The Total Synthesis of (±)-Scopadulcic Acids A and B and (±)-Scopadulciol

Frederick E. Ziegler* and Owen B. Wallace

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06520-8107

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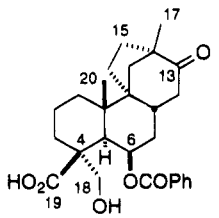
The total syntheses of (±)-scopadulcic acids A (**1**) and B (**2a**) and (±)-scopadulciol (**2b**) from the late, common intermediate **3** are described. The route provides a chemical correlation of the structures of the three natural products.

Introduction

In 1987 Hayashi *et al.*[1] reported the isolation and characterization of scopadulcic acid A (SDA) (**1**) and scopadulcic acid B (SDB) (**2a**) from the Paraguayan medicinal plant "Typychá Kuratû" (*Scoparia dulcis* L., Scrophuraliaceae). The gross structure of SDA was determined by a combination of MS, UV, IR, and one- and two-dimensional NMR spectroscopy; the relative stereochemistry was revealed through NOE studies. The structure of SDB was assigned by comparison of its spectral data with that of SDA. The structure of SDA was later confirmed by single crystal X-ray crystallography of its methanol solvate.[2] The absolute stereochemistry of SDA and SDB was assigned on the basis of a positive Cotton effect in their CD spectra.[1] No chemical correlation between SDA and SDB was established.[3]



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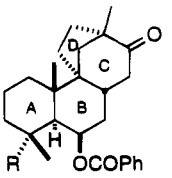

2a, R = CO_2H
b, R = CH_2OH

Scopadulciol (**2b**) was isolated from *Scoparia dulcis* indigenous to Taiwan.[4] Its structure was assigned by comparison of its spectral data with that of SDB. In addition, scopadulciol and SDB were reduced with $LiAlH_4$ to the same triol. Bangladeshi *S. dulcis* has yielded dulcinol,[5] a substance whose identity with scopadulciol has been suggested based on comparison of ^1H NMR spectra.[6]

Because *S. dulcis* had been used as a crude drug preparation for hypertension and stomach ailments in the aforementioned nations, Hayashi[7,8] initiated studies to determine if the scopadulan diterpenes were responsible for the ameliorating effects of the crude preparation. Scopadulcic acid B proved to be a powerful *in vitro* inhibitor of H^+,K^+-ATPase, the proton pump for gastric acid secretion.[7] In addition, SDB was found to be an effective antiviral agent against herpes simplex virus type 1 (HSV-1).[9] SDB was also shown to display antitumor activity in human cell lines[10] and to inhibit the action of tumor-promoting phorbol esters.[11]

Two studies have addressed the synthesis of SDB as its enantiomer. Meyers[12] has employed his chiral oxazoline methodology to produce a tetracyclic model while investigators at Schering-Plough have explored the possible conversion of the resin acid, abietic acid, into SDB.[13]

Overman was able to demonstrate that aryl iodides cyclize with dienes in the presence of a palladium catalyst to give the tetracyclic scopadulan ring system.[14] This clever strategy was applied successfully to the synthesis of (±)-SDB wherein introduction of the functionality of ring A required the elaboration of an aromatic ring.[15] A subsequent report[16] from the same laboratory detailed the total synthesis of (±)-SDA employing the palladium cyclization approach; however, ring A was formed *via* an intramolecular aldol condensation followed by subsequent functional group manipulation.

Our strategy for the synthesis of SDA and SDB was to produce racemic product such that the route would be amenable to the preparation of chiral, nonracemic product.[17] Secondly, an advanced intermediate that serves as the precursor of both substances was considered an important goal. Because oxidation of the neopentyl

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(2) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Morita, N. *J. Nat. Prod.* **1988**, *51*, 360.

(3) Numbering in the text follows the scopadulan nucleus. See structure **1**.

(4) Hayashi, T.; Asano, S.; Mizutani, M.; Takeguchi, N.; Kojima, T.; Okamura, K.; Morita, N. *J. Nat. Prod.* **1991**, *54*, 802.

(5) Ahmed, M.; Jakupovic, J. *Phytochemistry* **1990**, *29*, 3035.

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(9) Hayashi, K.; Niwayama, S.; Hayashi, T.; Nago, R.; Ochiai, H.; Morita, N. *Antiviral Res.* **1988**, *9*, 345.

(10) Hayashi, K.; Hayashi, T.; Morita, N. *Phytother. Res.* **1992**, *6*, 6.

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(15) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042.

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(17) Preliminary studies have provided diketone **3b** (76% ee) by the procedure described for the asymmetric preparation of the Wieland–Miescher ketone (**3a**) using L-proline. A CD spectrum confirmed the same absolute configuration for both diketones, Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Organic Syntheses*; Freeman, J. P., Ed.; Wiley: New York, 1990; Coll. Vol. 7; p 368.

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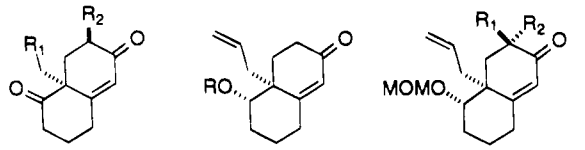
hydroxyl of scopadulciol (**2b**) would lead to SDB (**2a**), a synthetic scheme passing through scopadulciol was developed.

Results

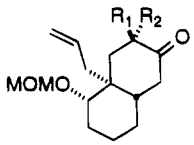
The known[18] diketone **3b**, which was prepared by Robinson annulation of 2-allyl-1,3-cyclohexanedione[19] with methyl vinyl ketone (MVK), was chosen as the precursor to rings B and C. The allyl residue would conveniently serve as the carbon source of ring D. The yield of diketone **3b** (77%) was improved by ~50% by modification of the literature conditions.[20] The saturated carbonyl of **3b** required protection to permit methylation at the enone methylene group. While the Wieland–Miescher ketone **3a** can be ketalized selectively at the saturated carbonyl,[21] efforts to effect this transformation with diketone **3b** were unsuccessful. The increased steric hindrance created by the allyl group in **3b** was responsible for the lack of selectivity. Consequently, the Boyce–Whitehurst protocol ($NaBH_4$)[22] for the selective reduction of the Wieland–Miescher ketone **3a** was applied to dione **3b** to afford stereoselectively the equatorial alcohol **4a**. Subsequent protection of the hydroxyl group as its methoxymethyl derivative (MOM) achieved the goal that was unattainable through selective ketalization.



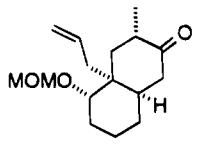
3a, $R_1 = R_2 = H$
b, $R_1 = CH{=}CH_2$, $R_2 = H$
c, $R_1 = CH{=}CH_2$, $R_2 = CH_3$

4a, R = H
b, R = MOM

5a, $R_1 = CH_3$, $R_2 = H$
b, $R_1 = H$, $R_2 = CH_3$



6a, $R_1 = CH_3$, $R_2 = H$
b, $R_1 = H$, $R_2 = CH_3$



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Incorporation of the future C_{17} methyl group of the diterpenes into the bicyclic nucleus was achieved by kinetic deprotonation[18] of enone **4b** with LDA at −78 °C followed by alkylation with methyl iodide at −20 °C. Flash chromatography removed unreacted enone **4b** and provided a chromatographically inseparable mixture of monomethylated enones **5a** and **5b** (~5.7:1; 85% yield) that was contaminated with ~2% of a dimethylated enone. The major, equatorially methylated diastereomer **5a** was obtained pure by recrystallization at the expense of yield. The separation proved unnecessary because subsequent over-reduction of the enones with Li bronze/MeOH[23] led to chromatographically separable alcohols **9** and **11**, which were readily freed of dimethylated alcohol.

The stereochemical assignments of **5a** and **5b** were based upon subsequent chemical transformations and the assumption that the enolate was methylated distal to the allyl and MOM ether substituents. The option of a more convergent approach, *i.e.*, annulation of 2-allyl-1,3-cyclohexanedione with methyl isopropenyl ketone, was attempted under basic, protic conditions and under acid catalysis;[24] the yield of **5a,b** was, at best, a meager 10%.

Initial studies on the reduction of the enone mixture **5a,b** were conducted with Li bronze/*tert*-BuOH,[23] a procedure that led to a mixture of saturated ketones in approximately the same ratio as was present in the enones themselves. Our initial assumption was that the saturated ketones were both *trans*-fused diastereomers, **5a** leading to equatorial methyl isomer **6a**, and **5b** providing its axial epimer **6b**. This hypothesis quickly became suspect when the mixture failed to undergo equilibration.[25] Because the ~6:1 mixture may already have been at equilibrium, the major saturated ketone **6a** was subjected to equilibration conditions (CD_3ONa/CD_3OD); no change in the ^1H NMR spectrum occurred other than deuterium incorporation. Thus, both major and minor components of the mixture were presumed to be thermodynamically stable, bearing equatorial methyl groups, and that the stereochemical difference lay in the ring fusions. Thus, the stereochemistry of the major component was satisfied by the stereochemistry present in structure **6a** while the structure of the minor component was reassigned as *cis*-fused isomer **7**. This hypothesis would receive confirmation in later transformations.

Although hexahydronaphthalen-2(3H)-ones give *trans*-fused products upon metal/NH_3 reduction[26] as the rule rather than the exception, an appropriately positioned substituent can produce a *cis*-fused product.[27] Addition of an electron to the major enone **5a** (Scheme 1) produces radical anion **8**, which can exist in the cisoid (**8c**) or the transoid (**8t**) conformation, both of which maintain orbital overlap.[28] The pseudoaxial methyl group in **8c** suffers a 1,3-diaxial interaction with ring B thereby favoring conformation **8t** for protonation at the ring junction. Further protonation of the enolate and reduction affords the single alcohol **9**, which was presumed to have an equatorial hydroxyl group.[29,30] On the other hand, the radical anion **10**, derived from the minor enone **5b**, disfavors conformation **10t** because of the 1,3-allyl/Me interaction. Consequently, the cisoid conformation **10c** undergoes protonation and reduction to form **11**. Thus, the methyl group dictates the stereochemical course of the reduction.

Our first attempt at the construction of the eventual D-ring focused upon an aldol strategy. Ketone **6a**, obtained at the time *via* the Li bronze/*tert*-BuOH procedure, was subjected to ozonolysis in MeOH followed by reductive workup with dimethyl sulfide in the presence of sodium carbonate. These conditions were sufficient to produce a β-hydroxy ketone **12a** of undefined stereochemistry at the hydroxyl center. That the aldol con-

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(20) MVK was added dropwise over 4 h at room temperature. An added precaution was to wrap the flask in Al foil.
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(25) This experiment was conducted on the THP ether derivatives.
(26) For a review on the reduction of α,β-unsaturated compounds with metals in liquid ammonia, see Caine, D. *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1976; 23; pp 1.
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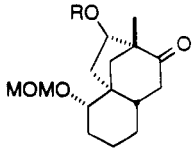
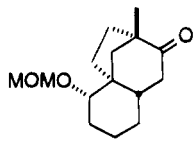
(29) Chetty, G. l.; Krishna Rao, G. S.; Dev, S.; Banerjee, D. K. *Tetrahedron* **1966**, *22*, 2311.
(30) Huffman, J. W.; Charles, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 6486.

Scheme 1

densation occurred at the methine center was apparent from the presence of a methyl singlet at δ 1.14 in the ^{1}H NMR spectrum. The aldol product failed to react with the Burgess reagent[31] in an effort to effect dehydration. Moreover, attempts to convert the hydroxyl group to a halide (PCl_3, pyr; PBr_3, pyr; $POCl_3$, pyr; $SOCl_2$, pyr) were uniformly unsuccessful. Eventually, mesylate **12b** was formed upon exposure of ketol **12a** to excess $MeSO_2Cl$ (7 equiv) and Et_3N (10 equiv) for 12 h at room temperature.[32] The mesylate failed to undergo elimination (DBU, toluene, reflux; *tert*-BuOK, DMSO, 90 °C).



