Synthesis of 15-Deoxy-16β-Ethoxybruceantin and Synthetic Efforts toward Bruceantin

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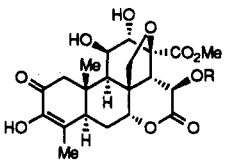
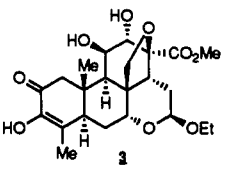
Utilization of asymmetric Michael addition leads to chiral phenanthrenone (+)-4 suitable for the synthesis of Bruceantin. The D-ring is assembled by means of an intramolecular alkylation of the bromoacetals **25** while only the axial diastereomer **25ax** proceeds smoothly. The formation of the cyanohydrin introduces the C-13 carboxyl group and tandem intramolecular alkylation provides the furan E-ring. The C-11,12 *cis*-diol **39** is readily transformed to the *trans*-diol **42** *via* an unusual Swern-type oxidation/reduction sequence. The C-2,3 olefin proves to be an efficient progenitor for the A-ring diosphenol function which can be introduced at the late stage of the synthesis. 15-Deoxy-16β-ethoxybruceantin **3** is accordingly prepared. Attempts to elaborate common intermediates toward the synthesis of bruceantin are described. The presence of an oxygen function at C-15 drastically changes the relative reactivity of the C-2,3 and C-11,12 olefinic bonds.

The quassinoids are a broad group of bitter principles isolated from the botanical family *Simaroubaceae*, which have been used for centuries in the folk medicine of Asia and Africa.[1] These materials are reportedly effective against a variety of ailments such as cancer, certain intestinal disorders, and even alcoholism.[2] Until the discovery in 1970 by Wall and Wani[3] that halocanthone, a member of the quassinoidal family, possessed antineoplastic activity, there had been no systematic investigation into the therapeutic benefits of quassinoids. Bruceantin (1) and bruceantinol (2) were isolated from *Brucea antidysenterica* in 1975 by Kupchan[4] as a result of an extensive search for new anticancer agents. Bruceantin (1) was the most potent therapeutic agent from the quassinoid family and underwent clinical testing at the U. S. National Cancer Institute. Despite its failure in Phase II clinical trials, bruceantin still attracts intensive synthetic efforts from various laboratories worldwide.[5] This enthusiasm undoubtedly arises from the synthetic challenge presented by the structural complexity of bruceantin and other members of the quassinoid family. An excellent comprehensive review of the synthetic achievements in this area has been published by Watt.[6]

A formal synthesis of bruceantin reported by Murae[7a] in 1989 and a recent total synthesis by Grieco[7b] prompts us to update our own synthetic efforts in this area. This paper reports on the preparation of optically active pentacyclic intermediate **3** which possesses all the requisite functionalities embodied in bruceantin, with the exception of the D-ring oxidation state. Our overall strategy for the synthesis of bruceantin, as depicted in Scheme 1, was to utilize olefins as progenitors for the A-ring diosphenol (enolized α-diketone), the C-ring *trans*-diol, and the D-ring α-acyloxy lactone. The elaboration of an olefinic bond into the diosphenol and *trans*-diol functionalities had been successfully demonstrated in model studies published from our laboratory.[8,9] It was our intention to effect sequential functionalization of these olefins in a stepwise, stereo- and chemoselective manner, i.e. a D-C-A sequence. Intramolecular oxygen alkylation of a leaving group (i.e. mesylate) at C-17 by a cyanohydrin anion generated by the addition of a cyanide anion to the carbonyl at C-13 forms the E-ring tetrahydrofuran bridge. Synthesis of the D-ring was achieved by intramolecular enolate alkylation of a bromoacetal. The E-ring carbon moiety was introduced at C-8 by means of a Nagata-type hydrocyanation[10] of a protected hydroxy enone. The ABC-ring skeleton was derived from the well-known enone **4**.[11]





3

R		
(*E*)-COCH=C(Me)CHMe$_2$	Bruceantin	**1**
H	Bruceolide	
COCH$_2$CHMe$_2$	Brucein A	
COMe	Brucein B	
(E)-COCH=C(Me)C(Me)$_2$OH	Brucein C	
COCH=CMe$_2$	Brusatol	
COPh	Bruceantarin	
(*E*)-COCH=C(Me)C(Me)$_2$OAc	Bruceantinol	**2**

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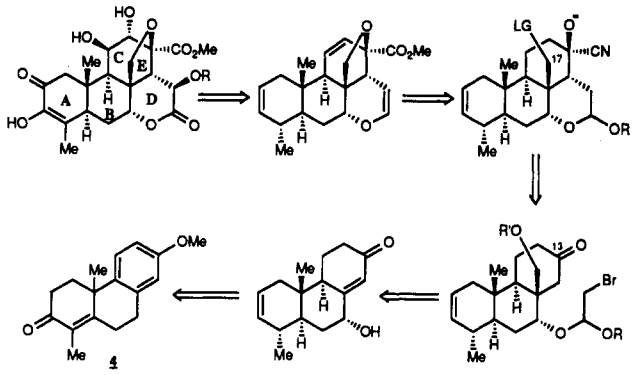
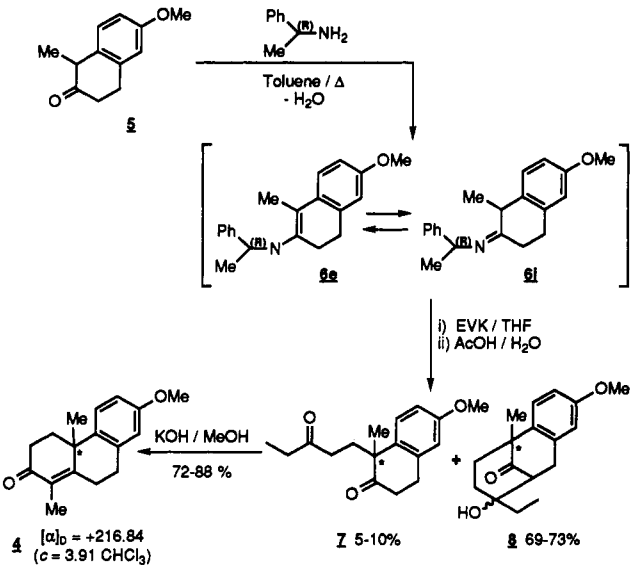
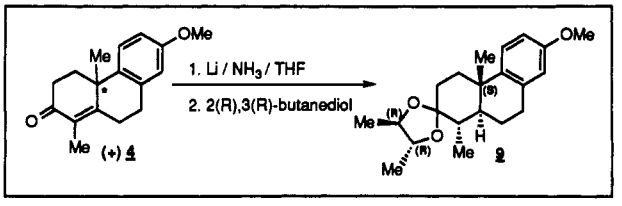
Scheme 1



Scheme 2





The enantioselective Robinson annulation, developed by d'Angelo,[12] was identified as the vehicle for the preparation of our tricyclic substrate **4** in optically active form (Scheme 2). Thus, condensation of the β-tetralone **5**[11] with (*R*)-α-methyl benzylamine presumably led to a mixture of imine **6i** and enamine **6e** which was not isolated but treated directly with ethyl vinyl ketone to afford a mixture of the diketone **7** (5–10%) and the ketol **8** (69–80%, single diastereomer of unknown relative stereochemistry). Stirring the **7**/**8** mixture with methanolic KOH afforded homochiral tricyclic enone (+)-**4** in high yield (72–88%) with optical purity in the excess of 95% ee.[13] The absolute configuration of (+)-**4** at C-10 was established as (*S*) by X-ray crystallography of the derived acetal **9**.[14]

Exhaustive Birch reduction of the enone **4** afforded exclusively the equatorial hydroxy dienyl ether **10** in 59% yield after recrystallization (Scheme 3).[15] The alcohol **10** was subsequently converted to the mesylate **11**, which was found to be extremely labile due to the sensitive dienyl ether function. Careful azeotropic removal of water from the crude mesylate **11** was crucial. Under strictly anhydrous conditions, isomerization of **11** to the thermodynamically more stable conjugated dienyl ether **12** using pyridinium *p*-toluenesulfonate occurred without incidence. Without purification, the dienyl ether **12** was oxidized with buffered persulfate (oxone)[15] to the γ-hydroxy enone **13** stereoselectively in 67% overall yield from the alcohol **10** for the three-step transformation. It is worth noting that a substantial amount (0–30% yield) of the enol lactone **14** was produced when the oxidation reaction was not efficiently stirred, which apparently allowed higher localized oxidant concentrations within the reaction medium resulting in overoxidation. The axial hydroxy group of **13** was then protected as the TBDMS ether **15**[16] in 70–85% yield. Incorporation of the C-2,3 olefinic bond in the A-ring required displacement of the mesylate at C-3 by sodium phenylselenide[17] to give the selenide **16** which was not isolated and subsequent syn elimination[18] effected by oxidation of the seleno moiety in **16** to give the olefin **17** in a one-pot operation (64% yield). It is worth noting that buffering the oxidation/elimination step with sodium bicarbonate significantly improved the yield to 82–89%, presumably by neutralization of the acidic phenylselenenic acid generated in the reaction.

Having secured the A-ring olefin, our attention was directed toward the introduction of the E-ring element, i.e. an oxymethyl fragment, at C-8 (Scheme 4). Hydrocyanation[10] of the enone **17** with diethylaluminum cyanide, in the presence of a catalytic amount of potassium cyanide and 18-crown-6 ether,[15] provided the axial nitrile **18ax** as the major product (65–87% yield). Combined crops of the minor equatorial isomer **18eq** (2–3% yield) can be recycled to enone **17** *via* a retro-Michael reaction effected by potassium *tert*-butoxide (57% unoptimized yield). After protecting the keto function in **18ax** as the TBDMS enol ether **19** under Mander's conditions,[19] the nitrile was reduced to the aldehyde **20** *via* hydrolysis of the imine intermediate followed by a second reduction to the neopentyl alcohol **21**.

The crude neopentyl alcohol **21** was subsequently protected as the benzyl ether **22**. The C-ring ketone was regenerated by acid hydrolysis (aqueous HCl/THF) of the TBDMS enol ether function to furnish the tricyclic ketone **23** in 60–72% overall yield from the nitrile **18ax**. The TBDMS ether at C-7 survived the acidic hydrolytic conditions and had to be separately unmasked by treatment with tetra-*n*-butylammonium fluoride[16] to provide the alcohol **24** in 78–95% yield.

Assembly of the D-ring rudiment was accomplished following the protocol of Schlessinger,[20] i.e. treatment of the alcohol **24** in the presence of *N*,*N*-dimethylaniline with 1-ethoxy-1,2-dibromoethane generated *in situ*. A mixture of diastereomeric bromoacetals **25ax** and **25eq** in the ratio of 6:4 was obtained in 80% yield (Scheme 5). It had been

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(12) Volpe, T.; Revial, G.; Pfau, M.; d'Angelo, J. *Tetrahedron Lett.* **1987**, *28*, 2367.
(13) The enantiomeric excess of the tricyclic enone was determined by assaying the Mosher ester of the corresponding allylic alcohol prepared by reduction ($CeCl_3/NaBH_4$) of the enone.
(14) Full X-ray data on compound **9** can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Tel. No. 44-223-336408; Fax No. 44-223-336033.
(15) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902.
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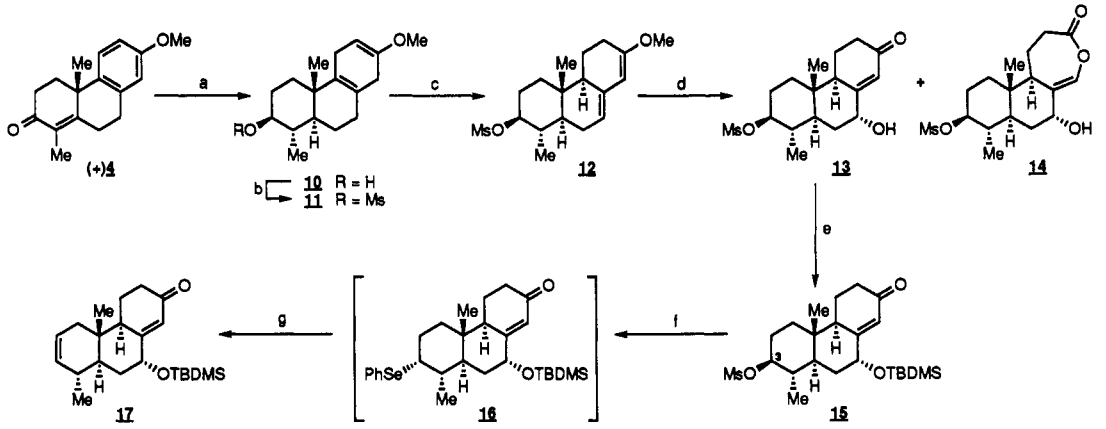
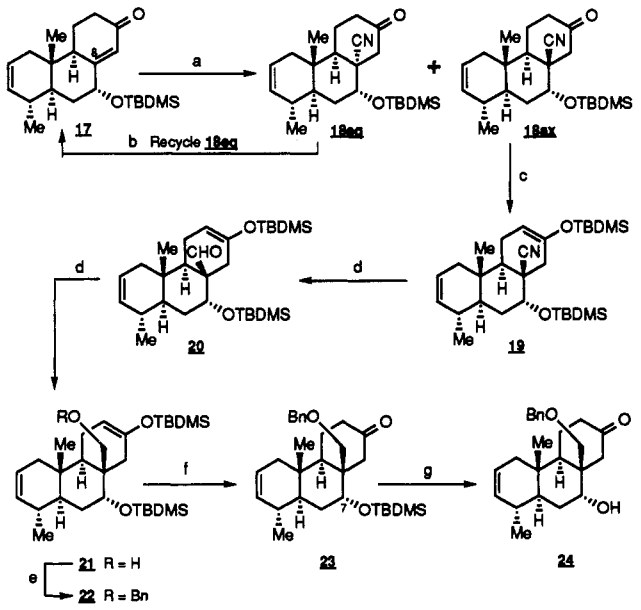
Scheme 3



[a] (i) Li/^{t}BuOH/NH_3/THF/−78 °C, (ii) Li/EtOH/NH_3/THF/−78 °C, 59%; (b) MsCl/Et_3N/CH_2Cl_2/−20 → 0 °C, crude quant yield; (c) PPTS/CH_2Cl_2, crude quant yield; (d) Oxone/K_2CO_3/THF/dioxane/H_2O, 67% for three steps b–d; (e) TBDMSCl/imidazole/DMF, 74%; (f) PhSeSePh/$NaBH_4$/EtOH/d; (g) H_2O_2/$NaHCO_3$/EtOH, 82% for two steps f–g.

