert*-butyldimethylsiloxy)-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-7*H*-2β,10aβ-(epoxymethano)phenanthrene-7,10(9*H*)-dione 7-(Ethylene acetal) (20). To a solution of lithium (ca. 270 mg, 39 mmol) in ammonia (200 mL) at −78 °C was added dropwise a solution of **19** (3.495 g, 5.73 mmol) in THF (40 mL) containing *tert*-butyl alcohol (0.4 mL). The reaction mixture was stirred at −78 °C for 10 min and warmed to −33 °C. After 1 h, the reaction was quenched by addition of isoprene (2 mL). Addition of solid NH_4Cl (6 g) and evaporation of the ammonia gave a residue, which was taken up in saturated aqueous NH_4Cl (70 mL) and extracted with CH_2Cl_2 (100 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 100 g, 20–30% EtOAc/hexane) of the residue afforded ketone **20** (1.9496 g, 37% yield from **18**) as colorless crystals. An analytical sample was obtained by recrystallization from ether–hexane as colorless prisms: mp 152–153 °C; IR (KBr) 1690 cm^{-1}; ^1H NMR (90 MHz) δ 0.80–0.95 (12 H), 0.97 (s, 3 H), 3.33 (s, 3 H), 3.35 (s, 3 H), 3.93 (m, 4 H), 4.15 (d, J = 8 Hz, 1 H), 4.49 (s, 2 H), 4.63 (s, 2 H); MS, m/z (rel intensity) 580 (0.1), 555 (1.8), 551 (2), 479 (22), 449 (over), 99 (100). Anal. Calcd for $C_{32}H_{56}O_9Si$: C, 62.71; H, 9.21. Found: C, 63.00; H, 9.03.

1,2,3,4,4a,4b,5,6,8,8a,9,10-Dodecahydro-3α-(*tert*-butyldimethylsiloxy)-10α-hydroxy-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (21). To a cold (−78 °C) solution of lithium bromide (38 mg, 0.44 mmol) in THF (2.5 mL) was added dropwise a solution of **20** (262 mg, 0.43 mmol) in THF (10 mL). After the mixture was stirred at −78 °C for 1 h, $LiEt_3BH$ (ca. 1 M THF solution, 3.5 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by the careful addition of water, followed by the addition of 3 M NaOH solution and 30% H_2O_2 solution. The resulting mixture was stirred at room temperature for 1 h, poured into brine, extracted with $CHCl_3$, and dried ($MgSO_4$). Removal of the solvent followed by chromatography (SiO_2, 10 g, 1:2–2:1 EtOAc/hexane) afforded, in order of elution, 7α-alcohol **21** (235 mg, 89% yield) and 7β-alcohol **22** (25.8 mg, 10% yield). An analytical sample of **21** was obtained by recrystallization from hexane as colorless prisms: mp 110–113 °C; IR (neat) 3500 cm^{-1}; ^1H NMR (90 MHz) δ 0.75–1.00 (15 H), 3.37 (s, 6 H), 3.92 (m, 4 H), 4.11 (d, J = 8 Hz, 1 H), 4.34 (m, 1 H, OH exchangeable with D_2O), 4.61 (s, 2 H), 4.63 (s, 2 H); MS, m/z (rel intensity) 614 (M^+, 0.1), 553 (3), 526 (7), 481 (24), 463 (15), 451 (100), 433 (26), 389 (22), 99 (over), 73 (76); exact mass calcd for $C_{30}H_{53}O_7Si$ ($M - CH_3OCH_2O$) 553.3562, found 553.3584. 7β-alcohol **22**: IR (neat) 3470 cm^{-1}; ^1H NMR (90 MHz) δ 0.8–0.95 (15 H), 3.37 (s, 6 H), 3.92 (br s, 4 H), 4.58 (s, 2 H), 4.64 (s, 2 H); MS, m/z (rel intensity) 583 (0.8), 553 (0.2), 495 (7), 481 (14), 463 (14), 451 (23), 99 (100).

Oxidation of 22 into 20. To a solution of the 7β-alcohol **22** (312.4 mg, 0.509 mmol) in CH_2Cl_2 (10 mL) containing 3A molecular sieves was added PDC (390 mg, 1.03 mmol). The resulting suspension was stirred at room temperature for 18 h, diluted with ether, and passed through a florisil column (10 g) that was washed further with EtOAc. The filtrate and the washes were combined and concentrated in vacuo. Chromatography (SiO_2, 10 g, 1:3–1:2 EtOAc/hexane) yielded **20** (262 mg, 84% yield).

1,2,3,4,4a,4b,5,6,8,8a,9,10-Dodecahydro-10α-acetoxy-3α-(*tert*-butyldimethylsiloxy)-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (23). To a solution of **21** (2.0661 g, 3.36 mmol), DMAP (50 mg, 0.41 mmol), and pyridine (3 mL, 37 mmol) in CH_2Cl_2 (50 mL) was added acetic anhydride (2 mL, 21 mmol), and the mixture was stirred at room temp overnight. Methanol was added to the mixture at 0 °C, and the volatiles were removed in vacuo. The residue was purified by SiO_2 column chromatography (50 g, 1:2 EtOAc/hexane) to yield acetate **23** (2.1531 g, 97% yield) as a colorless oil that crystallized upon standing. An analytical sample was obtained by recrystallization from hexane as colorless needles: mp 113–116 °C; IR (neat) 1730 cm^{-1}; ^1H NMR (90 MHz) δ 0.8–1.0 (15 H), 2.08 (s, 3 H), 3.31 (s, 3 H), 3.35 (s, 3 H), 3.93 (m, 4 H), 4.18 (d, J = 8 Hz, 1 H), 4.53 (s, 2 H), 4.62 (s, 2 H), 5.00 (m, 1 H); MS, m/z (rel intensity) 656 (M^+, 0.2), 624 (0.4), 599 (0.5), 523 (26), 492 (34), 463 (100), 433 (81), 99 (over), 73 (79); exact mass calcd for $C_{34}H_{60}O_{10}Si$ 656.3955, found 656.3915.

1,2,3,4,4a,4b,5,6,8,8a,9,10-Dodecahydro-10α-acetoxy-1α-[2-(methoxymethoxy)ethyl]-3α-hydroxy-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (24). To a solution of **23** (2.1531 g, 3.28 mmol) in THF (20 mL) under argon was added a solution of *n*-Bu_4NF (2.67 g, 10.4 mmol) in THF (20 mL). After being stirred at 50 °C for 3 h, the mixture was cooled to room temperature, poured into saturated aqueous $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (100 mL × 3). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography

(50 g, 15–20% acetone in CH_2Cl_2) to give **24** (1.7854 g, quantitative) as colorless amorphous solids: IR (neat) 3480, 1730 cm^{-1}; ^1H NMR (90 MHz) δ 0.72 (d, J = 6 Hz, 3 H), 0.95 (s, 3 H), 2.10 (s, 3 H), 3.34 (s, 3 H), 3.38 (s, 3 H), 3.92 (m, 4 H), 4.18 (d, J = 8 Hz, 1 H), 4.55 (s, 2 H), 4.64 (s, 2 H), 4.97 (m, 1 H); MS, m/z (rel intensity) 542 (M^+, 0.8), 524 (0.1), 510 (3), 480 (8), 405 (42), 345 (36), 100 (100), 99 (over); exact mass calcd for $C_{27}H_{42}O_9$ ($M^+ - CH_3OH$) 510.2829, found 510.2810.

1,2,4a,4b,5,6,8,8a,9,10-Decahydro-10α-acetoxy-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-7*H*-2β,10aβ-(epoxymethano)phenanthrene-3,7-(4*H*)-dione 7-(Ethylene acetal) (26). To a flask containing pyridine (4 mL, 49 mmol) and CH_2Cl_2 (50 mL) was added portionwise chromium trioxide (1.98 g, 19.8 mmol) over 5 min. After the mixture was stirred for 1 h, a solution of **24** (1.7854 g, 3.29 mmol) in CH_2Cl_2 (30 mL) was added. After being stirred for 30 min, the reaction mixture was diluted with EtOAc (100 mL), and the organic phase was separated. The brown residue was dissolved in saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (100 mL × 2), and the combined organic extract was washed with aqueous $NaHSO_3$ (50 mL × 2), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 50 g, 5–10% acetone in CH_2Cl_2) of the residue yielded ketone **26** (1.7604 g, 99%) as colorless crystals. An analytical sample was obtained by recrystallization from ether–hexane as colorless needles: mp 85–87 °C; IR (neat) 1720, 1740 cm^{-1}; ^1H NMR (90 MHz) δ 0.74 (d, J = 6 Hz, 3 H), 1.05 (s, 3 H), 2.12 (s, 3 H), 3.34 (s, 3 H), 3.39 (s, 3 H), 3.93 (m, 4 H), 4.51 (d, J = 8 Hz, 1 H), 4.53 (s, 2 H), 4.62 (s, 2 H), 5.12 (m, 1 H); MS, m/z (rel intensity) 540 (M^+, 7), 508 (4), 478 (8), 464 (15), 433 (50), 419 (16), 392 (28), 100 (100), 99 (over); exact mass calcd for $C_{28}H_{44}O_{10}$ 540.2934, found 540.2913.

1,2,4a,4b,5,6,8,8a,9,10-Decahydro-10α-hydroxy-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (28). A solution of **26** (198.8 mg, 0.368 mmol), $TsNHNH_2$ (350 mg, 1.88 mmol), $TsOH·H_2O$ (20 mg, 0.1 mmol), and anhydrous magnesium sulfate (450 mg, 3.74 mmol) in THF (8 mL) was stirred at room temperature for 2 days. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (40 mL) and extracted with $CHCl_3$ (50 mL × 3). Drying ($MgSO_4$) followed by evaporation of the solvent afforded crude tosylhydrazone **27**, which was dried over P_2O_5 under reduced pressure for 1 h.

The crude tosylhydrazone **27** was dissolved in THF (25 mL) and treated with methyllithium (1.06 M ether solution, 10 mL, 10.6 mmol) at 0 °C. After being stirred at 0 °C for 1 h and at room temperature for 2 h, the reaction was quenched by the careful addition of water at 0 °C. The solution was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (50 mL × 3). The combined extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (SiO_2, 20 g, 10–15% acetone/benzene) to afford olefin **28** (163 mg, 92%) as colorless solids. An analytical sample was obtained by recrystallization from EtOAc–hexane as colorless plates: mp 136.5–137.5 °C; IR (KBr) 3500 cm^{-1}; ^1H NMR (90 MHz) δ 0.80 (d, J = 6 Hz, 3 H), 0.94 (s, 3 H), 3.44 (s, 6 H), 3.93 (m, 4 H), 4.28 (d, J = 9 Hz, 1 H), 4.64 (s, 2 H), 4.68 (s, 2 H), 5.57 (br d, J = 10 Hz, 1 H, 11-H), 5.89 (br d, J = 10 Hz, 1 H, 12-H); MS, m/z (rel intensity) 482 (M^+, 0.2), 450 (4.7), 420 (0.5), 419 (0.5), 406 (1.7), 99 (100); exact mass calcd for $C_{26}H_{42}O_8$ 482.2879, found 482.2890.

