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Total Synthesis of (±)-Scopadulcic Acid B

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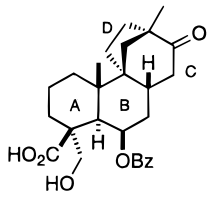
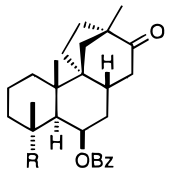
Abstract: The first total synthesis of a scopadulan diterpene is described. The key step is a double Heck cyclization of dienyl aryl iodide **8** to form tetracyclic enones **24** and **25** in 80−85% combined yield.

Introduction

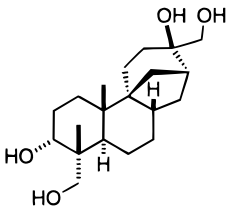
The widely distributed plant *Scoparia dulcis* L. has long been considered by native populations to posses medicinal properties. It is used to improve digestion and protect the stomach in Paraguay, as a cure for hypertension in Taiwan, and for treating toothaches, blennorhagia, and stomach disorders in India.[2−4] In recent screenings of the Paraguayan crude drug "Typychá Kuratû", Hayashi and co-workers isolated a number of structurally unique tetracyclic diterpenes, exemplified by scopadulcic acids A (**1**, SDA), B (**2**, SDB), and scopadulciol (**3**), that are active ingredients.[5,6] Scopadulciol has also been isolated from a Bangladeshi collection of *S. dulcis* L.[7] The structure of SDA was established by X-ray analysis of the crystalline methanol solvate,[8] while SDB and other scopadulan diterpenes were characterized through a combination of NMR, MS, UV and IR data.[5−7,9] The absolute stereochemistries of SDA and SDB have been proposed on the basis of their positive Cotton effects in the CD spectra.[5] The tetracyclic scopadulan ring system is new, although it is related to that of other diterpenes containing a bicyclo[3.2.1]octane substructure, such as aphidicolin (**4**)[10] and stemarin (**5**).[11]



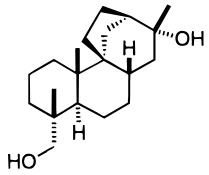
scopadulcic acid A (**1**)



scopadulcic acid B (**2**) R = CO_2H
scopadulciol (**3**) R = CH_2OH



aphidicolin (**4**)



stemarin (**5**)

A broad pharmacological profile has been observed for scopadulan diterpenes. SDB and **3** are powerful inhibitors of H^+,K^+-adenosine triphosphatase.[9,12,13] Since their mode of inhibition of this enzyme is different from that of omeprazole, a widely used clinical proton pump inhibitor, they represent new

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(2) Gonzales Torres, D. M. *Cattalogo de Plantas Medicinales (y Alimenticias y Utiles) Usada en Paraguay; Asunción: Paraguay, 1986; p 349.*

(3) Chow, S. Y.; Chen, S. M.; Yang, C. M.; Hsu, H. *J. Formosan Med. Assoc.* **1974**, *73*, 729.

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leads for developing agents to treat peptic ulcers, gastritis, and esophagitis.[12] SDA and SDB also show good activity against herpes simplex virus type 1 (HSV-1),[14,15] and SDB and some semisynthetic analogs show antitumor activity in several human cell lines as well as inhibition of the action of tumor-promoting phorbol esters.[16,17] In recent studies, SDB has been shown to inhibit bone resorption by osteoclast cells, and, thus, the scopadulan diterpenes warrant further evaluation as possible therapeutic agents for treating osteoporosis.[18]

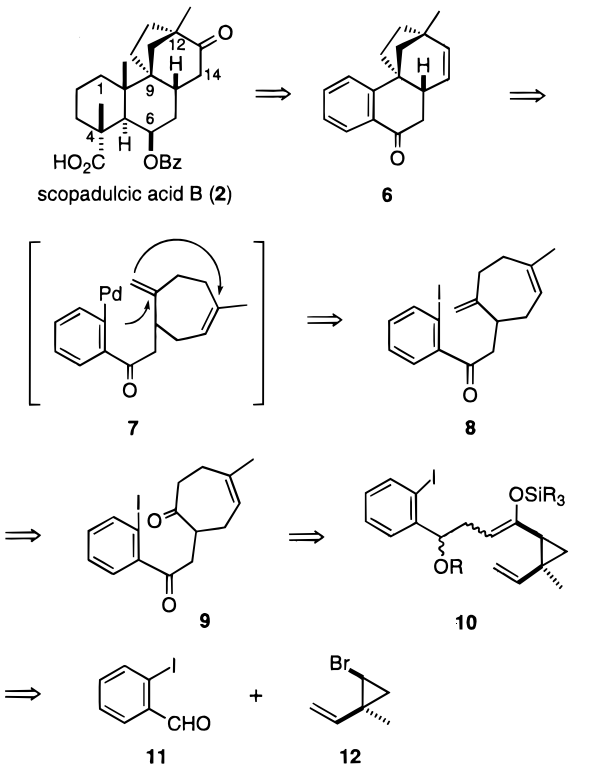
The unusual structure of scopadulan diterpenes and their extensive medicinal potential has prompted considerable synthetic work in this area. Total syntheses of (±)-SDB[19] and (±)-SDA[20] were reported from our laboratories in 1993 and constituted the first total synthesis accomplishments in the scopadulan diterpene area. In 1995, Ziegler and Wallace reported total syntheses of (±)-SDB and (±)-SDA, as well as the first total synthesis of scopadulciol.[21] The use of an advanced common intermediate in these latter syntheses provided further confirmation of the structural relationship of these three scopadulan diterpenes.

In this paper, we provide full details of the first total synthesis of (±)-scopadulcic acid B.

Results and Discussion

A. Synthesis Plan. Extensive investigations during the last decade have established the immense utility of intramolecular Heck reactions in the construction of complex molecules.[22] Our own studies in this area have focused on the remarkable ability of intramolecular Heck reactions to form quaternary carbon centers, even in highly congested arenas.[23,24] Our plan for preparing the scopadulan diterpenes aimed to exploit this facility by assembling the scopadulan B, C, and D rings by tandem intramolecular Heck cyclization of a 5-methylenecycloheptene precursor (**8** → **6**, Scheme 1). At the time our investigations began, this was a quite bold strategy, since sequential Heck cyclizations of simple dienes had been described only earlier

Scheme 1



that year.[25] We initially chose to examine this plan in a series having an aryl A ring, since this choice would allow us to more quickly examine the critical cyclization step. We were mindful from the outset, however, that this template might not be ideal for developing the full functionality of the scopadulan A ring.

Our initial model studies in a system lacking the C(6) oxygen and bridgehead C(12) methyl functionality have been summarized and provided requisite encouragement to undertake the total synthesis of SDB.[25,26] We envisaged constructing cyclization substrate **8** from 2-iodobenzaldehyde (**11**) and vinylcyclopropyl bromide **12**[27] using a divinylcyclopropane rearrangement of an enoxysilane intermediate (**10** → **9**) to develop the seven-membered ring.[28] If tetracycle **6** could be reached, we hoped to reduce this intermediate, or a derivative, as a prelude to introducing the final two quaternary centers of the A ring. We anticipated that the facial bias provided by the bicyclooctane substructure of **6** would provide the crucial initial stereocontrol element in this functionalization; that the two carbon bridge should direct introduction of the angular methyl group from the β face is apparent in a molecular model (Figure 1).

B. Preparation of Dienyl Aryl Iodide 8. The convergent assembly of cyclization precursor **8** began with 4-arylbutanal **15** and the known *cis*-cyclopropyl bromide **12**.[27−29] Aldehyde **15** was readily prepared on a large scale from commercially available 2-iodobenzaldehyde (**11**) as follows. Treatment of **11** with allylmagnesium bromide followed by *tert*-butyldimethyl-

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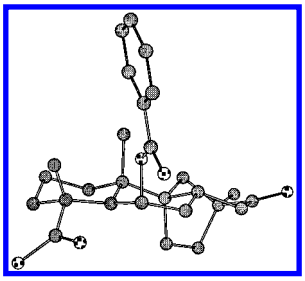

Figure 1. Molecular mechanics model SDB (**2**); hydrogens are omitted for clarity.

silyl (TBDMS) protection of the hydroxy group delivered **13**. Hydroboration-oxidation of the terminal vinyl group of **13** yielded **14**, which furnished aldehyde **15** upon Swern oxidation.[30] This four-step sequence was performed routinely on a 0.5 mol scale without purification of intermediates and provided **15** in 44% overall yield from **11**.

A 3:2 mixture of cyclopropyl bromides **12** and **16** is available in two steps from isoprene according to the procedure of Skattebol.[27] The required *cis*-isomer **12** was initially separated from this mixture by column chromatography. However, due to the volatility of **12**, it was subsequently found preferable to couple the **12**/**16** mixture with aldehyde **15** and defer separation of stereoisomers to a later stage.

Metalation of the **12**/**16** mixture with *t*-BuLi, followed by condensation of the resulting lithium reagents with **15**, provided the desired alcohols **17** in low yield. Apparently, these lithium reagents react with the aryl iodide functionality of **15** faster than with the aldehyde carbonyl group. It was eventually found that metathesis of the cyclopropyllithium reagents with $MgBr_2 \cdot OEt_2$ produced an organometallic species with the desired nucleophilic properties. Thus, treatment of a solution of the 3:2 mixture of bromides **12**/**16** with *t*-BuLi in ether at −78 °C, followed by sequential addition of a freshly prepared solution of $MgBr_2 \cdot OEt_2$ and aldehyde **11** provided **17** in good yield. These alcohols were not purified, but rather submitted directly to oxidation with pyridinium chlorochromate (PCC)[31] to furnish an inseparable mixture of *cis*- and *trans*-cyclopropyl ketones **18** in 75−85% overall yields from **15** (33−37% overall yields over five steps from 2-iodobenzaldehyde).

