

## Total Synthesis of Dumsin. 1. Retrosynthetic Strategy and the **Elaboration of Key Intermediates from (–)-Bornyl Acetate**

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An intramolecular anionic oxy-Cope rearrangement  $(44 \rightarrow 46)$  serves as the key step in a synthetic approach to the insect antifeedant dumsin. Initial investigations clarified the manner in which (-)-bornyl acetate may be transformed into the exo-norbornenol 44. Two routes were developed to advance beyond 46. The first involved acetal 51 as a matrix that was expected to allow the elaboration of rings D and E. The second plan deferred oxidation of the cyclopentene ring in 46 to a later stage of molecular construction. The latter experiments formed the basis of a protocol that led to the successful acquisition of keto aldehydes typified by 108 and 114.

Numerous plants native to the African and Asian continents contain limonoid triterpenes as their principal biologically active ingredient.<sup>1</sup> Many of these sources have historically been extensively utilized as traditional medicines and valued for their ability to cure or alleviate a variety of symptoms including fever, tuberculosis, hemorrhoids, and snake bite.<sup>2</sup> More recently, the evolutionary diversification of limonoids has become regarded as profitable for further investigation. Indeed, promising antifungal, anticancer, and insect antifeedant activities continue to be uncovered. Some of the more recently characterized members of this class are represented by 1-9 (Chart 1).<sup>2-9</sup>

Two lines of synthetic effort have been explored in this area. The first is, of course, the de novo assembly of these complex structures, remarkably few examples of which have appeared in the literature.<sup>10,11</sup> More often, attention has been focused on simplified or degraded limonoids

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references therein.

with a view to producing effective probes, identifying structure-activity relationships, and enhancing biological activity.<sup>12-19</sup> To us, the lineage of dumsin (2) and its eye-catching molecular intricacy were sufficient to engage our curiosity and attention. The Kubo group was successful in isolating 2 from the bitter root bark of the East African plant known in Swahili as "Msinduzi".9 The natives valued its extracts for alleviating stomach aches and warding off the symptoms of the common cold. More recent screening efforts have shown dumsin to possess remarkably potent insect antifeedant properties. On the basis of detailed spectroscopic analysis and a singlecrystal X-ray determination performed by Clardy,<sup>9</sup> 2 was identified to be a tetranortriterpenoid housing a highly oxygenated central core compactly accommodating four quaternary carbon atoms and nine additional stereogenic centers. The absolute configuration was also defined to be as shown. Also noteworthy is the presence of a hemiacetal of an  $\alpha$ -diketone embedded in the western ABC sector.

Synthetic Strategy. Since no chemistry has been recorded for **2**, our preoccupation with its construction, colloquially referred to in these laboratories as "The Dumsinthesis", was forced to proceed without any prior insight into its chemical idiosyncrasies. One point of

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<sup>3580</sup> 

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**SCHEME 1** 



concern was the projected sensitivity of the oxygenated A/B ring system. Although it seemed appropriate to delay its installation as long as possible, we remained concerned as to whether the concept of intramolecular condensation of a silyl-protected cyanohydrin anion<sup>20</sup> with a lactone carbonyl as envisioned for  $10 \rightarrow 2$  (Scheme 1) could in fact be exploited. Accordingly, this step was initially modeled with a structurally simpler prototype.<sup>21</sup> Two approaches to **11** were also initially scrutinized. The

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**SCHEME 2** 



first routing was via ketal **12**, an intermediate considered to have substantial potential as a consequence of its high conformational rigidity and functional group constitution. The alternative sequence was to be channeled through **13**, a compound anticipated to be readily available and whose oxidation within the cyclopentene ring was projected to set the proper level of oxygenation required of the target. The likely prospect that **12** could materialize as one of the oxidatively cleaved end-products of **13** did not escape our notice.

One of the more interesting underlying opportunities that would allow us to take advantage of this strategy was considered to be the facile charged-accelerated operation of an oxy-Cope rearrangement within a suitably substituted norbornene exemplified by **14** (Scheme 2). The ring strain resident in **14** was certain to represent a contributory factor to an enhanced rate for the [3,3] sigmatropic shift. Furthermore, it would be particularly advantageous to have access to **14** from a readily available, chiral nonracemic, and inexpensive commodity such as (-)-bornyl acetate (**15**). By judicious selection of this terpenoid ester, one introduces absolute configuration directly relatable to that resident in dumsin (**2**) from the very outset of the undertaking.

Efficient Stereocontrolled Synthesis of the ABC Subunit. Although examples of ring closures based on

**SCHEME 3** 



the nucleophilic addition of a protected cyanohydrin to a ketone<sup>22</sup> or aldehyde group have been documented in the context of natural products synthesis,<sup>23</sup> no reports of analogous cyclization onto a lactone carbonyl had been reported. To ensure the feasibility of this step and hence our entire tactical design, the previously described lactone 16<sup>24</sup> was deprotonated with LDA and alkylated with 2-(2-bromoethyl)-1,3-dioxolane. The angular side chain was thereby introduced to give 17 in 77% yield (Scheme 3), but only when standard conditions<sup>25</sup> were avoided and use was made of HMPA as cosolvent. This adjustment was necessary in order to accommodate the limited solubility of the lithium salt of 16 in THF alone. Deprotection of the acetal and Lewis acid-promoted conversion of aldehyde 18 to the TBS-cyanohydrin<sup>26</sup> set the stage for the key cyclization step. Following dropwise treatment of a cold (-78 °C) THF solution of 19 with 1.1 equiv of potassium hexamethyldisilazide, 20 was indeed produced in a highly diastereoselective manner. Only the  $\alpha$ -cyanosubstituted tricyclic hemiacetal was detected. Corroboration of the stereochemical assignment, initially based on the assumption that the larger substituent would be positioned on the less crowded exo surface, was achieved by X-ray crystallographic analysis of 21 (Figure 1).<sup>21,27</sup>

Arrival at **22** was accomplished by stirring an ethereal solution of **21** with 1 N sodium hydroxide solution at room temperature for 30 min. This simple procedure delivered the colorless crystalline dumsin ABC prototype in quantitative yield. Advantageously, if the last three steps in Scheme 3 are performed without the isolation of inter-

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**FIGURE 1.** Computer-generated perspective drawing of the final X-ray model of **21**.

**SCHEME 4** 



mediates, the overall yield of this conversion is increased to a satisfying 61% level.

**Evaluation of Enantiodefined Oxy-Cope Rearrangements.** The remote oxidation of (–)-**15** followed by a protecting group exchange has been reported by Money and by Ward to be a reliable means for generating ketone 23.28 The organocerate species generated by transmetalation of 3-benzyloxy-1-propyllithium with anhydrous cerium trichloride<sup>29</sup> added to 23 in an efficient manner (Scheme 4). Endo attack was assumed to prevail as commonly observed with camphor derivatives. When attempts to effect the dehydration of 24 invariably led to the undesired exo-methylene derivatives typified by 25-27, our attention was redirected to elaboration of functionalized norbornenes instead. To this end, 23 was transformed into triflate 28 by trapping of the enolate anion with Comins' reagent (Scheme 5). The corresponding vinyl stannane 29, bromide 30, and iodide 31 could subsequently be formed without difficulty in conventional fashion.<sup>31</sup> These attractive intermediates did not react universally as originally anticipated. However, palladiumcatalyzed reaction of 28 with other vinylic and allylic stannanes proceeded smoothly to afford 32, 34, and 35,

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### **SCHEME 5**



from which the terminal carbinols 33 and 36 were regioselectively crafted.

To set the stage for demonstrating the feasibility of the oxy-Cope isomerization, the functionalized alkenyllithium  $38^{32}$  was coupled to 37 at -78 °C. During subsequent warming to room temperature, the lithium alkoxide so formed underwent spontaneous electronic reorganization to furnish 39 after acidification (Scheme 6). Carbinol 40 proved to be isolable by quenching the same reaction mixture with saturated NH<sub>4</sub>Cl in the cold. The rearrangement reaction could then be independently performed by subjecting 40 to a basic environment about 0 °C. The stereochemical features of 39 were ascertained by detailed NOE analysis (see the Experimental Section).

To incorporate a side chain that would ultimately evolve into the A ring of dumsin, it becomes necessary to position a three-carbon unit in the norbornenone as reflected in 43. The precise location of this R group brings added steric compression to the oxy-Cope rearrangement since C-C bond formation necessarily must occur at that





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site. The allyl derivative and the terminally oxygenated equivalent (OMOM) were both examined (Scheme 7). These options conveniently allowed for selective cleavage of the tetrahydropyranyl ether (as  $41 \rightarrow 42$ ) with pyridinium tosylate in methanol followed by perruthenate oxidation.33 As before, 43a and 43b could be converted smoothly into 45 and 46, respectively. This structural isomerization could be interrupted at the stage of carbinol 44, but this alternative was not routinely practiced.

**Generation of Tricyclic Acetals and Elucidation** of Their Reactivity. Having learned how to assemble 46 in an expedient manner, we now were positioned to examine various oxidative protocols aimed at transforming its cyclopentene ring into a properly substituted tetrahydrofuran. According to plan, the initial focus was on tricyclic acetals such as 12. Ozonolysis of 46 under pyridine-modulated conditions<sup>34</sup> provided not the keto

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**SCHEME 9** 



aldehyde but its hydrated form **47** (Scheme 8). NOE measurements on **47** demonstrated that, at least in solution, the two hydroxy groups are oriented syn to each other in a way that allows a double-anomeric effect and intramolecular hydrogen bonding to operate. As a consequence, **47** is formed exclusively relative to the other possible diastereomers. Although **46** could be reduced cleanly to  $\beta$ -alcohol **49**, and access to **48–55** was as readily achieved, none of these proved to be targets of opportunity for more extensive scrutiny (Scheme 9).

