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Divergent Synthesis of Trans-Fused Polycyclic Ethers by a Convergent Oxiranyl Anion Strategy

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Supporting Information

ABSTRACT: Octacyclic polyethers that correspond to the CDEFGHIJ-ring system of yessotoxin as well as G- and/or I-ring-modified analogues were synthesized in a divergent manner, starting from a common intermediate, using an [X + 2 + Y]-type convergent method. Reaction of a triflate with the oxiranyl anion generated from an epoxy sulfone, followed by ring expansion, allowed for the incorporation of medium-sized ring ethers into the key intermediate. Subsequent acetal formation and reductive etherification afforded various octacycles containing seven- and eight-membered ether rings.

INTRODUCTION

Polycyclic ethers are one of the most representative classes of marine toxins produced by dinoflagellates.[1,2] Ingestion of fish and shellfish contaminated with dinoflagellate toxins causes serious seafood poisoning such as ciguatera fish poisoning and diarrhetic shellfish poisoning (DSP).[3] The origin of ciguatera toxins has been identified in the dinoflagellate *Gambierdiscus toxicus*, which produces maitotoxin,[4] ciguatoxins,[5] gambierol,[6] and gambieric acids[7] (Figure 1). The characteristic trans-fused ladder-shaped molecular structures and strong biological activity of these toxins continue to stimulate the development of new synthetic routes and their application in natural product synthesis.[8] Ciguatoxin (CTX), for example, is a lipophilic sodium channel activator that binds to site 5 on voltage-dependent Na^+ channels in excitabe cells and induces the influx of Na^+ ions, causing cell depolarization.[9] The total syntheses[10] and subsequent structure−activity relationship (SAR) study of CTXs[11] revealed that modification of the ring size strongly influences the biological activity: two F-ring-modified CTX3Cs, i.e., an eight-membered and an open-chain O-linked analogue, showed markedly diminished biological activity, while the ten-membered F-ring analogue of 51-hydroxy-CTX3C retained 2% of the cytotoxicity of CTX. A recent SAR study of an artificial polycyclic ether demonstrated that a 6/7/6/6/7/6/6 heptacyclic ring system inhibits maitotoxin-induced Ca^{2+} influx in rat glioma C6 cells.[12]

Another intriguing example of polycyclic ethers is yessotoxin (YTX) (Figure 1), which was first isolated as a diarrheic polyether toxin from the digestive gland of the scallop *Patinopecten yessoensis*[13] and later reported to be produced by the dinoflagellates *Protoceratium reticulatum* and *Lingulodinium polyedrum*.[14] Since the discovery of YTX, about 40 derivatives have been characterized by NMR and LC-MS techniques.[15] Although YTX was originally classified among the toxins responsible for DSP, YTX proved not to be diarrheagenic or lethal to mice after oral administration.[16] YTX has been found to exhibit multiple biological activities, including in vitro induction of apoptosis,[17] modulation of cellular calcium levels of human lymphocytes,[18] and enhancement of phosphodiesterase activity.[19] An SAR study of YTXs revealed that the C_9 terminal chain is important for fragmentation of E-cadherin in MCF-7 breast cancer cells.[20] However, despite extensive biological studies, the precise mechanism of action of YTX is not yet fully understood.[21] The high structural variability of YTX, furthermore, demands further chemical and biological studies.[22]

Marine polycyclic ethers, as mentioned above, vary in chemical structure and mode of action and exhibit distinct biological activities, because of which they may find potential applications in pharmacology. However, their limited availability, which is due to the extremely low abundance of standard toxins in natural sources, has hampered SAR studies. Chemical synthesis offers a powerful alternative to biosynthesis for supplying standard materials and their analogues. The aim of this study is to develop a flexible and divergent method for the synthesis of polycyclic ethers containing medium ring ethers, which in turn can be applied to the synthesis of natural toxins as well as their analogues.

The strategy we pursued is a novel [X + 2 + Y] convergent approach,[8a,23] where a nucleophilic substitution reaction of the oxiranyl anion **I**[24] with triflate **II** affords the coupling product **III** (Scheme 1, step 1).[25] Intramolecular hydroxy−epoxide cyclization affords the six-membered ketone **IV** (step 2), while an ensuing ring expansion reaction yields the seven-membered ketone **V** (step 3). Finally, reductive etherification of **IV** and **V** yields polycyclic ethers **VI** and **VII**, respectively, which feature new six−six- and six−seven-membered ether rings (step 4).[26] The advantage of this strategy is its flexibility, which allows for the generation of two different ring systems (**VI** and **VII**) from the common ketone intermediate **IV**. Using this strategy, we were also interested in deliberately creating new ring-modified and desmethyl analogues useful for biological studies, because

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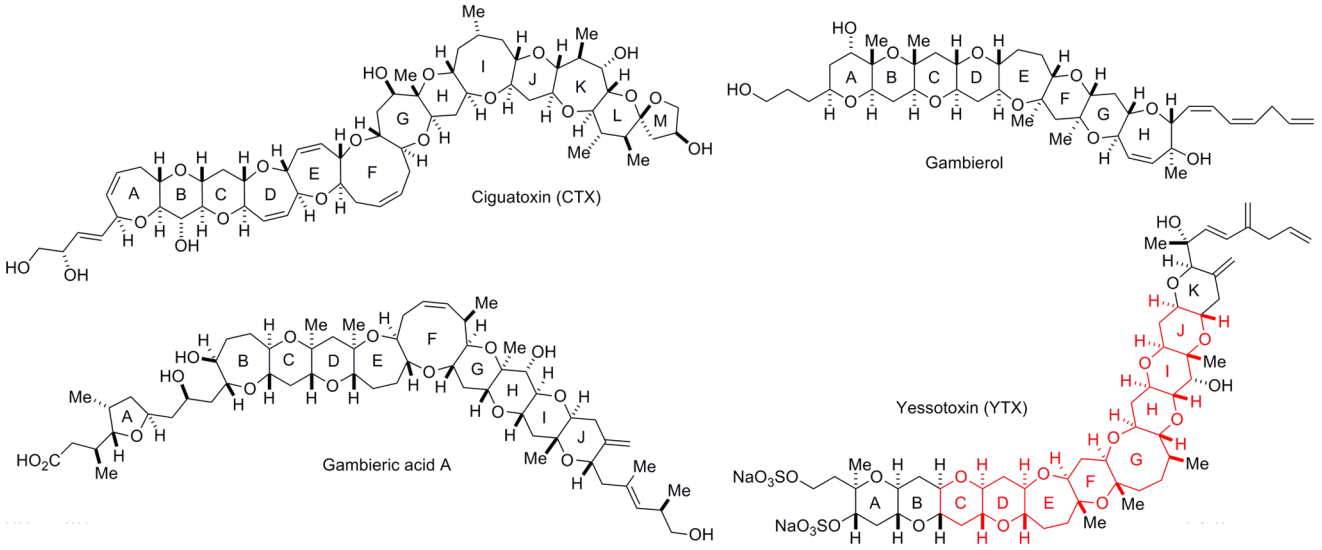
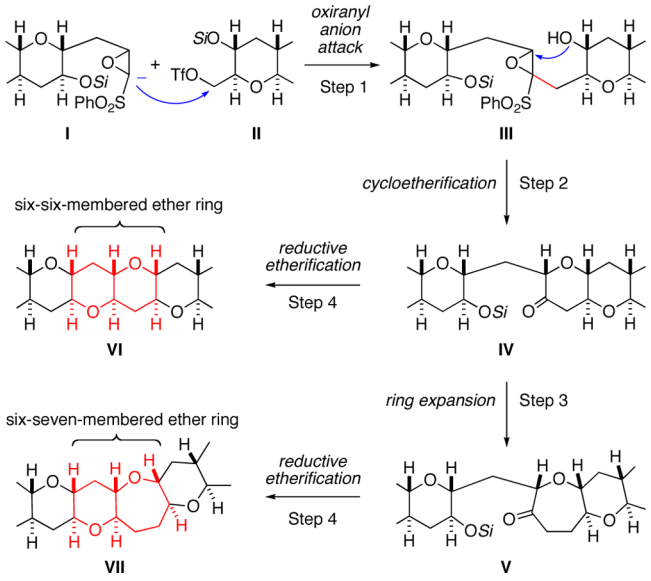
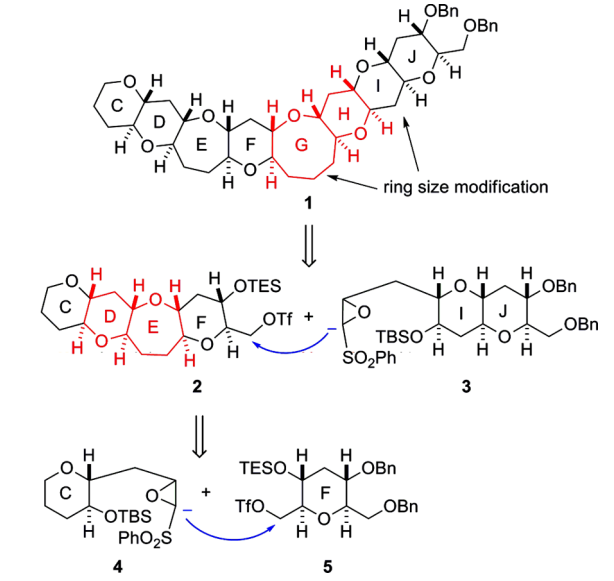