12a, R = H
b, R = Ms
c, R = CS_2Me



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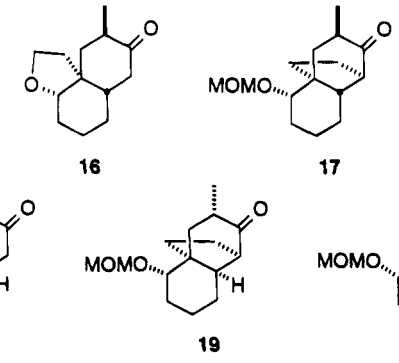
The keto alcohol **12a** also proved inert to NaH (THF, 0 °C) in spite of the concern for retroaldolization. Fortunately, treatment of the substance with LDA under the same conditions of solvent and temperature followed by successive quenching with CS_2 and MeI gave rise to xanthate **12c** albeit in less than ~40% yield. Reduction of the xanthate with *n*-Bu_3SnH in refluxing benzene[33] afforded an intractable mixture. Although the desired tricyclic product could be detected by GC/MS and its presence inferred by ^{1}H NMR when an eventually efficient preparation of ketone **13** was achieved, the aldol route was abandoned in favor of an alternative strategy.

Ozonolysis of unsaturated alcohol **9** followed by reductive workup with $NaBH_4$ provided diol **14a** without incident (Scheme 2). Selective oxidation of the secondary alcohol was achieved by the method of Stevens (NaOCl/HOAc; 85%).[34] Formation of mesylate **14c** from keto alcohol **14b** was straightforward although the chemistry of the mesylate would prove to be more complex.

Intramolecular alkylation of keto mesylate **14c** in the presence of MeONa/MeOH afforded an ~10:1 mixture (83%) of tricyclic ketones **13** and **17**, respectively, in

Scheme 2

addition to 8% of tetrahydrofuran **16**. Ketone **13** could be isolated by crystallization of the mixture. The minor ketone **17** was identified by GC/MS and by a doublet at δ 1.02 in a ^{1}H NMR spectrum of a chromatographed mixture that contained ketone **13**. The tetrahydrofuran **16**, which arises from intramolecular displacement of the mesylate group by the MOM ether, is formed in MeOH in the absence of base and in THF more slowly. This reactivity required the immediate use of the keto mesylate after its preparation. The ratio of ketones **13**:**17** was a function of the base system employed. The ratio decreased with increased base strength and poorer solvating properties of the alcohol: EtONa/EtOH (61:39), *tert*-BuOK/*tert*-BuOH (34:66). An interpretation of these results argues that the bulkier the base, the greater the tendency to deprotonate the methylene site rather than the methine position. Alkylation at the methylene site competes favorably with enolate equilibration. In the case of MeONa/MeOH, equilibration may



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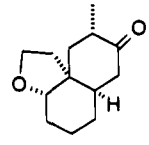

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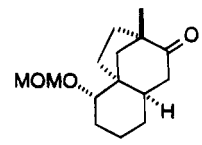

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(31) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224.
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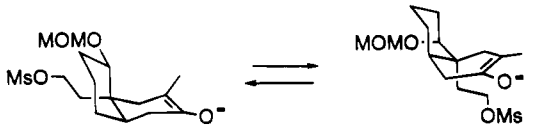
be more rapid than alkylation and/or the less hindered base may deprotonate more effectively at the methine site.

The *cis*-fused alcohol **11** was converted into keto mesylate **15c** (Scheme 2) using the same sequence of reactions employed for the *trans* isomer. Treatment of the keto mesylate with MeONa/MeOH gave tricyclic ketone **20** (67%) and tetrahydrofuran **18** (20%). The ketone arising from the undesired mode of alkylation—namely, **19**—was not detected. The higher yield of tetrahydrofuran **18** produced in the *cis* series relative to tetrahydrofuran **16** in the *trans* series (8%) is real; it is not an artifact of reaction prior to exposure to base. The rate of formation of tetrahydrofuran **18** is relatively unaffected by the conformational flexibility of the *cis*-decalone ring system (**21a** ⇆ **21b**) while the rate of C-alkylation is dependent on access to the conformation



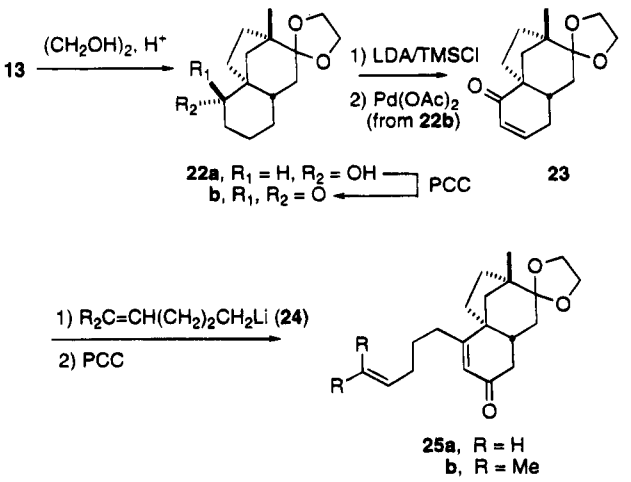
21a **21b**

21b. In addition, the nonidentity of ketones **13** and **20** and the inability to interconvert tetrahydrofurans **16** and **18** in the presence of base confirmed the earlier stereochemical ring junction assignments.

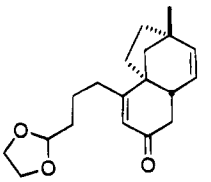
With the foregoing stereochemical issues resolved, construction of ring A was explored. Simultaneous protection of the ketone function of **13** and liberation of the protected alcohol was achieved by ketalization with ethylene glycol in the presence of acid (Scheme 3). The resultant alcohol **22a**, whose structure was confirmed by single crystal X-ray analysis,[35] was readily oxidized with pyridinium chlorochromate (PCC/NaOAc)[36] to afford ketone **22b**. Although formation of α,β-unsaturated ketone **23** could be achieved by selenenylation methods[37-39] from ketone **22b** (LDA; PhSeBr; O_3; Δ) in 76% yield, an operationally simpler strategy was used. The TMS enol ether of ketone **22b**, which proved to be quite stable to aqueous workup, was prepared (LDA; TMSCl) and oxidized with stoichiometric $Pd(OAc)_2$ in CH_3CN. Although the oxidation was sluggish, the desired product was obtained in 90% yield.[40] Efforts to employ catalytic $Pd(OAc)_2$ in the presence of stoichiometric oxidants were unrewarding.[41]

1,2-Addition of 4-pentenyllithium (**24a**)[42] to enone **23** followed by Dauben-Michno oxidative rearrangement[43] provided the transposed enone **25a**. Contrary to Overman's observation in his synthesis of SDA that Me_2CuLi

Scheme 3



was able to undergo 1,4-addition to enone **26**, the use of Me_2CuLi, $Me_2CuCNLi_2/BF_3{\cdot}Et_2O$,[44] or $Me_3Al/Ni(acac)_2$[45] gave either 1,2-addition products or recovered enone. Consequently, Overman's method of choice, the Luche protocol (Me_2Zn, $Ni(acac)_2$, LiBr),[46] was investigated. Although this reagent proved to be reactive toward enone **26** in the Overman study when Et_2O was used as a



26

solvent, to our dismay only an intractable mixture was obtained containing no 1,4-adduct. The use of THF as a solvent afforded only the product of 1,2-addition. The marked difference in regioselectivity of two structurally related enones led us to spectulate that the nickel reagent was coordinating with the monosubstituted olefin in enone **25a**, thereby affecting the course of the reaction. The presence of alkyl substituents on the double bond was considered likely to suppress complexation[47] while their location would have to be at the terminus of the chain to assure that a subsequent ozonolysis would afford an aldehyde. To test this hypothesis, enone **25b** was prepared from enone **23** with 5-methyl-4-hexenyllithium (**24b**), which was prepared by transmetalation[48,49] of the iodide.[50] Rewardingly, the Luche procedure performed admirably providing ketone **27** *via* axial addition of the methyl group from the less congested β-face of the enone (Scheme 4).

Ozonolysis of unsaturated ketone **27** afforded keto aldehyde **28**, which when exposed to KOH in aqueous MeOH at room temperature, gave, in addition to baseline material (TLC), a new substance that was presumed to

(35) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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(47) Conjugate addition under Luche conditions was successful with the 4-methyl-4-pentenyl and (*E*)-4-methyl-4-hexenyl side chain analogs of enone **25a**.

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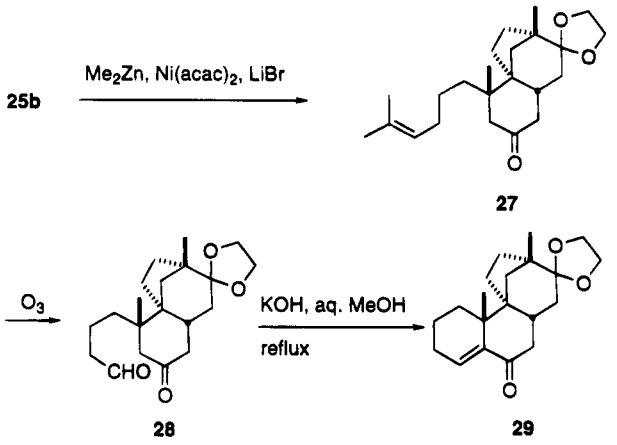
Scheme 4



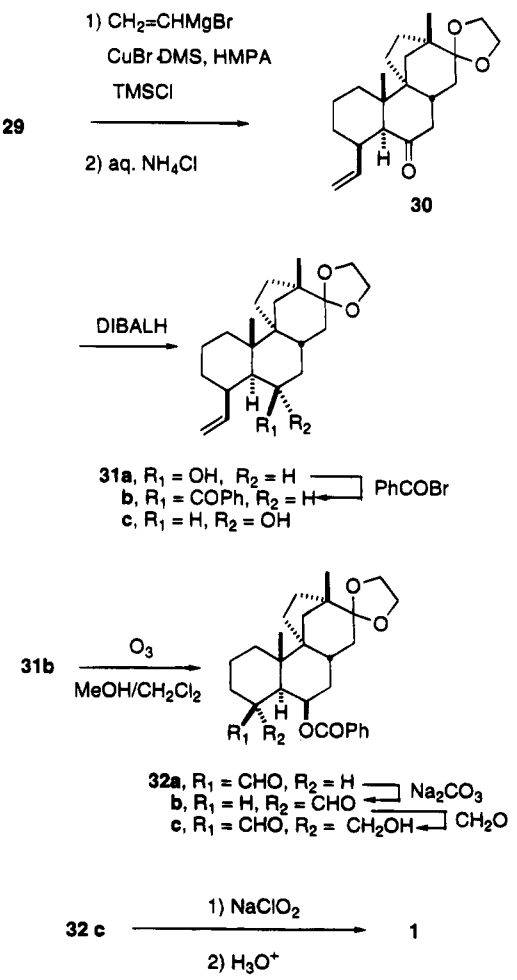
be a tetracyclic aldol product. When the reaction mixture was heated at reflux, a new less polar, UV-active spot appeared on TLC. This substance proved to be the desired enone **29**, albeit isolated in less than 30% yield. Acid-catalyzed cyclodehydration (*p*-TsOH, benzene, reflux) of keto aldehyde **28** was efficient but the formation of enone **29** was accompanied by its deprotected diketone, a product that would not lend itself to an expeditious completion of the syntheses.

Reconsidering the base-catalyzed cyclization, we suspected that at room temperature bimolecular condensations (base line material) were competing with cyclization and that elimination of water from the desired aldol was slow. The solution to the former problem was to decrease the concentration of the substrate while the solution to the latter problem was to increase the rate of dehydration. Consequently, when a solution of the keto aldehyde was added slowly to a refluxing solution of KOH in aqueous MeOH, enone **29** was isolated in 80% yield!

