Synthesis of a Model for the BCE Ring System of Bruceantin. A Caveat on the Cyclohexene → Trans Diaxial Diol Conversion

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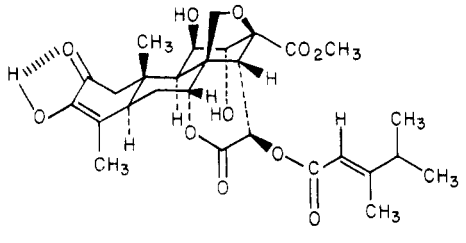
A BCE ring model (**2**) of the quassinoidal antileukemia agent bruceantin (**1**) has been prepared. The key features of the synthesis include formation of the tetrahydrofuran **19** (or **21**) from the tosyloxy enone **17** through alcohol tosylate **18** (or **20**) via an intramolecular solvolytic ring closure; direct cyclization to **19** under basic conditions failed due to the unfavorable geometric constraints imposed by the olefinic moiety of **17**. Tosyloxy ketone **31**, a saturated version of **17**, smoothly cyclized under basic conditions. Attempts to introduce the requisite trans diol functionality from tricyclic **21** by epoxide opening or Prevost reactions were completely unsuccessful; numerous examples of the intervention of the tetrahydrofuran oxygen were documented. The olefin → trans diol conversion was eventually achieved in high overall yield by a three-step procedure: (i) cis hydroxylation of **21** to **52**; (ii) regiospecific oxidation of **52** to ketol **53** via an intramolecular, tetrahydrofuran-assisted, decomposition of a sulfoxonium ion under nonbasic conditions; followed by (iii) stereospecific reduction of **53** to trans diol **2**. ^{13}C NMR correlation was made between trans diol **2** and its mono- and diacetate derivatives with natural bruceantin **1** and its derivatives. Cytological evaluation showed trans diol **2** to be inactive in the KB system.

Bruceantin (**1**), a promising antitumor agent, was isolated by Kupchan et al.[3,4] from *Brucea antidysenterica*, a tree indigenous to Ethiopia. The leaves and roots of this plant have been used in the treatment of cancer in Ethiopia for centuries.[5] Bruceantin has shown cytotoxic activity in vitro against human carcinoma of the nasopharynx (KB) at the 10^{-3} μg/mL level and has exhibited potent inhibitory activity against the P-388 lymphocytic leukemia in the mouse over a broad dosage range at the μg/kg level.[3] Bruceantin has also shown considerable inhibitory activity against Walker 256 intramuscular carcinosarcoma and the L-1210 lymphoid leukemia, but it is perhaps of greatest interest that bruceantin is active against two solid murine tumor systems,[4] a property not common in antitumor compounds.

In support of our efforts directed toward the total synthesis of bruceantin,[6] we initially elected to undertake the synthesis of BCE ring model system **2**. This paper details the results of that study.



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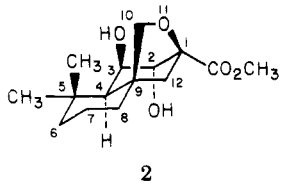

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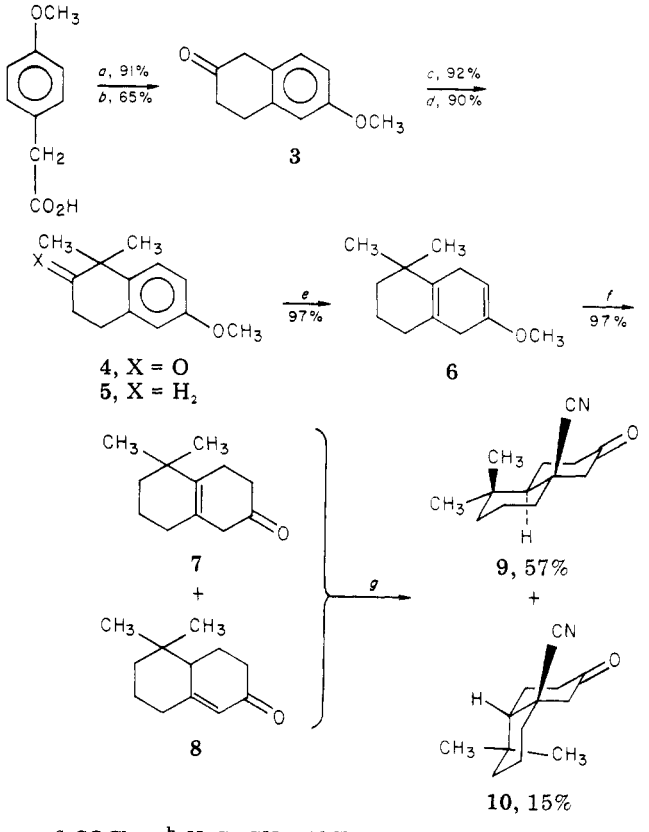
Scheme I



[a] $SOCl_2$. [b] $H_2C{=}CH_2$, $AlCl_3$, CH_2Cl_2. [c] NaH, CH_3I, benzene, room temperature. [d] KOH, NH_2NH_2, $HOCH_2CH_2OH$, 215 °C, 21 h. [e] Li, NH_3(l), EtOH. [f] Concentrated HCl, THF. [g] Et_3Al/HCN, THF.

Synthesis of Tricyclic Tetrahydrofuran 21. The synthetic approach to **2** chosen employed (4-methoxyphenyl)acetic acid as starting material (Scheme I).

6-Methoxy-2-tetralone (**3**) was prepared in 65% yield (after distillation) from (4-methoxyphenyl)acetyl chloride by the *Organic Synthesis* method[7] on a 0.30-mol scale. The yield was reduced substantially when the synthesis was performed on a larger 0.53-mol scale.

The conversion of **3** to **8** followed established literature procedures[8] with some modifications. A marked im-

(1) Postdoctoral Research Associate, 1977-1979.
(2) Alfred P. Sloan Fellow, 1977-1979.
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(6) For other studies directed toward the synthesis of bruceantin and other quassinoids see: (a) Stojanac, N.; Sood, A.; Stojanac, Z.; Valenta, A. *Can. J. Chem.* **1975**, *53*, 619. (b) Dias, J. R.; Ramachandra, R. *Tetrahedron Lett.* **1976**, 3685. (c) *J. Org. Chem.* **1977**, *42*, 1613. (d) *Synth. Commun.* **1977**, 293. (e) *J. Org. Chem.* **1977**, *42*, 3584. (f) Snitman, D. L.; Tsai, M.-Y.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 195.
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provement in the yield of 6-methoxy-1,1-dimethyl-2-tetralone (4) was effected by allowing the reaction to proceed at room temperature for 15 h after adding 3 to a mixture of sodium hydride and iodomethane in benzene instead of heating the reaction mixture at reflux.[8] Wolff–Kishner reduction of 4 afforded 6-methoxy-1,1-dimethyltetralin (5) in 90% yield, whereas Clemmensen reduction[8] produced only a 69.5% yield. Birch reduction of 5 to 6 was effected in 92–97% yield.

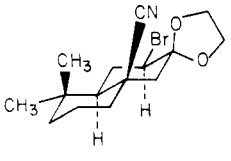
It has been reported that treatment of a THF solution of 6 with sulfuric acid resulted in the almost exclusive formation of unconjugated enone 7.[8] However, treatment of a THF solution of 6 with concentrated HCl afforded a mixture consisting of approximately 90% 8 and 10% 7. The enones could be separated by column chromatography but a better overall yield could be obtained if the mixture of enones was subjected to the subsequent reaction.

The elaboration of 8 to 2 requires the axial introduction at C-9 of a functional group convertible to a hydroxymethyl group. Hydrocyanation of enone 8 with triethylaluminum–hydrogen cyanide[9,10] was well-suited to meet this requirement. This method effects 1,4-addition to α,β-unsaturated ketones in an irreversible manner to give kinetically controlled products.[9a] In cyclic α,β-unsaturated ketones only axial addition of cyanide is observed and the trans isomer predominates.[9b]

Treatment of a 9:1 mixture of 8 and 7 with triethylaluminum–hydrogen cyanide afforded a 4:1 mixture of cyano ketones 9 and 10. Column chromatography gave a 56.6% yield of 9 and 15.1% of 10. It was hoped that 7 might be isomerized to 8 under the reaction conditions, but this did not occur. When pure enone 8 was subjected to the hydrocyanation conditions, a slightly higher yield (83.5%) of 9 and 10 was obtained. Column chromatography afforded 9 in 64.4% yield and 10 in 16.0% yield.

The synthetic route to the key tricyclic compound 21 is outlined in Scheme II. Excellent yields are obtained for all reactions employed in this sequence.

The bromo ketal 12 could be obtained directly from 9 by treatment with bromine in ethylene glycol at 60–85 °C.[11] Unfortunately, some equatorial bromo ketal 22 was also



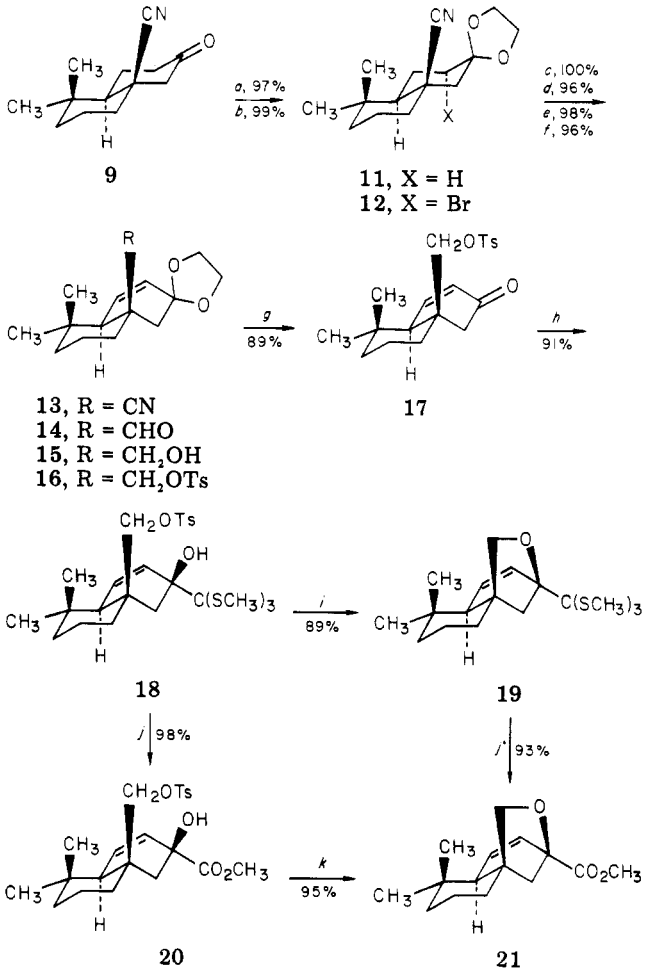
22

formed. The two isomers could not be separated without considerable loss of material, and 22 was not convertible to 13 under the reaction conditions employed for 12.

The nitrile 13 was converted smoothly to aldehyde 14 upon treatment with a large excess of lithium aluminum hydride in THF.[12] Interestingly, when 13 was treated with diisobutylaluminum hydride,[13] only starting material was isolated.

Conversion of the hydroxyl group of the "neopentyl" alcohol 15 to a suitable leaving group initially proved to

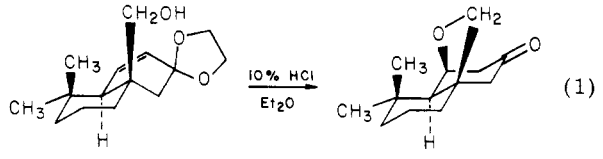
Scheme II



9; 11, X = H; 12, X = Br; 13, R = CN; 14, R = CHO; 15, R = CH_2OH; 16, R = CH_2OTs; 17; 18; 19; 20; 21

[a] $HOCH_2CH_2OH$, TsOH, toluene, reflux 4 h. [b] $C_6H_5N^+(CH_3)_3Br_3^-$, CH_2Cl_2, −10 → +13 °C. [c] DBU, 150 °C. [d] (1) $LiAlH_4$, THF; (2) 5% HOAc, MeOH. [e] $NaBH_4$, 95% EtOH, reflux. [f] (1) *n*-BuLi, THF; (2) TsCl. [g] 3.5% $HClO_4$, THF. [h] $LiC(SCH_3)_3$, THF, −70 → −60 °C. [i] HMPA, 90–95 °C, 24 h. [j] $HgCl_2$, HgO, 12:1 MeOH-H_2O. [k] HMPA, 120 °C, 24 h.

be problematic. Attempts to form the mesylate using the method of Crossland and Servis[14] were totally unsuccessful, even with prolonged reaction times at room temperature. The standard procedure for preparation of tosylates[15] afforded none of the desired product. An attempted preparation of the corresponding bromide using carbon tetrabromide and triphenylphosphine[16] also was fruitless. However, a product was isolated in the latter two reactions. This material was identified as the tetrahydrofuran 23, presumably formed by acid-catalyzed deketalization and intramolecular addition of the alcohol moiety to the incipient enone. Treatment of 15 with 10% HCl afforded 23 in 78.5% yield (eq 1).



15 → 23 (1)

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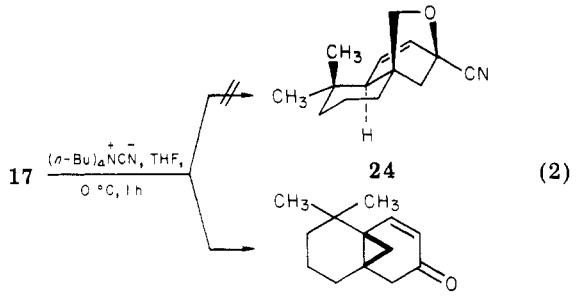
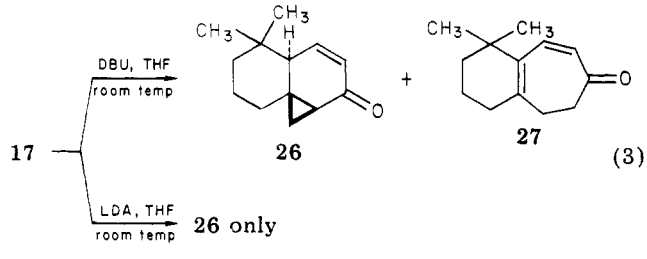
It was originally planned to use cyanide as a nucleophile to convert **17** to the tetrahydrofuran **24** (eq 2) via reversible addition, the nitrile subsequently being convertible to the desired methyl ester **21**. However, treatment of **17** with tetra-*n*-butylammonium cyanide[17] in THF at 0 °C afforded no **24**. The compound formed was identified as the cyclopropane **25**, based on its NMR spectrum and molecular ion (eq 2). The reaction is apparently thermodynamically



(2)

controlled with the product being formed from the more stable enolate. These results have some precedent in that tetraethylammonium cyanide has been implicated in the catalyzed dimerization of cyclohexenone via γ-deprotonation.[18]

Reaction of **17** with an excess of 2-lithio-1,3-dithiane gave a mixture of products consisting of small amounts of **25** and a second cyclopropane, identified as **26**, formed from the kinetic enolate of **17**. A pure sample of **26** was obtained in 77% yield by treatment of **17** with a sixfold excess of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in THF at room temperature for 5.5 h. A second product, assigned structure **27**, was isolated in 15% yield (eq 3). The

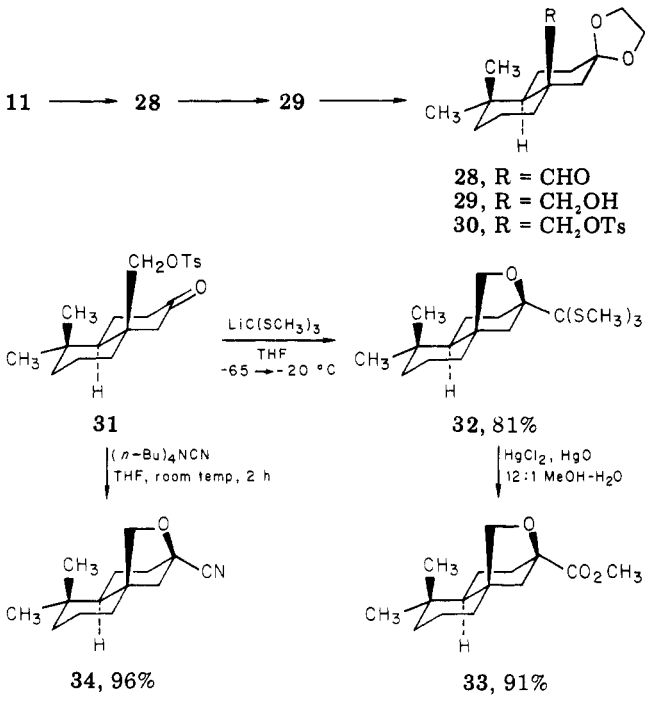


(3)

structure of cycloheptadienone **27** was confirmed by its ^{13}C NMR spectrum. An increase in reaction time resulted in an increase in the proportion of dienone, but the total yield of **26** and **27** declined markedly. For instance, treatment of **17** with a sixfold excess of DBU in THF at room temperature for 42 h afforded **26** and **27** in 23.4 and 26.6% isolated yields, respectively. When **26** was similarly treated with DBU for 90 h, **27** and **26** were isolated in only 15.4 and 4.6% yields, respectively. The bulk of the material isolated in the latter two reactions consisted of more polar colored compounds which in all likelihood arose from further reaction of **27**.

The assignment of structure **25** to the tetra-*n*-butylammonium cyanide product and of structure **26** to the initial DBU product was further substantiated by treatment of **17** with lithium diisopropylamide in THF at room temperature for 16 h. The product expected (**26**) from the kinetic enolate was formed exclusively (86% yield following distillation). It is noteworthy that the reaction proceeded at a negligible rate at 0 °C and that there was still a trace

Scheme III



of unreacted starting material after 16 h at room temperature.

The desired nucleophilic attack at the carbonyl carbon of **17** was effected by treatment with [tris(methylthio)methyl]lithium[19] in THF. However, the desired product **19** was not formed directly. If the reaction mixture was quenched with saturated ammonium chloride at −60 °C, alcohol **18** was obtained in excellent yield (91%). If the reaction mixture was warmed to room temperature before quenching, extensive decomposition took place (**25** was identified as one of the products) but no **19** was formed. Alcohol tosylate **18** was efficiently converted to **19** by heating in hexamethylphosphoramide (HMPA) at 90–95 °C for 24 h.[20] Treatment of **19** with mercuric chloride and mercuric oxide in aqueous methanol[21] afforded methyl ester **21** in 93% yield. An equally efficient route to **21** involved conversion of **18** to methyl ester **20** (98%) and cyclization to **21** (95%). In the latter case, a temperature of 120 °C was necessary to effect smooth conversion.

As stated previously, it was anticipated that treatment of enone tosylate **17** with [tris(methylthio)methyl]lithium would yield the tricyclic compound **19** directly under the reaction conditions. However, the alcohol tosylate **18** was formed exclusively. It was felt that the failure to cyclize directly was due to an unfavorable orientation of the tosylate group with respect to the incipient alkoxide ion imposed by the C-3, C-4 unsaturation in **17**. Examination of models showed the corresponding orientation to be much more favorable for the saturated keto tosylate **31** (Scheme III). It was expected that **31** would be smoothly converted to the tricyclic compound by treatment with [tris(methylthio)methyl]lithium. To test this postulate the conversion of **11** to **33** was undertaken (Scheme III). The reactions paralleled those employed in the conversion of **13** to **21**.

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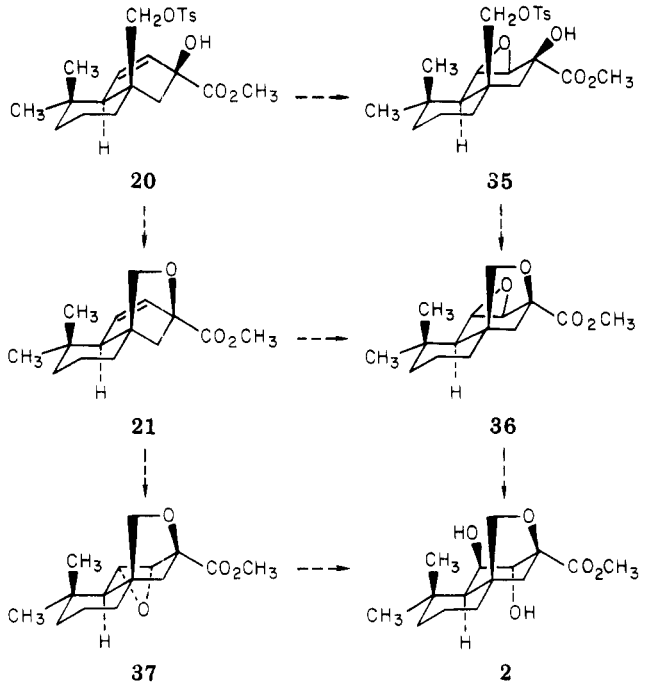
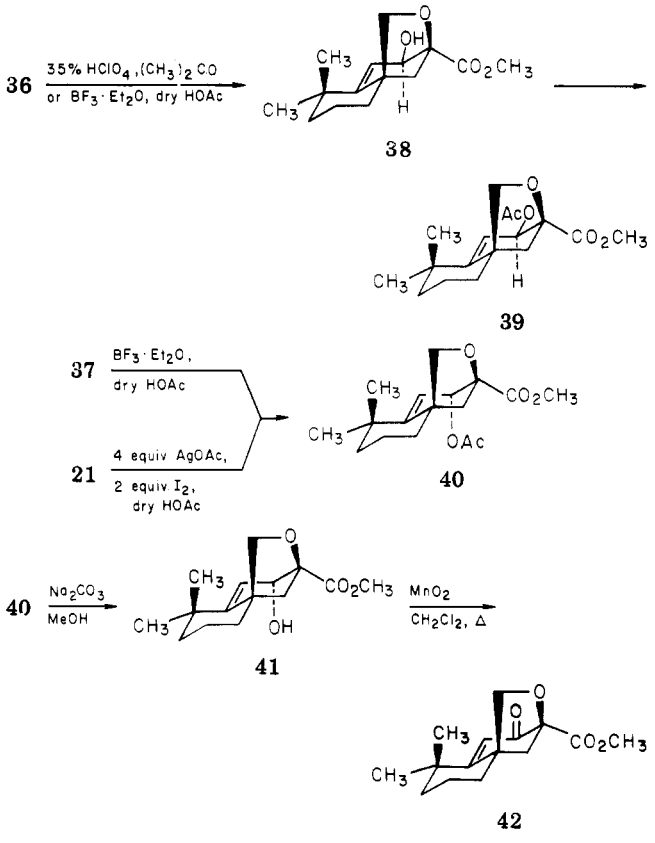
Scheme IV



Scheme V



When a solution of **31** in THF was added to a solution of [tris(methylthio)methyl]lithium at −65 to −60 °C, the reaction to produce **32** appeared to be complete within 0.5 h. The reaction mixture was stirred at −60 °C for 1.5 h and then warmed to −20 °C over a 1-h period before quenching with water. After thin layer chromatography of the crude product on silica gel, **32** was isolated in 81% yield. Furthermore, treatment of **31** with a slight excess of tetra-*n*-butylammonium cyanide in THF at room temperature afforded the nitrile **34** in 96% yield.