Figure 1. Chemical structure of representative polycyclic ethers.

Scheme 1. Convergent Synthetic Strategy for the Construction of Polycyclic Ethers



Scheme 2. Retrosynthetic Analysis of Octacyclic Polyether 1



bioactivities of polycyclic ethers are known to be influenced by the conformation and substituents of the ring systems.[27]

In this article, we report a convergent−divergent approach to the synthesis of the octacyclic CDEFGHIJ-ring skeleton **1** of yessotoxin and its G- and I-ring-modified analogues having different conformations.[28] Our convergent strategy was applied to the construction of the GH-ring of octacyclic ether **1**, after connection of the CDEF-ring triflate **2** and the bicyclic epoxy sulfone **3** (Scheme 2). Our flexible approach may be readily applied to octacyclic systems with combinations of different-sized G- and/or I-rings in **1**, by including ring expansion at a suitable stage of the synthesis. The tetracyclic compound **2** can then be conveniently synthesized by the same convergent strategy from epoxy sulfone **4** and monocyclic triflate **5**.

RESULTS AND DISSCUSSION

Convergent Synthesis of a Tetracyclic Ether Containing a Seven-Membered Ring. The synthesis of the CDEF-ring fragment **10**, a precursor of **2**, commenced with the coupling of **4**[26] with **5**[22c] (Scheme 3). The reaction proceeded optimally through the formation of the oxiranyl anion of **4** in the presence of **5**, when carried out using *n*-BuLi at −100 °C in THF/HMPA for 30 min, to afford **6** in 85% yield. Removal of the triethylsilyl (TES) group with TsOH, followed by exposure of the product to $MgBr_2{\cdot}OEt_2$ in the presence of LiBr, gave bromo ketone **7** as a mixture of two diastereoisomers. DBU-mediated cyclization of **7** afforded the six-membered ketone **8** in good yield, as a single isomer. This cyclization has the advantage that neither the stereochemistry of the bromo ketone **7**, in turn, nor that of epoxy sulfone **6** is relevant, because the initial cyclization products undergo facile DBU-promoted equilibration to afford a thermodynamically more stable isomer possessing an equatorial side chain. The ketone was then subjected to the ring expansion reaction with trimethylsilyldiazomethane (TMS-diazomethane)[29] in the presence of $BF_3{\cdot}OEt_2$, and the TMS group of the resulting α-trimethylsilyl ketone was removed with PPTS to furnish the

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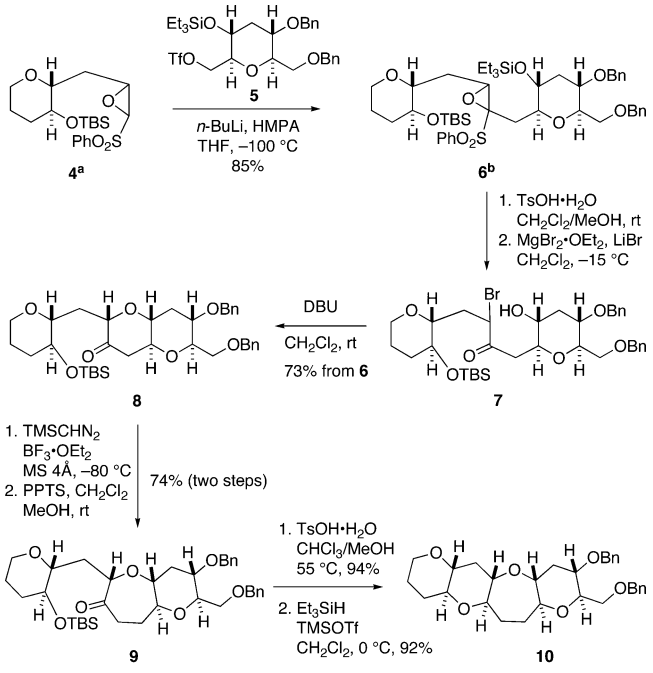
Scheme 3. Synthesis of Tetracyclic Ether 10



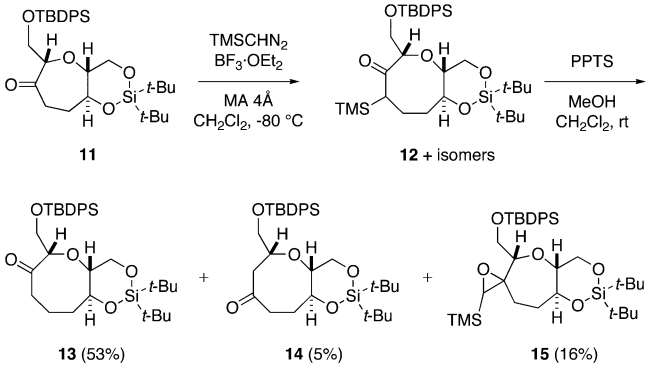
[a] A 64:36 mixture of α- and β-epoxides. [b] A 58:42 mixture of α- and β-epoxides

desired seven-membered ketone **9** in 74% yield over the two steps. Sequential cleavage of the TBS group and acetalization was accomplished by the treatment of **9** with TsOH in $CHCl_3$/MeOH at 55 °C, to give the corresponding methyl acetal in 94% yield. Finally, reductive etherification of the methyl acetal with Et_3SiH in the presence of trimethylsilyl triflate (TMSOTf) afforded the tetracyclic ether **10** containing a seven-membered ether ring, in 92% yield.

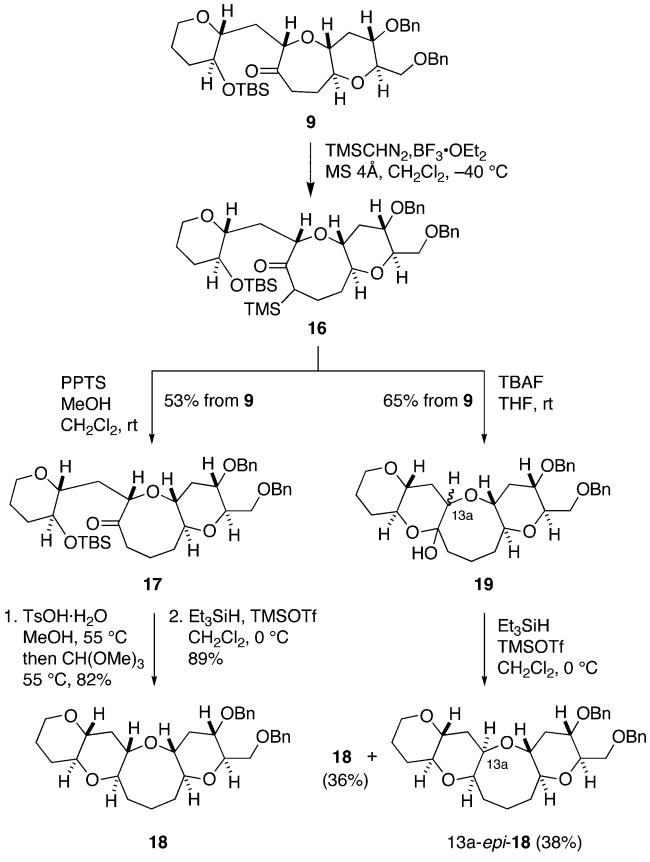
Synthesis of a Tetracyclic Ether Containing an Eight-Membered Ring Ether. Apart from seven-membered ring ethers, eight-membered ether rings are also commonly encountered structural units of polycyclic ether marine toxins. Because we established the synthetic route to seven-membered ether rings by ring expansion, we anticipated that further carbon homologation of a seven-membered ring would provide a concise route to eight-membered ether rings. Hirama and co-workers recently attempted the $AlMe_3$-mediated ring expansion reaction with TMS-diazomethane to construct the eight-membered E-ring of ciguatoxins; the reaction afforded the desired E-ring ketone and the byproduct, a seven-membered spiroepoxide, in 1.5:1 ratio.[30] Under our conditions (TMS-diazomethane and $BF_3{\cdot}OEt_2$ at −80 °C), ring expansion of the seven-membered ketone **11**[22b] afforded the desired eight-membered ketone **13** in 53% yield, along with 5% of the regioisomeric ketone **14** and 16% of spiroepoxide **15**, after mild acid treatment (Scheme 4).