Preliminary studies using the pure *cis*-cyclopropane isomer of **18** (obtained from pure **12**) and the mixture of isomers **18** demonstrated, as expected,[28] that enoxysilane derivatives of only the *cis*-isomer underwent [3,3]-sigmatropic rearrangement in refluxing benzene. Thus, the mixture of stereoisomeric cyclopropyl ketones **18** was treated with trimethylsilyl triflate (TMSOTf) and Et_3N, and the resulting enoxysilane derivatives **19** were heated for 1 h in refluxing benzene. Selective cleavage of the resulting trimethylsilyl enol ethers **20** and **21** with pyridinium *p*-toluenesulfonate (PPTS) in EtOH−H_2O provided Δ^4-cycloheptenone **22** in 51% yield, together with 26% of the *trans*-isomer of cyclopropyl ketone **18**. Separation of *trans*-**18** from cycloheptenones **22** on silica gel was possible at this stage, and recovered *trans*-**18** could be recycled to a 1:1.5 mixture of *cis*- and *trans*-**18** by exposure to NaOMe in refluxing MeOH. Two recycles allowed cycloheptenones **22** to be obtained in 60−65% overall yield from the mixture of *cis*- and *trans*-cyclopropyl ketones **18**.

The cycloheptenone ring was further elaborated by reaction of **22** with $Ph_3P{=}CH_2$, followed by removal of the silyl ether protecting group to provide **23**. Oxidation of **23** with PCC[31] then gave the desired methylenecycloheptene ketone **8** in 77% overall yield from **22**. After careful optimization, the sequence summarized in Scheme 2 provided Heck cyclization precursor **8** on multigram scales in 22% overall yield from 2-iodobenzaldehyde.

Palladium-Catalyzed Cyclization of 8 and Conversion of 24 and 25 to Ketone 31. The critical cyclization of dienyl aryl iodide **8** could be accomplished with a variety of Pd(0) catalysts. Cyclizations conducted with a catalyst system[32] that we had previously found effective at minimizing double bond migration (10% $Pd(OAc)_2$, 2−4 equiv of Ph_3P, 2 equiv of Ag_2CO_3 in refluxing MeCN) afforded variable yields (30−60%) of a ∼3:1 mixture of enones **24** and **25** (Scheme 3). Reproducibly high yields were obtained using 10% $Pd(OAc)_2$, 20% Ph_3P, and an excess of Et_3N in refluxing MeCN. This procedure provided enones **24** and **25** in 80−85% combined yield on scales as large as 14 g. The unconjugated enone **24** predominated to the extent of 1.3−1.8:1, although this ratio decreased at longer reaction times. No conditions we examined completely suppressed double bond migration. Face selection in the initial insertion step was not high, since the $\Delta^{13,14}$-enone **24** was formed as a 1.2−1.5:1 mixture of stereoisomers.

With gram quantities of the tetracyclic nucleus in hand, we directed our attention toward introducing oxidation at C(13), as well as converging the two stereoisomers of **24** and **25** into a common intermediate. Dehydrogenation of the **24**/**25** mixture with dichlorodicyanoquinone (DDQ) in refluxing chlorobenzene readily accomplished the latter objective and provided dienone **26** in 63% yield. Subsequent oxidation of **26** with 1.1 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature occurred at the distal double bond, and exclusively from the β face, to form epoxide **27**. Selective reduction of this intermediate with NaTeH[33] then delivered hydroxy enone **28** in 42% overall yield from the mixture of Heck cyclization products.

Our initial attempts to saturate the double bond of **28** met with difficulties. Hydrogenation of **28** with Pd/C resulted in significant deoxygenation of the benzylic ketone. This problem could be minimized by using transfer hydrogenation conditions (Pd/C, HCO_2NH_4); however, **29** was the major product. Stereoselection in this reduction was somewhat solvent dependent, with a 2:1 mixture of ketones **29** and **30** being produced in MeOH or EtOH and an 8:1 mixture in DMF. Single-crystal X-ray analysis of **30** allowed unambiguous confirmation of the unanticipated diastereoselection in this catalytic hydrogenation. Fortunately, the desired stereochemical outcome could be realized by utilizing the β-alcohol at C(13) as a stereodirecting element. Following precedents of Liotta, Maryanoff, and coworkers,[34] enone **28** was reduced with $LiAlH_4$ in THF at −78 °C to provide ketone **30** as a single diastereomer in 73% yield. Attempted protection of this alcohol as a methyl ether by treatment with excess KH and CH_3I resulted in concomitant methylation at C(7). However, exposure of **30** to methyl trifluoromethanesulfonate and 2,6-di-*tert*-butylpyridine in CH_2Cl_2 did provide **31** in satisfactory yield. The stage was now set for functionalization of the A ring.

Elaboration of Ring A. Having established rings B, C, and D of the scopadulan skeleton, we next focused on functionalization of ring A. As a prelude to attempted Birch reduction, the benzylic ketone functionality of **31** was protected as imidazolidine.[35] This transformation was best accomplished

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(31) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
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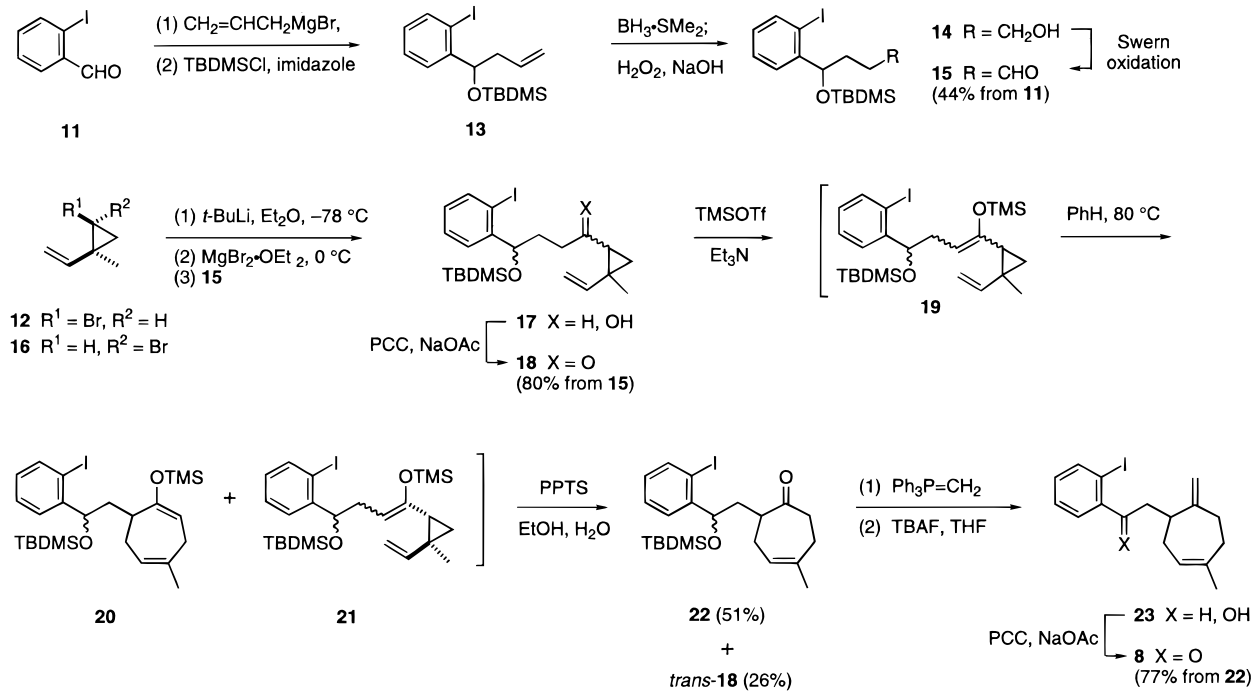
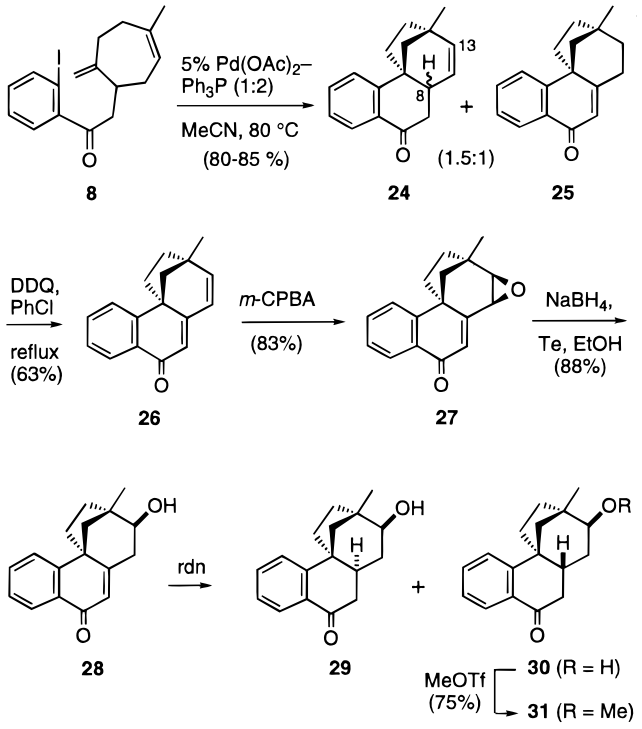
(35) Birch, A. J.; Dastar, K. P. *Aust. J. Chem.* **1973**, *26*, 1363.