Unsuccessful Attempts at Synthesis of the Trans Diol 2. Initially, two possible routes to target diol **2** through epoxide intermediates were envisaged (Scheme IV).

The epoxide **36** was preferred to **37** since the attacking nucleophile would not have to contend with three 1,3-diaxial interactions at C-3 in the hydrolysis to diol **2**. It was felt that the hydroxyl group in **20** would direct the oxygen to the β face. However, attempts to convert **20** to **35** with *m*-chloroperoxybenzoic acid (MCPBA) and peracetic acid at temperatures ranging from −20 to 65 °C were unsuccessful. Mostly starting material was recovered in each case. Treatment of **20** with peroxytrifluoroacetic acid in the presence of sodium carbonate or disodium hydrogen phosphate[22] resulted in extensive decomposition.

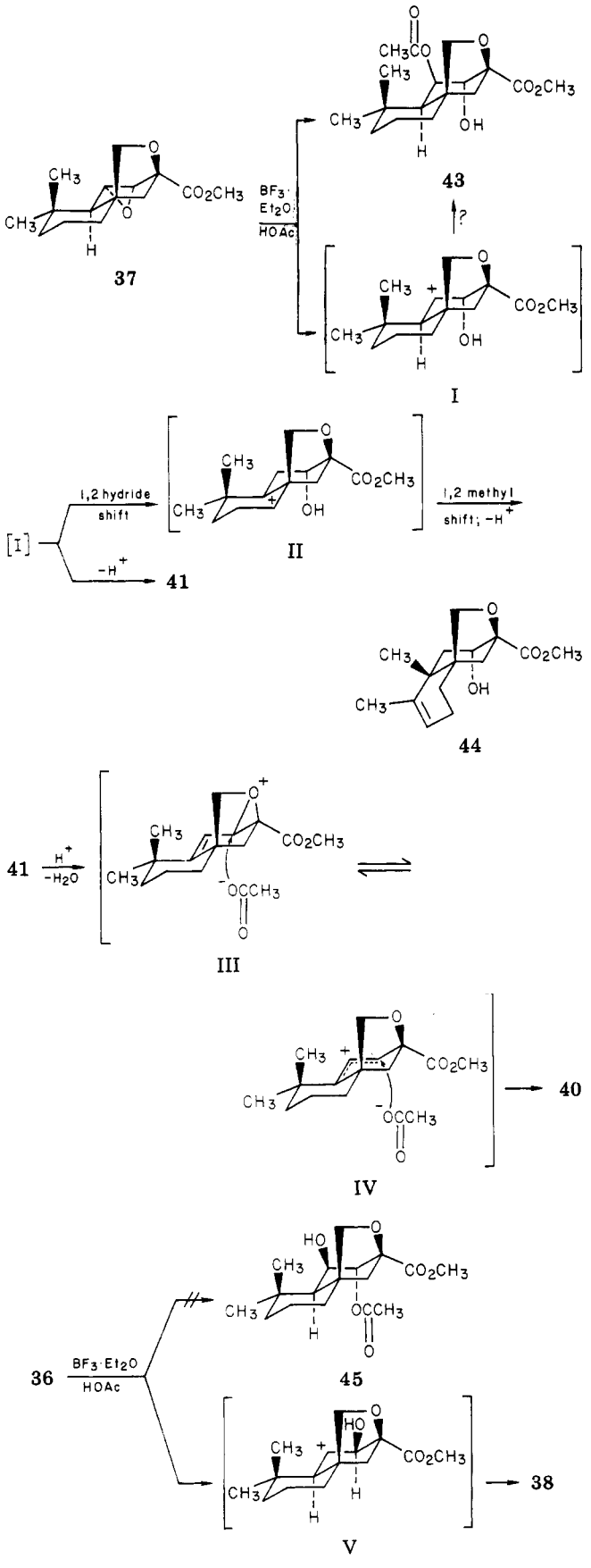
Compound **21** was successfully converted to a 3:1 mixture of epoxides **37** and **36** in 93–98% yield by treatment with 1.5 equiv of peroxytrifluoroacetic acid in dichloromethane in the presence of sodium carbonate. Previously, attempts to effect this conversion with MCPBA and with peracetic acid in ethyl acetate[23] had failed. The epoxides **36** and **37** were obtained in pure form by column chromatography or by a combination of recrystallization from petroleum ether–ether and subjecting the residue from the mother liquors to high performance liquid chromatography (LC). *There is strong evidence that the formation of the minor epoxide* ***36*** *is in large measure due to the directive effect of the tetrahydrofuran oxygen.* A THF solution of olefin **21** was treated with a total of 6 equiv of peroxytrifluoroacetic acid at four intervals over a period of 18 h. The isolated material consisted of 62% **37** and 38% starting material (NMR analysis). Neither the NMR spectrum nor TLC indicated the presence of any **36**.

A number of conditions for hydrolysis of the epoxides **36** and **37** were investigated on the 10-mg scale (for example: 35% aqueous perchloric acid in acetone, THF, and methanol and 9.5 M fluoboric acid in the same solvents). In most cases, **36** gave a mixture of products on hydrolysis while the major epoxide **37** reacted sluggishly if at all. Best results were obtained upon treatment of **36** (44 mg) with 0.5 mL of 35% aqueous perchloric acid in 3 mL of acetone at room temperature for 1 h. The sole identifiable product was the equatorial allylic alcohol **38** (Scheme V), isolated in 29% yield following column chromatography. Alcohol **38** presumably arises from scission of the protonated epoxide and concurrent loss of the axial C-4 hydrogen. The structure of **38** was confirmed by experimental evidence which will be described shortly. The reaction of **37** under the above conditions required approximately five times as much 35% aqueous perchloric acid and 8 h for completion. At least seven products were formed, none predominating. There was no indication of the desired trans diol **2** or axial allylic alcohol **41** in the NMR spectrum of the crude product mixture.

Several attempts were made to open the epoxides **36** and **37** with acetate. In only one case was the reaction clean enough to warrant isolation and characterization of the products. Epoxide **37** was treated with 9 equiv of boron trifluoride etherate (added in two portions) in acetic acid at room temperature for 5.5 h. The crude product mixture was subjected to column chromatography. The three major products were identified as axial allylic acetate **40** (Scheme V), the desired monoacetate **43**, and the rearrangement product **44** (Scheme VI), isolated in 38, 18, and 24% yields, respectively. Also isolated was a trace (<0.1%) of equatorial allylic acetate **39**. Although the product which we were seeking was formed in the reaction, the yield (18%) was far too low to be useful.

In a companion experiment, epoxide **36** was treated with 11 equiv of boron trifluoride etherate (added in two por-

Scheme VI



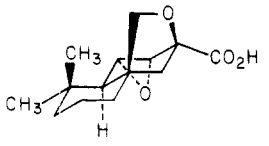
tions) in acetic acid at room temperature for 5 h. The major product was equatorial allylic alcohol **38**, isolated in 41% yield after column chromatography. Also isolated was a mixture of three more polar compounds, which was not investigated further. However, the desired acetate **45** (Scheme VI) definitely was not among the products. *No* allylic acetate was formed under the reaction conditions, nor was there any indication of the ketone which one might reasonably expect to arise from intermediate carbonium ion V (Scheme VI).

An explanation for the formation of axial allylic acetate **40** and alcohol **44** upon treatment of major epoxide **37** with excess boron trifluoride etherate is offered in Scheme VI. Boron trifluoride mediated opening of the epoxide leads to intermediate carbonium ion I. Elimination of the sterically hindered C-4 proton gives allylic alcohol **41**. Alternatively, a 1,2-hydride shift gives the more stable carbonium ion II, which can either revert to **41** or undergo a subsequent 1,2-methyl shift and proton loss to form **44**. Protonation of allylic alcohol **41** followed by loss of water, facilitated through neighboring-group participation from the tetrahydrofuran oxygen, leads to an intermediate represented by the equilibrium between III and IV. Although we cannot ascertain the true position of the equilibrium, there is a considerable body of evidence (much of which will be discussed later) that oxonium ion III is the major contributor. Attack of either III or IV by acetate ion provides axial allylic acetate **40**. The fact that **40** was formed to the near exclusion of equatorial allylic acetate **39** strongly suggests that the tetrahydrofuran oxygen is blocking approach of acetate from the β face under the conditions employed.

The mechanism presented in Scheme VI requires the conversion of alcohol **41** to acetate **40**. In order to confirm this transformation, a solution of **41** in acetic acid was treated with 9 equiv of boron trifluoride etherate at room temperature. Indeed the formation of **40** was observed to occur within 1 h. Since starting material remained after 2.5 h, an additional 9 equiv of boron trifluoride etherate was added. No starting material remained after 1 h, but now a second product, equatorial allylic acetate **39**, was observed. NMR analysis of the crude product indicated approximately 68% **40** and 32% **39**. In further experiments, a solution of pure **40** in acetic acid was treated with 9 equiv of boron trifluoride etherate. Only negligible conversion to **39** took place after 14 h at room temperature. An additional 9 equiv of boron trifluoride etherate was added. Substantial conversion to **39** was observed after 1 h. After 2 days, a final 9 equiv of boron trifluoride etherate was added and the mixture was stirred for 24 h. The isolated product consisted of approximately 57% **40** and 43% **39** (NMR analysis). Comparable results were eventually obtained when either equatorial alcohol **38** or **39** were subjected to similar reaction conditions. A solution of **38** in dry acetic acid was stirred at room temperature for 21 h, with no change occurring. Addition of 9 equiv of boron trifluoride etherate still effected no change after 3 h. The slow conversion of **38** to a mixture of **39** and **40** was observed after the addition of a second 9 equiv and stirring for 21 h. A large excess (25 equiv) of BF_3 was then added and the mixture stirred for 3 days. The isolated product consisted of 55% **40** and 45% **39** (NMR analysis). Finally, pure **39** was subjected to conditions identical with those employed for **40**. The isolated material consisted of 57% **40** and 43% **39**. The above results indicate that under the solvolytic conditions employed, oxonium ion III predominates at lower BF_3 concentrations (comparable to those employed in the reactions of epoxides **37** and **36**), whereas carbonium ion IV predominates in the presence of very large excesses of BF_3. At the higher concentrations presumably the extent of coordination of the tetrahydrofuran oxygen to BF_3 approaches 100% and neighboring-group participation is effectively precluded. Eventually,

the thermodynamic equilibrium mixture (ca. 57% **40**, 43% **39**) is attained.

The opening of the major epoxide **37** under basic conditions was also investigated. Treatment of **37** with 10% potassium hydroxide in dimethyl sulfoxide (Me_2SO)[24] at 100–110 °C for 6 days gave the carboxylic acid **46** as sole product (73% yield). The conversion to the acid was



46

complete in less than 1 day. The use of Me_2SO as solvent has been demonstrated to favor diaxial cleavage under basic conditions.[24] (A mixture of the two isomers of 1-phenyl-4-*tert*-butylcyclohexene oxide was converted completely to the corresponding trans diaxial diol by heating in a mixture of Me_2SO and 2 N potassium hydroxide at 100 °C for 60 h.[24])

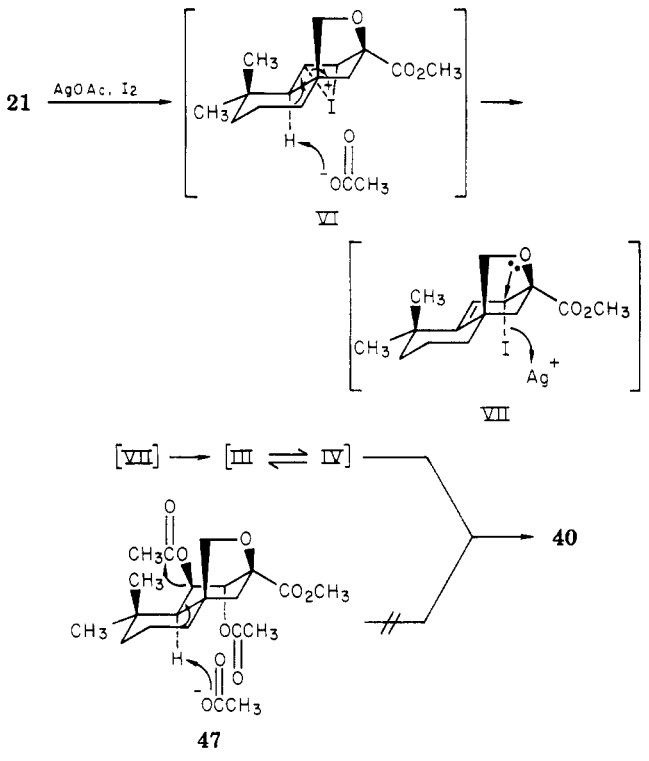
The above reaction was not performed on the minor epoxide **36**, which was in short supply. The prospects of trans diaxial opening of **36** under alkaline conditions (along with unavoidable saponification) should be much better than for **37**. However, even should the reactions prove successful, the results would be of questionable value in the transformation of olefin **21** to diol **2** since **36** presently represents only 25% of the epoxidation product.

Since the preparation of the desired trans diol **2** through the epoxides **36** and **37** did not appear feasible, the introduction of acetate (or benzoate) groups in a trans diaxial manner by subjecting the olefin **21** to Prevost conditions[25] was considered. The introduction of **21** to a mixture of bromine and silver benzoate in benzene and subsequent heating at reflux[26] gave a mixture of products, none of which was the desired dibenzoate. Similar results were obtained for the precursors **14**, **15**, and **19**.

Generally, only trans dibenzoates are prepared via the Prevost reaction. There are virtually no instances in which trans diacetates have been prepared by this method.[25d] In the Woodward modification of the Prevost reaction an olefin is treated with iodine and silver acetate in dry acetic acid at room temperature, water is added, and the mixture is heated at reflux, resulting in overall cis addition of hydroxyl and acetate.[25e,26]

In an attempt to prepare the trans diaxial diacetate, **21** was subjected to Prevost conditions in dry acetic acid. Accordingly, when 2 equiv of iodine was added to a solution of **21** and 4 equiv of silver acetate in dry acetic acid[27,28] and the mixture was heated at reflux for 0.5 h, the axial allylic acetate **40** was obtained in 94% yield. It is notable that when 4 equiv of sodium acetate was included in the reaction mixture, the reaction was greatly accelerated and **40** was obtained in excellent yield (78–96%) after stirring at room temperature for 2–6 h. Furthermore, there was no reaction when **21** was treated with iodine and the sparingly soluble silver acetate in dry benzene.

Scheme VII

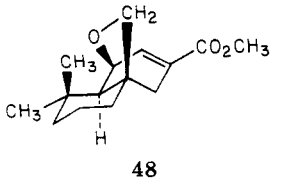


47

A proposed mechanism to account for the formation of **40** is presented in Scheme VII.

Another possible mechanism for the formation of **40** entails initial formation of the trans diaxial diacetate (**47**) and subsequent acetate-catalyzed elimination of acetic acid, thus removing the 1,3-diaxial interactions experienced by the acetate at C-3. Later in the course of our investigations, an authentic sample of **47** was prepared and subsequently treated with 4 equiv of sodium acetate in acetic acid at room temperature for 24 h and in acetic acid at reflux for 0.5 h, without any change occurring. Addition of silver acetate (4 equiv) followed by iodine (2 equiv) at room temperature and subsequent stirring at room temperature for 24 h and heating under reflux for 0.5 h also resulted in no appreciable change. Consequently, the intermediacy of **47** in the formation of **40** can be ruled out (Scheme VII).

At the outset, it was felt that if such a mechanism were indeed operative, the corresponding trans diaxial bis(trifluoroacetate) should be isolable if silver trifluoroacetate and trifluoroacetic acid (TFA) were used instead of silver acetate and acetic acid. Trifluoroacetate should not be a strong enough base to catalyze elimination of TFA. Accordingly, a mixture of **21**, 2 equiv of iodine, and 4 equiv of silver trifluoroacetate was heated at reflux in TFA for 0.5 h. Unexpectedly, the rearrangement product **48** was isolated in 87% yield. It was subsequently shown that trifluoroacetic acid alone effected this transformation.

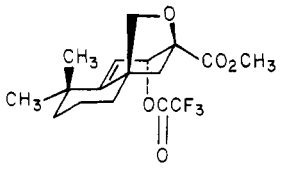


48

When **21** was stirred with silver trifluoroacetate (4 equiv) and iodine (2 equiv) in benzene at room temperature for 2–3 h and then at 60 °C for 0.5 h, allylic trifluoroacetate **49** was obtained as the sole product (94% crude yield; 70%

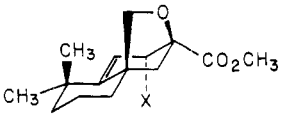
(24) Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron* **1968**, *24*, 1755.
(25) (a) Prévost, C. *C. R. Hebd. Seances Acad. Sci.* **1933**, *196*, 1129. (b) Prévost, C. *Ibid.* **1933**, *197*, 1661. (c) Prévost, C.; Wiemann, J. *Ibid.* **1935**, *204*, 989. (d) Wilson, C. V. *Org. React.* **1957**, *9*, 332. (e) Gunstone, F. D. *Adv. Org. Chem.* **1960**, *1*, 117.
(26) McCasland, G. E.; Horswill, E. C. *J. Am. Chem. Soc.* **1954**, *76*, 1654.
(27) Ellington, P. S.; Hey, D. G.; Meakins, G. D. *J. Chem. Soc. C* **1966**, 1327.
(28) (a) Rahman, A.; Waheed, N.; Ghazala, M. *Z. Naturforsch. B* **1976**, *31*, 264. (b) Parilli, M.; Adinolfi, M.; Dovinola, V.; Mangoni, L. *Gazz. Chim. Ital.* **1974**, *104*, 819.

yield of pure **49**). However, when **21** was stirred with silver



49

trifluoroacetate (2 equiv) and iodine (1 equiv) in acetic acid at 70 °C for 2.5 h, allylic acetate **40** was obtained as sole product (94% crude yield).



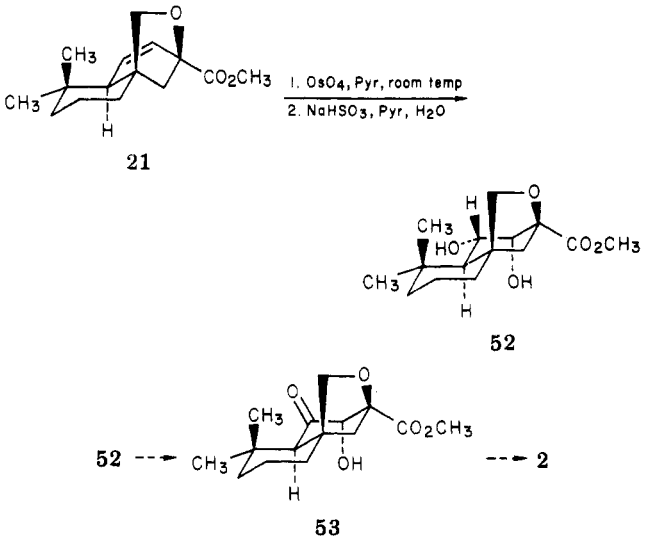
40, X = $OCOCH_3$
50a, X = I
b, X = OMs
c, X = Cl
d, X = Br

All of the aforementioned results are consistent with the mechanism presented in Scheme VII. The role of acetate anion in the conversion of the intermediate iodonium ion to allylic iodide is substantiated by the fact that the reaction is greatly accelerated by added sodium acetate.

There is considerable supporting evidence that the tetrahydrofuran oxygen is lending anchimeric assistance in the reaction. An attempt was made to prepare the mesylate **50b** in the usual manner[14] from **41**. Instead of the expected product, allylic chloride **50c** was isolated in 69% yield following column chromatography. It should be noted that a considerable excess of triethylamine and methanesulfonyl chloride was required to effect completion of the reaction. Mesylate **50b** is evidently initially formed under the reaction conditions. Elimination of mesylate via neighboring-group participation from the tetrahydrofuran oxygen and subsequent attack by chloride anion provides **50c**. Treatment of **50c** with a fourfold excess of sodium acetate in dry acetic acid at room temperature afforded allylic acetate **40** as sole product (TLC), but only after addition of a twofold excess of silver acetate. In another experiment, bromine (2 equiv) was added to a mixture of olefin **21** and sodium acetate (4 equiv) in acetic acid and the mixture was stirred at room temperature for 2.5 h. The NMR spectrum of the crude product indicated 60% allylic bromide **50d** and 40% **40**. Complete conversion to **40** could be effected by heating a solution of the initial product mixture in acetic acid at 70 °C for 2 h in the presence of excess sodium acetate. Unlike **50c**, the addition of silver ion was not required for conversion of **50d** to **40**. Since iodide is a better leaving group than bromide, it can be concluded that the major factor in the conversion of **50a** to **40** (Scheme VII) is neighboring-group participation of the tetrahydrofuran oxygen. As in the case of the previously discussed opening of epoxide **37** in acetic acid in the presence of boron trifluoride etherate, contribution of carbonium ion IV (Scheme VI) cannot be ruled out and the extent of its contribution cannot be estimated. Under the Prevost conditions, silver ion probably serves to remove iodide ion from the reaction medium. However, the observed conversion of allylic bromide **50d** to **40** (discussed above) suggests that the presence of silver ion is not essential.

The structures of allylic alcohols **38** and **41** and allylic acetates **39** and **40** were established by their NMR spectra. The C-2 and C-3 protons in the axial compounds **40** and **41** had coupling constants of 4.5 Hz corresponding to a

Scheme VIII



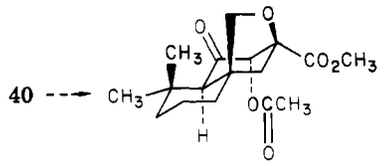
dihedral angle of 48°, whereas these protons in the equatorial compounds **38** and **39** exhibited coupling constants of ca. 2.5 Hz, corresponding to a dihedral angle of ca. 60°. These calculated values are in accord with the dihedral angles observed in molecular models.

Further substantiation of the structural assignments was provided by the unequivocal synthesis of equatorial allylic alcohol **38**. Either acetate **40** or trifluoroacetate **49** was convertible to alcohol **41** by transesterification in methanol in the presence of sodium carbonate. Treatment of **41** with activated manganese dioxide in dichloromethane at reflux afforded enone **42** (Scheme V) in 83% yield.[29] Stereoselective reduction from the less hindered α face should afford equatorial allylic alcohol **38**. A number of reducing agents were examined. Best results were obtained with sodium cyanoborohydride in trifluoroacetic acid (TFA).[30] Treatment of **42** with 7.7 equiv of sodium cyanoborohydride (added in three portions at 40-min intervals at 0–5 °C) afforded **38** in 48% isolated yield. The NMR spectrum of this material was identical with that of the alcohol obtained from epoxide **36**. At least seven other products were formed, but none of these was the isomeric alcohol **41**. Treatment of **42** with L-Selectride[31] in THF at −60 °C for 1 h followed by quenching with water at 0 °C also afforded **38** as the only identifiable product. The customary workup (treatment with 30% hydrogen peroxide and 10% aqueous sodium hydroxide) gave a complex mixture containing no allylic alcohol.