Having developed the ring-expansion methodology, we next examined the BF_3-mediated ring expansion reaction of ketone **9** (Scheme 5). In this case, a higher temperature (−40 °C) was required to achieve the desired conversion to silyl ketone **16**. Removal of the TMS group of **16** with PPTS afforded the eight-membered ketone **17** in 53% yield over the two steps. Acid-catalyzed deprotection of the TBS ether, followed by heating in trimethyl orthoformate at 55 °C (both steps in one pot), gave the methyl acetal in 82% yield. Reduction with Et_3SiH and TMSOTf afforded tetracyclic ether **18**, which

Scheme 4. Ring Expansion of Seven-Membered Ether Ring 11



Scheme 5. Synthesis of Tetracyclic Ether 18



contained an eight-membered ether ring, in 89% yield. An attempt for simultaneous removal of the TMS and TBS groups in **16** with TBAF, however, caused concomitant epimerization at C13a to give an inseparable diastereomeric mixture of hemiacetal **19**, probably because of the basic nature and the presence of a hydroxide in commercial TBAF. Reductive etherification, followed by careful separation of the products by column chromatography, afforded tetracycles **18** and 13a-*epi*-**18** in 36% and 38% yields, respectively.

Divergent Synthesis of Octacyclic Ring Systems. Our newly developed [X + 2 + Y]-type convergent approach allowed for the construction of six-, seven-, and eight-membered polycyclic ethers from the same intermediate. To demonstrate the utility of our method, we focused on higher polycyclic ethers. We therefore implemented our approach in

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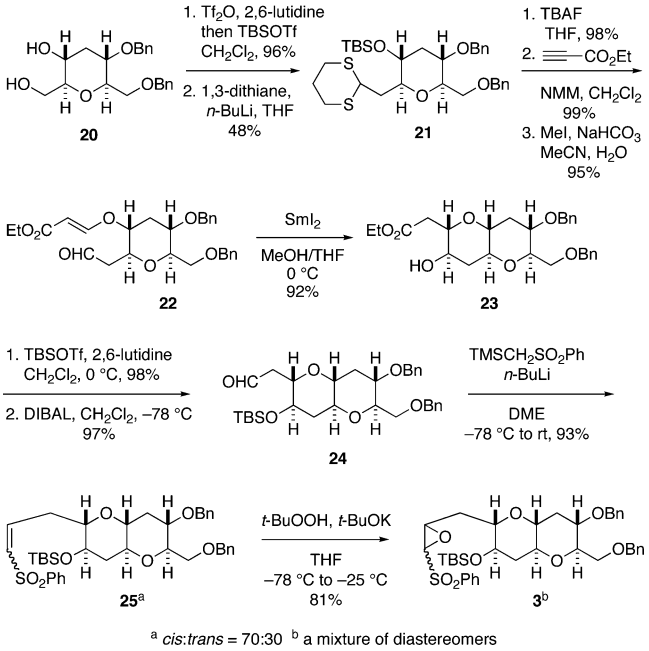
the synthesis of the octacyclic framework corresponding to the CDEFGHIJ-ring **1** of yessotoxin and its G- and/or I-ring-modified analogues.

Monocyclic diol **20**[31] was selected as the starting material for the preparation of epoxy sulfone **3** (Scheme 6). One-pot

Scheme 6. Synthesis of Epoxy Sulfone 3

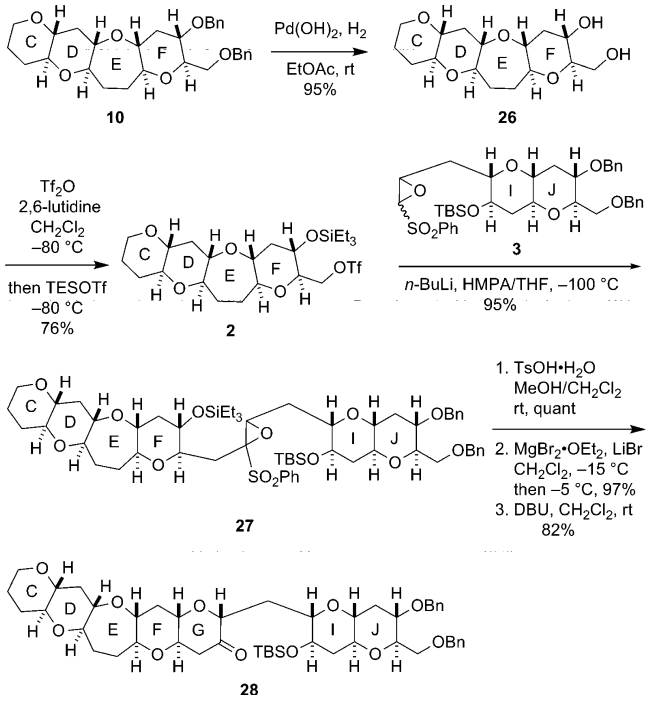


[a] *cis*:*trans* = 70:30 [b] a mixture of diastereomers

triflation of the primary hydroxy group and *tert*-butyldimethylsilylation of the secondary hydroxy group of **20**, followed by triflate displacement with 2-lithio-1,3-dithiane, gave dithioacetal **21**. Removal of the TBS group with TBAF, hetero-Michael addition of the resulting secondary alcohol to ethyl propiolate in the presence of *N*-methylmorpholine, and subsequent alkylative hydrolysis of the dithioacetal with MeI and $NaHCO_3$ in aqueous acetonitrile afforded *β*-alkoxyacrylate aldehyde **22** in high yield. Reductive radical cyclization of **22** using SmI_2[32] allowed for the efficient synthesis of the stereochemically defined bicyclic hydroxy ester **23** as the sole product in 92% yield. Protection of the hydroxy group as the TBS ether, followed by reduction of the ester with DIBALH, gave aldehyde **24**, which was then subjected to Peterson olefination[33] using (trimethylsilyl)methyl phenyl sulfone and *n*-BuLi to give cis-enriched vinyl sulfone **25** in 93% yield (cis–trans ratio = 70:30). Subsequent epoxidation with *t*-BuOOH and *t*-BuOK in THF afforded the bicyclic epoxy sulfone **3** in good yield.[26]

Toward the convergent synthesis of octacyclic ethers, triflate **2** was prepared from tetracyclic benzyl ether **10** in two steps: (1) hydrogenolysis of the two benzyl ether protecting groups, and (2) one-pot triflate and triethylsilyl ether formation (Scheme 7). The ensuing second convergent synthesis was achieved by treating a mixture of the tetracyclic triflate **2** and the bicyclic epoxy sulfone **3** with *n*-BuLi in THF at −100 °C, to afford epoxy sulfone **27** as a mixture of diastereoisomers in 95% yield. The same three-step sequence used earlier in this study (see Scheme 3), which involved deprotection of the TES ether of **27** with TsOH, epoxide opening with $MgBr_2·OEt_2$, and DBU-mediated cyclization of the resulting hydroxy bromo ketone, led to the formation of the six-membered ring ether

Scheme 7. Synthesis of Ketone 28



ketone **28**, a key intermediate in the present divergent synthesis, in good overall yield.