Introduction of the remaining carbons at C_4 and manipulation of the functionality at this site were the remaining operations to be accomplished. Copper-catalyzed 1,4-addition of vinylmagnesium bromide[51] to enone **29** gave rise to the single, saturated ketone **30** (Scheme 5). At this juncture the stereochemistry of this substance could not be ascertained although exposure of the adduct to CD_3ONa/CD_3OD incorporated three atoms of deuterium adjacent to the carbonyl. Apart from the deuterium incorporation, the ^1H NMR spectrum was unaltered indicating that the more stable C_5 epimer had been formed. Molecular mechanics calculations performed on the two C_5 epimers of ketone **30** showed an energy difference of ~0.6 kcal/mol, a value that predicts a mixture upon equilibration. Calculations on the C_4 epimers were ignored because the α-face addition of the cuprate to enone **29** was considered unlikely. Moreover, Overman[16] in his work observed β-face addition of cyanide under similar circumstances.

Reduction of ketone **30** with DIBALH gave a mixture (>3:1) of alcohols wherein the desired axial isomer predominated over the equatorial isomer **31c**.[52] Benzoylation of axial alcohol **31a** was sluggish at room temperature; benzoyl bromide in refluxing pyridine was required. ^1H NMR spectroscopy did not prove useful in

Scheme 5



assessing the C_6 stereochemistry in either the alcohols or the benzoate. In the alcohols the methine hydrogen were masked by the ketal signal while the benzoate methine appeared as a narrow, apparent doublet (J = 2.2 Hz). While this signal was not meaningful for the interpretation of stereochemistry, it was the pattern present in the natural products.

Ozonolysis of benzoate **31b** in CH_2Cl_2/MeOH in the presence of Na_2CO_3 led to a mixture of aldehydes **32a,b**. Prolonged exposure to the buffered conditions produced only the more stable aldehyde **32b**. Deuteration ($NaHCO_3$, $CD_3OD/CDCl_3$) provided the d_1-aldehyde, whose aldehyde proton in its ^1H NMR spectrum collapsed from a doublet to a singlet. Had the AB-ring juncture of these two aldehydes been *cis*, then the kinetic and thermodynamic aldehydes would have been the same equatorial aldehyde. This observation coupled with the successful syntheses demonstrated that aldehyde **32b** was the more stable equatorial isomer and that the AB-ring juncture was indeed *trans*.

After several failed attempts to introduce the remaining carbon of the diterpene skeleton using the kinetic enolate of aldehyde **32b** and formaldehyde equivalents, e.g., (benzyloxy)methyl chloride (BOMCl), a more classical approach prevailed. Exposure of aldehyde **32b** to formalin in the presence of aqueous base produced the single β-hydroxy aldehyde **32c**, the product of equatorial electrophilic addition. In practice, formalin was added to the crude reaction mixture subsequent to ozonolysis to afford the aldol in 80% yield.

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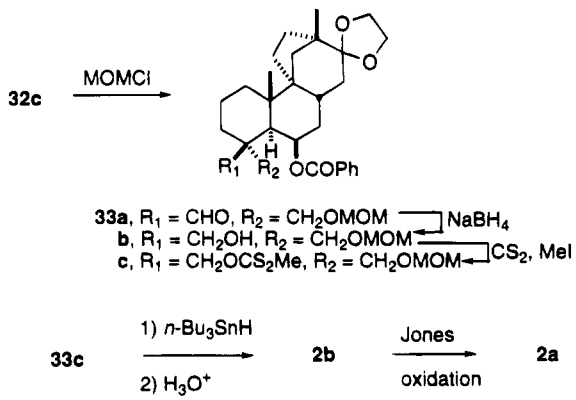
(52) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, *26*, 3307.

Scheme 6



Selective oxidation of the aldehyde group of **32c** with $NaClO_2$,[53,54] and subsequent ketal hydrolysis provided scopadulcic acid A (**1**), whose ^1H and ^{13}C NMR spectra were identical to literature values[7] and spectra of the natural product provided by Professor Hayashi.

Formation of SDB required inversion of the oxidation levels of C_{18} and C_{19} of aldol **32c**. This end was readily achieved (Scheme 6) by protection of the hydroxyl group and conversion of the aldehyde to a methyl group by *n*-Bu_3SnH reduction of the xanthate ester **33c**.[33] This route produced the first synthesis of scopadulciol (**2b**), whose high field ^1H NMR spectrum was identical to a spectrum provided by Professor Hayashi and whose ^{13}C NMR spectrum agreed with reported values.[4,55] Jones oxidation[56] of scopadulciol readily afforded scopadulcic acid B (**2a**), which was identical to a sample of natural material by comparison of ^1H NMR spectra; the ^{13}C NMR spectrum was in accord with literature values.[4,7] The use of the common intermediate, aldol **32c**, confirmed by chemical synthesis the structures of the three natural products, which had been previously interrelated by NMR studies.

Experimental Section

Unless otherwise stated, all reactions were carried out in flame-dried glassware, under a N_2 atmosphere. Ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under N_2. Methylene chloride (CH_2Cl_2), benzene (PhH), diisopropylamine (*i*-Pr_2NEt), hexanes, pyridine, and triethylamine (Et_3N) were distilled from CaH_2. Other solvents (ACS photometric grade) were used without further purification. Commercially available reagents were used as received. Alkyllithiums were titrated by the method of Lipton.[57] Workup means drying over Na_2SO_4 (unless stated otherwise), filtration, and concentration *in vacuo*. Flash chromatography was conducted by the method of Still.[58] Melting points are uncorrected. Infrared spectra (IR) were recorded in $CHCl_3$. Gas chromatography (GC) and GC/MS were conducted with a 0.25 μm film SE-30 column. Low resolution mass spectra (LRMS) were run at 70 eV or 20 eV (EI). High resolution mass spectra were recorded at the University of Illinois, Urbana–Champaign. ^1H NMR spectra were recorded at 300 MHz ($CDCl_3$, δ 7.26); ^{13}C NMR spectra were recorded at 75 MHz ($CDCl_3$, 77.00 ppm) unless otherwise noted. Elemental analyses were conducted by Atlantic Microlabs, Inc., Atlanta, GA.

(±)-(4a*R,5*S**)-4,4a,5,6,7,8-Hexahydro-5-hydroxy-4a-(2-propenyl)naphthalen-2(3*H*)-one (4a).** To a stirred solution of diketone **3b** (61.2 g, 0.3 mol) in 600 mL of EtOH/THF (5:1) at 0 °C was added a solution of $NaBH_4$ (3.4 g, 0.089 mol in 500 mL of EtOH/THF (5:1)) dropwise over 8 h. Acetic acid (10 mL) was added, and the solvent was removed in vacuo. The resulting semisolid mass was dissolved in $CHCl_3$ and washed with water, saturated $NaHCO_3$, and brine. Workup gave a dark red oil (60.5 g, 98%) which solidified on refrigeration for 12 h. The solid was sufficiently pure for the subsequent reaction. A recrystallized sample gave keto alcohol **4a** as a white solid: mp 71.5–72.5 °C (Et_2O/hexanes). IR: 3425, 1662, 1620 cm^{-1}. ^1H NMR: δ 5.84 (s, 1H), 5.72–5.86 (m, 1H), 5.11 (d, *J* = 16.9 Hz, 1H), 5.01 (d, *J* = 9.9 Hz, 1H), 3.52 (dd, *J* = 11.0, 4.9 Hz, 1H), 2.63 (br s, 1H), 2.40–2.60 (m, 3H), 2.25–2.40 (m, 3H), 2.14–2.21 (m, 1H), 1.70–2.00 (m, 4H), 1.38 (qt, *J* = 13.1, 4.6 Hz, 1H). ^{13}C NMR: 200.13, 167.28, 134.55, 126.33, 117.70, 77.62, 44.95, 35.80, 34.05, 32.28, 30.92, 29.94, 23.90. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.72; H, 8.84.

(±)-(4a*R,5*S**)-4,4a,5,6,7,8-Hexahydro-5-[(methoxymethyl)oxy]-4a-(2-propenyl)naphthalen-2(3*H*)-one (4b).** To a stirred solution of keto alcohol **4a** (8.24 g, 40 mmol) and *i*-Pr_2NEt (17.5 mL, 100 mmol) in 170 mL of CH_2Cl_2 at room temperature was added (chloromethyl)methyl ether (MOMCl, 5 mL, 66 mmol) dropwise over 4 h. After stirring the reaction mixture for 12 h an additional 1.1 mL of MOMCl (13 mmol) was added. Stirring was continued for 12 h. Excess NH_4OH was added, and the reaction mixture was diluted with CH_2Cl_2 and washed with water, ice-cold 5% HCl, water, and brine. Workup and flash chromatography (0–10% EtOAc/hexanes) yielded 7.60 g (76%) of a pale yellow oil that solidified on refrigeration. Recrystallization afforded acetal **4b** as a colorless solid: mp 39.5–40 °C (Et_2O/hexanes). IR: 1662, 1620 cm^{-1}. ^1H NMR: δ 5.75 (s, 1H), 5.62–5.75 (m, 1H), 5.01 (d, *J* = 16.8 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 6.9 Hz, 1H), 4.49 (d, *J* = 6.9 Hz, 1H), 3.32 (dd, *J* = 11.6, 4.7 Hz, 1H), 3.27 (s, 3H), 2.32–2.52 (m, 3H), 2.06–2.29 (m, 4H), 1.76-1.93 (m, 3H), 1.63 (qd, *J* = 12.4, 4.0 Hz, 1H), 1.26 (qt, *J* = 13.3, 4.3 Hz, 1H). ^{13}C NMR: 199.01, 165.63, 134.55, 126.33, 117.28, 95.50, 83.09, 55.40, 44.28, 36.41, 33.98, 32.14, 31.10, 26.84, 23.61. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.83; H, 8.85.

(±)-(3*R,4a*S**,5*S**)-4,4a,5,6,7,8-Hexahydro-5-[(methoxymethyl)oxy]-3-methyl-4a-(2-propenyl)naphthalen-2(3*H*)-one (5a).** LDA was prepared by adding *n*-BuLi (16.2 mL, 1.31 M, 21 mmol) dropwise to a stirred solution of *i*-Pr_2NH (3.15 mL, 22.5 mmol) in 30 mL of THF at 0 °C. The solution was cooled to −78 °C, and a solution of enone **4b** (3.73 g, 15 mmol) in 25 mL of THF was added dropwise over 10 min. After stirring the mixture for an additional 15 min, MeI (1.9 mL, 30 mmol) was added in one portion and stirring was continued for 12 h at −20 °C. Saturated $NaHCO_3$ (2 mL) was added and the solvent was removed. The residue was dissolved in CH_2Cl_2 and washed with ice-cold 5% HCl, saturated $NaHCO_3$, water, and brine. Workup gave a yellow semisolid that was purified by flash chromatography (0–20% EtOAc/hexanes), yielding 0.34 g of unreacted starting material and 3.35 g (85% yield) of an inseparable, solid mixture, which was analyzed by GC/MS and found to be a mixture (~5.7:1) of monomethylated diastereomers. The product was also contaminated by ~2% of a dimethylated product. Recrystallization gave the major diastereomer **5a** as white crystals: mp 49–50 °C (Et_2O/hexanes). IR: 1667, 1626 cm^{-1}. ^1H NMR: δ 5.84–5.96 (m, 1H), 5.83 (s, 1H), 5.12 (br d, *J* = 16.9 Hz, 1H), 5.00 (br d, *J* = 9.7 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.38 (s, 3H), 3.27 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.49–2.67 (m, 3H), 2.40 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.15–2.35 (m, 2H), 1.86–2.00 (m, 2H), 1.72 (qd, *J* = 12.4, 3.8 Hz, 1H), 1.56 (t, *J* = 14.0 Hz, 1H), 1.37 (qt, *J* = 13.1, 4.2 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: 201.28, 164.26, 135.53, 126.13, 116.78, 95.91, 86.08, 55.52, 45.07, 42.71, 37.47, 36.79, 31.94, 27.18, 23.19, 14.79. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.68; H, 9.16.