Scheme 4



[a] (a) Et_2AlCN/KCN/18-crown-6/benzene/toluene, 87% of β-nitrile (**18ax**) and 3% of α-nitrile (**18eq**); (b) ^{t}BuOK/THF, 57%; (c) TBDMSOTf/Et_3N/CH_2Cl_2/0 °C, crude quant yield; (d) DIBAL-H/ether, crude quant yields; (e) (i) NaH/$PhCH_2Br$/$^n Bu_4NI$/THF, crude quant yield; (f) aqueous HCl, 68% for five steps c–f; (g) $^n Bu_4NF$/THF, 95%.

demonstrated in a similar model system[9a] that both of the diastereomeric bromoacetals **28ax/28eq** cyclized to give the tetracyclic ketone **29ax/29eq**, albeit with a 10-fold difference in reaction rate. In the present A-ring olefin series the axial bromoacetal **25ax** readily underwent cyclization to the tetracyclic ketone **26** upon treatment with potassium *tert*-butoxide, while the equatorial bromoacetal **25eq** was extremely slow to cyclize to **27**. The cyclization product **26** decomposed when exposed to the reaction conditions for an extended period of time, during which the equatorial isomer did not cyclize at any appreciable rate. The total ineptness of the equatorial isomer to cyclize could be due to the highly unfavorable interaction involved in eclipsing the bromo and ethoxy groups as was required to provide the proper orbital alignment for the C-14,15 bond formation. A similar observation had also been made by Schlessinger in his synthesis of bisnorvernolepin.[20] It was obvious that the equatorial isomer **25eq** could not be fully utilized in our synthetic sequence due to its sluggishness toward cyclization. The axial isomer **25ax** could, however, be separated from the equatorial isomer **25eq** by means of preparative HPLC. Generation of the incommodious equatorial isomer **25eq** presented only a minor inconvenience, since this material could be easily recycled by heating with freshly activated zinc in ethanol (80% yield) or preferably by hydrolysis[21] with amberlyst-15[22] in aqueous acetonitrile at reflux to regenerate the alcohol **24** in quantitative yield. Subsequent treatment of the pure axial bromoacetal **25ax** with potassium *tert*-butoxide in benzene readily provided the tetracyclic ketone **26** in 90% yield.

Having constructed the D-ring skeleton, our effort was directed toward the elaboration of the tetrahydrofuran E-ring (Scheme 6). After masking of the C-13 carbonyl of the ketone **26** as its TBDMS enol ether **30**,[19] the benzyl protecting group was removed by dissolving metal reduction,[23] and the resulting neopentyl alcohol **31** was immediately converted to the mesylate **32** in 70–96% chromatographed yield. As anticipated, the mesylate **32** was found to be extremely labile and could only be purified with silica gel deactivated by triethylamine. Selenylation of the TBDMS enol ether **32** with phenylselenyl chloride at low temperatures (slowly warmed up from −35 °C to −15 °C) afforded the α-seleno ketone **33** in 81–88% yield. Extreme caution had to be exercised in handling the α-seleno ketone **33**, since it was prone to cyclize to the undesired cyclopropyl ketone **34**.[24] Upon exposure of the α-seleno ketone **33** to potassium cyanide in the presence of 18-crown-6 ether, the transient cyanohydrin was generated and immediate ring-closure led to 57–73% yield of the pentacyclic nitrile **35**. Under the reaction conditions, the C-12 phenyl selenide was readily epimerized to the more stable equatorial position[9a] which was not detrimental to the synthetic effort. Oxidation of the C-12 seleno function of **35** with hydrogen peroxide effected syn elimination[18] to furnish the C-11,12 olefinic bond in the

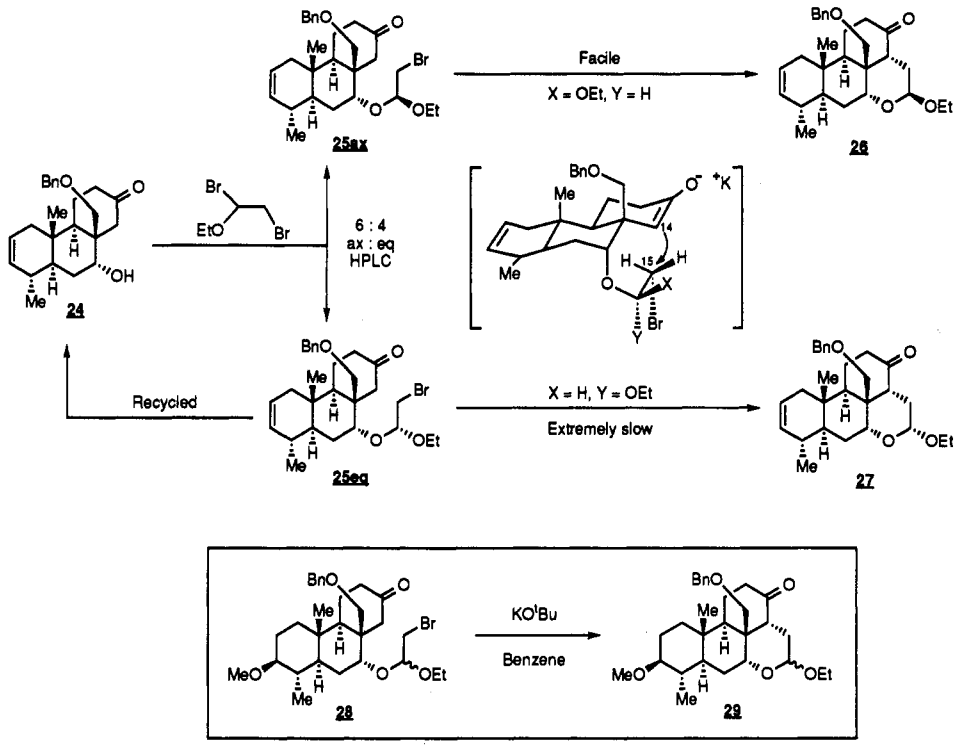
(21) Use of other acids (hydrochloric, sulfuric, *p*-toluenesulfonic, methanesulfonic) had uniformly failed to effect the hydrolysis of the bromoacetal **25eq**.

(22) Rowlands, D. C.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E. *J. Org. Chem.* **1952**, *17*, 807–811.

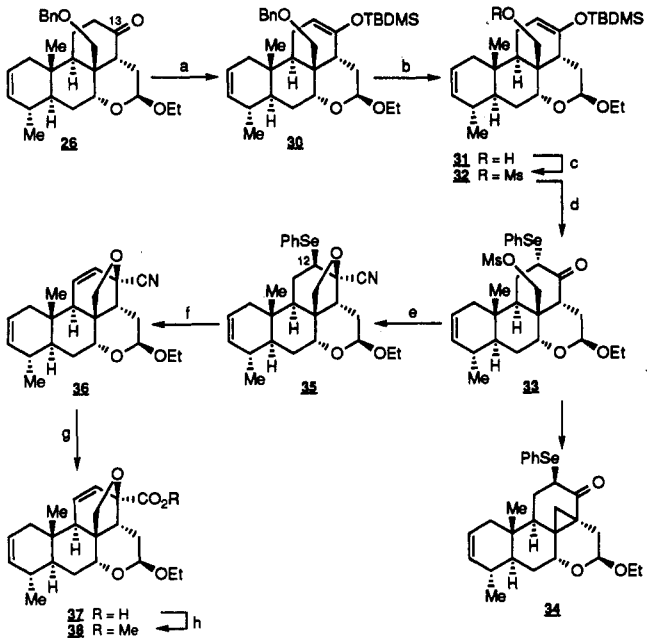
(23) Reist, E. J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 3725–3726.

(24) The assigned structure of the cyclopropyl ketone **34** is consistent with ^{1}H NMR, mass spec. IR (ν 1675 cm^{-1}, indicative of a carbonyl α to a cyclopropane ring). Upon treatment with hydrogen peroxide, syn elimination of the selenide occurs and the carbonyl stretching shifted further to 1660 cm^{-1}.

Scheme 5



Scheme 6



[a] (a) TBDMSOTf/Et_3N/CH_2Cl_2/0 °C, crude quant yield; (b) Li/NH_3/THF/−78 °C, crude quant yield; (c) MsCl/Et_3N/CH_2Cl_2, 85% for three steps a–c; (d) PhSeCl/THF/−35 → −15 °C, crude quant yield; (e) KCN/18-crown-6/CH_3CN, crude quant yield; (f) H_2O_2/$NaHCO_3$/THF, 62% for three steps d–f; (g) (i) KOH/H_2O_2/dioxane, (ii) NaH_2PO_4, crude quant yield; (h) CH_2N_2/ether, 91% for two steps g–h.

diene **36**, thereby setting the stage for the introduction of the requisite vicinal diol. Nitrile **36** was subjected to basic hydrolysis[25] to provide the acid **37** upon acidification, followed by methylation with diazomethane to give the methyl ester **38** in quantitative yield.

At this point the synthetic strategy demanded stepwise functionalization of the two olefinic bonds in the pentacyclic diene **38**, preferably beginning with the C-ring. Osmylation[26] of the diene **38** with 1 equiv of osmium tetraoxide in THF at room temperature provided one major product in 60–70% yield (Scheme 7). Exclusive osmylation of the C-ring olefinic bond had occurred in a stereochemically defined manner, while the relatively more exposed A-ring olefinic bond remained intact. The greater reactivity of the C-ring olefin was presumably a consequence of ring strain imparted by the bridging tetrahydrofuran moiety. This selectivity was much appreciated, since assembly of the most labile A-ring diosphenol function could be postponed until later in the synthetic sequence.

Subjecting the *cis*-diol **39** to nonbasic Swern oxidation conditions, as previously developed in a model system,[9] generated the bis-oxosulfonium salt **40** which was *warmed in the absence of added triethylamine* to afford α-hydroxy ketone **41** in 82–99% yield with complete C-11 selectivity. The mechanism of this intriguing reaction presumably involves intramolecular deprotonation of the C-11 axial methine hydrogen by the proximal lone pair of the bridging tetrahydrofuran oxygen moiety.[9] Sodium triacetoxyborohydride was found to be superior to tetra-*n*-butylammonium borohydride which was previously employed in the model system,[9,27] and effected the reduction of **41** to the *trans*-diol **42** in 88–99% yield. The diol **42** was subsequently derivatized as the bis-dichloroacetate **43** in 83–92% yield. In turn, the A-ring olefinic bond in **43** was subjected to osmylation in a mixture of pyridine–THF[28] at room temperature to afford the β-*cis*-diol **44** in 89% yield together with trace amount of the corresponding α-isomer. Following our previously disclosed protocol,[8] treatment of the A-ring diol **44** with standard Swern oxidation conditions[29] (oxalyl chloride–DMSO–triethyl-

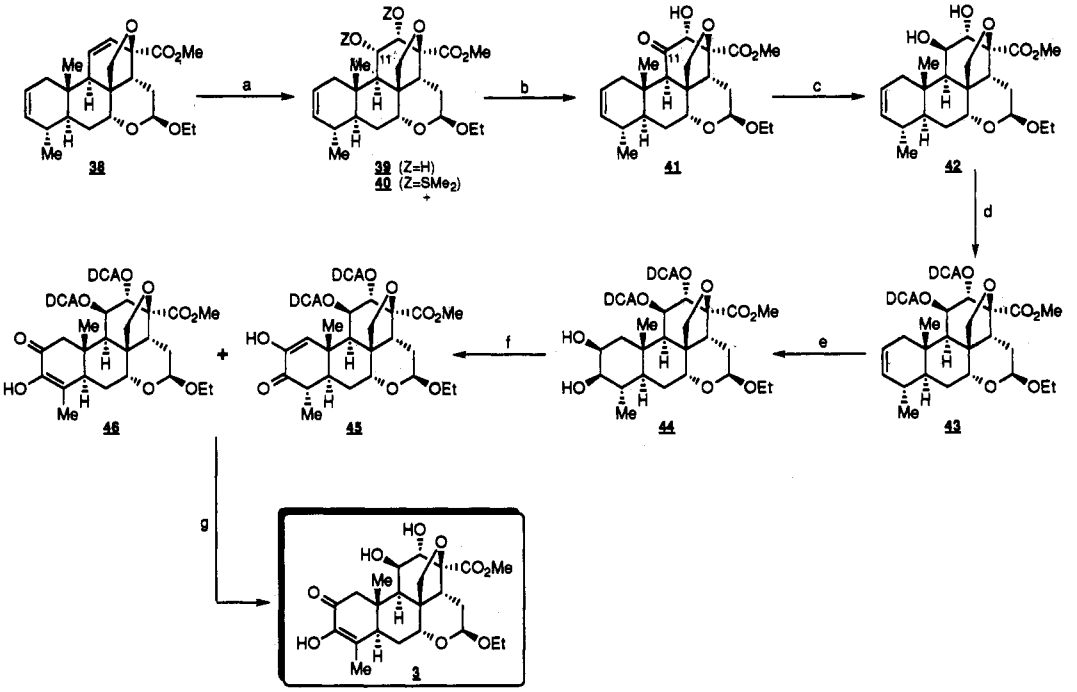
(25) Hartley, D. J. *J. Chem. Soc.* **1962**, 4722–4723.

(26) Criegee, R. *Ann.* **1936**, *522*, 75–96.

(27) With tetra-*n*-butylammonium borohydride, reduction of the C-13 methyl ester was observed, which was totally suppressed when triacetoxyborohydride was employed.

(28) Rate of osmylation was greatly enhanced in the presence of pyridine.

Scheme 7



[a] (a) 1 equiv of OsO_4/THF, 60%; (b) $(CF_3CO)_2O/CH_2Cl_2$/−78 °C, 82%, without Et_3N; (c) $Na(AcO)_3BH$/EtOAc/0 °C, 88%; (d) DCACl/Pyr/CH_2Cl_2, 92%; (e) OsO_4/Pyr/THF, 89%; (f) (i) $(COCl)_2$/DMSO/CH_2Cl_2/−78 °C, (ii) Et_3N, 59%; (g) DBU/CH_2Cl_2, 75%.

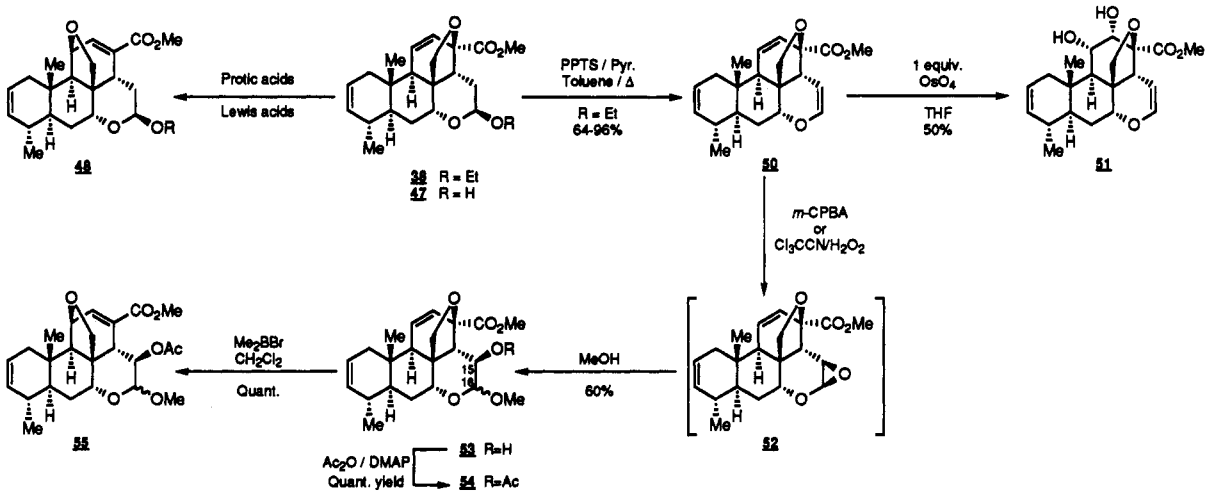
amine) gave an inseparable 2:1 mixture of kinetic and thermodynamic diosphenols (**45** and **46**, respectively) in 59% unoptimized yield. In this series, DBU was a better base than sodium methoxide, which was employed in the earlier model study,[8] to equilibrate the isomeric diosphenols. Hence, exposure of a mixture of the diosphenols **45** and **46** to DBU in methylene chloride resulted in isomerization of the kinetic isomer to the thermodynamically more stable isomer with concomitant removal of the dichloroacetyl protecting groups[30] at C-11 and 12 to furnish in one-pot the diosphenol **3** in 75% yield.