1,2,4a,4b,5,6,8,8a,9,10-Decahydro-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-10α-[((2,2,2-trichloroethoxy)carbonyl)oxy]-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (29). To a cold (0 °C) solution of **28** (1.1549 g, 2.40 mmol) and DMAP (60 mg, 0.49 mmol) in pyridine was added dropwise 2,2,2-trichloroethyl chloroformate (1.65 mL, 12.0 mmol). After being stirred at 0 °C for 10 min and at room temperature overnight, the reaction was quenched by the addition of water (2 mL) at 0 °C. The solvent of the reaction mixture was evaporated in vacuo. The residue was taken up in saturated aqueous $NaHCO_3$ (50 mL), extracted with CH_2Cl_2 (100 mL × 3), and dried. Removal of the solvent followed by chromatography (SiO_2, 50 g, 5–10% acetone/benzene) yielded trichloroethyl carbonate **29** (1.4632 g, 93%) as a colorless viscous oil: IR (neat) 1750 cm^{-1}; ^1H NMR (90 MHz) δ 0.74 (d, J = 6 Hz, 3 H), 0.98 (s, 3 H), 3.38 (s, 3 H), 3.42 (s, 3 H), 3.94 (br s, 4 H), 4.32 (d, J = 9 Hz, 1 H), 4.57 (s, 2 H), 4.68 (s, 2 H), 4.77 (ABq, J = 12 Hz, $\Delta\nu_{AB}$ = 17 Hz, 2 H, OCH_2CCl_3), 5.63 (br d, J = 10 Hz, 1 H), 5.89 (br d, J = 10 Hz, 1 H); MS, m/z (rel intensity) 660 ($[M + 4]^+$, 0.3), 658 ($[M + 2]^+$, 0.8), 656 (M^+, 0.8), 99 (100); exact mass calcd for $C_{29}H_{43}O_{10}Cl_3$ 656.1922, found 656.1966.

1,2,3,4,4a,4b,5,6,8,8a,9,10-Dodecahydro-3α,4α-dihydroxy-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-10α-[((2,2,2-trichloroethoxy)carbonyl)oxy]-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (30). To a solution of **29** (1.513 g, 2.31 mmol) in THF (20 mL) and pyridine (4 mL) was added osmium tetroxide (715.3 mg, 2.81 mmol) in one portion, and the mixture was stirred at room temperature overnight. A solution of $NaHSO_3$ (1.8 g, 17.3 mmol) in water (10 mL) and pyridine (2 mL) was added, and the resulting mixture was stirred at room temperature for 3 h. The solution was poured into brine (50 mL) and extracted with EtOAc (70 mL × 4). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL) and then dried ($MgSO_4$). Concentration in vacuo followed by chromatography (SiO_2, 50 g, 2–3% $MeOH/CH_2Cl_2$) afforded **30** (1.4016 g, 88%) as a colorless viscous oil, which crystallized upon standing. An analytical sample was obtained by recrystallization from ether as colorless prisms: mp 141.5–143 °C; IR (neat) 3430, 1755 cm^{-1}; ^1H NMR (90 MHz) δ 0.72 (d, J = 5 Hz, 3 H), 1.14 (s, 3 H), 3.36 (s, 3 H), 3.40 (s, 3 H), 3.91 (br s, 4 H), 4.15 (d, J = 8 Hz, 1 H), 4.54 (s, 2 H), 4.65 (s, 2 H), 4.75 (ABq, J = 12 Hz, $\Delta\nu_{AB}$ = 15 Hz, 2 H); MS, m/z (rel intensity) 674 ($[M - H_2O + 2]^+$, 0.4), 672 (0.4), 6.42 (0.5), 640 (0.5), 100 (100), 99 (over); exact mass calcd for $C_{28}H_{39}O_{10}Cl_3$ ($M - CH_3OH - H_2O$) 640.1609, found 640.1586.

1,2,3,4,4a,4b,5,6,8,8a,9,10-Dodecahydro-3α,4α-diacetoxy-1α-[2-(methoxymethoxy)ethyl]-2α-((methoxymethoxy)methyl)-4bβ,8α-dimethyl-10α-[((2,2,2-trichloroethoxy)carbonyl)oxy]-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (31). To a solution of **30** (1.3761 g, 1.99 mmol) and DMAP (0.74 g, 6.1 mmol) in CH_2Cl_2 (40 mL) was added acetic anhydride (1.9 mL, 20 mmol). After being stirred at room temperature for 100 min (TLC monitoring), the reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with $CHCl_3$ (50 mL × 3). Drying ($MgSO_4$) of the combined organic extract was followed by removal of the solvent in vacuo and chromatography (SiO_2, 50 g, 10–15% acetone/benzene) to give **31** (1.5022 g, 97%) as colorless crystals. An analytical sample was obtained by recrystallization from ether as colorless prisms: mp 136–139 °C; IR (neat) 1755 cm^{-1}; ^1H NMR (90 MHz) δ 0.72 (d, J = 6 Hz, 3 H), 1.05 (s, 3 H), 1.94 (s, 3 H), 2.07 (s, 3 H), 2.22 (d, J = 5 Hz, 1 H, 9-H), 3.33 (s, 3 H), 3.36 (s, 3 H), 3.90 (br s, 4 H), 4.26 (d, J = 8 Hz, 1 H), 4.56 (s, 4 H, 2 × OCH_2O), 4.77 (ABq, J = 12 Hz, $\Delta\nu_{AB}$ = 16 Hz, 2 H), 5.33 (br d, J = 5 Hz, 1 H), 5.58 (dd, J = 5, 12 Hz, 1 H, 11-H); MS, m/z (rel intensity) 778 ($[M + 4]^+$, 0.1), 776 ($[M + 2]^+$, 0.2), 774 (M^+, 0.2), 99 (100). Anal. Calcd for $C_{33}H_{49}O_{14}Cl_3$: C, 51.07; H, 6.36; Cl, 13.70. Found: C, 50.89; H, 6.36; Cl, 13.63.

1,2,3,4,4a,4b,5,6,8,8a,9,10-Dodecahydro-3α,4α-diacetoxy-1α-(2-hydroxyethyl)-2α-(hydroxymethyl)-4bβ,8α-dimethyl-10α-[((2,2,2-trichloroethoxy)carbonyl)oxy]-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one (33). To a solution of **31** (1.4697 g, 1.90 mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C was added ethanedithiol (1.4 mL, 16 mmol) and then $BF_3·OEt_2$ (0.5 mL, 4.1 mmol). After stirring at 0 °C for 1 h, additional $BF_3·OEt_2$ (1.8 mL, 15 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min and warmed to room temperature, and the stirring was continued for 40 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (40 mL) and extracted with $CHCl_3$ (50 mL × 3). The combined organic extract was dried ($MgSO_4$) and evaporated. Chromatography (SiO_2, 40 g, 3% $MeOH/CH_2Cl_2$) afforded **32** (1.324 g, 97%) as colorless crystals, which was used in the next reaction without further purification.

To a solution of **32** (1.324 g) and calcium carbonate (1.48 g, 14.8 mmol) in 20% aqueous MeCN (70 mL) was added *N*-bromosuccinimide (1.33 g, 7.19 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with Na_2SO_3 (1.94 g, 15.4 mmol) and stirred for a further 5 min. Insoluble solids were filtered off, and the filtrate was concentrated in vacuo. The

residue was taken up in 1 M HCl solution (40 mL) and extracted with $CHCl_3$. The organic extract was washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent followed by chromatography (SiO_2, 40 g, 4% MeOH in CH_2Cl_2) yielded **33** (1.0857 g, 89% from **31**) as colorless crystals. An analytical sample was obtained by recrystallization from acetone–hexane as colorless prisms: mp 189–191 °C; IR (KBr) 3470, 1750, 1710 cm^{-1}; ^1H NMR (90 MHz) δ 0.94 (d, J = 6 Hz, 3 H), 1.22 (s, 3 H), 1.97 (s, 3 H), 2.11 (s, 3 H), 4.24 (d, J = 8 Hz, 1 H), 4.78 (s, 2 H), 4.88 (m, 1 H, 7-H), 5.06 (d, J = 5 Hz, 1 H), 5.56 (dd, J = 11 and 5 Hz, 1 H); MS, m/z (rel intensity) 626 ([M – H_2O + 2]$^+$, 0.7), 624 (1), 566 (1.9), 564 (1.7), 553 (4), 551 (4), 77 (100). Anal. Calcd for $C_{27}H_{37}O_{11}Cl_3$: C, 50.36; H, 5.79; Cl, 16.52. Found: C, 50.09; H, 5.78; Cl, 16.16.

1,2,3,4,4a,4b,5,6,8,8a,9,10-Dodecahydro-3α,4α-diacetoxy-2α-(methoxycarbonyl)-1α-((methoxycarbonyl)methyl)-4bβ,8α-dimethyl-10α-[((2,2,2-trichloroethoxy)carbonyl)oxy]-7*H*-2β,10aβ-(epoxymethano)phenanthren-7-one 7-(Ethylene acetal) (34). To a cold (–78 °C) solution of oxalyl chloride (0.06 mL, 0.69 mmol) in CH_2Cl_2 (1 mL) was added dropwise a solution of DMSO (0.08 mL, 1.1 mmol) in CH_2Cl_2 (1 mL). After 3 min, a solution of the diol **33** (101 mg, 0.16 mmol) in CH_2Cl_2 (4 mL) was added dropwise to the mixture. After this was stirred at –78 °C for 15 min, to the reaction mixture was added triethylamine (0.3 mL, 2.2 mmol), and the stirring was continued for 15 min at –78 °C. The reaction mixture was allowed to warm to room temperature over 30 min, whereupon the reaction quenched by addition of water (10 mL). The mixture was extracted with CH_2Cl_2 (20 mL × 2), and combined organic extract was dried over $MgSO_4$. Removal of the solvent gave the crude dialdehyde, which was immediately used in the next reaction without further purification.