Scheme 2



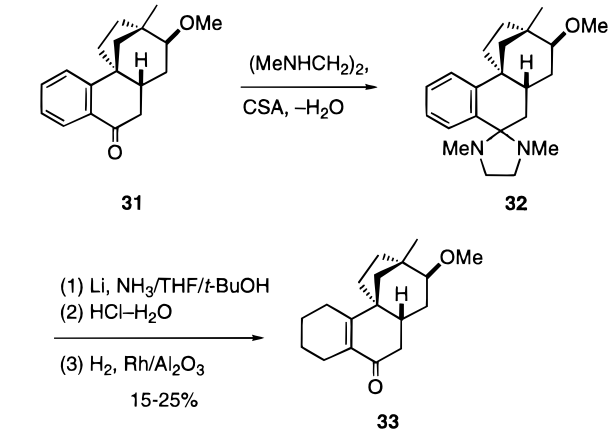
Scheme 3



reduction conditions	29		30
Pd/C, HCO_2NH_4, 23 °C	2-8	:	1
$LiAlH_4$, THF, –78 °C	–		only (73%)

using a large excess of *N*,*N*′-dimethylethylenediamine (TMEDA) and catalytic amount of camphorsulfonic acid (CSA) in toluene under Dean−Stark conditions (Scheme 4). Reduction of the crude imidazolidine **32** with excess Li in NH_3−THF containing *t*-BuOH, followed by cleavage of the diamine protecting group and selective catalytic hydrogenation of the disubstituted double bond (H_2, Rh/Al_2O_3), gave the desired enone **33**, albeit in low yield (15−25% from **31**). All attempts to improve the efficiency

Scheme 4



of this reduction sequence, including employing potassium or sodium as reductants, proved unfruitful.

It is well appreciated that aromatic derivatives containing two or more electron-donating substituents reluctantly undergo Birch reduction.[36] Thus, a better substrate for dearomatization would be benzoic acid **36**. Furthermore, the dianion generated from Birch reduction of **36** could be amenable to methylation[37] to introduce directly the C(4) geminal substituents of SDB (Scheme 5). To reach carboxylic acid **36**, ketone **31** was initially reduced with $LiAlH_4$ at −78 °C to provide **34** in high yield. We hoped to use the equatorial alcohol of **34** to direct functionalization to C(4) of the aromatic ring. Although *ortho* metalation of benzyl alcohols is well-known,[38,39] this transformation has rarely been employed in complex molecule construction. Thus, we were pleased to find that the desired benzoic acid **36** could be

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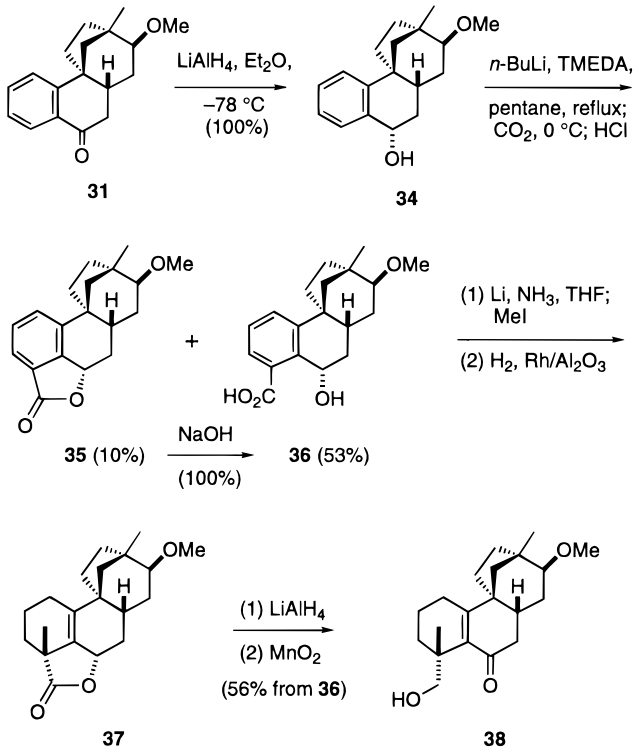
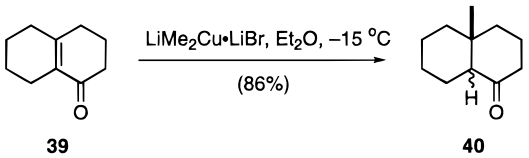
Scheme 5



accessed from **34**. The optimal procedure was to expose alcohol **34** to excess *n*-BuLi in refluxing TMEDA−pentane to produce a red solution of the dianion,[40] which was quenched at 0 °C with solid CO_2. After acidification, benzoic acid **36** was obtained in 53% yield, together with 10% of lactone **35** (which could be efficiently converted to **36**) and 30% of recovered **34**.

Finally, Birch reduction of **36** and *in situ* methylation[41] generated a 1,4-cyclohexadiene, which was not isolated, but immediately hydrogenated over Rh/Al_2O_3 to afford lactone **37** in ∼65% yield from **36**. Reduction of this intermediate with $LiAlH_4$, followed by oxidation of the allylic alcohol with MnO_2-provided enone **38**. This four-step conversion was typically accomplished without isolation or purification of intermediates and provided **38** in up to 56% overall yield. The good efficiency of this conversion requires that face selectivity in the pivotal methylation step is high. That the methyl group had indeed been introduced from the required β-face was apparent from isolation of lactone **37**.

Introduction of the Quaternary Methyl Group at C(10) and Completion of the Total Synthesis of (±)-SDB. Having developed a viable route to pentacyclic enone **38**, we were now confronted with the formidable task of introducing the remaining quaternary methyl group. From the outset we had anticipated that this functionalization would be difficult, since C(10) was adjacent to a quaternary center of the bicyclo[3.2.1]octane unit. Although β,β-disubstituted enones are known to be poor Michael acceptors, we found that 1,4-adduct **40** could be obtained in good yield when model enone **39** was treated with 5 equiv of lithium dimethylcuprate in ether at −15 °C (eq 1). However, attempts to effect this transformation in the scopadulan series (with enone **38** or the corresponding methyl ester) were unrewarding. Many conjugate addition procedures were surveyed,[42] including lithium dimethylcuprate/trimethylsilyl chloride,[43] methyl copper tri-*n*-butylphosphine,[44] "higher order" cyano methyl cuprates,[45] $BF_3{\cdot}Et_2O$-catalyzed cuprate addition,[46] and nickel acetylacetonate-catalyzed addition of dimethylzinc.[47] Typically, the starting enone and/or the 1,2-adduct were obtained in these reactions.



(1)

We finally turned to diethylaluminium cyanide, which has proven to be an excellent reagent for effecting conjugate addition of a carbon nucleophile at highly encumbered centers.[48] Treatment of enone **38** with Et_2AlCN at room temperature for 12 h provided cyano ketone **41** in 48% yield (92% based on consumed **38**) (Scheme 6). The efficiency of this conversion could be raised to 85% yield with two recycles of recovered enone **38**. The stereochemical outcome of this reaction was tentatively assigned on the basis of substantial literature precedent that CN addition would occur in an axial fashion.[48]

The conversion of **41** to SDB was greatly simplified by the observation that exposure of **41** to an excess of $LiAlH_4$ in refluxing THF gave rise to pentacyclic aminal **42** in essentially quantitative yield. This propitious reduction introduces the required β-alcohol at C(6) and captures the C(10) substituent at the aldehyde oxidation state. Aminal **42** was not purified, but directly subjected to Wolff−Kishner reduction under forcing conditions to provide tetracycle **43** in 74% overall yield from **41**.

Completion of the synthesis of SDB (**2**) from **43** required benzoylation of the secondary alcohol, oxidation of the primary alcohol to a carboxylic acid, and conversion of the methyl ether to a ketone. To achieve these functional group modifications, the primary alcohol was first protected by treatment of **43** with *tert*-butyldimethylsilyl triflate and 2,6-lutidine in CH_2Cl_2 at −78 °C to afford **44**. Conventional benzoylation of the hindered axial secondary alcohol of **44** with benzoyl chloride and pyridine was unsuccessful. However, when **44** was treated with benzoyl triflate in the presence of 2,6-lutidine,[49] followed by desilylation with tetra-*n*-butylammonium fluoride (TBAF), hydroxy benzoate **45** was obtained in good yield (78% from **43**). Finally, oxidation of **45** with RuO_4[50] afforded (±)-scopadulcic acid B (**2**) in 60% yield. Synthetic **2** showed 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, and chromatographic properties that were indistinguishable from those of an authentic sample of SDB.

Conclusion

The first total synthesis of (±)-scopadulcic acid B was accomplished in 30 steps and with an overall yield of 0.5% from 2-iodobenzaldehyde. The central strategic element of this

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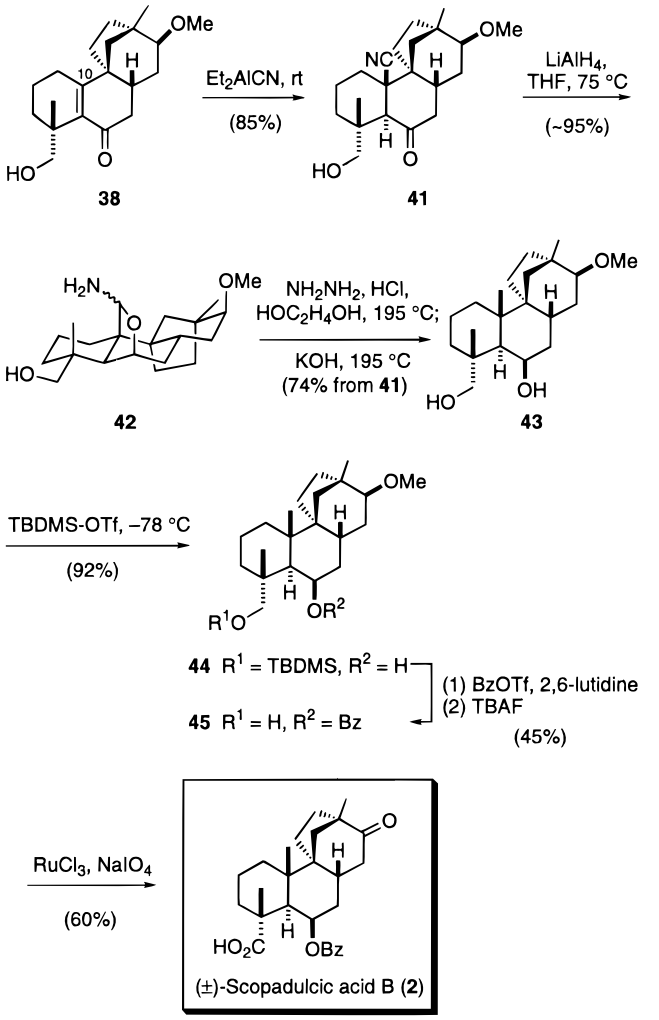
Scheme 6



synthesis is the palladium-catalyzed biscyclization of dienyl aryl iodide **8** which occurs with complete regioselectivity and in high yield to form the core scopadulan ring system.