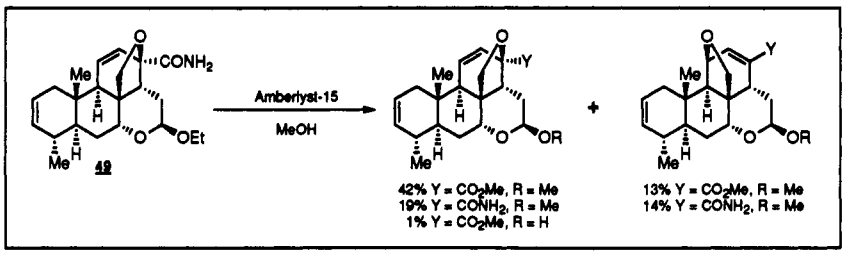
Having demonstrated the feasibility of sequential functionalization of the olefinic bonds in the C and A rings, our attention was directed toward the preparation of the pentacyclic triene **50**. The dehydration of the lactol **47** or elimination of ethanol from the acetal **38** was not as straightforward as might be expected. In particular, under acidic conditions the reaction was hampered by the lability of the bridging allylic ether as demonstrated in the acidic hydrolysis of the amide **49**. The desired transformation was eventually achieved by employing a modification of the conditions used by the Corey group in their synthesis of ginkgolide-B.[31] The acetal **38** was heated with a catalytic amount of pyridinium *p*-toluenesulfonate in toluene at reflux moderated by additional pyridine, to afford the triene **50** in high yield (>90%) (Scheme 8). Treatment of the triene **50** with 1 equiv of osmium tetraoxide once again underwent selective oxidation at the C-ring, yielding the diol **51** as the major product (50%). On the other hand, oxidation of the triene **50** with *m*-CPBA or trichloroacetonitrile/hydrogen peroxide[32] in methanol was sluggish but found to be chemoselective. The presumed epoxide intermediate (not observed) **52** was trapped *in situ* by the nucleophilic solvent employed (methanol) to furnish the hydroxyacetal **53** (60%) as a 4:6 diastereomeric mixture at the C-16 center. As expected, oxidation occurred stereoselectively at C-15 to provide the requisite β-stereochemistry, which was confirmed by examination of the coupling constants ($J_{15,14}$ = 11.7 Hz and $J_{15,16}$ = 7.5 Hz in one diastereomer and 12.4 Hz and 3.6 Hz, respectively, in the other) in the corresponding ^1H NMR spectrum. The stereoselectivity at C-15 was further substantiated in the β-TMS-ethyl acetal series (Scheme 9 *vide infra*). The C-15 hydroxy group was temporarily derivatized as the acetate **54** in order to facilitate the subsequent exploratory chemistry. Attempts to transform the D-ring acetal to the lactol uniformly failed due to the facile E-ring rearrangement to **55** (quantitative yield) under the acidic conditions employed, as previously observed.

It became apparent that a different acetal which would undergo hydrolysis without invoking the E-ring rearrangement was in order. Hence, oxidation of the triene **50** with *m*-CPBA was carried out in dichloromethane in the presence of excess β-TMS-ethanol (30 equiv) (Scheme 9). The stereoselectivity at C-15 was maintained while the addition of the β-TMS-ethanol was also stereochemically controlled to give the hydroxyacetal **56** in 38% yield as a single diastereomer (^1H NMR $J_{15,14}$ = 11.6 Hz, $J_{15,16}$ = 7.4 Hz). The chemoselectivity suffered, however, resulting in epoxidation of the A-ring olefinic bond as well to provide the epoxyacetal **57** (33%) along with a small amount of the hydroxybenzoate **58** (8%). The decrease in reactivity of the C-ring olefin presumably is due to the introduction of the electronegative oxygen function at C-15 in combination with the equatorial C-16 alkoxy group. It should be noted that compound **38** bears a C-16 alkoxy group, but in this instance, it is axially disposed and therefore in a less ideal position to provide inductive deactivation *via* the σ system. This decrease in C-ring reactivity is further seen in the osmylation of the diene **59**

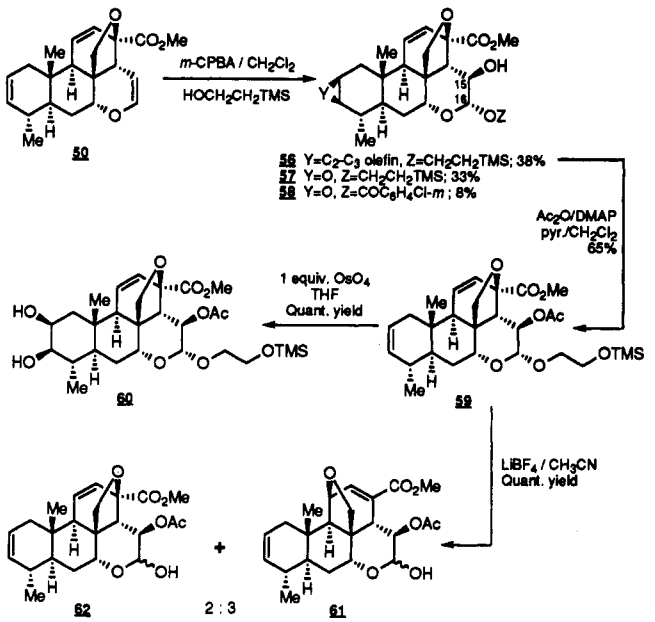
(29) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
(30) It is believed that the presence of adventitous water assisted in the hydrolysis of the dichloroacetoxy moiety *via* the dichloroketene intermediacy.
(31) Corey, E. J.; Kang, M.-c.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649–651.
(32) Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888–890.

Scheme 8

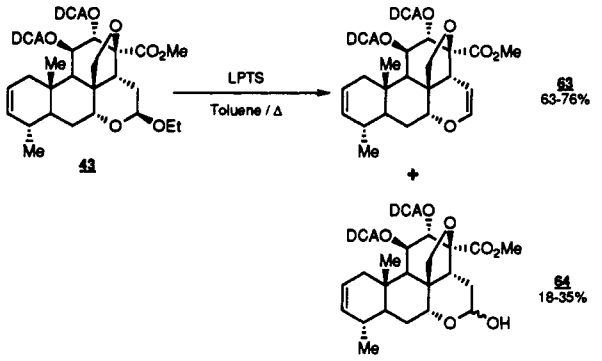




Scheme 9



Scheme 10



which leads to exclusive bis-hydroxylation of the A-ring olefin, and the diol **60** was isolated as the sole product in crude quantitative yield. More disappointingly, attempts to liberate the β-TMS-ethyl acetal under the mild conditions reported by Lipshutz[33] ($LiBF_4$ in acetonitrile at reflux) failed to obviate the E-ring rearrangement and provided quantitatively a 3:2 mixture of the isomeric lactols (**61**:**62**) in favor of the undesired isomer **61**.

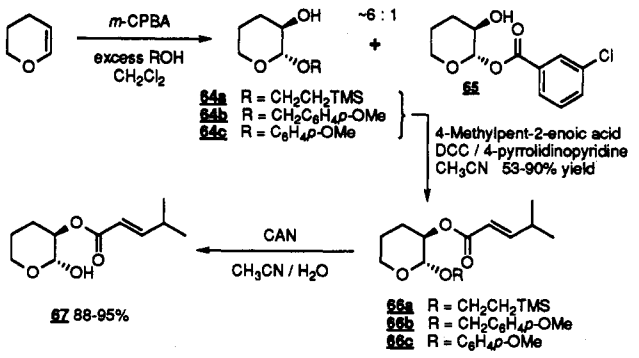
The facile rearrangement of the E-ring coupled with the reversal in the reactivity of the olefinic bonds in A and C rings after the introduction of the C-15 oxygen function demands initial functionalization of the C-ring olefin bond first, followed by sequential oxidation of the D and then A rings, i.e. C-D-A sequence. To this end, the acetal **43** was subjected to the previously described conditions (pyridinium *p*-toluenesulfonate/toluene/Δ) but without pyridine to provide the diene **63** in only moderate yield, presumably due to the instability of the dichloroacetoxy moiety to the reaction conditions. Furthermore, the dihydropyran moiety of **63** was found to be extremely prone to hydration leading to the formation of the lactol **64** in significant quantities during any synthetic operation involving **63**. The switch to 2,6-lutidinium *p*-toluene sulfonate,[34] however, greatly enhanced the rate of reaction and yielded 63–76% of the diene **63** along with 18–35% of the lactol **64** (Scheme 10). Before committing the precious diene **63** to the epoxidation sequence, further studies into the generation of the D-ring pyran epoxide and its ring-opening by an oxygen function, which can be more readily unmasked at a later stage, were warranted.

The problems encountered in the placement of the D-ring lactol led us to reexamine the generation and trapping of the transient D-ring pyran epoxide. Epoxi-

(33) Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* 1981, *22*, 4603–4606.

(34) Nitz, T. J.; Paquette, L. A. *Tetrahedron Lett.* 1984, *25*, 3047–3050.

Scheme 11

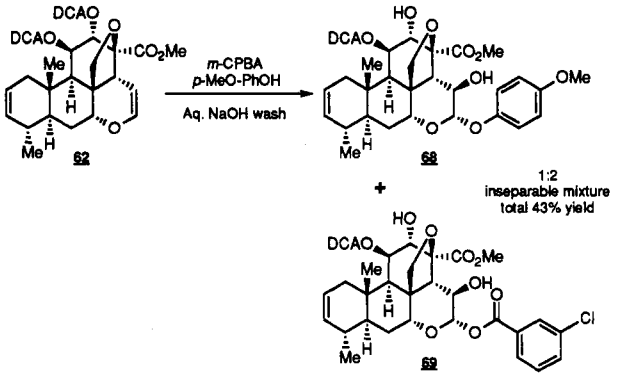


dation of the commercially available 3,4-dihydro-2*H*-pyran as a model substrate (Scheme 11) with *m*-CPBA in the presence of excess (5–6 equiv) β-TMS-ethanol, *p*-methoxybenzyl alcohol, or *p*-methoxyphenol, each afforded approximately a 6:1 mixture of hydroxyacetal **64a–c** and hydroxybenzoate **65** in good yield, with predominantly *trans* stereochemistry. The separation of the excess alcohols from the hydroxyacetals **64a–c** could be achieved by evacuation (β-TMS-ethanol), column chromatography (*p*-methoxybenzyl alcohol), or base wash (*p*-methoxyphenol). The α,β-unsaturated acyl side chain[35] was incorporated under modified Murae's conditions[5e] (4-pyrrolidinopyridine/DCC/acetonitrile) to give the ester **66a–c** in good yield (53–90%). Attempts to cleave the β-TMS acetal **66a** with tetra-*n*-butylammonium fluoride in HMPA[36] only led to hydrolysis of the acyl side chain. Other fluoride sources (LiF, CsF, $LiBF_4$, CeF_3, TiF_4) either resulted in no change or decomposition of the substrate **66a**. On the other hand, ceric ammonium nitrate[37] readily cleaved the *p*-methoxybenzyl (**66b**) and -phenyl (**66c**) acetals to furnish the lactol **67** in high yield (88 and 95%, respectively). The facile oxidative cleavage of these acetals **66b,c** promised a new way of refunctionalization.

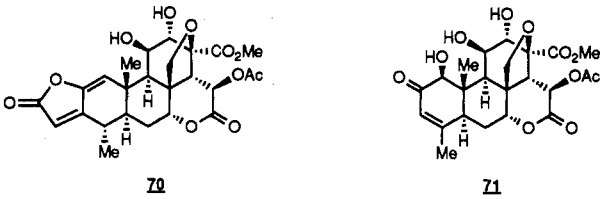
A new practical problem was, however, soon realized. The similar R_f of the product and the excess *p*-methoxybenzyl alcohol prevented easy separation by column chromatography. On the other hand, *p*-methoxyphenol (26 equiv) employed in the epoxidation of the dihydropyran **62** (Scheme 12) was readily removed by means of sodium hydroxide wash, which also hydrolyzed one of the dichloroacetoxy functions, leading to the monodichloroacetate **68**. More disappointingly, the interception of the transient epoxide favored formation of benzoate **69** over acetal **68** in the ratio of 2:1 and they appeared as an inseparable mixture (total 43% yield). The root of the problem arose from the use of *m*-CPBA, leading to competitive interception of the transient epoxide by the resulting *m*-chlorobenzoic acid byproduct. A return to this research arena would appear to profit from generation of the α-alkoxy epoxide intermediate *via* the use of dimethyldioxirane[38] as an oxidant since in this case, the byproduct is the nonnucleophilic acetone.

Compound Testing. Approximately 5 years ago[39] the National Cancer Institute instituted a new *in vitro* human disease antitumor screening program which features the use of a panel of 60 human tumor cell lines which now screen for 9 major cancer types (leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast). In the course of bioassay-guided fractionation, Tischler, Cardellina, Boyd, and Cragg at the National Cancer Institute recently reported that the quassinoids sergiolide **70** and isobrucein B **71** showed activity at concentrations between 10^{-5} to 10^{-8} M (Scheme 13).[40] On the basis of these results, we submitted a selection of pentacyclic intermediates (**36–38, 41–44, 3**) for assay by the Boyd group at the NCI. These each were tested against all 60 cell lines in duplicate at 10^{-5} M and in quadruplicate at both 10^{-7} and 10^{-8} M.[41] Unfortunately, they all appear to be essentially devoid of activity at these concentrations.

Scheme 12



Scheme 13



Experimental Section

All reactions were conducted under nitrogen and stirred magnetically, unless otherwise stated. When anhydrous conditions were required, the glassware was flame-dried under a positive pressure of dry nitrogen, or under high vacuum and then filled with dry nitrogen upon cooling. Reaction temperatures refer to external or bath temperatures, unless indicated otherwise. Temperatures of −78 °C and 0 °C refer to dry ice–acetone and ice–water baths, respectively. Solvents, i.e. hexanes, EtOAc, CH_2Cl_2, and $CHCl_3$, were distilled prior to use. In particular THF and diethyl ether were freshly distilled from the ketyl formed by the reaction of sodium with benzophenone; benzene, toluene, and CH_2Cl_2 were distilled from CaH_2. MeOH, EtOH, DMF, and DMSO were stored over molecular sieves before use. Analytical TLC was performed on precoated (0.25 mm) silica gel 60F-254 plates from EM Reagents and visualized under UV (254 nm) as required. The TLC plates were developed with acidified alcoholic *p*-anisaldehyde solution and heated on a hot plate at approximately 200 °C. Flash column chromatography was carried out using silica gel 60 (60–200 mesh) unless stated otherwise. HPLC was carried out on Waters Prep-500 using prepacked columns. All compounds reported have been analyzed by elemental analysis, exact mass, and/or appear homogeneous by ^1H and ^{13}C NMR (copies of the proton NMR spectra of compounds **3, 4, 7, 8, 10, 12, 13, 15, 17, 18ax, 18eq, 20, 23, 24, 25eq, 25ax, 26, 32, 33, 35–46, 50, 56, 57, 59,** and **63** can be found in the supplementary material. Melting points were determined with a Fisher-Johns

(35) Okano, M.; Lee, K.-H. *J. Org. Chem.* **1981**, *46*, 1138–1141.
(36) Kan, T.; Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417–5418.
(37) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291–6292.
(38) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205–211.
(39) Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abbott, B. J.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 589–601.
(40) Tischler, M.; Cardellina, J. H., II; Boyd, M. R.; Cragg, G. M. *J. Nat. Prod.* **1992**, *55*, 667–671.
(41) Boyd, M. R. Personal communication May 30, 1993.

melting point apparatus. Melting points (mp) and boiling points (bp) in degrees are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 267 grating infrared spectrometer as solutions in $CHCl_3$. NMR spectra were obtained in $CDCl_3$, unless otherwise stated, on a QE-300 spectrometer. Data were reported in ppm downfield from tetramethylsilane (δ 0.00 ppm). Low-resolution electron impact mass spectra were recorded on a Finnigan 4121 GC-mass spectrometer. High-resolution mass spectra (exact mass) were obtained on a CEC-21-110-B mass spectrometer at the Purdue Pharmacy Department. Microanalyses were conducted by Dr. H. D. Lee of the Purdue Microanalytical Laboratory.