The dialdehyde was dissolved in acetone (5 mL) cooled to 0 °C and treated with Jones' reagent (0.3 mL). After the mixture was stirred at room temperature for 3 h, the reaction was quenched by addition of isopropyl alcohol. The solvent was removed in vacuo, and the residue was taken up in 1 M HCl solution (5 mL) and extracted with EtOAc (15 mL × 3). Drying ($MgSO_4$) and evaporation of the solvent gave the crude diacid, which was dissolved in EtOAc cooled to 0 °C and treated with ethereal diazomethane. After 5 min, excess diazomethane was decomposed by addition of acetic acid, and the solvent was removed in vacuo to give the crude diester, which was immediately used in the next reaction.

A mixture of the above diester, a catalytic amount of $TsOH·H_2O$, and ethylene glycol (0.1 mL) in benzene (10 mL) was heated at reflux for 40 min. The reaction mixture was cooled to room temperature, poured into saturated aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc (30 mL × 1, 15 mL × 1). The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (SiO_2, 10 g, 1:9 acetone/benzene) to give diester **34** (95.6 mg, 82% overall yield from **33**). An analytical sample was obtained by recrystallization from ether–EtOAc as colorless prisms: mp 224–226 °C; IR (neat) 1755 cm^{-1}; ^1H NMR (270 MHz) δ 0.65 (d, J = 7 Hz, 3 H), 1.01 (s, 3 H), 1.91 (s, 3 H), 2.04 (s, 3 H), 3.62 (s, 3 H), 3.68 (s, 3 H), 3.78–3.96 (m, 4 H), 4.32 (d, J = 9 Hz, 1 H), 4.47 (d, J = 12 Hz, 1 H), 4.82 (br d, J = 2 Hz, 1 H, 7-H), 5.01 (d, J = 12 Hz, 1 H), 5.46–5.59 (m, 2 H); MS, m/z (rel intensity) 746 ([M + 4]$^+$, 0.8), 7.44 ([M + 2]$^+$, 2.4), 742 (M$^+$, 2.5), 673 (0.8), 671 (2.6), 669 (2.5), 627 (0.5), 625 (0.4), 613 (0.6), 611 (1.8), 609 (2.0), 99 (100). Anal. Calcd for $C_{31}H_{41}O_{14}Cl_3$: C, 50.04; H, 5.55; Cl, 14.29. Found: C, 49.80; H, 5.54; Cl, 13.87.

11α,12α-Diacetoxy-13,20-epoxy-3,3-(ethylenedioxy)-16-oxopicrasan-21-oic Acid Methyl Ester (36). To a solution of **34** (807.2 mg, 1.09 mmol) in THF (18 mL) and acetic acid (2 mL) was added freshly activated zinc powder. After 2 h, pyridine (3 mL) was added to the reaction mixture, and insoluble solids were filtered through Celite that was washed with EtOAc. The filtrate and the washes were combined, and toluene was added to the combined solution, which was then concentrated in vacuo. The addition and evaporation of toluene were repeated three times. Column chromatography (SiO_2, 30 g, 2% MeOH/$CHCl_3$) followed by crystallization from ether–CH_2Cl_2 to give lactone **36** (0.55 g, 94%) as colorless crystals. An analytical sample was obtained by recrystallization from ether–EtOAc as colorless prisms: mp 248–249 °C; IR (KBr) 1740 cm^{-1}; ^1H NMR (270 MHz) δ 0.82 (d, J = 6.5 Hz, 3 H), 1.06 (s, 3 H), 1.95 (s, 3 H), 2.06 (s, 3 H), 2.60 (dd, J = 14, 5.5 Hz, 1 H, 14-H), 2.96 (dd, J = 19, 5.5 Hz, 1 H, 15β-H), 3.41 (dd, J = 19, 14 Hz, 1 H, 15α-H), 3.56 (br d, J = 9 Hz, 1 H), 3.76 (s, 3 H), 3.89–4.00 (m, 4 H), 4.44–4.54 (m, 2 H), 5.59–5.68 (m, 2 H); MS, m/z (rel intensity) 536 (M$^+$, 1), 99 (100); exact mass calcd for $C_{27}H_{36}O_{11}$ 536.2257, found 536.2267.

13,20-Epoxy-3,3-(ethylenedioxy)-11α,12α-dihydroxy-16-oxopicrasan-21-oic Acid Methyl Ester (37). To a solution of **36** (460.8 mg, 0.86 mmol) in methanol (20 mL) was added 0.5 M potassium methoxide in methanol (2.5 mL), and the resultant mixture was stirred at room temperature for 43 h. Acetic acid (0.7 mL) and then pyridine (3.5 mL) were added to the reaction mixture, and the solvent was removed in vacuo. The residue was taken up in saturated aqueous $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (50 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by SiO_2 chromatography (30 g, 3% MeOH/$CHCl_3$) to give diol **37** (292.7 mg, 75%) as colorless crystals. An analytical sample was obtained by recrystallization from ether–EtOAc as colorless prisms: mp 241–245 °C; IR (KBr) 3450, 1740 cm^{-1}; ^1H NMR (270 MHz) δ 0.80 (d, J = 6 Hz, 3 H), 1.11 (s, 3 H), 2.45 (br dd, J = 13.5, 5.5 Hz, 1 H, 14-H), 2.76 (dd, J = 18.5, 5.5 Hz, 1 H, 15β-H), 3.43 (m, 1 H, OH), 3.51 (br d, J = 8 Hz, 1 H), 3.55 (dd, J = 18.5, 13.5 Hz, 1 H, 15α-H), 3.83 (s, 3), 3.86–4.02 (m, 4 H), 4.19 (m, 2 H), 4.36 (d, J = 8 Hz, 1 H), 4.44 (t-like, J = 3 Hz, 1 H, 7-H); MS, m/z (rel intensity) 452 (M$^+$, 0.8), 99 (100); exact mass calcd for $C_{23}H_{32}O_9$ 452.2046, found 452.2041.

13,20-Epoxy-3,3-(ethylenedioxy)-12α-hydroxy-11,16-dioxopicrasan-21-oic Acid Methyl Ester (38). (a) Oxidation with $(COCl)_2$–DMSO–iPr_2NEt. To a cold (–78 °C) solution of oxalyl chloride (0.07 mL, 0.8 mmol) in CH_2Cl_2 (2 mL) was added dropwise a solution of DMSO (0.11 mL, 1.6 mmol) in CH_2Cl_2 (2 mL). After 3 min at –78 °C, a solution of **37** (191.1 mg, 0.42 mmol) in CH_2Cl_2 (7 mL) and DMSO (0.4 mL) was added dropwise to the reaction mixture. After the mixture was stirred at –78 °C for 30 min, *N*,*N*-diisopropylethylamine (0.55 mL, 3.2 mmol) was added, stirring was continued at the same temperature for 5 min, and then the reaction was allowed to warm to room temperature over 30 min, whereupon saturated aqueous $NaHCO_3$ (20 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (40 mL × 3). The combined organic layer was washed with 1% HCl solution (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (30 mL) and dried ($MgSO_4$). After concentration in vacuo, the residue was purified by SiO_2 chromatography (20 g, 20% acetone/benzene) to give ketol **38** (187.6 mg, 98%) as colorless crystals. An analytical sample was obtained by recrystallization from acetone–hexane as colorless plates: mp 248–250 °C (dec); IR (KBr) 3400, 1730 cm^{-1}; ^1H NMR (270 MHz) δ 0.81 (d, J = 6 Hz, 3 H), 1.18 (s, 3 H), 2.06 (ddd, J = 15, 3, 3 Hz, 1 H, 6α-H), 2.49 (ddd, J = 13, 3.5, 3.5 Hz, 1 H, 1β-H), 2.69 (d, J = 1.5 Hz, 1 H, 9-H), 2.80 (ddd, J = 14, 6, 2 Hz, 1 H), 2.98 (dd, J = 19, 6 Hz, 1 H), 3.18 (d, J = 4.5 Hz, 1 H, OH), 3.63 (dd, J = 8.5, 1.5 Hz, 1 H), 3.67 (dd, J = 19, 14 Hz, 1 H), 3.85 (s, 3 H), 3.91 (m, 4 H), 4.19 (dd, J = 4.5, 2 Hz, 1 H), 4.32 (d, J = 8.5 Hz, 1 H), 4.61 (t, J = 3 Hz, 1 H, 7-H); MS, m/z (rel intensity) 450 (M$^+$, 0.3), 99 (100); exact mass calcd for $C_{23}H_{30}O_9$ 450.1889, found 450.1909.

13,20-Epoxy-3,3-(ethylenedioxy)-11β,12α-dihydroxy-16-oxopicrasan-21-oic Acid Methyl Ester (12). To a cold (0 °C) solution of **38** (181.6 mg, 0.40 mmol) in EtOAc (30 mL) was added n-Bu_4NBH_4 (210 mg, 0.82 mmol). After the mixture was stirred for 2 h (TLC monitoring) at 0 °C, additional n-Bu_4NBH_4 (210 mg, 0.82 mmol) was added, and stirring was continued for 2 h. The reaction was quenched by addition of aqueous NaH_2PO_4 (10 mL). The mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (40 mL × 3). The combined organic extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and SiO_2 chromatography (15 g, 20% acetone/benzene, then 3% MeOH/$CHCl_3$) of the residue afforded *trans*-diol **12** (109.4 mg, 60%) as colorless crystals. An analytical sample was obtained by recrystallization from acetone–hexane as colorless prisms: mp 292–293 °C; IR (KBr) 3450, 1730, 1705 cm^{-1}; ^1H NMR (270 MHz) δ 0.82 (d, J = 7 Hz, 3 H), 1.34 (s, 3 H), 1.95 (ddd, J = 12.5, 3.5, 3.5 Hz, 1 H, 1β-H), 2.05 (ddd, J = 14, 2.5, 2.5 Hz, 1 H, 6α-H), 2.45 (m, 1 H, OH), 2.60 (ddd, J = 14, 5.5, 1.5 Hz, 1 H, 14-H), 2.71 (dd, J = 18.5, 5.5 Hz, 1 H, 15β-H),

3.30 (br d, J = 3 Hz, 1 H, OH), 3.53 (dd, J = 18.5, 14 Hz, 1 H, 15α-H), 3.63 (dd, J = 8, 1.5 Hz, 1 H, 20-H), 3.85 (s, 3 H), 3.89–4.02 (m, 4 H), 4.14 (m, $W_{1/2}$ = 6 Hz, 1 H, 12-H), 4.21 (m, $W_{1/2}$ = 14 Hz, 1 H, 11-H), 4.54 (t, J = 2.5 Hz, 1 H, 7-H), 4.72 (d, J = 8 Hz, 1 H, 20-H); MS, m/z (rel intensity) 452 (M^+, 2.2), 99 (100); exact mass calcd for $C_{23}H_{32}O_9$ 452.2046, found 452.2033.