Synthesis of Trans Diol 2. The results thus far presented strongly indicate that any scheme for conversion of olefin **21** to trans diaxial diol **2** which necessitates attack of a nucleophile (or electrophile) from the β face at C-3 is doomed to failure. A synthetic strategy which utilizes this stereochemical reality is therefore indicated. This criterion is met by the reduction of a ketone at C-3 from the less hindered side.

To this end, our attention was initially directed toward the conversion of the readily available allylic acetate **40** to **51** (eq 4). However, several attempts at the conversion, most notably hydroboration in ether followed by treatment with aqueous chromic acid,[32] gave complex mixtures.

(29) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.
(30) For other examples of reduction of enones with sodium cyanoborohydride see: Boutique, M. H.; Jacquesy, R.; Petit, Y. *Bull. Soc. Chim. Fr.* **1973**, 3062.
(31) (a) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. (b) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2196.



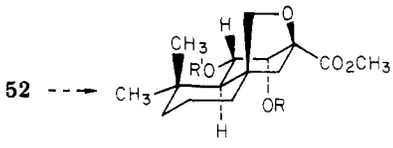
51 (4)

The approach which ultimately resulted in the successful synthesis of diol **2** is shown in Scheme VIII.

The preparation of cis diol **52** was best accomplished by treatment of **21** with a slight excess of osmium tetroxide in pyridine at room temperature[33] (93% yield). Catalytic osmium tetroxide oxidation of **21** using *N*-methylmorpholine *N*-oxide as oxidant[34] also afforded **52** in high yield (89%). The material from the latter reaction contained a small amount of brown impurity but was of sufficient purity that it could be used in subsequent reactions without any adverse effects.

At the outset, we felt that the best prospects for conversion of **52** to **2** lay in protection of the axial hydroxyl group and inversion of the unprotected alcohol, followed by deprotection.

Attempts to prepare *tert*-butyldimethylsilyl ether **54a** (eq 5) were completely fruitless. There was only negligible



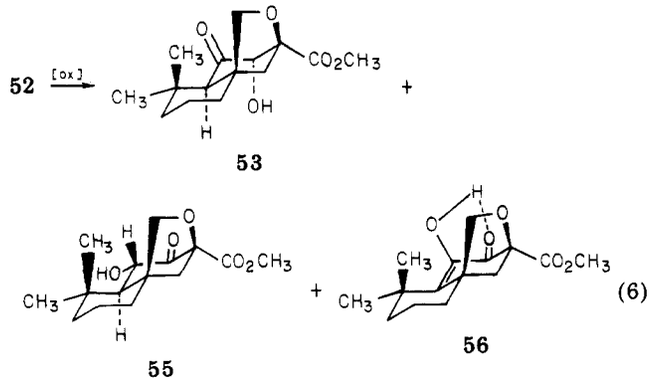
(5)

54a, R = $Si(CH_3)_2$-*t*-Bu; R′ = H
b, R′ = R = CH_3CO
c, R′ = CH_3CO; R = H

reaction upon treating **52** with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide at room temperature for 25 h as well as at elevated temperatures.[35] Similar results were obtained when 4-(dimethylamino)-pyridine (DAP) was used as catalyst and dichloromethane as solvent[36] (no reaction after 60 h at room temperature). However, reaction of **52** with acetic anhydride in dichloromethane in the presence of 1.1 equiv of DAP afforded a mixture of diacetate **54b** and a monoacetate **54c**. Since reaction takes place preferentially at the equatorial hydroxyl instead of the axial as we required, the attractiveness of the contemplated route was greatly diminished, and we directed our efforts toward the more direct approach of Scheme VIII. The successful completion of the cis diol → trans diol transformation requires regiospecific oxidation of **52** to ketol **53** followed by chemoselective stereoselective reduction to **2**.

There are a number of procedures in the literature for conversion of vicinal diols to α-hydroxy ketones without any competitive carbon–carbon bond cleavage occurring.[37-39] It was therefore our expectation that the oxidation products of **52** could at least be restricted to α-ketols **53** and **55** (eq 6).

It has been reported that a number of α-diols could be converted to α-hydroxy ketones in good yield by treatment with 1.3 equiv of bis(tributyltin) oxide and bromine in dichloromethane at room temperature for 1–3 h. When **52** was subjected to these conditions there was little reaction. Eventually, after heating at reflux for 3 h, addition of more reagents, and continued heating for 12 h, a mixture of **52**, **53**, and **55** (as indicated by TLC) was obtained. However, isolation of the products was not nearly as simple as inferred.[37] Utilization of the workup employed in a very similar procedure[40] failed to remove the considerable side product, presumably primarily tributyltin bromide. Since the reaction did not proceed to completion and since it was not selective, chromatographic isolation of the products was not attempted.



(6)

The use of silver carbonate on Celite was also investigated.[38] Treatment of 1,2-cyclohexanediol with an excess of this reagent has been reported to give 2-hydroxycyclohexanone in 45% yield. In our hands, treatment of **52** with 4 equiv of silver carbonate on Celite in benzene at reflux for 22.5 h gave a 2:1 mixture (NMR) of **52** and undesired α-ketol **55** (eq 6). When this mixture was subjected to more forcing conditions (10 equiv of silver carbonate, reflux in toluene for 1.5 h), conversion to **55** was essentially complete with only trace amounts of **53** and α-dione **56** (eq 6) being formed. These results are not surprising since the proposed mechanism for silver carbonate oxidation[41] and experimental evidence[42] require preferential oxidation of the alcohol with the more accessible α proton.

The reagent formed by complexation of a methyl sulfide with either chlorine or *N*-chlorosuccinimide has found utility in the oxidation of secondary and tertiary 1,2-diols to α-ketols.[39] It is believed that treatment of an alcohol with this reagent forms the sulfoxonium derivative VIII (Scheme IX).[39,43] Treatment of VIII with triethylamine produces the ylide IX, which undergoes internal elimination to yield ketone.

The Corey–Kim procedure (NCS variant) for oxidation of secondary and tertiary 1,2-diols[39] was applied to cis diol **52**. We hoped that the sulfoxonium intermediate VIII would be preferentially formed at the less hindered equatorial hydroxyl and that abstraction of the highly hindered axial proton via intermediate ylide IX would be feasible by virtue of the intramolecular nature of the process. However, no significant reaction occurred, even though the reaction mixture was warmed from −25 to 10 °C over a 5-h period before addition of triethylamine.

Our expectation that the Corey–Kim procedure could be employed to selectively convert **52** to **53** was based in part on the earlier studies of Pfitzner and Moffatt[44] on the

(32) (a) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2951. (b) Lane, C. F. *J. Org. Chem.* **1974**, *39*, 1437.
(33) Baran, J. S. *J. Org. Chem.* **1960**, *25*, 257.
(34) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(35) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(36) Hernandez, O.; Chaudhary, S. K. *Tetrahedron Lett.* **1979**, 99.
(37) Ueno, Y.; Okawara, M. *Tetrahedron Lett.* **1976**, 4597.
(38) Fêtizon, M.; Golfier, M.; Louis, J.-M. *Chem. Commun.* **1969**, 1102.
(39) Corey, E. J.; Kim, C. U. *Tetrahedron Lett.* **1974**, 287.
(40) Saigo, K.; Morikawa, A.; Makaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1656.
(41) Fêtizon, M.; Golfier, M.; Mourques, P. *Tetrahedron Lett.* **1972**, 4445.
(42) Bastard, J.; Fêtizon, M.; Gramain, J. C. *Tetrahedron* **1973**, 2867.
(43) (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. (b) Corey, E. J.; Kim, C. U.; Takeda, Makoto *Tetrahedron Lett.* **1972**, 4339.

Scheme IX

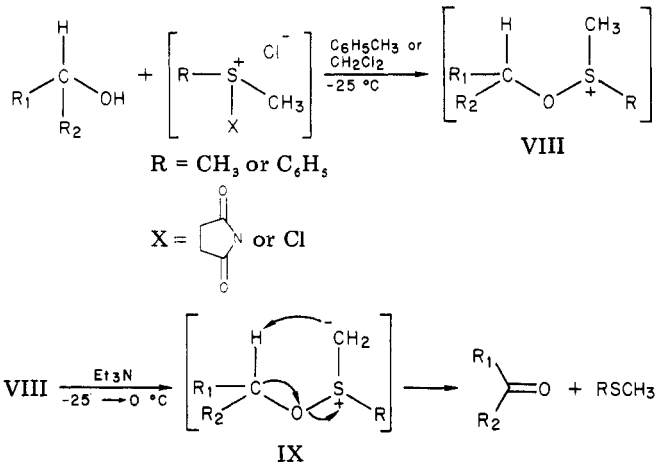


Table I. Oxidation of Cis Diol 52 with Me_2SO/TFAA and Me_2SO/ClC(O)C(O)Cl in CH_2Cl_2

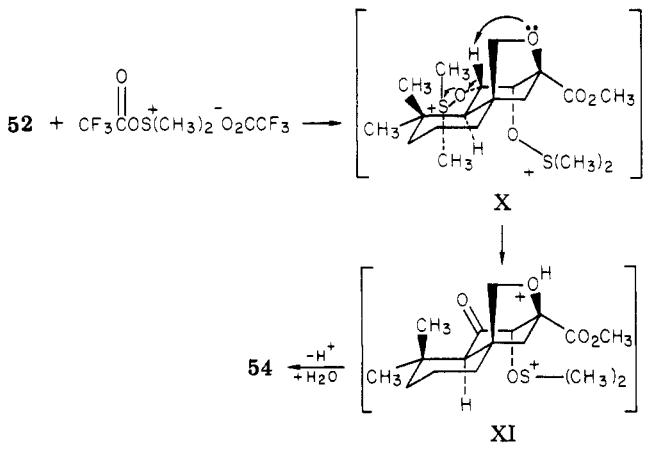
reaction conditions	isolated yield, % 52	53	55	56
1.3 equiv TFAA, −60 °C, inverse addition;[a] 2.3 equiv Et_3N, −60 °C → room temp	24.8	42.8	20.1	
as above; 2.3 equiv TFAA; 2.9 equiv Et_3N	20.4	32.3	18.9	21.7
1.5 equiv TFAA, −60 °C, normal addition;[b] 5.2 equiv Et_3N, −60 → 0 °C				77.9
1.5 equiv TFAA, −60 °C, normal addition; 2.8 equiv Et_3N followed in 5 min by 5% HCl, −60 °C	54[c]	46[c]		
1.67 equiv TFAA, normal addition, −60 → 0 °C; 5% HCl, 0 °C	12.5	84.0		
5.6 equiv ClC(O)C(O)Cl, inverse addition, −60 °C → room temp		2.8	29.5	40.6
1.4 equiv ClC(O)C(O)Cl, normal addition, −60 °C; excess Et_3N, −60 °C → room temp		40[c]		60[c]

[a] Addition of preformed reagent to substrate. [b] Addition of substrate to reagent. [c] Determined by NMR.

oxidation of alcohols with dicyclohexylcarbodiimide (DCC) in Me_2SO in the presence of certain acids. The reaction is thought to proceed through the same intermediates VIII and IX (Scheme IX) as discussed previously. Significantly, 11α-hydroxyprogesterone was smoothly converted to the corresponding ketone with DCC in Me_2SO in the presence of pyridinium trifluoroacetate, whereas the 11β-epimer was inert under these conditions.[44b] Since the reaction proceeded for the isomer with the less hindered hydroxyl (and consequently the more hindered C-11 hydrogen) the rate determining step might well be formation of the sulfoxonium intermediate VIII. By analogy, the expected product upon oxidation of **52** would be the required α-ketol **53**. However, treatment of **52** with 3 equiv of DCC in Me_2SO in the presence 1 equiv of pyridinium trifluoroacetate at room temperature for 22.5 h and then at 65 °C for 20 h furnished essentially unchanged starting material.

The procedure which showed the most promise and which eventually led to success utilizes the reagent gen-

Scheme X



erated by addition of trifluoroacetic anhydride (TFAA) to Me_2SO in dichloromethane at −60 °C.[45] The product distribution was highly dependent on the precise reaction conditions employed (Table I). It was felt that the prospects of selective conversion of **52** to **53** would be improved by inverse addition (i.e., addition of the preformed reagent to a solution of the diol substrate). However, the exact opposite proved to be the case. A dichloromethane solution of the reagent formed at −60 °C was added portionwise to a solution of **52** at −60 °C until all starting material "appeared" to be consumed (TLC). Thereupon excess triethylamine was added and the mixture was warmed to room temperature. The isolated material generally consisted of all possible products as well as starting material (Table I). It was, however, encouraging that the major product was the desired α-ketol.

We next investigated the usual procedure wherein a solution of substrate is added to a solution of the Me_2SO–TFAA reagent (normal addition). Accordingly **52** was allowed to react with 1.5 equiv of reagent at −60 °C and 5.2 equiv of triethylamine was added at −60 °C. Following workup, the only identifiable product proved to be α-dione **56**, isolated in 78% yield following column chromatography. Since the reaction was run on a small (0.28 mmol) scale it is conceivable that more than 1.5 equiv (0.06 mL) of TFAA was actually used. At least 2 equiv of TFAA should be required for the exclusive formation of **56**. In any event, the formation of **56** appeared to be enhanced by prolonged contact with triethylamine. In another experiment, the reaction was quenched at −60 °C with 5% HCl 5 min after addition of triethylamine. The isolated material consisted of nearly equal amounts of starting material and **53** (no **56**).

In monitoring the reactions of **52** with the Me_2SO–TFAA reagent by TLC, it had been noted that complete conversion to the desired α-ketol **53** generally appeared to take place within 10 min after addition of **52** to the reagent (*before addition of the base*). Yet upon workup, the reaction proved to be incomplete or other products were formed. In further experiments, the reaction of the Me_2SO–TFAA complex with cis diol **52** was quenched with water at −60 °C and at room temperature (no triethylamine added). In the first case, only starting material was recovered. In the second case, the product consisted of **53** and uncharacterized material which upon standing was converted to α-dione **56**. It is noteworthy that the reaction mixture began to turn yellow at around 0 °C. Conversion of **52** to **53** did take place without addition of the supposedly essential base. Under optimum conditions, **52** was

(44) (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661. (b) *Ibid.* **1965**, *87*, 5670.

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

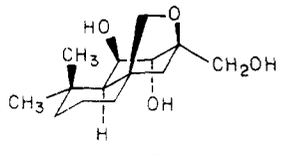
added at −60 °C to a solution of reagent prepared by addition of 1.67 equiv of TFAA to excess Me_2SO. The reaction was quenched with 5% HCl after stirring at −60 °C for 0.5 h and −15 to 0 °C for 1.5 h. Following column chromatography, **53** was isolated in 84% yield and 12.5% of starting material was recovered. Complete conversion to **53** could not be accomplished without further or competing reactions taking place.

An explanation for the formation of α-ketal **53** under acidic conditions is offered in Scheme X. At low temperature, the bis-sulfoxonium intermediate X should be the predominant species in solution. The tetrahydrofuran oxygen is ideally situated to serve as an internal base in the removal of the highly hindered axial hydrogen, thus facilitating decomposition to the desired ketol and dimethyl sulfide. Since only starting material was recovered when the Corey–Kim and Pfitzner–Moffatt procedures were employed it seems reasonable that no intermediate sulfoxonium intermediate was formed. The efficiency of the Me_2SO–TFAA reagent in the oxidation of highly hindered alcohols has been stressed.[45]

The utility of the recently reported Me_2SO oxalyl chloride reagent[46] in the oxidation of **52** was also investigated. The results are reported in Table I.

With ketol **53** available from **52** in high yield, only selective reduction to **2** remained to complete the synthesis of the model system. Considering the steric constraints, reduction of **53** was expected to furnish **2** exclusively.

A number of reducing agents were investigated for the conversion of **53** to **2**. Among these were sodium borohydride in methanol, lithium tri-*tert*-butoxyaluminum hydride,[47] and tetra-*n*-butylammonium borohydride in dichloromethane.[48] The reactions were generally sluggish and required treatment with a large excess of reducing agent at room temperature for at least 2 h before all (or most) starting material was consumed. In all cases, the desired trans diol was obtained in low yield. In addition, a second product, identified as triol **57** was formed at a competitive rate.



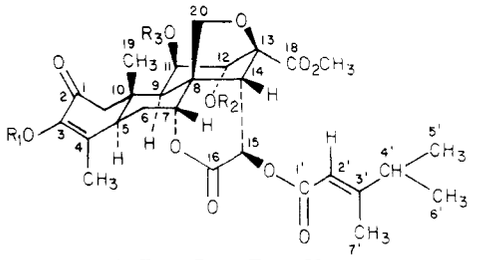
57

Of the aforementioned reagents, tetra-*n*-butylammonium borohydride offered the most promise. Treatment of **53** with 6 equiv of borohydride in dichloromethane at room temperature for 2 h followed by quenching with 5% aqueous HCl[49] gave a mixture which afforded 18% **53**, 33% **2**, and 12% **57** upon column chromatography. It had been observed "that the addition of an equivalent amount of ethanol results in a substantial (ca. twofold) increase in the rate of reduction of cyclohexanone by tetrabutylammonium borohydride in dichloromethane."[48] In our hands, treatment of **53** with 5.5 equiv of borohydride in 5% methanol–dichloromethane at room temperature for 20 h afforded triol **57** as sole product (75% yield). Running the reaction in pure methanol also gave **57** as sole product (87% yield), but more reducing reagent (10 equiv) and a longer reaction time (25 h) were required.

It has been observed that some diborane is generated by a solution of tetra-*n*-butylammonium hydride in dichloromethane. It is possible that diborane generated under the reaction conditions is responsible for the formation of triol **57**. In an attempt to eliminate the production of diborane (or at least to minimize its effect) a solution of **53** in ethyl acetate was treated with 4.5 equiv of tetra-*n*-butylammonium borohydride at 0 °C for 80 min. The material isolated proved to be the desired diol **2** (91%, >95% pure) uncontaminated by **57**. Not only was the reaction cleaner, but it proceeded at a faster rate at a lower temperature.

Although the above results were quite gratifying, still better results were obtained using sodium cyanoborohydride[50–52] in trifluoroacetic acid as reducing agent. Treatment of a solution of **53** in trifluoroacetic acid with 9–10 equiv of sodium cyanoborohydride (added portionwise at intervals over 3 h) at 0–5 °C afforded **2** free of any impurities in 92–96% yield. The use of trifluoroacetic acid as solvent is critical. Treatment of **53** with sodium cyanoborohydride at pH 3 according to a literature procedure[51] gave no reaction. When acetic acid was used as solvent,[52] the rate of formation of **2** was too slow to be of synthetic use.

Spectral Correlations. The tricyclic model compound **2** was further characterized by detailed comparison of the proton and ^{13}C NMR characteristics of this compound, its monoacetate **45**, and its diacetate **47** with those of authentic bruceantin **1** and its acetates **58a** and **58c**.



1, $R_1 = R_2 = R_3 = H$
58a, $R_1 = Ac$; $R_2 = R_3 = H$
b, $R_1 = R_2 = Ac$; $R_3 = H$
c, $R_1 = R_2 = R_3 = Ac$

The 90-MHz proton NMR of bruceantin (**1**) showed a doublet at δ 2.58 (J = 8 Hz) corresponding to the C-11 hydroxyl, a doublet at δ 3.44 (J = 2.5 Hz) corresponding to the C-12 hydroxyl, and a complex multiplet at δ 4.1–4.4 due to the C-11 and C-12 protons. The 90-MHz NMR spectrum of **2** showed peaks at δ 2.70 (d, J = 11 Hz) and 3.11 (d, J = 2.5 Hz) which were assigned to the C-3 and C-2 hydroxyls, respectively. The C-2 and C-3 protons appeared as a complex multiplet at δ 4.0–4.3. In the 360-MHz spectrum of **1**, the multiplet at δ 4.1–4.4 was revealed to consist of a broad undefined multiplet at δ 4.20 (C-12 proton) and a broad doublet of doublets at δ 4.26 (J = 8.1 and 3.6 Hz) corresponding to the C-11 proton. It may be concluded that the coupling constant between the C-11 hydrogen and hydroxyl is 8.1 Hz and that the value for C-11 and C-9 is 3.6 Hz. The expected coupling constant

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(47) (a) Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1958**, *80*, 5372. (b) Fajkos, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2284.
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Table II. ^{13}C Chemical Shifts for Compounds of General Structure A[a]

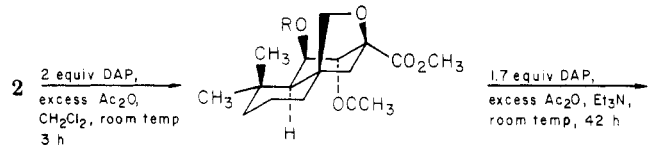
	9	10	11	12	13	14	15	18[b]	20[c]	25	26
C-1	53.2	51.1	46.4	(41.2)	47.2	47.9	45.3	44.2	44.0	44.7	47.8
C-2	205.5	206.1	107.0	106.3	104.1	104.1	105.8	(80.1)	72.0	196.9	193.9
C-3	41.2	(39.9)	36.2	54.8	(128.8)	(129.7)	127.2	(129.7)	(128.1)	124.4	127.7
C-4	24.2	24.1	22.1	31.0	(130.4)	(130.7)	132.5	(130.7)	(129.5)	156.9	144.5
C-5	33.4	34.2	33.2	32.6	32.8	32.8	32.2	32.0	32.2	32.8	35.2
C-6	41.2	(33.6)	41.4	(41.4)	40.6	41.2	41.4	40.9	41.0	36.3	41.3
C-7	19.5	19.9	19.4	19.3	19.3	18.8	18.4	17.6	17.5	(31.3)	(22.2)
C-8	38.4	30.9	39.4	39.1	37.4	33.2	34.3	34.4	34.0	(32.3)	37.0
C-9	40.8	39.8	38.0	37.8	38.6	51.4	42.0	38.6	36.9	29.9	24.7
C-10	50.8	45.9	52.4	45.5	51.4	52.4	53.8	52.0	52.0	23.0	30.1
C-11	122.0	125.0	123.5	123.4	123.0	207.1	60.8	69.5	68.8	17.4	(20.1)
CH_3 (ax)	20.0	29.0	19.9	20.3	20.2	21.0	22.0	(22.2)	(22.2)	(27.5)	21.2
CH_3 (eq)	31.8	30.9	32.1	31.6	31.4	30.8	32.2	32.6	32.5	(28.1)	30.0
$-OCH_2CH_2O-$			64.7	65.9	65.3	64.8	64.7				
			64.2	64.8	64.4		64.2				

[a] ppm from Me_4Si. Similar values in parentheses may be reversed. [b] δ 15.7 (SCH_3), (21.6) (tosyl CH_3), (80.2) [$C(SCH_3)_3$], 127.9 (d), 129.7 (d), 135.5 (s), 144.4 (s). [c] δ (21.6) [tosyl CH_3]; 53.0 (OCH_3), 127.8 (d), 133.4 (s), 144.4 (s).

between the C-11 and C-12 protons was not discernible. In the 360-MHz spectrum of **2** the signals due to the C-2 and C-3 protons appeared as a singlet and broad singlet, respectively, the coupling with the hydroxyls having been eliminated. The high degree of similarity found in the proton NMR spectra of **1** and **2** demonstrates that vicinal trans diaxial diols are present in both. The large coupling constants for the β hydroxyls can be attributed to strong hydrogen bonding to the tetrahydrofuran oxygen.