(4a*S*)-2,3,4,4a,9,10-hexahydro-7-methoxy-1,4a-dimethylphenanthren-2-one (4). To a flask equipped with magnetic stirrer, Dean–Stark trap, and condenser, were charged the β-tetralone 5 (64 g, 0.34 mol), (*R*)-α-methylbenzylamine (48 mL, 0.37 mol), and anhydrous toluene (300 mL). The resulting golden yellow solution was stirred under N_2 and heated under reflux for 24 h while the water generated was collected in the Dean–Stark trap. Most of the toluene (~250 mL) was distilled off, and the resulting yellow syrup was cooled and diluted with anhydrous THF (250 mL) followed by addition of ethyl vinyl ketone (40 mL, 0.4 mol). The mixture was stirred at rt for 4 days under N_2. The excess ethyl vinyl ketone was removed along with THF (~100 mL) under reduced pressure (rotavap). To the remaining solution was added a mixture of AcOH (25 mL) and water (75 mL) and stirred for 3 h at rt. The organic layer was separated from the aqueous layer which was extracted twice with ether (2 × 100 mL). The extracts and organic layer were combined and washed successively with 10% aqueous NaOH, 5% aqueous HCl, water, and then brine. After drying over Na_2SO_4, solvent was removed under reduced pressure (rotavap) to provide an orange syrup (90 g). The crude syrup was purified by column chromatography to afford the diketone 7 (7.3g, 8%) as a white solid: R_f = 0.39 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.18 (d, 1H, J = 8.7 Hz), 6.82 (dd, 1H, J = 2.5 and 8.7 Hz), 6.71 (d, 1H, J = 2.5 Hz), 3.81 (s, 3H), 3.14–1.96 (m, 10H), 1.40 (s, 3H), 0.96 (t, 3H, J = 7.3 Hz). The ketol 8 (74.3 g, 80%) was isolated as a pale yellow solid: R_f = 0.24 (30% EtOAc/hexanes); mp = 95–97 °C; $[\alpha]^{25}_D$ = +32.63° (c = 6.90, $CHCl_3$); IR (thin film) 3479 (br), 1717 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.14 (d, 1H, J = 8.7 Hz), 6.80 (dd, 1H, J = 2.1 and 8.7 Hz), 6.61 (d, 1H, J = 2.1 Hz), 3.79 (s, 3H), 3.30 (dd, 1H, J_{ABX} = 7.2 and 18 Hz), 3.10 (d, 1H, J_{AB} = 18 Hz), 2.65 (d, 1H, J = 6.4 Hz), 2.14 (dt, 1H, J = 4.2 and 13.0 Hz), 1.84 (br s, 1H), 1.74–1.42 (m, 5H), 1.46 (s, 3H), 0.94 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 158.23, 135.08, 134.63, 126.43, 113.33, 111.83, 80.40, 55.22, 54.62, 48.66, 40.48, 34.33, 32.21, 31.40, 20.01, 6.54; MS (EI) m/z 274 (M^+), 189, 161; MS (CI/NH_3) m/z 292 (M + NH_4), 263, 248; HRMS $C_{17}H_{22}O_3$ calcd 274.1563, found 274.1564.

A solution of the ketol 8 (48 g, 0.17 mol) in MeOH (150 mL) was treated with powdered KOH (5 g) and stirred under N_2 at rt for 2 days. Most of the MeOH was removed under reduced pressure (rotavap) and the brown residue was taken into water and extracted with 30% EtOAc in hexanes. The extract was washed with water and then brine, dried over Na_2SO_4, and concentrated to a yellow syrup which solidified on standing (41.5 g, 93% yield). An analytical sample was prepared by recrystallization from acetone/hexanes to give the enone 4 as a white solid: R_f = 0.42 (30% EtOAc/hexanes); mp = 72–73.5 °C; $[\alpha]^{25}_D$ = +216.84° (c = 3.91, $CHCl_3$); IR (thin film) 1660 (s), 1617 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 1H, J = 8.7 Hz), 6.80 (dd, 1H, J = 2.5 and 8.7 Hz), 6.65 (d, 1H, J = 2.5 Hz), 3.79 (s, 3H), 3.01–2.00 (m, 8H), 1.84 (s, 3H), 1.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.16, 162.28, 157.49, 137.02, 136.87, 128.47, 126.63, 112.85, 96.00, 55.17, 39.17, 36.32, 34.20, 30.16, 27.29, 27.09, 10.84; MS (EI) m/z 256 (M^+), 241, 213; MS (CI) m/z 257 (M + H), 189; HRMS $C_{17}H_{20}O_2$ calcd 256.1458, found 256.1505.

(1*S*,4a*S*)-2,2-(Ethylenedioxy)-1,2,3,4,4a,9,10,10a-octahydro-7-methoxy-1,4a-dimethylphenanthrene (9). To a flask equipped with magnetic stirrer, dry ice condenser, and N_2 inlet was charged liquid NH_3 (20 mL) at –78 °C. Lithium wire (42 mg, 6 mmol) was added and the resulting dark blue solution was stirred for 30 min. The enone 4 (130 mg, 0.5 mmol) in THF (5 mL) was added and the mixture was stirred under reflux (–33 °C) for 2 h. Isoprene (1 mL) was added dropwise to discharge the blue color and the NH_3 was allowed to evaporate at rt under a stream of N_2. The white residue was dissolved in water and extracted with ether. The extract was washed with water and brine and dried over Na_2SO_4. The solvent was removed to afford a syrup which was passed through a plug of silica gel to provide the ketone as a colorless syrup (60 mg, 46%): ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 1H, J = 8.7 Hz), 6.74 (dd, 1H, J = 2.5 and 8.7 Hz), 6.61 (d, 1H, J = 2.5 Hz), 3.78 (s, 3H), 2.96–2.83 (m, 2H), 2.68–2.49 (m, 4H), 1.99–1.59 (m, 4H), 1.35 (s, 3H), 1.12 (d, 3H, J = 6.4 Hz). A solution of the ketone (60 mg, 0.23 mmol) in toluene (3 mL) was treated with (2*R*,3*R*)-2,3-butanediol (0.1 mL, 1.1 mmol), *p*-TsOH, and $MgSO_4$ (0.5 g). The mixture was heated under gentle reflux overnight under N_2. After cooling, the mixture was passed through a plug of cotton wool to remove the $MgSO_4$ and concentrated to an oil. The oil was chromatographed to provide the ketal 9 as a crystalline solid (73 mg, 95%). The crystalline solid was subjected to X-ray analysis. R_f = 0.64 (30% EtOAc/hexanes): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 1H, J = 8.7 Hz), 6.59 (dd, 1H, J = 2.5 and 8.7 Hz), 6.58 (d, 1H, J = 2.5 Hz), 3.82–3.76 (m, 1H), 3.78 (s, 3H), 3.59–3.51 (m, 1H), 2.88–2.85 (m, 2H), 2.20–1.48 (m, 8H), 1.30 (d, 3H, J = 6.3 Hz), 1.19 (d, 3H, J = 6.3 Hz),1.35 (s, 3H), 0.98 (d, 3H, J = 6.4 Hz).

(1*S*,2*S*,4a*S*,10a*S*)-1,2,3,4,4a,5,8,9,10,10a-decahydro-2-hydroxy-7-methoxy-1,4a-dimethylphenanthrene (10). A 5-L three-necked round-bottom flask equipped with a dropping funnel, dry ice condenser, N_2 inlet, and mechanical stirrer was cooled to –78 °C and charged with liquid NH_3 (1 L). Lithium in small pieces (14 g, 2 mol) was added over 15 min, and the resulting deep blue solution was stirred for 30 min. A solution of the enone 4 (50 g, 0.2 mol) in THF (450 mL) was added over 1 h, followed by addition of a solution of *t*-BuOH in THF (80 mL) over 30 min. The cooling bath was removed and the reaction mixture was stirred under reflux (–33 °C) for 2.5 h. EtOH (250 mL) was added slowly (exothermic) over 45 min while the blue color gradually disappeared, and the mixture was stirred for 10 min upon complete addition. Lithium in small pieces (14 g, 2 mol) was added portionwise (exothermic) over 1.25 h to give a deep blue solution again. The reaction mixture was stirred for 1 h as the blue color gradually faded. The condenser was removed and the NH_3 was allowed to evaporate overnight under a stream of N_2 at ambient temperature. The residue was cooled to 0 °C with stirring and water (1 L) was added over 1 h. The THF layer was separated and the aqueous layer was extracted with ether (3 × 400 mL). The ethereal extracts were combined with the THF layer and washed once with water (500 mL) then brine. After drying over Na_2SO_4, the solvent was evaporated to afford an orange oil (76 g) which solidified on standing in freezer. The solid was recrystallized from ether/pentane to give in 3 crops, 15.0, 4.5, and 6.5 g (50.8%) of the alcohol 10 as a colorless solid. The mother liquor was subjected to HPLC to provide an additional 7.5 g (14.7%) of the alcohol 10: R_f = 0.31 (30% EtOAc/hexanes); mp = 97–99 °C; $[\alpha]^{25}_D$ = +77.76° (c = 7.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.64 (t, 1H, J = 3.0 Hz), 3.55 (s, 3H), 3.13 (dt, 1H, J = 5.0 and 10.1 Hz), 2.26–0.91 (m, 15H), 1.01 (d, 3H, J = 6.4 Hz), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.08 (s), 133.84 (s), 123.28 (s), 90.27 (d), 75.85 (d), 53.28 (q), 47.05 (d), 38.58 (d), 35.95 (s), 34.06 (t), 33.70 (t), 30.68 (t), 30.39 (t), 25.19 (t), 20.38 (t), 18.22(q), 14.71 (q); MS (EI) m/z 262 (M^+), 247, 229, 134, 122; MS (CI/NH_3) m/z 263 (M + H), 250, 223, 186, 169; HRMS $C_{17}H_{26}O_2$ calcd 262.1926, found 262.1930.

(1*S*,2*S*,4a*S*,10a*S*)-1,2,3,4,4a,5,8,9,10,10a-decahydro-2-(methanesulfonyl)-7-methoxy-1,4a-dimethylphenanthrene (11). A solution of the alcohol 10 (29.5 g, 112 mmol) and Et_3N (30 mL, 215 mmol) in CH_2Cl_2 (250 mL) was cooled to –35 °C (dry ice/acetone bath) and methanesulfonyl chloride (12 mL, 155 mmol) was added (exothermic) as the temperature rose up to –20 °C and precipitation of white solids was observed. The resulting suspension was stirred for 50 min while the reaction temperature gradually rose up to –5 °C. The reaction mixture was poured into ice-cooled 10% aqueous $NaHCO_3$ solution and extracted with ether. The extract was washed with water and then brine and dried over Na_2SO_4. Upon evaporation of solvent, the mesylate 11 was obtained as a yellow syrup which was azeotroped with benzene (2 × 100 mL) and used directly for the next reaction without further purification: R_f = 0.39 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 4.63 (t, 1H, J = 2.8 Hz), 4.23 (dt, 1H, J = 5.6 and 11.3 Hz), 3.55 (s, 3H), 3.03 (s, 3H), 2.80–1.13 (m, 14H), 1.03 (d, 3H, J = 6.6 Hz), 1.01 (s, 3H); MS (EI) m/z 340 (M^+), 124, 79; HRMS $C_{18}H_{28}O_4S$ calcd 340.1708, found 340.1704.

(1*S*,2*S*,4a*S*,4b*R*,10a*S*)-1,2,3,4,4a,4b,5,6,10,10a-decahydro-2-(methanesulfonyl)-7-methoxy-1,4a-dimethylphenanthrene (12). A solution of the crude dienol ether **11** (112 mmol) in CH_2Cl_2 (100 mL) was treated with PPTS (0.85 g, 3.1 mmol) and stirred at rt for 3.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ether. The extract was washed sequentially with water and then brine and dried over Na_2SO_4. The conjugate dienol ether **12** was obtained as an orange viscous oil (38.5 g) on removal of solvent and was used directly for the next reaction: R_f = 0.39 (30% EtOAc/hexanes): ^1H NMR ($CDCl_3$) δ 5.28 (m, 1H), 5.21 (s, 1H), 4.26 (dt, 1H, J = 4.8 and 10.8 Hz), 3.56 (s, 3H), 3.01 (s, 3H), 2.31–1.03 (m, 13H), 0.99 (d, 3H, J = 6.4 Hz), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.6 (s), 134.1 (s), 116.9 (d), 99.3 (d), 87.5 (d), 54.3 (q), 47.5 (q), 46.7 (d), 38.8 (d), 37.6 (d), 36.1 (t), 34.1 (s), 28.7 (t, 2×), 27.6 (t), 22.3 (t), 15.2 (q), 12.6 (q); MS (EI) m/z 340 (M^+), 201, 137, 124; HRMS $C_{18}H_{28}O_4S$ calcd 340.1708, found 340.1705.

(1*S*,2*S*,4a*S*,4b*R*,9*R*,10a*S*)-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydro-9-hydroxy-2-(methanesulfonyl)-1,4a-dimethylphenanthren-7-one (13). The crude dienol ether **12** (112 mmol) in a mixture of dioxane (200 mL) and THF (300 mL) in a three-necked round-bottom flask, equipped with dropping funnel and mechanical stirrer, was cooled to 0 °C and a solution of $NaHCO_3$ (17g, 0.2 mol) in water (100 mL) was added. A solution of oxone (83 g, 135 mmol) in water (230 mL) was added dropwise over 1 h and the resulting suspension was vigorously stirred at 0 °C for 2.5 h. The reaction mixture was poured into 20% aqueous $NaHCO_3$ solution and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and concentrated to an orange syrup (39 g). Flash chromatography (ether and then 5% MeOH/ether) of the crude syrup furnished the hydroxy enone **13** (30 g, 78.2%) as a syrup: R_f = 0.32 (3% MeOH/ether); IR ($CHCl_3$) 3590 (s), 3420 (b), 1670 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.99 (d, 1H, J = 1.4 Hz), 4.34 (br s, 1H), 4.29 (dt, 1H, J = 3.8 and 12.6 Hz), 3.02 (s, 3H), 2.54 (m, 1H), 2.43 (dt, 1H, J = 4.2 and 16.0 Hz), 2.32–1.62 (m, 10H), 1.50 (dt, 1H, J = 3.3 and 14.6 Hz), 1.34 (dt, 1H, J = 3.3 and 14.6 Hz),1.04 (d, 3H, J = 5.6 Hz), 0.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 200.7 (s), 163.4 (s), 127.5 (d), 87.0 (d), 70.6 (d), 44.4 (q), 43.2 (d), 38.8 (d), 38.4 (t), 36.4 (d), 36.4 (s), 35.7 (t), 31.8 (t), 28.4 (t), 20.7 (t), 15.3 (q), 14.0 (q); MS (EI) m/z 342 (M^+), 246, 213, 150, 121, 107, 93, 79, 67, 55, 41; HRMS $C_{17}H_{26}O_5S$ calcd 342.1501, found 342.1493.