Although this synthesis is too lengthy to provide practical access to SDB, it did yield several simpler analogs that proved to be inhibitors of H^+,K^+-ATPase.[51] Surprisingly, the most effective was siloxy enone **22**, which inhibited hog gastric H^+,K^+-ATPase in a dose-dependent fashion with $IC_{50} = 8.2$ μM.[51]

Two aspects of this first generation entry to the scopadulan terpenes would merit attention if an efficient total synthesis of these potentially pharmacologically significant materials were to be realized. First, an aromatic ring is not an ideal structural template for developing the two quaternary centers of the scopadulan A ring. Second, some improvement in synthetic efficiency would result if the initial step of the double Heck cyclization occurred stereoselectively to form the required *cis*-arrangement of the angular C(8) hydrogen and the one carbon bridge of the bicyclo[3.2.1]octane unit. These objectives were ultimately realized in a second generation strategy, culminating in the first total synthesis of (±)-scopadulcic acid A.[20]

Experimental Section

General Experimental Details. An ~1.5:1 mixture of *cis*- and *trans*-1-bromo-2-methyl-2-vinylcyclopropanes (**12** and **16**) was prepared from isoprene as described by Skattebol.[27] The major (more polar) *cis*-bromide could be separated on silica gel (Waters LC 500 preparative chromatograph) using hexane as the eluent: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.80 (dd, J = 17.1, 10.8 Hz, 1H), 5.17 (dd, J = 10.8, 1.1 Hz, 1H), 5.13 (dd, J = 17.1, 1.1 Hz, 1H), 3.00 (dd, J = 7.5, 4.7 Hz, 1H), 1.25 (t, J = 6.4 Hz, 1H), 1.24 (s, 3H), 1.05 (dd, J = 6.4, 4.7 Hz, 1H). Other general experimental details have been described.[52]

4-(2-Iodophenyl)-4-(*tert*-butyldimethylsiloxy)-1-butene (13). To a cooled (ice bath) solution of aldehyde **11** (56.3 g, 243 mmol) and THF (475 mL) was added dropwise a solution of allylmagnesium bromide (300 mL, 1.0 M in Et_2O). After 0.5 h, the reaction mixture was allowed to warm to room temperature (rt); saturated aqueous NH_4Cl (200 mL) was then added, and the resulting mixture was poured into a mixture of Et_2O (250 mL) and H_2O (250 mL). The organic layer was washed with H_2O (200 mL), dried over ($MgSO_4$), and concentrated to give a golden yellow oil (63.8 g, 96%), which could be used without purification in the subsequent step.

This material eventually crystallized; recrystallization from hexanes afforded colorless needles: mp 44−45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.9, 1.1 Hz, 1H), 7.51 (dd J = 7.8, 1.7 Hz, 1H), 7.35 (td, J = 7.6, 0.9 Hz, 1H), 6.97 (td, J = 7.6, 1.7 Hz, 1H), 5.96−5.82 (m, 1H), 5.24−5.16 (m, 2H), 4.92 (br d J = 6.0 Hz, 1H), 2.65−2.55 (m, 1H), 2.40 (s, 1H), 2.35−2.25 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.4, 139.2, 134.2, 129.1, 128.4, 126.9, 118.6, 97.3, 76.2, 42.7; IR (KBr) 3332−3227, 988, 920 cm^{-1}; MS (CI) *m*/*z* 257, 233, 186, 131, 130, 129.

To a solution of this alcohol (63.8 g, 232 mmol), DMF (650 mL), and imidazole (25.8 g, 379 mmol) was added *tert*-butyldimethylchlorosilane (47.9 g, 318 mmol) portionwise over 0.5 h. The reaction was allowed to stir at rt overnight and then at 65 °C for 2 h. After cooling to rt, the solution was partitioned between hexanes (500 mL) and H_2O (500 mL). The organic layer was washed with H_2O (500 mL), saturated aqueous $NaHCO_3$ (300 mL) and brine (300 mL), dried ($MgSO_4$), and concentrated to give 91.6 g, (86%) of **13** as a colorless oil, which could be used in the subsequent step without purification.

A pure sample of **13** was obtained by radial chromatography on silica gel (97:3 hexanes−EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.9, 1.1 Hz, 1H), 7.55 (dd, J = 7.8, 1.7 Hz, 1H), 7.37 (td, J = 7.6, 1.1 Hz, 1H), 6.97 (td, J = 7.6, 1.7 Hz, 1H), 6.00−5.87 (m, 1H), 5.15−5.08 (m, 2H), 4.94 (dd, J = 8.0, 3.8 Hz, 1H), 2.51−2.42 (m, 1H), 2.37−2.28 (m, 1H), 0.93 (s, 9H), 0.09 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 146.9, 138.8, 134.9, 128.7, 128.1, 127.9, 117.2, 96.9, 78.0, 43.6, 25.8, 18.2, −4.6, −4.9; IR (film) 992, 914 cm^{-1}; MS (EI) *m*/*z* 347, 331, 163, 99, 75, 73.

4-(2-Iodophenyl)-4-(*tert*-butyldimethylsiloxy)butanal (15). An adaptation of a published procedure was employed.[53] To a cooled solution (ice bath) of alkene **13** (91.6 g, 236 mmol) and hexane (80 mL) was added dropwise $BH_3{\cdot}SMe_2$ (8.5 mL, 10 M in BH_3), and the resulting solution was maintained at rt overnight. EtOH (80 mL) was then added to quench the excess hydride and to facilitate stirring, followed by sequential addition at 0 °C of 3 M NaOH (30 mL) and 30% H_2O_2 (34 mL); H_2O_2 was added at such a rate that the internal temperature did not exceed 40 °C. The resulting solution was heated under gentle reflux with vigorous stirring for 5 h. After cooling to rt, the reaction mixture was poured into cold H_2O (1 L) and extracted with Et_2O (750 mL). The organic layer was washed with H_2O (150 mL), brine (150 mL), dried ($MgSO_4$), and concentrated to give an orange liquid (85.4 g, 89%), which was purified by flash chromatography (4:1 hexanes−EtOAc) to give 60.3 g (63%) of alcohol **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.9, 1.1 Hz, 1H), 7.49 (dd, J = 7.8, 1.7 Hz, 1H), 7.33 (td, J = 7.6, 1.0 Hz, 1H), 6.92 (td, J = 7.7, 1.7 Hz, 1H), 4.88 (m, 1H), 3.65 (m, 2H), 1.82 (br s, 1H), 1.8−1.6 (m, 4H), 0.89 (s, 9H), 0.06 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.0, 138.8, 128.7, 128.1, 127.9, 96.8, 77.9, 62.8, 35.4, 28.7, 25.8, 18.1, −4.6, −5.0; HRMS (EI) *m*/*z* 349.0116 (349.0120 calcd for $C_{12}H_{18}IO_2Si$).

Alcohol **14** was oxidized on a 150 g scale using the procedure of Swern.[30] Purification of the crude product by flash chromatography (9:1 hexanes−EtOAc) afforded 119 g (80%) of **15** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, J = 1.7 Hz, 1H), 7.76 (dd, J = 7.9, 1.2 Hz, 1H), 7.48 (dd, J = 7.8, 1.7 Hz, 1H), 7.34 (td, J = 7.4, 1.2 Hz, 1H), 6.95 (td, J = 7.4, 1.7 Hz, 1H), 4.92 (dd, J = 7.3, 4.0 Hz, 1H), 2.51 (td, J = 7.4, 1.7 Hz, 1H), 2.1−1.8 (m, 3H), 0.88 (s, 9H),

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0.05 (s, 3H), −0.16 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.3, 146.1, 139.0, 129.0, 128.2, 127.9, 96.7, 77.0, 39.7, 31.2, 25.8, 18.0, -4.7, −5.1; IR (film) 1727 cm^{-1}; HRMS (EI) *m*/*z* 404.0667 (404.0668 calcd for $C_{16}H_{25}IO_2Si$).

***cis*- and *trans*-[4-(*tert*-Butyldimethylsiloxy)-4-(2-iodophenyl)-1-oxobutyl]-2-methyl-2-vinylcyclopropane (18).** A solution of the 3:2 diastereomeric mixture of *cis*- and *trans*-cyclopropyl bromides **12** and **16** (41.6 g, 0.258 mol) and Et_2O (500 mL) were cooled to −78 °C, and then *tert*-butyllithium (400 mL, 1.7 M in pentane) was added dropwise. The resulting solution was maintained at −78 °C for 1.5 h, freshly prepared $MgBr_2$·OEt_2 (170 mL, 0.45 mol, 2.6 M in Et_2O) was added, and the solution was warmed to 0 °C for 0.5 h. A solution of the aldehyde **15** (83.6 g, 0.207 mol) and Et_2O (200 mL) was then added dropwise. The resulting solution was maintained at 0 °C for 15 min and then allowed to warm to rt for 15 min before the reaction was quenched with saturated aqueous NH_4Cl (300 mL). Ether (500 mL) and H_2O (500 mL) were then added, the layers were separated, the aqueous layer was extracted with EtOAc (700 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to give alcohols **17** as a pale yellow oil.

This oil was immediately taken up in CH_2Cl_2 (1.5 L), and PCC (54 g, 0.26 mol), NaOAc (27 g, 0.33 mol), and powdered 3 Å molecular seives (170 g) were added. The resulting dark mixture was stirred at rt overnight and then diluted with Et_2O (2 L) and filtered through Florisil. Concentration and filtration of the resulting residue through silica gel (20:1 hexane-EtOAc) afforded an inseparable mixture of the *cis*- and *trans*-cyclopropyl ketones **18** (80 g, 75%) as a clear oil (90% pure by GLC analysis).