The monoacetate **45** was prepared by treatment of **2** with 2 equiv of DAP[53] and 8 equiv of acetic anhydride in dichloromethane at room temperature for 3 h (eq 7). No diacetate **47** was formed. This result attests to the steric environment of the C-3 hydroxyl. There are a number of examples in which the C-12 hydroxyls of quassinoids containing the trans diaxial diol system can be selectively acetylated and in which acetylation of the C-11 hydroxyl is very difficult.[4,54] In these examples, an acetate group at C-1 causes even greater steric hindrance at the C-11 hydroxyl than experienced by the C-3 hydroxyl in **2**.

Formation of the diacetate **47** could be accomplished only after prolonged stirring of a mixture of **45**, 1.7 equiv of DAP, and excess acetic anhydride in triethylamine[53b] at room temperature (eq 7).



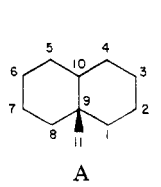
45, R = H

47, R = $COCH_3$ (7)

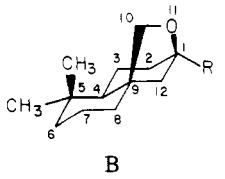
The selective preparation of bruceantin monoacetate (**58a**) was easily accomplished by treating bruceantin with a total of 4.6 equiv of acetic anhydride in pyridine at 0 °C over 3.5 h and refrigeration at −20 °C overnight. The selective monoacetylation of brusatol, a quassinoid of structure similar to **1**, has been accomplished by treatment with excess acetic anhydride in pyridine at room temperature for 1.5 h.[55]

We had felt that the selective formation of the diacetate **58b** might also be possible. Treatment of **58a** with 4.5 equiv of acetic anhydride in pyridine at room temperature for 2 h gave no reaction. An additional 9 equiv of acetic anhydride and stirring for 4 h resulted in no discernible change. In another experiment, 0.0169 mmol of **58a** was treated with 0.0164 mmol of DAP and 0.2 mmol of acetic anhydride in dichloromethane. There was virtually no reaction at 0 °C for 1 h. After 5 h at room temperature, a small amount of **58b** (assumed) and **58c** was observed to have formed. Twenty-four hours later, after periodic addition of a total 0.0164 mmol of DAP and 1.1 mmol of acetic anhydride, unreacted **58a** was still present but the major product was **58c**. Treatment of bruceantin with 3.03 equiv of DAP and excess acetic anhydride for 12 h gave exclusively triacetate **58c**. The presence of the bulky axial substituent at C-14 of **58a** accounts for the difference in reactivity between **58a** and **2**. Apparently, a β substituent at C-1 of a quassinoid[54] is necessary to preclude competitive acetylation at the C-11 hydroxyl. Only the monoacetate and triacetate were reported for brusatol, a quassinoid lacking a C-1 substituent.[55]

During the course of our model studies, the ^{13}C NMR spectra of a number of compounds synthesized were recorded.[56] The results are presented in Tables II and III. In Table II the chemical shift values for compounds of general structure A are listed. The data for tricyclic compounds of general structure B are given in Table III. The chemical shifts for compounds **27** and **48** are listed in the Experimental Section.



A



B

The *trans*- and *cis*-cyano ketones **9** and **10** can be readily distinguished by their ^{13}C NMR spectra (Table II). In particular, the C-8 carbon appears 7.5 ppm further downfield in **9** than in **10**, and the C-10 carbon appears 4.9 ppm further downfield in **9**. The corresponding values for

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Table III. ^{13}C Chemical Shifts for Tricyclic Compounds of Structure B[a]

	19	21	36	37	38	39	40	41	42	49
C-1	74.3	80.4	80.0	82.9	84.9	83.5	82.7	83.8	88.3	81.9
C-2	(128.4)	(127.5)	52.9	(52.1)	73.6	76.2	71.3	70.2	192.7	74.6
C-3	(130.8)	(130.1)	50.1	(51.6)	120.6	116.7	116.3	119.4	122.0	114.2
C-4	56.1	55.7	54.5	54.7	152.3	154.0	154.9	152.8	168.7	158.0
C-5	33.1	33.1	34.3	33.2	35.0	35.2	35.2	35.0	36.7	35.4
C-6	41.0	40.9	42.1	41.3	39.5	39.4	39.5	39.6	38.6	39.4
C-7	20.6	20.6	20.8	20.8	19.8	19.7	19.8	19.9	19.4	19.8
C-8	36.8	36.2	36.9	36.1	31.6	31.5	31.8	31.8	31.6	31.7
C-9	45.6	46.4	42.5	44.6	44.5	44.9	45.2	45.8	47.6	45.6
C-10	73.7	74.2	75.0	74.8	82.0	82.6	80.5	80.9	79.3	80.5
C-11	48.9	48.5	48.9	43.3	48.1	48.6	41.8	41.4	49.3	41.8
CH_3 (ax)	22.4	22.4	22.8	22.3	30.5	30.6	30.3	30.4	29.9	30.3
CH_3 (eq)	32.2	32.2	32.4	32.1	31.8	31.6	31.8	31.8	32.0	31.8
OCH_3		52.4	52.6	52.6	52.5	52.5	52.3	52.4	52.5	52.6
C=O methyl ester		172.3	172.0	171.3	172.2	(171.4)	(170.6)	173.0	175.9	169.8
other	$C(SCH_3)_3$, 89.5 SCH_3, 15.1					(170.9) 21.2	(169.5) 20.9			156.3[b] 114.6[c]

	52	53	51	55	56	2	43	45	47	57
C-1	83.9	83.5	82.4	87.4	87.0	84.5	82.9	83.2	81.9	85.2
C-2	72.4	77.4	75.9	206.7	188.0	74.6	(73.0)	74.2	72.3	74.0
C-3	69.5	206.0	201.2	74.0	(143.1)	72.5	(72.7)	71.3	71.2	73.0
C-4	52.0	59.5	61.0	59.1	(142.4)	49.9	49.0	50.9	50.1	50.6
C-5	33.4	32.6	32.8	35.1	35.4	34.1	33.7	34.2	33.7	34.2
C-6	(43.6)	(42.8)	(42.8)	42.1	41.5	(44.4)	(44.6)	(44.4)	(44.9)	(43.5)
C-7	20.8	20.1	20.0	20.5	19.9	20.6	20.5	20.5	20.3	20.6
C-8	35.8	34.3	34.2	34.7	33.3	34.3	34.9	34.3	35.0	34.9
C-9	44.4	46.4	46.3	45.1	47.2	45.2	44.8	44.6	44.0	44.8
C-10	76.4	76.7	76.7	78.8	80.0	76.9	76.5	76.7	76.4	75.7
C-12	(44.0)	(43.6)	(44.2)	49.8	49.7	(45.1)	(45.6)	(45.2)	(45.7)	(44.6)
CH_3 (ax)	21.6	20.6	20.5	21.7	27.4	23.5	23.7	23.4	23.5	23.5
CH_3 (eq)	35.3	32.6	32.6	34.7	29.9	31.3	31.1	31.4	31.2	31.5
OCH_3	52.6	52.7	52.7	52.8	52.7	52.7	52.7	52.6	52.8	
C=O methyl ester	173.5	171.8	(169.7)	167.4	168.0	174.2	(171.6)	(170.9)	(171.0)	
other			(168.3) 20.6				(170.2) 21.7	(170.2) 21.0	(168.4) (169.7) 20.9 21.7	CH_2OH, 65.8

[a] ppm from Me_4Si. Similar values in parentheses may be reversed. [b] C=O, J_{CCF} = 42.0 Hz. [c] CF_3, J_{CF} = 285.6 Hz.

the isomeric 9-methyldecalins were reported as 6.05 and 4.41 ppm, respectively.[56c]

It has been observed that the carbinyl carbon atoms appear at higher field in cyclohexanols bearing axial hydroxy groups than those in the corresponding isomers bearing equatorial hydroxyls.[56e,57] Similar observations have been made with isomeric axial and equatorial acetates.[56e,58] The chemical shift values for the allylic alcohols **38** and **41** (Table III) are in agreement with these observations. The C-2 carbon in the axial isomer **41** is more shielded (by 3.4 ppm) than the C-2 carbon in the equatorial isomer **38**. The results are similar for **39** and **40** (δ_e–δ_a = 4.9 ppm).

A study of cyclohexanediols[59] has similarly shown that the carbinyl carbons are more shielded in the cis isomers (which contain one axial hydroxy group) than in the corresponding trans isomers (with two equatorial hydroxyls). However, this trend does not continue when one compares the cis diol **52** with the trans diaxial diol **2** (Table III). The C-2 and C-3 carbon atoms are both more shielded in **52**.

It has been well established that β-carbon atoms are more shielded in compounds containing axial hydroxy groups than in the equatorial isomers.[57b,e,58,59] Indeed, the C-4 carbon does appear at higher field (by 2.1 ppm) in **2** than in **52**.

The chemical shifts for bruceantin (**1**), its monoacetate (**58a**), and its triacetate (**58c**) are listed in Table IV. Assignments are based in large measure on the chemical shifts reported for brucein C (which differs from bruceantin only at C–4′) and its triacetate.[60] As expected, there is excellent correlation between the ^{13}C NMR spectra of bruceine C and bruceantin, with significant differences occurring only on the side chain. Monoacetylation of **1** produced significant changes in chemical shifts only in the A ring. The chemical shifts for C-11 and C-12 in **1** and **58c** are essentially identical with the corresponding chemical shifts for bruceine C and its triacetate. Finally, the ^{13}C chemical shifts for C-11 and C-12 of **1** compare favorably with those for C-3 and C-2 of **2**.

It has been recently reported that the epoxymethano bridge was essential for biological activity in quassinoids

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Table IV. ^{13}C Chemical Shifts for 1, 58a, and 58c[a]

	1	58a	58c		1	58a	58c
C-1	48.7	50.1	50.3	C-18	171.9	171.6	(170.0)
C-2	192.2	189.5	187.8	C-19	15.5	15.5	15.7
C-3	144.2	142.4	142.5	C-20	74.1	78.8	73.6
C-4	127.9	145.7	144.7	4-Me	13.3	14.5	14.4
C-5	41.9	42.9	43.0	OMe	52.9	52.8	52.8
C-6	29.2	28.9	28.8	C-1′	(167.1)	(167.2)	[167.7]
C-7	82.4	82.4	82.3	C-2′	111.8	111.9	111.7
C-8	45.5	45.5	45.1	C-3′	(165.1)	(165.1)	[164.8]
C-9	41.9	41.6	41.4	C-4′	38.4	38.3	38.4
C-10	41.2	40.8	40.3	C-5′	20.8	20.8	20.9
C-11	71.1	71.1	69.2	C-6′	20.8	20.8	20.9
C-12	75.9	75.8	71.0	C-7′	17.0	17.0	16.9
C-13	81.4	81.4	80.0	3-OAc		20.2	20.2
						(168.7)	(168.6)
C-14	51.7	51.2	51.6				
				11-OAc			21.4
C-15	65.9	66.2	65.4				(168.9)
C-16	169.8	169.4	169.9	12-OAc			20.6
							(169.0)

[a] ppm from Me_4Si. Similar values in parentheses or brackets may be exchanged.

such as bruceantin (1) and that the C-12 hydroxy moiety was desirable.[61] The model system **2** has these two features, and it was tested for in vitro activity against human carcinoma of the nasopharynx (KB).[3,4] Diol **2** as well as **21**, **52**, and **56** was found to be completely inactive, indicating that the presence of the epoxymethano bridge and C-12 hydroxy group alone is not adequate for activity.

Experimental Section

General. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in chloroform-*d* solution on Varian A60A, Perkin-Elmer R-32, and Nicolet NT-360 spectrometers; chemical shifts are reported in parts per million (δ) from internal tetramethylsilane (Me_4Si). Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Carbon-13 NMR experiments were performed using a Varian CFT-20 NMR spectrometer. Typically, a 7- or 9-μs pulse width was used with a pulse repitition rate of 1–3 s; 8K data points were employed in the time domain. Carbon-13 chemical shifts are referenced in parts per million (ppm) from internal Me_4Si. Mass spectra were recorded on a CEC-21-110-B high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 μA. Infrared (IR) spectra were obtained on a Perkin-Elmer 137 sodium chloride spectrometer and were calibrated with the 6.25- and 9.73-μm bands of polystyrene. Melting points were determined on a Fisher-Johns melting point apparatus. Molecular distillations were performed on a Büchi GKR-50 Kugelrohr. All melting points and boiling points are uncorrected. High-performance liquid chromatography (LC) was performed on a Waters Associates Prep LC/System 500 instrument. Microanalyses were performed by C. S. Yeh of the Purdue Chemistry Department microanalytical services.

All experiments in nonaqueous media were carried out under a positive pressure of dry nitrogen. All reactions were done in oven-dried glassware. Unless otherwise stated, all transfers of liquids or solutions were made via syringe. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Benzene, dichloromethane, dimethyl sulfoxide (Me_2SO), and diisopropylamine were distilled from calcium hydride and stored over 4A molecular sieves. Acetic acid (500 mL) was distilled from 10 g of chromium trioxide and 5 mL of acetic anhydride and stored over 4A molecular sieves. Acetic anhydride was dried over potassium carbonate and phosphorus pentoxide and distilled. Triethylamine was distilled from potassium hydroxide and stored over 4A molecular sieves. Boron trifluoride etherate was freshly distilled. Analytical thin-layer chromatography (TLC) was performed on Sil G-25 UV_{254} plates obtained from Brinkmann Instruments, Inc.

Thick-layer plates were made from silica gel PF-254 containing $CaSO_4$, from EM Reagents. Column chromatography was done on silica gel (60–200 mesh) obtained from Sargent-Welch or silica gel 60 (230–400 mesh ASTM) from EM Reagents. TLC data for compounds in the synthesis section are reported as (solvent system, R_f). The following solvent systems were used: 1, 30% THF/hexane; 2, 20% ether/chloroform; 3, 5% ethanol/chloroform; 4, 15% methanol/chloroform.

3,4-Dihydro-1,1-dimethyl-6-methoxy-2(1*H*)-naphthalenone (4).[8] A solution of **3** (51.1 g, 0.290 mol) in 175 mL of benzene was added dropwise to a suspension of sodium hydride (17.6 g, 0.73 mol) and iodomethane (56.0 mL, 0.90 mol) in 300 mL of benzene at 5 → 10 °C over a 40-min period. The mixture was stirred at 5 → 10 °C for 30 min and then at room temperature for 15 h. Wet ether (200 mL) was added, and the organic phase was washed with 240-mL portions of water, 10% sodium hydroxide solution, and brine and dried ($MgSO_4$). Removal of solvent in vacuo and subsequent distillation afforded 54.2 g (91.5%) of **4**: TLC (1, 0.45); bp 115–116 °C (0.60–0.65 torr) [lit.[8] bp 108–113 °C (0.5–0.6 torr)].

6-Methoxy-1,1-dimethyltetralin (5). A mixture of 47.6 g (0.233 mol) of **4**, 45 g of 85% KOH, and 60 mL (1.8 mol) of 97% hydrazine in 500 mL of ethylene glycol was heated to 130 °C over 1 h and then heated at reflux (oil bath temperature 215 °C) for 21 h. After cooling the mixture was poured into 600 mL of water and extracted with hexane (5 × 300 mL). The combined organic layers were washed with brine (225 mL) and dried ($MgSO_4$). Removal of solvent in vacuo yielded 40.0 g (90.3%) of **5** as a pale yellow liquid; TLC (1, 0.58).

1,2,3,4,5,8-Hexahydro-1,1-dimethyl-6-methoxynaphthalene (6).[8] A 250-mL three-neck flask was equipped with a dry-ice condenser, an ammonia inlet, and a septum. Lithium metal (40 cm; 1.69 g, 0.244 mol) was added portionwise to a solution of 9.29 g (48.8 mmol) of tetralin **5** in 10 mL of ether and 100 mL of liquid ammonia at reflux. After 30 min, 14.2 mL (0.244 mol) of ethanol was added via a dropping funnel over 0.5 h. After 15 min, 10 mL of ethanol was added to the still blue mixture. The ammonia was allowed to evaporate from the colorless mixture. The residue was partitioned between 100 mL of water and 50 mL of ether. Layers were separated and the aqueous layer was extracted with ether (3 × 50 mL). The organic phase was washed with 50 mL of brine and dried ($MgSO_4$). Evaporation of solvent afforded 9.15 g (97.4%) of **6** as a soft white solid: mp 33–36 °C [lit.[8] bp 68–72 °C (0.1 torr)]; TLC (1, 0.61).

When the reaction was performed on a 0.25-mole scale, **6** was obtained in 95% yield.

Acid Hydrolysis of 6. Isolation of a Mixture of 3,4,5,6,7,8-Hexahydro-5,5-dimethyl-2(1*H*)-naphthalenone (7) and 4,4a,5,6,7,8-Hexahydro-5,5-dimethyl-2(3*H*)-naphthalenone (8). A solution of 9.08 g (47.2 mmol) of **6** in 200 mL of THF was stirred with 5 mL of concentrated HCl for 2 h.

(64) Seebach, D.; Geiss, K. H.; Beck, A. K.; Graf, B.; Daum, H. *Chem. Ber.* **1972**, *105*, 3280.
(65) Eliel, E. L.; Hartmann, A. A.; Abatjoglu, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807.

There was no apparent change after 20 min. The reaction mixture was quenched with 120 mL of saturated sodium bicarbonate solution, layers were separated, and the aqueous layer was extracted with 120 mL of ether. Combined organic layers were washed with 80 mL of brine and dried ($MgSO_4$). Evaporation of solvent gave 8.13 g (96.6%) of a mixture of approximately 90% 8 and 10% 7 (as shown by NMR): TLC for 7 (1, 0.50); TLC for 8 (1, 0.38).

When the reaction was performed on a 0.19-mol scale, a 99.0% yield of enones 7 and 8 was attained.

Generation of Hydrogen Cyanide Gas. The reaction was done under a good hood on a 7.5% scale as described by Brauer.[62] The liquid HCN (28.05 g) collected was dissolved in 350 mL of THF at 0 °C, affording a 2.67 M solution. The solution was kept sealed in two containers in the refrigerator when not being used.

Hydrocyanation of 8.[10] Isolation of *trans*-Octahydro-8a-cyano-5,5-dimethyl-2(1*H*)-naphthalenone (9) and *cis*-Octahydro-8a-cyano-5,5-dimethyl-2(1*H*)-naphthalenone (10). Triethylaluminum (157 mmol, 108 mL of a 1.45 M solution in hexane) was added to 100 mL of THF under nitrogen at 0–5 °C, followed by 44 mL (118 mmol) of 2.67 M HCN in THF. A solution of enones 7 and 8 (7.76 g, 43.5 mmol) in 125 mL of THF was added rapidly via a dropping funnel. The dark yellow solution was stirred at 0 °C for 2 h and then at room temperature for 18 h. The resulting dark red solution was poured cautiously into 1 L of 5% aqueous sodium hydroxide at 5 °C and extracted with ether (4 × 500 mL). The combined ether extracts were washed with water (2 × 500 mL) and brine (500 mL) and dried (K_2CO_3). Removal of solvent yielded 9.66 g of red oil which was chromatographed on a column containing 200 g of silica gel. Unreacted enones 7 and 8 were eluted with the first 2 L of 3% THF/hexane. Elution with a further 875 mL of 3% THF/hexane gave 1.35 g (15.1%) of crude 10. Continued elution with 3% THF/hexane (2 L), 5% THF/hexane (3 L), and 10% THF/hexane (750 mL) afforded 5.06 g (56.6%) of crude *trans*-cyano ketone 9 as a white solid. Recrystallization of crude 9 from hexane and a trace of ether gave 4.37 g (48.9%) of pure material: TLC (1, 0.24); mp 80.5–81.5 °C; IR (KBr) 3.41, 4.48 (C≡N), and 4.81 μm (C=O); NMR ($CDCl_3$) δ 1.03 (s, 3, CH_3), 1.08 (s, 3, CH_3), 2.13 (t, 1, J = 3 Hz, C-4a H), 1.2–2.0 (m, 8, C-4, C-6, C-7, and C-8 H), 2.30–2.65 (m, 2, C-3 H), and 2.30–2.83 (2 overlapping d, 2, C-1 H); mass spectrum m/e (rel intensity) 205 (30), 190 (13), 178 (10), 163 (32), 69 (53), 55 (99), 41 (100), 39 (46).

Exact Mass. Calcd for $C_{13}H_{19}NO$: 205.147. Found: 205.147.

The crude cis isomer 10 was purified by preparative TLC (silica gel; 25% THF/hexane) and triturated with hexane and a trace of ether to yield the analytical sample: mp 52–53.5 °C; IR (KBr) 3.41, 4.48 (CN), and 5.80 μm (C=O); NMR ($CDCl_3$) δ 0.98 (s, 6, CH_3), 1.15–1.45 (m, 4, C-6 and C-7 H), 1.45–1.9 (m, 4, C-4 and C-8 H), 1.9–2.55 (m, 2, C-3 H), 2.04 (t, 1, C-4a H), 2.45 [d, 1, J = 14 Hz, C-1(ax) H], and 2.91 [d, 1, J = 14 Hz, C-1(eq) H]; mass spectrum m/e (rel intensity) 205 (92), 190 (27), 178 (14), 163 (24), 162 (32), 83 (48), 69 (58), 55 (52), 41 (100), 39 (58).

Exact Mass. Calcd for $C_{13}H_{19}NO$: 205.147. Found: 205.149.

***trans*-8a-Cyano-5,5-dimethyl-2,2-ethylenedioxydecahydronaphthalene (11).** A mixture of 7.85 g (38.2 mmol) of 9, 600 mg of *p*-toluenesulfonic acid monohydrate, 145 mL of dry ethylene glycol, and 575 mL of dry toluene was heated at reflux under nitrogen for 4 h in a 1-L flask equipped with a Dean–Stark trap. The reaction mixture was allowed to cool to room temperature and then washed with saturated sodium bicarbonate solution (500, 300 mL) and water (300 mL). The aqueous layers were extracted with ether (2 × 400 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo and the product was further dried via a vacuum pump overnight at 50 °C. The isolated white solid (10.0 g, mp 87–87.2 °C) was recrystallized from hexane to yield 9.28 g (97.4%) of 11: TLC (1, 0.35; 2, 0.50); mp 86.8–87.2 °C; IR (KBr) 3.45, 3.51, 4.50 (CN), 8.99, and 9.24 μm; NMR ($CDCl_3$) δ 0.94 (s, 3, CH_3), 1.09 (s, 3, CH_3), 3.99 (m, 4, $-OCH_2CH_2O$), and 1.15–2.3 (m, 13, remaining H); mass spectrum m/e (rel intensity) 249 (11), 195 (6), 100 (15), 99 (100), 86 (41), 55 (22), 41 (32).