Finally, five different octacyclic ethers, including the CDEFGHIJ-ring skeleton **1** of yessotoxin, were synthesized from the key intermediate **28** (Scheme 8). First, desilylative acetalization, followed by reductive etherification of the resulting methyl acetal **29** with Et_3SiH and TMSOTf, gave octacyclic ether **30** in good yield. To introduce an angular methyl group at the acetal carbon atom, mixed thioacetal **31** was prepared by removal of the TBS group with TsOH in aqueous THF at 65 °C, followed by reaction with EtSH in the presence of $Zn(OTf)_2$. Oxidation of **31** to the corresponding sulfone with *m*-CPBA, followed by methylation with $AlMe_3$,[34] allowed for the stereoselective introduction of the angular methyl group, and cyclic ether **32** was obtained as a single isomer in 73% yield.

In addition, the ring expansion approach enabled access to octacyclic derivatives containing seven- and eight-membered ether rings at the center of the molecule. Thus, treatment of **28** with TMS-diazomethane and subsequent removal of the TMS group gave the seven-membered ketone **33** in 87% yield. The one-pot removal of the TBS group and cyclic acetal formation was followed by reductive etherification with Et_3SiH and TMSOTf to afford the seven-membered G-ring analogue **34** in good yield. A second BF_3-mediated ring expansion reaction of **33** with TMS-diazomethane afforded the eight-membered ketone **35**, after removal of the TMS group. Cyclic acetal formation and subsequent reductive etherification gave octacyclic ether **1**, which corresponds to the CDEFGHIJ-ring system of yessotoxin.

The utility of the present divergent approach was further demonstrated by repositioning the carbonyl group in **28** to the I-ring. Reduction of ketone **28** with $NaBH_4$, followed by acetylation of the resulting alcohol, gave the G-ring acetate, where the TBS ether on the I-ring was cleaved by the action of TBAF in the presence of acetic acid. Oxidation of the resulting

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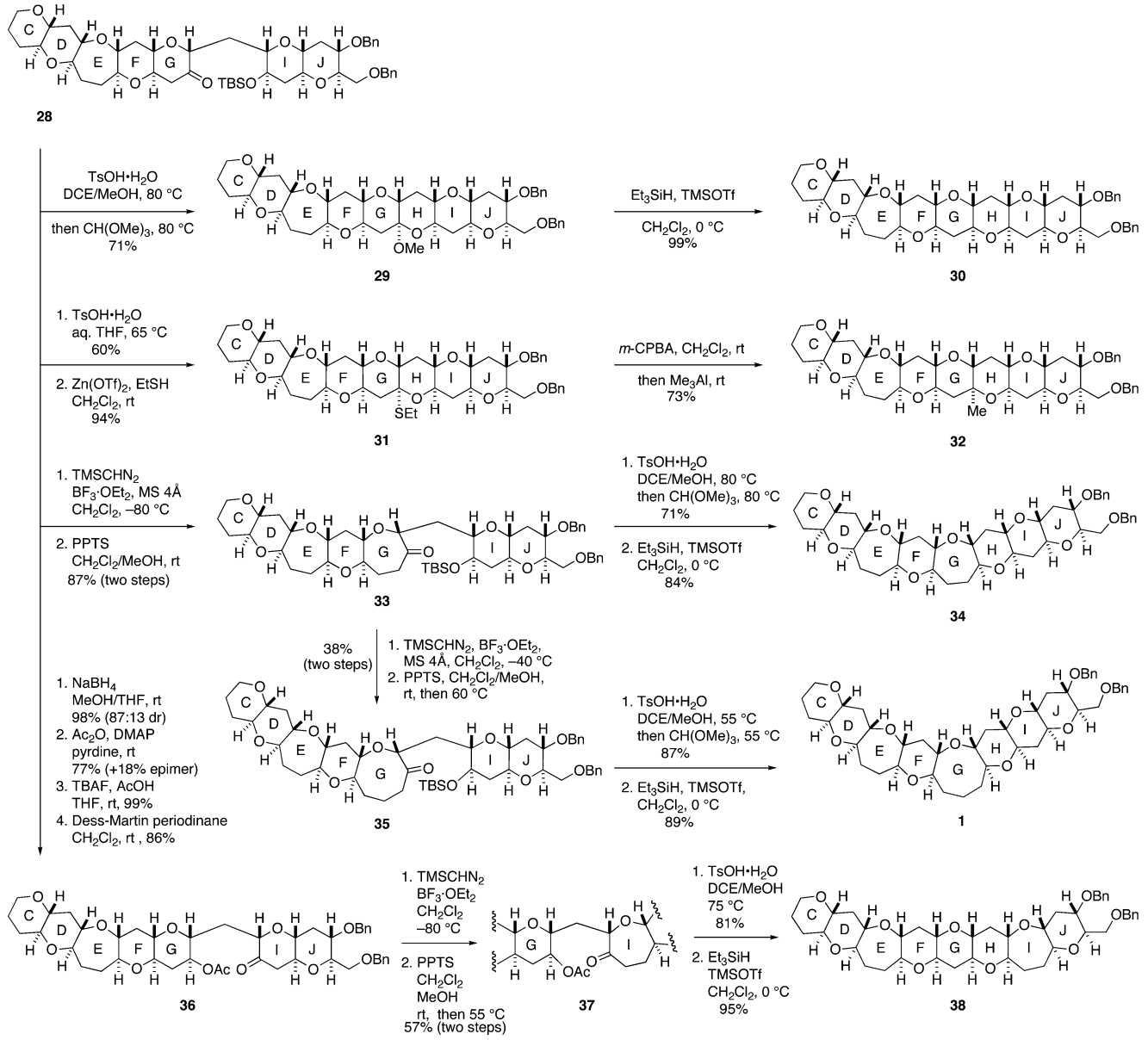
Scheme 8. Synthesis of Octacyclic Ether 1 and Its Ring-Modified Analogues



alcohol with Dess–Martin periodinane[35] gave the I-ring ketone **36**. Ring expansion of **36** was then accomplished by using the same conditions as those employed for ketone **33**, giving the seven-membered ketone **37** in moderate yield. Heating of the ketone with TsOH in dichloroethane (DCE)/MeOH at 75 °C led to simultaneous deacetylation and cyclic methyl acetal formation. Finally, reductive etherification afforded octacyclic ether **38**, a positional isomer of the seven-membered ring of **34**.

■ CONCLUSION

We have demonstrated a divergent synthesis of trans-fused polycyclic ethers by a new [X + 2 + Y]-type convergent method based on an oxiranyl anion strategy. The key feature of this method is that seven- and eight-membered ether rings can readily be constructed by introducing ring expansion at the stage where intermediate ketones are formed. The ensuing intramolecular acetalization and reductive etherification reactions allow for the construction of various types of octacyclic polyethers. The present method provides a flexible and divergent synthetic route to polycyclic ethers consisting of six-, seven-, and eight-membered ether rings, as they can be synthesized from the same starting material. Further application of this method to the synthesis of marine polycyclic ethers and their analogues is in progress.

■ EXPERIMENTAL SECTION

General. All air- and moisture-sensitive reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions. The term "dried" refers to the drying of an organic solution over $MgSO_4$ followed by filtration. Flash chromatography was carried out with silica gel (spherical, neutral, particle size 40–50 μm). Melting points are uncorrected. Chemical shifts are reported in ppm relative to internal TMS (δ 0.00 ppm) for ^{1}H NMR spectra and to the solvent signals (δ 77.0 ppm for $CDCl_3$, δ 128.39 ppm for C_6D_6, and δ 123.87 ppm for pyridine-d_5) for ^{13}C NMR spectra. Coupling constants (J) are reported in hertz. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =

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broad). ^{1}H and ^{13}C spectra are provided in Supporting Information. The low- and high-resolution mass spectra were recorded on magnetic sector FAB or EI mass spectrometers.