Spectral data for *cis*-**18** (a mixture of benzylic silyl ether diastereomers that was obtained from pure *cis*-cyclopropyl bromide **12**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 1H), 7.47 (dd, J = 7.8, 1.7 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 6.95 (td, J = 7.5, 1.6 Hz, 1H), 5.80 (dd, J = 17.4, 10.7 Hz) and 5.79 (dd, J = 17.4, 10.8 Hz, 1H total), 5.1−5.0 (m, 2H), 4.9−4.8 (m, 1H), 2.7−2.5 (m, 2H), 2.1−2.0 (m, 1H), 2.0−1.8 (m, 1H), 1.57 (t, J = 4.8 Hz, 1H), 1.31 and 1.30 (s, 3H total), 1.06 (dd, J = 7.6, 4.3 Hz, 1H), 0.98 (s, 3H), 0.051 and 0.046 (s, 3H total), −0.16 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.9, 146.7, 138.9, 128.9, 128.3, 128.2, 127.9, 113.4, 96.9, 77.7, 40.5, 36.9, 32.7, 31.0, 30.9, 29.7, 25.8, 23.1, 22.1, 18.0, 0.0, −4.7, −4.96, −5.01; IR (film) 1698, 973, 905 cm^{-1}; HRMS (EI) *m*/*z* 484.1262 (484.1294 calcd for $C_{22}H_{33}IO_2Si$).

2-[2-(*tert*-Butyldimethylsiloxy)-2-(2-iodophenyl)ethyl]-5-methylcyclohept-4-en-1-one (22). The mixture of cyclopropyl ketones **18** (104 g, 0.215 mol) was dissolved in CH_2Cl_2 (1 L) and cooled to 0 °C, and Et_3N (62 mL, 0.44 mol) and TMSOTf (64 mL, 0.33 mol) were then added sequentially. The resulting solution was maintained at 0 °C for 0.5 h, diluted with pentane (2.5 L), and washed with saturated aqueous $NaHCO_3$ (500 mL). The organic layers were dried (K_2CO_3), concentrated, and the resulting oil was taken up in benzene (1 L) and heated to reflux (100 °C external bath) for 1.5 h. After cooling to rt, the reaction was concentrated, and the resulting pale yellow oil (a mixture of **20** and **21**) was dissolved in EtOH (800 mL). Water was added until the solution just turned cloudy, and then additional EtOH was added until the solution cleared. After the addition of PPTS (6.4 g), the resulting solution was maintained at rt for 20 h. After concentration, the residue was dissolved in Et_2O (1 L), and the organic layer was washed with brine (200 mL), dried ($MgSO_4$), and concentrated. The resulting pale yellow oil was purified on silica gel using a Waters LC 500 chromatograph (20:1 hexane−EtOAc) to afford 53 g (51%, 92% pure by GLC analysis) of cycloheptenone **22**, a pale yellow oil that was a ∼1:1 mixture of benzylic silyl ether epimers, and 27 g (26%) of recovered *trans*-**18**. Spectral data for cycloheptenone **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.9, 1.1 Hz, 1H), 7.48 (dd J = 7.4, 1.6 Hz, 1H), 7.32 (td, J = 6.9, 1.1 Hz, 1H), 6.92 (td, J = 7.5, 1.6 Hz, 1H), 5.55 (br t, J = 5.1 Hz) and 5.47 (br t, J = 5.3 Hz, 1H total), 4.94−4.85 (m, 1H), 3.12−3.03 (m, 1H), 2.74−2.54 (m, 1H), 2.53−2.43 (m, 2H), 2.23−1.97 (m, 4H), 1.75 (br s, 3H), 1.57−1.38 (m, 1H), 0.87 and 0.86 (s, 3H total), 0.06 and 0.03 (s, 3H total), −0.19 and −0.23 (s, 9H total); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 214.1, 213.5, 147.5, 147.3, 138.9, 138.7, 137.6, 137.5, 128.9, 128.8, 128.3, 128.1, 128.0 127.9, 122.6, 122.5, 96.7, 76.3, 75.7, 47.5, 47.1, 41.6, 41.4, 40.8, 39.7, 31.9, 29.5, 29.3, 29.2, 26.1, 26.0, 25,8, 18.0, −4.5, −4.7, −5.0; IR (film) 1707 cm^{-1}; HRMS (CI) *m*/*z* 485.1364 (485.1349 calcd for $C_{12}H_{33}O_2SiI$).

Epimerization of *trans*-18 to a Mixture of *cis*- and *trans*-Isomers. To a solution of *trans*-cyclopropyl ketone **18** (4.0 g, 8.3 mmol) and methanol (20 mL) at rt was added sodium metal (0.38 g, 17 mmol) in small portions over 15 min. The resulting solution was heated at reflux for 1 d and allowed to cool to rt, and brine (7 mL) was added. The layers were separated, the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a light brown oil. Purification of the residue on silica gel (20:1 hexane−EtOAc) afforded 3.8 g (95%) of a 1:1.5 mixture of the *cis*- and *trans*-cyclopropyl ketones **18** (90% pure by GLC analysis).

2-[2-Hydroxy-2-(2-iodophenyl)ethyl]-5-methyl-1-methylenecyclohept-4-ene (23). Oven-dried methyltriphenylphosphonium bromide (50.1 g, 0.140 mol) was suspended in THF (1.5 L), the mixture was cooled to 0 °C, and *n*-BuLi (76 mL, 0.124 mol, 1.63 M in hexane) was added dropwise. The resulting bright yellow solution was maintained at 0 °C for 0.5 h, and a solution of cycloheptenone **22** (40.0 g, 0.083 mol) and THF (120 mL) was added dropwise. The reaction was maintained at 0 °C for 0.5 h and allowed to warm to rt for an additional 0.5 h. The reaction was then quenched by the addition of acetone (100 mL), solvents were removed under reduced pressure, and the residue was dissolved in methanol (500 mL) and extracted with pentane (5 × 800 mL). The combined pentane extracts were dried ($MgSO_4$) and concentrated to give (32 g, 80%) of crude 2-[2-(*tert*-butyldimethylsiloxy)-2-(2-iodophenyl)ethyl]-5-methyl-1-methylenecyclohept-4-ene as thick orange syrup, which was used directly in the next step without purification. A sample purified by flash chromatography (hexane) showed the following diagnostic data: ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.6, 154.3, 148.3, 148.0, 140.1, 139.6, 138.8, 128.7, 128.3, 128.2, 128.1, 127.0, 122.8, 122.5, 110.7, 108.6, 96.7, 76.5, 76.2, 43.8, 43.0, 41.6, 41.1, 34.8, 34.7, 34.2, 33.0, 32.3, 30.5, 25.9, 18.0, −4.2, −4.4, −4.7, −5.0; MS (CI) *m*/*z* 483, 407, 351, 224.

To a solution of the crude diene (32 g) and THF (350 mL) at rt was added a solution of TBAF (124 mL, 1 M solution in THF), and the resulting solution was maintained at rt for 8 h. Brine (50 mL) was added, the layers were separated, the aqueous layer was extracted with Et_2O (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (3:1 hexane−EtOAc) to afford 22 g (90%) of alcohol **23**, a 1:1 mixture of benzylic alcohol epimers, as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.75 (m, 1H), 7.6−7.5 (m, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.0−6.9 (td, J = 7.6, 1.7 Hz, 1H), 5.54 (br t, J = 6.5 Hz, 1H), 5.42 (br t, J = 6.7 Hz, 1H), 5.0−4.7 (m, 3H), 2.9−2.7 (m, 1H), 2.5−2.1 (m, 7H), 1.9−1.8 (m, 1H), 1.75 and 1.73 (br s, 3H total), 1.7−1.6 and 1.5−1.4 (m, 1H total); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.4, 153.9, 146.6, 140.1, 139.2, 129.0, 128.5, 127.1, 127.0, 122.3, 122.1, 111.3, 110.1, 97.3, 76.5, 75.5, 43.1, 42.0, 41.5, 40.4, 34.5, 32.8, 32.0, 31.6, 31.5, 29.7, 25.8; IR (film) 3415, 1635, 892 cm^{-1}; HRMS (CI) *m*/*z* 368.0632 (368.0637 calcd for $C_{17}H_{21}IO$).

2-[2-(2-Iodophenyl)-2-oxoethyl]-5-methyl-1-methylenecyclohept-4-ene (8). A solution of **23** (22.0 g, 0.060 mol) and CH_2Cl_2 (250 mL) was cooled to 0 °C, and PCC (17.6 g. 0.083 mol), NaOAc (10.1 g, 0.124 mol), and powdered 3 Å molecular sieves (50 g) were added portionwise over 15 min.[31] The dark solution was maintained at 0 °C for 0.5 h and then at rt for 14 h. The reaction was diluted with Et_2O (800 mL) and filtered through Florisil, and the filtrate was concentrated and the residue was purified by flash chromatography (20:1 hexanes−EtOAc) to afford 20 g (90%) of ketone **8** as a colorless oil that was 90% pure by GLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.9, 1.0 Hz, 1H), 7.4−7.3 (m, 2H), 7.10 (ddd, J = 7.9, 7.2, 2.0 Hz, 1H), 5.45 (br t, J = 6.5 Hz, 1H), 4.72 (br s, 2H), 3.1−2.9 (m, 3H), 2.37−2.25 (m, 4H), 2.17−2.07 (m, 2H), 1.74 (br d, J = 0.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.1, 154.0, 144.7, 140.5, 133.4, 127.8, 122.0, 110.1, 91.1, 45.7, 40.8, 34.5, 32.7, 32.0, 25.9; IR (film) 1698, 1638, 895 cm^{-1}; HRMS (EI) *m*/*z* 366.0499 (366.0481 calcd for $C_{17}H_{19}IO$).