11β,12α-Diacetoxy-13,20-epoxy-3,3-(ethylenedioxy)-16-oxopicrasan-21-oic Acid Methyl Ester (39). To a solution of the diol **12** (20 mg, 0.044 mmol) and DMAP (30 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) was added acetic anhydride (0.06 mL, 0.64 mmol). After being stirred at room temperature for 18 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 5 g, 20% acetone/benzene) of the residue yielded diacetate **39** (20.2 mg, 85%) as colorless solids. An analytical sample was obtained by recrystallization from ether–EtOAc: mp 311–315 °C; IR (KBr) 1730 cm^{-1}; ^1H NMR (270 MHz) δ 0.84 (d, J = 6.5 Hz, 3 H), 1.16 (s, 3 H), 1.79 (dq, J = 11.5, 6.5 Hz, 1 H, 4-H), 1.89 (dd, J = 5, 1 Hz, 1 H, 9-H), 2.05 (s, 3 H), 2.15 (s, 3 H), 2.62 (ddd, J = 14, 6, 1.5 Hz, 1 H), 3.15 (dd, J = 18.5, 6 Hz, 1 H), 3.19 (dd, J = 18.5, 14 Hz, 1 H), 3.67 (dd, J = 8, 1.5 Hz, 1 H), 3.74 (s, 3 H), 3.88–4.01 (m, 4 H), 4.61 (t, J = 2.5 Hz, 1 H), 4.79 (d, J = 8 Hz, 1 H), 5.12 (t, J = 1.5 Hz, 1 H), 5.24 (br d, J = 5 Hz, 1 H); MS, m/z (rel intensity) 536 (M^+, 0.4), 477 (0.8), 460 (0.7), 99 (100); exact mass calcd for $C_{27}H_{36}O_{11}$ 536.2257, found 536.2227.

11β,12α-Diacetoxy-13,20-epoxy-3,16-dioxopicrasan-21-oic Acid Methyl Ester (40). A solution of **39** (74.5 mg, 0.14 mmol) in THF (5 mL) and 2 M HCl (1 mL) was stirred at room temperature overnight. The solvent was evaporated in vacuo, and the residue was taken up in saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (20 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 10 g, 20–30% acetone/benzene) of the residue yielded ketone **40** (64.3 mg, 94%) as colorless crystals. An analytical sample was obtained by recrystallization from methanol as colorless prisms: mp 319–320 °C; IR (KBr) 1740, 1716 cm^{-1}; ^1H NMR (270 MHz) δ 1.03 (d, J = 6 Hz, 3 H), 1.40 (s, 3 H), 1.90 (br d, J = 5 Hz, 1 H, 9-H), 2.06 (s, 3 H), 2.19 (s, 3 H), 2.68 (ddd, J = 14, 6, 1 Hz, 1 H, 14-H), 3.03 (dd, J = 19, 6 Hz, 1 H, 15β-H), 3.20 (dd, J = 19, 14 Hz, 1 H, 15α-H), 3.72 (dd, J = 8, 1.5 Hz, 1 H), 3.75 (s, 3 H), 4.64 (m, 1 H), 4.81 (d, J = 8 Hz, 1 H), 5.13 (m, 1 H), 5.27 (br d, J = 5 Hz, 1 H, 11-H); MS, m/z (rel intensity) 492 (M^+, 34), 464 (3), 432 (25), 390 (93), 231 (66), 55 (100); exact mass calcd for $C_{25}H_{32}O_{10}$ 492.1995, found 492.2008.

11β,12α-Diacetoxy-13,20-epoxy-2α-hydroxy-3,16-dioxopicrasan-21-oic Acid Methyl Ester (41). To a cold (−10 °C) solution of **40** (22.2 mg, 0.045 mmol) and triethylamine (0.05 mL, 0.36 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (0.04 mL, 0.21 mmol). After being stirred at the same temperature for 40 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo to give a residue, which was dissolved in CH_2Cl_2 (1.5 mL) containing solid $NaHCO_3$ (40 mg). The solution was cooled to 0 °C and treated with MCPBA (80% purity, 15 mg, 0.07 mmol). After being stirred at 0 °C for 40 min, the reaction was quenched by addition of saturated aqueous Na_2SO_3, and stirring was continued for 5 min. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in THF (2 mL) and 2 M HCl (2 mL), and the mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo to give a residue, which was taken up in saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 4 g, 0.5–1% MeOH/$CHCl_3$) of the residue afforded α-hydroxy ketone **41** (9 mg, 39%) as colorless crystals. An analytical sample was obtained by recrystallization from acetone–hexane as colorless fine needles: mp 258–260 °C; IR (KBr) 3456, 1748, 1730 cm^{-1}; ^1H NMR (270 MHz) δ 1.12 (d, J = 6.4 Hz, 3 H), 1.48 (s, 3 H), 1.89 (br d, J = 5 Hz, 1 H), 2.06 (s, 3 H), 2.20 (s, 3 H), 2.44 (dd, J = 12.4, 6.8 Hz, 1 H, 1β-H), 2.66 (ddd, J = 14, 6, 1.5 Hz, 1 H), 3.05 (dd, J = 18.8, 6 Hz, 1 H), 3.19 (dd, J = 18.8, 14 Hz, 1 H), 3.57 (br d, J = 3 Hz, 1 H, 2-OH), 3.72 (dd, J = 8, 1.5 Hz, 1 H), 3.75 (s, 3 H), 4.29 (br dd, J = 12, 7 Hz, 1 H, 2-H), 4.65 (m, 1 H), 4.81 (d, J = 8 Hz, 1 H), 5.16 (m, 1 H), 5.23 (br d, 1 H); MS, m/z (rel intensity) 508 (M^+, 7), 480 (16), 448 (12), 406 (78), 247 (90), 115 (78), 73 (100); exact mass calcd for $C_{25}H_{32}O_{11}$ 508.1944, found 508.1926.

11β,12α-Diacetoxy-13,20-epoxy-3-hydroxy-2,16-dioxopicras-3-en-21-oic Acid Methyl Ester (42). A solution of **41** (16.7 mg, 0.033 mmol) and bismuth trioxide (25 mg, 0.054 mmol) in acetic acid was heated at reflux for 30 min. After cooling to room temperature, the reaction mixture was passed through a pad of Celite with $CHCl_3$. The solvent was evaporated in vacuo to give a residue, which was purified by column chromatography (SiO_2, 3 g, 1% MeOH/$CHCl_3$) to afford diosphenol **42** (12 mg, 72%) as white solids. An analytical sample was obtained by recrystallization from acetone–hexane as colorless fine needles: mp 249–250 °C; IR (KBr) 3430, 1740, 1668, 1646 cm^{-1}; UV (EtOH) 274 (ε 7500), (EtOH + NaOH) 322 nm; ^1H NMR (270 MHz) δ 1.23 (s, 3 H), 1.73 (ddd, J = 15, 13, 2.5 Hz, 1 H, 6β-H), 1.86 (d, J = 2.2 Hz, 3 H), 2.08 (s, 3 H), 2.15 (s, 3 H), 2.33 (br d, J = 16 Hz, 1 H, 1α-H), 2.37 (ddd, J = 15, 2.5, 2.5 Hz, 1 H, 6α-H), 2.62 (d, J = 16 Hz, 1 H, 1β-H), 2.69 (br dd, J = 13.5, 6 Hz, 1 H), 2.91 (br d, J = 13 Hz, 1 H, 5-H), 3.10 (dd, J = 19, 6 Hz, 1 H, 15β-H), 3.26 (dd, J = 19, 13.5 Hz, 1 H, 15α-H), 3.71 (dd, J = 8, 1.5 Hz, 1 H), 3.75 (s, 3 H), 4.73 (m, 1 H, 7-H), 4.77 (d, J = 8 Hz, 1 H, 20-H), 5.13–5.20 (m, 2 H, 11-H, 12-H), 6.06 (m, 1 H, 3-OH); MS, m/z (rel intensity) 506 (M^+, 11), 464 (91), 446 (22), 444 (13), 297 (47), 296 (56), 295 (48), 281 (40), 201 (47), 151 (100); exact mass calcd for $C_{25}H_{30}O_{11}$ 506.1788, found 506.1795.

11β,12α-Diacetoxy-3-(*tert*-butyldimethylsiloxy)-13,20-epoxy-2,16-dioxopicras-3-en-21-oic Acid Methyl Ester ((±)-9). To a solution of **42** (3.9 mg, 0.008 mmol) and imidazole (10 mg, 0.15 mmol) in DMF (0.4 mL) was added TBSCl (15 mg, 0.1 mmol). After being stirred at room temperature for 2 days, the reaction mixture was poured into water (10 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 2 g, 20% acetone in benzene) to afford TBS ether **9** (4 mg, 84%) as colorless crystals. An analytical sample was obtained by recrystallization from acetone–hexane as colorless needles: mp 305–306 °C (decomp); IR (KBr) 1745, 1680 cm^{-1}; UV (EtOH) 271 nm (ε 8300); ^1H NMR (270 MHz) δ 0.13 (s, 3 H), 0.14 (s, 3 H), 0.94 (s, 9 H), 1.22 (s, 3 H), 1.72 (ddd, J = 14.5, 13, 2.5 Hz, 1 H, 6β-H), 1.86 (d, J = 1.5 Hz, 3 H), 2.08 (s, 3 H), 2.13 (1 H, 9-H, overlapped with other signal), 2.14 (s, 3 H), 2.27 (br d, J = 16 Hz, 1 H), 2.37 (ddd, J = 14.5, 2.5, 2.5 Hz, 1 H), 2.53 (d, J = 16 Hz, 1 H), 2.68 (ddd, J = 14, 6, 1 Hz, 1 H), 2.89 (br d, J = 13 Hz, 1 H), 3.10 (dd, J = 19, 6 Hz, 1 H), 3.26 (dd, J = 19, 14 Hz, 1 H), 3.70 (dd, J = 8, 1.5 Hz, 1 H), 3.75 (s, 3 H), 4.72 (t, J = 2.5 Hz, 1 H), 4.78 (d, J = 8 Hz, 1 H), 5.11–5.18 (m, 2 H); MS, m/z (rel intensity) 621 ($[M + H]^+$, 1.6), 6.05 (3), 563 (100); exact mass calcd for $C_{30}H_{41}O_{11}Si$ (M − CH_3) 605.2418, found 605.2388.