A noteworthy observation was made during the oxidation of **47** with trifluoroperacetic acid.<sup>35</sup> Thereby initiated





was a stereoselective tandem bicycloacetalization process that formally includes MOM deprotection and several ensuing steps on the way to generating **51** in one pot. A synopsis of the possible sequence of chemical events is provided in Scheme 10. X-ray diffraction analysis of **51** (Figure 2)<sup>36</sup> indicated clearly that the  $-CH_2OTBDPS$ substituent is projected axially from the cyclohexanone ring and provides confirmation of the fact that **47** was produced by way of a fully stereocontrolled oxy-Cope reaction. Close stoichiometric control of the proportion of trifluoroacetic anhydride is highly desirable in order to preclude any visible signs of conversion to **52**. This lactone was the only insoluble product when a significant excess of the oxidant was employed.

Attention is also drawn to the outcome of heating **47** with a catalytic quantity of *p*-toluenesulfonic acid in benzene. These conditions led efficiently to the free keto aldehyde **53** (92%) with only minimal epimerization  $\alpha$  to the ketone carbonyl (2% of **54**). The premixing of **51** with acetic acid at 0 °C followed by the introduction of TBAF gave rise to **56** (Scheme 11). This carbinol was subjected to photoinduced oxidative cyclization by irradiation with a tungsten lamp at 45 °C in the presence of iodosobenzene diacetate and iodine.<sup>37</sup> Abstraction by the photogenerated oxo radical of a proximate hydrogen atom generates a C-centered radical amenable to intra- or intermolecular interception.<sup>38</sup> In the present circumstance, the ortho ester **57** was isolated in 52% yield.

It was our hope to exploit the arrival at **56** and **57** by means of one or another hydrolytic reaction, precedent for which was available.<sup>39</sup> Should the conversion of **57** to **58** occur uneventfully, we would find ourselves ready for construction of the CD rings of dumsin. However, the production of this dihydroxy keto lactone did not materialize. The cyclic compound **57** 

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FIGURE 2. Computer-generated perspective drawing of the final X-ray model of 51.





appears to have the enthalpic advantage, the proclivity for existing in cyclic forms being also noted in the quantitative conversion of **56** into **59** with 5% HCl in aqueous acetone and the unoptimized intramolecular closure to generate **60** in the presence of trimethyl orthoformate.

Notwithstanding, the predescribed results lent credence to the working hypothesis that the acetal moiety in **51** would prove to be a robust protecting group for the primary alcohol and lactal functional groups, and that

### **SCHEME 12**



unmasking later in the synthesis could prove feasible. The perruthenate oxidation of **56** was sluggish but gave aldehyde **61** cleanly in 78% yield (Scheme 12). The first chain extension option to be explored consisted of application of the Wadsworth–Emmons protocol to furnish **62**, followed by acetalization and reduction with Dibal-H. As expected, the carbomethoxy group emerged as a primary alcohol, which was transformed by  $S_N^2$  chemistry into nitrile **65**. While the reduction of these steps to practice proceeded with reasonable efficiency, the elaboration of diol **66** and more advanced intermediates



was characterized by low yields at every step. An alternative mode of construction of the dumsin D ring was consequently explored.

4-Butenylmagnesium bromide proved to be an acceptable elongation element to couple with aldehyde 70. At -78 °C, the  $\alpha$ -alcohol **71** proved to be the predominant product ( $\alpha/\beta$  = 10:1, Scheme 13). Protection of the secondary alcohol as the TBS ether 72 followed by a hydrolysis-oxidation sequence led to the unsaturated ketone 74. Ozonolysis was successful in delivering keto aldehyde 75a, thereby setting the stage for cycloaldolization chemistry. The use of potassium carbonate in methanol at room temperature generated predominantly the thermodynamic aldol product 76, whereas the kinetic isomer 77 dominated when the cyclization was performed with sodium methoxide in methanol at approximately -10 °C for 120 h. When 77 was heated with sodium hydroxide in aqueous methanol, conversion to 76 was observed.



**FIGURE 3.** Computer-generated perspective drawing of the final X-ray model of **76**.

The stereochemical assignments to aldol products **76** and **77** were elucidated by NOE methods applied to **76** and **79** (see the Experimental Section), and the relative stereochemistry of **76** was confirmed by X-ray crystallographic evidence (Figure 3).<sup>36</sup> The ORTEP diagram clearly shows that the newly formed cyclohexanol ring adopts a chair conformation housing a bulky axially disposed OTBS group. We consider it remarkable that diastereomers **80a** and **80b** in which the bulky siloxy substituent occupies an equatorial position were not formed at detectable levels.



The dilemma that we now faced could arise by virtue of severe steric repulsion between the equatorial protecting group and the adjacent tetrahydropyran ring. On this basis, it was considered appropriate to orient the siloxy group axially as in **81** or to drastically reduce the size of the oxygenated carbon by placing a ketone carbonyl at that site (see **82**). We opted to examine the latter alternative.

The discovery that the oxidation of **71**, when performed with pyridinium chlorochromate, resulted in formation of the rearranged aldehyde **83** was only a temporary setback (Scheme 14). Alternate use of the Dess-Martin



periodinane<sup>40</sup> gave rise to **84**. The latter on reduction with Dibal-H simply reinstated the  $\alpha$ -hydroxyl as in **85**. On the other hand, hydrolytic removal of the acetate, oxidation to diketone **87**, and ozonolysis resulted in the efficient formation of **88**. While this was a key advance, we were disappointed to find that subsequent aldolization gave rise to a mixture of **89/90** or only **90** depending upon conditions. As before, the relative stereochemistry of **90** was elucidated by NOE experiments. Having encountered this obstacle, we departed from this plan and returned to probe the prospects held by ketones of the generic family **13**.

**Implementation of the Alternative Plan Based on 46.** The feasibility of involving **46** was next accorded prime consideration. This readily accessible intermediate was quickly noted to be base-sensitive. For example, epimerization could not be skirted during desilylation with TBAF. Although this complication could be circumvented through the utilization of buffers, it proved more advisable to engage **46** in ketalization as the initial maneuver (Scheme 15). Standard oxidation of **92** with a catalytic amount of perruthenate salt in the presence of NMO as the co-oxidant followed by nucleophilic sidechain elongation of aldehyde **93** furnished **94** in quite

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respectable yield. This secondary alcohol was expeditiously silylated with TBSOTf in advance of acidcatalyzed intramolecular aldol cyclization. The use of 2% HCl in THF at room temperature (72 h) gave rise to the desired products **96a** and **96b** in a 7:1 ratio.

The crossover in stereoselectivity observed for the 4-butenylmagnesium bromide addition to **70** leading to **71** and for the conversion of **93** to **94** prompted examination of the analogous Grignard coupling to **70** (Scheme 16). In so doing, we discovered that **98** was formed exclusively (70% isolated) in line with earlier observations. These findings are explainable in terms of the Cram model. Should steric constraints cause orientation of the carbonyl oxygen away from these regions, the

**SCHEME 17** 



illustrated conformations are likely to be adopted. Nucleophilic attack by the organometallic species from the less hindered direction (as denoted by the arrows) eventuates in the involvement of opposite faces of the carbonyl  $\pi$  cloud.

Before carrying the silyl ethers **97a** and **97b** forward, we were prompted to examine the consequences of the exposure of these intermediates to ozonolysis conditions. For this purpose, keto alcohol **96a** was reduced to **100** in diastereocontrolled fashion and protected as the acetonide **101** (Scheme 17). The conformational rigidity imposed on **101** as a consequence of the presence of the dioxane ring was of advantage to stereochemical assignment by means of NOE studies. Unlike the behavior of **46**, which leads to **47** on oxidative cleavage, **101** reacts more sluggishly to generate a labile ozonide amenable to clean conversion to keto aldehyde **102**.

The successful screening of the  $96a \rightarrow 102$  conversion prompted a detailed analysis of the response of the three substrates compiled in Scheme 18 to the identical oxidative cleavage conditions. Although a product of the same type as **102** made its appearance in each of the examples, the over-oxidized  $\alpha$ -hydroxy keto aldehydes 111, 113, and 115 unexpectedly materialized as the major products. No improvement was realized by modifying the ozonolysis solvent from polar (CH<sub>3</sub>OH, CH<sub>2</sub>Cl<sub>2</sub>, etc.) to nonpolar (pentane). Ultimately, a more broadly based investigation turned up the fact that ruthenium tetraoxide at room temperature<sup>41</sup> smoothly transformed **104** into **110** without detectable contamination from the over-oxidized product (Scheme 19). Prolonged reaction times have been shown not to generate the corresponding keto acid. Furthermore, there exists no need for prior reduction of the ketone carbonyl group as reflected in the rather efficient conversion of 97b to 116 without visible signs of **117**.

With these observations in hand, only two steps were believed to separate us from a presumed key lactone







precursor to dumsin, viz. **119** or a closely related structure (Scheme 20). In principle, two sequential oxidations would allow us to access this advanced intermediate and allow in-depth investigation of E-ring incorporation. While the exact order of these two steps is not likely of direct importance, the regioselectivity of the Baeyer– Villiger oxidative insertion is most crucial. With these guidelines in mind, extensive investigation was made of a broad spectrum of intermediates, the oxidation levels in which were varied in order to uncover an optimal substrate/functional group interrelationship if such existed.