(±)-(6a*R,9*R**,11a*R**)-$\Delta^{7(8)}$-9,11a-Methano-9-methyl-5-oxo-5,6,6a,11a-tetrahydro-11a*H*-cyclohepta[*a*]naphthalene (24) and (9*R**,11a*R**)-9,11a-Methano-9-methyl-5-oxo-5,11a-dihydro-11a*H*-**

cyclohepta[*a*]naphthalene (25). A solution of iodide **8** (6.12 g, 0.017 mol), $Pd(OAc)_2/Ph_3P$ (1:2, 327 mg, 0.425 mmol), Et_3N (12 mL, 0.085 mol), and MeCN (150 mL) was heated at reflux for 4 h. After cooling, the solution was diluted with Et_2O (500 mL) and extracted with saturated aqueous $NaHCO_3$ (150 mL) and brine (70 mL). After drying ($MgSO_4$), concentration afforded a dark oil. Purification of this material by flash chromatography (20:1 hexanes−EtOAc) gave 3.86 g (97%, 83% pure by GLC analysis) of tetracyclic products as a 1.5:1 mixture of the unconjugated and conjugated enones **24** and **25**, respectively. This mixture was resolved by careful flash chromatography (25:1 hexanes−EtOAc) for characterization. Unconjugated enone **24**, a mixture of C(8) epimers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.55 (m, 2H), 7.31 (m, 1H), 5.80 (dt, J = 9.5, 1.5 Hz) and 5.74 (m, 1H total), 5.47 (dd, J = 9.5, 3.7 Hz) and 5.29 (dd, J = 9.5, 1.9 Hz, 1H total), 3.16 (m, 1H), 2.8−2.3 (m, 2H), 2.0−1.4 (m, 6H), 1.25 and 1.22 (s, 3H total); ^{13}C NMR (major isomer, 300 MHz, $CDCl_3$) δ 197.9, 150.9, 138.8, 133.8, 132.2, 127.3, 126.7, 126.5, 126.0, 47.6, 46.1, 43.6, 43.4, 42.4, 41.7, 32.7, 23.5; IR (film) 1695, 1599 cm^{-1}; HRMS (EI) *m*/*z* 238.1357 (238.1356 calcd for $C_{17}H_{18}O$). Conjugated enone **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, J = 8.2, 0.8 Hz, 1H), 7.60−7.53 (m, 2H), 7.35 (td, J = 7.9, 2.1 Hz, 1H), 6.21 (d, J = 1.9 Hz, 1H), 2.73 (dddd, J = 15.4, 10.6, 2.7, 1.9 Hz, 1H), 2.52 (dd, J = 15.4, 5.9 Hz, 1H), 2.36 (ddd, J = 11.7, 10.6, 5.9 Hz, 1H), 2.20 (dd, J = 11.7, 2.7 Hz, 1H), 2.06−1.86 (m, 3H), 1.75−1.68 (m, 1H), 1.6−1.5 (m, 2H), 1.17 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 184.9, 167.3, 148.1, 132.2, 131.8, 126.4, 126.1, 126.0, 121.6, 55.7, 50.0, 41.9, 39.7, 29.5, 37.1, 31.0, 25.9; IR (film) 1661, 1601 cm^{-1}; HRMS (EI) *m*/*z* 238.1371 (94, 238.1357 calcd for $C_{17}H_{18}O$).

(±)-(9*R,11a*R**)Δ$^{7(8)}$-9,11a-Methano-9-methyl-5-oxo-5,11a-dihydro-11a*H*-cyclohepta[*a*]naphthalene (26).** A solution of tetracyclic ketones **24**/**25** (3.5 g, 1.5:1), DDQ (10 g, 45 mmol), and PhCl (150 mL) was heated at reflux (160 °C oil bath) for 7 h. The cooled reaction mixture was filtered through a plug of Celite, and the filtrate was concentrated. The residue was dissolved in $CHCl_3$ (200 mL) and washed with H_2O (3 × 100 mL), and the combined aqueous washes were back-extracted with $CHCl_3$ (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The resulting dark oil was adsorbed on 5 g of silica gel, layered on a silica gel flash column, and eluted with 3:2 hexanes−EtOAc to afford dienone **26** (1.95 g, 95% pure by GLC analysis) as an oil, which solidified upon standing: mp 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (td, J = 7.7, 1.0 Hz, 1H), 7.65−7.55 (m, 2H), 7.38 (ddd, J = 8.2, 5.6, 2.7 Hz, 1H), 6.37 (dd, J = 9.3, 1.0 Hz, 1H), 6.22 (d, J = 9.3 Hz, 1H), 6.17 (s, 1H), 2.29−2.17 (m, 2H), 2.02−1.75 (m, 5H), 1.37 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 185.0, 163.0, 149.6, 147.7, 132.3, 132.0, 126.5, 126.3, 126.0, 125.4, 120.5, 52.8, 48.7, 45.0, 41.3, 38.5, 23.8; IR (KBr) 1645 cm^{-1}; HRMS (EI) *m*/*z* 236.1210 (236.1201 calcd for $C_{17}H_{16}O$). Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.23; H, 6.84.

(±)-(7*R,8*S**,9*R**,11a*R**)-7,8-Epoxy-9,11a-methano-9-methyl-5-oxo-5,11a-dihydro-11a*H*-cyclohepta[*a*]naphthalene (27).** A solution of dieneone **26** (1.9 g, 8.0 mmol), *m*-chloroperoxybenzoic acid (2.0 g, titrated at 74%, 8.6 mmol), and CH_2Cl_2 (100 mL) was maintained at rt for 48 h and then quenched with 10% aqueous $Na_2S_2O_3$ (100 mL). After 1 h, the layers were separated, and the organic layer was washed with 15% NaOH (50 mL) and dried ($MgSO_4$). Concentration and purification of the residue by radial chromatography (9:1 hexanes−EtOAc) gave 1.7 g (83%) of epoxy enone **27** as a colorless oil that solidified upon standing: mp 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J = 8.1, 1.2 Hz, 1H), 7.61−7.51 (m, 2H), 7.37 (td, J = 8.1, 1.2 Hz, 1H), 6.55 (s, 1H), 3.60 (d, J = 3.6 Hz, 1H), 3.28 (d, J = 3.6 Hz, 1H), 2.25−1.82 (m, 6H), 1.39 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 184.3, 159.6, 147.3, 132.9, 131.5, 128.2, 126.7, 126.5, 125.3, 60.1, 51.9, 47.5, 42.8, 42.3, 41.7, 35.3, 22.6; IR (KBr) 1670, 1600 cm^{-1}; HRMS (EI) *m*/*z* 252.1136 (252.1140 calcd for $C_{17}H_{16}O_2$). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.28; H, 6.41.

(±)-(8*R,9*R**,11a*R**)-8-Hydroxy-9,11a-methano-9-methyl-5-oxo-5,11a-dihydro-11a*H*-cyclohepta[*a*]naphthalene (28).** A slight adaptation of a general procedure was employed.[33] Tellurium powder (1.85 g, 14.5 mmol) and $NaBH_4$ (1.1 g, 29.1 mmol) were added to EtOH (50 mL), and the resulting solution was degassed and then heated at 80 °C for 1 h with vigorous stirring. After 1 h, the pale purple solution was cooled to 0 °C, and a solution of epoxide **27** (913 mg, 3.62 mmol) and EtOH (11 mL) was added dropwise. After 10 min, H_2O (10 mL) was added, and after an additional 1 h, the reaction mixture was passed through a plug of Celite and the filtrate was concentrated. This residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (40 mL), and the organic layer was separated and dried ($MgSO_4$). After concentration, the residue was purified by radial chromatography (9:1 hexanes−*i*-PrOH) to provide alcohol **28** (806 mg, 88%) as a pale yellow powder: mp 189−190 °C (from $CHCl_3$−hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, J = 7.5, 2.0 Hz, 1H), 7.64−7.54 (m, 2H), 7.37 (ddd, J = 8.1, 6.0, 2.3 Hz, 1H), 6.26 (d, J = 2.0 Hz, 1H), 3.81 (br t, J = 4.0 Hz, 1H), 2.93 (ddd, J = 16.0, 4.8, 2.1 Hz, 1H), 2.53 (dd, J = 16.0, 0.7 Hz, 1H), 2.45−2.35 (m, 2H), 2.11 (d, J = 12.0 Hz, 1H), 2.01−1.79 (m, 4H), 1.24 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 184.7, 165.0, 147.7, 132.4, 131.7, 126.6, 126.3, 125.9, 123.6, 75.2, 50.1, 48.9, 46.1, 39.4, 38.1, 35.9, 22.1; IR (KBr) 1645, 1595 cm^{-1}; HRMS (EI) *m*/*z* 254.1301 (254.1307 calcd for $C_{17}H_{18}O_2$); MS (CI) *m*/*z* 255, 237. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.17; H, 7.15.

(±)-(6a*R,8*S**,9*S**,11a*S**)-8-Hydroxy-9,11a-methano-9-methyl-5-oxo-5,6,6a,11a-tetrahydro-11a*H*-cyclohepta[*a*]naphthalene (30).** Hydroxy enone **28** (452 mg, 1.78 mmol) was dissolved in THF (50 mL) and cooled in a −78 °C bath, and $LiAlH_4$ (2.5 mL, 1.0 M in Et_2O) was added dropwise over 5 min. The reaction was maintained at −78 °C for 1 h, and the −78 °C bath was replaced with a −23 °C bath. After 1 h, the reaction was poured into a mixture of EtOAc (100 mL) and 5% HCl (25 mL) and the organic layer was separated and dried ($MgSO_4$). Concentration and purification of the residue by radial chromatography (95:5 hexanes−*i*-PrOH) provided keto alcohol **30** (334 mg, 73%) as a thick oil, which solidified upon standing: mp 110−111 °C (from $CHCl_3$−hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.7 Hz, 1H), 7.55−7.53 (m, 2H), 7.29 (ddd, J = 8.1, 5.4, 3.0 Hz, 1H), 3.59 (br s, 1H), 2.55−2.40 (m, 3H), 2.17−2.10 (m, 1H), 2.02−1.90 (m, 2H), 1.77−1.51 (m, 6H), 1.20 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.9, 149.5, 133.9, 132.0, 126.9, 126.2, 125.3, 74.2, 47.3, 45.1, 44.7, 41.3, 36.4, 36.0, 35.7, 32.7, 23.8; IR (film) 3465, 1671 cm^{-1}; HRMS (EI) *m*/*z* 256.1467 (256.1453 calcd for $C_{17}H_{20}O_2$). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.55; H, 7.82.