Exact Mass. Calcd for $C_{15}H_{23}NO_2$: 249.173. Found: 249.174.

***trans*-3α-Bromo-9-cyano-5,5-dimethyl-2,2-ethylenedioxydecahydronaphthalene (12).[63]** Phenyltrimethylammonium perbromide (PTAB, Aldrich) was recrystallized from acetic acid, giving material with mp 115–117 °C. To a solution of 11 (5.59 g, 22.4 mmol) in 125 mL of dichloromethane was added 8.59 g (22.8 mmol) of PTAB at −10 to −8 °C over a 10-min period. The mixture was stirred at 0 °C for 80 min and then gradually warmed to 13 °C over 2.5 h. A trace of starting material was still detectable. An additional 95 mg of PTAB was added and the mixture was stirred at −5 °C to complete the reaction. The mixture was warmed to 10 °C and poured into 125 mL of 10% sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were washed with 100 mL of 10% sodium thiosulfate and 50 mL of brine and dried ($MgSO_4$). Removal of solvent yielded 7.29 g (99.1%) of 12, mp 141–144.5 °C. Recrystallization from hexane/ether afforded the analytical sample: TLC (1, 0.35; 2, 0.60); mp 145–146.5 °C; IR (KBr) 3.52, 4.51, 7.00, 7.39, 8.32, 8.72, 8.82, 8.95, 9.07, 9.32, 9.77, 10.07, and 10.50 μm; NMR ($CDCl_3$) δ 0.93 (s, 3, CH_3), 1.10 (s, 3, CH_3), 4.07 (m, 4, $-OCH_2CH_2O-$), 4.30 (m, 1, HCBr), and 1.3–2.4 (m, 13, remaining H); mass spectrum m/e (rel intensity) 329 (41), 327 (42), 249 (19), 248 (100), 209 (22), 150 (35), 137 (21), 99 (24), 86 (24).

Exact Mass. Calcd for $C_{15}H_{22}NO_2Br$: 327.083. Found: 327.083.

***trans*-1,2,3,4,4a,5,6,8a-Octahydro-4a-cyano-1,1-dimethyl-6,6-ethylenedioxynaphthalene (13).** A mixture of 6.23 g (19.0 mol) of 12 and 12 mL of DBU was stirred under nitrogen at 120–150 °C for 1.5 h and 150 °C for 0.5 h. After cooling, the mixture was partitioned between 100 mL of water and 100 mL of ether. The layers were separated and the aqueous layer was extracted with 100 mL of ether. The combined organic layers were washed with 100 mL of brine and dried ($MgSO_4$). Evaporation of solvent afforded 4.73 g (~100%) of white solid, mp 105–108.5 °C. Recrystallization from hexane gave 4.37 g (93.0%) of 13: TLC (1, 027; 2, 0.50); mp 109–110.5 °C; IR (KBr) 3.45, 4.48 (CN), 8.71, 8.81, 8.91, 9.17, 9.25, 10.08, and 10.73 μm; NMR ($CDCl_3$) δ 1.00 (s, 3, CH_3), 1.12 (s, 3, CH_3), 2.27 (d of d, 1, J = 14 and 1.5 Hz, C-5(eq) H), 3.75–4.25 (m, 4, $-OCH_2CH_2O-$), 4.72 (ddd, 1, J = 10, 3, and 1.5 Hz, olefinic H), 6.03 (dd, 1, J = 10 and 1.5 Hz, olefinic H), and 1.2–2.15 (m, 8, remaining H); mass spectrum m/e (rel intensity) 247 (32), 232 (12), 154 (14), 153 (100), 112 (41).

Exact Mass. Calcd for $C_{15}H_{21}NO_2$: 247.157. Found: 247.156.

***trans*-1,2,3,4,4a,5,6,8a-Octahydro-1,1-dimethyl-6,6-ethylenedioxynaphthalene-4a-carboxaldehyde (14).[12]** Lithium aluminum hydride (1.03 g, 27 mmol) was added portionwise to a solution of nitrile 13 (4.26 g, 17.2 mmol) in 125 mL of THF over a 10-min period. The mixture was stirred at room temperature 4 h and then heated from 30 to 60 °C over 1 h and at 60–65 °C for 0.5 h. The mixture was cooled, and a mixture of 120 mL of 5% acetic acid and 120 mL of methanol was added via a dropping funnel over 10 min. The mixture was stirred for 10 h and then extracted with 150 mL of chloroform. The organic phase was washed with 150 mL of saturated sodium bicarbonate and 100 mL of brine and dried ($MgSO_4$). Removal of solvent in vacuo afforded 4.16 g (96.2%) of crude 14, mp 50–53 °C. Recrystallization from petroleum ether gave 3.77 g of 14: TLC (1, 0.41); mp 54.5–56 °C; IR (KBr) 3.45, 3.65, 5.85 (C=O), 8.70, 9.02, 9.11, 10.00, and 10.60 μm; NMR ($CDCl_3$) δ 0.75 (s, 3, CH_3), 1.03 (s, 3, CH_3), 1.1–1.85 (m, 5), 1.89 (s, 2), 1.97–2.37 (m, 2), 3.92 (m, 4, $-OCH_2CH_2O-$), 5.75 (ddd, 1, J = 10.5, 3, and 1 Hz, olefinic H), 6.15 (d of d, 1, J = 10.5 and 2 Hz, olefinic H), and 9.98 (d, 1, J = 1.2 Hz, CHO); mass spectrum m/e (rel intensity) 250 (2), 222 (100), 207 (44), 163 (21), 153 (35), 152 (37), 108 (39), 107 (34), 91 (58), 79 (42), 77 (49), 55 (49), 41 (92).

Exact Mass. Calcd for $C_{15}H_{22}O_3$: 250.157. Found: 250.157.

***trans*-1,2,3,4,4a,5,6,8a-Octahydro-1,1-dimethyl-6,6-ethylenedioxy-4a-(hydroxymethyl)naphthalene (15).** Sodium borohydride (800 mg; 21 mmol) was added to a solution of 4.00 g (16.0 mmol) of aldehyde 14 in 125 mL of 95% ethanol over a period of 10 min at room temperature. The mixture was stirred under nitrogen at 30 to 70 °C for 1 h and then heated at reflux 1 h. After cooling, solvent was removed in vacuo. The residue was partitioned between 100 mL of brine and 100 mL of ether. The aqueous layer was extracted with a second 100-mL portion of ether. The organic extract was washed with 50 mL of brine and dried ($MgSO_4$). Evaporation of solvent furnished 3.95 g (98.0%) of crude alcohol, mp 61–64 °C. Recrystallization from

hexane gave the analytical sample: TLC (1, 0.29; 2, 0.41); mp 70–70.5 °C; IR ($CHCl_3$) 2.88, 3.44, 8.77, 9.17, 9.73, 10.02, and 10.53 μm; NMR ($CDCl_3$) δ 0.77 (s, 3, CH_3), 0.94 (s, 3, CH_3), 2.22 (dd, 1, J = 14 and 2 Hz, C-5(eq) H), 3.08 (s, 1, **OH**), 3.72 (br s, 2, $\mathbf{CH_2}$OH), 3.98 (m, 4, $-OCH_2CH_2O-$), 5.64 (ddd, 1, J = 10.5 and 3 Hz, J = 2 Hz, olefinic H), 6.00 (dd, 1, J = 10.5 and 2 Hz, olefinic H), and 1.05–2.1 (m, 8, remaining H); mass spectrum m/e (rel intensity) 252 (0.4), 222 (1.3), 153 (1.2), 150 (1.0), 43 (14), 41 (17), 33 (36), 31 (100), 29 (19).

Exact Mass. Calcd for $C_{15}H_{24}O_3$: 252.176. Found: 252.175.

***trans*-1,2,3,4,4a,5,6,8a-Octahydro-1,1-dimethyl-6,6-ethylenedioxy-4a-(tosyloxymethyl)naphthalene (16).** *n*-Butyllithium (65.9 mmol, 36.0 mL of a 1.83 M solution) was added to a solution of 16.4 g (65.0 mmol) of **15** in 200 mL of THF at −60 to −50 °C over a 5-min period. The solution was stirred at −50 to −60 °C for 0.5 h, 13.1 g (68.7 mmol) of tosyl chloride (dissolved in 60 mL of THF) was added at −50 to −30 °C, and the mixture was stirred at −35 to −15 °C for 1 h. Water (200 mL) was added at −15 °C (temperature rising to 15 °C), and the mixture was stirred at room temperature for 3 h. The mixture was extracted with ether (2 × 200 mL), and the combined ether layers were washed with 200 mL of brine and dried (Na_2SO_4/K_2CO_3). Evaporation of solvent afforded 26.4 g (100%) of **16**: TLC (1, 0.30; 2, 0.60); mp 74–76 °C dec; IR (KBr) 3.0, 3.42, 3.49, 7.75, 8.41, 8.48, 9.18, 10.37, 11.64, 11.75, and 12.29 μm; NMR ($CDCl_3$) δ 0.70 (s, 3, CH_3), 0.89 (s, 3, CH_3), 2.22 (dd, 1, J = 14 and 2 Hz, C-5(eq) H), 2.38 (s, 3, tosyl CH_3), 3.80 (m, 4, $-OCH_2CH_2O-$), 4.14 (d, 1, J = 10 Hz, $CHOSO_2-$), 4.36 (dd, 1, J = 10 and 2 Hz, $CHOSO_2-$), 5.86 (dd, 1, J = 10 and 2 Hz, olefinic H), 5.52 (ddd, 1, J = 10, 3, and 2 Hz, olefinic H), 7.32 (d, 2, J = 9 Hz, arom), 7.79 (d, 2, J = 9 Hz, arom), and 1.0–2.05 (m, 8, remaining H); mass spectrum m/e (rel intensity) 406 (22), 362 (1.0), 360 (0.8), 346 (1.5), 344 (1.4), 236 (1.9), 216 (3), 173 (20), 172 (30), 155 (30), 108 (61), 107 (85), 91 (95), 65 (100).

Exact Mass. Calcd for $C_{22}H_{30}O_5S$: 406.181. Found: 406.182.

***trans*-4a,5,6,7,8,8a-Hexahydro-5,5-dimethyl-8a-(tosyloxymethyl)-2(1*H*)-naphthalenone (17).** Ketal **16** (25.9 g, 63.7 mmol) was dissolved in 300 mL of THF at −5 °C and 150 mL of 3.5% perchloric acid was added. The mixture was stirred at 0–5 °C for 1.5 h and then quenched with 250 mL of saturated sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with ether (2 × 250 mL). Combined organic extracts were washed with 200 mL of brine and dried (K_2CO_3/Na_2SO_4). Removal of solvent yielded a pale yellow oil which was dissolved in petroleum ether and a minimum volume of ether at room temperature and refrigerated overnight. The product was isolated as 20.6 g (89%) of white crystals, mp 97–99 °C. Recrystallization from petroleum ether/ether afforded the analytical sample: mp 99.5–102 °C; TLC (1, 0.24; 2, 0.55); IR (KBr) 2.90, 3.43, 5.98, 7.40, 8.40, 8.50, 10.36, 11.41, 11.7, and 12.26 μm; NMR ($CDCl_3$) δ 0.81 (s, 3, CH_3), 1.02 (s, 3, CH_3), 1.96 (dd, 1, J = 17 and 1.5 Hz, C-1(ax) H), 2.38 (dd, 1, J = 2.5 and 3.2 Hz, C-4a H), 2.73 (dd, J = 17 and 1 Hz, C-1(eq) H), 2.43 (s, 3, tosyl CH_3), 3.90 (d, 1, J = 9.5 Hz, $-CHOSO_2-$), 4.40 (dd, 1, J = 9.5 Hz, $-CHOSO_2-$), 5.95 (ddd, 1, J = 10, 3.2, and 1 Hz, C-3 H), 6.87 (dd, 1, J = 10 and 2.5 Hz, C-4 H), 7.31 (d, 2, J = 8.5 Hz, arom), 7.71 (d, 2, J = 8.5 Hz, arom), and 1.5–2.10 (m, 6, remaining H); mass spectrum m/e (rel intensity) 3.62 (<1), 190 (10), 175 (6), 147 (98), 134 (29), 133 (42), 122 (35), 121 (26), 119 (29), 107 (29), 105 (38), 92 (33), 91 (100), 79 (40), 77 (49), 65 (49), 41 (58), 39 (65).

Exact Mass. Calcd for $C_{20}H_{26}O_4S$: 362.159. Found: 362.158.

Preparation of Tris(methylthio)methane.[64] Chloroform (100 mL) was saturated with gaseous HCl at −20 °C. Methyl mercaptan (17.9 g, 0.372 mol) was condensed in 20 mL of chloroform at −60 °C and added to the HCl solution. Trimethyl orthoformate (13.4 g, 0.126 mol) was added rapidly by syringe. The mixture was stored at −20 °C for 3 days and then stirred at room temperature 1.5 days. The chloroform solution was washed with 7% KOH (4 × 100 mL) and dried (K_2CO_3). Removal of solvent gave a colorless liquid which was distilled to yield 15.1 g (93.7%) of orthothioformate: bp 62 °C (0.6 torr) [lit.[65] bp 102 °C (15 torr)].

***trans*-1,2,3,4,4a,5,6,8a-Octahydro-1,1-dimethyl-4a-(tosyloxymethyl)-6α-tris(methylthio)methylnaphthalen-6β-ol (18).** *n*-Butyllithium (5.1 mmol, 2.7 mL of a 1.9 M solution) was added to a solution of tris(methylthio)methane (828 mg, 5.37 mmol) in 20 mL of THF. The mixture was stirred at −70 °C for 15 min, and a solution of **17** (1.60 g, 4.41 mmol) in 20 mL of THF was added. The mixture was stirred at −65 to −60 °C for 1 h. The reaction was quenched with 50 mL of saturated ammonium chloride solution at −60 °C. After warming to room temperature, the layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Evaporation of solvent yielded 2.07 g (90.8%) of white solid, mp 103–106 °C. Recrystallization from petroleum ether/dichloromethane afforded 1.63 g of pure **18**: TLC (1, 0.37; 2, 0.71); mp 109.5–111 °C; IR ($CHCl_3$) 2.86, 3.47, 7.46, 8.54, 10.43, 11.65, and 12.3 μm; NMR ($CDCl_3$) δ 0.71 (s, 3, CH_3), 0.89 (s, 3, CH_3), 2.21 (s, 9, $\mathbf{SCH_3}$), 2.38 (d, 1, J = 11.5 Hz, C-5(eq) H), 2.40 (s, 3, tosyl CH_3), 4.26 (s, 2, $\mathbf{CH_2}OSO_2-$), 5.76 (d, 1, J = 2 Hz, olefinic H), 6.01 (d, 1, J = 2 Hz, olefinic H), 7.30 (d, 2, J = 8.5 Hz, arom), and 7.78 (d, 2, J = 8.5 Hz, arom); mass spectrum m/e (rel intensity) 452 (5), 375 (5), 373 (5), 363 (12), 248 (39), 229 (37), 201 (100), 173 (92), 172 (93), 108 (63), 107 (80), 92 (58), 91 (96), 79 (55), 77 (63), 65 (66).

Exact Mass. Calcd for $C_{23}H_{32}O_3S_3$ ($M^+ - CH_3SOH$): 452.151. Found: 452.153.

(4α)-5,5-Dimethyl-1α-tris(methylthio)methyl-11-oxatricyclo[7.2.1.0^{4,9}]dodec-2-ene (19).[20] Alcohol tosylate **18** (1.09 g, 2.12 mmol) was heated in 25 mL of HMPA at 90–95 °C for 24 h. The mixture was poured into 100 mL of water and extracted with ether (100, 100, 50 mL). Ether layers were washed with 5% aqueous sodium bicarbonate (2 × 50 mL), water (2 × 50 mL), and brine (50 mL) and dried ($MgSO_4$). Removal of solvent yielded 729 mg of crude product. This material was chromatographed on 50 g of silica gel. Elution with 2% THF/hexane afforded 652 mg (89.7%) of pure **19**: TLC (1, 0.58); bp 108–110 °C (0.45 torr); mp 54–57 °C; IR (KBr) 3.49, 6.96, 7.29, 8.57, 9.54, 9.95, 10.43, 12.16, 13.42, and 14.37 μm; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 0.99 (s, 3, CH_3), 2.22 (s, 9, $\mathbf{SCH_3}$), 2.39 (dd, 1, J = 4 and 2 Hz, C-4 H), 3.50 (dd, 1, J = 9 and 2 Hz, $-CHO$), 4.23 (d, 1, J = 9 Hz, $-CHO$), 5.81 (dd, 1, J = 10 and 2 Hz, C-2 H), 6.38 (ddd, 1, J = 10, 4, and 2 Hz, C-3 H), and 1.05–2.35 (m, 8, remaining H); mass spectrum m/e (rel intensity) 344 (0.7), 297 (53), 179 (19), 166 (21), 135 (38), 121 (100).

Exact Mass. Calcd for $C_{17}H_{28}OS_3$: 344.134. Found: 344.133.

Methyl *trans*-1,2,3,4,4a,5,6,8a-Octahydro-1,1-dimethyl-6β-hydroxy-4a-(tosyloxymethyl)naphthalene-1-carboxylate (20).[21] A mixture of 902 mg (1.75 mmol) of **18**, 1.98 g (7.11 mmol) of mercuric chloride, and 636 mg (2.94 mmol) of mercuric oxide in 43 mL of 12:1 methanol/water was stirred at room temperature for 4 h. The mixture was filtered and the solid residue was washed with dichloromethane (2 × 25 mL). Combined filtrates were diluted with 50 mL of water and extracted with dichloromethane (2 × 50 mL). The organic layer was washed with 75% ammonium acetate solution (2 × 50 mL) and saturated ammonium chloride solution (2 × 50 mL) and dried ($MgSO_4$). Evaporation of solvent gave 723 mg (98.1%) of **20** as a white foam: TLC (1, 0.22; 2, 0.48); mp 34–36 °C; IR (thin film) 2.88, 3.44, 5.77, 7.40 (br), 7.99, 8.49, 10.37 (br), and 11.7 μm (br); NMR ($CDCl_3$) δ 0.77 (s, 3, CH_3), 0.95 (s, 3, CH_3), 2.42 (s, 3, tosyl CH_3), 3.20 (s, 1, OH), 3.74 (s, 3, CH_3), 4.22 (d, 1, J = 9.5 Hz, $-CHOTs$), 4.43 (d, 1, J = 9.5 Hz, $-CHOTs$), 5.57 (ddd, 1, J = 10, 3, and 1.5 Hz, olefinic H), 5.90 (dd, 1, J = 10 and 2 Hz, olefinic H), 7.31 (d, 2, J = 8.5 Hz, arom), 7.80 (d, 2, J = 8.5 Hz, arom), and 1.2–2.4 (m, 9, remaining H); mass spectrum m/e (rel intensity) 404 (9), 372 (69), 304 (22), 91 (100).

Exact Mass. Calcd for $C_{22}H_{28}O_5S$ ($M^+ - H_2O$): 404.166. Found: 404.166.

When the reaction was repeated on a 10.5-mmol scale, 4.38 g (99%) of **20**, mp 38–42 °C, was obtained.

Conversion of 19 to Methyl (4α)-5,5-Dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodec-2-ene-1α-carboxylate (21). A mixture of 542 mg (1.57 mmol) of **19**, 1.73 g (6.37 mmol) of mercuric chloride, and 571 mg (2.63 mmol) of mercuric oxide in 39 mL of 12:1 methanol/water and 5 mL of ether was stirred for 4 h at room temperature. Workup was as in the previous experiment. The product was isolated as 368 mg (93.4%) of colorless oil. Molecular distillation at 84–86 °C (0.50 torr) afforded the analytical sample: TLC (1, 0.42; 2, 0.57); mp 55.5–58 °C; IR (KBr) 3.48, 5.72, 6.91, 7.72, 7.98, 8.65, and 9.34 μm; NMR ($CDCl_3$) δ 0.93 (s, 3, CH_3), 1.00 (s, 3, CH_3), 2.02 (apparent s, 2, C-12 H), 2.25 (dd, 1, J = 1.5 and 1.5 Hz, C-4 H), 3.65 (dd, 1, J = 8.5 and 2 Hz, HCO), 3.76 (s, 3,

OCH_3), 4.34 (d, 1, J = 8.5 Hz, HCO), 5.92 (m, 2, overlapping olefinic H), and 1.1–1.83 (m, 6, remaining H); mass spectrum m/e (rel intensity) 250 (47), 220 (100), 150 (25), 149 (15), 91 (18).

Exact Mass. Calcd for $C_{15}H_{22}O_3$: 250.157. Found: 250.155.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.76; H, 8.58.

Conversion of 20 to 21. A mixture of 587 mg (1.39 mmol) of **20** and 15 mL of HMPA was heated at 120 °C for 24 h. Workup was as for conversion of **18** to **19** (×0.6). Evaporation of solvent furnished 332 mg (95.4%) of pure **21** as a white solid. On a larger scale, 4.79 g of brown oil was obtained upon heating a mixture of 7.55 g (17.9 mmol) of **20** and 100 mL of HMPA at 120 °C for 25 h. Column chromatography (silica gel; 3–5% THF/hexane) afforded 3.04 g (68%) of **21**, mp 47–47.5 °C. Recrystallization from petroleum ether gave material with mp 58.5–59.5 °C.

(1α,2α)-3,3-Dimethyl-11-oxatricyclo[5.3.2.$0^{2,7}$]dodecan-9-one (23). A solution of 56.5 mg (0.224 mmol) of **15** in 10 mL of ether was shaken with 10% HCl (2 × 10 mL) in a separatory funnel. After drying ($MgSO_4$), evaporation of ether yielded 36.6 mg (78.5%) of **23** as an oil: TLC (1, 0.37); IR (thin film) 3.40, 5.83, and 9.82 μm; NMR ($CDCl_3$) δ 0.99 (s, 3, CH_3), 1.02 (s, 3, CH_3), 1.68 (s, 1, C-2 H), 2.24 (dd, 1, J = 17 and 2.5 Hz, C-10(ax) H), 2.33 (dd, 1, J = 14 and 2 Hz, C-8(ax) H), 2.53 (dd, 1, J = 14 and 2 Hz, C-8(eq) H), 2.74 (dd, 1, J = 17 and 4 Hz, C-10(eq) H), 3.59 (d, 1, J = 8 Hz, C-12 H), 3.87 (dd, 1, J = 8 and 2 Hz, C-12 H), 4.42 (dd, 1, J = 4 and 2.5 Hz, C-1 H), and 1.1–1.8 (m, 6, remaining H); mass spectrum m/e (rel intensity) 208 (43), 193 (7), 178 (17), 163 (13), 152 (59), 151 (100), 81 (47).