3,11β,12α-Triacetoxy-13,20-epoxy-2,16-dioxopicras-3-en-21-oic Acid Methyl Ester ((±)-43). To a solution of **42** (8.5 mg, 0.017 mmol), a catalytic amount of DMAP, and pyridine (0.1 mL, 1.2 mmol) in CH_2Cl_2 (1 mL) was added acetic anhydride (0.05 mL, 0.5 mmol). After being stirred at room temperature for 1.5 h, the reaction mixture was poured into 2 M HCl (10 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (15 mL), dried ($MgSO_4$), and evaporated. Chromatography (SiO_2, 2 g, 0.5–1% MeOH/$CHCl_3$) of the residue afforded triacetate **43** (7.8 mg, 85%) as colorless solids. An analytical sample was obtained by recrystallization from ether–methanol: mp 302 °C (dec); IR (KBr) 1765, 1745, 1685 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 1.44 (s, 3 H), 1.72 (d, J = 1.5 Hz, 3 H), 1.82 (ddd, J = 14.5, 13, 2.5 Hz, 1 H), 1.87 (s, 3 H), 1.88 (s, 3 H), 2.21 (s, 3 H), 2.28 (ddd, J = 14.5, 3, 3 Hz, 1 H), 2.60 (br d, J = 16 Hz, 1 H), 2.74 (br d, J = 4.7 Hz, 1 H, 9-H), 2.83 (d, J = 16 Hz, 1 H), 3.11 (dd, J = 14, 5.5 Hz, 1 H), 3.23 (br d, J = 13 Hz, 1 H, 5-H), 3.28 (dd, J = 18, 5.5 Hz, 1 H), 3.66 (dd, J = 18, 14 Hz, 1 H), 3.69 (s, 3 H), 3.87 (dd, J = 8, 1 Hz, 1 H), 4.88 (d, J = 8 Hz, 1 H), 5.55–5.62 (m, 2 H); MS, m/z (rel intensity) 548 (M^+, 1), 506 (11), 464 (27), 446 (14), 78 (100); exact mass calcd for $C_{25}H_{30}O_{11}$ (M − CH_2CO) 506.1788, found 506.1773.

3-(*tert*-Butyldimethylsiloxy)-13,20-epoxy-11β,12α-dihydroxy-2,16-dioxopicras-3-en-21-oic Acid Methyl Ester (44). To a cold (0 °C) solution of **45** (230.5 mg, 0.418 mmol) and DMAP (10 mg, 0.082 mmol) in pyridine (5 mL) under argon was added dropwise phenyl chlorothionoformate (0.25 mL, 1.8 mmol). The mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and stirred overnight. The reaction was quenched by addition of water (0.5 mL) at 0 °C, and the solvent was removed in vacuo. The residue was taken up in 1 M HCl solution (20 mL) and extracted with EtOAc (20 mL × 2). The combined organic extract was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (SiO_2, 20 g, 2% MeOH/$CHCl_3$) gave thionocarbonate **46**, which was used in the next reaction without further purification.

To a solution of the above **46** and AIBN (12 mg, 0.07 mmol) in toluene (10 mL) under argon was added dropwise tributyltin hydride (0.5 mL, 1.9 mmol). After being heated under reflux for 2 h, the reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, 30 g, 10–15% acetone/benzene) to give **44** (145.3 mg, 65% from **45**). An analytical sample was obtained by recrystallization from acetone–$CHCl_3$ as colorless needles: mp 291–292.5 °C; IR (KBr) 3540, 3470, 1730, 1710, 1675 cm^{-1}; ^1H NMR (270 MHz) δ 0.13 (s, 3 H), 0.16 (s, 3 H), 0.95 (s, 9 H), 1.39 (s, 3 H), 1.75 (ddd, J = 14.5, 13, 2.5 Hz, 1 H), 1.85 (d, J = 1.5 Hz, 3 H), 1.96 (br d, J = 4 Hz, 1 H, 9-H), 2.35 (d, J = 16 Hz, 1 H, 1α-H), 2.35 (ddd, J = 14.5, 2.5, 2.5 Hz, 1 H), 2.57 (d, J = 8 Hz, 1 H), 2.68 (ddd, J = 13.5, 6, 1 Hz, 1 H), 2.80 (dd, J = 19, 6 Hz, 1 H), 2.81–2.92 (m, 2 H), 3.51 (d, J = 4 Hz, 1 H, OH), 3.59 (dd, J = 19, 13.5 Hz, 1 H), 3.68 (dd, J = 8, 1 Hz, 1 H), 3.86 (s, 3 H), 4.13–4.22 (m, 2 H), 4.66 (t, J = 2.5 Hz, 1 H), 4.72 (d, J = 8 Hz, 1 H); MS, m/z (rel intensity) 521 ($[M - CH_3]^+$, 3), 479 (100); exact mass calcd for $C_{23}H_{31}O_9Si$ ($M - C_4H_9$) 479.1737, found 479.1742

Preparation of (−)-9 from 44. Acetic anhydride (0.45 mL, 4.8 mmol) was added to a solution of **44** (187.5 mg, 0.350 mmol) and DMAP (250 mg, 2.05 mmol) in CH_2Cl_2 (10 mL). After being stirred at room temperature for 15 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (50 mL × 3). The combined organic extract was washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (SiO_2, 20 g, 20% EtOAc/CH_2Cl_2) of the residue afforded diacetate **9a** (157.9 mg, 73%) as colorless crystals: $[\alpha]^{26}_D$ −22° (c 0.44, $CHCl_3$).

Conversion of (−)-9 to (−)-43. To a cold (0 °C) solution of (−)-**9** (369.5 mg, 0.596 mmol) in THF (7 mL) was added a solution of n-Bu_4NF (360 mg, 1.38 mmol) in THF (5 mL). After being stirred at 0 °C for 30 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with $CHCl_3$ (30 mL × 3). Drying ($MgSO_4$) followed by evaporation of the solvent gave a residue, which was passed through a florisil short column with 5% MeOH in $CHCl_3$ to afford the diosphenol **42**.

Acetic anhydride (0.3 mL) was added to a solution of the above **42**, DMAP (9 mg, 0.07 mmol), and pyridine (0.5 mL, 6.2 mmol) in CH_2Cl_2 (10 mL). After being stirred at room temperature for 1.5 h, the reaction mixture was poured into 1 M HCl (20 mL) and extracted with $CHCl_3$ (30 mL × 3). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 20 g, 1–2% MeOH/$CHCl_3$) to yield the triacetate **43** (284.5 mg, 87%) as colorless solids.

11β,12α-Diacetoxy-3-(*tert*-butyldimethylsiloxy)-13,20-epoxy-16-hydroxy-2-oxopicras-3-en-21-oic Acid Methyl Ester (51). To a cold (0 °C) solution of (−)-**9** (502.7 mg, 0.81 mmol) in ethanol (6 mL) and CH_2Cl_2 (3 mL) was added sodium borohydride (31 mg, 0.82 mmol). After being stirred at 0 °C for 5 h, the reaction was quenched by addition of aqueous NaH_2PO_4 (3 mL). The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with $CHCl_3$ (40 mL × 5). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 30 g, 1–2% MeOH/$CHCl_3$) of the residue gave hemiacetal **51** (441.8 mg, 87%) as colorless amorphous solids (a mixture of diastereomers at C-16, α:β = ca. 2:3 by ^1H NMR): IR (KBr) 3470, 1750, 1680, 1615 cm^{-1}; ^1H NMR (270 MHz) δ 0.12, 0.13, 0.14, and 0.15 (each s, 6 H), 0.94 (s, 9 H), 1.20 (s, 3 H), 1.84 (br s, 3 H), 2.05 (s, 3 H), 2.11 (s, 3 H), 3.14 (br d, J = 12.5 Hz, 0.6 H, 5-H of 16β-OH epimer), 3.28 (br d, J = 12.5 Hz, 0.4 H, 5-H of 16α-OH epimer), 3.54 (dd, J = 8, 1 Hz, 0.4 H, 20-H of 16α-OH epimer), 3.63 (dd, J = 8, 1 Hz, 0.6 H, 20-H of 16β-OH epimer), 3.72 and 3.73 (each s, ca. 3:2 ratio, 3 H), 3.82 (m, 0.4 H, 7-H of 16α-OH epimer), 4.24 (m, 0.6 H, 7-H of 16β-OH epimer), 4.62 and 4.64 (each d, J = 8 Hz, 1 H, 20-H), 4.71 (dd, J = 9, 1.5 Hz, 0.4 H, 16-H of 16α-OH epimer), 5.02–5.15 (m, 2 H, 11-H, 12-H), 5.47 (br d, J = 2 Hz, 0.6 H, 16-H of 16β-OH epimer); MS, m/z (rel intensity) 623 ($[M + H]^+$, 0.5), 607 (1.5), 589 (2.5), 579 (7.5), 565 (62), 561 (15), 547 (100); exact mass calcd for $C_{27}H_{37}O_{11}Si$ ($M - C_4H_9$) 565.2325, found 565.2079.

11β,12α-Diacetoxy-3-(*tert*-butyldimethylsiloxy)-13,20-epoxy-2-oxopicrasane-3,15-dien-21-oic Acid Methyl Ester (52). To a solution of **51** (93.7 mg, 0.15 mmol) in pyridine (5 mL) was added phosphoryl chloride (0.1 mL, 1.07 mmol). After being stirred at 100 °C for 4 h, the reaction mixture was cooled to room temperature, poured into saturated aqueous $NaHCO_3$ (10 mL), and extracted with $CHCl_3$ (30 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 15 g, 15% acetone/benzene) of the residue gave vinyl ether **52** (61.3 mg, 67%) as colorless crystals. An analytical sample was obtained by recrystallization from EtOAc–hexane as colorless needles: mp 159–160 °C; IR (KBr) 1755, 1745, 1675, 1640, 1615 cm^{-1}; ^1H NMR (270 MHz) δ 0.13 (s, 3 H), 0.15 (s, 3 H), 0.95 (s, 9 H), 1.22 (br s, 3 H), 1.67 (ddd, J = 15, 13, 2 Hz, 1 H), 1.86 (d, J = 2 Hz, 3 H), 2.06 (s, 3 H), 2.11 (s, 3 H), 2.15–2.33 (m, 3 H), 2.49 (d, J = 15.5 Hz, 1 H, 1β-H), 2.93 (m, 1 H), 3.00 (br d, J = 13 Hz, 1 H), 3.60 (dd, J = 7.5, 1.5 Hz, 1 H), 3.74 (s, 3 H), 4.42 (dd, J = 3, 2 Hz, 1 H), 4.70 (d, J = 7.5 Hz, 1 H), 5.03 (dd, J = 5, 1.5 Hz, 1 H, 11-H), 5.10 (t, J = 1.5 Hz, 1 H, 12-H), 5.12 (dd, J = 6, 2 Hz, 1 H), 6.42 (dd, J = 6, 3 Hz, 1 H); MS, m/z (rel intensity 589 ($[M - CH_3]^+$, 2.6), 561 (3), 547 (100); exact mass calcd for $C_{27}H_{35}O_{10}Si$ ($M - C_4H_9$) 547.2000, found 547.2031.