However, all trials have so far failed to yield positive results. The principal complicating factor behind these difficult experiments is the substantive steric congestion in the  $\beta$ -region of these compounds. Reagents cannot perform their normal, anticipated function because of an

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### SCHEME 19



#### SCHEME 20



inability to become covalently linked to the substrate in question. This deterrent mandates that very special tactics be fruitfully applied in order to achieve the targeted goal. Undertakings of this type are currently in progress.

#### **Experimental Section**

(±)-(3a*R*\*,7a*R*\*)-7a-[2-(1,3-Dioxolan-2-yl)ethyl]hexahydro-3,3-dimethylphthalide (17). To a stirred solution of diisopropylamine (1.0 mL, 6.6 mmol) in THF (10 mL) was added *n*-butyllithium (4.2 mL, 1.6 M in hexanes, 6.6 mmol) at 0 °C. Stirring was continued for 15 min, and the temperature was lowered to -78 °C, and then 2 mL of HMPA was added. This reaction mixture was added dropwise to a solution of lactone **16**<sup>24</sup> (1.01 g, 6.0 mmol) in a mixed solvent system consisting of THF (10 mL) and HMPA (2 mL). The resulting yellow solution was stirred at -78 °C for 1 h followed by the addition of 2-(2-bromoethyl)-1,3-dioxolane (1.187 g, 6.6 mmol) in THF (10 mL). The mixture was allowed to warm to room temperature, stirred for another 30 min, and quenched with saturated NH<sub>4</sub>Cl solution. The separated aqueous layer was extracted with ether (50 mL × 3), and the combined organic layers were washed with brine, dried, and concentrated under reduced pressure to afford 1.53 g of viscous product. Purification of this residue by flash chromatography (ethyl acetate/hexanes, 1:5) provided **17** as a colorless waxy solid (1.24 g, 77%): IR (neat, cm<sup>-1</sup>) 2937, 1757, 1145; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.87–4.84 (m, 1 H), 3.96–3.81 (m, 4 H), 2.14 (d, J = 2.7 Hz, 1 H), 1.82–1.47 (series of m, 12 H), 1.46 (s, 3 H), 1.40 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  180.5, 104.2, 85.0, 69.5, 45.0, 44.6, 30.9, 30.4, 29.1, 28.9, 25.8, 21.2, 20.6, 20.1; MS *m*/*z* (M<sup>+</sup>) calcd 268.1674, obsd 268.1669. Anal. Calcd for C<sub>15</sub>H<sub>24</sub>O<sub>4</sub>: C, 67.12; H, 9.02. Found: C, 66.57; H, 9.03.

(±)-(3aR\*,7aR\*)-7a-(2-Formylethyl)hexahydro-3,3-dimethylphthalide (18). To a stirred solution of 17 (2.15 g, 8.04 mmol) in wet acetone (270 mL, 20% water) was added a catalytic amount of TsOH (4.02 g), and the resulting mixture was stirred at room temperature for 72 h or heated to reflux for 7 h. The solvent was volatilized under reduced pressure, and the residue was partitioned between water and ether (100 mL of each). The separated aqueous phase was extracted with ether (100 mL  $\times$  3), and the combined organic phases were washed with brine, dried, and evaporated to give 18 (1.75 g, 97%) as a colorless oil: IR (neat, cm<sup>-1</sup>) 1755, 1722, 1266; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.79 (s, 1 H), 2.59 (m, 2 H), 2.15 (d, J = 2.9 Hz, 1 H), 2.14–1.85 (series of m, 2 H), 1.77–1.48 (series of m, 8 H), 1.46 (s, 3 H), 1.40 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  201.2, 180.2, 85.2, 45.8, 44.5, 39.4, 30.5, 30.1, 26.6, 25.7, 21.1, 20.4, 19.8; MS m/z (M<sup>+</sup>) calcd 224.1412, obsd 224.1395.

(±)-(3aR\*,7aR\*)-7a-[3-(tert-Butyldimethylsiloxy)-3-cyanopropyl]hexahydro-3,3-dimethylphthalide (19). To a solution of 18 (1.30 g, 5.8 mmol) in anhydrous acetonitrile (29 mL) was added sequentially potassium cyanide (1.51 g, 20.2 mmol), anhydrous zinc iodide (29 mg, 0.09 mmol), and tertbutyldimethylsilyl chloride (1.044 g, 20.2 mmol) at room temperature. The mixture was stirred for 24 h and evaporated under reduced pressure to afford a residue which was redissolved in ether (25 mL). The undissolved material was removed by filtration and rinsed with more ether (15 mL). The filtrate was washed with water, dried, and concentrated in vacuo. Isolation of the mixture of diastereomers 19 as a colorless oil (1.76 g, 83%) was accomplished by column chromatography (silica gel, ethyl acetate/hexanes, 1:6): IR (neat, cm<sup>-1</sup>) 1759, 1263, 1114; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) & 4.44 (m, 1 H), 2.08 (d, J = 5.9 Hz, 2 H), 1.98-1.49 (series of m, 11 H), 1.46 (s, 3 H), 1.41 (s, 3 H), 0.89 (s, 9 H), 0.15 (s, 6 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) & 180.0, 178.9, 119.6, 85.1, 62.0, 61.7, 45.5, 44.8, 44.7, 31.4, 30.5, 30.4, 29.8, 29.5, 25.7, 25.5, 21.1, 20.5, 19.8, 18.0, 17.9, -5.3, -5.4; MS m/z (M<sup>+</sup>) calcd 365.2386, obsd 365.2356. Anal. Calcd for C<sub>20</sub>H<sub>35</sub>NO<sub>3</sub>Si: C, 65.71; H, 9.66. Found: C, 65.8; H, 9.68.

(±)-(3aR\*,3aS\*,5aR\*,9aR\*)-3-(tert-Butyldimethylsiloxy)decahydro-3a-hydroxy-5,5-dimethylcyclopent[c]isobenzofuran-3-carbonitrile (20). To a stirred solution of TBScyanohydrin 19 (30.2 mg, 0.083 mmol) in THF (1 mL) was added KHMDS (0.5 M in toluene, 0.19 mL) dropwise at -78 °C. After 10 min of stirring, water (1 mL) was introduced in one portion and the whole system was allowed to warm to room temperature. The resulting solution was diluted with ether (1 mL), and the aqueous phase was extracted with ether (1 mL  $\times$  3). The organic solutions were dried, filtered, and concentrated to yield a pale yellow residue which was subjected to flash chromatography (ethyl acetate/hexanes, 1:5) to afford 20 (18.7 mg, 62%) as a colorless wax: IR (neat, cm<sup>-1</sup>) 3591, 3453, 2257; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.61 (s, 1 H), 2.12 (m, 1 H), 1.89 (m, 2 H), 2.28 (m, 4 H), 1.46 (series of m, 6 H), 1.28 (s, 3 H), 1.24 (s, 3 H), 0.92 (s, 9 H), 0.24 (s, 3 H), 0.22 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 120.5, 111.9, 86.6, 81.4, 55.7, 51.6, 36.4, 35.4, 29.6, 29.0, 25.8, 25.7, 21.8, 20.7, 19.7, 18.2, -3.3,-3.5; MS m/z (M<sup>+</sup> + 1) calcd 366.2646, obsd 366.2632.

(±)-(3a*R*\*,3a*S*\*,5a*R*\*,9a*R*\*)-Decahydro-3-3a-dihydroxy-5,5-dimethylcyclopent[*c*]isobenzofuran-3-carbonitrile (21). To a solution of 20 (18.7 mg, 0.051 mmol) in dry THF (1 mL) was added a solution of TBAF (1.0 M in THF, 56  $\mu$ L) and stirred for 30 min at room temperature. After a water quench (1 mL) and dilution with ether (1 mL), the separated aqueous layer was extracted with ether (1 mL  $\times$  3), and the combined organic layers were washed with brine, dried, and concentrated under reduced pressure to afford a viscous product. Purification of this residue by flash chromatography (ethyl acetate/ hexanes, 1:5) provided pure 21 (8.8 mg, 77%) as a colorless crystalline solid: mp 112-114 °C (from ethyl acetate-hexanes); IR (neat, cm<sup>-1</sup>) 3418, 1256, 1225; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.48 (d, J = 1.6 Hz, 1 H), 2.67 (s, 1 H), 2.00–1.98 (series of m, 2 H), 1.90-1.65 (series of m, 5 H), 1.63 (s, 1 H), 1.62-1.35 (series of m, 5 H), 1.32 (s, 3 H), 1.30 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 119.8, 112.9, 87.7, 76.9, 54.4, 52.9, 37.9, 52.9, 30.3, 28.8, 25.2, 21.9, 20.7, 20.0; MS m/z (M<sup>+</sup>) calcd 251.1521, obsd 251.1524.