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(±)-(3*R,4a*S**,5*S**,8a*S**)-5-[(Methoxymethyl)oxy]-3-methyl-1,4,4a,5,6,7,8,8a-octahydro-4a-(2-propenyl)naphthalen-2(3*H*)-one (6a).** To a three-necked flask fitted with a dry ice condenser was added freshly cut and washed (hexanes) Li wire (300 mg, 43 mmol). The flask was cooled to −78 °C and enough anhydrous NH_3 was condensed to dissolve the lithium.[23] After adding THF (20 mL), a solution of enones **5a,b** (GC, 4.5:1; 2.64 g, 10 mmol) and *tert*-BuOH (3.8 mL, 40 mmol) in THF (20 mL) was then added dropwise to the Li bronze with stirring. The mixture was stirred for an additional 20 min. Solid NH_4Cl was added to destroy excess Li, and the NH_3 was allowed to evaporate at room temperature under a stream of N_2. The THF was removed, and the resulting white residue was diluted with CH_2Cl_2 and water. The organic phase was washed with water and brine. Workup and flash chromatography (0−10% EtOAc/hexanes) gave 2.21 g (83%) of ketones **6a** and **7** (4.5:1) as a white solid. Recrystallization of a sample gave white crystals of ketone **6a**: mp 63−64 °C (Et_2O/hexanes). IR: 1703, 1636 cm^{-1}. ^1H NMR: δ 6.23 (dtd, *J* = 17.2, 10.1, 4.3 Hz, 1H), 4.91−5.01 (m, 2H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.50 (d, *J* = 6.8 Hz, 1H), 3.29 (s, 3H), 3.15 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.58 (br d, *J* = 14.7 Hz, 1H), 2.16−2.44 (m, 4H), 2.09 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.49−1.87 (m, 4H), 1.13−1.32 (m, 3H), 0.90−1.01 (m, 1H), 0.89 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR: 212.28, 137.10, 115.43, 95.50, 85.78, 55.32, 46.23, 43.66, 43.35, 40.70, 40.31, 30.69, 27.03, 26.96, 24.11, 14.27. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.88.

(±)-(4*S,4a*R**,7*R**,9a*S**)-6-Hydroxy-4-[(methoxymethyl)oxy]-7-methyl-1,4,4a,5,6,7,9,9a-octahydro-[4a,7]-methano-[4a*H*]benzocyclohepten-8(5*H*)-one (12a).** Ozone was passed through a solution of ketone **6a** (1.60 g, 6 mmol) and Na_2CO_3 (150 mg, 1.4 mmol) in 30 mL of MeOH at −78 °C until a blue color persisted. The flask was purged with N_2 for 10 min before the addition of dimethyl sulfide (4.43 mL, 60 mmol). After stirring the reaction mixture at −78 °C for 30 min, it was allowed to warm to room temperature for 12 h. The solvent was removed, and the resulting white solid was dissolved in CH_2Cl_2 and washed with water. Workup and flash chromatography (0−50% EtOAc/hexanes) gave 1.02 g of ketol **12a** (63% yield) and 0.48 g of an inseparable mixture that presumably contained other cyclization isomers. A sample of **12a** was recrystallized affording white crystals: mp 110−111 °C (Et_2O/hexanes). IR: 3454, 1703 cm^{-1}. ^1H NMR: δ 4.77 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.15 (dd, *J* = 10.7, 4.7 Hz, 1H), 3.38 (s, 3H), 3.28 (dd, *J* = 11.0, 4.0 Hz, 1H), 2.15−2.51 (m, 4H), 1.94 (br d, *J* = 8.9 Hz, 1H), 1.60−1.79 (m, 4H), 1.46 (br d, *J* = 7 Hz, 1H), 1.17−1.37 (m, 4H), 1.14 (s, 3H). ^{13}C: 211.42, 95.42, 79.68, 79.14, 57.43, 55.27, 47.16, 45.32, 44.23, 43.52, 31.73, 29.09, 28.77, 23.53, 17.68. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.14; H, 9.00.

(±)-(2*R,3*R**,4a*S**,5*S**,8a*S**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5-[(methoxymethyl)oxy]-3-methyl-4a-(2-propenyl)-naphthalen-2-ol (9) and (±)-(2*S**,3*S**,4a*S**,5*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5-[(methoxymethyl)oxy]-3-methyl-4a-(2-propenyl)naphthalen-2-ol (11).** Li bronze[23] was prepared from Li wire (3.86 g, 0.55 mol) (vide supra). THF (130 mL) was added to the stirred mixture followed by the dropwise addition over 30 min of a solution of enones **5a,b** (5.7:1; 18.2 g, 0.07 mol) and MeOH (16.7 mL, 0.41 mol) in 100 mL of THF. The reaction mixture was stirred at −78 °C for 4 h. Excess Li bronze was destroyed by the addition of MeOH (10 mL). The dry ice/acetone bath was removed, and the excess NH_3 was allowed to evaporate in a stream of N_2. The reaction mixture was concentrated and diluted with CH_2Cl_2 and water. The organic phase was washed with water and brine. Workup and flash chromatography (0−30% EtOAc/hexanes) gave 14.4 g (78%) of alcohol **9**, which solidified on prolonged refrigeration to give a white, waxy solid. Recrystallization gave pure material: mp 54−56 °C (Et_2O/hexanes). IR: 3618, 3464, 1634 cm^{-1}. ^1H NMR: δ 6.14 (dtd, *J* = 17.1, 10.1, 4.6 Hz, 1H), 4.91−5.00 (m, 2H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 3.35 (s, 3H), 3.11−3.17 (m, 2H), 2.44 (br d, *J* = 14.6 Hz, 1H), 2.04−2.14 (m, 2H), 1.15−1.87 (m, 11H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.64 (t, *J* = 12.0 Hz, 1H). ^{13}C NMR: 137.15, 114.71, 95.43, 86.44, 76.13, 55.13, 43.71, 41.39, 40.81, 36.98, 34.24, 30.91, 27.12, 26.64, 24.34, 18.55. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.66; H, 10.56. Further elution gave 2.44 g (13%) of alcohol **11** as a white solid, which was recrystallized from Et_2O: mp 59−60 °C. IR: 3620, 3466, 1636 cm^{-1}. ^1H NMR: δ 5.72−5.86 (m, 1H), 5.00−5.06 (m, 2H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.51 (d, *J* = 6.9 Hz, 1H), 3.94 (dd, *J* = 10.4, 4.7 Hz, 1H), 3.35 (s, 3H), 3.12 (td, *J* = 10.0, 4.5 Hz, 1H), 2.40 (dd, *J* = 14.1, 8.0 Hz, 1H), 2.10 (dd, *J* = 14.1, 7.1 Hz, 1H), 1.48−1.84 (m, 11H), 1.15 (br d, *J* = 13.0 Hz, 1H), 0.89−1.00 (m, 4H). ^{13}C NMR: 134.67, 117.06, 94.72, 76.24, 73.97, 55.18, 40.07, 38.29, 36.72, 36.19, 35.51, 34.28, 26.59, 25.53, 19.81, 18.23. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.69; H, 10.50.

(±)-(2*R,3*R**,4a*R**,5*S**,8a*S**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-4a-(2-hydroxyethyl)-5-[(methoxymethyl)oxy]-3-methylnaphthalen-2-ol (14a).** Ozone was passed through a solution of alcohol **9** (13.9 g, 52 mmol) in 300 mL of EtOH at −78 °C until a blue color was visible. The solution was purged with N_2 for 10 min before $NaBH_4$ (4.8 g, 130 mmol) was added. The reaction mixture was stirred while warming to room temperature over 12 h. The solvent was removed, and the white solid was dissolved in CH_2Cl_2 and was washed with water and brine. Workup and flash chromatography (0−60% EtOAc/hexanes) yielded 10.58 g (75%) of diol **14a**. Recrystallization of a sample gave white crystals: mp 98−99 °C (Et_2O). IR: 3620, 3424, 1452 cm^{-1}. ^1H NMR: δ 4.73 (d, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 4.05 (dd, *J* = 9.7, 1.3 Hz, 1H), 3.56−3.76 (m, 2H), 3.37 (s, 3H), 3.10−3.21 (m, 2H), 2.15 (dd, *J* = 13.9, 3.4 Hz, 1H), 1.61−1.97 (m, 7H), 1.14−1.45 (m, 6H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.73 (t, *J* = 13.0 Hz, 1H). ^{13}C NMR: 95.22, 85.84, 75.77, 57.86, 55.52, 44.24, 40.45, 36.61, 34.60, 27.84, 26.64, 26.20, 24.25, 18.56. Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.15; H, 10.36. Found: C, 66.04; H, 10.39.

(±)-(2*S,3*S**,4a*R**,5*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-4a-(2-hydroxyethyl)-5-[(methoxymethyl)oxy]-3-methylnaphthalen-2-ol (15a).** Alcohol **11** (2.05 g, 7.6 mmol) was ozonized and reduced as described for alcohol **9**. The product was purified by flash chromatography (0−60% EtOAchexanes) to yield 1.73 g (83%) of diol **15a** as a white solid. A sample was recrystallized from MeOH/Et_2O: mp 95−96 °C. IR: 3622, 3425 cm^{-1}. ^1H NMR: δ 4.74 (d, *J* = 7.1 Hz, 1H), 4.54 (d, *J* = 7.1 Hz, 1H), 3.97 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.76 (br t, *J* = 9.8 Hz, 1H), 3.67 (br d, *J* = 10.0 Hz, 1H), 3.44−3.58 (m, 1H), 3.35 (s, 3H), 3.15 (br m, 1H), 2.37 (ddd, *J* = 14.6, 9.7, 4.6 Hz, 1H), 2.11 (dd, *J* = 14.0, 3.5 Hz, 1H), 1.92 (br s, 1H), 1.72−1.87 (m, 2H), 1.50−1.70 (m, 7H), 1.14−1.24 (m, 2H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.73 (t, *J* = 13.3 Hz, 1H). ^{13}C NMR: 94.60, 75.96, 74.61, 58.05, 55.56, 42.29, 39.61, 39.01, 38.94, 36.63, 34.08, 26.82, 25.71, 20.38, 18.33. Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 65.96; H, 10.41.

(±)-(3*S,4a*R**,5*S**,8a*R**)-4a-(2-Hydroxyethyl)-5-[(methoxymethyl)oxy]-3-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1*H*)-one (15b).** To a stirred solution of diol **15a** (1.45 g, 5.3 mmol) in 30 mL of glacial HOAc at room temperature was added 10 mL of commercial bleach (5.25% NaOCl, ~7 mmol) dropwise over 1 h.[34] The reaction mixture was stirred for an additional 1 h before 15 mL of *i*-PrOH was added. The solution was concentrated, and the resulting residue was dissolved in CH_2Cl_2 and was washed with water, aqueous $NaHCO_3$, water, and brine. Workup and flash chromatography (0−50% EtOAc/hexanes) gave 1.15 g (80%) of keto alcohol **15b** as a colorless oil that solidified on prolonged refrigeration. Recrystallization gave analytical material: mp 56−58 °C (Et_2O/hexanes). IR: 3442, 1708 cm^{-1}. ^1H NMR: δ 4.82 (d, *J* = 7.2 Hz, 1H), 4.58 (d, *J* = 7.2 Hz, 1H), 4.18 (dd, *J* = 11.5, 4.7 Hz, 1H), 3.76 (br t, *J* = 9.1 Hz, 1H), 3.51−3.62 (m, 1H), 3.41 (s, 1H), 3.38 (s, 3H), 2.57−2.70 (m, 2H), 2.47 (dd, *J* = 13.7, 5.5 Hz, 1H), 2.37 (ddd, *J* = 14.7, 9.3, 5.1 Hz, 1H), 1.67−2.05 (m, 6H), 1.56 (app tt, *J* = 13.8, 4.3 Hz, 1H), 1.32 (dt, *J* = 15.0, 4.6 Hz, 1H), 1.07−1.18 (m, 2H), 0.99 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR: 212.83, 94.40, 73.73, 57.88, 55.59, 44.34, 42.52, 41.26, 39.57, 39.25, 37.41, 26.22, 25.28, 19.49, 13.90. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.52; H, 9.69.