(2*S*,3*R*,5*S*,6*R*)-5-(Benzyloxy)-6-((benzyloxy)methyl)-2-(((((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)-2-(phenylsulfonyl)oxiran-2-yl)methyl)-3-((triethylsilyl)oxy)tetrahydropyran (6). To a solution of epoxy sulfones **4**[26] (214 mg, 0.519 mmol, 64:36 mixture of isomers) and triflate **5**[22c] (209 mg, 0.346 mmol) in THF (6 mL) and HMPA (0.241 mL, 1.38 mmol) at −100 °C was added dropwise *n*-BuLi (0.346 mL of a 1.6 M solution in *n*-hexane, 0.554 mmol). The reaction mixture was stirred at −100 °C for 30 min, and then the reaction was quenched with saturated aqueous NH_4Cl solution. The resulting mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc in hexane) afforded a 58:42 mixture of epoxy sulfones **6** (255 mg, 85%) as a pale yellow oil. $[\alpha]^{28}_D$ −15.5 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 1454, 1324, 1098, 838 cm^{-1}; ^{1}H NMR for the major isomer ($CDCl_3$, 600 MHz) δ 7.96−7.92 (2H, m), 7.65−7.60 (1H, m), 7.54−7.51 (2H, m), 7.34−7.20 (10H, m), 4.67 and 4.49 (each 1H, d, *J* = 12.1 Hz), 4.51 and 4.44 (each 1H, d, *J* = 11.5 Hz), 3.88 (1H, m), 3.79 (1H, dd, *J* = 11.0, 3.3 Hz), 3.65−3.51 (4H, m), 3.40 (1H, ddd, *J* = 13.2, 8.8, 4.4 Hz), 3.33−3.11 (4H, m), 2.81 (1H, m), 2.48 (1H, dd, *J* = 15.0, 2.2 Hz), 2.39 (1H, ddd, *J* = 15.7, 9.5, 7.3 Hz), 2.32−2.26 (1H, m), 2.08−1.99 (1H, m), 1.69−1.59 (2H, m), 1.48−1.38 (2H, m), 1.19 (1H, dd, *J* = 15.0, 11.0 Hz), 0.91 (9H, s), 0.83 (9H, t, *J* = 8.0 Hz), 0.439 (3H, dq, *J* = 15.0, 8.0 Hz), 0.436 (3H, dq, *J* = 15.0, 8.9 Hz), 0.14 (3H, s), 0.09 (3H, s); ^{13}C NMR for the major isomer ($CDCl_3$, 150 MHz) δ 138.5, 138.4, 138.1, 133.8, 129.0 (×2), 128.4 (×2), 127.8 (×2), 127.64, 127.56, 81.9, 79.9, 78.8, 73.6, 72.7, 71.7, 71.4, 71.0, 70.3, 69.0, 67.7, 64.1, 39.6, 35.8, 33.5, 30.5, 25.8, 25.5, 17.9, 6.7, 4.9, −4.2, −4.7; ^{1}H NMR for the minor isomer ($CDCl_3$, 600 MHz) δ 7.96−7.92 (2H, m), 7.65−7.60 (1H, m), 7.54−7.51 (2H, m), 7.34−7.20 (10H, m), 4.64 and 4.51 (each 1H, d, *J* = 12.1 Hz), 4.50 and 4.42 (each 1H, d, *J* = 11.5 Hz), 3.76 (1H, m), 3.71 (1H, dd, *J* = 8.4, 2.6 Hz), 3.70 (1H, dd, *J* = 10.6, 3.7 Hz), 3.65−3.51 (2H, m), 3.33−3.11 (6H, m), 2.93 (1H, ddd, *J* = 15.0, 8.4, 2.2 Hz), 2.79 (1H, ddd, *J* = 15.0, 2.6, 2.6 Hz), 2.32−2.26 (1H, m), 2.13 (1H, dd, *J* = 15.0, 9.5 Hz), 2.08−1.99 (2H, m), 1.69−1.59 (2H, m), 1.48−1.38 (2H, m), 1.32 (1H, q, *J* = 11.7 Hz), 0.91 (9H, s), 0.78 (9H, t, *J* = 8.0 Hz), 0.36 (1H, dq, *J* = 15.1, 8.0 Hz), 0.33 (1H, dq, *J* = 15.1, 8.0 Hz), 0.12 (3H, s), 0.08 (3H, s); ^{13}C NMR for the minor isomer ($CDCl_3$, 150 MHz) δ 138.5, 138.33, 138.28, 133.7, 129.04, 129.0, 128.3 (×2), 127.8 (×2), 127.7, 127.5, 80.4, 79.8, 77.0, 75.2, 73.4, 71.6, 71.5, 71.4, 69.0, 68.5, 67.4, 62.5, 39.6, 33.4, 31.5, 30.4, 25.8, 25.6, 17.9, 6.7, 4.8, −4.3, −4.7; HRFABMS *m*/*z* calcd for $C_{47}H_{71}O_9SSi_2$ (MH^+) 867.4357, found 867.4356.

(2*S*,4a*S*,6*R*,7*S*,8a*R*)-7-(Benzyloxy)-6-((benzyloxy)methyl)-2-(((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)hexahydropyrano[3,2-*b*]pyran-3(2*H*)-one (8). A solution of the TES ether **6** (255 mg, 0.294 mmol) and $TsOH·H_2O$ (5.6 mg, 0.029 mmol) in CH_2Cl_2 (2.5 mL) and MeOH (2.5 mL) was stirred at room temperature for 1 h. The reaction was quenched with Et_3N, and the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (50→80% EtOAc in hexane) afforded 201 mg of the secondary alcohol as a colorless oil.

The secondary alcohol (201 mg, 0.267 mmol) prepared in the previous step was dissolved in CH_2Cl_2 (5 mL), and the solution was cooled to −15 °C. LiBr (46 mg, 0.53 mmol) and $MgBr_2·OEt_2$ (138 mg, 0.534 mmol) were added and the reaction mixture was stirred at −15 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (40% EtOAc in hexane) provided bromo ketone **7** (171 mg) as a colorless oil.

To a solution of bromo ketone **7** (171 mg, 0.248 mmol) in CH_2Cl_2 (5 mL) was added DBU (0.039 mL, 0.26 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water, dried, and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexane) gave ketone **8** (131 mg, 73% overall yield for the three steps) as a colorless oil. $[\alpha]^{23}_D$ +50.9 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1719, 1455, 1364, 1254, 1098, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (10H, m, Ar), 4.62 and 4.55 (each 1H, d, *J* = 12.2 Hz), 4.59 and 4.42 (each 1H, d, *J* = 11.2 Hz), 3.99 (1H, dd, *J* = 6.4, 2.9 Hz), 3.80 (1H, m), 3.76 (1H, dd, *J* = 10.7, 1.5 Hz), 3.67 (1H, dd, *J* = 10.7, 4.9 Hz), 3.58 (1H, ddd, *J* = 10.7, 9.3, 4.4 Hz), 3.47 (1H, ddd, *J* = 9.3, 4.9, 1.5 Hz), 3.41 (1H, ddd, *J* = 10.7, 9.3, 6.3 Hz), 3.36−3.18 (4H, m), 2.98 (1H, dd, *J* = 17.1, 5.9 Hz), 2.65 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 2.45−2.37 (2H, m), 1.96 (1H, m), 1.81 (1H, ddd, *J* = 14.2, 9.3, 3.4 Hz), 1.68−1.57 (2H, m), 1.55 (1H, q, *J* = 11.2 Hz), 1.39 (1H, m), 0.87 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 138.1, 137.9, 128.4, 128.3, 127.9, 127.8 (×2), 127.6, 79.8, 79.4, 78.5, 75.6, 74.0, 73.5, 72.1, 71.9, 71.1, 69.1, 67.3, 44.2, 35.2, 33.9, 33.5, 25.8, 25.6, 17.9, −4.1, −4.7; HRFABMS *m*/*z* calcd for $C_{35}H_{51}O_7Si$ (MH^+) 611.3404, found 611.3420.

(2*R*,3*S*,4a*R*,6*S*,9a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)hexahydro-2*H*-pyrano[3,2-*b*]oxepin-7(3*H*)-one (9). To a suspension of ketone **8** (120 mg, 0.197 mmol) and powdered 4 Å molecular sieves (600 mg) in CH_2Cl_2 (6 mL) at −80 °C were added $BF_3·OEt_2$ (0.121 mL, 0.983 mmol) and trimethylsilyldiazomethane (0.493 mL of a 2.0 M solution in hexanes, 0.986 mmol). After being stirred at −80 °C for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure to afford 139 mg of the crude TMS ketone, which was immediately used in the next reaction without further purification.