(±)-(6a*R,8*R**,9*R**,11a*R**)-8-Hydroxy-9,11a-methano-9-methyl-5-oxo-5,6,6a,11a-tetrahydro-11a*H*-cyclohepta[*a*]naphthalene (29).** A mixture of hydroxy enone **28** (165 mg, 0.65 mmol), Pd/C (165 mg), HCO_2NH_4 (410 mg, 6.5 mmol), and DMF (7 mL) was stirred for 1 h at rt and then filtered through Celite. The eluent was partitioned between CH_2Cl_2 (100 mL) and H_2O (25 mL), and the organic layer was dried ($MgSO_4$). Concentration gave an oil that was 8:1 mixture of **29** and **30** (^{1}H NMR analysis). This mixture could be separated by radial chromatography (95:5 hexanes−*i*-PrOH) to give a pure sample of **29** which deposited crystals suitable for single-crystal X-ray analysis.[54]

(±)-(6a*R,8*S**,9*S**,11a*S**)-9,11a-Methano-8-methoxy-9-methyl-5-oxo-5,6,6a,11a-tetrahydro-11a*H*-cyclohepta[*a*]naphthalene (31).** To a solution of alcohol **30** (659 mg, 2.57 mmol), dry hexane (51 mL), and CH_2Cl_2 (13 mL) at rt were added sequentially 2,6-di-*tert*-butylpyridine (2.3 mL, 10.3 mmol) and methyl trifluoromethanesulfonate (0.6 mL, 5 mmol). The reaction was maintained at rt for 1h and then heated at reflux for 15 h. After cooling, the reaction mixture was partitioned between Et_2O (100 mL) and 1 M HCl (15 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by radial chromatography (15:1 hexane−EtOAc) to afford 519 mg (75%) of ketone **31** as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 1H), 7.53−7.50 (m, 2H), 7.29−7.25 (m, 1H), 3.33 (s, 3H), 2.96 (br s, 1H), 2.50−2.38 (m, 3H), 2.15−2.08 (m, 1H), 1.97−1.86 (m, 3H), 1.66 (dd, J = 12.4, 4.5 Hz, 1H), 1.58 (dd, J = 13.0, 4.4 Hz, 1H), 1.48−1.56 (m, 1H), 1.38 (ddd, J = 15.0, 12.0, 3.5 Hz, 1H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 149.6, 133.7, 131.9, 126.7, 126.0, 125.3, 83.6, 57.1, 46.9, 45.4, 45.0, 41.3, 36.5, 36.1, 32.7, 30.2, 23.8; IR (film) 1686 cm^{-1}; HRMS

(54) The authors have deposited atomic coordinates for this compound 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, U.K.

(EI) *m*/*z* 270.1598 (270.1620 calcd for $C_{18}H_{22}O_2$). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.98; H, 8.17.

(±)-(5*R,6a*S**,8*R**,9*R**,11a*R**)-5-Hydroxy-9,11a-methano-8-methoxy-9-methyl-5,6,6a,11a-tetrahydro-11a*H*-cyclohepta[*a*]naphthalene-4-carboxylic acid (36).** To a solution of ketone **31** (1.52 g, 5.62 mmol) and dry THF (250 mL) at −78 °C was added $LiAlH_4$ (8.4 mL, 1.5 equiv, 1.0 M in Et_2O) dropwise. The resulting solution was maintained at −78 °C for 30 min, and then poured into a rapidly stirring mixture of EtOAc (250 mL) and 1 M HCl (75 mL). The layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated to provide 1.50 g (98%, 96% pure by GC analysis) of alcohol **34** as a thick crude oil, which was not purified but employed directly in the next reaction. Alcohol **34** showed a diagnostic doublet of doublets (J = 10.9, 5.9 Hz) at δ 4.78 for the axial C(6) methine hydrogen.

An adaptation of a published procedure was employed.[35] A solution of this crude alcohol (102 mg, 0.375 mmol), dry pentane (4 mL) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (freshly distilled from CaH_2 and then from Na, 0.23 mL, 1.49 mmol) was treated dropwise with *n*-BuLi (0.89 mL, 1.6 M in hexane) at rt. After 20 min, the resulting pink mixture was heated at reflux for 3 h. The resulting deep red mixture was cooled to 0 °C, and solid CO_2 was added in small portions over 3 h. The heterogeneous mixture was stirred at rt under a balloon of CO_2 for 16 h. The reaction mixture was then diluted with Et_2O (35 mL) and acidified with 1 M HCl to pH 1−2. The layers were separated, the aqueous layer was extracted with EtOAc (5 × 25 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting solid residue was recrystallized from hexane−ether to afford 63 mg (53%) of acid **36** as a colorless solid. The mother liquors were purified on silica gel (3:1 hexane−EtOAc) to give 11 mg (9.8%) of lactone **35** as a colorless solid and 33 mg (32%) of the starting alcohol **34**. Acid **36**: mp 158−159 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.52 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 5.16 (dd, J = 10.5, 6.7 Hz, 1H), 3.33 (s, 3H), 2.95 (br s, 1H), 2.04 (t, J = 9.6 Hz, 1H), 1.90−1.80 (m, 4H), 1.71−1.64 (m, 4H), 1.36−1.58 (m, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 145.7, 141.1, 134.3, 130.0, 128.0, 128.1, 85.8, 67.9, 57.5, 48.3, 46.4, 37.4, 36.5, 36.4, 31.0, 24.2, two carbons buried under solvent peaks; IR (film) 3344, 1659 cm^{-1}; HRMS (CI) *m*/*z* 299.1658, (299.1647 calcd for $C_{19}H_{24}O_4$). Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.10; 7.68. Lactone **35**: mp 150−152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.3 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 5.30 (dd, J = 11.7, 5.3 Hz, 1H), 3.38 (s, 3H), 2.95 (s, 1H), 2.20 (ddd, J = 16.2, 12.8, 3.9 Hz, 1H), 2.22 (dd, J = 11.2, 5.3 Hz, 1H), 2.02 (d, J = 11.5, 1H), 1.95−1.75 (m, 3H), 1.65−1.35 (m, 5H), 1.18 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.5, 148.5, 141.1, 130.1, 130.0, 124.5, 122.8, 84.1, 78.7, 57.6, 48.1, 46.8, 45.3, 38.1, 37.6, 36.1, 31.5, 30.0, 23.5; IR (film) 1760 cm^{-1}; HRMS (CI) *m*/*z* 299.1659 (299.1627 calcd for $C_{19}H_{22}O_3$).

(±)-(4*R,6a*R**,8*S**,9*S**,11a*S**)-4,9-Dimethyl-4-hydroxymethylene-9,11a-methano-8-methoxy-5-oxo-1,2,3,4,5,6,6a,11a-octahydro-11a*H*-cyclohepta[*a*]naphthalene (38).** A slight modification of a general procedure was employed.[41b] Liquid ammonia (60 mL, dried for 30 min over $NaNH_2$) was distilled under Ar into a predried, three-necked flask. Dry THF (12 mL) was added, and the resulting solution was cooled to −78 °C. Lithium metal (108 mg, 15.5 mmol, containing 0.02% Na) was added in small pieces, and then a solution of acid **36** (288 mg, 0.911 mmol) and THF (1.5 mL) was added slowly by syringe. The resulting deep blue solution was allowed to reflux for 20 min and was then cooled to −78 °C. Isoprene (∼1 mL) then was added to quench excess Li, and the resulting mixture was allowed to warm to rt. After the NH_3 had evaporated, the reaction mixture was recooled to 0 °C and CH_3I (2.1 mL) was added. The resulting mixture was stirred at 0 °C for 15 min, Et_2O (100 mL) and H_2O (20 mL) were added, and the aqueous layer was acidified to pH 1 with HCl. The layers were separated, the aqueous layer was extracted with Et_2O (3 × 25 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated.

This crude residue was taken up in EtOAc (5 mL), Rh/Al_2O_3 (30 mg) was added, and the vessel was fitted with a H_2 balloon and stirred under a H_2 atmosphere for 12 h. The reaction was then filtered through a plug of Celite, and the filtrate was concentrated to provide crude **37**, which was immediately dissolved in Et_2O (5 mL) and cooled to −78 °C. A solution of $LiAlH_4$ (1.6 mL, 1.0 M in Et_2O) was added dropwise, and the resulting mixture was then allowed to warm to 0 °C for 20 min and then to rt over 15 min. The reaction was quenched by successive addition of H_2O (65 μL), 2 M NaOH (65 μL), and H_2O (190 μL). The resulting heterogeneous mixture was stirred at rt for 2 h and filtered, and the filtrate was concentrated to afford the corresponding diol as a colorless oil.

A mixture of this crude diol, MnO_2 (55 mg, 0.63 mmol), and CH_2Cl_2 (5 mL) was stirred at rt for 15 h and then filtered through a plug of Celite. The filtrate was concentrated, and the residue was purified by radial chromatography (3:1 hexane−EtOAc) to afford 160 mg (56% over four steps) of enone **38** as a colorless solid: mp 125−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (AB q, $\Delta\upsilon$ = 103 Hz, J_{AB} = 10.6 Hz, 2H), 3.31 (s, 3H), 2.88 (br s, 1H), 2.3−2.1 (m, 5H), 1.83−1.55 (m, 8H), 1.55−1.40 (m, 4H), 1.3−1.2 (m, 1H), 1.18 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 165.1, 138.2, 83.4, 70.9, 57.2, 49.2, 44.9, 42.9, 41.9, 38.7, 36.9, 35.9, 35.5, 30.0, 27.9, 27.2, 24.0, 18.5; IR (film) 1662, 1610 cm^{-1}; HRMS (CI) *m*/*z* 319.2247 (319.2273 calcd for $C_{20}H_{30}O_3$). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.48; H, 9.55.