(±)-(4*S,4a*S**,7*S**,9a*R**)-4-[(Methoxymethyl)oxy]-7-methyl-1,2,3,4,6,7,9,9a-octahydro-[4a,7]methano-[4a*H*]benzo-

cyclohepten-8(5*H*)-one (20) and (±)-(3a*S,6a*R**,9*S**,-10a*R**)-1,2,4,5,6,6a,7,8,9,10-Decahydro-9-methyl[10a*H*]-naphtho[1,8a-b]furan-8(3a*H*)-one (18).** To a stirred solution of keto alcohol **15b** (0.756 g, 2.8 mmol) and Et_3N (0.78 mL, 5.6 mmol) in 25 mL of CH_2Cl_2 at 0 °C was added MsCl (0.28 mL, 3.6 mmol). After 20 min, the mixture was diluted with CH_2Cl_2 and washed with water, ice cold 5% HCl, water, and brine. Workup gave the crude mesylate **15c** as a pale yellow oil. ^{1}H NMR: δ 4.75 (d, *J* = 7.1 Hz, 1H), 4.51 (d, *J* = 7.1 Hz, 1H), 4.45 (td, *J* = 10.2, 5.9 Hz, 1H), 4.27 (td, *J* = 10.2, 5.6 Hz, 1H), 4.10–4.15 (m, 1H), 3.35 (s, 3H), 2.97 (s, 3H), 2.54–2.68 (m, 2H), 2.32–2.42 (m, 2H), 1.94–2.07 (m, 3H), 1.49–1.85 (m, 5H), 1.15–1.24 (m, 2H), 0.99 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR: 212.10, 94.37, 73.29, 67.16, 55.52, 43.26, 42.42, 41.10, 39.80, 39.22, 37.09, 33.66, 26.32, 25.38, 19.20, 13.86. LRMS (CI): 348 (M^+).

The crude mesylate in 2.5 mL of dry THF was added dropwise over 3 h to a solution containing 1.5 mL of 25% NaOMe/MeOH in 30 mL of MeOH. The solution was stirred for an additional 3 h. Acetic acid (1.5 mL) was added, and the solvent was removed. The residue was dissolved in CH_2Cl_2 and was washed with water, aqueous $NaHCO_3$, water, and brine. Workup and flash chromatography (0–20% EtOAc/hexanes) afforded 0.474 g (67%) of tricyclic ketone **20** as a colorless oil. IR: 1701, 1462 cm^{-1}. ^{1}H NMR: δ 4.70 (d, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 6.9 Hz, 1H), 3.51 (br s, 1H), 3.38 (s, 3H), 2.70 (dd, *J* = 16.3, 8.7 Hz, 1H), 2.20–2.30 (br m, 1H), 1.88–1.99 (m, 4H), 1.73–1.82 (m, 2H), 1.27–1.68 (m, 7H), 1.07 (s, 3H). ^{13}C NMR: 214.50, 94.83, 79.98, 55.40, 53.68, 48.15, 43.85, 42.07, 38.42, 36.31, 35.05, 28.98, 26.91, 19.92, 19.62. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.23; H, 9.62. Further elution gave 0.116 g (20%) of ether **18** as a colorless oil, which solidified on prolonged refrigeration. Recrystallization gave a white solid: mp 40–40.5 °C (Et_2O–hexanes). IR: 1709, 1456 cm^{-1}. ^{1}H NMR: δ 3.89–4.06 (m, 2H), 3.46 (br s, 1H), 2.73 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.50 (app septet, *J* = 6.5 Hz, 1H), 2.32–2.40 (m, 1H), 2.07 (dd, *J* = 13.9, 1.6 Hz, 1H), 1.72–1.97 (m, 4H), 1.41–1.58 (m, 5H), 1.13 (td, *J* = 9.0, 4.0 Hz, 1H), 0.99 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR: 212.27, 81.11, 64.78, 44.20, 43.14, 42.36, 39.54, 38.57, 37.31, 28.30, 25.18, 20.33, 14.15. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.08; H, 9.77.

(±)-(3*R,4a*R**,5*S**,8a*S**)-4a-(2-Hydroxyethyl)-5-[(methoxymethyl)oxy]-3-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1*H*)-one (14b).** Diol **14a** (5.1 g, 18.7 mmol) was oxidized as described for diol **15a** (vide supra) to give 3.96 g (78%) of keto alcohol **14b** as a white solid after flash chromatography (0–50% EtOAc/hexanes). A sample was recrystallized from Et_2O/MeOH: mp 78.5–80 °C. IR: 3426, 1706 cm^{-1}. ^{1}H NMR: δ 4.75 (d, *J* = 7.0 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 3.95 (dd, *J* = 9.8, 2.0 Hz, 1H), 3.70–3.90 (m, 2H), 3.38 (s, 3H), 3.25 (dd, *J* = 11.1, 4.1 Hz, 1H), 2.51 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.27–2.38 (m, 2H), 2.08–2.19 (m, 2H), 1.61–1.92 (m, 5H), 1.20–1.41 (m, 3H), 1.11 (t, *J* = 15.5 Hz, 1H), 1.02 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR: 211.36, 95.40, 85.41, 58.20, 55.65, 46.76, 43.35, 42.33, 40.52, 27.54, 26.57, 24.08, 14.25. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.75; H, 9.76.

(±)-(4*S,4a*S**,7*S**,9a*S**)-4-[(Methoxymethyl)oxy]-7-methyl-1,2,3,4,5,6,7,8,8a-octahydro-[4a,7]methano[4a*H*]benzocyclohepten-8(5*H*)-one (13) and (±)-(3a*S**,6a*S**,9*R**,-10a*R**)-1,2,4,5,6,6a,7,8,9,10-Decahydro-9-methyl-[10a*H*]-naphtho[1,8a-*b*]furan-8(3a*H*)-one (16).** Keto alcohol **14b** (2.92 g, 10.8 mmol) was derivatized as described for keto alcohol **15b** to afford mesylate **14c** as a pale yellow oil. ^{1}H NMR: δ 4.73 (td, *J* = 10.5, 6.0 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 4.51 (d, *J* = 6.9 Hz, 1H), 4.39 (td, *J* = 10.5, 5.7 Hz, 1H), 3.32 (s, 3H), 3.18 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.00 (s, 3H), 2.01–2.52 (m, 6H), 1.79–1.92 (m, 2H), 1.50-1.63 (m, 2H), 1.24–1.37 (m, 3H), 1.09 (t, *J* = 13.8 Hz, 1H), 1.02 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR: 210.78, 95.18, 84.97, 67.94, 55.36, 46.18, 43.33, 42.23, 40.36, 37.12, 26.67, 26.61, 25.08, 23.76, 14.22. LRMS (CI): 253 (M^+ − OMs).

Cyclization of the mesylate was accomplished as described for mesylate **15c**. The crude product was purified by flash chromatography (0–20% EtOAc/hexanes) to give 2.26 g (83%) of tricyclic ketones **13** and **17** (~10:1) as an inseparable mixture along with ether **16**. An analytical sample of ketone **13** was prepared by crystallization: mp 34–34.5 °C (Et_2O/hexanes). IR: 1701, 1459 cm^{-1}. ^{1}H NMR: δ 4.75 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 3.36 (s, 3H), 3.34 (m, 1H), 2.27 (dd, *J* = 15.8, 6.1 Hz, 1H), 1.87–2.15 (m, 4H), 1.59–1.77 (m, 5H), 1.42 (br d, *J* = 12 Hz, 1H), 1.18–1.30 (m, 4H), 1.08 (s, 3H). ^{13}C NMR: 213.54, 95.39, 78.69, 55.28, 52.21, 49.30, 47.63, 44.61, 42.26, 35.94, 28.99, 28.86, 23.59, 22.13, 19.42. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.33; H, 9.54. Further elution gave 177 mg (8%) of ether **16** as a colorless oil: IR: 1702, 1455 cm^{-1}. ^{1}H NMR: δ 3.92–4.05 (m, 2H), 3.50–3.55 (m, 1H), 2.45 (app septet, *J* = 6.4 Hz, 1H), 2.00–2.26 (m, 4H), 1.85–1.93 (m, 1H), 1.64–1.79 (br m, 3H), 1.16–1.37 (m, 5H), 1.00 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR: 211.10, 82.66, 64.40, 46.24, 46.05, 44.74, 42.14, 41.32, 27.97, 27.25, 25.60, 22.60, 14.09. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found C, 74.76; H, 9.69.

(±)-(4′*S,4a′*S**,7′*S**,9′a*S**)-7′-Methyl-1′,2′,3′,4′,6′,7′,9′,9′a-octahydro-spiro[1,3-dioxolane-2,8′(5′*H*)-[4a′,7′]methano-[4a′*H*]benzocycloheptenl-4′-ol (22a).** A solution of tricyclic ketones **13** (2.09 g, 8.3 mmol, contaminated with ketone **17**) in 40 mL of benzene containing ethylene glycol (4.6 mL, 83 mmol) and *p*-toluenesulfonic acid (79 mg, 0.4 mmol) was heated at refux for 12 h using a Dean–Stark trap. The solvent was removed and the resulting white solid was dissolved in CH_2Cl_2. The solution was washed with saturated $NaHCO_3$, water, and brine. Workup and flash chromatography (0–20% EtOAc/hexanes) gave 1.93 g (92%) of ketal alcohol **22a** as a white solid. Recrystallization gave colorless needles: mp 127–129 °C (Et_2O). IR: 3615, 1451 cm^{-1}. ^{1}H NMR: δ 3.76–4.00 (m, 4H), 3.45 (dd, *J* = 11.4, 3.9 Hz, 1H), 1.58–1.78 (m, 7H), 1.02–1.49 (m, 9H), 0.96 (s, 3H). ^{13}C NMR: 112.93, 73.28, 65.20, 64.81, 49.34, 47.18, 45.37, 41.23, 37.64, 34.43, 32.30, 28.64, 23.95, 21.01, 19.15. LRMS (EI): 252 (M^+). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.67.

(±)-(4a′*S,7′*S**,9a′*S**)-1′,2′,6′,7′,9′,9′a-Hexahydro-7′-methyl-8-oxo-spiro[1,3-dioxolane-2,8′(5′*H*)-[4a′,7′]methano[4a′*H*]-benzocyclohepten]-4′(3′*H*)-one (22b).** To a stirred solution of ketal alcohol **22a** (1.23 g, 4.9 mmol) and NaOAc (0.64 g, 7.8 mmol) in 35 mL of CH_2Cl_2 was added pyridinium chlorochromate (1.58 g, 7.3 mmol).[36] The reaction mixture was stirred at room temperature for 12 h. The product was diluted with Et_2O, filtered through a pad of Florisil and washed with Et_2O until no product was detected in the washings by TLC. Removal of the solvent and flash chromatography (0–10% EtOAc/hexanes) yielded 1.19 g (98%) of ketone **22b** as a white solid. A sample was recrystallized from Et_2O/hexanes: mp 71–72 °C. IR: 1698, 1454 cm^{-1}. ^{1}H NMR: δ 3.75–4.00 (m, 4H), 2.22–2.31 (m, 2H), 1.37–2.01 (m, 13H), 0.97 (s, 3H). ^{13}C NMR: 213.43, 111.93, 65.19, 64.81, 56.69, 47.79, 43.17, 42.84, 39.86, 37.25, 34.10, 29.13, 28.16, 25.54, 18.78. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.84; H, 8.90.