Exact Mass. Calcd for $C_{13}H_{20}O_2$: 208.146. Found: 208.149.

Preparation of Tetra-*n*-butylammonium Cyanide.[66] A solution of 44.6 g (52 mmol) of $(n\text{-Bu})_4NF{\cdot}34H_2O$[67,68] in 100 mL of 10% acetonitrile/toluene was shaken with 100 mL of 50% aqueous sodium hydroxide and 7.35 g (0.15 mol) of sodium cyanide. Following separation of layers, the organic solvent was removed in vacuo. Further drying via a vacuum pump afforded 11.8 g (84%) of tetra-*n*-butylammonium cyanide.

Reaction of 17 with Tetra-*n*-butylammonium Cyanide. Formation of 7,7-Dimethyltricyclo[4.4.1.$0^{1,6}$]undec-4-en-3-one (25). Tetra-*n*-butylammonium cyanide (1.00 mmol, 1.29 mL of 0.778 M solution in THF) was added to a solution of enone tosylate **17** in 20 mL of THF at −8 °C. The solution was stirred at −3 °C for 1 h. Thereupon, 20 mL of 5% aqueous sodium bicarbonate was added, and the mixture was extracted with ether (2 × 20 mL). Ether layers were washed with 20 mL of brine and dried ($MgSO_4$). Removal of solvent yielded 218 mg of yellow oil. Molecular distillation gave 113 mg (65%) of **25**: TLC (1, 0.50); bp 125 °C (1.3 torr); IR (thin film) 3.46, 5.99, 6.33, 6.83, 7.06, 7.84, 8.16, and 12.3 μm; NMR ($CDCl_3$) δ 1.09 (s, 6, 2 CH_3), 2.47 (d, 1, J = 18 Hz, C-2(ax) H), 2.84 (d, 1, J = 18 Hz, C-2(eq) H), 5.76 (d, 1, J = 11 Hz, C-4 H), 7.48 (d, 1, J = 11 Hz, C-5 H), and 1.0-2.2 (m, 9, remaining H); mass spectrum m/e (rel intensity) 190 (25), 175 (22), 147 (70), 133 (43), 129 (41), 105 (48), 101 (40), 91 (100), 79 (41), 77 (49).

Exact Mass. Calcd for $C_{13}H_{18}O$: 190.136. Found: 190.135.

Reaction of 17 with Lithium Diisopropylamide. Formation of (3α,7α)-8,8-Dimethyltricyclo[5.4.0.$0^{1,3}$]undec-5-en-4-one (26). *n*-Butyllithium (0.35 mmol, 0.18 mL of a 1.94 M solution) was added to a solution of 0.07 mL (0.50 mmol) of diisopropylamine in 10 mL of THF at −35 °C. The mixture was warmed to room temperature and then cooled to −65 °C. A solution of 113 mg (0.31 mmol) of **17** in 5 mL of THF was added. The mixture was stirred at −65 °C for 0.5 h, at 0 °C for 0.5 h, and finally at room temperature for 16 h. Saturated ammonium chloride solution (20 mL) was added and the mixture was extracted with ether (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). Removal of solvent gave 62.1 mg of oil, still containing a trace of starting material. Molecular distillation afforded 51.0 mg (86.0%) of pure **26**: TLC (1, 0.43); bp 110 °C (0.2 torr); IR (thin film) 3.48, 6.00, and 11.96 μm; NMR ($CDCl_3$) δ 0.94 (s, 3, CH_3), 1.10 (s, 3, CH_3), 2.43 (dd, 1, J = 3 and 2 Hz, C-7 H), 4.83 (dd, 1, J = 11, 3, and 1.5 Hz, C-4 H), 6.59 (dd, 1, J = 11 and 2 Hz, C-6 H) and 1.0–2.7 (m, 9, remaining H); mass spectrum m/e (rel intensity) 190 (19), 162 (16), 147 (22), 122 (29), 107 (27), 105 (21), 91 (81), 69 (63), 41 (100), 39 (68).

Exact Mass. Calcd for $C_{13}H_{18}O$: 190.136. Found: 190.137.

Reaction of 17 with DBU in THF. Isolation of 26 and 1,2,3,4,5,6-Hexahydro-1,1-dimethyl-7*H*-benzocyclohepten-7-one (27). DBU (0.70 mL, 4.7 mmol) was added to a solution of 497 mg (1.37 mmol) of **17** in 20 mL of THF at room temperature. The mixture was stirred for 3 h, and an additional 0.50 mL (3.3 mmol) of DBU was added. After 2.5 h, the mixture was partitioned between 40 mL of water and 40 mL of ether. The layers were separated, and the aqueous layer was extracted with 40 mL of ether. Combined organic layers were washed with 10 mL of brine and dried ($MgSO_4$). Evaporation of solvent provided 272 mg of crude products, which were chromatographed on 12 g of silica gel. Elution with 2% THF/hexane afforded 38.6 mg (14.8%) of **27** as a pale yellow oil: TLC (1, 0.49); IR (thin film) 3.46, 6.00, 6.34, 6.85, 7.06, 7.82, 8.16, and 8.50 μm; NMR ($CDCl_3$) δ 1.08 (s, 6, 2 CH_3), 6.05 (d, 1, J = 14 Hz, C-8 H), 6.71 (d, 1, J = 14 Hz, C-9 H), and 1.2–2.65 (m, 10, remaining H); ^{13}C NMR ($CDCl_3$) δ 33.6 (C-1), 38.9 (C-2), 18.9 (C-3), 42.7 (C-6), 202.6 (C-7), 128.5 (C-8), 140.6 (C-9), 28.9 (2 CH_3), 29.4, 33.8, 137.3, and 144.8; mass spectrum m/e (rel intensity) 190 (67), 175 (52), 147 (66), 91 (54), 55 (50), 41 (97), 39 (77), 27 (100).

Exact Mass. Calcd for $C_{13}H_{18}O$: 190.136. Found: 190.133.

Further elution with 2% THF/hexane and 5% THF/hexane gave 199.9 mg (76.6%) of **26**. In another experiment, a mixture of 470 mg (1.30 mmol) of **17**, 1.2 mL (8.0 mmol) of DBU, and 10 mL of THF was stirred at room temperature for 42 h. The isolated brown oil was chromatographed as before to afford 65.6 mg (26.6%) of **27** and 57.7 mg (23.4%) of **26**.

***trans*-5,5-Dimethyl-2,2-ethylenedioxydecahydronaphthalene-8a-carboxaldehyde (28).** Lithium aluminum hydride (600 mg, 15.8 mmol) was added over a 15-min period to a solution of 2.45 g (9.81 mmol) of **11** in 60 mL of THF at room temperature. The mixture was stirred at room temperature for 7 h. Thereupon, a mixture of 60 mL of 5% acetic acid, 60 mL of methanol, and 60 mL of THF was added, and the mixture stirred for 20 h. An additional 40 mL of 5% acetic acid was added and the mixture extracted with chloroform (3 × 80 mL). The last two organic extracts (plus some emulsion) were washed with 80 mL of saturated aqueous sodium bicarbonate. Combined organic layers were then washed with saturated sodium bicarbonate solution (80 mL) and brine (2 × 80 mL) and dried ($MgSO_4$). Removal of solvent afforded 2.59 g of white solid, mp 79–80 °C. Recrystallization from petroleum ether gave 2.45 g (98.9%) of **28**: TLC (1, 0.44); mp 79–80 °C; IR (KBr) 3.47, 4.89, 8.93, and 9.17 μm; NMR ($CDCl_3$) δ 0.80 (s, 3, CH_3), 0.97 (s, 3, CH_3), 3.87 (m, 4, $-OCH_2CH_2O-$), 10.1 (s, 1, CHO), and 1.1–2.37 (m, 13, remaining H); mass spectrum m/e (rel intensity) 252 (0.4), 237 (1), 224 (59), 181 (42), 147 (15), 99 (100), 86 (36), 69 (19), 67 (25), 55 (19), 21 (18).

Exact Mass. Calcd for $C_{15}H_{24}O_3$: 252.173. Found: 252.170.

***trans*-5,5-Dimethyl-2,2-ethylenedioxy-8a-(hydroxymethyl)decahydronaphthalene (29).** Sodium borohydride (464 mg, 12.3 mmol) was added to a solution of 2.32 g (9.20 mmol) of **28** in 100 mL of 95% ethanol. The mixture was heated at reflux for 5.5 h. After cooling, 50 mL of brine was added and the mixture was extracted with ether (2 × 100 mL). After drying ($MgSO_4$), the ether was evaporated to yield 2.5 g of white solid, which was extracted with dichloromethane–hexane (1:1). Removal of solvent afforded 1.45 g (62%) of pure **29**: mp 68–69 °C; IR ($CHCl_3$) 2.82, 3.39, 8.86, 9.16, 9.67, and 10.57 μm; NMR ($CDCl_3$) δ 0.77 (s, 3, CH_3), 0.88 (s, 3, CH_3), 2.07 (dd, 1, J = 14 and 2.5 Hz, C-1(eq) H), 2.52 (s, 1, OH), 3.62 (d, 1, J = 12 Hz, CHOH), 3.88 (d, 1, J = 12 Hz, CHOH), 3.83, 4.13 (m, 4, $-OCH_2CH_2O-$), and 1.0–2.08 (m, 12, remaining H); mass spectrum m/e (rel intensity) 254 (100), 224 (75), 223 (80), 209 (25), 181 (34), 99 (52), 86 (61), 55 (60), 41 (82).

Exact Mass. Calcd for $C_{15}H_{26}O_3$: 254.188. Found: 254.185.

***trans*-5,5-Dimethyl-2,2-ethylenedioxy-8a-(tosyloxymethyl)decahydronaphthalene (30).** At −55 °C, *n*-butyllithium (3.9 mmol) was added to a solution of 1.000 g (3.93 mmol) of **29** in 30 mL of THF. The solution was stirred at −55 to −45 °C for 25 min. Thereupon 957 mg (5.02 mmol) of tosyl chloride in 10 mL of THF was added (temperature rising to −30 °C). The

(66) Makosza, M.; Bialecka, E. *Synth. Commun.* **1976**, *6*, 313.
(67) Prepared by R. E. Donaldson.
(68) McMullan, R.; Jeffrey, G. A. *J. Chem. Phys.* **1959**, *31*, 1231.

mixture was stirred at −30 to −20 °C for 1 h and −20 to +20 °C for 4 h. The reaction was still incomplete, and an additional 0.50 mmol of *n*-butyllithium was added. After stirring at −45 to −20 °C for 1 h, there was no change. The reaction was quenched with 50 mL of water. Layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). Combined organic layers were washed with 50 mL of brine and dried (K_2CO_3/Na_2SO_4). Removal of solvent in vacuo gave 2.19 g of light yellow oil. Crystallization from petroleum ether plus a trace of ether at −78 °C afforded 691 mg (43.0%) of **30**: TLC (1, 0.37); mp 87–88 °C; NMR ($CDCl_3$) δ 0.72 (s, 3, CH_3), 0.88 (s, 3, CH_3), 2.43 (s, 3, tosyl CH_3), 3.83 (s, 4, $-OCH_2CH_2O-$), 4.27 (dd, 1, J = 9 and 1 Hz, CHOTs), 4.49 (d, 1, J = 9 Hz, CHOTs), 7.33 (d, 2, J = 8 Hz, arom), 7.80 (d, 2, J = 8 Hz, arom), and 0.97–2.27 (m, 13, remaining H); mass spectrum m/e (rel intensity) 408 (16), 323 (1), 309 (1), 255 (18), 254 (100), 223 (21), 163 (14), 99 (92), 91 (58), 86 (38), 55 (36), 41 (31).

Exact Mass. Calcd for $C_{22}H_{32}O_5S$: 408.197. Found: 408.199.

***trans*-Octahydro-5,5-dimethyl-8a-tosyloxymethyl-2-(1*H*)-naphthalenone (31).** A mixture of 667 mg (1.63 mmol) of **30** in 25 mL of THF and 15 mL of 3.5% perchloric acid was stirred at room temperature for 12 h. Saturated sodium bicarbonate solution (20 mL) was added, and the mixture was extracted with ether (2 × 25 mL). Combined ether layers were washed with 20 mL of brine and dried (K_2CO_3/Na_2SO_4). Evaporation of solvent gave 549 mg (92.2%) of crude **31**. Recrystallization from petroleum ether afforded 391 mg of the analytical sample: TLC (1, 0.26); mp 92.5–94 °C; IR (KBr) 3.43, 5.88, 7.41, 8.41, 8.49, 9.12, 10.25, 10.66, 11.6, 11.77, and 12.26 μm; NMR ($CDCl_3$) δ 0.78 (s, 3, CH_3), 0.96 (s, 3, CH_3), 2.43 (s, 3, tosyl CH_3), 3.85 (d, 1, J = 10 Hz, CHOTs), 4.25 (d, 1, J = 10 Hz, CHOTs), 7.35 (d, 2, J = 8.5 Hz, arom), 7.76 (d, 2, J = 8.5 Hz, arom), and 1.05–2.57 (m, 13, remaining H); mass spectrum m/e (rel intensity) 364 (42), 253 (15), 252 (16), 236 (18), 192 (34), 149 (25), 135 (27), 124 (48), 123 (28), 122 (41), 121 (44), 107 (62), 93 (69), 91 (94), 79 (71), 77 (68), 69 (74), 55 (62), 41 (100).

Exact Mass. Calcd for $C_{20}H_{28}O_4S$: 364.171. Found: 364.171.

(4α)-5,5-Dimethyl-1α-tris(methylthio)methyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecane (32). *n*-Butyllithium (0.60 mL, 1.1 mmol) was added to a solution of 204 mg (1.32 mmol) of tris(methylthio)methane in 15 mL of THF at −65 °C. After 15 min, a solution of 299.4 mg (0.821 mmol) of **31** in 3 mL of THF was added; the solution turned pink-orange. The mixture was stirred at −65 to −60 °C for 1.5 h and then warmed to −20 °C over a 1-h period. The deep red mixture was quenched with 25 mL of water and extracted with ether (2 × 40 mL). Combined ether layers were washed with 25 mL of brine and dried ($MgSO_4$). Removal of solvent gave 395 mg of colorless liquid which was chromatographed on silica gel (30% THF/hexane). Extraction of the least polar material in ether afforded 230 mg (80.9%) of crude **32** as a yellowish white solid. Recrystallization from petroleum ether afforded the analytical sample: TLC (1, 0.65); mp 72–73 °C; IR (KBr) 3.49, 7.00, 9.86, 9.97, 10.60, and 12.32 μm; NMR ($CDCl_3$) δ 0.90 (s, 6, CH_3), 2.19 (s, 9, SCH_3), 3.37 (d, 1, J = 8 Hz, −CHO−), 4.23 (d, 1, J = 8 Hz, −CHO−), and 1.07–2.63 (m, 13, remaining H); mass spectrum m/e (rel intensity) 346 (0.6), 299 (55), 153 (53), 107 (43), 91 (30), 43 (100), 42 (47), 41 (46).

Exact Mass. Calcd for $C_{17}H_{30}OS_3$: 346.146. Found: 346.145.

Methyl (4α)-5,5-Dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (33). A mixture of 58.4 mg (0.169 mmol) of **32**, 175 mg (0.645 mmol) of mercuric chloride, and 58.1 mg (0.268 mmol) of mercuric oxide in 4 mL of 12:1 methanol/water was heated at reflux for 1 h. The reaction mixture was cooled and filtered. The residue was washed with dichloromethane (2 × 5 mL). Combined filtrates were diluted with 10 mL of water and extracted with dichloromethane (2 × 10 mL). The organic layer was washed with 75% aqueous ammonium acetate (2 × 10 mL) and saturated ammonium chloride solution (2 × 10 mL) and dried ($MgSO_4$). Removal of solvent gave 47.6 mg of colorless liquid. Molecular distillation afforded 38.8 mg (91.3%) of **33**: TLC (1, 0.45); bp 109 °C (0.5 torr); IR ($CHCl_3$) 3.42, 3.52, 5.76, 6.90, 7.95, 8.68, 9.37, and 9.82 μm; NMR ($CDCl_3$) δ 0.91 (s, 3, CH_3), 3.54 (d, 1, J = 8 Hz, −CHO−), 3.72 (s, 3, CO_2CH_3), 4.34 (d, 1, J = 8 Hz, −CHO−), and 1.0–2.1 (m, 13, remaining H); mass spectrum m/e (rel intensity) 252 (100), 222 (27), 220 (19), 193 (25), 153 (25), 147 (20), 140 (89).

Exact Mass. Calcd for $C_{15}H_{24}O_3$: 252.173. Found: 252.175.

(4α)-1α-Cyano-5,5-dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecane (34). A solution of 33.5 mg (0.092 mmol) of **31** and 0.12 mmol of tetra-*n*-butylammonium cyanide in 5 mL of THF was stirred at room temperature for 2 h. The mixture was quenched with 10 mL of 5% sodium bicarbonate solution and extracted with ether (2 × 10 mL). Ether layers were washed with 10 mL of brine and dried ($MgSO_4$). Evaporation of solvent yielded 19.3 mg (96%) of **34**, mp 81–83.5 °C. Recrystallization from petroleum ether gave the analytical sample: TLC (1, 0.43); mp 89–91 °C; IR (KBr) 3.47, 4.47 (w), 6.89, 8.45, 9.84, 10.08, and 10.14 μm; NMR ($CDCl_3$) δ 0.90 (s, 6, 2 CH_3), 3.55 (d, 1, J = 8.5 Hz, C-10 H), 4.31 (d, 1, J = 8.5 Hz, C-10 H), and 1.1–2.5 (m, 13, remaining H); mass spectrum m/e (rel intensity) 219 (3), 189 (4), 172 (15), 91 (50), 41 (100), 39 (83), 27 (100).

Exact Mass. Calcd for $C_{14}H_{21}NO$: 219.162. Found: 219.164.

Preparation of Pertrifluoroacetic Acid.[22,69] Trifluoroacetic anhydride (7.0 mL, 49.6 mmol) was added to a mixture of 1.00 mL (27.8 mmol) of 73% hydrogen peroxide and 25 mL of dichloromethane at 0 °C. The mixture was stirred at 0 °C until homogeneous (0.5 h). The exact concentration of peracid was determined iodometrically.[70]

Epoxidation of 21. Isolation of Methyl (4α)-5,5-Dimethyl-2,3β-oxido-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (36) and Methyl (4α)-5,5-Dimethyl-2,3α-oxido-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (37).[22] Pertrifluoroacetic acid (3.47 mL of a 0.84 M solution, 3.00 mmol) was added to a slurry of 954 mg (9.00 mmol) of sodium carbonate in a solution of 500 mg (2.00 mmol) of **21** in 20 mL of dry dichloromethane. The mixture was stirred at room temperature for 1 h (no starting material remained). Water (50 mL) was added and the mixture was extracted with dichloromethane (2 × 50 mL). Combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Removal of solvent in vacuo furnished 524 mg (98.5%) of white solid. The NMR spectrum indicated that this material consisted of about 76% **37** and 24% **36**. The mixture was placed upon a column containing 30 g of silica gel G (230–400 mesh) and eluted with 10% THF/hexane to afford 332 mg (62.4%) of **37**: TLC (1, 0.37; 2, 0.50); mp 113.5–114 °C; IR ($CHCl_3$) 3.37, 3.41, 5.73, 6.90, 6.95, 7.70, 7.96, 8.65, and 9.26 μm; NMR ($CDCl_3$) δ 1.01 (s, 3, CH_3), 1.11 (s, 3, CH_3), 1.77 (d, 1, J = 1 Hz, C-4 H), 1.58 [dd, 1, J = 11 and 2 Hz, C-12(ax) H], 1.93 [d, 1, J = 11 Hz, C-12(eq) H], 3.08 (d, 1, J = 4.5 Hz, C-2 H), 3.36 (dd, 1, J = 4.5 and 1 Hz, C-3 H), 3.67 (dd, 1, J = 9 and 2 Hz, C-10 H), 3.83 (s, 3, OCH_3), 4.33 (d, 1, J = 9 Hz, C-10 H), and 1.2–1.7 (m, 6, remaining H); mass spectrum m/e (rel intensity) 266 (2), 151 (100).

Exact Mass. Calcd for $C_{15}H_{22}O_4$: 266.152. Found: 266.155.

Continued elution with 10% THF/hexane gave 93.0 mg (17.5%) of **36**: TLC (1, 0.31; 2, 0.41); mp 79–79.5 °C; IR ($CHCl_3$) 3.36, 3.40, 5.76, 6.88, 6.94, 7.65, 7.90, 8.65, and 9.29 μm; NMR ($CDCl_3$) δ 1.14 (s, 6, 2 CH_3), 1.66 (d, 1, J = 3 Hz, C-4 H), 1.68 [d, 1, J = 11 Hz, C-12(ax) H], 1.88 [d, 1, J = 11 Hz, C-12(eq) H], 3.31 (dd, 1, J = 4 and 3 Hz, C-3 H), 3.54 (d, 1, J = 8 Hz, C-10 H), 3.60 (d, 1, J = 4 Hz, C-2 H), 3.84 (s, 3, OCH_3), 4.43 (d, 1, J = 8 Hz, C-10 H), and 1.2–1.7 (m, 6, remaining H); mass spectrum m/e (rel intensity) 266 (4), 251 (13), 151 (77), 41 (100).

Exact Mass. Calcd for $C_{15}H_{22}O_4$: 266.152. Found: 266.152.

In a reaction using 738 mg (6.96 mmol) of **21**, run under essentially identical conditions, 384 mg (93.3%) of **36** and **37** was obtained. Recrystallization twice from petroleum ether–ether afforded 92 mg of **37**, mp 108–109.5 °C. The bulk of the material obtained from the mother liquors (259 mg) was subjected to high performance liquid chromatography (silica gel column, 30 atm nitrogen pressure, 15% THF/hexane, 250 mL/min flow rate). The first fraction eluted yielded 144 mg of **37**. The second fraction consisted of 83.4 mg of **36**, mp 71–74 °C. Analytical TLC indicated

(69) Emmons, W. D. *J. Am. Chem. Soc.* **1954**, *76*, 3468.

(70) Böhme, H. "Organic Synthesis"; Wiley: New York, 1955; Collect. Vol. 3, p 619.

(71) The 90-MHz NMR spectrum of a more concentrated sample of **2** showed additional coupling constants of ca. 2 Hz for the C-12 equatorial proton, 1.5 Hz for the C-12 axial and C-10 protons, 11 Hz for the C-3 hydroxyl, and 2.5 Hz for the C-2 hydroxyl. The splitting pattern for the C-2 and C-3 protons was considerably more complex than in the 360-MHz spectrum.

that each of the two fractions isolated contained a trace of the lesser isomer, but the amount was too small to be detectable in the NMR spectra.