(±)-(3aR\*,5aS\*,9aS\*)-Octahydro-3a-hydroxy-5,5-dimethylcyclopent[c]isobenzofuran-3(3aH)-one (22). A solution of 21 (6.4 mg, 0.026 mmol) in ether (0.5 mL) was treated with 1 N aqueous NaOH solution (0.04 mL), stirred vigorously at room temperature for 30 min, and diluted with brine (1 mL). The separated organic layer was dried and concentrated under reduced pressure to furnish 22 (3.9 mg, 100%) as a colorless crystalline solid: mp 72-75 °C (from ethyl acetate/hexanes); IR (neat, cm<sup>-1</sup>) 3432, 1755; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.39 (s, 1 H), 2.67 (m, 1 H), 2.28 (ddd, J = 18.0, 8.1, 3.4 Hz, 1 H), 2.05 (ddd, J = 18.0, 8.1, 3.4 Hz, 1 H), 1.89 (m, 2 H), 1.75-1.46 (series of m, 6 H), 1.39-1.37 (m, 2 H), 1.34 (s, 3 H), 1.28 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  212.0, 104.3, 87.0, 53.6, 50.8, 32.5, 32.0, 30.0, 29.3, 26.1, 22.3, 21.4, 19.8; MS m/z (M<sup>+</sup>) calcd 224.1412, obsd 224.1381. Anal. Calcd for C13H20O3: C, 69.60; H, 8.99. Found: C, 69.57; H, 9.10.

(1S,4S,5R)-4,7,7-Trimethyl-5-(tetrahydro-2H-pyran-2yl)oxy]bicyclo[2.2.1]hept-2-en-2-ol Trifluoromethanesulfonate (28). To a stirred solution of 23 (8.4 g, 0.034 moL) in anhydrous THF (180 mL) was added slowly via addition funnel a solution of KHMDS (0.5 M in toluene, 100 mL, 0.05 mol) at 0 °C during 40 min. The resulting brown solution was stirred at the same temperature for another 1 h, allowed to warm to room temperature overnight, treated slowly with N-(5-chloro-2-pyridyl)triflimide (17.5 g, 0.044 mol) in THF (120 mL) at 0 °C during 45 min, and allowed to gradually warm to room temperature during 4 h. The mixture was diluted with water (50 mL) and ether (100 mL), and the separated organic layer was washed with 5% NaOH solution and brine and then dried. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (ethyl acetate/hexanes, 1:40) to provide 28 (9.96 g, 78%) as a colorless oil containing two inseparable acetals; IR (neat, cm<sup>-1</sup>) 1460, 1399; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.38 (d, J = 1.0 Hz, 1 H, minor isomer), 5.34 (d, J = 0.5 Hz, 1 H, major isomer), 4.65 (t, J = 3.4 Hz, 1 H, minor isomer), 4.56 (t, J = 3.2 Hz, 1 H, major isomer), 4.33 (dd, J = 7.0, 2.4 Hz, 1 H, minor isomer), 4.11 (dd, J = 7.5, 2.6 Hz, 1 H, major isomer), 3.82 and 3.52 (two sets of m, 2 H), 2.51-2.31 (two sets of m, 2 H), 1.78-1.30 (series of m, 7 H), 1.18, 1.11 and 0.81 (three sets of s, 9 H, major isomer), 0.97, 0.96, and 0.82 (three sets of s, 9 H, minor isomer); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 154.7, 154.0, 121.3, 120.6, 100.7, 95.9, 84.9, 80.8, 62.4, 61.9, 57.9, 57.8, 57.5, 57.4, 53.3, 53.2, 35.8, 33.7, 30.8, 30.7, 25.5, 25.4, 19.5, 19.4, 19.3, 19.1, 18.9, 18.8, 11.4; MS m/z (M<sup>+</sup>) calcd 384.1216, obsd 384.1249.

**2-[[(1.5,2,R,4,R)-5-Allyl-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-yl]oxy]tetrahydro-2***H***-pyran (<b>35**). Flame-dried lithium chloride (86 mg, 2 mmol) was added to dry DMF (10 mL), followed by **28** (153 mg, 0.4 mmol), allyltributylstannane (134 mg, 0.4 mmol), and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (14 mg, 0.02 mmol). The bright yellow solution was heated at 100 °C until the formation of a black precipitate was complete (2 h). After being cooled to room temperature, the mixture was poured into a mixture of ether (15 mL) and saturated KF solution (20 mL) and stirred vigorously for at least 20 min. The organic layer was washed with brine and dried. The filtrate was concentrated under reduced pressure to give a yellow oil which was subjected to flash chromatographic purification (ethyl acetate/hexanes, 1:40) to yield **35** (98 mg, 89%) as a colorless oil: IR (neat, cm<sup>-1</sup>) 1642, 1137, 1117; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.89–5.77 (m, 1H), 5.23 (d, J = 14.0 Hz, 1 H), 5.10 (dd, J = 3.3, 1.6 Hz, 1 H), 5.03 (m, 1 H), 4.56 (m, 1 H), 4.27 (dd, J = 7.0, 2.8 Hz, 0.5 H), 3.92–3.80 (m, 1 H), 3.47 (m, 1 H), 2.87 (m, 2 H), 2.25 (m, 1 H), 2.11 (dd, J = 11.1, 3.7 Hz, 1 H), 1.81–1.41 (m, 6 H), 1.33 (m, 1 H), 1.09 (s, 3 H), 0.82 (s, 3 H), 0.81 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  147.1, 146.2, 136.03, 136.01, 129.6, 128.8, 115.5, 115.4, 101.0, 96.0, 86.1, 81.8, 62.9, 61.9, 57.4, 57.3, 57.0, 56.8, 54.48, 54.46, 35.7, 35.1, 33.8, 31.10, 31.07, 25.6, 25.5, 20.04, 20.00, 19.40, 19.37, 19.26, 11.50, 11.48; MS m/z (M<sup>+</sup>) calcd 276.2090, obsd 276.2085.

(1*R*,4*S*,5*R*)-4,7,7-Trimethyl-5-[(tetrahydro-2*H*-pyran-2yl)oxy]bicyclo[2.2.1]hept-2-ene-2-propanol (36). A solution of 2,3-dimethyl-2-butene (42 mL, 1.0 M in THF) was treated with BH<sub>3</sub>-THF complex (42 mL, 1.0 M in THF) at 0 °C, and the solution was stirred for 1.5 h prior to the addition of a solution of **35** (11.50 g, 0.042 mol) at the same temperature. The resulting mixture was stirred for another 2 h, treated with 15% NaOH solution (42 mL) followed by H<sub>2</sub>O<sub>2</sub> (aq, 30%, 42 mL) at 0 °C, and allowed to warm to room temperature during 1.5 h. The mixture was extracted with ether (40 mL × 3), and the combined organic layers were dried and evaporated to leave a colorless oil, which was purified by flash chromatography (ethyl acetate/hexanes, 1:4) to give colorless oily **36** (as two separable diastereomeric alcohols **36a** and **36b**, 1:1, 10.70 g, 87%).

For **36a**: IR (neat, cm<sup>-1</sup>) 3461, 1137, 1062; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.23 (s, 1H), 4.59 (m, 1 H), 4.07 (dd, J = 7.5, 2.6 Hz, 1 H), 3.82 (m, 1 H), 3.69 (t, J = 6.1 Hz, 2 H), 3.45 (m, 1 H), 2.33 (ddd, J = 12.6, 7.5, 3.9 Hz, 1 H), 2.19 (m, 2 H), 2.08 (d, J = 3.5 Hz, 1 H), 1.80–1.59 (series of m, 5 H), 1.48 (m, 4 H), 1.10 (dd, J = 12.1, 2.8 Hz, 1 H), 1.02 (s, 3 H), 0.79 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  148.5, 128.4, 101.0, 86.0, 63.2, 62.9, 57.2, 57.1, 55.2, 35.8, 31.0, 30.0, 27.0, 25.5, 20.0, 19.9, 19.3, 11.6; MS m/z (M<sup>+</sup>) calcd 294.2159, obsd 294.2188.

For **36b**: IR (neat, cm<sup>-1</sup>) 3406, 1060, 1036; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.27 (d, J = 0.8 Hz, 1 H), 4.53 (t, J = 3.4 Hz, 1 H), 4.25 (dd, J = 7.1, 2.5 Hz, 1 H), 3.87 (m, 1 H), 3.65 (t, J = 6.1 Hz, 2 H), 3.48 (m, 1 H), 2.25–2.14 (m, 3 H), 2.10 (d, J = 3.8 Hz, 1 H), 1.84 (br s, 1 H), 1.82–1.67 (series of m, 3 H), 1.65–1.42 (series of m, 5 H), 1.07 (s, 3 H), 0.90 (dd, J = 12.2, 2.5 Hz, 1 H), 0.80 (s, 3 H), 0.76 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  147.9, 128.9, 96.0, 81.8, 63.2, 61.8, 57.3, 56.6, 55.2, 33.8, 30.9, 29.9, 27.2, 25.6, 20.0, 19.3, 19.2, 11.5; MS *m*/*z* (M<sup>+</sup>) calcd 294.2159, obsd 294.2192.