11β,12α-Diacetoxy-3-(*tert*-butyldimethylsiloxy)-13,20-epoxy-15β,16-dihydroxy-2-oxopicras-3-en-21-oic Acid Methyl Ester (56) and 11β,12α-Diacetoxy-3-(*tert*-butyldimethylsiloxy)-13,20:3α,4α-diepoxy-15β,16-dihydroxy-2-oxopicras-3-en-21-oic Acid Methyl Ester (59). To a vigorously stirred solution of **52** (27.8 mg, 0.046 mmol) in CH_2Cl_2 (1 mL) and saturated aqueous $NaHCO_3$ (1 mL) was added dropwise a solution of MCPBA (80% purity, 15 mg, 0.11 mmol) in CH_2Cl_2 (1 mL). After being stirred at room temperature for 2 h, the reaction was quenched by addition of aqueous Na_2SO_3 (10 mL), and the reaction mixture was extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (SiO_2, 3 g, 2–5% MeOH/$CHCl_3$) of the residue gave an inseparable complex mixture of hydroxy hemiacetal **56** and the corresponding epoxide **59** (17.9 mg, ca. 61%). Each of them consisted of a mixture of diastereomers at C-16. The mixture was used in the next reaction without further confirmation (IR (KBr) 3450, 1745, 1670 cm^{-1}). The mass spectrum of the mixture showed a strong fragment ion peak corresponding to a loss of a *tert*-butyl group from the molecular ion of **56** at m/z 563.1921 (calcd for $C_{27}H_{35}O_{11}Si$: 563.1948).

11β,12α-Diacetoxy-3-(*tert*-butyldimethylsiloxy)-13,20-epoxy-15β-hydroxy-2,16-dioxopicras-3-en-21-oic Acid Methyl Ester (57) and 11β,12α-Diacetoxy-3-(*tert*-butyldimethylsiloxy)-13,20:3α,4α-diepoxy-15β-hydroxy-2,16-dioxopicras-3-en-21-oic Acid Methyl Ester (60). A mixture of the hemiacetal **56** and its epoxide **59** (100 mg, 0.15 mmol) and freshly prepared silver(I) oxide (650 mg, 2.8 mmol) in MeCN (10 mL) was heated at reflux for 4.5 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The filtrate and washes were combined and concentrated in vacuo. Chromatography (SiO_2, 10 g, 1–2% MeOH/$CHCl_3$) of the residue gave an inseparable mixture of lactone **57** and the corresponding epoxide **60** (64.7 mg, ca. 1:1 mixture by ^1H NMR analysis, 65%) as white solids: IR (KBr) 3480, 1760, 1680 cm^{-1}; ^1H NMR (270 MHz, signals due to 57) δ 0.13 (s, 3 H), 0.15 (s, 3 H), 0.94 (s, 9 H), 1.22 (br s, 3 H), 1.85 (d, J = 1.8 Hz, 3 H), 2.11 (s, 3 H), 2.14 (s, 3 H), 2.40 (br d, J = 15 Hz, 1 H, 6α-H), 2.54 (d, J = 15.8 Hz, 1 H, 1α-H), 2.81 (dd, J = 12.5, 1.5 Hz, 1 H, 14-H), 2.93 (br d, J = 13 Hz, 1 H, 5-H), 3.76 (dd, J = 8, 1 Hz, 1 H, 20-H), 3.81 (s, 3 H), 4.32 (br s, 1 H, OH),

4.73 (d, J = 8 Hz, 1 H, 20-H), 4.77 (m, 1 H, 7-H), 5.02 (d, J = 12.5 Hz, 1 H, 15-H), 5.20 (br d, J = 5 Hz, 1 H, 11-H), 5.27 (t, J = 1.5 Hz, 1 H, 12-H); ^{1}H NMR (270 MHz, signals due to **60**) δ 0.06 (s, 3 H), 0.24 (s, 3 H), 0.90 (s, 9 H), 1.11 (br s, 3 H), 1.39 (s 3 H), 2.09 (s, 3 H), 2.13 (s, 3 H), 3.79 (s, 3 H), 4.18 (d, J = 1.5 Hz, 1 H, OH), 4.67 (d, J = 8 Hz, 1 H, 20-H), 4.70 (m, 1 H), 4.97 (dd, J = 12.5, 1.5 Hz, 1 H, 15-H), 5.14 (br d, J = 5 Hz, 1 H, 11-H), 5.25 (m, 1 H, 12-H); MS, m/z (rel intensity) 595 (a loss of a *tert*-butyl group from the molecular ion of **60**, 9.8), 579 (a loss of a *tert*-butyl group from the molecular ion of **57**, 98), 75 (100); exact mass calcd for $C_{27}H_{35}O_{12}Si$ (**60**, M − C_4H_9) 579.1897, found 579.1897.

11β-Acetoxy-3-(*tert*-butyldimethylsiloxy)-13,20-epoxy-12α,15β-dihydroxy-2,16-dioxopicras-2-en-21-oic Acid Methyl Ester (58). A mixture of **57** and **60** (30.3 mg, 0.048 mmol) was dissolved in 1 M potassium methoxide in methanol (1 mL). After stirring at room temperature for 2 h, the reaction was quenched by addition of concentrated HCl–methanol (1:2, 0.25 mL). Insoluble solids were filtered and washed thoroughly with methanol. The filtrate and washes were combined and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 3 g, 2–5% MeOH/$CHCl_3$) to afford monoacetate **58** (9.7 mg, 34%): ^{1}H NMR (270 MHz) δ 0.14 (s, 3 H), 0.15 (s, 3 H), 0.95 (s, 9 H), 1.22 (br s, 3 H), 1.85 (d, J = 2 Hz, 3 H), 2.10 (s, 3 H), 2.28–2.46 (3 H), 2.57 (d, J = 16 Hz, 1 H), 2.82 (dd, J = 12.5, 1.5 Hz, 1 H, 14-H), 2.92 (br d, J = 12.5 Hz, 1 H, 5-H), 3.44 (br, 1 H, OH), 3.80 (dd, J = 8, 1 Hz, 1 H), 3.84 (s, 3 H), 4.13 (m, 1 H), 4.70 (d, J = 8 Hz, 1 H), 4.79 (t, J = 2.5 Hz, 1 H), 5.26 (d, J = 12.5 Hz, 1 H), 5.26 (dd, J = 5, 1 Hz, 1 H).

3,11,12-Tri-*O*-acetylbrusatol (61) and 11-*O*-Acetylbrusatol (62). Acetic anhydride (0.1 mL, 1.06 mmol) was added to a mixture of brusatol (**3**, 54.5 mg, 0.10 mmol) and DMAP (50 mg, 0.41 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into 2 M HCl solution and extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 5 g, 2% MeOH/$CHCl_3$) to afford 3,11,12-*O*-triacetylbrusatol (**61**).

A solution of the above triacetate **61** in 3 M H_2SO_4–methanol (1:1, 8 mL) was heated at reflux for 30 h. Methanol was removed in vacuo, and the resulting aqueous solution was extracted with $CHCl_3$ (20 mL × 3). The organic extract was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (SiO_2, 5 g, 1–2% MeOH/$CHCl_3$) of the residue afforded, in order of elution, 11-*O*-acetylbrusatol (**62**, 25.2 mg, 43%) and brusatol (**3**, 11 mg, 20%). 3,11,12-Tri-*O*-acetylbrusatol (**61**): ^{1}H NMR (270 MHz) δ 1.30 (br s, 3 H), 1.81 (d, J = 1 Hz, 3 H), 1.93 (d, J = 0.7 Hz, 3 H, 3′-CH_3), 2.02 (s, 3 H), 2.12 (s, 3 H), 2.19 (br s, 3 H, 3′-CH_3), 2.25 (s, 3 H), 2.33–2.48 (3 H), 2.61 (d, J = 16 Hz, 1 H), 3.11 (br d, J = 12 Hz, 1 H, 14-H), 3.29 (br d, J = 12 Hz, 1 H, 14-H), 3.71 (s, 3 H), 3.85 (br d, J = 7.7 Hz, 1 H), 4.75 (d, J = 7.7 Hz, 1 H), 4.86 (m, 1 H), 5.23 (d, J = 5 Hz, 1 H, 11-H), 5.30 (br s, 1 H, 12-H), 5.61 (br s, 1 H, 2′-H), 6.09 (br, 1 H, 15-H). 11-*O*-Acetylbrusatol (**62**): ^{1}H NMR (270 MHz) δ 1.23 (br s, 3 H), 1.86 (d, J = 1.8 Hz, 3 H), 1.93 (d, J = 1.5 Hz, 3 H, 3′-CH_3), 2.09 (s, 3 H), 2.19 (d, J = 1.1 Hz, 3 H, 3′-CH_3), 2.35–2.48 (3 H), 2.65 (d, J = 16 Hz, 1 H, 1-H), 3.00 (br d, J = 12.8 Hz, 1 H, 5-H), 3.21 (br d, J = 12.8 Hz, 1 H, 14-H), 3.48 (m, 1 H, OH), 3.77 (s, 3 H), 3.82 (dd, J = 7.7, 1 Hz, 1 H, 20-H), 4.13 (m, 1 H, 12-H), 4.73 (d, J = 7.7 Hz, 1 H, 20-H), 4.85 (m, 1 H), 5.31 (br d, J = 4.5 Hz, 1 H, 11-H), 5.63 (m, 1 H, 2′-H), 6.09 (s, 1 H, 3-OH), 6.19 (br, 1 H, 15-H).