(1*S*,2*S*,4a*S*,4b*R*,9*R*,10a*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydro-2-(methanesulfonyl)-1,4a-dimethylphenanthren-7-one (15). A solution of the alcohol **13** (11 g, 3.2 mmol) in DMF (50 mL) was treated sequentially with imidazole (4.5 g, 66 mmol) and TBDMS chloride (7.3 g, 48 mmol) and the mixture was stirred at rt for 3 days. The resulting orange reaction mixture was poured into 10% aqueous $NaHCO_3$ solution and extracted with ether. The ethereal extract was washed with water and then brine and dried over Na_2SO_4. Removal of solvent afforded a red oil which was filtered through a plug of silica gel with ether and then concentrated to an orange oil. HPLC (25% EtOAc/hexanes) of the crude oil provided the silyloxy enone **15** (10.8 g, 73.6%) as a white solid: R_f = 0.49 (50% EtOAc/hexanes); mp =111–113 °C; $[\alpha]^{25}_D$ = −38.16° (c = 3.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.91 (d, 1H, J = 1.9 Hz), 4.30 (dt, 1H, J = 4.7 and 10.8 Hz), 4.26 (t, 1H, J = 2.4 Hz), 3.03 (s, 3H), 2.48 (m, 1H), 2.40 (dt, 1H), 2.30–1.60 (m, 9H), 1.42 (m, 1H), 1.33 (dt, 1H), 1.00 (d, 3H, J = 6.1 Hz), 0.85 (s, 9H), 0.78 (s, 3H), 0.05 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 200.2 (s), 162.8 (s), 126.5 (d), 87.0 (d), 71.7 (d), 44.1 (q), 43.6 (d), 38.9 (d), 38.9 (t), 36.4 (s), 36.2 (d), 36.0 (t), 33.6 (t), 28.5 (t), 25.7 (q, 3 × CH_3), 20.6 (t), 18.0 (s), 15.5 (q), 14.1 (q), −4.6 (q), −5.0 (q); MS (CI) m/z; 457 (M + H), 399, 361, 343, 229; HRMS (CI) $C_{23}H_{41}O_5SSi$ (M + H) calcd 457.2444, found 457.2426. Anal. ($C_{23}H_{40}O_5SSi$) Calcd. C, 60.48; H, 8.82; S, 7.02. Found: C, 60.61; H, 9.23; S, 7.00.

(1*R*,4a*S*,4b*R*,9*R*,10a*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-1,4,4a,4b,5,6,7,9,10,10a-decahydro-1,4a-dimethylphenanthren-7-one (17). A suspension of diphenyl diselenide in EtOH (80 mL) was cooled to 0 °C and treated with portionwise addition of $NaBH_4$ (2.5 g, 65 mmol) over 1 h. The resulting clear, pale yellow solution was stirred at rt for 1.75 h and then a solution of the mesylate **15** (19.5g, 42.7 mmol) in EtOH (70 mL) was added. The mixture was heated under gentle reflux for 5.5 h as white solid was observed to precipitate out. After cooling to 0 °C, THF (50 mL), solid $NaHCO_3$ (8.3 g, 99 mmol), and 30% H_2O_2 (60 mL) were added sequentially. The mixture was allowed to warm up to rt gradually and stirred for 1.5 days. After removal of most of the EtOH by rotavap, the residue was diluted with ether, washed with water and then brine, and dried over Na_2SO_4. The solvent was evaporated to provide a pale yellow syrup (16.21 g) which was subjected to flash chromatography eluted with 10% EtOAc/hexanes to furnish the dienone **17** as a white crystalline solid (12.6 g, 81.6%): R_f = 0.53 (50% ether/hexanes): mp = 53–54 °C (racemate mp = 72.5–73.5 °C); $[\alpha]^{25}_D$ = −148.29° (c = 3.08 $CHCl_3$); IR (thin film) 1678 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.91 (d, 1H, J = 1.7 Hz), 5.61–5.46 (m, 2H), 4.27 (t, 1H, J = 2.4 Hz), 2.59 (dt, 1H, J = 1.7 and 6.9 Hz), 2.50–2.40 (m, 1H), 2.33–2.22 (m, 1H), 2.10–1.68 (m, 7H), 1.40 (tm, 1H), 1.00 (d, 3H, J = 6.5 Hz), 0.86 (s, 9H), 0.76 (s, 3H), 0.06 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.5 (s), 164.1 (s), 132.4 (d), 125.1 (d), 123.4 (d), 72.0 (d), 43.2 (d), 41.6 (d), 39.1 (t), 36.1 (t), 34.9 (t), 32.8 (d), 25.5 (q, 3 × CH_3), 20.2 (t), 19.2 (q), 17.8 (s), 13.5 (q), −4.8 (q), −5.2 (q); MS (EI) m/z 360 (M^+), 345, 303, 75; HRMS $C_{22}H_{36}O_2Si$ calcd 360.2485, found 360.2478. Anal. ($C_{22}H_{36}O_2Si$) Calcd: C, 73.28; H, 10.07. Found: C, 73.22; H, 10.38.

(1*R*,4a*S*,4b*R*,8a*S*,9*R*,10a*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-8a-cyano-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-1,4a-dimethylphenanthren-7-one (18ax) and (1*R*,4a*S*,4b*R*,8a*R*,9*R*,10a*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-8a-cyano-1,4,4a,-4b,5,6,7,8,8a,9,10,10a-dodecahydro-1,4a-dimethylphenanthren-7-one (18eq). To the dienone (14.2 g, 39 mmol) **17** in a mixture of benzene and toluene (20 mL) was added 18-crown-6 ether (155 mg) followed by KCN (58 mg). The mixture was cooled to 0 °C and a 1.4 M solution of Et_2AlCN in toluene (150 mL, 210 mmol) was added. The resulting yellow solution was allowed to warm up to rt and stirred for 24 h. The reaction mixture was slowly poured into an iced 5% aqueous NaOH solution (800 mL) with vigorous stirring inside an efficiently ventilated hood. After the evolution of gas subsided, the mixture was extracted with ether. The extract was washed with water and then brine and dried over Na_2SO_4. Upon evaporation of solvent, a yellow solid (19.3 g) was obtained. The crude solid was purified by HPLC, eluted with 10% EtOAc in hexanes to give in order of elution, the β-nitrile **18ax** (11.7 g) contaminated with a small amount of unchanged starting material dienone **17** (3.3%) as a white solid, and a fraction of the pure β-nitrile **18ax** (2.05 g) which was collected as a white solid (total yield 87%). An analytical sample of the β-nitrile **18ax** was prepared by recrystallization from hexanes: mp = 124–125 °C (racemate mp = 142–143 °C); $[\alpha]^{25}_D$ = −33.54° (c = 3.32, $CHCl_3$); IR ($CHCl_3$) 2240 (w), 1720 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.57–5.47 (m, 2H), 3.90 (br s, 1H), 2.82 (d of AB_q, 1H, J_{AB} = 14.3 Hz), 2.58–2.50 (dm, 1H), 2.33–1.54 (m, 11H), 1.03 (s, 3H,), 0.98 (d, 3H, J = 6.8 Hz), 0.90 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.8 (s), 132.7 (d), 123.2 (d), 121.1 (s), 70.7 (d), 49.1 (t), 45.9 (d), 45.4 (s), 40.7 (t), 40.7 (d), 40.0 (t), 35.7 (s), 31.8 (d), 30.1 (t), 25.7 (q, 3 × CH_3), 23.1 (t), 19.2 (q), 17.9 (s), 11.9 (q), −4.5 (q), −5.1 (q); HRMS (CI) $C_{23}H_{38}NO_2Si$ (M + H) calcd 388.2672, found 388.2662. Anal. ($C_{23}H_{37}NO_2Si$) Calcd: C, 71.27; H, 9.63; N, 3.62. Found: C, 70.76; H, 9.97; N, 3.26. The α-nitrile **18eq** (0.39 g, 2.5%) was isolated as a white solid: R_f = 0.29 (20% EtOAc/hexanes); mp = 128–130 °C; $[\alpha]^{25}_D$ = −47.04° (c = 2.41 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.57–5.47 (m, 2H), 3.85 (br s, 1H), 2.67 (d of AB_q, 1H, J_{AB} = 16.5 Hz), 2.61–1.39 (m, 12H), 0.99 (d, 3H, J = 6.6 Hz), 0.97 (s, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 200.0 (s), 132.6 (d), 123.3 (d), 122.5 (s), 70.7 (d), 47.7 (s), 45.1 (t), 42.1 (d), 41.0 (t), 40.3 (d), 38.0 (t), 36.4 (s), 32.1 (d), 28.2 (t), 25.8 (q, 3 × CH_3), 21.2 (t), 19.2 (q), 18.0 (s), 15.8 (q), −4.4 (q), −4.9 (q); HRMS $C_{23}H_{37}NO_2Si$ calcd 387.2594, found 387.2579.

(1*R*,4a*S*,4b*R*,8a*S*,9*R*,10a*S*)-8a-[(Benzyloxy)methyl]-9-[(*tert*-butyldimethylsilyl)oxy]-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-1,4a-dimethylphenanthren-7-one (23). A mixture of the ketone **18ax** in CH_2Cl_2 (50 mL) and Et_3N (3.6 mL, 25.7 mmol) was cooled to 0 °C under N_2. TBDMS triflate (2.5 mL, 10.9 mmol) was added and the reaction mixture was stirred for 1.5 h at 0 °C. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ether. The extract was washed with water and then brine and dried over Na_2SO_4. Upon evaporation of solvent, the TBDMS enol ether **19** was obtained as a pale yellow amorphorous solid (4.7 g) which was used directly in the next reaction. R_f = 0.67 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 5.52–5.46 (m, 2H), 4.89 (m, 1H), 3.98 (m, 1H), 2.75–

1.50 (m, 11H), 1.04 (s, 3H), 0.97 (d, 3H, J = 6.6 Hz), 0.91 (s, 9H); 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H); MS (EI) m/z 501 (M^+), 475, 444, 417, 303, 285, 73, 57; HRMS $C_{29}H_{51}NO_2Si_2$ calcd 501.3458, found 501.3453.

A solution of the crude nitrile **19** (4.7 g) in ether (80 mL) was cooled to 0 °C under N_2 and treated with a 1 M solution of DIBAL-H in hexanes (13 mL, 13 mmol). The mixture was stirred at 0 °C for 1 h and quenched by addition of a solution of 6% AcOH in water (50 mL) saturated with NaOAc. The mixture was diluted with THF (50 mL) and stirred for 3 min and then extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ solution and brine and dried over Na_2SO_4. Removal of the solvent afforded the aldehyde **20** as a pale yellow, amorphous solid (4.34 g) which was used for the following reaction without further purification: R_f = 0.71 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 9.95 (s, 1H), 5.52–5.45 (m, 2H), 4.92 (dt, 1H, J = 2.4 and 5.2 Hz), 4.11 (m, 1H), 2.80 (m, 1H), 2.40–1.20 (m, 10H), 0.94 (d, 3H, J = 6.6 Hz), 0.90 (s, 9H), 0.89 (s, 9H), 0.70 (s, 3H), 0.10 (s, 6H), 0.09 (s, 3H), 0.04 (s, 3H); MS (CI) m/z 505 (M + H), 133; HRMS $C_{29}H_{52}O_3Si_2$ calcd 504.3455, found 504.3471.

The crude aldehyde **20** in ether (60 mL) was cooled to −78 °C under N_2 and stirred with a 1 M solution of DIBAL-H in hexanes (13.5 mL, 13.5 mmol) for 1 h. After removal of cooling bath, the reaction mixture was diluted with THF (30 mL) and stirred for 10 min with a solution of 6% AcOH in water (50 mL) saturated with NaOAc. The mixture was extracted with EtOAc, and the extract was washed with saturated aqueous $NaHCO_3$ and then brine. After drying over Na_2SO_4, the solvent was evaporated to provide the alcohol **21** as a white foam (4.4 g) which was used directly in the subsequent reaction: R_f = 0.52 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 5.51–5.45 (m, 2H), 4.83 (dt, 1H, J = 2.4 and 4.7 Hz), 3.96 (m, 1H), 3.71 (s, 2H), 2.43 (br d, 1H, J = 16.0 Hz), 2.20–1.50 (m, 11H), 0.96 (d, 3H, J = 6.6 Hz), 0.91 (s, 9H), 0.90 (s, 9H), 0.78 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H); MS (EI) m/z 506 (M^+), 449, 185, 73, 57; HRMS $C_{29}H_{54}O_3Si_2$ calcd 506.3611, found 506.3607. A mixture of the crude alcohol **21**, benzyl bromide (4 mL, 33.6 mmol), and ^{n}Bu$_4$NI (3.1g, 8.5 mmol) in THF (80 mL) was stirred with NaH (0.8 g, 33.3 mmol) for 45 h. The reaction was cautiously quenched by addition of 10% aqueous HCl (80 mL), and the mixture was stirred for 20 h at rt. The organic layer was separated, and the aqueous layer was extracted with ether. The extract was combined with the organic layer and washed sequentially with 20% aqueous $NaHSO_3$ solution, saturated aqueous $NaHCO_3$ solution, and brine. After drying over Na_2SO_4, the solvent was removed to furnish a yellow oil which was subjected to flash chromatography. The benzyl ether **23** was obtained as a syrup (2.8 g) in 68.1% overall yield from the nitrile **18ax**: R_f = 0.37 (20% EtOAc/hexanes); $[\alpha]^{25}_D$ = −24.50° (c = 3.47 $CHCl_3$); IR (thin film) 1720 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37–7.24 (m, 5H), 5.54–5.45 (m, 2H), 4.46 (d of AB_q, 1H, J_{AB} = 12.3 Hz), 4.39 (d of AB_q, 1H, J_{AB} = 12.3 Hz), 3.69 (br s, 1H), 3.54 (d of AB_q, J_{AB} = 9.7 Hz), 3.40 (d of AB_q, J_{AB} = 9.7 Hz), 2.58 (d of AB_q, 1H, J_{AB} = 14 Hz), 2.44–1.56 (m, 11H), 1.26 (tm, 1H), 0.95 (d, 3H, J = 6.7 Hz), 0.90 (s, 9H), 0.75 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 212.6 (s), 138.1 (s), 133.3 (d), 128.2 (d, 2×), 127.3 (d, 3×), 123.9 (d), 73.5 (t), 72.3 (t), 70.1 (d), 48.9 (t), 47.8 (s), 46.6 (d), 41.6 (d), 41.2 (t), 40.9 (t), 35.5 (s), 32.0 (d), 29.1 (t), 25.9 (q, 3 × CH_3), 21.6 (t), 19.2 (q), 18.0 (s), 13.7 (q), −4.4 (q), −4.9 (q); MS (CI) m/z 483 (M + H), 425, 375, 351, 243; HRMS $C_{30}H_{46}O_3Si$ calcd 482.3216, found 482.3230.