Tetrahydro-2-[[(1S,2R,4R)-5-[3-[(methoxymethoxy)propyl-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-yl]oxy]-2H**pyran (41).** A stirred solution of **36** (3.7 g, 1.3 mmol) in  $CH_2Cl_2$ (40 mL) was cooled to 0 °C, treated with diisopropylethylamine (11.0 mL, 0.06 mol) and dropwise with chloromethyl methyl ether (2.9 mL, 0.04 mol), allowed to warm to room temperature overnight, diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and washed with brine (15 mL). The separated organic phase was dried and concentrated to yield a brown residue that was subjected to flash chromatography (ethyl acetate/hexanes, 1:20 with 1% of triethylamine) to provide 41 (3.87 g of a mixture of two isomers, 91%) as a colorless oil: IR (neat, cm<sup>-1</sup>) 1442, 1384, 1118; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.22 (s, 1 H, minor isomer), 5.18 (s, 1 H, major isomer), 4.62 (s, 2 H, major isomer), 4.61 (s, 2 H, minor isomer), 4.60-4.53 (m, 1 H), 4.25 (dd, J = 7.0, 2.4 Hz, 1 H, minor isomer), 4.06 (dd, J = 7.6, 2.6 Hz, 1 H, major isomer), 3.91-3.79 (m, 1 H), 3.60-3.38 (m, 4 H), 3.36 (s. 3 H. major isomer), 3.35 (s, 3 H, minor isomer), 2.23 (ddd, J = 12.0, 7.6, 3.8 Hz, 1 H), 2.24-2.07 (m, 4 H), 1.83-1.42 (series of m, 7 H), 1.09 (dd, J = 12.1, 2.5 Hz, 1 H, major isomer), 1.08 (s, 3 H, minor isomer), 1.00 (s, 3 H, major isomer), 0.86 (dd, J =12.1, 2.5 Hz, 1 H, minor isomer), 0.81 (s, 3 H, minor isomer), 0.79 (s, 3 H, major isomer), 0.77 (s, 3 H);  $^{13}\mathrm{C}$  NMR (75 MHz,

CDCl<sub>3</sub>)  $\delta$  148.4, 147.5, 128.9, 128.2, 100.9, 96.4, 96.0, 86.0, 81.8, 67.6, 67.5, 62.8, 61.9, 57.2, 57.0, 56.7, 55.1, 55.0, 35.8, 33.9, 31.1, 27.8, 26.8, 25.7, 25.5, 20.1, 20.0, 19.4, 19.3, 11.6, 11.5; MS *m*/*z* (M<sup>+</sup>) calcd 338.2457, obsd 338.2464.

(1S,2R,4R)-5-[3-[(Methoxymethoxy)propyl]-1,7,7trimethylbicyclo[2.2.1]hept-5-en-2-ol (42b). A mixture of 41 (3.87 g, 0.011 mol) and *p*-toluenesulfonic acid (0.11 g, 0.58 mmol) in methanol (150 mL) was stirred at room temperature for 1 h, and the resulting pale yellow solution was diluted with saturated sodium bicarbonate solution (50 mL) and extracted with ether (75 mL  $\times$  3). The combined organic layers were washed with brine, dried, and concentrated under reduced pressure. The crude product (3.21 g) was purified by flash chromatography (ethyl acetate/hexanes, 1:2 with 1% triethylamine) to afford deprotected alcohol 42b (ca. 3.0 g, 100%) as a colorless oil: IR (neat, cm<sup>-1</sup>) 3450, 1148, 1113; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.23 (s, 1 H), 4.59 (s, 2 H), 4.08 (br m, 1 H), 3.54 (t, J = 6.4 Hz, 2 H), 3.34 (s, 3 H), 2.39 (ddd, J = 12.7, 7.7, 3.6 Hz, 1 H), 2.20 (ddd, J = 7.7, 7.7, 1.3 Hz, 2 H), 2.11 (d, J = 3.6 Hz, 1 H), 1.84-1.67 (m, 2 H), 1.03 (s, 3 H), 0.80 (s, 3 H), 0.77 (m, 1 H), 0.75 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 152.9, 126.0, 96.3, 78.9, 67.6, 58.2, 57.7, 55.2, 55.1, 37.9, 27.3, 27.1, 20.3, 19.0, 10.8; MS m/z (M<sup>+</sup>) calcd 254.1882, obsd 254.1873.

(1S,4R)-5-[3-(Methoxymethoxy)propyl]-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-one (43b). A solution of **42b** (3.0 g, 0.01 mol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was charged with powdered 4 Å molecular sieves (ca. 2.0 g) and 4-methylmorpholine N-oxide (2.08 g, 0.018 mol). The resulting suspension was slightly cooled in a water bath, treated with tetrapropylammonium perruthenate (TPAP, 0.21 g, 0.59 mmol) slowly at room temperature (slightly exothermic), stirred for 2 h until the starting material was completely consumed (TLC analysis), and passed through a short pad of Florisil and Celite (1:1). The filter cake was washed several times with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were concentrated to give a green-yellowish oil which was purified by flash chromatography (ethyl acetate/ hexanes, 1:5 with 1% of trithylamine) to afford 43b (2.68 g, 90%) as a colorless liquid: IR (neat, cm<sup>-1</sup>) 1746, 1112, 1040; <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 4.86 (s, 1 H), 4.46 (s, 2 H), 3.35 (t, J = 1.7 Hz, 2 H), 3.17 (s, 3 H), 2.00–1.88 (m, 4 H), 1.66–1.49 (series of m, 3 H), 0.98 (s, 3 H), 0.83 (s, 3 H), 0.63 (s, 3 H); 13C NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  213.5, 156.2, 124.7, 96.5, 67.3, 65.4, 58.9, 54.8, 52.2, 35.9, 27.9, 26.9, 19.4, 19.2, 7.5; MS m/z (M<sup>+</sup>) calcd 252.1725, obsd 252.1724; [a]<sup>24</sup> D +594.1 (c 0.41, CHCl<sub>3</sub>). Anal. Calcd for C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>: C, 71.38; H, 9.59. Found: C, 71.48; H, 9.66.

(3aR,6R,7S,7aR)-7-[(tert-Butyldiphenylsiloxy)methyl]-3,3a,4,6,7,7a-hexahydro-7a-[3-(methoxymethoxy)propyl]-2,3,6,6-tetramethyl-5H-inden-5-one (46) and (1S,2R,4R)-2-[(E)-3-(tert-Butyldiphenylsiloxy)-1-methyl-1-propenyl]-5-[3-(methoxymethoxy)propyl]-1,7,7-trimethylbicyclo[2.2.1]-hept-5-en-2-ol (44b). A flame-dried 25 mL round-bottomed flask was charged with (E)-2-bromo-4-(tertbutyldimethylsilyloxy)-2-butene (0.59 g, 1.53 mmol) in THF (6 mL), cooled to -78 °C, and treated dropwise with a solution of tert -butyllithium (1.8 mL, 1.7 M in pentane, 3.06 mmol) dropwise. After 15 min, the resulting homogeneous yellow solution was added a solution of 43b (0.17 g, 0.77 mmol) in THF (3 mL) slowly, and the reaction mixture was allowed to warm to room temperature overnight, recooled to -78 °C, and finally quenched with 2 mL of saturated NH<sub>4</sub>Cl solution. After returning to room temperature, the mixture was diluted with brine and ether (5 mL of each), and the aqueous layer was extracted with ether (10 mL  $\times$  2). The combined organic layers were dried, and the filtrate was concentrated to give a pale yellow oil that was purified by flash chromatography (ethyl acetate/hexanes, 1:20 then 1:10) to afford 46 (0.318 g, 78%) as a colorless oil accompanied by trace amounts of **44b** ( $\leq$  5%), which was isolated as the exclusive product when the reaction was performed at -78 °C for 2 h and quenched at the same temperature.

For **46**: IR (neat, cm<sup>-1</sup>) 1714, 1112; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.67–7.63 (m, 4 H), 7.45–7.37 (m, 6 H), 5.15 (d, J= 1.1 Hz, 1 H), 4.58 (s, 2 H), 3.64 (dd, J = 10.4, 5.3 Hz, 1 H), 3.56 (dd, J = 16.6, 6.2 Hz, 1 H), 3.43 (m, 2 H), 3.39 (s, 3 H), 2.60 (dd, J = 7.1, 5.5 Hz, 1 H), 2.30 (dd, J = 11.6, 7.6 Hz, 2 H), 2.18 (dd, J = 11.9, 6.2 Hz, 1 H), 2.07 (t, J = 7.3 Hz, 1 H), 1.56 (d, J = 1.3 Hz, 3 H), 1.51 (m, 4 H), 1.12 (d, J = 7.1 Hz, 3 H), 1.09 (s, 3 H), 1.03 (s, 9 H), 0.85 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  216.2, 145.6, 135.64, 135.56, 135.1, 133.37, 133.36, 129.7, 127.9, 127.67, 127.65, 96.4, 68.3, 62.3, 55.1, 51.8, 51.7, 48.3, 46.1, 42.6, 40.6, 38.8, 30.7, 26.8, 25.2, 22.5, 19.1, 12.6, 12.4.; MS *m*/*z* (M<sup>+</sup> - C<sub>4</sub>H<sub>9</sub>) calcd 505.2774, obsd 505.2738; [ $\alpha$ ]<sup>24</sup> D - 5.4 (*c* 0.50, CHCl<sub>3</sub>). Anal. Calcd for C<sub>35</sub>H<sub>52</sub>O<sub>4</sub>Si: C, 74.69; H. 8.96. Found: C, 74.76; H. 8.94.

74.69; H, 8.96. Found: C, 74.76; H, 8.94. For **44b**: IR (neat, cm<sup>-1</sup>) 3475, 1112, 1039; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.70–7.66 (m, 4 H), 7.43–7.36 (m, 6 H), 5.44 (t, J = 6.8 Hz, 1 H), 5.06 (d, J = 1.1 Hz, 1 H), 4.60 (s, 2 H), 4.24 (dd, J = 5.9, 1.1 Hz, 1 H), 3.50 (t, J = 6.4 Hz, 2 H), 3.34 (s, 3 H), 2.13–2.00 (series of m, 4 H), 1.79–1.60 (series of m, 4 H), 1.41 (s, 3 H), 1.14 (s, 3 H), 1.04 (s, 9 H), 1.02 (s, 3 H), 0.91 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  147.2, 140.8, 135.6, 134.0, 131.2, 129.6, 127.6, 126.1, 96.4, 86.3, 67.6, 61.6, 60.8, 59.9, 55.1, 54.2, 38.4, 27.2, 26.9, 26.8, 22.3, 21.5, 19.1, 15.4, 8.83; MS *m*<sub>Z</sub> (M<sup>+</sup>) calcd 562.3478, obsd 562.3479; [ $\alpha$ ]<sup>24</sup> D +36.2 (c 0.63, CHCl<sub>3</sub>). Anal. Calcd for C<sub>35</sub>H<sub>50</sub>O<sub>4</sub>Si: C, 74.69; H, 8.96. Found: C, 74.63; H, 8.89.