(±)-(4*R,4a*S**,6a*R**,8*S**,9*S**,11a*S**11b*R**)-11b-Cyano-4,9-dimethyl-4-(hydroxymethylene)-9,11a-methano-8-methoxy-5-oxo-1,2,3,4,4a,5,6,6a,11a,11b-decahydro-11a*H*-cyclohepta[*a*]naphthalene (41).** A solution of enone **38** (115 mg, 0.362 mmol), Et_2AlCN (1.1 mL, 1.0 M in toluene), and dry toluene (5 mL) was maintained at rt for 24 h. The reaction was then diluted with Et_2O (50 mL) and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 15 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography (3:1 hexane−EtOAc) afforded 55 mg (48%) of recovered starting material **38** and 60 mg (48%) of nitrile **41** as a clear oil. Recovered **38** was recycled two times to obtain a total of 106 mg (85%) of nitrile **41**: ^{1}H NMR (500 MHz) δ 3.77 (d, J = 10.6 Hz, 1H), 3.30 (s, 3H), 3.15 (d, J = 10.6 Hz, 1H), 2.88 (br s, 1H), 2.54 (m, 1H), 2.44 (s, 1H), 2.35 (dd, J = 15.3, 5.0 Hz, 1H), 2.20−2.10 (m, 2H), 1.95−1.85 (m, 2H), 1.80−1.16 (m, 12H), 1.29 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz) δ 207.3, 122.7, 83.0, 71.0, 57.1, 53.0, 50.8, 45.7, 45.6, 44.0, 39.9, 37.7, 37.3, 36.0, 35.9, 31.0, 30.1, 23.8, 23.0, 18.2, 16.7; IR (film) 3463, 2231, 1714 cm^{-1}; HRMS (CI) *m*/*z* 346.2373 (346.2382 calcd for $C_{21}H_{31}NO_3$).

(±)-(4*R,4a*R**,5*R**,6a*R**,8*S**,9*S**,11a*S**11b*S**)-5-Hydroxy-4-(hydroxymethylene)-9,11a-methano-8-methoxy-4,9,11b-trimethyl-1,2,3,4,4a,5,6,6a,11a,11b-decahydro-11a*H*-cyclohepta[*a*]naphthalene (43).** To a solution of nitrile **41** (31 mg, 0.09 mmol) and THF (3.2 mL) at −78 °C was added a solution of $LiAlH_4$ (1.4 mL, 1.0 M in Et_2O), and the resulting solution was allowed to warm to rt and then heated at reflux for 4 h. The reaction was cooled to 0 °C and quenched by successive addition of H_2O (55 μL), 2 M NaOH (55 μL), and H_2O (170 μL). The resulting heterogeneous mixture was stirred at rt for 2 h and filtered, and the solid was washed with EtOAc. Concentration of the filtrate afforded 36 mg of crude aminal **42** as viscous oil, which was used directly in the next reaction: HRMS (CI) *m*/*z* 350.2678 (350.2695 calcd for $C_{21}H_{36}NO_3$).

A mixture of this sample of crude aminal **42** (17 mg, 0.05 mmol), ethylene glycol (1 mL), hydrazine dihydrochloride (50 mg, 0.48 mmol), and hydrazine monohydrate (0.2 mL) was placed in a tightly sealed vial and heated in a 195 °C oil bath for 5 h. The reaction mixture was cooled to 0 °C, KOH pellets (320 mg, excess) were carefully added, and this mixture was placed in the 195 °C oil bath for an additional 12 h. After the reaction was allowed to cool to rt, Et_2O (10 mL) and H_2O (3 mL) were added, the layers were separated, the aqueous layer was extracted with EtOAc (6 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue on silica gel (3:1 hexane−EtOAc) gave 12 mg (75%) of the diol **43** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (app d, J = 2.3 Hz, 1H), 3.53 (d, J = 11.0 Hz, 1H), 3.31 (s, 3H), 3.15 (d, J = 11.0 Hz, 1H), 2.80 (br s, 1H), 2.18−2.26 (m, 1H), 1.75−1.62 (m, 3H), 1,01−1.55 (m, 16H), 1.33 (s, 3H), 1.18 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.6, 72.3, 67.8, 62.2, 57.2, 53.1, 44.5, 43.4, 39.4, 38.6, 38.5, 37.8, 36.5, 34.3, 31.1, 28.8, 24.1, 22.3, 22.1, 20.8,

18.2; IR (film) 3438 cm^{-1}; HRMS (CI) *m*/*z* 319.2628 (319.2637 calcd for $C_{21}H_{36}O_3$).

(±)-(4*R,4a*R**,5*R**,6a*R**,8*S**,9*S**,11a*S**,11b*S**)-4-((*tert*-Butyldimethylsiloxy)methylene)-5-hydroxy-9,11a-methano-8-methoxy-4,9,11b-trimethyl-1,2,3,4,4a,5,6,6a,11a,11b-decahydro-11a*H*-cyclohepta[*a*]naphthalene (44).** To a solution of diol **43** (38 mg, 0.11 mmol) and CH_2Cl_2 (5 mL) at −78 °C was added dropwise a solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (74 μL, 0.34 mmol), 2,6-lutidine (83 μL, 0.67 mmol), and CH_2Cl_2 (1 mL). The reaction was maintained at −78 °C for 10 min, and then brine (1 mL) was added. After the mixture was allowed to warm to rt, it was diluted with Et_2O (15 mL), the layers were separated, the aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue on silica gel (15:1 hexane−EtOAc) gave 41 mg (92%) of silyl ether **44** as a viscous colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (app br s, 1H), 3.50 (d, *J* = 9.8 Hz, 1H), 3.31 (s, 3H), 2.93 (d, *J* = 9.8 Hz, 1H), 2.80 (br s, 1H), 2.22 (m, 1H), 1.75−1.00 (m, 18H), 1.32 (s, 3H), 1.10 (s, 3H), 1.00 (s, 3H), 0.87 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.6, 71.0, 67.9, 57.2, 53.1, 43.4, 43.1, 39.3, 38.8, 38.5, 38.4, 37.9, 36.7, 34.4, 31.1, 28.9, 25.8, 25.7, 24.1, 22.2, 21.1, 18.3, 18.1, −5.6, −5.7; IR (film) 3486 cm^{-1}; HRMS (CI) *m*/*z* 433.3486 (433.3493 calcd for $C_{27}H_{50}O_3Si$).

(±)-(4*R,4a*R**,5*R**,6a*R**,8*S**,9*S**,11a*S**,11b*S**)-5-Benzoyl-4-(hydroxymethylene)-9,11a-methano-8-methoxy-4,9,11b-trimethyl-1,2,3,4,4a,5,6,6a,11a,11b-decahydro-11a*H*-cyclohepta[*a*]naphthalene (45).** A solution of alcohol **44** (26 mg, 0.058 mmol) and dry CH_2Cl_2 (1 mL) at 0 °C was treated dropwise with 2,6-lutidine (140 μL, 1.2 mmol) and benzoyl triflate (94 μL, 0.58 mmol), and the resulting solution was maintained at 0 °C for 2 h.[49] Ether (5 mL) and saturated aqueous $NaHCO_3$ (0.5 mL) were then added, and the aqueous layer was separated and extrated with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified on silica gel (20:1 hexane−EtOAc) to provide 15.7 mg of the C(6) benzoate (49%, 85% based on consumed **44**) as a thick oil, together with 11 mg of recovered **44**. The crude benzoate was used immediately in the next reaction: HRMS (CI) *m*/*z* 555.3833 (555.3869 calcd for $C_{34}H_{55}O_4Si$).

A solution of tetrabutylammonium fluoride (0.5 mL, 1.0 M in THF) was added to this crude benzoate, the resulting solution was maintained at rt for 16 h, and Et_2O (5 mL) and brine (1 mL) were added. The resulting mixture was stirred at rt for 1 h, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel (10:1 hexane−EtOAc) to afford 12 mg of alcohol **45** (45%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 5.57 (app d, *J* = 2.0 Hz, 1H), 3.55 (d, *J* = 10.9 Hz, 1H), 3.27 (s, 3H), 3.10 (d, *J* = 10.9 Hz, 1H), 2.80 (br s, 1H), 2.21−2.15 (m, 1H), 1.78−1.85 (m, 1H), 1.74−1.04 (m, 17H), 1.52 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 132.8, 130.9, 129.7, 128.4, 84.6, 71.5, 70.7, 57.5, 52.9, 43.5, 43.2, 38.7, 38.5, 38.4, 37.8, 36.5, 35.4, 34.1, 31.1, 29.6, 24.1, 22.4, 22.3, 20.3, 18.2; IR (film) 3463, 1712 cm^{-1}; HRMS (CI) *m*/*z* 441.2959 (441.3004 calcd for $C_{28}H_{40}O_4$).

(±)-Scopadulcic acid B (2). To a solution of alcohol **45** (12.5 mg, 0.025 mmol), CCl_4 (0.2 mL), MeCN (0.2 mL), and H_2O (0.3 mL) at rt was added $NaIO_4$ (91 mg, 0.43 mmol). After 15 min of stirring, $RuCl_3 \cdot 3H_2O$ (∼1 mg) was added, and the reaction mixture was stirred at rt overnight.[50] After 16 h, the mixture was filtered through a plug of Celite, and the filter cake was washed with EtOAc. The filtrate was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified on silica gel (2:1 hexane−EtOAc) to provide 7.5 mg (60%) of (±)-scopadulcic acid B as a colorless solid: mp 230−232 °C. Synthetic (±)-scopadulcic acid B (**2**) was in all respects (500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, TLC mobility in three solvent systems), except optical rotation, indistinguishable from an authentic sample of scopadulcic acid B provided by Professor T. Hayashi.

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