11,12-Di-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)bruceantin (63) and 11,12-Di-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)-3α,4α-epoxybruceantin (65). To a solution of the inseparable mixture of the lactone **57** and its epoxide **60** (38 mg), *N*,*N*′-dicyclohexylcarbodiimide (DCC, 19 mg, 0.092 mmol), and DMAP (15 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added dropwise a solution of 3,4-dimethyl-2-pentenoic acid (13 mg, 0.10 mmol) in CH_2Cl_2 (1 mL). After being stirred at room temperature overnight, the reaction mixture was poured into 1 M HCl solution (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (SiO_2, 5 g, 3-5% acetone/benzene) of the residue gave an inseparable mixture of protected bruceantin **63** and its epoxide **65** (32 mg, ca. 1:1 mixture by ^{1}H NMR analysis, 72%) as colorless amorphous solids: IR (KBr) 1760, 1685 cm^{-1}; ^{1}H NMR (270 MHz, signals due to **63**) δ 0.13 (s, 3 H), 0.16 (s, 3 H), 0.95 (s, 9 H), 1.06 (d, J = 7 Hz, 6 H, 2 × 4′-CH_3), 1.20 (br s, 3 H, 10-CH_3), 1.85 (d, J = 1.8 Hz, 3 H, 4-CH_3), 2.03 (s, 3 H, $OCOCH_3$), 2.11 (s, 3 H, $OCOCH_3$), 2.16 (d, J = 1.1 Hz, 3 H, 3′-CH_3), 2.57 (d, J = 15.8 Hz, 1 H, 1α-H), 2.96 (br d, J = 13 Hz, 1 H, 5-H), 3.27 (br d, J = 13 Hz, 1 H, 14-H), 3.70 (s, 3 H, CO_2CH_3), 3.84 (br d, J = 8 Hz, 1 H, 20-H), 4.75 (d, J = 8 Hz, 1 H, 20-H), 4.84 (m, 1 H, 7-H), 5.20 (br d, J = 5 Hz, 1 H, 11-H), 5.33 (br s, 1 H, 12-H), 5.62 (br s, 1 H, 2′-H), 6.07 (br, 1 H, 15-H); ^{1}H NMR (270 MHz, signals due to **65**) δ 0.07 (s, 3 H), 0.24 (s, 3 H), 0.90 (s, 9 H), 1.06 (d, J = 7 Hz, 6 H, 2 × 4′-CH_3), 1.09 (br s, 3 H, 10 -CH_3), 1.40 (s, 3 H, 4-CH_3), 2.02 (s, 3 H, $OCOCH_3$), 2.10 (s, 3 H, $OCOCH_3$), 2.16 (br s, 3 H, 3′-CH_3), 2.50 (br d, J = 14.5 Hz, 1 H, 1α-H), ca. 3.26 (br, 1 H, 14-H), 3.69 (s, 3 H, CO_2CH_3), 3.82 (br d, J = 7.7 Hz, 1 H, 20-H), 4.70 (d, J = 7.7 Hz, 1 H, 20-H), 4.80 (m, 1 H, 7-H), 5.14 (br d, J = 5 Hz, 1 H, 11-H), 5.29(br s, 1 H, 12-H), 5.62 (br s, 1 H, 2′-H), 6.06 (br, 1 H, 15-H).

Bruceantin (1) and 11-*O*-Acetylbruceantin (64). A mixture of the protected bruceantin **63** and its epoxide **65** (44.5 mg, 2.2:1 mixture) in 3 M H_2SO_4 (3 mL) and methanol (3 mL) was heated at reflux for 29 h. Methanol was removed in vacuo, and the aqueous residue was extracted with $CHCl_3$ (15 mL × 3). The organic extract was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (SiO_2, 3 g, 1–2% MeOH/$CHCl_3$) of the residue afforded, in order of elution, 11-*O*-acetylbruceantin (**64**, 11.4 mg, 47% based on **63**) and bruceantin (**1**, 3.4 mg, 15% based on **63**). 11-*O*-acetylbruceantin (**64**): IR (KBr) 3450, 1748, 1672, 1644 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.07 (d, J = 7 Hz, 6 H, 2 × 4′-CH_3), 1.23 (br s, 3 H, 10-CH_3), 1.73 (ddd, J = 15, 13, 2.5 Hz, 1 H, 6β-H), 1.86 (d, J = 1.8 Hz, 3 H, 4-CH_3), 2.09 (s, 3 H, $OCOCH_3$), 2.15 (d, J = 1.1 Hz, 3 H, 3′-CH_3), 2.35–2.46 (3 H, 1α-H, 6α-H, 9-H), 2.65 (d, J = 16 Hz, 1 H, 1β-H), 3.00 (br d, J = 12.5 Hz, 1 H, 5-H), 3.22 (br d, J = 12.5 Hz, 1 H, 14-H), 3.41 (m, 1 H, 12-OH), 3.75 (s, 3 H, CO_2CH_3), 3.82 (br d, J = 7.7 Hz, 1 H, 20-H), 4.13 (m, 1 H, 12-H), 4.72 (d, J = 7.7 Hz, 1 H, 20-H), 4.86 (m, 1 H), 5.31 (br d, J = 5 Hz, 1 H, 11-H), 5.64 (m, 1 H, 2′-H), 6.08 (s, 1 H, 3-OH), 6.17 (br, 1 H, 14-H); MS, m/z (rel intensity) 590 (M^+, 0.2), 530 (0.1), 480 (0.7), 462 (0.2), 434 (0.6), 402 (1), 291 (1.7), 201 (1.4), 151 (1.6), 111 (100); exact mass calcd for $C_{30}H_{38}O_{12}$ 590.2363, found 590.2354. Bruceantin (**1**): ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), IR, and mass spectra of the synthetic bruceantin (**1**) was identical with those of the authentic substance.

3,11β,12α-Triacetoxy-13,20-epoxy-16-hydroxy-2-oxopicras-3-en-21-oic Acid Methyl Ester (66). To a cold (0 °C) suspension of the triacetate (−)-**56** (79.7 mg, 0.15 mmol) in ethanol (3 mL), CH_2Cl_2 (3 mL), and THF (1 mL) was added sodium borohydride (6 mg, 0.16 mmol). After the mixture was stirred at 0 °C for 6 h, the reaction was quenched by addition of aqueous NaH_2PO_4 (2 mL). The reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (20 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (SiO_2, 10 g, 1–3% MeOH/$CHCl_3$) of the residue gave hemiacetal **66** (67.1 mg, 84%) as colorless amorphous solids (a mixture of diastereomers at C-16, α:β = ca. 2:3): IR (KBr) 3450, 1756, 1744, 1682 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.31 (br s, 3 H, 10-CH_3), 1.79 (br s, 3 H, 4-CH_3), 2.05 (s, 3 H, $OCOCH_3$), 2.118 and 2.122 (each s, total 3 H, $OCOCH_3$), 2.25 (s, 3 H, $OCOCH_3$), 3.28 (br d, J = 12.5 Hz, 0.6 H, 5-H of 16β-OH isomer), 3.41 (br d, J = 12.5 Hz, 0.4 H, 5-H of 16α-OH isomer), 3.56 (dd, J = 8, 1 Hz, 0.4 H, 20-H of 16α-OH isomer), 3.64 (dd, J = 7.7, 1 Hz, 0.6 H, 20-H of 16β-OH isomer), 3.73 and 3.75 (each s, ca. 3:2, total 3 H, CO_2CH_3), 3.84 (m, 0.4 H, 7-H of 16α-OH isomer), 4.25 (m, 0.6 H, 7-H of 16β-OH isomer), 4.62 and 4.64 (each d, J = 8, 7.7 Hz, total 1 H, 20-H), 4.84 (br d, J = 8.5 Hz, 0.4 H, 16-H of 16α-OH isomer), 5.03–5.15 (m, 2 H, 11-H, 12-H), 5.46 (m, 0.6 H, 16-H of 16β-OH isomer); MS, m/z (rel intensity) 550 (M^+, 5), 532 (12), 508 (12), 490 (14), 476 (10), 472 (23), 448 (22), 430 (32), 388 (65), 201 (100), 193 (50), 151 (75).

3,11β,12α-Triacetoxy-13,20-epoxy-2-oxopicrasane-3,15-dien-21-oic Acid Methyl Ester (67). To a soltuion of **66** (61.5 mg, 0.11 mmol) in pyridine (4 mL) was added phosphoryl chloride (0.1 mL, 1.1 mmol). The mixture was stirred at 100 °C for 4 h

and then cooled to room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (20 mL × 4). The combined organic extract was washed with saturated aqueous $CuSO_4$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 5 g, 15% acetone/benzene) to afford vinyl ether **67** (37.4 mg, 63%) as colorless solids. An analytical sample was obtained by recrystallization from EtOAc–hexane as colorless prisms: mp 276–278 °C; IR (KBr) 1760, 1740, 1688, 1648, 1372, 1140, 1048 cm^{-1}; ^1H NMR (270 MHz) δ 1.32 (s, 3 H), 1.81 (d, J = 1.5 Hz, 3 H), 2.06 (s, 3 H), 2.12 (s, 3 H), 2.25 (s, 3 H), 2.33 (br d, J = 16 Hz, 1 H), 2.33 (dd, J = 5.5, 1.5 Hz, 1 H), 2.56 (d, J = 16 Hz, 1 H), 2.95 (m, 1 H), 3.14 (br d, J = 12.5 Hz, 1 H), 3.61 (dd, J = 7.7, 1.5 Hz, 1 H), 3.75 (s, 3 H), 4.44 (m, 1 H), 4.70 (d, J = 7.7 Hz, 1 H), 5.05 (br d, J = 5.5 Hz, 1 H), 5.11 (m, 1 H), 5.13 (dd, J = 6, 2 Hz, 1 H), 6.41 (dd, J = 6, 3 Hz, 1 H, 16-H); MS, m/z (rel intensity) 532 (M^+, 4), 490 (8), 472 (51), 201 (100); exact mass calcd for $C_{27}H_{32}O_{11}$ 532.1944, found 532.1943.