(±)-(4a′*S,7′*S**,9a′*S**)-7′-Methyl-6′,7′,9′,9′a-tetrahydro-spiro[1,3-dioxolane-2,8′(5′*H*)-[4a′,7′]methano[4a′*H*]-benzocyclohepten]-4′(1′*H*)-one (23).** To a solution of dry diisopropylamine (0.39 mL, 2.8 mmol) in 15 mL of THF at 0 °C was added *n*-BuLi (1.8 mL of 1.45M, 2.6 mmol) dropwise. A solution of ketone **22b** (500 mg, 2.0 mmol) in THF (5 mL) was added dropwise to the LDA solution at −78 °C. After stirring the reaction mixture for 20 min, TMSCl (0.36 mL, 2.8 mmol) was added in one portion. The reaction mixture was warmed to 0 °C and was quenched with saturated $NaHCO_3$. The solvent was removed, and the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ and water. Workup gave the crude silyl enol ether, which was dissolved in 15 mL of dry CH_3CN. $Pd(OAc)_2$ (0.54 g, 2.4 mmol) was added, and the mixture was stirred at room temperature for 36 h and then was heated at ~50 °C for 8 h. The reaction mixture was cooled, concentrated, and purified by flash chromatography (0–10% EtOAc/hexanes), yielding 444 mg (90%) of enone **23** as a yellow solid. Recrystallization gave **23** as a white solid: mp 102–103 °C (Et_2O). IR: 1663, 1454 cm^{-1}. ^{1}H NMR: δ 6.82–6.88 (m, 1H), 5.95–5.99 (m, 1H), 3.76–4.01 (m, 4H), 2.08–2.26 (m, 4H), 1.70–1.91 (m, 3H), 1.40–1.64 (m, 4H), 1.02 (s, 3H). ^{13}C NMR: 202.27, 148.35, 129.26, 111.77, 65.23, 64.84, 52.84, 48.37, 44.01, 38.45, 37.12, 34.11, 29.48,

27.94, 18.72. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.48; H, 8.17.

(±)-(4a′S*,7′S*,9a′S*)-7′-Methyl-4′-[4″-pentenyl]-6′,7′,9′,9′a-tetrahydrospiro[1,3-dioxolane-2,8′(5′H)-[4a′,7′]methano-[4a′H]benzocycloheptenl-2′(1′H)-one (25a). A solution of 4-pentenyllithium[42] was prepared by adding a solution of 5-bromo-1-pentene (1 mL, 8.4 mmol) in 3 mL of dry Et_2O to a sonicated suspension of finely cut Li wire (0.25 g) in 4 mL of Et_2O. The mixture was sonicated for 1 h. Approximately 2 mL of the lithium reagent was added to a solution of enone **23** (225 mg, 0.9 mmol) in dry Et_2O (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature before quenching with saturated NH_4Cl. Dilution with CH_2Cl_2 and washing with water and brine followed by workup ($MgSO_4$) gave a crude product that was dissolved in CH_2Cl_2 (4.8 mL) and DMF (0.2 mL). Pyridinium chlorochromate (600 mg, 2.8 mmol)[36] was added, and the reaction mixture was heated at reflux for 12 h. Dilution of the mixture with EtOAc, washing with water, workup ($MgSO_4$), and flash chromatography (0–15% EtOAc/hexanes) gave 228 mg (80%) of enone **25a**. Recrystallization from Et_2O/hexanes gave white crystals: mp 63–64 °C. IR: 1659, 1611 cm^{-1}. ^1H NMR: δ 5.84 (s, 1H), 5.74–5.85 (m, 1H), 4.97–5.05 (m, 2H), 3.79–4.02 (m, 4H), 2.06-2.25 (m, 7H), 1.40–1.90 (m, 10H), 1.04 (s, 3H). ^{13}C NMR: 198.55, 168.89, 137.74, 125.84, 115.10, 111.58, 65.32, 64.90, 48.80, 47.95, 46.04, 40.16, 40.06, 37.32, 34.24, 33.17, 31.00, 28.06, 27.03, 19.24. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.80; H, 8.99.

(±)-(4a′S*,7′S*,9a′S*)-7′-Methyl-4′-(5″-methyl-4″-hexenyl)-6′,7′,9′,9′a-tetrahydrospiro[1,3-dioxolane-2,8′(5′H)-[4a′,7′]-methano[4a′H]benzocyclohepten]-2′(1′H)-one (25b). To a stirred solution of 6-iodo-2-methyl-2-hexene (1.08 g, 4.8 mmol) in 35 mL of Et_2O at −78 °C was added *tert*-BuLi (6.5 mL of 1.5 M, 9.7 mmol) dropwise over 5 min.[48,49] After stirring the reaction mixture at −78 °C for 20 min and at room temperature for 45 min, a solution of enone **23** (600 mg, 2.4 mmol) in 5 mL of Et_2O was added to the lithium reagent. Stirring was continued at room temperature for 20 min before the addition of aqueous $NaHCO_3$. The reaction mixture was diluted with Et_2O and washed with water and brine. Workup gave a crude product that was dissolved in 20 mL of CH_2Cl_2 containing ~1 mL of DMF. Pyridinium chlorochromate (1.57 g, 7.3 mmol)[36] was added, and the reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with ether and passed through a short column of Florisil until the Et_2O washings were free of product by TLC. Flash chromatography (0–30% EtOAc/hexanes) yielded 32 mg (4%) of pure 1,4-adduct as a colorless oil: IR: 2931, 1696, 1452 cm^{-1}. ^1H NMR: δ 5.02–5.09 (m, 1H), 3.78–4.02 (m, 4H), 2.46 (dd, J = 13.6, 5.7 Hz, 1H), 2.19 (br d, J = 13.6 Hz, 1H), 1.67 (s, 3H), 1.58 (s, 3H), 1.58–2.07 (m, 10H), 1.24–1.50 (m, 8H), 0.99 (s, 3H). ^{13}C NMR: 214.02, 131.53, 124.38, 112.25, 65.41, 65.09, 56.81, 48.21, 44.58, 42.88, 38.02, 37.50, 35.56, 34.23, 32.35, 32.10, 29.41, 27.87, 27.73, 25.70, 18.97, 17.71. HRMS (CI) Calcd for $C_{22}H_{35}O_3$ $(M + H)^+$: 347.2586. Found: 347.2587.

Further elution gave 695 mg (84%) of enone **25b** as a colorless oil. IR: 2959, 1658, 1613 cm^{-1}. ^1H NMR: δ 5.83 (s, 1H), 5.09 (br t, J = 6.8 Hz, 1H), 3.79–4.02 (m, 4H), 1.98–2.25 (m, 7H), 1.69 (s, 3H), 1.59 (s, 3H), 1.36–1.90 (m, 10H), 1.04 (s, 3H). ^{13}C NMR: 198.72, 169.32, 132.25, 125.83, 123.62, 111.69, 65.40, 64.93, 48.83, 48.00, 46.12, 40.23, 40.12, 37.38, 34.31, 31.34, 28.20, 28.11, 27.62, 25.63, 19.31, 17.69. Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.44; H, 9.37.

(±)-(4′S*,4a′S*,7′S*,9a′S*)-3′,4′,6′,7′,9′,9′a-Hexahydro-4′-(5″-methyl-4″-hexenyl)-4′,7′-dimethylspiro[1,3-dioxolane-2,8′(5′H)-[4a′,7′]methano[4a′H]benzocyclohepten]-2′(1′H)-one (27). To a stirred solution of enone **25b** (660 mg, 1.9 mmol) in Et_2O (15 mL) containing LiBr (500 mg, 5.6 mmol) and $Ni(acac)_2$ (49 mg, 10 mol %) was added Me_2Zn (4.8 mL of 2 M solution in toluene, 9.6 mmol) dropwise over 10 min.[46] The reaction mixture was stirred at room temperature for 36 h followed by the addition of aqueous $NaHCO_3$ and dilution with CH_2Cl_2. The organic phase was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0–20% EtOAc/hexanes) afforded 586 mg (85%) of ketone **27** as a white solid. A sample was recrystallized from Et_2O/hexanes: mp 100.5–101.5 °C. IR: 2968, 1701, 1454 cm^{-1}. ^1H NMR: δ 5.09 (br t, J = 6.8 Hz, 1H), 3.77–4.01 (m, 4 H), 1.82–2.29 (m, 9H), 1.68 (s, 3H), 1.59 (s, 3H), 1.34–1.70 (m, 8H), 1.16–1.31 (m, 2H), 0.99 (s, 3H), 0.83 (s, 3H). ^{13}C NMR: 211.09, 131.55, 124.25, 112.05, 65.28, 64.90, 49.95, 49.70, 47.69, 44.43, 42.48, 40.90, 39.05, 38.65, 35.69, 34.82, 28.80, 25.59, 24.23, 23.72, 20.55, 19.32, 17.64. Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.45; H, 10.06. Further elution yielded 35 mg of enone **25b**.

(±)-(4′S*,4a′S*,7′S*,9a′S*)-3′,4′,6′,7′,9′,9′a-Hexahydro-4′,7′-dimethyl-4′-(4″-oxobutyl)spiro[1,3-dioxolane-2,8′-(5′H)-[4a′,7′]methano[4a′H]benzocyclohepten]-2′(1′H)-one (28). A solution of ketone **27** (90 mg, 0.25 mmol), containing Na_2CO_3 (~5 mg) in CH_2Cl_2 (6 mL) at −78 °C was ozonized until a blue color was visible. The solution was purged with N_2 for 10 min before the addition of dimethyl sulfide (0.5 mL). The solution was warmed to room temperature and stirred for 12 h. Removal of solvent and flash chromatography (0–30% EtOAc/hexanes) yielded 75.1 mg (90%) of keto aldehyde **28** as a white solid. Recrystallization afforded an analytical sample: mp 80–81 °C (Et_2O). IR: 2960, 1718, 1701 cm^{-1}. ^1H NMR: δ 9.76 (br s, 1H), 3.77–4.01 (m, 4H), 2.45 (td, J = 6.7, 1.1 Hz, 2H), 2.05–2.30 (m, 5H), 1.79–1.89 (m, 2H), 1.34–1.70 (m, 10H), 0.98 (s, 3H), 0.87 (s, 3H). ^{13}C NMR: 210.71, 202.14, 112.00, 65.36, 64.97, 49.89, 49.51, 47.76, 44.43, 44.36, 42.49, 41.00, 39.03, 38.64, 35.46, 34.78, 23.82, 20.52, 19.33, 16.60. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.87; H, 9.11.

(±)-(6a′S*,9′S*,11a′S*,11b′R*)-9′,11b′-Dimethyl-1′,2′,3′,6′a,7′,10′,11′,11b′-octahydrospiro[1,3-dioxolane-2,8′(9′H)-[9′,11a′]methano[11a′H]cyclohept[a]naphthalen]-5′(6′H)-one (29). To a vigorously refluxing solution of KOH (0.47 g, 7 mmol) in MeOH/water (1:1; 90 mL) was added a solution of keto aldehyde **28** (1.61 g, 4.82 mmol) in MeOH (15 mL) dropwise over 90 min. The reaction mixture was heated at reflux for 12 h. The mixture was cooled to room temperature, aqueous NH_4Cl was added, and the solvent was removed. The residue was dissolved in CH_2Cl_2 and was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0–20% EtOAc/hexanes) gave 1.21 g (80%) of enone **29** as a white solid. Recrystallization gave an analytical sample: mp 138.5–140 °C (Et_2O). IR: 2946, 1676, 1618 cm^{-1}. ^1H NMR: δ 6.61 (dd, J = 5.7, 2.4 Hz, 1H), 3.78–4.03 (m, 4H), 2.58 (dd, J = 10.0, 7.4 Hz, 1H), 2.29–2.40 (m, 1H), 1.97–2.21 (m, 3H), 1.23–1.87 (m, 12H), 1.07 (s, 3H), 0.98 (s, 3H). ^{13}C NMR: 201.57, 142.60, 134.75, 112.23, 65.40, 65.04, 49.80, 47.89, 42.33, 42.10, 39.51, 38.25, 35.15, 34.99, 29.65, 25.47, 25.03, 24.48, 19.46, 18.30. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.78; H, 8.87.