(4aS,6aR,9R,10S,10aS)-10-[(tert-Butyldiphenylsiloxy)methyl]hexahydro-6,6,9-trimethyl-1*H*,4a*H*-pyrano[2,3-*c*]isobenzofuran-8(6H)-one (51) and (1S,2R,5aR,7aS,11aS)-1-[(tert-Butyldiphenylsiloxy)methyl]hexahydro-2,6,6trimethyl-7aH,9H-pyrano[2',3',2,3]furo[3,4]oxepin-4(5H)one (52). To a stirred suspension of 47 (61 mg, 0.1 mmol) and freshly grounded urea-hydrogen peroxide powder (47 mg, 0.5 mmol) in anhydrous CH<sub>2</sub>Čl<sub>2</sub> (2 mL) was added dropwise freshly distilled trifluoroacetic anhydride (56  $\mu$ L, 0.4 mmol) at 0 °C, and the resulting slurry was stirred at this temperature for 2 h prior to being neutralized with saturated sodium bicarbonate solution. The separated aqueous phase was extracted with  $CH_2Cl_2$  (5 mL  $\times$  2), and the combined organic layers were washed with brine, dried, concentrated under reduced pressure, and subjected to flash chromatography (ethyl acetate/ hexanes, 1:5) to provide 51 (31 mg, 62%) as a colorless solid and 52 (1.2 mg, 2%) as a colorless oil.

For **51**: mp 134–135 °C (from ethyl acetate/hexanes); IR (neat, cm<sup>-1</sup>) 1715, 1112, 1062; <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  7.87–7.72 (m, 4 H), 7.28–7.17 (m, 6 H), 5.72 (s, 1 H), 4.10 (dd, J = 11.4, 2.1 Hz, 1 H), 4.00 (m, 1 H), 3.61 (dd, J = 11.4, 3.6 Hz, 1 H), 2.97 (dd, J = 17.3, 4.3 Hz, 1 H), 2.10 (dd, J = 17.3, 5.3 Hz, 1 H), 1.88 (q, J = 6.5 Hz, 1 H), 1.64 (td, J = 13.5, 4.2 Hz, 1 H), 1.53 (q, J = 2.7 Hz, 1 H), 1.39 (dd, J = 14.2, 5.2 Hz, 1 H), 1.28 (m, 2 H), 1.24 (s, 3 H), 1.15 (s, 9 H), 1.11 (s, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.95 (m, 2 H); 13C NMR (75 MHz, C6D6) d 210.6, 136.4, 136.0, 132.7, 132.5, 130.0, 129.8, 128.2, 128.1, 99.3, 76.4, 60.0, 59.5, 49.8, 45.8, 43.3, 41.7, 39.7, 32.8, 31.8, 26.9, 25.3, 21.3, 19.1, 11.6; FAB MS m/z (M<sup>+</sup>) calcd for C<sub>31</sub>H<sub>42</sub>O<sub>4</sub>Si: C, 73.48; H, 8.36. Found: C, 73.52; H, 8.33.



For **52**: IR (neat, cm<sup>-1</sup>) 1732, 1112, 1068; <sup>1</sup>H NMR (300 MHz,  $C_6D_6$ )  $\delta$  7.85–7.75 (m, 4 H), 7.23–7.17 (m, 6 H), 4.78 (s,

1 H), 4.17 (d, J = 5.2 Hz, 2 H), 3.17–3.06 (m, 2 H), 2.90 (td, J = 11.0, 2.6 Hz, 1 H), 2.33 (dd, J = 15.9, 4.2 Hz, 1 H), 2.16 (dd, J = 15.8, 5.2 Hz, 1 H), 1.91 (t, J = 4.7 Hz, 1 H), 1.64 (t, J = 5.1 Hz, 1H), 1.35 (d, J = 6.6 Hz, 3 H), 1.32 (s, 3 H), 1.30–1.18 (m, 4 H), 1.20 (s, 3 H), 1.16 (s, 9 H); <sup>13</sup>C NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  171.7, 135.9, 135.8, 133.5, 133.4, 129.84, 129.80, 127.89, 127.85, 102.9, 84.6, 71.7, 63.3, 60.7, 56.1, 48.5, 45.7, 33.7, 33.0, 30.6, 26.8, 25.2, 21.6, 21.0, 19.0; FAB MS m/z (M<sup>+</sup>) calcd 522.28, obsd 522.43.

(3aR,5aR,6R,9S,9aR,9bR)-9-(tert-Butyldimethylsiloxy)-3,3a,4,5a,6,7,8,9,9a,9b-decahydro-6-hydroxy-9b-[3-(methoxymethoxy)propyl]-2,3,3, 5a-tetramethyl-5H-benz[e]inden-5-one (96a) and (3aR,5aR,6S,9S,9aR,9bR)-9-(tert-Butyldimethylsiloxy)-3,3a,4,5a,6,7,8,9,9a,9b-decahydro-6-hydroxy-9b-[3-(methoxymethoxy)propyl]-2,3,3,5atetramethyl-5H-benz[e]inden-5-one (96b). A solution 95 (20 mg, 0.045 mmol) in THF (10 mL) was treated with 0.1 mL of 2 N aqueous HCl solution, stirred for 72 h at 20-25 °C, diluted with water and ethyl acetate (2 mL of each), and extracted with ethyl acetate (4 mL  $\times$  3). The combined organic layers were washed with water, saturated sodium bicarbonate solution, and brine, dried, and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexanes, 1:3) to furnish 96a (12 mg, 71%) and 96b (ca. 1 mg, 7%), both as colorless oils.

For **96a**: IR (neat, cm<sup>-1</sup>) 3483, 1686, 1253; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.62 (d, J = 1.2 Hz, 1 H), 4.63 (s, 2 H), 4.39 (d, J = 2.0 Hz, 1 H), 3.97 (t, J = 2.5 Hz, 1 H), 3.54 (m, 2 H), 3.37 (s, 3 H), 2.50 (dd, J = 5.5, 0.7 Hz, 1 H), 2.37 (d, J = 8.4 Hz, 1 H), 2.32 (dd, J = 13.8, 1.5 Hz, 1 H), 2.30 (m, 1 H), 2.16–2.03 (m, 1 H), 1.94–1.81 (m, 2 H), 1.66–1.30 (series of m, 6 H), 1.53 (d, J = 1.3 Hz, 3 H), 1.28 (s, 3 H), 1.06 (s, 3 H), 0.94 (s, 9 H), 0.84 (s, 3 H), 0.15 (s, 3 H), 0.12 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  224.2, 142.8, 132.0, 96.6, 74.2, 68.2, 67.7, 55.3, 51.4, 50.7, 50.2, 48.9, 46.2, 39.9, 38.4, 32.8, 31.4, 26.0, 24.8, 23.9, 21.9, 18.0, 15.0, 12.2, -3.6, -4.3; MS m/z (M<sup>+</sup> + 1) calcd 495.3505, obsd 495.3464.

For **96b**: IR (neat, cm<sup>-1</sup>) 3457, 1712, 1255; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.62 (d, J = 1.2 Hz, 1 H), 4.62 (s, 2 H), 4.38 (d, J = 1.8 Hz, 1 H), 3.98 (s, 1 H), 3.53 (m, 2 H), 3.37 (s, 3 H), 2.54–1.80 (series of m, 7 H), 1.68–1.30 (series of m, 6 H), 1.53 (d, J = 1.2 Hz, 3 H), 1.28 (s, 3 H), 1.06 (s, 3 H), 0.94 (s, 9 H), 0.84 (s, 3 H), 0.15 (s, 3 H), 0.11 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  221.5, 142.5, 135.5, 96.5, 75.1, 68.4, 68.3, 55.2, 52.1, 50.6, 50.4, 48.7, 42.3, 40.2, 38.1, 31.5, 28.8, 26.0, 24.9, 23.6, 21.9, 21.3, 18.0, 12.2, -3.6, -4.4; MS *m*/*z* (M<sup>+</sup>) calcd 494.3428, obsd 494.3417.