A solution of the above TMS ketone (139 mg, 0.197 mmol) and PPTS (50 mg, 0.199 mmol) in CH_2Cl_2 (2.5 mL) and MeOH (2.5 mL) was stirred at room temperature for 1 h. The reaction was quenched with Et_3N, and the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc in hexane) to give ketone **9** (91 mg, 74%) as a colorless oil. $[\alpha]^{24}_D$ +10.5 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 1711, 1454, 1256, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.20 (10H, m, Ar), 4.60 and 4.54 (each 1H, d, *J* = 12.2 Hz), 4.58 and 4.39 (each 1H, d, *J* = 11.2 Hz), 3.96 (1H, dd, *J* = 6.8, 3.9 Hz), 3.78 (1H, m), 3.74 (1H, dd, *J* = 10.7, 1.5 Hz), 3.61 (1H, dd, *J* = 10.7, 4.9 Hz), 3.49−3.39 (2H, m), 3.37−3.19 (4H, m), 3.03 (1H, ddd, *J* = 11.2, 9.3, 4.4 Hz), 2.87 (1H, ddd, *J* = 13.7, 12.9, 2.0 Hz), 2.55 (1H, ddd, *J* = 11.7, 4.4, 3.9 Hz), 2.32 (1H, dd, *J* = 11.2, 6.8 Hz), 2.24 (1H, ddd, *J* = 9.2, 7.3, 2.4 Hz), 2.19 (1H, m), 1.96 (1H, m), 1.76 (1H, ddd, *J* = 13.7, 9.3, 3.9 Hz), 1.67−1.49 (4H, m), 1.40 (1H, m), 0.88 (9H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 138.2, 138.0, 128.4, 128.3, 127.9, 127.7 (×2), 127.6, 83.9, 80.7, 80.3, 80.0, 78.1, 73.5, 72.4, 71.3, 71.0, 69.2, 67.4, 37.1, 36.5, 36.3, 33.5, 29.2, 25.8, 25.5, 17.9, −3.9, −4.7; HRFABMS *m*/*z* calcd for $C_{36}H_{53}O_7Si$ (MH^+) 625.3561, found 625.3580.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,10a*S*,11a*R*,13a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)tetradecahydro-2*H*-pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepine (10). *i. Acetalization of Ketone* ***9****.* A solution of **9** (438 mg, 0.701 mmol) and $TsOH·H_2O$ (2.2 mg, 0.012 mmol) in $CHCl_3$ (10 mL) and MeOH (10 mL) was stirred at 55 °C for 7 h. The reaction mixture was cooled to room temperature, and the reaction was quenched with Et_3N. The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (40% EtOAc in hexane) afforded methyl acetal 11a-OMe-**10** (347 mg, 94%) as a colorless oil. (2*R*,3*S*,4a*R*,5a*S*,6a*R*,10a*S*,11a-*R*,13a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-11a-methoxytetradecahydro-2*H*-pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepine (11a-OMe-**10**): $[\alpha]^{24}_D$ +4.7 (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 1454, 1242, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.18 (10H, m, Ar),

4.61 and 4.54 (each 1H, d, J = 12.2 Hz), 4.57 and 4.37 (each 1H, d, J = 11.2 Hz), 3.91 (1H, m), 3.73 (1H, dd, J = 10.7, 1.5 Hz), 3.61 (1H, dd, J = 10.7, 5.4 Hz), 3.46 (1H, ddd, J = 11.2, 9.8, 4.9 Hz), 3.42 (1H, dd, J = 10.7, 4.9 Hz), 3.41−3.25 (4H, m), 3.25 (3H, s), 3.21 (1H, ddd, J = 13.2, 9.3, 3.9 Hz), 2.98 (1H, ddd, J = 10.7, 9.3, 4.9 Hz), 2.58 (1H, ddd, J = 11.2, 4.4, 4.4 Hz), 2.14 (1H, m), 2.08−1.70 (8H, m), 1.59 (1H, q, J = 11.2 Hz), 1.41 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 138.0, 128.4, 128.3, 127.8, 127.7, 127.7, 127.6, 100.0, 82.0, 81.1, 80.2, 79.1, 77.6, 73.5, 72.5, 70.8, 70.2, 69.3, 67.9, 47.3, 36.9, 32.3, 31.0, 28.9, 27.6, 25.7; HREIMS m/z calcd for $C_{31}H_{40}O_7$ (M^+) 524.2774, found 524.2750.

*ii. Reductive Etherification of Acetal 11a-OMe-**10**.* To a solution of 11a-OMe-**10** (347 mg, 0.662 mmol) in CH_2Cl_2 (15 mL) at 0 °C were added Et_3SiH (0.529 mL, 3.312 mmol) and TMSOTf (0.360 mL, 1.986 mmol), and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (40% EtOAc in hexane) afforded the tetracyclic polyether **10** (302 mg, 92%) as a colorless solid. Mp 144−147 °C; $[\alpha]^{25}_D$ +30.9 (c 0.39, $CHCl_3$); IR ($CHCl_3$) 1496, 1455, 1338, 1281, 1073 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.34−7.06 (10H, m, Ar), 4.50 and 4.43 (each 1H, d, J = 12.7 Hz), 4.47 and 4.28 (each 1H, d, J = 12.2 Hz), 3.80 (1H, dd, J = 10.7, 2.0 Hz), 3.74 (1H, dd, J = 10.7, 4.4 Hz), 3.70 (1H, m), 3.50 (1H, ddd, J = 11.2, 9.3, 4.9 Hz), 3.40 (1H, ddd, J = 9.3, 4.4, 2.0 Hz), 3.15 (1H, ddd, J = 10.7, 9.3, 3.9 Hz), 3.12−3.04 (3H, m), 3.10 (1H, ddd, J = 9.3, 9.3, 4.4 Hz), 2.89 (1H, ddd, J = 11.2, 11.2, 3.9 Hz), 2.84 (1H, ddd, J = 10.2, 10.2, 4.4 Hz), 2.47 (1H, ddd, J = 11.7, 4.4, 4.4 Hz), 2.46 (1H, ddd, J = 11.2, 4.4, 4.4 Hz), 1.95−1.85 (5H, m), 1.75 (1H, q, J = 11.2 Hz), 1.55 (1H, q, J = 11.2 Hz), 1.49−1.25 (2H, m), 1.19 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 138.0, 128.4, 128.3, 127.8, 127.7, 127.7, 127.6, 82.1, 81.8, 80.2, 79.5, 78.8, 77.9, 77.2, 73.5, 72.6, 70.9, 69.4, 67.9, 37.5, 37.1, 29.3, 29.3, 29.2, 25.5; HREIMS m/z calcd for $C_{30}H_{38}O_6$ (M^+) 494.2668, found 494.2650.

Ring Expansion Reaction of the Seven-Membered Ketone 11. To a suspension of ketone **11**[22b] (357 mg, 0.629 mmol) and powdered 4 Å molecular sieves (12.9 g) in CH_2Cl_2 (12 mL) at −80 °C were added $BF_3{\cdot}OEt_2$ (0.232 mL, 1.89 mmol) and trimethylsilyldiazomethane (1.57 mL of a 2.0 M solution in hexanes, 3.14 mmol). The reaction mixture was stirred at −80 °C for 2.3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure to afford the crude TMS ketone **12** (441 mg), which was immediately used in the next reaction without further purification.

A solution of the TMS ketone **12** (441 mg, 0.629 mmol) and PPTS (152 mg, 0.629 mmol) in CH_2Cl_2 (3 mL) and MeOH (3 mL) was stirred at room temperature for 20 h. The reaction was quenched with Et_3N, and the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (5→10% EtOAc in n-hexane) gave ketone **13** (194 mg, 53%), the regioisomer **14** (18 mg, 5%), and a 57:43 mixture of epoxides *cis*- and *trans*-**15** (69 mg, 16%).