3,11β,12α-Triacetoxy-13,20-epoxy-15β,16-dihydroxy-2-oxopicras-3-en-21-oic Acid Methyl Ester (68). (a) Oxidation with Osmium Tetroxide. To a solution of **67** (31.5 mg, 0.059 mmol) in THF (1.5 mL) and pyridine (0.3 mL) was added osmium tetroxide (20 mg, 0.079 mmol). After this was stirred at room temperature for 1 h, additional osmium tetroxide (16 mg, 0.06 mmol) was added and the mixture was stirred for 20 min. A solution of $NaHSO_3$ (135 mg, 1.30 mmol) in water (0.8 mL) and pyridine (0.2 mL) was added to the reaction mixture, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was poured into saturated aqueous $CuSO_4$ (10 mL) and extracted with $CHCl_3$ (20 mL × 3). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (SiO_2, 5 g, 5% MeOH/$CHCl_3$) of the residue afforded hydroxy hemiacetal **68** (28.7 mg, 85%) as white amorphous solids (a 1:1 mixture of diastereomers at C-16): IR (KBr) 3450, 1748, 1682 cm^{-1}; ^1H NMR (270 MHz) δ 1.31 (br s, 3 H, 10-CH_3), 1.79 (d, J = 1.1 Hz, 3 H, 10-CH_3), 2.111 and 2.115 (each s, total 3 H, $OCOCH_3$), 2.14 (s, 3 H, $OCOCH_3$), 2.25 (s, 3 H, $OCOCH_3$), 3.31 (d, J = 12.5 Hz, 0.5 Hz, 5-H), 3.42 (d, J = 12.5 Hz, 1 H, 5-H), 3.61 (dd, J = 8, 1 Hz, 0.5 H, 20-H), 3.65 (dd, J = 8, 1 Hz, 0.5 H, 20-H), 3.82 and 3.83 (each s, total 3 H, CO_2CH_3), 3.91 (m, 0.5 H, 7-H of 16α-OH isomer), 4.14 (dd, J = 11.5, 7 Hz, 0.5 H, 15-H of 16α-OH isomer), 4.28 (m, 0.5 H, 7-H of 16β-OH isomer), 4.40 (dd, J = 11.5, 3.7 Hz, 0.5 H, 15-H of 16β-OH isomer), 4.60 (d, J = 7 Hz, 0.5 H, 16α-H), 4.61 (d, J = 8 Hz, 0.5 H, 20-H), 4.63 (d, J = 8 Hz, 1 H, 20-H), 5.09–5.20 (m, 2 H, 11-H, 12-H), 5.35 (d, J = 3.7 Hz, 0.5 H, 16-H of 16β-H isomer); MS, m/z (rel intensity) 548 ([M – H_2O]$^+$, 29), 525 (7), 506 (53), 464 (36), 446 (27), 404 (50), 386 (47), 297 (88), 201 (62), 151 (91), 60 (100); exact mass calcd for $C_{27}H_{32}O_{12}$ (M – H_2O) 548.1894, found 548.1909.

(b) Oxidation with *m*-CPBA. To a solution of **67** (27.9 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) and saturated aqueous $NaHCO_3$ (2 mL) was added MCPBA (80% purity, 16 mg, 0.074 mmol). After being stirred vigorously at room temperature for 3 h, the reaction was quenched by addition of Na_2SO_3 and stirred for 15 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (SiO_2, 5 g, 2–4% MeOH in $CHCl_3$) of the residue afforded **68** (16.8 mg, 56%).

3,11β,12α-Triacetoxy-13,20-epoxy-15β-hydroxy-2,16-dioxopicras-3-en-21-oic Acid Methyl Ester (69). A mixture of **68** (26.2 mg, 0.046 mmol) and freshly prepared silver(I) oxide (100 mg) in MeCN (3 mL) was stirred at 80 °C for 1 h. The reaction mixture was filtered through a pad of Celite, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (SiO_2, 5 g, 1–2% methanol/$CHCl_3$) to afford lactone **69** (19 mg, 73%) as colorless solids. An analytical sample was obtained by recrystallization from EtOAc–hexane as colorless prisms: mp 280 °C (dec); IR (KBr) 3450, 1748, 1684 cm^{-1}; ^1H NMR (270 MHz) δ 1.33 (s, 3 H, 10-CH_3), 1.80 (d, J = 1.5 Hz, 3 H, 4-CH_3), 2.11 (s, 3 H, $OCOCH_3$), 2.15 (s, 3 H, $OCOCH_3$), 2.25 (s, 3 H, $OCOCH_3$), 2.29 (br d, J = 5.5 Hz, 1 H, 9-H), 2.36 (br d, J = 15.6 Hz, 1 H, 1α-H), 2.41 (ddd, J = 14.5, 3, 3 Hz, 1 H, 6α-H), 2.61 (d, J = 15.6 Hz, 1 H, 1β-H), 2.83 (dd, J = 12.5, 1.5 Hz, 1 H, 14-H), 3.04 (br d, J = 12.7 Hz, 1 H, 5-H), 3.77 (dd, J = 7.8, 1 Hz, 1 H, 20-H), 3.81 (s, 3 H, CO_2CH_3), 4.33 (br s, 1 H, 15-OH), 4.74 (d, J = 7.8 Hz, 1 H, 20-H), 4.78 (m, 1 H, 7-H), 5.03 (br d, J = 12.5 Hz, 1 H, 15-H), 5.21 (br d, J = 5.5 Hz, 1 H, 11-H), 5.27 (m, 1 H, 12-H); MS, m/z (rel intensity) 564 (M^+, 6), 522 (12), 504 (8), 494 (52), 452 (20), 434 (33), 402 (14), 392 (27), 374 (19), 354 (22), 297 (59), 200 (42), 151 (54), 139 (56), 69 (100); exact mass calcd for $C_{27}H_{32}O_{13}$ 564.1843, found 564.1833.

3,11,12-Tri-*O*-acetylbruceantin (71). To a solution of **69** (26.5 mg, 0.047 mmol), DMAP (12 mg, 0.098 mmol), and DCC (15 mg, 0.073 mmol) in CH_2Cl_2 (1 mL) was added dropwise a solution of 3,4-dimethyl-2-pentenoic acid (10 mg, 0.078 mmol) in CH_2Cl_2 (1 mL). After being stirred at room temperature overnight, the solution was filtered through a pad of Celite, and the pad was washed with a mixture of ether and CH_2Cl_2. The filtrate and washes were combined and concentrated in vacuo. The residue was taken up in 1 M HCl (10 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 5 g, 0.5% MeOH/$CHCl_3$) to yield 3,11,12-*O*-triacetylbruceantin (**71**, 25.5 mg, 81%) as colorless solids. An analytical sample was obtained by recrystallization from CH_2Cl_2–ether: mp 273–275 °C (lit.[4b] mp 268–269 °C); IR (KBr) 1756, 1688, 1644 cm^{-1}; ^1H NMR (270 MHz) δ 1.07 (d, J = 6.6 Hz, 6 H, 2 × 4′-CH_3), 1.31 (s, 3 H, 10-CH_3), 1.81 (d, J = 1.5 Hz, 3 H, 4-CH_3), 2.03 (s, 3 H, $OCOCH_3$), 2.12 (s, 3 H, $OCOCH_3$), 2.16 (d, J = 1.1 Hz, 3 H, 3′-CH_3), 2.26 (s, 3 H, $OCOCH_3$), 2.63 (d, J = 15.8 Hz, 1 H, 1β-H), 3.08 (br d, J = 12.5 Hz, 1 H, 5-H), 3.29 (br d, J = 12.5 Hz, 1 H, 14-H), 3.70 (s, 3 H, CO_2CH_3), 3.85 (br d, J = 8 Hz, 1 H, 20-H), 4.76 (d, J = 8 Hz, 1 H, 20-H), 4.86 (m, 1 H, 7-H), 5.22 (br d, J = 5 Hz, 1 H, 11-H), 5.32 (m, 1 H, 12-H), 5.62 (br s, 1 H, 2′-H), 6.07 (br, 1 H, 15-H); MS, m/z (rel intensity) 632 ([M – CH_2CO]$^+$, 0.8), 111 (100); exact mass calcd for $C_{32}H_{40}O_{13}$ (M – CH_2CO) 632.2469, found 632.2475.

Bruceantin (1). A solution of **71** (70.3 mg, 0.104 mmol) in 12 M HCl (0.5 mL), 3 M H_2SO_4 (4 mL), and methanol (4 mL) was heated at reflux for 30 h. Methanol in the reaction mixture was removed in vacuo, and the remaining layer was extracted with $CHCl_3$ (20 mL × 3). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a SiO_2 column (5 g, 1% MeOH/$CHCl_3$) to yield bruceantin (**1**, 11.1 mg, 19%).

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Registry No. **1**, 41451-75-6; **3**, 14907-98-3; (±)-**9**, 122554-54-5; (–)-**9**, 122818-14-8; (±)-**12**, 122554-63-6; (±)-**16**, 116216-47-8; (±)-**17**, 122554-55-6; (±)-**18**, 116216-48-9; (±)-**19**, 122554-56-7; (±)-**20**, 122554-57-8; (±)-**21**, 122554-58-9; (±)-**22**, 122620-77-3; (±)-**23**, 116216-49-0; (±)-**24**, 122554-70-5; (±)-**26**, 116216-50-3; (±)-**27**, 122554-67-0; (±)-**28**, 116216-51-4; (±)-**29**, 116216-58-1; (±)-**30**, 122554-71-6; (±)-**31**, 116216-59-2; (±)-**32**, 123964-06-7; (±)-**33**, 122577-00-8; (±)-**34**, 122554-59-0; (±)-**35**, 122554-73-8; (±)-**36**, 122554-60-3; (±)-**37**, 122554-61-4; (±)-**38**, 122554-62-5; (±)-**39**, 122554-64-7; (±)-**40**, 122554-74-9; (±)-**41**, 122554-65-8; **42**, 123427-40-7; (±)-**42**, 122554-66-9; (–)-**43**, 123964-08-9; (±)-**43**, 123964-07-8; **44**, 122554-76-1; **45**, 92116-32-0; **46**, 122577-01-9; α-**51**, 123535-82-0; β-**51**, 123991-89-9; **52**, 123485-08-5; **55**, 124094-08-2; α-**56**, 123535-83-1; β-**56**, 123535-84-2; **57**, 123485-09-6; **58**, 123485-10-9; α-**59**, 123964-09-0; β-**59**, 123964-10-3; **60**, 123964-11-4; **61**, 14907-99-4; **62**, 123964-12-5; **63**, 123427-42-9; **64**, 123485-11-0; **65**, 123964-13-6; α-**66**, 123964-14-7; β-**66**, 123964-15-8; **67**, 123964-16-9; α-**68**, 123964-17-0; β-**68**, 123991-90-2; **69**, 123991-91-3; **70**, 25514-28-7; **71**, 55812-88-9; **72**, 123964-18-1; (*E*)-$(Me)_2CHC(Me)=CHCO_2H$, 38972-59-7.

Supplementary Material Available: ^1H NMR spectra for compounds **1**, **9**, **12**, **17–21**, **23**, **24**, **26**, **28–34**, **36–44**, **51**, **52**, **58**, **64**, **66–69**, **71**, and **72** and ^{13}C NMR spectrum for the compound **1** (38 pages). Ordering information is given on any current masthead page.