(3aR,5aR,6R,9S,9aR,9bR)-9-(tert-Butyldimethylsiloxy)-3,3a,4,5a,6,7,8,9,9a,9b-decahydro-9b-[3-(methoxymethoxy)propyl]-2,3,3,5a-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]methoxy]-5H-benz[e]inden-5-one (97a). To a stirred solution of 96a (35 mg, 0.071 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) were added diisopropylethylamine (0.25 mL, 1.43 mmol), SEMCl (0.13 mL, 0.71 mmol), and tetrabutylammonium iodide (cat). The reaction mixture was stirred overnight prior to being quenched with saturated NaHCO<sub>3</sub> solution and diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The separated aqueous solution was extracted with CH<sub>2</sub>- $Cl_2$  (5 mL  $\times$  3), and the combined organic phases were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexanes, 1:5) to provide **97a** (42 mg, 77%) as a colorless syrup: IR (neat, cm<sup>-1</sup>) 1709, 1038; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.51 (d, J = 1.1 Hz, 1 H), 4.64 (d, J = 7.4 Hz, 1 H), 4.61 (s, 2 H), 4.40 (d, J = 7.4 Hz, 1 H), 4.28 (br s, 1 H), 3.67-3.37 (series of m, 5 H), 3.36 (s, 3 H), 2.53 (dd, J = 13.8, 8.8 Hz, 1 H), 2.37 (d, J = 13.8 Hz, 1 H), 2.32 (d, J = 8.8 Hz, 1 H), 2.29–1.53 (series of m, 8 H), 1.50 (d, J = 1.1 Hz, 3 H), 1.37 (s, 3 H), 1.30 (m, 1 H), 1.05 (s, 3 H), 0.93 (s, 9 H), 0.91 (s, 3 H), 0.86 (m, 2 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.00 (s, 9 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 216.2, 143.1, 131.6, 96.5, 94.5, 79.2, 68.1, 67.4, 64.9, 55.2, 52.2, 51.3, 50.9, 48.2, 47.3, 39.4, 37.0, 33.3, 31.6, 25.9, 24.9, 24.3, 21.8, 18.2,

18.0, 15.4, 12.3, -1.4, -3.9, -4.4; FAB MS m/z (M<sup>+</sup>) calcd 624.42, obsd 624.39;  $[\alpha]^{24}$   $_{\rm D}$  +116.6 (c 0.35, CHCl<sub>3</sub>).

(3aR,5aR,6S,9S,9aR,9bR)-9-(tert-Butyldimethylsiloxy)-3,3a,4,5a,6,7,8,9,9a,9b-decahydro-9b-[3-(methoxymethoxy)propyl]-2,3,3,5a-tetra-methyl-6-[[2-(trimethylsilyl)ethoxy] methoxy]-5H-benz[e]inden-5-one (97b). A solution of 96b (16 mg, 0.032 mmol) in  $CH_2Cl_2$  (0.5 mL) was treated with diisopropylethylamine (0.3 mL, excess), SEMCl (0.12 mL, 20 equiv), and a catalytic amount of tetrabutylammonium iodide as described above to provide 97b (20 mg, quantitative) as a pale yellow oil: IR (neat, cm<sup>-1</sup>) 1710, 1026; <sup>1</sup>H NMR (300 MHz,  $(CDCI_3) \delta$  5.59 (d, J = 1.3 Hz, 1 H), 4.63 (s, 2 H), 4.53 (d, J =6.8 Hz, 1 H), 4.48 (d, J = 6.8 Hz, 1 H), 4.35 (d, J = 1.3 Hz, 1 H), 3.73 (s, 1 H), 3.64-3.40 (series of m, 4 H), 3.37 (s, 3 H), 2.42 (br s, 1 H), 2.35 (br s, 1 H), 2.28 (dd, J = 7.0, 3.1 Hz, 1 H), 1.93–1.53 (series of m, 9 H), 1.51 (d, J = 1.3 Hz, 3 H), 1.32 (m, 1 H), 1.26 (s, 3 H), 1.05 (s, 3 H), 0.99-0.85 (m, 2 H), 0.93 (s, 9 H), 0.84 (s, 3 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.01 (s, 9 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 219.6, 142.5, 132.5, 96.5, 94.3, 81.8, 68.4, 68.3, 65.0, 55.2, 51.2, 50.8, 50.4, 48.6, 42.0, 40.8, 37.8, 31.6, 29.4, 26.0, 24.9, 21.9, 21.2, 20.7, 18.0, 17.9, 12.3, -1.4, -3.7, -4.4; MS m/z (M<sup>+</sup> - C<sub>3</sub>H<sub>5</sub>O) calcd 567.3902, obsd 567.3895;  $[\alpha]^{24}_{D}$  +117.0 (*c* 0.50, CHCl<sub>3</sub>). Anal. Calcd for C<sub>34</sub>H<sub>64</sub>O<sub>6</sub>Si<sub>2</sub>: C, 65.34; H, 10.33. Found: C, 65.43; H, 10.27.

(3aR,5S,5aS,6R,9S,9aR,9bR)-9-(tert-Butyldimethylsiloxy)-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-9b-[3-(methoxymethoxy)propyl]-2,3,3,5a-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]methoxy]-3*H*-benz[*e*]inden-5-ol (103) and (3a*R*,5*R*,5a*S*,6*R*,9*S*,9a*R*,9b*R*)-9-(*tert*-Butyldimethylsiloxy)-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-9b-[3-(methoxymethoxy)propyl]-2,3,3,5a-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]methoxy]-3H-benz[e]inden-5-ol (105). To a stirred solution of 97a (24 mg, 0.038 mmol) in THF (1 mL) was added DIBAL-H solution (1.0 M in hexanes, 0.5 mL, excess) at -78 °C. After being stirred at this temperature for 1 h, the reaction mixture was carefully quenched with saturated sodium sulfate solution until a solid precipitate formed, was allowed to warm to room temperature, and was filtered. The filter cake was washed several times with ethyl acetat, e and the combined filtrates were concentrated to give a colorless residue that was subjected to flash chromatographic purification (ethyl acetate/ hexanes, 1:5) to yield 103 (14 mg, 58 %) and 105 (3.5 mg, 15%), both as colorless oils.

For **103**: IR (neat, cm<sup>-1</sup>) 3495, 1054; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.91 (m, 1 H), 4.68 (d, J = 6.5 Hz, 1 H), 4.61 (d, J = 6.5 Hz, 1 H), 4.58 (s, 2 H), 4.33 (br s, 1 H), 3.74 (m, 1 H), 3.57 (m, 1 H), 3.51–3.35 (series of m, 4 H), 3.34 (s, 3 H), 3.09 (d, J = 4.2 Hz, 1 H), 2.08–1.56 (series of m, 8 H), 1.53 (d, J = 1.2 Hz, 3 H), 1.48–1.18 (series of m, 6 H), 1.16 (s, 3 H), 1.03 (s, 3 H), 0.95 (s, 9 H), 0.94 (s, 3 H), 0.12 (s, 3 H), 0.09 (s, 3 H), 0.01 (s, 9 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  141.2, 133.3, 96.3, 94.1, 79.8, 70.7, 68.4, 67.2, 65.9, 55.1, 50.0, 46.9, 45.3, 42.0, 41.3, 36.7, 33.4, 28.5, 28.1, 26.1, 25.1, 24.0, 22.0, 18.1, 17.8, 16.1, 12.3, -1.5, -3.2, -4.4; MS *m/z* (M<sup>+</sup> – C<sub>5</sub>H<sub>11</sub>O<sub>2</sub>) calcd 523.3639, obsd 523.3665; [ $\alpha$ ]<sup>24</sup> D = 36.7 (*c* 0.45, CHCl<sub>3</sub>).



For **105**: IR (neat, cm<sup>-1)</sup> 3496, 1033; 1<sup>H</sup> NMR (300 MHz, CDCl3) d 5.89 (d, J = 1.2 Hz, 1 H), 4.85 (d, J = 6.9 Hz, 1 H), 4.71 (d, J = 6.9 Hz, 1 H), 4.60 (s, 1 H), 4.53 (s, 1 H), 4.23 (m, 1 H), 3.74-3.51 (m, 2 H), 3.49-3.37 (two sets of m, 3 H), 3.35

(s, 3 H), 2.17–1.57 (series of m, 6 H), 1.54 (d, J = 1.2 Hz, 3 H), 1.51–1.18 (series of m, 5 H), 1.17 (s, 3 H), 1.14 (s, 3 H), 0.98 (s, 3 H), 0.96 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H), 0.02 (s, 9 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  141.7, 132.9, 96.4, 92.3, 87.0, 79.6, 68.2, 66.5, 66.1, 55.2, 50.2, 49.4, 47.8, 46.9, 42.4, 36.2, 33.2, 30.9, 28.5, 26.1, 25.2, 24.2, 21.0, 18.2, 18.1, 12.3, 9.4, -1.3, -3.3, -4.3; MS m/z (M<sup>+</sup> – C<sub>6</sub>H<sub>12</sub>O) calcd 526.3510, obsd 526.3499; [ $\alpha$ ]<sup>24</sup>  $_{\rm D}$  –40.0 (c 0.035, CHCl<sub>3</sub>).