(4a*R*,6*S*,10a*S*)-2,2-Di-*tert*-butyl-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)hexahydro[1,3,2]dioxasilino[5,4-*b*]oxocin-7(6*H*)-one (13). Colorless oil; $[\alpha]^{27}_D$ −85.6 (c 1.28, $CHCl_3$); IR ($CHCl_3$) 2933, 2860, 1713, 1473, 1110, 1069 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70−7.67 (2H, m), 7.65−7.62 (2H, m), 7.46−7.36 (6H, m), 4.12 (1H, dd, J = 10.7, 4.9 Hz), 4.03 (1H, ddd, J = 9.3, 8.0, 1.5 Hz), 3.89 (1H, dd, J = 10.7, 10.3 Hz), 3.87 (1H, dd, J = 11.2, 5.6 Hz), 3.7943 (1H, dd, J = 11.2, 2.8 Hz), 3.7942 (1H, dd, J = 5.6, 2.8 Hz), 3.22 (1H, ddd, J = 10.3, 9.3, 4.9 Hz), 3.20 (1H, td, J = 11.5, 5.8 Hz), 2.21 (1H, ddd, J = 11.5, 5.6, 4.7 Hz), 2.05 (1H, m), 1.97 (1H, m), 1.87 (1H, m), 1.71 (1H, m), 1.06 (9H, s), 1.02 (9H, s), 0.96 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.0, 135.7, 135.6, 133.00, 132.96, 129.8 (×2), 127.8, 127.7, 89.5, 82.3, 77.4, 67.2, 65.9, 38.5, 36.4, 27.4, 27.0, 26.6, 22.6, 22.5, 19.8, 19.1; HRFABMS m/z calcd for $C_{33}H_{51}O_5Si_2$ (MH^+) 583.3275, found 583.3280.

(4a*R*,6*R*,10a*S*)-2,2-Di-*tert*-butyl-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)hexahydro-[1,3,2]dioxasilino[5,4-*b*]oxocin-8(9*H*)-one (14). Colorless oil; $[\alpha]^{29}_D$ +11.2 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 2961, 2933, 2860, 1697, 1473, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66−7.64 (4H, m), 7.45−7.36 (6H, m), 4.05 (1H, ddd, J = 9.5, 5.0, 2.9 Hz), 3.98 (1H, dd, J = 10.5, 5.1 Hz), 3.84 (1H, dddd, J = 10.3, 5.6, 5.1, 2.4 Hz), 3.67 (1H, dd, J = 10.5, 10.2 Hz), 3.65 (1H, dd, J = 10.7, 5.6 Hz), 3.55 (1H, dd, J = 10.7, 5.1 Hz), 3.10 (1H, ddd, J = 10.2, 9.5, 5.1 Hz), 2.95 (1H, dd, J = 10.9, 10.3 Hz), 2.73 (1H, ddd, J = 16.1, 12.4, 1.9 Hz), 2.57 (1H, dddd, J = 15.1, 12.4, 2.9, 2.2 Hz), 2.43 (1H, dd, J = 10.9, 2.4 Hz), 2.41 (1H, ddd, J = 16.1, 7.1, 2.2 Hz), 2.00 (1H, dddd, J = 15.1, 7.1, 5.0, 1.9 Hz), 1.05 (9H, s), 1.02 (9H, s), 0.98 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.6, 135.69, 135.66, 133.28, 133.25, 129.83, 129.81, 127.8 (×2), 82.7, 77.0, 76.2, 67.3, 66.7, 45.0, 39.3, 29.4, 27.4, 27.0, 26.7, 22.5, 20.1, 19.1; HRFABMS m/z calcd for $C_{33}H_{51}O_5Si_2$ (MH^+) 583.3275, found 583.3267.

(4a*R*,6*S*,9a*S*)-2,2-Di-*tert*-butyl-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3′-(trimethylsilyl)hexahydrospiro[[1,3,2]-dioxasilino[5,4-*b*]oxepine-7,2′-oxirane] (*cis*-15 and *trans*-15). A 57:43 mixture of *cis*-**15** and *trans*-**15**. Colorless oil; $[\alpha]^{29}_D$ −39.7 (c 1.23, $CHCl_3$); IR ($CHCl_3$) 2960, 2933, 2889, 2860, 1115 cm^{-1}; ^{1}H NMR of the major *cis*-**15** ($CDCl_3$, 500 MHz) δ 7.74−7.67 (4H, m), 7.42−7.34 (6H, m), 4.06 (1H, dd, J = 10.8, 5.3 Hz), 3.89−3.84 (1H, m), 3.83 (1H, dd, J = 10.8, 10.3 Hz), 3.78 (2H, d, J = 4.4 Hz), 3.61 (1H, t, J = 4.4 Hz), 3.37 (1H, ddd, J = 10.3, 9.4, 5.3 Hz), 2.53 (1H, td, J = 13.5, 1.8 Hz), 2.26−2.20 (1H, m), 2.09 (1H, s), 1.43 (1H, tdd, J = 13.5, 11.5, 1.5 Hz), 1.06 (9H, s), 1.03 (9H, s), 0.98 (9H, s), 1.00−0.97 (1H, m), 0.13 (9H, s); ^{13}C NMR of the major *cis*-**15** ($CDCl_3$, 125 MHz) δ 135.8, 135.7, 133.9, 133.6, 129.5, 129.53, 129.48, 127.52, 127.50, 79.9, 77.1 (×2), 67.0, 65.5, 64.9, 57.9, 36.3, 31.4, 27.5, 27.1, 26.7, 22.6, 19.9, 19.3, −1.9; ^{1}H NMR of the minor *trans*-15 ($CDCl_3$, 500 MHz) δ 7.74−7.67 (4H, m), 7.42−7.34 (6H, m), 4.13 (1H, dd, J = 10.8, 5.3 Hz), 3.89−3.84 (2H, m), 3.74 (1H, dd, J = 11.5, 7.1 Hz), 3.65 (1H, dd, J = 11.5, 2.5 Hz), 3.57 (1H, dd, J = 7.1, 2.5 Hz), 3.30 (1H, ddd, J = 10.1, 9.4, 5.3 Hz), 2.26−2.20 (1H, m), 2.16 (1H, dddd, J = 13.8, 7.3, 5.2, 1.2 Hz), 1.81 (1H, d, J = 0.9 Hz), 1.46 (1H, tdd, J = 13.5, 11.5, 1.6 Hz), 1.19 (1H, ddd, J = 14.0, 7.3, 1.6 Hz), 1.06 (9H, s), 1.04 (9H, s), 1.00 (9H, s), 0.12 (9H, s); ^{13}C NMR of the minor *trans*-15 ($CDCl_3$, 125 MHz) δ 135.75, 135.72, 134.0, 133.6, 129.6, 129.5, 127.6, 127.5, 85.0, 79.6, 77.4, 67.3, 65.7, 64.1, 58.8, 35.0, 27.5, 27.1, 26.9, 26.8, 22.6, 19.9, 19.2, −2.0; HRFABMS m/z calcd for $C_{36}H_{58}O_5Si_3Na$ (MNa^+) 677.3490, found 677.3488. The stereochemistry of the epoxides *cis*- and *trans*-**15** was determined by difference NOE experiments as shown in Figure 2.

(2*R*,3*S*,4a*R*,6*S*,10a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)octahydropyrano[3,2-*b*]oxocin-7(6*H*)-one (17). To a suspension of ketone **9** (29.7 mg, 0.048 mmol) and powdered 4 Å molecular sieves (148 mg) in CH_2Cl_2 (2.5 mL) at −80 °C were

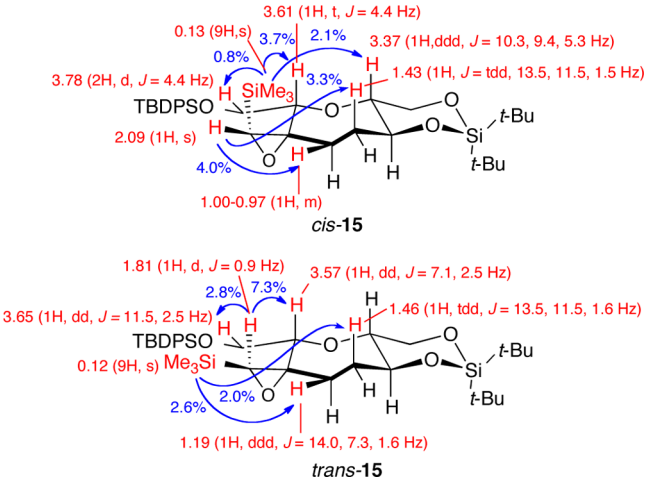

Figure 2. Difference NOE experiments of *cis*-**15** and *trans*-**15**.

added $BF_3{\cdot}OEt_2$ (0.029 mL, 0.238 mmol) and trimethylsilyldiazomethane (0.238 mL of a 2.0 M solution in hexanes, 0.476 mmol). After being stirred at −80 °C for 1 h, the reaction mixture was warmed to −40 °C and stirring was continued for another 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure to afford the crude TMS ketone **16**, which was immediately used in the next reaction without further purification.