(1*R*,4a*S*,4b*R*,8a*S*,9*R*,10a*S*)-8aβ-[(Benzyloxy)methyl]-1,4,-4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-9α-hydroxy-1α,4aβ-dimethylphenanthren-7-one (24). A solution of the TBDMS ether **23** (4.5 g, 9.3 mmol) in THF (60 mL) was treated with a 1 M solution of ^{n}Bu$_4$NF in THF (30 mL, 30 mmol). The mixture was stirred at rt overnight then poured into water and extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Removal of solvent gave an orange-red syrup which was subjected to flash chromatography eluted with 20% and then 50% EtOAc/hexanes to give the alcohol **24** (3.28 g, 95.5%) as a white solid. An analytical sample was prepared by recrystallization from CH_2Cl_2/hexanes as needle-shaped crystals: R_f = 0.19 (30% EtOAc/hexanes); mp = 149–150 °C (racemate mp = 151–152 °C; $[\alpha]^{25}_D$ = −0.82° (c = 3.17 $CHCl_3$); IR (thin film) 3499 (br), 1697 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.23 (m, 5H), 5.54–5.46 (m, 2H), 4.44 (d of AB_q, 1H, J_{AB} = 12.0 Hz), 4.38 (d of AB_q, 1H, J_{AB} = 12.0 Hz), 3.77 (br s, 1H), 3.53 (d of AB_q, 1H, J_{AB} = 9.7 Hz), 3.43 (d of AB_q, 1H, J_{AB} = 9.7 Hz), 2.66 (d of AB_q, 1H, J_{AB} = 14.0 Hz), 2.46–1.30 (m, 13H,), 0.97 (d, 3H, J = 6.7 Hz), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 213.0 (s), 138.0 (s), 133.2 (d), 128.1 (d, 2×), 127.3 (d, 3×), 123.8 (d), 73.4 (t), 72.4 (t), 68.9 (d), 48.2 (t), 47.1 (s), 46.2 (d), 41.6 (d), 40.9 (t, 2×), 35.4 (s), 31.8 (d), 29.1 (t), 21.5 (t), 19.1 (q), 13.6 (q); MS (CI) m/z 369 (M + H), 261; HRMS (CI) $C_{24}H_{33}O_3$ (M + H) calcd 369.2430, found 369.2381. Anal. ($C_{24}H_{32}O_3$) Calcd: C, 78.21; H, 8.76. Found: C, 78.31; H, 8.89.

(1*R*,4a*S*,4b*R*,8a*S*,9*R*,10a*S*)-8a-[(Benzyloxy)methyl]-9-(2-bromo-1(*R*)-ethoxyethoxy)-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-1,4a-dimethylphenanthren-7-one (25eq) and (1*R*,-4a*S*,4b*R*,8a*S*,9*R*,10a*S*)-8a-[(benzyloxy)methyl]-9-(2-bromo-1(*S*)-ethoxyethoxy)-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-1,4a-dimethylphenanthren-7-one (25ax). To bromine (1.5 mL, 29.1 mmol) at −25 °C (dry ice/acetone bath) was added dropwise ethyl vinyl ether (3 mL, 31.3 mmol) over 30 min. The resulting pale yellow solution was stirred at −25 °C for 30 min and then cooled to −60 °C, which solidified and was evacuated under high vacuum for 45 min. The cooling bath was replaced by an ice–water bath. The solid thawed into a pale yellow liquid which was transferred *via* cannula to a solution of the alcohol **24** (2.1 g, 5.7 mmol) in a mixture of dimethylaniline (4.0 mL, 31.5 mmol) and CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was allowed to gradually warm to rt and was stirred for 2.5 h. The resulting clear, orange solution was poured into a 20% aqueous $NaHCO_3$ solution and extracted with ether. The extract was washed with cold 10% aqueous HCl, saturated aqueous $NaHCO_3$, and then brine and dried over Na_2SO_4. Evaporation of solvent afforded an orange oil which was filtered through a short column of silica gel to remove residual dimethylaniline. A ~3:2 mixture of the diastereomeric acetal was obtained as a yellow oil (2.9 g) upon concentration. Purification by HPLC (15% EtOAc/hexanes) initially provided the equatorial acetal **25eq** (1.12 g, 38%). An analytical sample was prepared by recrystallization from hexanes/CH_2Cl_2: R_f = 0.50 (30% EtOAc/hexanes); mp = 124–125 °C (racemate mp = 125–126 °C; $[\alpha]^{25}_D$ = +0.48° (c = 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36–7.26 (m, 5H), 5.50–5.46 (m, 2H), 4.60 (t, 1H, J = 5.2 Hz), 4.48 (d of AB_q, 1H, J_{AB} = 12.0 Hz), 4.38 (d of AB_q, 1H, J_{AB} = 12.0 Hz), 3.69 (m, 1H), 3.56 (m, 2H), 3.48 (d of AB_q, 1H, J_{AB} = 9.9 Hz), 3.43 (d of AB_q, 1H, J_{AB} = 9.9 Hz), 3.34 (m, 2H), 2.77 (d of AB_q, 1H, J_{AB} = 13.6 Hz), 2.45 (br d of AB_q, 1H, J_{AB} = 13.6 Hz), 2.40 (m, 1H), 2.27 (m, 1H), 2.00–1.70 (m, 8H), 1.58 (m, 1H), 1.23 (t, 3H, J = 7.1 Hz), 0.96 (d, 3H, J = 6.6 Hz), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 211.9 (s), 138.1 (s), 133.3 (d), 128.3 (d, 2×), 127.5 (d, 3×), 123.9 (d), 102.7 (d), 76.5 (d), 73.6 (t), 71.2 (t), 62.0 (t), 48.1 (t), 47.5 (s), 47.1 (d), 42.1 (d), 41.0 (d, 2×), 35.4 (s), 32.0 (d), 31.8 (t), 26.6 (t), 21.6 (t), 19.1 (q), 15.1 (q), 14.0 (q); HRMS $C_{28}H_{39}BrO_4$ calcd 519.2110, found 519.2076. Anal. ($C_{28}H_{39}BrO_4$) Calcd: C, 64.84; H, 7.58; Br, 15.23. Found: C, 64.56; H, 7.79; Br, 15.11.

The slower-eluted axial acetal **25ax** (1.63 g, 55%) was isolated as a white solid: R_f = 0.47 (30% EtOAc/hexanes); mp = 75–77 °C; $[\alpha]^{25}_D$ = −31.45° (c = 3.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35–7.25 (m, 5H), 5.52–5.46 (m, 2H), 4.69 (dd, 1H, J = 5.2 and 6.1 Hz), 4.48 (d of AB_q, 1H, J_{AB} = 12.2 Hz), 4.39 (d of AB_q, 1H, J_{AB} = 12.2 Hz), 3.72 (m, 1H), 3.62–3.54 (m, 2H), 3.49 (m, 2H), 3.39–3.31 (m, 2H), 2.78 (d of AB_q, 1H, J_{AB} = 14.6 Hz), 2.47 (dd of ABX, 1H, J_{AX} = 2.4 Hz, J_{AB} = 14.6 Hz), 2.43 (m, 1H), 2.30 (m, 1H), 2.00–1.60 (m, 9H), 1.18 (t, 3H, J = 7.1 Hz), 0.99 (d, 3H, J = 6.6 Hz), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 212.5 (s), 138.2 (s), 133.3 (d), 128.2 (d, 2×), 127.4 (d, 3×), 123.9 (d), 100.1 (d), 74.2 (d), 73.5 (t), 71.5 (t), 62.6 (t), 48.1 (s), 47.0 (d), 41.5 (d), 41.0 (t, 2×), 35.5 (s), 32.3 (t), 32.0 (d), 24.7 (t), 21.6 (t), 19.2 (q), 15.3 (q), 14.0 (q).

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,14*R*,16*S*)-20-[(Benzyloxy)methyl]-16-ethoxy-13-oxo-21-norpicras-2-ene (26). The axial acetal **25ax** (2.26 g) in benzene (50 mL) was stirred with potassium t-BuOK under N_2 at rt for 1.5 h. The reaction was quenched by addition of water and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and then concentrated to an orange syrup. Purification by flash chromatography (20% EtOAc/hexanes) led to the isolation of the tetracyclic ketone **26** as a colorless syrup (1.71 g, 89.6%): R_f = 0.45 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = −0.63° (c = 4.22 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34–7.24 (m, 5H), 5.51–5.45 (m, 2H), 4.86 (br d, 1H, J = 3.8 Hz), 4.45 (d of AB_q, 1H, J_{AB} = 12.2 Hz), 4.38 (d of AB_q, 1H, J_{AB} = 12.2

Hz), 3.77 (d of AB_q, 1H, J_{AB} = 9.4 Hz) 3.73 (m, 1H) 3.63 (m, 1H), 3.41 (m, 1H), 3.25 (d of AB_q, 1H, J_{AB} = 9.4 Hz), 2.94 (dd, 1H, J = 5.2 and 13.6 Hz), 2.45–2.30 (m, 2H), 2.15 (m, 1H), 2.05 (m, 1H), 1.99 (dt, 1H, J = 3.8 and 13.6 Hz), 1.80 (m, 1H), 1.64 (br dd, 1H, J = 5.2 and 13.6 Hz), 1.49 (dt, 1H, J = 3.3 and 11.8 Hz), 1.26 (m, 1H), 1.18 (t, 3H, J = 7.1 Hz), 0.97 (d, 3H, J = 7.1 Hz), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 213.1 (s), 138.1 (s), 133.5 (d), 128.3 (d, 2×), 127.4 (d, 3×), 123.8 (d), 95.5 (d), 74.8 (t), 73.7 (t), 66.1 (d), 62.3 (t), 48.7 (d), 42.4 (d), 41.7 (s), 41.4 (t), 40.8 (d), 37.4 (t), 35.4 (s), 32.1 (d), 30.0 (t), 27.5 (t), 21.2 (t), 19.2 (q), 15.1 (q), 13.8 (q).

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,14*R*,16*S*)-20-[(Benzyloxy)methyl]-13-[(*tert*-butyldimethylsilyl)oxy]-16-ethoxy-21-norpicrasa-2,12-diene (30). A solution of the ketone **26** (1.01 g, 2.3 mmol) in CH_2Cl_2 (30 mL) and Et_3N (0.7 mL, 5 mmol) was cooled to 0 °C under N_2. TBDMS triflate (0.7 mL, 3 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. The mixture was then poured into 5% aqueous $NaHCO_3$ solution and extracted with ether. The ethereal extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent provided the TBDMS enol ether **30** as an orange syrup which was used for the next reaction without further purification: R_f = 0.72 (30% EtOAc/hexanes).

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,14*R*,16*S*)-20-(Methanesulfonyl)-13-[(*tert*-butyldimethylsilyl)oxy]-16-ethoxy-21-norpicrasa-2,-12-diene (32). Liquid NH_3 (~150 mL) was condensed in a three-necked flask equipped with mechanical stirrer, addition funnel, and dry ice condenser at −78 °C under N_2. Lithium wire (0.16 g, 23 mmol) was added in small pieces and stirred mechanically for 40 min. To the resulting dark blue solution was added a solution of the benzyl ether **30** in THF (40 mL). The reaction mixture was stirred at −78 °C for 1.5 h and then quenched by addition of water (50 mL). The cooling bath and condenser were removed and liquid NH_3 was allowed to evaporate under a stream of N_2 for 3 h at ambient temperature. The residue was diluted with water and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Et_3N (0.5 mL) was added prior to concentration to ensure neutralization of any adventitious acid. The alcohol **31** was obtained as a pale yellow syrup which was used immediately for the following reaction without further purification: R_f = 0.48 (20% EtOAc/hexanes). A solution of the alcohol **31** in CH_2Cl_2 (20 mL) was chilled to 0 °C under N_2 and treated sequentially with Et_3N (5 mL, 36 mmol) and methanesulfonyl chloride (0.7 mL, 9 mmol). Precipitation of white solid was observed immediately, and the mixture was stirred for 1.25 h as reaction temperature gradually rose to rt. The reaction mixture was poured into 5% aqueous $NaHCO_3$ solution and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent gave an orange oil which was purified by flash chromatography (5% and then 10% ether/hexanes) on silica gel previously deactivated by washing with Et_3N/hexanes. The mesylate **32** was obtained as a white amorphous solid (1.06 g) in 85% overall yield for the three-step transformation from the benzyl ether **26**: R_f = 0.50 (20% EtOAc/hexanes); mp = 126–127 °C; $[\alpha]^{25}_D$ = +19.55° (c = 3.07 $CHCl_3$); IR ($CHCl_3$) 1677 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.40 (m, 2H), 4.81 (br d, 1H, J = 3.3 Hz), 4.75 (m, 1H), 4.53 (d of AB_q, 1H, J_{AB} = 9.9 Hz), 4.19 (d of AB_q, 1H, J_{AB} = 9.9 Hz), 4.05 (t, 1H, J = 2.8 Hz) 3.66 (m, 1H), 3.43 (m, 1H), 3.00 (s, 3H), 2.64 (dd, 1H, J = 4.7 and 12.5 Hz), 2.12–1.45 (m, 11H), 1.20 (t, 3H, J = 7.1 Hz), 0.99 (d, 3H, J = 7.1 Hz), 0.91 (s, 9H), 0.84 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.29, 133.02, 123.37, 103.66, 100.20, 95.60, 68.52, 63.61, 63.42, 61.68, 58.39, 45.26, 41.60, 40.41, 34.45, 33.99, 31.80, 31.62, 26.43, 25.41, 20.14, 18.85, 18.04, 17.72, 15.09, 14.81, 13.63, 8.82, 7.97, −4.56, −4.89.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,12*S*,14*R*,16*S*)-20-(Methanesulfonyl)-16-ethoxy-13-oxo-12-(phenylseleno)-21-norpicras-2-ene (33). A stirred solution of the TBDMS enol ether **32** (0.55 g, 1.0 mmol) in THF (10 mL) was cooled to −35 °C under N_2 and treated with dropwise addition of a solution of phenylselenenyl chloride (0.24 g, 1.2 mmol) in THF (10 mL) over 25 min. Upon complete addition, the resulting mixture was gradually warmed up to −10 °C over 30 min and then poured into a 5% aqueous $NaHCO_3$ solution and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and concentrated to provide the seleno ketone **33** as a yellow syrup (0.78 g, 131% crude weight) which was used directly for the next transformation: R_f = 0.26 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 2H), 7.34 (m, 3H), 5.53 (br s, 2H), 4.89 (d, 1H, J = 3.4 Hz), 4.39 (d of AB_q, 1H, J_{AB} = 11.3 Hz), 4.16 (d of AB_q, 1H, J_{AB} = 11.3 Hz), 4.00 (d, 1H, J = 4.2 Hz), 3.79 (br s, 1H), 3.71–3.61 (m, 1H), 3.50–3.39 (m, 1H), 2.94 (s, 3H), 2.70 (dt, 1H, J = 4.6 and 14.6 Hz), 2.52–1.31 (m, 11H), 1.21 (t, 3H, J = 7.0 Hz), 1.03 (d, 3H, J = 7.3 Hz), 0.89 (s, 3H); MS (EI) m/z 582 (M^+), 537, 425, 379, 314, 283, 269, 255, 157, 107, 91; MS (CI) m/z 583 (M + H), 537, 441, 425, 415, 381, 351, 313, 285.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,12*R*,13*R*,14*R*,16*S*)-13,20-Epoxy-16-ethoxy-12-(phenylseleno)-21-nitrilopicrasa-2-ene (35). A solution of the keto mesylate **33** (~1.0 mmol) in acetonitrile (20 mL) was stirred under N_2 with 18-crown-6 ether (0.32 g, 1.2 mmol) and KCN (0.1 g, 1.5 mmol) for 15 h at rt. The reaction mixture was poured into 10% aqueous $NaHCO_3$ solution and extracted with ether. The extract was washed with brine then dried over Na_2SO_4. Evaporation of solvent afforded the nitrile **35** as an orange oil (0.55 g, 106% crude yield) which was used directly for the subsequent reaction: R_f = 0.56 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.70 (m, 2H), 7.33 (m, 3H), 5.45 (br s, 2H), 4.96 (br s, 1H), 4.34 (d, 1H, J = 8.6 Hz), 3.78 (br s, 1H), 3.73–3.63 (m, 1H), 3.57 (d, 1H, J = 8.6 Hz), 3.50–3.39 (m, 1H), 3.09 (m, 1H), 2.69 (dd, 1H, J = 5.5 and 13.8 Hz), 2.18–1.08 (m, 11H), 1.20 (t, 3H, J = 7.1 Hz), 0.96 (d, 3H, J = 6.9 Hz), 0.83 (s, 3H); MS (EI) m/z 513 (M^+), 486, 468, 283, 255, 157, 119, 107, 91; MS (CI) m/z 514 (M + H), 468, 310; HRMS $C_{28}H_{35}O_3NSe$ calcd 513.1782, found 513.1788.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,13*R*,14*R*,16*S*)-13,20-Epoxy-16-ethoxy-21-nitrilopicrasa-2,11-diene (36). A solution of the selenide **35** (~1.0 mmol) in THF (20 mL) was chilled to 0 °C and treated sequentially with solid $NaHCO_3$ powder (0.3 g) and 30% H_2O_2 in water (2 mL). The mixture was stirred for 30 h at rt and then quenched with a mixture of aqueous $NaHSO_3$ and $NaHCO_3$ solution and extracted with ether. The ethereal extract was washed with brine and dried over Na_2SO_4. Removal of the solvent gave the dienic nitrile **36** as a yellow syrup (0.55 g) which solidified on standing in the fridge. Purification by flash chromatography (silica gel, 10% EtOAc/hexanes) furnished the nitrile **36** as a colorless solid (62% overall yield, three steps from the mesylate **32**): R_f = 0.58 (30% EtOAc/hexanes); IR ($CHCl_3$) 2245 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.90 (br s, 2H), 5.50 (br s, 2H), 5.03 (d, 1H, J = 3.4 Hz), 4.56 (d, 1H, J = 8.6 Hz), 3.80 (br s, 1H), 3.80–3.70 (m, 1H), 3.61 (dd, 1H, ^4J_w = 2.3 Hz, J = 8.6), 3.51–3.46 (m, 1H), 2.77 (br s, 1H), 2.60 (dd, 1H, J = 4.2 and 13.5 Hz), 2.12–1.74 (m, 6H), 1.45 (m, 1H), 1.22 (t, 3H, J = 7.1 Hz), 1.14–1.08 (m, 1H), 0.97 (d, 3H, J = 6.9 Hz), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 133.63, 130.36, 125.47, 122.93, 118.82, 95.66, 72.64, 72.36, 70.88, 62.75, 46.28, 44.43, 44.22, 42.43, 39.73, 35.22, 32.02, 28.81, 25.98, 18.89, 15.72, 15.12; MS (EI) m/z 355 (M^+), 337, 310, 279, 264, 246, 238, 193, 156, 119, 107, 93, 91; MS (CI) m/z 356 (M + H), 338, 310, 292,236; HRMS $C_{22}H_{29}O_3N$ calcd 355.2148, found 355.2148.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,13*R*,14*R*,16*S*)-13,20-Epoxy-16-ethoxypicrasa-2,11-dien-21-oic Acid (37). The dienic nitrile **36** (0.36 g, 1 mmol) in a mixture of dioxane (10 mL) and 10% aqueous KOH (10 mL) was treated with 30% H_2O_2 in water. Liberation of gas (oxygen) was observed and the mixture was allowed to stir at rt for 15 min. The reaction mixture was heated under gentle reflux for 18 h, then cooled, and quenched with saturated aqueous Na_2HPO_4 solution. The mixture was extracted with $CHCl_3$ and the extract was dried over Na_2SO_4. Upon evaporation of the solvent, the acid **37** was obtained as a colorless oil (0.38 g, 100% crude yield) of very high purity: ^{1}H NMR ($CDCl_3$) δ 5.96–5.91 (br m, 2H), 5.58-5.48 (br m, 2H), 5.01 (d, 1H, J = 3.1 Hz), 4.62 (d, J = 8.6 Hz), 3.82 (br s, 1H), 3.78-3.64 (m, 2H), 3.53–3.41 (m, 1H), 2.81 (br s, 1H), 2.39 (dd, 1H, J = 4.5 and 14.2 Hz), 2.17–1.03 (m, 8H), 1.20 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7 Hz), 0.99 (d, 3H, J = 6.7 Hz), 0.93 (s, 3H); MS (EI) m/z 374 (M^+), 356, 329, 311, 297, 280, 269, 255, 202, 175, 107, 91, 73; MS (CI) m/z 357, 329, 311, 299, 293, 255; HRMS $C_{22}H_{30}O_5$ calcd 374.2093, found 374.2088.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,13*R*,14*R*,16*S*)-13,20-Epoxy-16-ethoxypicrasa-2,11-dien-21-oic Acid, Methyl Ester (38). A solution of the acid **37** (0.38 g, 1 mmol) in a mixture of ether (3 mL) and CH_2Cl_2 (3 mL) was cooled to 0 °C and treated with excess ethereal diazomethane. After stirring for 1 h, the reaction mixture was gently warmed to remove the excess diazomethane. Removal of the solvent provided the methyl ester **38** as a colorless oil (0.36 g, 91% yield, two steps from the nitrile **36**): R_f = 0.39 (30%

EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 5.96–5.84 (m, 2H), 5.51 (br m, 2H), 4.97 (br s, 1H), 4.56 (d, 1H, J = 8.6 Hz), 3.80 (s, 3H), 3.77–3.63 (m, 3H), 3.55–3.33 (m, 1H), 2.80 (br s, 1H), 2.47 (m, 1H), 2.11 (m, 1H), 1.92–1.70 (m, 5H), 1.48 (m, 1H), 1.20 (t, 3H, J = 7.0 Hz), 1.11 (m, 1H), 0.97 (d, 3H, J = 6.7 Hz), 0.93 (s, 3H); MS (EI) m/z 388 (M^+), 357, 340, 329, 311, 280, 269, 255, 216, 189, 107, 93; MS (CI) m/z 357, 343, 325, 313, 269; HRMS $C_{23}H_{32}O_5$ calcd 388.2250, found 388.2256.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,11*S*,12*S*,13*S*,14*R*,16*S*)-13,20-Epoxy-16-ethoxy-11,12-dihydroxypicras-2-en-21-oic Acid, Methyl Ester (39). A solution of the diene **38** (73 mg, 0.19 mmol) in THF (3 mL) was cooled to 0 °C under N_2 and treated with a 51 mM solution of OsO_4 in THF (3.8 mL, 0.19 mmol). The resulting dark solution was allowed to warm up to rt gradually and stirred for 12 h. The reaction mixture was quenched with aqueous $NaHSO_3$ solution, diluted with THF (3 mL), and stirred for 30 min, and then extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and then concentrated to an oil. The crude oil was subjected to flash chromatography (50% and then 75% EtOAc/hexanes) to recover starting material diene **38** (3 mg, 4%) and the diol **39** (48 mg, 60%) as a white solid: R_f = 0.45 (75% EtOAc/hexanes); mp 177–179 °C; $[\alpha]^{25}_D$ = +54.01° (c = 2.25 $CHCl_3$); IR ($CHCl_3$) 3560 (br), 3400 (br),1720 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.54–5.41 (m, 2H), 4.91 (d, 1H, J = 3.3 Hz), 4.26 (d, 1H, J = 8.1 Hz), 4.22–4.07 (m, 2H), 3.84 (s, 3H), 3.75 (m, 1H), 3.70–3.62 (m, 1H), 3.52–3.41 (m, 2H), 3.33 (d, 1H, J = 1.9 Hz), 2.67 (dd, 1H, J = 4.8 Hz and 17.9 Hz), 2.53 (dt, 1H, J = 3.6 and 13.7 Hz), 2.41 (d, 1H, J = 10.6 Hz), 2.32 (dd, 1H, J = 2.6 and 13.8 Hz), 2.03–1.72 (m, 4H), 1.57 (m, 1H), 1.29–1.06 (m, 1H), 1.20 (t, 3H, J = 7.1 Hz), 1.04 (s, 3H), 0.99 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 173.23, 131.69, 124.86, 95.61, 83.13, 73.30, 72.76, 69.96, 68.11, 62.24, 52.79, 44.57, 43.87, 42.75, 42.41, 41.50, 36.08, 32.39, 29.39, 26.80, 19.54, 15.09, 13.23; MS (EI) m/z 422 (M^+), 404, 386, 376, 358, 343, 119, 105, 91; MS (CI) m/z 423 (M + H), 405, 377, 359, 299; HRMS $C_{23}H_{34}O_7$ calcd 422.2304, found 422.2306.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,12*R*,13*S*,14*R*,16*S*)-13,20-Epoxy-16-ethoxy-12-hydroxy-11-oxopicras-2-en-21-oic Acid, Methyl Ester (41). A mixture of DMSO (0.5 mL) and CH_2Cl_2 (3 mL) was cooled to −78 °C under N_2 and treated with dropwise addition of TFAA (0.35 mL, 2.5 mmol). A white suspension resulted and was stirred for 20 min at −78 °C followed by dropwise addition of the diol **39** (48 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) over 5 min. The suspension was stirred for 30 min as temperature gradually rose from −65 to −60 °C. The reaction mixture turned into a clear solution as the temperature was allowed to rise up to −25 °C rapidly and stirred for 40 min. The reaction was complete as shown on TLC and was quenched by addition of an aqueous solution of Na_2HPO_4 (2 mL). After stirring for 10 min, the mixture was poured into water and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ and then brine and dried over Na_2SO_4. Removal of solvent afforded a pale yellow solid which was purified by flash chromatography (30% and then 50% EtOAc/hexanes) to give the hydroxy ketone **41** as a white powder (39 mg, 81.6%): R_f = 0.70 (75% EtOAc/hexanes); mp = 184–187 °C; $[\alpha]^{25}_D$ = +67.03° (c = 1.85 $CHCl_3$); IR ($CHCl_3$) 3600 (br), 3540 (br), 3360 (br), 1745 (sh), 1730 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.53–5.42 (m, 2H), 5.00 (d, 1H, J = 1.7 Hz), 4.26 (d, 1H, J = 8.1 Hz), 4.02 (s, 1H), 3.91 (m, 1H), 3.85 (s, 3H), 3.77–3.66 (m, 1H), 3.59–3.48 (m, 2H), 3.14 (br s, 1H), 2.96 (s, 1H), 2.89 (m, 1H), 2.64 (m, 2H), 1.97–1.79 (m, 4H), 1.53 (m, 1H), 1.28–1.13 (m, 1H), 1.23 (t, 3H, J = 7.1Hz), 1.09 (s, 3H), 0.98 (d, 3H, J = 6.7Hz); ^{13}C NMR ($CDCl_3$) δ 206.09, 171.94, 132.30, 124.26, 95.61, 82.86, 78.07, 73.82, 68.83, 62.48, 52.79, 51.09, 46.38, 44.10, 41.30, 39.75, 34.89, 31.49, 28.85, 26.65, 19.10, 14.90, 12.6; MS (EI) m/z 420 (M^+), 402, 374, 356, 219, 185, 153, 139, 128, 105, 91; MS (CI) m/z 421 (M + H), 403, 375, 357, 345, 327; HRMS $C_{23}H_{32}O_7$ calcd 420.2148, found 420.2146.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,11*R*,12*S*,13*S*,14*R*,16*S*)-13,20-Epoxy-16-ethoxy-11,12-dihydroxypicras-2-en-21-oic Acid, Methyl Ester (42). A solution of the hydroxy ketone **41** (31 mg, 0.07 mmol) in EtOAc (5 mL) was cooled to 0 °C and treated with $Na(AcO)_3BH$ (50 mg). The suspension was stirred at 0 °C for 12 h, and then diluted with EtOAc, and quenched with water. The mixture was extracted with EtOAc and the extract was dried over Na_2SO_4. Evaporation of solvent provided an oil (30 mg) which was subjected to flash chromatography (30% and then 50% EtOAc/hexanes) to recover starting material **41** (2.5 mg, 8%) and the *trans*-diol **42** (25 mg, 80.3% yield) as a white powder: R_f = 0.48 (75% EtOAc/hexanes); $[\alpha]^{25}_D$ = +44.57° (c = 1.40 $CHCl_3$); IR ($CHCl_3$) 3550 (s), 1720 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.59–5.43 (m, 2H), 4.88 (br s, 1H), 4.56 (d, 1H, J = 8.0 Hz), 4.09 (dd, 1H, J = 4.3 and 12.9 Hz), 4.01 (br s, 1H), 3.87 (s, 3H), 3.79 (br s, 1H), 3.72–3.58 (m, 2H), 3.51–3.40 (m, 1H), 3.18 (s, 1H), 2.57–2.41 (m, 3H), 2.26 (dd, 1H, J = 4.8 and 14.2 Hz), 1.98–1.68 (m, 5H), 1.53 (br t, 1H), 1.41–1.23 (m, 5H), 1.31 (s, 3H), 1.20 (t, 3H, J = 7.2 Hz), 0.99 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 174.01, 132.35, 123.62, 95.39, 83.42, 76.57, 74.55, 71.77, 69.68, 62.28, 52.86, 44.37, 43.94, 42.92, 40.35, 38.77, 36.29, 32.00, 30.13, 26.93, 19.26, 15.10, 14.69, 14.67.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,11*R*,12*S*,13*S*,14*R*,16*S*)-11,12-Bis(dichloroacetoxy)-13,20-epoxy-16-ethoxypicras-2-en-21-oic Acid, Methyl Ester (43). A solution of the *trans* diol **42** (25 mg, 0.059 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.3 mL) was cooled to 0 °C under N_2 and added to dichloroacetyl chloride (60 mL, 0.62 mmol). The mixture was allowed to warm up to rt and stirred for 3 h. TLC showed a 2:1 mixture of the bis- and monodichloroacetate. More dichloroacetyl chloride (30 mL, 0.31 mmol) was added at 0 °C and stirred for 5 h. The reaction mixture was diluted with 75% EtOAc/hexanes, washed with 10% aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to a yellow syrup. Purification by flash chromatography (20% EtOAc/hexanes) provided the bis-dichloroacetate **43** as a foam (35 mg, 92%): R_f = 0.64 (75% EtOAc/hexanes); $[\alpha]^{25}_D$ = +26.77° (c = 4.65, $CHCl_3$); IR ($CHCl_3$) 1770 (s), 1750 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.00 (s, 1H), 5.94 (s, 1H), 5.47 (br s, 2H), 5.21 (d, 1H, J = 5.4 Hz), 5.14 (s, 1H), 4.94 (d, 1H, J = 2.8 Hz), 4.61 (d, 1H, J = 7.6 Hz), 3.90 (br s, 1H), 3.73 (s, 3H), 3.71–3.64 (m, 2H), 3.53–3.45 (m, 1H), 2.71 (dd, 1H, J = 2.5 and 13.5 Hz), 2.28–2.16 (m, 2H), 1.98–1.77 (m, 5H), 1.63–1.55 (tm, 1H), 1.40–1.30 (tm, 1H), 1.20 (t, 3H, J = 7.0 Hz), 1.17 (s, 3H), 0.99 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 169.85, 163.19, 161.55, 132.68, 122.50, 95.28, 80.48, 73.94, 73.82, 73.57, 69.64, 65.12, 64.14, 63.94, 62.57, 52.88, 43.48, 43.07, 42.92, 40.22, 38.67, 36.06, 31.95, 29.91, 26.77, 19.17, 15.29, 15.10; MS (EI) m/z 642 (M^+, isotope pattern 642, 644, 646, 648, 650), 599, 515, 496, 481, 353, 341, 325, 280, 263, 251, 171, 119, 107, 93, 83; MS (CI) m/z 643, 627, 599, 515, 387, 357, 341, 325, 311.