(±)-(4′R*,4a′S*,6a′S*,9′S*,11a′S*,11b′S*)-1′,2′,3′,4′,6a′,-6a′,7′,10′,11′,11b′-Decahydro-9′,11b′-dimethyl-4′-vinylspiro-[1,3-dioxolane-2,8′(9′H)-[9′,11a′]methano[11a′H]cyclohept-[a]naphthalen]-5′(4a′H)-one (30). A stirred suspension of CuBr·DMS complex (163 mg, 0.79 mmol) in THF (23 mL) was cooled to −78 °C. Vinylmagnesium bromide (4.75 mL, 1 M in THF, 4.75 mmol) was added dropwise followed by HMPA (1.1 mL, 6.3 mmol). The mixture was stirred for 20 min before a solution of enone **29** (500 mg, 1.58 mmol) and TMSCl (0.71 mL, 5.5 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 30 min, excess aqueous NH_4Cl was added, and the mixture was stirred for 1 h at room temperature. The solvent was removed, and the residue was dissolved in CH_2Cl_2. The organic phase was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0–10% EtOAc/hexanes) yielded 472 mg (87%) of ketone **30** as a white solid. Recrystallization gave an analytical sample: mp 135.5–137 °C (Et_2O/hexanes). IR: 2949, 1700, 1604 cm^{-1}. ^1H NMR: δ 6.20 (ddd, J = 17.7, 10.8, 4.0 Hz, 1H), 4.98–5.11 (m, 2H), 3.78–4.02 (m, 4H), 2.85 (br m, 1H), 2.23–2.37 (m, 3H), 1.83–2.09 (m, 4H), 1.53–1.72 (m, 5H), 1.23–1.51 (m, 6H), 0.97 (s, 3H), 0.95 (s, 3H). ^{13}C NMR: 210.68, 140.49, 112.32, 112.10, 65.33, 65.00, 56.08, 51.19, 47.50, 44.31, 41.49, 41.07, 38.80, 36.83, 34.88, 34.15, 31.53, 28.63, 32.22, 20.01, 19.45, 16.81. Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.62; H, 9.32.

(±)-(4′R*,4a′S*,5′R*,6a′S*,9′S*,11a′S*,11b′S*)-1′,2′,3′,4′,-4a′,5′,6′,6a′,7′,10′,11′,11b′-Dodecahydro-9′,11b′-dimethyl-4′-vinylspiro[1,3-dioxolane-2,8′(9′H)-[9′,11a′]methano-[11a′H]cyclohept[a]naphthalen]-5′-ol (31a) and (±)-(4′R*,-4a′S*,5′S*,6a′S*,9′S*,11a′S*,11b′S*)-1′,2′,3′,4′,4a′,5′,6′,6a′,7′,-10′,11′,11b′-Dodecahydro-9′,11b′-dimethyl-4′-vinylspiro-[1,3-dioxolane-2,8′(9′H)-[9′,11a′]methano[11a′H]cyclohept-[a]naphthalen]-5′-ol (31c). To a solution of ketone **30** (470 mg, 1.37 mmol) in THF (20 mL) at −78 °C was added DIBALH (4 mL, 1 M in THF, 4 mmol). The reaction mixture was stirred for 15 min before the addition of aqueous $NaHCO_3$. The THF was removed, and residue was dissolved in CH_2Cl_2 and was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0−20% EtOAc/hexanes) gave 330 mg (70%) of axial alcohol **31a**. An analytical sample was recrystallized from Et_2O: mp 166−168 °C. IR: 3555, 2937, 1625 cm^{-1}. ^1H NMR: δ 6.58 (app dt, J = 16.9, 10.2 Hz, 1H), 5.24 (dd, J = 16.9, 2.1 Hz, 1H), 5.07 (dd, J = 10.2, 2.1 Hz, 1H), 3.74−4.01 (m, 5H), 2.45−2.50 (br m, 1H), 2.23−2.33 (m, 1H), 1.30−1.83 (m, 16H), 1.27 (s, 3H), 1.13−1.22 (m, 1H), 0.94 (s, 3H). ^{13}C NMR: 144.70, 115.90, 112.80, 72.57, 65.16, 64.78, 51.83, 48.08, 46.89, 45.82, 42.52, 38.26, 38.09, 36.90, 35.08, 33.95, 33.23, 32.26, 22.92, 22.23, 19.43, 18.20. Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.24; H, 9.91. Found: C, 76.38; H, 9.92. Further elution yielded 106 mg (22%) of equatorial alcohol **31c**. An analytical sample was recrystallized from Et_2O: mp 153.5−155 °C. IR: 3608, 3468, 2936, 1631 cm^{-1}. ^1H NMR: δ 6.16 (ddd, J = 17.8, 10.3, 8.2 Hz, 1H), 5.02−5.15 (m, 2H), 3.70−4.00 (m, 5H), 2.72−2.78 (br m, 1H), 1.91−2.03 (m, 1H), 1.19−1.85 (m, 18H), 0.96 (s, 3H), 0.93 (s, 3H). ^{13}C NMR: 140.62, 114.46, 112.77, 67.46, 65.26, 64.97, 51.45, 49.08, 47.21, 42.14, 38.78, 38.67, 36.96, 35.89, 35.08, 32.70, 30.53, 23.57, 19.50, 19.49, 17.62. Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.24; H, 9.91. Found: C, 76.07; H, 9.94.

(±)-(4′R*,4a′S*,5′R*,6a′S*,9′S*,11a′S*,11b′S*)-5′-(Benzoyloxy)-1′,2′,3′,4′,4a′,5′,6′,6a′,7′,10′,11′,11b′-dodecahydro-9′,11b′-dimethyl-4′-vinylspiro[1,3-dioxolane-2,8′(9′H)-[9′,11a′]methano[11a′H]cyclohept[a]naphthalene] (31b). A solution of alcohol **31a** (325 mg, 0.94 mmol), DMAP (23 mg, 20 mol %), and benzoyl bromide (0.22 mL, 1.87 mmol) in pyridine (9 mL) was heated at reflux for 4 h. Excess pyridine was removed, and the residue was dissolved in CH_2Cl_2 and was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0−10% EtOAc/hexanes) yielded 380 mg (90%) of benzoate **31b** as a white solid: Recrystallization gave colorless needles: mp 212−214 °C (Et_2O). IR: 2937, 1706, 1601 cm^{-1}. ^1H NMR: δ 7.99 (d, J = 7.5 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 6.26 (app dt, J = 16.7, 10.0 Hz, 1H), 5.22 (br d, J = 2.2 Hz, 1H), 4.78 (dd, J = 16.7, 1.5 Hz, 1H), 4.42 (dd, J = 11.7, 1.5 Hz, 1H), 3.74−3.98 (m, 4H), 2.42−2.48 (br m, 1H), 2.14−2.25 (m, 1H), 1.47 (s, 3H), 1.33−1.92 (m, 16H), 1.22 (t, J = 13.1 Hz, 1H), 0.96 (s, 3H). ^{13}C NMR: 166.23, 141.65, 132.36, 131.14, 129.59, 128.14, 112.89, 112.67, 74.50, 65.22, 64.93, 51.76, 47.04, 45.91, 44.87, 42.51, 38.35, 38.24, 34.99, 34.26, 33.81, 32.91, 23.01, 22.20, 19.45, 18.22. Anal. Calcd for $C_{29}H_{38}O_4$: C, 77.28; H, 8.52. Found: C, 77.21; H, 8.42.

(±)-(4′S*,4a′S*,5′R*,6a′S*,9′S*,11a′S*,11b′S*)-5′-(Benzoyloxy)-1′,2′,3′,4′,4a′,5′,6′,6a′,7′,10′,11′,11b′-dodecahydro-4′-(hydroxymethyl)-9′,11b′-dimethylspiro[1,3-dioxolane2,8′(9′H)-[9′,11a′]methano[11a′H]cyclohept[a]-naphthalene]-4′-carboxaldehyde (32c). Ozone was passed through a stirred solution cooled to −78 °C of unsaturated benzoate **31b** (350 mg, 0.78 mmol) in $MeOH/CH_2Cl_2$ (1:1, 12 mL) containing Na_2CO_3 (8 mg) until a blue color became visible. The solution was purged with N_2 for 10 min before the addition of dimethyl sulfide (0.57 mL, 7.8 mmol). The mixture was stirred for 12 h while warming to room temperature. Sodium carbonate (15 mg) and aqueous formaldehyde (2 mL of 37% solution) were added, and the mixture was stirred at room temperature for 9 h. The reaction mixture was diluted with CH_2Cl_2 and was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0−10% EtOAc/hexanes) afforded 300 mg (80%) of aldol **32c** as a solid. Recrystallization was accomplished with Et_2O/MeOH/hexanes: mp 196−198 °C dec. IR: 2945, 1711, 1600 cm^{-1}. ^1H NMR (CD_2Cl_2): δ 10.02 (s, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 5.63 (br s, 1H), 3.71−3.95 (m, 5H), 3.54 (d, J = 11.0 Hz, 1H), 2.13−2.24 (m, 1H), 2.04 (br d, J = 13.7 Hz, 1H), 1.73−1.94 (m, 6H), 1.41 (s, 3H), 1.44−1.66 (m, 9H), 1.15−1.37 (m, 2H), 0.95 (s, 3H). ^{13}C NMR (CD_2Cl_2): 206.73, 166.07, 133.47, 130.82, 129.91, 128.97, 112.80, 70.53, 67.48, 65.71, 65.32, 54.42, 52.25, 48.40, 47.46, 43.30, 38.86, 38.48, 35.41, 34.50, 33.94, 32.62, 31.20, 23.37, 22.46, 19.63, 18.81. HRMS (CI) Calcd for $C_{29}H_{39}O_6$ (M + H)$^+$: 483.2746. Found: 483.2726.

If desired, aldehyde **32b** can be isolated before the addition of formaldehyde as a colorless solid after crystallization: mp 198−200 °C (Et_2O/CH_2Cl_2/hexanes). IR: 2944, 1711, 1602 cm^{-1}. ^1H NMR : δ 10.02 (d, J = 1.3 Hz, 1H), 7.98 (d, J = 7.3 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.3 Hz, 2H), 5.41 (br d, J = 2.6 Hz, 1H), 3.74−4.00 (m, 4H), 2.50 (br m, 1H), 2.16−2.24 (br d, J = 12.6 Hz, 2H), 1.32 (s, 3H), 1.19−1.95 (m, 16H), 0.96 (s, 3H). LRMS (EI): 452 (M^+).

(±)-(4S*,4aS*,5R*,6aS*,9S*,11aS*,11bS*)-5-(Benzoyloxy)-4-(hydroxymethyl)-9,11b-dimethyl-8-oxo-1,2,3,4,4a,5,6,-6a,7,8,9,10,11,11b-tetradecahydro-9,11a-methano-11aH-cyclohept[a]naphthalen]-4-carboxylic Acid. (±)-Scopadulcic Acid A (1). To a stirred solution of aldol **32c** (100 mg, 0.21 mmol) in *tert*-BuOH (1.5 mL), THF (0.5 mL), and 2-methyl-2-butene (0.5 mL) at room temperature was added a solution of $NaClO_2$ (116 mg of 80% purity, 1.03 mmol) and NaH_2PO_4 (120 mg) in water (0.6 mL). The reaction mixture was stirred at room temperature until no starting material was visible by TLC (approximately 6 h). The reaction mixture was acidified to pH 2 with 1 M HCl, stirred for 12 h, and then heated at a gentle reflux for 1 h. The volatile components were removed, and the residue was dissolved in CH_2Cl_2 and was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0−50% EtOAc/hexanes) gave 61 mg (65%) of scopadulcic acid A as a white solid. Recrystallization gave colorless crystals: mp 251−253 °C dec (acetone/MeOH) (lit.[16] 237−239 °C, dec). IR (KBr disc): 3482, 2934, 1717, 1700 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.96 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 2H), 5.60 (br s, 1H), 3.80 (d, J = 11.0 Hz, 1H), 3.58 (d, J = 11.0 Hz, 1H), 2.28−2.55 (m, 2H), 2.22 (br t, J = 13.4 Hz, 1H), 2.01−2.15 (m, 3 H), 1.90 (d, J = 12.1 Hz, 1H), 1.80−1.95 (m, 3H), 1.59 (s, 3H), 1.55−1.79 (m, 7H), 1.46 (d, J = 12.2 Hz, 1H), 1.01 (s, 3H). ^{13}C NMR (acetone-d_6): 212.65, 178.20, 166.65, 133.66, 132.50, 130.76, 129.50, 70.36, 68.10, 54.13, 53.12, 48.73, 46.33, 44.88, 43.36, 39.93, 37.60, 36.92, 35.69, 35.08, 33.44, 24.37, 21.56, 20.42, 20.10. HRMS (CI) Calcd for $C_{27}H_{35}O_6$ (M + H)$^+$: 455.2433. Found: 455.2438.