Treatment of 36 with 35% Aqueous Perchloric Acid in Acetone. Isolation of Methyl 5,5-Dimethyl-2β-hydroxy-11-oxatricyclo[7.2.1.0^{4,9}]dodec-3-ene-1α-carboxylate (38). A mixture of 43.9 mg (0.165 mmol) of **36**, 0.5 mL of 35% aqueous perchloric acid, and 3 mL of acetone was stirred at room temperature for 1 h (all starting material was consumed). The reaction was quenched with 20 mL of saturated sodium bicarbonate solution and extracted with ether (2 × 20 mL). The organic phase was washed with 20 mL of brine and dried ($MgSO_4$). Removal of solvent gave 22.4 mg of white solid which was chromatographed on 7 g of silica gel. Elution with 20% ether/chloroform afforded 17.2 mg (28.7%) of **38**, mp 115–118 °C. There were at least three minor more polar products, none of which were characterized. However, trans diol **2** definitely was not among them.

Treatment of 36 with Excess Boron Trifluoride Etherate in Acetic Acid. Isolation of 38. A solution of 30.7 mg (0.115 mmol) of **36** in 4 mL of dry acetic acid was treated with 0.10 mL (0.8 mmol) of boron trifluoride etherate. The mixture was stirred at room temperature for 4 h, an additional 0.05 mL (0.4 mmol) of boron trifluoride etherate was added, and the mixture was stirred for 1 h (no remaining starting material). Water (20 mL) was added, and the mixture was extracted with dichloromethane (2 × 20 mL). Combined organic extracts were washed with 5% sodium bicarbonate solution (2 × 20 mL) and brine (20 mL) and dried (K_2CO_3). Evaporation of solvent furnished 32.1 mg of a soft white solid which was chromatographed on 10 g of silica gel. Elution with 10% ether/chloroform afforded 19.3 mg (41.0%) of **38**, mp 122–123 °C. Recrystallization from hexanes plus a trace of dichloromethane gave the analytical sample: TLC (1, 0.17; 2, 0.18); mp 124–125.5 °C; IR (KBr) 2.96, 3.46, 5.71, 5.78, 7.17, 7.85, 8.62, 9.35, 9.47, 9.68, and 11.67 μm; NMR ($CDCl_3$) δ 1.03 (s, 6, 2 CH_3), 2.62 (br s, 1, OH), 3.75 (d, 1, J = 7.5 Hz, C-10 H), 3.79 (s, 3, OCH_3), 4.07 (dd, 1, J = 7.5 and 1.5 Hz, C-10 H), 4.71 (dd, 1, J = 2.5 and 2 Hz, C-2 H), 5.45 (d, 1, J = 2.5 Hz, C-3 H), and 1.1–2.4 (m, 8, remaining H); mass spectrum m/e (rel intensity) 266 (69), 237 (38), 207 (50), 203 (100), 189 (46), 177 (52), 107 (99).

Exact Mass. Calcd for $C_{15}H_{22}O_4$: 266.152. Found: 266.152.

Preparation of Methyl 2β-Acetoxy-5,5-dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodec-3-ene-1α-carboxylate (39). A mixture of 39.3 mg (0.148 mmol) of **38**, 0.25 mL of acetic anhydride, and 2.0 mL of pyridine was stirred at room temperature for 12 h. The reaction was incomplete; therefore 18.1 mg (0.148 mmol) of 4-(dimethylamino)pyridine (DAP)[53] and an additional 0.10 mL of acetic anhydride were added. The reaction was complete within 2 h. The mixture was partitioned between 10 mL of water and ether (2 × 10 mL). The ether layer was washed with 10-mL portions of 10% sodium bicarbonate solution, water, 10% HCl, and brine and dried ($MgSO_4$). Removal of solvent provided 39.7 mg (87.3%) of **39**. Recrystallization from petroleum ether afforded the analytical sample: TLC (1, 0.27; 2, 0.39); mp 84–84.5 °C; IR (KBr) 3.50, 5.78, 7.99, 8.11, and 9.65 μm; NMR ($CDCl_3$) δ 1.14 (s, 6, 2 CH_3), 2.09 (s, 3, acetate CH_3), 3.76 (s, 3, OCH_3), 3.79 (d, 1, J = 7.5 Hz, C-10 H), 4.24 (d, 1, J = 7.5 Hz, C-10 H), 5.40 (d, 1, J = 2.5 Hz, C-2 H), 5.95 (d, 1, J = 2.5 Hz, C-3 H), and 1.2–2.3 (m, 8, remaining H); mass spectrum m/e (rel intensity) 308 (2), 278 (44), 246 (19), 236 (61), 203 (32), 43 (100), 41 (38).

Exact Mass. Calcd for $C_{17}H_{24}O_5$: 308.162. Found: 308.162.

Treatment of 21 with Silver Acetate and Iodine in Acetic Acid. Isolation of Methyl 2α-Acetoxy-5,5-dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodec-3-ene-1α-carboxylate (40).[27,28] Iodine (852 mg, 3.36 mmol) was added to a mixture of 420 mg (1.68 mmol) of **21**, 1.120 g (6.71 mmol) of silver acetate, and 550.5 mg (6.71 mmol) of sodium acetate in 25 mL of dry acetic acid at room temperature. Precipitation of silver iodide was complete within 10 min. The reaction was complete after stirring at room temperature for 6 h. The mixture was filtered and the collected solids were washed with 60 mL of water. The filtrate was extracted with ether (3 × 50 mL). The ether solution was washed with saturated sodium bicarbonate solution (2 × 50 mL), water (50 mL), and brine (50 mL) and dried ($MgSO_4$). Evaporation of solvent in vacuo provided 560 mg of material which was placed on a column containing 25 g of silica gel. Elution with 2–4% THF/hexane furnished 403.5 mg (78.0%) of pure **40**: TLC (1, 0.42; 2, 0.49); bp 114 °C (1.0 torr); IR (neat) 3.40, 3.45, 3.49, 5.71, 5.78, 6.90, 6.97, 7.34, 7.99, 8.18, 8.62, 9.28, 9.49, 9.62, 9.77, and 9.89 μm; NMR ($CDCl_3$) δ 1.12 (s, 3, CH_3), 1.17 (s, 3, CH_3), 1.98 (s, 3, acetate CH_3), 3.56 (d, 1, J = 7 Hz, C-10 H), 3.75 (s, 3, OCH_3), 3.90 (d, 1, J = 7 Hz, C-10 H), 5.29 (s, 1, J = 4.5 Hz, C-2 H), 5.66 (d, 1, J = 4.5 Hz, C-3 H), and 1.2–2.2 (m, 8, remaining H).

Exact Mass. Calcd for $C_{17}H_{24}O_5$: 308.162. Found: 308.162.

Treatment of 37 with Excess Boron Trifluoride in Acetic Acid. Isolation of 40, Methyl (4β)-4,5-Dimethyl-2α-hydroxy-11-oxatricyclo[7.2.1.0^{4,9}]dodec-5-ene-1α-carboxylate (44), and Methyl (4α)-3β-Acetoxy-5,5-dimethyl-2α-hydroxy-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (43). To a solution of 134 mg (0.504 mmol) of **37** in 10 mL of dry acetic acid was added 0.35 mL (2.85 mmol) of boron trifluoride etherate. The resulting cloudy mixture was stirred at room temperature for 2.5 h, an additional 0.20 mL (1.62 mmol) of boron trifluoride etherate was added, and the mixture was stirred 3 h to ensure completion. The mixture was partitioned between 25 mL of water and dichloromethane (2 × 25 mL). The combined organic layers were washed with 5% sodium bicarbonate solution (2 × 25 mL) and brine (25 mL), dried (K_2CO_3), and evaporated in vacuo, affording 141 mg of pale yellow oil. The material was placed upon a column containing 10 g of silica gel. Elution with 5% ether/chloroform yielded 23.3 mg of **40**, 69.6 mg of a mixture of **40**, **44**, and a trace of **39**, and 7.1 mg of crude **44** (tentative structural assignment). Continued elution with 5% ether/chloroform and 10% ether/chloroform afforded 29.8 mg (18.0%) of **43**: TLC (2, 0.10); mp 95–96.5 °C; IR (KBr) 2.98, 3.48, 5.79, 8.03, 9.41, and 9.68 μm; NMR ($CDCl_3$) δ 0.95 (s, 3, CH_3), 1.07 (s, 3, CH_3), 1.80 (d, 1, J = 5.5 Hz, C-4 H), 2.01 [dd, 1, J = 13 and 2.5 Hz, C-12(ax) H], 2.07 (s, 3, acetate CH_3), 2.24 [d, 1, J = 13 Hz, C-12(eq) H], 3.35 (br m, 1, OH), 3.63 (dd, 1, J = 7.5 and 2.5 Hz, C-10 H), 3.79 (s, 3, OCH_3), 4.0 (m, 1, C-2 H), 4.57 (d, 1, J = 7.5 Hz, C-10), 5.26 (dd, 1, J = 5.5 and 1.5 Hz), and 1.2–1.9 (m, 6, remaining H); mass spectrum m/e (rel intensity) 326 (5), 284 (8), 266 (24), 238 (9), 85 (31), 83 (66), 43 (100).

Exact Mass. Calcd for $C_{17}H_{26}O_6$: 326.173. Found: 326.170.

The mixture of **40**, **44**, and **39** was rechromatographed on silica gel using 3% THF/hexane as the eluting solvent. First isolated was 36.1 mg of **40** for a total of 59.4 mg (38.2% yield). Continued elution afforded 25.1 mg (32.2 mg total, 24.0%) of crude **44** as a nearly colorless oil: TLC (2, 0.29); IR (thin film) 2.92, 3.46, 5.76, 6.92, 6.97, 7.88, 9.22, 9.62, and 9.67 μm; NMR ($CDCl_3$) δ 1.36 (s, 3, CH_3), 1.64 (d, 3, J = 2 Hz, CH_3), 2.73 (d, 1, J = 12 Hz, C-12(ax) H), 3.19 (br s, 1, OH), 3.81 (s, 3, OCH_3), and 5.27 (br m, 1, olefinic H); mass spectrum m/e (rel intensity) 266 (5), 219 (5), 167 (8), 43 (100), 41 (100), 29 (83), 27 (94).

Exact Mass. Calcd for $C_{15}H_{22}O_4$: 266.152. Found: 266.149.

Only a trace (<0.1 mg) of **39** was isolated.

Methyl (1α,2α)-3,3-Dimethyl-11-oxatricyclo[5.3.2.0^{2,7}]dodec-9-ene-9-carboxylate (48). A mixture of 112 mg (0.447 mmol) of **21** and 10 mL of trifluoroacetic acid was heated at reflux for 0.5 h. The resulting dark yellow solution was partitioned between 20 mL of dichloromethane and 20 mL of water. The aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (2 × 20 mL) and brine (20 mL) and dried ($MgSO_4$). Removal of solvent yielded 107.0 mg (95.6%) of **48** as a pale yellow oil which solidified upon refrigeration (mp 41.5–42 °C). Recrystallization from petroleum ether at −20 °C afforded the analytical sample: TLC (1, 0.48; 2, 0.54); mp 44–46 °C; IR (KBr) 3.43, 5.84, 7.91, 8.09, 8.59, 9.24, and 9.67 μm; NMR ($CDCl_3$) δ 0.97 (s, 6, 2 CH_3), 2.40 (m, 2, C-8 H), 3.58 (d, 1, J = 8.5 Hz, C-12 H), 3.71 (s, 3, OCH_3), 3.79 (dd, 1, J = 8.5 and 2.5 Hz, C-12 H), 4.32 (d, 1, J = 6 Hz, C-1 H), 7.12 (dd, 1, J = 6 and 2 Hz, olefinic H), and 1.1–1.85 (m, 6, remaining H); ^{13}C NMR ($CDCl_3$) δ 73.4 (C-1), 54.8 (C-2), 30.8 (C-3), 40.8 (C-4), 18.3 (C-5), 31.3 (C-6), 42.6 (C-7), 46.1 (C-8), 130.8 (C-9), 140.7 (C-10), 74.9 (C-12), 23.2 (ax CH_3), 33.4 (eq CH_3), 167.7 (C=O), and 51.7 (OCH_3); mass spectrum m/e (rel intensity) 250 (72), 123 (100), 122 (51), 91 (45).

Exact Mass. Calcd for $C_{15}H_{22}O_3$: 250.157. Found: 250.156.

Methyl 5,5-Dimethyl-2α-(trifluoroacetoxy)-11-oxatricyclo[7.2.1.0^{4,9}]dodec-3-ene-1α-carboxylate (49). Iodine (507.6 mg, 2.00 mmol) was added to a solution of 250.3 mg (1.00 mmol) of **21** and 883.5 mg (4.00 mmol) of silver trifluoroacetate in 20 mL of benzene. Precipitation of silver iodide was complete within

5 min. The mixture was stirred at room temperature for 3.5 h and then heated at 60–70 °C for 0.5 h. There was no significant change (TLC) after the first 1 h. Water (20 mL) was added, and the mixture was extracted with dichloromethane (2 × 20 mL). The organic extracts were washed with saturated sodium bicarbonate solution (20 mL), water (20 mL), saturated sodium thiosulfate solution (20 mL), and brine (20 mL) and dried ($MgSO_4$). Removal of solvent provided 377 mg of pale yellow oil which was chromatographed on 10 g of silica gel with 2% THF/hexane, affording 252.5 mg (69.7%) of pure **49**, mp 60–61.5 °C. Recrystallization from petroleum ether gave the analytical sample: TLC (1, 0.50; 2, 0.63); mp 64–67 °C dec; IR (KBr) 3.44, 5.61, 5.73, 6.90, 7.30, 7.68, 7.74, 7.83, 8.24, 8.46, 8.64 (br), 9.21, 9.61, 10.34, and 10.96 μm; NMR ($CDCl_3$) δ 1.14 (s, 3, CH_3), 1.18 (s, 3, CH_3), 1.97 [d, 1, J = 13 Hz, C-12(ax) H], 2.13 [d, 1, J = 13 Hz, C-12(eq) H], 3.62 (d, 1, J = 7.5 Hz, C-10 H), 3.75 (s, 3, OCH_3), 3.91 (d, 1, J = 7.5 Hz, C-10 H), 5.45 (d, 1, J = 4.5 Hz, C-2 H), 5.69 (d, 1, J = 4.5 Hz, C-3 H), and 1.3–1.9 (m, 6, remaining H); mass spectrum m/e (rel intensity) 362 (2), 347 (2), 322 (4), 203 (42), 91 (17), 81 (20), 79 (26), 69 (100), 58 (18), 43 (23).

Exact Mass. Calcd for $C_{17}H_{21}O_5F_3$: 362.134. Found: 362.134.

Methyl 5,5-Dimethyl-2α-hydroxy-11-oxatricyclo-[7.2.1.0^{4,9}]dodec-3-ene-1α-carboxylate (41). A mixture of 344 mg (1.12 mmol) of **40** and 197 mg (1.86 mmol) of sodium carbonate in 5 mL of methanol was stirred at room temperature for 3 h. The mixture was partitioned between 20 mL of dichloromethane and 20 mL of water. The aqueous layer was extracted with dichloromethane (2 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$), and evaporated in vacuo to afford 265 mg (89%) of **41**, mp 76–80 °C. Recrystallization from hexanes plus a trace of dichloromethane provided the analytical sample: TLC (1, 0.24; 2, 0.26); mp 75–76 °C; IR (KBr) 2.88, 3.40, 3.49, 5.75, 7.96, 8.61, 9.28, 9.47, and 9.62 μm (br); NMR ($CDCl_3$) δ 1.09 (s, 3, CH_3), 1.17 (s, 3, CH_3), 1.99 (d, 1, J = 12 Hz, C-12 H), 2.02 (d, 1, J = 12 Hz, C-12 H), 2.77 (br d, 1, J = 4 Hz, OH), 3.58 (d, 1, J = 7 Hz, C-10 H), 3.78 (s, 3, CH_3), 3.87 (d, 1, J = 7 Hz, C-10 H), 4.17 (br dd, 1, J = 4.5 and 4 Hz, C-2 H), 5.64 (d, 1, J = 4.5 Hz, C-3 H), and 1.3–1.85 (m, 6, remaining H); mass spectrum m/e (rel intensity) 266 (99), 237 (51), 207 (61), 203 (94), 107 (93), 91 (100), 41 (77).

Exact Mass. Calcd for $C_{15}H_{22}O_4$: 266.152. Found: 266.152.

In a reaction similar to the above, 135 mg (0.37 mmol) of trifluoroacetate **49** was converted to 85.5 mg (86%) of **41**, isolated as a pale yellow oil.

Methyl 5,5-Dimethyl-11-oxa-2-oxotricyclo[7.2.1.0^{4,9}]dodec-3-ene-1α-carboxylate (42).[29] A mixture of 219.6 mg (0.825 mmol) of **41** and 2.20 g of activated manganese dioxide (Manganese Hydrate No. 37 from General Metallic Oxides Co.) in 25 mL of dichloromethane was stirred at room temperature for 16 h and then heated at reflux for 2 h. Filtration and removal of solvent in vacuo furnished 181.5 mg (83.3%) of **42**, mp 127–129 °C. Recrystallization from ether afforded the analytical sample: TLC (1, 0.20; 2, 0.42); mp 134–135.5 °C; IR (KBr) 3.45, 5.67, 6.00, 7.60, 7.91, 8.02, 8.64, 9.38, 9.61, 9.78, 11.43, and 12.78 μm; NMR ($CDCl_3$) δ 1.19 (s, 3, CH_3), 1.23 (s, 3, CH_3), 2.08 [d, 1, J = 12.5 Hz, C-12(ax) H], 2.36 [d, 1, J = 12.5 Hz, C-12(eq) H], 3.84 (s, 3, OCH_3), 3.94 (m, 2, C-10 H), 6.09 (s, 1, olefinic H), and 1.4–2.0 (m, 6, remaining H); mass spectrum m/e (rel intensity) 265 (100), 175 (38), 163 (56), 135 (42), 121 (74), 107 (69), 55 (40), 41 (56).

Exact Mass. Calcd for $C_{15}H_{20}O_4$: 264.136. Found: 264.136.

Selective Reduction of 42 to 38. Sodium cyanoborohydride (41.9 mg, 0.667 mmol) was added in three portions at approximate 40-min intervals to a solution of 84.9 mg (0.321 mmol) of **42** in 5 mL of TFA at 0–5 °C. After 2 h of reaction time, the mixture was partitioned between water (20 mL) and dichloromethane (3 × 20 mL). The combined organic layers were washed with 20-mL portions of saturated sodium bicarbonate solution and brine and dried (K_2CO_3). Removal of solvent gave 75.5 mg of material which was chromatographed on 10 g of silica gel. Upon elution with 5% ether/chloroform, a mixture of at least seven minor products was isolated. Continued elution with 5–10% ether/chloroform afforded 40.9 mg (47.8%) of **38** as a white solid. No axial allylic alcohol **41** was isolated.

(4α)-5,5-Dimethyl-2,3-oxido-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylic Acid (46).[24] A mixture of 23.1 mg (0.087 mmol) of **37**, 1.7 mL of Me_2SO, and 0.30 mL of 2 N KOH was heated at 100 °C for 24 h. After cooling, 15 mL of 10% HCl was added, and the mixture was extracted with ether (3 × 10 mL). The combined ether layers were washed with water (2 × 10 mL) and brine (10 mL) and dried ($MgSO_4$). Removal of solvent in vacuo gave 21.9 mg (100%) of **46**, mp 115–119 °C. Recrystallization from petroleum ether/ether afforded the analytical sample: TLC (1, 0.0; 3, 0.02); mp 117.5–119 °C; IR (KBr) 3.0–3.6 (br), 3.76 (w), 3.94 (w), and 5.74 μm; NMR ($CDCl_3$) δ 1.00 (s, 3, CH_3), 1.10 (s, 3, CH_3), 1.73 [dd, 1, J = 12 and 1.5 Hz, C-12(ax) H], 2.00 [d, 1, J = 12 Hz, C-12(eq) H], 3.09 (d, 1, J = 4 Hz, C-2 H), 3.36 (d, 1, J = 4 Hz, C-3 H), 3.70 (dd, 1, J = 9 and 1.5 Hz, C-10 H), 4.36 (d, 1, J = 9 Hz, C-10 H), 7.70 (br s, 1, COOH), and 1.15–1.75 (m, 7, remaining H); mass spectrum m/e (rel intensity) 252 (3), 151 (100).

Exact Mass. Calcd for $C_{14}H_{20}O_4$: 252.136. Found: 252.135.

Attempted Preparation of Mesylate 50b. Isolation of Methyl 2α-Chloro-5,5-dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodec-3-ene-1α-carboxylate (50c). Triethylamine (0.10 mL, 0.72 mmol) and methanesulfonyl chloride (0.04 mL, 0.5 mmol) were added to a solution of 47.9 mg (0.18 mmol) of **41** in 2.0 mL of dichloromethane at 0 °C. No reaction occurred within 80 min. The mixture was warmed and stirred at room temperature for 20 min. Thereupon methanesulfonyl chloride (0.04, 0.10, and 0.04 mL) and the corresponding amounts of triethylamine were added at 0.5–h intervals. Thirty minutes after the last addition, 10 mL of dichloromethane was added and the mixture was washed with 10-mL portions of water, 10% HCl, saturated sodium bicarbonate solution, and brine. The dried solvent (K_2CO_3/Na_2SO_4) was evaporated and the residue was chromatographed on 8 g of silica gel. Elution with 2–5% THF/hexane afforded 35.5 mg (69.3%) of **50c** as a pale yellow oil: TLC (2, 0.68); NMR ($CDCl_3$) δ 1.10 (s, 3, CH_3), 1.18 (s, 3, CH_3), 2.05 (d, 1, J = 12 Hz, C-12 H), 2.18 (d, 1, J = 12 Hz, C-12 H), 3.61 (d, 1, J = 7.5 Hz, C-10 H), 3.80 (s, 3, OCH_3), 3.92 (d, 1, J = 7.5 Hz, C-10 H), 4.62 (d, 1, J = 4.5 Hz, C-2 H), 5.70 (d, 1, J = 4.5 Hz, C-3 H), and 1.2–1.9 (m, 6, remaining H); mass spectrum m/e (rel intensity) 284 (1), 269 (2), 219 (100), 203 (86), 187 (31).

Exact Mass. Calcd for $C_{13}H_{21}O_3Cl$: 284.118. Found: 284.120.