(2*S,3*R**,4*S**,5*S**,7*R**,8*R**,9*R**,10*S**,11*R**,12*S**,13*S**,14*R**,16*S**)-11,12-Bis(dichloroacetoxy)-2,3-dihydroxy-13,20-epoxy-16-ethoxypicrasan-21-oic Acid, Methyl Ester (44).** A solution of the olefin **43** (7 mg, 0.01 mmol) in THF (1 mL) and pyridine (0.5 mL) was cooled to 0 °C and treated with a 51 mM solution of OsO_4 in THF (0.85 mL, 0.043 mmol). The reaction mixture was stirred at rt for 6 h, diluted with THF (2 mL), quenched with aqueous $NaHSO_3$, and stirred for 2 h. The mixture was extracted with EtOAc and the extract was washed with brine and dried over Na_2SO_4. Removal of solvent provided an oil which was purified by flash chromatography (30% and then 50% EtOAc/hexanes) to give the β-*cis*-diol **44** as a colorless syrup (5 mg, 67.8%): R_f = 0.47 (75% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.03 (s, 1H), 5.95 (s, 1H), 5.21 (d, 1H, J = 5.0 Hz), 5.15 (d, 1H, J =1.0 Hz), 4.95 (d, 1H, J = 2.8 Hz), 4.67 (d, 1H, J = 7.8 Hz), 4.05 (m, 1H), 3.91 (bs, 1H), 3.73 (s, 3H), 3.72–3.63 (m, 2H), 3.53–3.43 (m, 1H), 3.17 (dd, 1H, J = 9.8 and 3.2 Hz), 2.75 (dm, 1H), 2.25–1.33 (m, 10H), 1.39 (s, 3H), 1.21 (t, 3H, J = 7.0 Hz), 1.01 (d, 3H, J = 6.3 Hz); MS (EI) m/z 630, 602, 572, 556, 538, 474, 440, 83, 45; MS (CI) m/z 677 (M + H, isotope pattern 673, 675, 677, 679), 631, 615, 595, 579, 561, 503, 375, 357, 343, 327, 317, 181.

(4*S,5*S**,7*R**,8*R**,9*R**,10*S**,11*R**,12*S**,13*S**,14*R**,16*S**)-11,12-Bis(dichloroacetoxy)-13,20-epoxy-16-ethoxy-2,3-dioxopicrasan-21-oic Acid, Methyl Ester (45 & 46).** A mixture of DMSO (70 mL, 0.98 mmol) and CH_2Cl_2 (1 mL) was cooled to −78 °C under N_2 and treated with oxalyl chloride (50 mL, 0.57 mmol) dropwise. The mixture was stirred at −78 °C for 20 min and then treated with a solution of the diol **44** (5 mg, 0.007 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was allowed to warm up to −65 °C over 40 min, and Et_3N (0.2 mL) was added dropwise and stirred for 10 min at −65 °C. Reaction was completed as judged by TLC, the mixture was diluted with 75% EtOAc/hexanes and poured into water. The mixture was extracted with 75% EtOAc/hexanes. The extract was washed with brine and then dried over Na_2SO_4. Removal of solvent provided an oil which was purified by flash chromatography (30% EtOAc/hexanes) to afford an inseparable mixture (~2:1) of the isomeric diosphenols, kinetic

(*k*) **45** vs thermodynamic (*t*) **46**, as an oil (3 mg, 60%): R_f = 0.65 (75% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.14(*k*) (s, 0.67H), 6.05(*t*) (s, 0.33H), 6.04(*k*) (s, 0.67H), 6.00 (s, 0.67H), 5.98(*t*) (s, 0.33H), 5.97(*k*) (s, 0.67H), 5.41(*k*) (d, 0.67H, *J* = 5.0 Hz), 5.24(*k*) (br s, 0.67H), 5.21(*t*) (br s, 0.33H), 5.13(*t*) (d, 0.33H, *J* = 5.0 Hz), 5.01(*t*) (d, 0.33H, *J* = 3.0 Hz), 4.96(*k*) (d, 0.67H, *J* = 2.8 Hz), 4.65(*t*) (d, 0.33H, *J* = 7.7 Hz), 4.64(*k*) (d, 0.67H, *J* = 7.7 Hz), 4.05(*t*) (br s, 0.33H), 3.97(*k*) (bs, 0.67H), 3.76 (s, 3H), 3.74–3.65 (m, 2H), 3.58–3.46 (m, 1H), 2.85–1.43 (m), 1.87(*t*) (d, 1H, *J* = 1.0 Hz), 1.48(*k*) (s, 2H), 1.30(*t*) (s, 1H), 1.26–1.20(*k*) (m, 5H).

(5*R,7*R**,8*R**,9*R**,10*S**,11*R**,12*S**,13*S**,14*R**,16*S**)-13,20-Epoxy-16-ethoxy-3,11,12-trihydroxy-2-oxopicras-3-en-21-oic Acid, Methyl Ester (3).** A mixture of the isomeric diosphenols **45** & **46** (3 mg, 0.004 mmol) in CH_2Cl_2 (1 mL) was stirred with DBU (2 drops) at rt overnight. The reaction mixture was diluted with EtOAc and washed with 1% aqueous HCl, water, and then brine. After drying over Na_2SO_4, the solvent was evaporated to provide an oil which was purified by flash chromatography (30% and then 50% EtOAc/hexanes) to furnish the diosphenol **3** as a foam (1.5 mg, 74.5% yield): R_f = 0.22 (75% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.05 (s, 1H), 4.94 (br s, 1H), 4.60 (d, 1H, *J* = 8.0 Hz), 4.05 (m, 1H), 4.03 (br s, 1H), 3.93 (br s, 1H), 3.88 (s, 3H), 3.75–3.62 (m, 1H), 3.55–3.45 (m, 2H), 3.19 (s, 1H), 2.96 (d, 1H, *J* = 14.2 Hz), 2.60–1.48 (m, 8H),1.87 (d, 3H, *J* = 1.1 Hz), 1.39 (s, 3H) 1.24 (t, 3H, *J* = 7.2 Hz); MS (EI) *m/z* 453, 452 (M^+), 438, 420, 406, 388, 371, 359, 298, 201, 200, 151, 55; MS (CI) *m/z* 453 (M + H), 435, 417, 407, 389, 281, 143, 127, 111, 97, 81, 69; HRMS calcd 453.2124, found 453.2135.

(4*R,5*S**,7*R**,8*R**,9*R**,10*S**,13*R**,14*R**)-13,20-Epoxypicras-2,11,15-trien-21-oic Acid, Methyl Ester (50).** A solution of the acetal **38** (10 mg, 0.026 mmol) in anhydrous toluene (10 mL) and pyridine (0.15 mL) was treated with PPTS (65 mg, 0.26 mmol) and heated under reflux overnight. The reaction mixture was cooled, treated with Et_3N (10 drops), poured into 1% aqueous $NaHCO_3$ solution, and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Removal of solvent provided an oil which was purified by flash chromatography (silica gel, 30% EtOAc/hexanes) to give the dihydropyran **50** as a white powder (8.5 mg, 96%): R_f = 0.58 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.34 (dd, 1H, *J* = 2.9 and 6.0 Hz), 5.98 (dd, 1H, *J* = 3.0 and 9.9 Hz), 5.85 (dd, 1H, *J* = 1.6 and 9.9 Hz), 5.51 (br s, 2H), 4.94 (dd, 1H, *J* = 1.5 and 6.0 Hz), 4.64 (d, 1H, *J* = 8.7 Hz), 4.28 (br s, 1H), 3.83 (s, 3H), 3.66 (dd, 1H, *J* = 2.1 and 8.7 Hz), 2.81 (br m, 2H), 2.14–2.06 (m, 2H),1.82–1.72 (m, 2H), 1.48–1.39 (tm, 1H), 1.25–1.15 (tm, 1H), 0.98 (d, 3H, *J* = 6.8 Hz), 0.96 (s, 3H); MS (EI) *m/z* 342 (M^+), 326, 312, 280, 269, 216, 189, 175, 131, 115, 105, 91; MS (CI) *m/z* 343 (M + H), 325, 311, 293, 269; HRMS $C_{21}H_{26}O_4$ calcd 342.1831, found 342.1830.

(4*R,5*S**,7*R**,8*R**,9*R**,10*S**,13*R**,14*S**,15*R**,16*R**)-13,20-Epoxy-15-hydroxy-16-[2-(trimethylsilyl)ethoxy]picrasa-2,-11-dien-21-oic Acid, Methyl Ester (56).** A solution of the triene **50** (8.5 mg, 0.025 mmol) and β-(trimethylsilyl)ethanol (0.1 mL, 0.7 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −10 °C under N_2 and treated with *m*-CPBA (6 mg, 0.028 mmol). After stirring at −10 °C for 1.5 h, the reaction mixture was allowed to warm up to rt and stirred for 12 h. The mixture was poured into a mixture of aqueous $NaHCO_3$ and $NaHSO_3$ solution and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of solvent provided an oil which was placed under high vacuum to remove the excess β-(trimethylsilyl)ethanol. The resulting syrup was subjected to flash chromatography (silica gel, 20, 30, and then 50% EtOAc/hexanes) to furnish, in order of elution,(i) a trace of unchanged starting material triene **50**; (ii) the alcohol **56** as a foam (4.5 mg, 38%): R_f = 0.56 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.14 (dd, 1H, *J* = 3.0 and 9.8 Hz), 5.93 (dd, 1H, *J* = 1.7 and 9.8 Hz), 5.50 (br s, 2H), 4.53 (d, 1H, *J* = 8.7 Hz), 4.25 (d, 1H, *J* = 7.1 Hz), 3.99 (m, 1H), 3.89–3.73 (m, 1H), 3.83 (s, 3H), 3.68–3.59 (m, 3H), 2.85 (br s, 1H), 2.15–0.85 (m, 7H), 0.98 (d, 3H, *J* = 6.9 Hz), 0.92 (s, 3H), 0.02 (s, 9H); (iii) the epoxy alcohol **57** as a foam (4.0 mg, 33%): R_f = 0.23 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.14 (dd, 1H, *J* = 2.9 and 9.9 Hz), 5.87 (dd, 1H, *J* = 1.6 and 9.9 Hz), 4.39 (d, 1H, *J* = 8.6 Hz), 4.21 (d, 1H, *J* = 7.0 Hz), 4.02–3.93 (m, 1H), 3.86–3.69 (m, 1H), 3.81 (s, 3H), 3.61–3.52 (m, 3H), 3.19 (dd, 1H, *J* = 4.1 and 5.6 Hz), 3.05 (d, 1H, *J* = 3.7 Hz), 2.75 (br s, 1H), 2.12 (d, 1H, *J* = 11.3 Hz), 2.06 (dd, 1H, *J* = 6.0 and 14.7 Hz), 1.92 (dm, 1H), 1.67–1.04 (m, 6H), 1.10 (d, 3H, *J* = 5.8 Hz), 0.90 (s, 3H), 0.03 (s, 9H); and (iv) the epoxy benzoate **58** (0.5 mg, 8%): R_f = 0.11 (50% EtOAc/hexanes).

(4*R,5*S**,7*R**,8*R**,9*R**,10*S**,13*R**,14*S**,15*R**,16*R**)-15-Acetoxy-13,20-epoxy-16-[2-(trimethylsilyl)ethoxy]-picrasa-2,-11-dien-21-oic Acid, Methyl Ester (59).** A solution of the alcohol **56** (1.5 mg, 0.003 mmol) in CH_2Cl_2 (1 mL) was treated with pyridine (0.1 mL), DMAP (1 mg) and Ac_2O (0.05 mL, 0.52 mmol) and stirred overnight at rt. The reaction was poured into water and extracted with ether. The extract was washed with water then brine. After drying over Na_2SO_4, solvent was removed to provide an oil which was flash chromatographed to afford the acetate **59** as a colorless foam (1.5 mg, 92% yield): R_f = 0.60 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.17 (dd, 1H, *J* = 3.0 and 9.8 Hz), 5.93 (dd, 1H, *J* = 1.7 and 9.7 Hz), 5.49 (br s, 2H), 5.14 (dd, 1H, *J* = 7.4 and 11.6 Hz), 4.52 (d, 1H, *J* = 8.7 Hz), 4.39 (d, 1H, *J* = 7.4 Hz), 3.99–3.90 (m, 1H), 3.79–3.62 (m, 3H), 3.77 (s, 3H), 3.58–3.50 (m, 1H), 2.94 (br s, 1H), 2.30 (d, 1H, *J* = 11.5 Hz), 2.17–0.83 (m, 8H), 1.99 (s, 3H), 0.96 (d, 3H, *J* = 6.9 Hz), 0.91 (s, 3H), 0.01 (s, 9H); MS (EI) *m/z* 490, 400, 358, 310, 269, 189, 73; MS (CI) *m/z* 491, 401, 341, 313, 269.

(4*R*,5*S*,7*R*,8*R*,9*R*,10*S*,11*R*,12*S*,13*S*,14*R*)-11,12-Bis(dichloroacetoxy)-13,20-epoxypicrasa-2,15-dien-21-oic Acid, Methyl Ester (63). To a flask equipped with a Dean–Stark trap and condenser was charged with 2,6-lutidinium *p*-toluenesulfonate (32 mg, 0.11 mmol) and anhydrous toluene (10 mL). The mixture was heated under argon for 2 h and then the bath temperature was raised as toluene (7 mL) was distilled off and collected in the Dean–Stark trap. The solution was cooled to rt, a solution of the acetal **43** (16 mg, 0.025 mmol) in anhydrous toluene (5 mL) was added, and the mixture was heated for 2 h as toluene (1 mL) was collected in the Dean–Stark trap. The reaction mixture was cooled to rt, poured into 1% aqueous $NaHCO_3$ solution, and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of solvent afforded an oil which was subjected to flash chromatography (silica gel, 10, 20, and then 50% EtOAc/hexanes) to provide in order of elution, the dihydropyran **63** as a colorless foam (7 mg, 47%), followed by the lactol **64** (5 mg, 33%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 6.40 (dd, 1H, *J* = 3.0 and 6.0 Hz), 6.01 (s, 1H), 5.95 (s, 1H), 5.49 (br s, 2H), 5.21 (d, 1H, *J* = 4.9 Hz), 5.20 (d, 1H, *J* = 0.8 Hz), 5.10 (dd, 1H, *J* = 1.8 and 6.0 Hz), 4.70 (d, 1H, *J* = 7.6 Hz), 4.36 (br s, 1H), 3.76 (s, 3H), 3.66 (dd, 1H, *J* = 1.5 and 7.6 Hz), 3.07 (br s, 1H), 2.15 (m, 1H), 2.08 (dd, 1H, *J* = 3.5 and 11.9 Hz), 2.04–1.83 (m, 3H),1.58–1.21 (m, 2H), 1.20 (s, 3H), 1.00 (d, 3H, *J* = 6.7 Hz); MS (EI) *m/z* 598 (M^+, isotope pattern 596, 598, 600, 602), 579, 539, 468, 406, 341, 325, 311, 279, 202, 189, 108, 93, 83; MS (CI) *m/z* 599 (M + H), 577, 564, 469, 341, 311, 181.

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Supplementary Material Available: Copies of the proton NMR spectra of compounds **3, 4, 7, 8, 10, 12, 13, 15, 17, 18ax, 18eq, 20, 23, 24, 25eq, 25ax, 26, 32, 33, 35–46, 50, 56, 57, 59,** and **63** (37 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.