(±)-(4′S*,4a′S*,5′R*,6a′S*,9′S*,11a′S*,11b′S*)-5′-(Benzoyloxy)-1′,2′,3′,4′,4a′,5′,6′,6a′,7′,10′,11′,11b′-dodecahydro-9′,11b′-dimethyl-4′-[[(methoxymethyl)oxy]methyl]-spiro[1,3-dioxolane-2,8′(9′H)-[9′,11a′]methano[11a′H]-cyclohept[a]naphthalene]-4′-carboxaldehyde (33a). To a stirred solution of aldol **32c** (250 mg, 0.52 mmol) and *i*-Pr_2-NEt (0.54 mL, 3.1 mmol) in CH_2Cl_2 (5 mL) at room temperature was added MOMCl (0.16 mL, 2.1 mmol) dropwise. The reaction mixture was stirred for 24 h and then diluted with water. After dilution with CH_2Cl_2, the organic phase was washed with water, ice-cold 5% HCl, water, and brine. Workup ($MgSO_4$) and flash chromatography (0−20% EtOAc/hexanes) yielded 249 mg (91%) of aldehyde **33a** as a white foam: IR: 2947, 1710, 1601 cm^{-1}. ^1H NMR: δ 9.95 (s, 1H), 7.98 (d, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 5.66 (br d, J = 2.4 Hz, 1H), 4.54 (s, 2H), 3.74−3.98 (m, 4H), 3.57 (d, J = 9.7 Hz, 1H), 3.51 (d, J = 9.7 Hz, 1H), 3.30 (s, 3H), 2.08−2.22 (m, 2H), 1.76−1.96 (m, 5H), 1.50−1.67 (m, 6H), 1.39−1.48 (m, 3H), 1.34 (s, 3H), 1.16−1.27 (m, 2H), 0.95 (s, 3H). ^{13}C NMR: 205.31, 165.65, 132.99, 130.16, 129.52, 128.45, 112.38, 96.72, 71.56, 70.07, 65.22, 64.89, 55.39, 53.09, 51.70, 47.66, 46.98, 42.87, 38.44, 38.05, 34.91, 34.04, 33.52, 32.10, 31.13, 22.87, 21.42, 19.36, 18.35. Anal. Calcd for $C_{31}H_{42}O_7$: C, 70.70; H, 8.04. Found: C, 70.57; H, 7.98.

(±)-(4′R*,4a′S*,5′R*,6a′S*,9′S*,11a′S*,11b′S*)-5′-(Benzoyloxy)-1′,2′,3′,4′,4a′,5′,6′,6a′,7′,10′,11′,11b′-dodecahydro-4′-(hydroxymethyl)-9′,11b′-dimethyl-4′-[[(methoxymethyl)oxy]methyl]spiro[1,3-dioxolane-2,8′(9′H)-

[9′,11a′]methano[11a′*H*]cyclohept[*a*]naphthalene]-4′-methanol (33b). To a stirred solution of aldehyde **33a** (235 mg, 0.45 mmol) in EtOH (4 mL) at 0 °C was added a solution of $NaBH_4$ (16.5 mg, 0.45 mmol) in EtOH (1 mL). After 30 min, the ice bath was removed and the reaction mixture was stirred for 6 h at room temperature. Aqueous NH_4Cl was added followed by dilution with CH_2Cl_2. The organic phase was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0–30% EtOAc/hexanes) afforded 234 mg (99%) of alcohol **33b** as a colorless oil: IR: 3518, 2945, 1707, 1600 cm^{-1}. ^1H NMR: δ 8.03 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 5.59 (br s, 1H), 4.57 (s, 2H), 3.68–4.07 (m, 6H), 3.57 (d, J = 9.4 Hz, 2H), 3.41 (d, J = 9.4 Hz, 1H), 3.33 (s, 3H), 2.06–2.18 (m, 3H), 1.48 (s, 3H), 1.37–1.91 (m, 14H), 1.18 (t, J = 12.8 Hz, 1H), 0.94 (s, 3H). ^{13}C NMR: 165.81, 132.69, 130.70, 129.44, 128.30, 112.45, 96.82, 76.37, 70.95, 65.11, 64.79, 63.35, 55.35, 52.36, 46.92, 46.66, 43.13, 42.55, 38.65, 38.06, 34.85, 34.62, 34.14, 32.27, 30.48, 23.18, 22.50, 19.35, 17.80. HRMS (CI) Calcd for $C_{31}H_{45}O_7$ (M + H)$^+$: 529.3165. Found: 529.3111.

(±)-*O*-(4′*S,4a′*S**,5′*R**,6a′*S**,9′*S**,11a′*S**,11b′*S**)-5′-(Benzoyloxy)-1′,2′,3′,4′,4a′,5′,6′,6a′,7′,10′,11′,11b′-dodecahydro-9′,11b′-dimethyl-4′-[[(methoxymethyl)oxy]methyl]-4′-spiro[1,3-dioxolane-2,8′(9′*H*)-[9′,11a′]methano[11a′*H*]-cyclohept[*a*]naphthyl]methyl *S*-Methyl Carbonodithioate (33c).** To a solution of alcohol **33b** (170 mg, 0.32 mmol) in THF (3 mL) cooled to −78 °C was added potassium hexamethyldisilazide (1.3 mL, 0.5 M solution in toluene, 0.65 mmol). After 5 min, CS_2 (0.20 mL, 3.3 mmol) was added in one portion followed by a single portion of MeI (0.21 mL, 3.3 mmol) 2 min later. The reaction mixture was warmed to 0 °C, quenched with aqueous NH_4Cl, and diluted with CH_2Cl_2. The organic phase was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0–30% EtOAc/hexanes) yielded 170 mg (85%) of xanthate **33c** as a colorless oil: IR: 2946, 1709, 1600, 1276 cm^{-1}. ^1H NMR: δ 8.07 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.3 Hz, 2H), 5.64 (br s, 1H), 5.31 (d, J = 11.4 Hz, 1H), 4.58 (s, 2H), 4.47 (d, J = 11.4 Hz, 1H), 3.74–3.98 (m, 4H), 3.57 (d, J = 9.9 Hz, 1H), 3.35 (s, 3H), 3.34 (d, J = 9.9 Hz, 1H), 2.43 (s, 3H), 2.10–2.19 (m, 1H), 1.75–1.94 (m, 5H), 1.53 (s, 3H), 1.51–1.66 (m, 7H), 1.15–1.49 (m, 5H), 0.95 (s, 3H). ^{13}C NMR: 215.21, 165.91, 132.78, 130.43, 129.77, 128.23, 112.45, 96.73, 74.75, 73.40, 71.12, 65.23, 64.87, 55.37, 52.45, 46.98, 46.18, 42.65, 42.41, 38.61, 38.16, 34.92, 34.37, 33.83, 32.24, 31.26, 23.25, 22.44, 19.43, 18.65, 18.00. HRMS (CI) Calcd for $C_{33}H_{47}O_7S_2$ (M + H)$^+$: 619.2763. Found: 619.2745.

(±)-(4*R,4a*S**,5*R**,6a*S**,9*S**,11a*S**,11b*S**)-5-(Benzoyloxy)-4-(hydroxymethyl)-4,9,11b-trimethyl-1,2,3,4,4a,5,6,6a,7,8,9,-10,11,11b-tetradecahydro-9,11a-methano-11a*H*-cyclohept-[*a*]naphthalene-8(9*H*)-one. (±)-Scopadulciol (2b).** To a solution of *n*-Bu_3SnH (0.21 mL, 0.78 mmol) and AIBN (8.5 mg, 0.052 mmol) in benzene (3 mL) maintained at a gentle reflux was added a solution of xanthate **33c** (160 mg, 0.26 mmol) in benzene (0.5 mL). The solution was heated at reflux for 1 h. The solution was cooled and the solvent removed. The resulting liquid was loaded on a short silica column and was eluted with 0–20% EtOAc/hexanes to remove tin salts. The semicrude product was dissolved in THF (3 mL). Aqueous HCl (4 drops; 1 M) was added, and the mixture was heated at reflux for 12 h. The solvent was removed, and the residue was dissolved in CH_2Cl_2. The organic phase was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0–30% EtOAc/hexanes) yielded 69.5 mg (63%) of scopadulciol (**2b**) as a white solid. A sample was rechromatographed (1% MeOH/$CHCl_3$) and recrystallized to give colorless crystals: mp 212–214 °C (Et_2O/$CHCl_3$). IR: 3635, 3480, 1706, 1601 cm^{-1}. ^1H NMR: δ 8.04 (d, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 5.63 (br d, J = 2.2 Hz, 1H), 3.59 (d, J = 10.9 Hz, 2H), 3.12 (d, J = 10.9 Hz, 1H), 2.43–2.54 (m, 1H), 2.13–2.27 (m, 2H), 1.99 (dd, J = 16.0, 12.0 Hz, 1H), 1.53 (s, 3H), 1.49–1.85 (m, 13H), 1.22 (br d, J = 12.4 Hz, 1H), 1.09 (s, 3H), 0.92 (s, 3H). ^{13}C NMR: 213.47, 166.27, 132.96, 130.70, 129.60, 128.49, 71.30, 70.24, 53.03, 52.29, 45.47, 43.17, 42.68, 38.96, 38.45, 37.70, 36.70, 35.86, 35.46, 34.27, 23.67, 21.75, 20.37, 19.72, 18.13. HRMS (CI) Calcd for $C_{27}H_{37}O_4$ (M + H)$^+$: 425.2692. Found: 425.2676.

(±)-(4*R,4a*S**,5*R**,6a*S**,9*S**,11a*S**,11b*S**)-5-(Benzoyloxy)-4,9,11b-trimethyl-8-oxo-1,2,3,4,4a,5,6,6a,7,8,9,10,11,11b-tetradecahydro-9,11a-methano-11a*H*-cyclohept[*a*]naphthalen-4-carboxylic Acid. (±)-Scopadulcic Acid B (2a).** Scopadulciol (**2b**) (29 mg, 0.068 mmol) was suspended in acetone (1 mL). Jones reagent was added dropwise until TLC indicated that no starting material was present. The reaction mixture was diluted with CH_2Cl_2, and the organic phase was washed with water and brine. Workup ($MgSO_4$) and flash chromatography (0–30% EtOAc/hexanes) gave 24.9 mg (83%) of scopadulcic acid B (**2a**) as a white solid. Recrystallization from CH_2Cl_2/Et_2O yielded white crystals, mp 252–253 °C dec. IR: 2945, 1707 (br), 1601 cm^{-1}. ^1H NMR: δ 8.02 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 5.33 (br d, J = 1.6 Hz, 1H), 2.42–2.52 (m, 1H), 2.17–2.28 (m, 3H), 2.01 (dd, J = 16.0, 12.0 Hz, 1H), 1.55 (s, 3H), 1.51–1.90 (m, 13H), 1.37 (s, 3H), 1.09 (s, 3H). ^{13}C NMR: 213.20, 183.17, 166.07, 132.99, 130.56, 129.59, 128.50, 72.88, 53.16, 52.32, 47.21, 45.20, 44.76, 42.56, 39.77, 38.83, 36.60, 35.99, 35.15, 34.01, 23.76, 21.59, 19.68, 19.36, 17.97. HRMS (CI) Calcd for $C_{27}H_{35}O_5$ (M + H)$^+$: 439.2485. Found: 439.2478.

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Supplementary Material Available: Copies of the ^1H NMR spectra of compounds **1**, **2a**, **2b**, **32b**, **32c**, **33b**, **33c**, which are lacking combustion analyses, and comparison ^1H NMR spectra of **2a** (natural vs synthetic) (8 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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