Preparation of Methyl (4α)-2α,3α-Dihydroxy-5,5-dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (52). Method A.[33] A solution of 866 mg (3.46 mmol) of **21** in 10 mL of pyridine was treated with 8.3 mL (3.5 mmol) of 0.423 M osmium tetroxide in pyridine at room temperature. The dark brown mixture was stirred at room temperature for 2 h. Thereupon a mixture of 1.6 g of sodium bisulfite, 18 mL of pyridine, and 27 mL of water was added. After stirring for 1.5 h, the resulting dark orange solution was extracted with dichloromethane (100, 50, 50 mL). The organic layer was washed with water (50 mL), saturated cupric sulfate solution (4 × 50 mL), and water (2 × 50 mL) and dried (K_2CO_3). Removal of solvent in vacuo and further drying via a vacuum pump afforded 911 mg (92.6%) of pure **52**: TLC (1, 0.16; 2, 0.12); mp 123–124 °C; IR (KBr) 2.96, 3.46, 5.75, 7.88, 8.20, 8.66, 8.86, 9.28, 9.33, 9.69, and 11.43 μm; NMR ($CDCl_3$) δ 1.06 (s, 3, CH_3), 1.17 (s, 3, CH_3), 1.74 [dd, 1, J = 12 and 1.5 Hz, C-12(ax) H], 2.24 [d, 1, J = 12 Hz, C-12(eq) H], 2.57 (d, 1, J = 11 Hz, OH), 3.51 (dd, 1, J = 9 and 1.5 Hz, C-10 H), 3.77 (s, 3, OCH_3), 3.9–4.1 (m, 2, C-2 and C-3 H), 4.23 (d, 1, J = 9 Hz, C-10 H), and 1.2–1.7 (7, m, remaining H); mass spectrum m/e (rel intensity) 284 (42), 207 (35), 206 (22), 181 (33), 131 (79), 123 (98), 81 (64), 69 (63), 55 (68), 43 (68), 41 (100).

Exact Mass. Calcd for $C_{15}H_{24}O_5$: 284.162. Found: 284.162.

Method B. Catalytic Osmium Tetroxide Oxidation of 21 Using *N*-Methylmorpholine *N*-Oxide as Oxidant.[34] Olefin **21** (523 mg, 2.09 mmol) was added portionwise over a 15-min period to a mixture of 10.0 mg (0.039 mmol) of osmium tetroxide, 299 mg (2.21 mmol) of *N*-methylmorpholine *N*-oxide, 10 mL of water, 4 mL of acetone, and 0.8 mL of *tert*-butyl alcohol at room temperature. The mixture was stirred overnight. Thereupon a mixture of 0.10 g of sodium dithionite, 1.2 g of Florisil, and 8.0 mL of water was added. The mixture was stirred and then filtered with washing with acetone. The filtrate was neutralized with 2 N sulfuric acid, and the acetone was evaporated in vacuo. The residue was extracted with dichloromethane (3 × 25 mL). The organic extracts were washed with 25 mL of 5% HCl, 25 mL of water, and 25 mL of brine and dried (K_2CO_3). Removal of solvent yielded 530 mg (89.3%) of **52**, contaminated with a brown im-

purity. However, no impurities could be detected in the NMR spectrum.

Preparation of Methyl (4α)-5,5-Dimethyl-2α-hydroxy-11-oxa-3-oxotricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (53) under Optimal Conditions. Trifluoroacetic anhydride (0.33 mL, 2.34 mmol) was added to a solution of 0.22 mL (3.1 mmol) of Me_2SO in 10 mL of dichloromethane at −60 °C. After 10 min, a solution of 398 mg (1.40 mmol) of **52** in 5 mL of dichloromethane was added. The mixture was stirred at −60 °C for 0.5 h and then warmed rapidly to −15 °C. The reaction mixture was allowed to warm slowly to −3 °C over a 1.5–h period, and then quenched with 10 mL of 5% HCl. The mixture was stirred at 0 °C for 0.5 h, 25 mL of water was added, and the cold mixture was extracted with dichloromethane (2 × 50 mL). Combined organic layers were washed with 20 mL of water and dried (Na_2SO_4). Evaporation of solvent provided 392 mg of white solid, which was chromatographed on 25 g of silica gel. Elution with chloroform afforded 332 mg (84.0%) of pure **53**: TLC (1, 0.30; 4, 0.64); mp 163.5–165 °C; IR (KBr) 3.10, 3.48, 5.74, 5.92, 7.86, 8.01, 8.67, 8.85, 9.36, and 9.53 μm; NMR ($CDCl_3$) δ 1.15 (s, 3, CH_3), 1.17 (s, 3, CH_3), 2.11 [dd, 1, J = 12 and 2 Hz, C-12(eq) H], 2.48 (d, 1, J = 1.5 Hz, C-4 H), 2.63 (dd, 1, J = 12 and 1.5 Hz, C-12(ax) H], 3.24 (br m, 1, OH), 3.57 (dd, 1, J = 8 and 1.5 Hz, C-10 H), 3.80 (s, 3, OCH_3), 4.08 (dd, 1, J = 3.5 and 2 Hz, C-2 H), 4.22 (dd, 1, J = 8 and 1.5 Hz, C-10 H), and 1.2–1.9 (m, 6, remaining H); mass spectrum m/e (rel intensity) 282 (19), 251 (7), 180 (19), 168 (100), 167 (81), 115 (48), 81 (30), 69 (47), 55 (35).

Exact Mass. Calcd for $C_{15}H_{22}O_5$: 282.147. Found: 282.148.

Continued elution with chloroform and 2% ether/chloroform provided 49.9 mg (12.5% recovery) of **52**.

Methyl 5,5-Dimethyl-3-hydroxy-11-oxa-2-oxotricyclo-[7.2.1.0^{4,9}]dodec-3-ene-1α-carboxylate (56). TFAA (0.06 mL, 0.42 mmol) was added to a solution of Me_2SO (0.04 mL, 0.56 mmol) in 8 mL of dichloromethane at −60 °C. After 10 min, a solution of 79.2 mg (0.279 mmol) of **52** in 4 mL of dichloromethane was added rapidly. The mixture was stirred at −60 °C for 40 min. Triethylamine (0.10 mL, 0.72 mmol) was added, the solution was stirred at −60 °C for 30 min, and a second 0.10 mL of triethylamine was added, raising the pH of the solution from 2 to 8. The mixture was stirred at −60 °C for 40 min and then warmed to 0 °C. Water (20 mL) was added and the mixture was extracted with dichloromethane (2 × 20 mL). Removal of solvent following drying ($MgSO_4$) yielded 82.3 mg of crude dione, mp 112–113 °C. The material was placed on a column containing 9 g of silica gel. Elution with chloroform and 4% ether/chloroform gave 60.8 mg (77.9%) of pure **56**: TLC (2, 0.52); mp 116–117 °C; IR (KBr) 3.03, 3.48, 5.79, 5.99, and 7.36 μm; NMR ($CDCl_3$) δ 1.23 (s, 3, CH_3), 1.46 (s, 3, CH_3), 2.06 (d, 1, J = 12 Hz, C-12 H), 2.34 (d, 1, J = 12 Hz, C-12 H), 3.84 (s, 3, OCH_3), 3.87 (m, 2, C-10 H), 6.13 (s, 1, OH), and 1.1–1.9 (m, 6, remaining H); mass spectrum m/e (rel intensity) 280 (6), 250 (24), 239 (31), 218 (49), 83 (46), 82 (37), 55 (80), 41 (100).

Exact Mass. Calcd for $C_{15}H_{20}O_5$: 280.131. Found: 280.129.

Treatment of 52 with the Me_2SO–Oxalyl Chloride Reagent.[46] Isolation of 53, 56, and Methyl (4α)-5,5-Dimethyl-3α-hydroxy-11-oxa-2-oxotricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (55). A solution of oxidizing reagent was prepared by adding 1.18 mL (1.66 mmol) of Me_2SO dropwise to a solution of 0.73 mL (8.4 mmol) of oxalyl chloride in 10 mL of dichloromethane at −55 to −60 °C. After 15 min of stirring, five 1.20-mL portions were added to a solution of 215 mg (0.756 mmol) of **52** in 10 mL of dichloromethane at −60 °C over a 4-h period (the reaction mixture was briefly warmed to −10 °C between the fourth and last additions of reagent). Triethylamine (2.8 mL, 20 mmol) was added at −60 °C and the mixture was warmed to room temperature. Water (25 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with 25-mL portions of 10% HCl, water, 5% sodium carbonate solution, and brine and dried ($MgSO_4$). Removal of solvent gave 266 mg of material which was chromatographed on 25 g of silica gel. Elution with chloroform and 1% ether/chloroform afforded 86.2 mg (40.6%) of α-dione **56**. Elution with 2% ether/chloroform furnished 62.9 mg (29.5%) of **55**, mp 116–117 °C. Recrystallization from petroleum ether–ether provided the analytical sample: TLC (2, 0.40); mp 124–125 °C; IR (KBr) δ 2.93, 3.45, 5.73, 5.80, 7.98, 8.97, 9.30, 9.55, and 9.87 μm; NMR ($CDCl_3$) δ 1.14 (s, 3, CH_3), 1.16 (s, 3, CH_3), 1.48 (dd, 1, J = 11 and 2 Hz, C-4 H), 1.95 (d, 1, J = 13.5 Hz, C-12 H), 2.38 (d, 1, J = 13.5 Hz, C-12 H), 3.31 (br s, 1, OH), 3.76 (dd, 1, J = 8.5 and 2 Hz, C-10 H), 3.83 (s, 3, OCH_3), 4.55 (d, 1, J = 8.5 Hz, C-10 H), 4.70 (d, 1, J = 11 Hz, C-3 H), and 1.2–1.8 (m, 6, remaining H); mass spectrum m/e (rel intensity) 282 (9), 254 (11), 152 (46), 151 (100).

Exact Mass. Calcd for $C_{15}H_{22}O_5$: 282.147. Found: 282.149.

Elution with 10% ether/chloroform gave 5.9 mg (2.8%) of **53**.

Methyl (4α)-2α-Acetoxy-5,5-dimethyl-11-oxa-3-oxotricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (51). Acetic anhydride (0.12 mL, 1.3 mmol) was added to a solution of 175.3 mg (0.621 mmol) of **53** and 76.1 mg (0.623 mmol) of DAP[53] in 6 mL of dichloromethane. After 2 h at room temperature, the solution was diluted with 20 mL of dichloromethane and washed with 10-mL portions of 10% sodium bicarbonate solution, saturated ammonium chloride solution, and brine and dried ($MgSO_4$). Evaporation of solvent in vacuo afforded 195.5 mg (97.1%) of pure **51**: TLC (2, 0.51); mp 180–180.5 °C; IR (KBr) 3.45, 5.74, 5.80, 7.81, 7.89, 8.26, 8.71, and 9.70 μm; NMR ($CDCl_3$) δ 1.15 (s, 6, 2 CH_3), 2.07 (s, 3, acetate CH_3), 2.14 [dd, 1, J = 13 and 2 Hz, C-12(eq) H], 2.34 (d, 1, J = 1.5 Hz, C-4 H), 2.50 [dd, 1, J = 13 and 1.5 Hz, C-12(ax) H], 3.56 (dd, 1, J = 8.5 and 1.5 Hz, C-10 H), 3.72 (s, 3, OCH_3), 4.25 (dd, 1, J = 8.5 and 1.5 Hz, C-10 H), 5.20 (d, 1, J = 2 Hz, C-2 H), and 1.2–1.9 (m, 6, remaining H); mass spectrum m/e (rel intensity) 326 (4), 284 (14), 266 (42), 85 (100).

Exact Mass. Calcd for $C_{17}H_{26}O_6$: 326.127. Found: 326.127.

Preparation of Methyl (4α)-2α,3β-Dihydroxy-5,5-dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (2) under Optimal Conditions. To a solution of 108.9 mg (0.386 mmol) of **53** in 6 mL of TFA at 0–5 °C was added a total of 69.7 mg (1.11 mmol) of sodium cyanoborohydride in three portions at 1-h intervals. One hour following the last addition, the reaction mixture was partitioned between 25 mL of water and dichloromethane (3 × 25 mL). The organic extracts were washed with 25 mL of saturated sodium bicarbonate solution and 25 mL of brine and dried (Na_2SO_4). Removal of solvent in vacuo yielded 105.4 mg (96.0%) of **2**, mp 105–107 °C. Recrystallization from hexanes/dichloromethane gave the analytical sample: TLC (2, 0.14; 4, 0.61); mp 123–124 °C; IR (KBr) 2.93, 3.10, 3.49, 5.76, 6.94, 7.85, 8.69, 9.42, 9.63, 10.56, and 10.73 μm; 360-MHz NMR ($CDCl_3$) δ 1.07 (s, 3, CH_3), 1.26 (s, 3, CH_3), 1.52 (d, 1, J = 3.0 Hz, C-4 H), 1.80 [d, 1, J = 11.6 Hz, C-12(eq) H], 2.32 (d, 1, J = 11.6 Hz, C-12(ax) H), 2.70 (br s, 1, C-3 OH), 3.11 (br s, 1, C-2 OH), 3.62 (d, 1, J = 7.9 Hz, C-10 H), 3.80 (s, 3, OCH_3), 4.07 (s, 1, C-2 OH), 4.12 (br s, 1, C-3 H), 4.50 (d, 1, J = 7.9 Hz, C-10 H), and 1.26–1.64 (m, 6, remaining H);[71] mass spectrum m/e (rel intensity) 284 (28), 151 (100), 123 (36), 81 (42), 55 (37), 43 (31), 41 (50).

Exact Mass. Calcd for $C_{15}H_{24}O_5$: 284.162. Found: 284.164.

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.12; H, 8.28.

Reaction of Tetra-n-butylammonium Borohydride with 53 in Ethyl Acetate at 0 °C. Isolation of 2. Tetra-n-butylammonium borohydride (25.0 mg, 1.03 mmol) was added to a solution of 26.0 mg (0.092 mmol) of **53** in 2 mL of ethyl acetate at 0 °C. The reaction was complete after 80 min at 0 °C. Following the addition of 10 mL of 5% HCl, the mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were washed with 10 mL of water and dried (K_2CO_3/Na_2SO_4). Evaporation of solvent gave 23.7 mg (90.5%) of crude **2**, mp 92–94 °C. The NMR spectrum indicated that the material was of 95% or better purity. No triol **57** was evident.

Prolonged Reaction of 53 with Excess Tetra-n-butylammonium Borohydride in Methanol at Room Temperature. Isolation of (4α)-5,5-Dimethyl-1α-(hydroxymethyl)-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-2α,3β-diol (57). Tetra-n-butylammonium borohydride (100 mg, 0.41 mmol) was added to a solution of 102.3 mg (0.362 mmol) of **53** in 5 mL of methanol at room temperature. The mixture was stirred for 6 h, an additional 70 mg (0.29 mmol) of borohydride was added, and the mixture was stirred for 15 h. The reaction was complete after a final addition of 50 mg (0.21 mmol) of borohydride and stirring for 4 h. The mixture was partitioned between 20 mL of water and dichloromethane (5 × 20 mL). The combined organic layers were washed with 40 mL of 5% HCl and 40 mL of brine and dried (K_2CO_3/Na_2SO_4). Removal of solvent in vacuo gave 234 mg of

material which was chromatographed on 10 g of silica gel. Elution with 10% ether/chloroform afforded 12.6 mg (12.2%) of crude **53**. Elution with 5% methanol/chloroform provided 80.8 mg (87.0%) of **57** as a colorless oil which solidified upon standing: TLC (2, 0.0; 4, 0.33); mp 142–143.5 °C; IR (KBr) 2.96, 3.46, 6.89, 7.95, 9.23 (br), 9.38, 9.60 (br), 9.88, 10.21, and 12.29 μm; NMR ($CDCl_3$) δ 1.05 (s, 3, CH_3), 1.27 (s, 3, CH_3), 1.79 (d, 1, J = 16 Hz, C-12 H), 2.10 (d, 1, J = 16 Hz, C-12 H), 3.42 (d, 1, J = 8 Hz, C-10 H), 3.54 (d, 1, J = 12 Hz, CHOH), 3.80 (d, 1, J = 12 Hz, CHOH), 3.95–4.20 (m, 2, C-2 and C-3 H), 3.20–4.20 (m, 3, OH), 4.39 (d, 1, J = 8 Hz, C-10 H), and 1.3–1.8 (m, 7, remaining H); mass spectrum m/e (rel intensity) 256 (0.3), 255 (0.8), 238 (9), 220 (51), 207 (11), 43 (92), 41 (100).

Exact Mass. Calcd for $C_{14}H_{24}O_4$: 256.167. Found: 256.164.

Methyl (4α)-2α-Acetoxy-5,5-dimethyl-3β-hydroxy-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (45). Acetic anhydride (0.20 mL, 2.1 mmol) was added to a solution of 75.6 mg (0.266 mmol) of **2** and 65.4 mg (0.535 mmol) of DAP[53] in 6 mL of dichloromethane at room temperature. The mixture was stirred for 3 h, and the workup procedure used in the preparation of **51** was followed, providing 79.4 mg (91.5%) of crude **45**. Recrystallization from hexanes plus a trace of dichloromethane afforded the analytical sample: TLC (2, 0.19; 3, 0.38; 4, 0.71); mp 102.5–104 °C dec; IR (KBr) 2.92, 3.46, 5.75, 7.85, 8.06, 8.21, 8.96, and 9.65 μm; 360-MHz NMR ($CDCl_3$) δ 1.05 (s, 3, CH_3), 1.29 (s, 3, CH_3), 1.40 (dd, 1, J = 4.3 and 1.2 Hz, C-4 H), 1.99 [dd, 1, J = 11.6 and 1.2 Hz, C-12(eq) H], 2.07 (s, 3, acetate CH_3), 2.11 [d, 1, J = 11.6 Hz, C-12(ax) H], 2.78 (d, 1, J = 10.4 Hz, OH), 3.58 (dd, 1, J = 8.5 and 1.2 Hz, C-10 H), 3.74 (s, 3, OCH_3), 4.05 (ddd, 1, J = 10.4, 4.3, and 1.5 Hz, C-3 H), 4.49 (d, 1, J = 8.5 H, C-10 H), 5.23 (dd, 1, J = 1.5 and 1.2 Hz, C-2 H), and 1.2–1.7 (6, m, remaining H); mass spectrum m/e (rel intensity) 326 (2), 284 (23), 266 (95), 151 (99), 133 (70), 55 (79), 43 (42), 29 (100), 27 (93).

Exact Mass. Calcd for $C_{17}H_{26}O_6$: 326.173. Found: 326.172.

Methyl (4α)-2α,3β-Diacetoxy-5,5-dimethyl-11-oxatricyclo[7.2.1.0^{4,9}]dodecane-1α-carboxylate (47). Acetic anhydride (0.51 mL, 5.3 mmol) was added to a solution of 71.6 mg (0.219 mmol) of **45** and 29.5 mg (0.241 mmol) of DAP in 2 mL of dichloromethane and 2 mL of triethylamine.[53b] The mixture was stirred at room temperature for 18 h. Since the reaction was incomplete, an additional 15.0 mg (0.123 mmol) of DAP and 0.25 mL of acetic anhydride were added, and the mixture was stirred for 24 h. The mixture was partitioned between water (25 mL) and ether (2 × 25 mL). The organic extracts were washed with 25-mL portions of 10% sodium bicarbonate, water, 10% HCl, and brine and dried ($MgSO_4$). Evaporation of solvent yielded 70.3 mg (87.0%) of crude **47**, mp 116–118 °C. Recrystallization from petroleum ether provided the analytical sample: TLC (2, 0.27; 3, 0.44; 4, 0.74); mp 137–138 °C; IR (KBr) 3.45, 5.70, 6.91, 7.32, 7.85, 8.07, 8.22, 8.65, 9.34, 9.60, 9.72, and 10.43 μm; 360-MHz NMR ($CDCl_3$) δ 0.95 (s, 3, CH_3), 1.08 (s, 3, CH_3), 1.68 (dd, 1, J = 4.3 and 1.2 Hz, C-4 H), 2.00 [d, 1, J = 11.6 Hz, C-12(eq) H], 2.07 (s, 3, acetate CH_3), 2.08 [d, 1, J = 11.6 Hz, C-12(ax) H], 2.12 (s, 3, acetate CH_3), 3.49 (dd, 1, J = 7.9 and 1.2 Hz, C-10 H), 3.70 (s, 3, OCH_3), 4.57 (d, 1, J = 7.9 Hz, C-10 H), 5.08 (d, 1, J = 1.2 Hz, C-2 H), 5.24 (dd, 1, J = 4.3 and 1.2 Hz, C-3 H), and 1.25–1.73 (m, 6, remaining H); mass spectrum m/e (rel intensity) 368 (23), 326 (41), 266 (84), 43 (48), 41 (100), 31 (69), 29 (82), 27 (74).

Exact Mass. Calcd for $C_{19}H_{28}O_7$: 368.183. Found: 368.184.

Preparation of Bruceantin Monoacetate (58a). A total of 0.11 mL (1.2 mmol) of acetic anhydride was added in three portions over a 3.5-h period to a solution of 140 mg (0.255 mmol) of **1** in 8 mL of pyridine at 0 °C. Following refrigeration at −20 °C overnight (necessary for completion of the reaction), 25 mL of water was added, and the mixture was extracted with dichloromethane (2 × 40 mL). The organic layers were washed with saturated cupric sulfate solution (2 × 25 mL), water (25 mL), 10% sodium bicarbonate solution (25 mL), and brine (25 mL) and dried ($MgSO_4$). Evaporation of solvent in vacuo afforded 151 mg (97%) of **58a**, mp 166–168 °C. Recrystallization from ether gave the analytical sample: TLC (3, 0.15); mp 166–168 °C, partial NMR ($CDCl_3$) δ 1.05 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 1.69 (s, 3, C-19 CH_3), 1.80 (s, 3, 4-CH_3), 2.14 (s, 3, C-7′ CH_3), 2.25 (s, 3, acetate CH_3), 3.75 (s, 3, OCH_3), 4.26 (br m, 2, C-11 and C-12 H), 5.65 (s, 1, C-2 H), and 6.21 (d, 1, J = 13 Hz, C-15 H); mass spectrum m/e (rel intensity) 590 (1.4), 546 (9), 438 (14), 420 (14), 402 (15), 392 (11), 297 (18), 151 (55), 112 (98), 111 (100), 110 (97), 43 (98).

Exact Mass. Calcd for $C_{30}H_{38}O_{12}$: 590.236. Found: 590.235.

Preparation of Bruceantin Triacetate (58c). Acetic anhydride (0.05 mL, 0.53 mmol) was added to a solution of 27.1 mg (0.049 mmol) of **1** and 18.3 mg (0.15 mmol) of DAP[53] in 2 mL of dichloromethane. The mixture was stirred at room temperature for 12 h (conversion to **58c** was nearly complete after 1.5 h). Dichloromethane (20 mL) was added and the organic phase was washed with 10-mL portions of saturated ammonium chloride solution, water, and 10% aqueous sodium bicarbonate. After drying ($MgSO_4$) the solvent was removed to yield 28.9 mg (87%) of crude **58c**. Recrystallization from ether plus a trace of dichloromethane gave the analytical sample: TLC (3, 0.35); mp 268–269 °C; partial NMR ($CDCl_3$) δ 1.06 [d, 6, J = 6.5 Hz, CH-(CH_3)$_2$], 1.30 (s, 3, C-19 CH_3), 1.80 (s, 3, 4-CH_3), 2.02 (s, 3, acetate CH_3), 2.10 (s, 3, acetate CH_3), 2.15 (s, 3, C-7′ CH_3), 2.23 (s, 3, acetate CH_3), 3.68 (s, 3, OCH_3), 5.2–5.4 (m, 2, C-11 and C-12 H), 5.64 (s, 1, C-2 H), and 6.07 (d, 1, J = 13 Hz, C-15 H).

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