(3aR,5S,5aR,6R,9S,9aR,9bR)-9-(tert-Butyldimethylsiloxy)-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-9b-[3-(methoxymethoxy)propyl]-2,3,3,5a-tetramethyl-5-(triethylsiloxy)-6-[[2-(trimethylsilyl)ethoxy]methoxy]-3Hbenz[e]indene (104). To a stirred solution of 103 (16.9 mg, 0.027 mmol) in CH<sub>2</sub>Cl<sub>2</sub> were added diisopropylethylamine (75 µL, 0.54 mmol), DMAP (catalytic amount), and chlorotriethylsilane (45  $\mu$ L, 0.27 mmol). The resulting mixture was stirred at 35-40 °C for 60 h prior to being quenched by saturated NaHCO<sub>3</sub> solution (2 mL) and extracted with  $CH_2Cl_2$  (2 mL  $\times$ 3). The combined organic layers were washed with brine, dried, and concentrated to provide a reddish brown residue that was purified by flash chromatography (ethyl acetate/hexanes, 1:15) to yield **104** as a pale yellow oil (15 mg, 75%): IR (neat,  $cm^{-1}$ ) 1472, 1372, 1251; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.91 (s, 1 H), 4.71 (s, 2 H), 4.59 (s, 2 H), 4.29 (br s, 1 H), 3.77 (td, J = 9.8, 6.7 Hz, 1 H), 3.70 (d, J = 2.7 Hz, 1 H), 3.60 (dd, J = 11.6, 4.5 Hz, 1 H), 3.44 (m, 3 H), 3.34 (s, 3 H), 2.05-1.56 (series of m, 9 H), 1.52 (d, J = 1.2 Hz, 3 H), 1.50-1.18 (series of m, 5 H), 1.14 (s, 3 H), 1.01 (s, 3 H), 0.98 (m, 9 H), 0.95 (s, 9 H), 0.90 (s, 3 H), 0.64 (m, 6 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.01 (s, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 140.7, 133.9, 96.3, 95.8, 80.7, 71.7, 68.4, 67.2, 64.7, 55.0, 50.1, 46.7, 45.6, 42.7, 41.0, 36.8, 33.2, 29.1, 28.8, 26.2, 25.0, 24.1, 23.4, 18.2, 18.1, 16.5, 12.2, 7.2, 5.4, -1.5, -3.1, -4.7; FAB MS *m*/*z* (M<sup>+</sup>) calcd 740.53, obsd 740.42;  $[\alpha]^{24}$  <sub>D</sub> +23.1 (*c* 1.78, CHCl<sub>3</sub>).

(1R,2R,4S,4aR,5R,8S,8aS)-8-(tert-Butyldimethylsiloxy)-2-(1,1,-dimethylacetonyl)decahydro-1-[3-(methoxymethoxy)propyl]-4a-methyl-4-(triethylsiloxy)-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1-naphthaldehyde (110) and (1R,2R,4S,4aR,5R,8S,8aS)-8-(tert-Butyldimethylsiloxy)decahydro-2-(3-hydroxy-1,1-dimethylacetonyl)-1-[3-(methoxymethoxy)propyl]-4a-methyl-4-(triethylsiloxy)-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1-naphthaldehyde (111). A. Via Ozonolysis. Into a stirred solution of 104 (46 mg, 0.062) mmol) in a mixture of methanol (4 mL), CH<sub>2</sub>Cl<sub>2</sub> (4 mL), and pyridine (4 drops) was bubbled ozone at -78 °C until a blue color persisted. The excess ozone was removed with nitrogen, the colorless solution was treated with dimethyl sulfide (excess), and the reaction mixture was allowed to warm to room temperature during 2 h. The crude syrup isolated by removing all of the volatile materials was subjected to flash chromatographic purification (ethyl acetate/hexanes, 1:1) to yield 110 (13 mg, 55%, colorless oil) along with 111 (27 mg, 27%, colorless oil).

For **110**: IR (neat, cm<sup>-1</sup>) 1707, 1108, 1055; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  10.37 (s, 1 H), 4.75 (s, 2 H), 4.73 (m, 1 H), 4.61 (d, J = 2.6 Hz, 1 H), 4.58 (m, 1 H), 4.07 (m, 1 H), 3.96 (d, J = 3.0 Hz, 1 H), 3.78 (m, 2 H), 3.66–3.33 (series of m, 5 H), 3.36 (s, 3 H), 2.87 (dd, J = 14.5, 3.0 Hz, 1 H), 2.16 (s, 3 H), 2.13 (t, J = 14.5 Hz, 1 H), 1.95–1.78 (series of m, 4 H), 1.56 (m, 3 H), 1.34 (s, 3 H), 1.25 (m, 4 H), 1.10 (s, 3 H), 1.01–0.89 (series of m, 12 H), 0.88 (s, 9 H), 0.64 (m, 6 H), 0.01 (s, 15 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  213.4, 207.3, 96.4, 95.0, 81.2, 71.7, 67.9, 66.7, 64.8, 56.4, 55.1, 50.7, 45.8, 43.5, 39.1, 32.0, 27.6, 27.1, 26.8, 26.6, 26.2, 23.3, 22.9, 22.8, 18.2, 18.1, 17.7, 7.2, 5.3, -1.5, -3.3, -4.9; FAB MS m/z (M<sup>+</sup>) calcd 772.52, obsd 772.32;  $[\alpha]^{24}$  D +24.3 (*c* 0.35, CHCl<sub>3</sub>).

For **111**: IR (neat, cm<sup>-1</sup>) 3378, 1707, 1108; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  10.37 (s, 1 H), 4.75 (s, 2 H), 4.65 (m, 2 H), 4.48 (d, J = 18.1 Hz, 1 H), 4.24 (d, J = 18.1 Hz, 1 H), 4.04 (s, 1 H), 3.98 (s, 1 H), 3.78 (m, 1 H), 3.59 (m, 1 H), 3.49–3.30 (series of m, 3 H), 3.37 (s, 3 H), 2.95 (dd, J = 13.4, 2.9 Hz, 1 H), 2.20 (t, J = 3.8 Hz, 1 H), 1.94–1.47 (series of m, 7 H), 1.35 (s, 3 H), 1.31–1.11 (series of m, 2 H), 1.06–0.90 (series of m, 19 H), 0.87 (s, 9 H), 0.65 (m, 6 H), 0.01 (s, 15 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  214.6, 207.3, 96.2, 95.0, 81.2, 71.7, 67.6, 66.7, 65.0, 64.9, 56.3, 55.1, 48.3, 45.9, 43.6, 40.4, 32.0, 28.4, 27.1, 26.9, 26.2, 22.9, 22.2, 20.2, 18.2, 17.7, 7.2, 5.3, -1.5, -3.3, -4.9; FAB MS m/z (M<sup>+</sup> + 1) calcd 788.51, obsd 788.31; [ $\alpha$ ]<sup>24</sup> <sub>D</sub> +15.6 (*c* 0.35, CHCl<sub>3</sub>).

**B. By Ruthenium Tetraoxide Oxidation**. A solution of **104** (20 mg, 0.027 mmol) in  $CCl_4-CH_3CN-H_2O$  (1:1:1.5, 7 mL) was charged with sodium periodiate (23 mg, 0.108 mmol) followed by a catalytic amount of ruthenium trichloride hydrate (1 mg) at room temperature, and the dark brown mixture was stirred for 2 h. The workup procedure described above was followed (flash chromatography, ethyl acetate/ hexanes, 1:8) to provide **110** (14.3 mg, 69%) as a single product.

(1R,2R,4aR,5S,8S,8aS)-8-(tert-Butyldimethylsiloxy)-2-(1,1-dimethylacetonyl)decahydro-1-[3-(methoxymethoxy)propyl]-4a-methyl-4-oxo-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1-naphthaldehyde (116). A vigorously stirred hetereogenous mixture of 97b (14 mg, 0.022 mmol) in CCl<sub>4</sub>-CH<sub>3</sub>CN-H<sub>2</sub>O (1:1:1.5, 7 mL) was charged with sodium periodiate (19 mg, 0.09 mmol) followed by ruthenium trichloride hydrate (1 mg, catalytic amount) at room temperature. The dark brown mixture was stirred for 2 h, diluted with water and CH<sub>2</sub>Cl<sub>2</sub> (1 mL of each), and extracted with  $CH_2Cl_2$  (2 mL  $\times$  3). The combined organic layers were washed with brine, dried, and concentrated under reduced pressure to give a residue that was subjected to flash chromatographic purification (ethyl acetate/hexanes, 1:5) to furnish 116 as a colorless oil (9.6 mg, 65%): IR (neat, cm<sup>-1</sup>) 1710, 1112, 1029; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  10.32 (s, 1 H), 5.05 (d, J = 6.7 Hz, 1 H), 4.77 (d, J =6.7 Hz, 1 H), 4.48 (dd, J = 10.4, 6.4 Hz, 1 H), 4.42 (m, 1 H), 4.27 (m, 1 H), 3.75 (m, 1 H), 3.64 (m, 1 H), 3.51 (m, 1 H), 3.28 (m, 1 H), 3.22 (s, 3 H), 2.83 (s, 1 H), 2.86-2.74 (m, 1 H), 2.71 (d, J = 1.3 Hz, 1 H), 2.43 (m, 2 H), 1.92-1.71 (series of m, 3 H), 1.70 (s, 3 H), 1.69–1.51 (m, 1 H), 1.50 (s, 3 H), 1.41–1.31 (series of m, 3 H), 1.17-1.00 (m, 2 H), 0.98 (s, 9 H), 0.74 (s, 3 H), 0.57 (s, 3 H), 0.22 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 9 H); 13C NMR (75 MHz, CDCl<sub>3</sub>) & 210.7, 210.6, 205.5, 96.6, 95.5, 79.0, 68.6, 67.7, 65.5, 54.9, 54.1, 52.7, 50.4, 45.6, 45.1, 37.5, 29.2, 28.3, 27.4, 26.3, 25.6, 23.5, 23.0, 22.5, 21.2, 18.4, 18.3, -1.3, -3.5, -4.7; MS m/z (M<sup>+</sup> - 1) calcd 655.4061, obsd 655.4096;  $[\alpha]^{24}$  <sub>D</sub> +11.1 (*c* 0.14, CHCl<sub>3</sub>).

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**Supporting Information Available:** Text presenting experimental details and full spectral data for all compounds for which information is not recorded in the Experimental Section, together with copies of the high-field <sup>1</sup>H NMR spectra of all intermediates and tables giving all of the crystallographic details and structure refinement infomation for **21**, **51**, and **76**. This material is available free of charge via the Internet at http://pubs.acs.org.

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