A solution of the above TMS ketone **16** and PPTS (25 mg, 0.099 mmol) in CH_2Cl_2 (1.0 mL) and MeOH (1.0 mL) was stirred at room temperature for 25 h. The reaction was quenched with Et_3N (0.1 mL), and the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc in hexane) to give ketone **17** (16.0 mg, 53%) as a colorless oil. $[\alpha]^{25}_D$ −18.4 (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) 1709, 1454, 1254, 1099 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.35−7.07 (10H, m, Ar), 4.49 and 4.42 (each 1H, d, *J* = 12.2 Hz), 4.41 and 4.24 (each 1H, d, *J* = 11.7 Hz), 3.90 (1H, dd, *J* = 7.3, 3.4 Hz), 3.78 (1H, d, *J* = 10.7 Hz), 3.70 (1H, dd, *J* = 10.7, 4.4 Hz), 3.61 (1H, m), 3.42−3.35 (3H, m), 3.28 (1H, ddd, *J* = 9.8, 9.8, 4.4 Hz), 3.17 (1H, ddd, *J* = 11.2, 11.2, 5.4 Hz), 3.12−3.03 (2H, m), 2.79 (1H, ddd, *J* = 11.7, 8.8, 4.4 Hz), 2.44 (1H, ddd, *J* = 12.2, 12.2, 3.9 Hz), 2.40 (1H, ddd, *J* = 13.7, 7.3, 2.4 Hz), 2.14−2.05 (2H, m), 1.98 (1H, m), 1.83−1.71 (2H, m), 1.67−1.51 (3H, m), 1.45−1.13 (3H, m), 0.97 (9H, s), 0.44 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 216.0, 139.3, 139.2, 128.7, 128.5, 128.4, 128.1, 127.9, 127.6, 85.5, 82.1, 81.6, 81.0, 78.5, 73.5, 72.8, 71.7, 70.9, 70.1, 67.4, 38.1, 37.6, 35.8, 33.9. 33.5, 26.0, 25.9, 23.7, 18.1, −3.9, −4.6; HRFABMS *m*/*z* calcd for $C_{37}H_{55}O_7Si$ (MH^+) 639.3717, found 639.3691.

(2*S*,3*R*,4a*S*,7a*R*,8a*S*,12a*R*,13a*S*,14a*R*)-2-(Benzyloxy)-3-((benzyloxy)methyl)hexadecahydropyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*g*]oxocine (18). *i. Acetalization of Ketone 17.* A solution of **17** (28.0 mg, 0.0439 mmol) and $TsOH{\cdot}H_2O$ (4.2 mg, 0.022 mmol) in 1,2-dichloroethane (1.0 mL) and MeOH (1.0 mL) was stirred at 55 °C for 1.5 h. An additional 4.2 mg of $TsOH{\cdot}H_2O$ (0.022 mmol) was added, and stirring was continued at 55 °C for another 4 h. Trimethyl orthoformate (0.50 mL, 4.6 mmol) was then added, and the mixture was stirred at 55 °C for 1 h. The reaction mixture was cooled to room temperature, and Et_3N (0.5 mL) was added. The resulting mixture was concentrated under reduced pressure to afford 37 mg of a pale yellow oil. Purification by flash chromatography (30% EtOAc in *n*-hexane) gave methyl acetal 7a-OMe-**18** (19.5 mg, 82%) as a colorless oil. (2*S*,3*R*,4a*S*,7a*R*,8a*S*,12a*R*,13a*S*,14a*R*)-2-(Benzyloxy)-3-((benzyloxy)methyl)-7a-methoxyhexadecahydropyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*g*]-oxocine (7a-OMe-**18**): $[\alpha]^{29}_D$ −6.8 (*c* 1.63, $CHCl_3$); IR ($CHCl_3$) 3010, 2946, 2867, 1454, 1100, 1082, 1062 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.20 (10H, m), 4.59 and 4.54 (each 1H, d, *J* = 12.4 Hz), 4.56 and 4.37 (each 1H, d, *J* = 11.3 Hz), 3.90 (1H, m), 3.72 (1H, dd, *J* = 10.6, 1.8 Hz), 3.58 (1H, dd, *J* = 10.6, 5.1 Hz), 3.43 (1H, dd, *J* = 10.6, 5.5 Hz), 3.42 (1H, ddd, *J* = 11.0, 9.2, 4.4 Hz), 3.35 (1H, dd, *J* = 11.0, 3.3 Hz), 3.34 (1H, ddd, *J* = 9.2, 5.1, 1.8 Hz), 3.22 (1H, ddd, *J* = 11.3, 9.1, 4.4 Hz), 3.19 (3H, s), 3.19−3.17 (2H, m), 2.93 (1H, ddd, *J* = 10.6, 9.1, 5.1 Hz), 2.44 (1H, ddd, *J* = 12.1, 4.4, 4.4 Hz), 2.30−2.24 (2H, m), 2.00−1.93 (3H, m), 1.84 (1H, m), 1.75−1.63 (4H, m), 1.45 (1H, m), 1.40−1.35 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 138.1, 128.33, 128.26, 127.8, 127.7, 127.6, 127.5, 98.5, 85.3, 84.7, 81.1, 79.7, 77.1, 73.4, 72.6, 70.9, 69.4, 69.3, 67.8, 47.5, 38.4, 37.4, 37.1, 34.3, 28.9, 25.6, 17.7; MS (EI) 538 (M^+), 506 (M − MeOH); HREIMS calcd for $C_{32}H_{42}O_7$ (M^+) 538.2931, found 538.2926.

ii. Reductive Etherification of Acetal 7a-OMe-18. To a solution of 7a-OMe-**18** (19.0 mg, 0.0353 mmol) and Et_3SiH (0.107 mL, 0.670 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added TMSOTf (0.032 mL, 0.177 mmol), and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (3 mL), and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure to afford 19.0 mg of a white solid. Purification by flash chromatography (30% EtOAc in *n*-hexane) gave **18** (15.9 mg, 89%) as a colorless solid. Mp 117−119 °C; $[\alpha]^{28}_D$ +27.8 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 1454, 1085 cm^{-1}; ^1H NMR (600 MHz, C_5D_5N) δ 7.49−7.29 (10H, m, Ar), 4.74 and 4.55 (each 1H, d, *J* = 11.7 Hz), 4.66 and 4.61 (each 1H, d, *J* = 11.7 Hz), 3.98 (1H, br d, *J* = 11.0 Hz), 3.86 (1H, dd, *J* = 11.0, 5.1 Hz), 3.85 (1H, m), 3.66 (1H, ddd, *J* = 11.0, 9.5, 4.4 Hz), 3.57 (1H, dd, *J* = 9.4, 5.1 Hz), 3.41 (1H, ddd, *J* = 11.7, 10.3, 4.4 Hz), 3.34 (1H, ddd, *J* = 10.2, 10.2, 4.4 Hz), 3.30 (1H, m), 3.22−3.15 (2H, m), 3.02 (1H, ddd, *J* = 11.0, 9.5, 4.4 Hz), 2.99 (1H, ddd, *J* = 11.0, 9.5, 4.4 Hz), 2.70 (1H, ddd, *J* = 11.0, 11.0, 4.4 Hz), 2.45 (1H, ddd, *J* = 11.7, 11.0, 4.4 Hz), 2.25−2.19 (2H, m), 2.03 (1H, m), 1.84 (1H, m), 1.74 (1H, q, *J* = 11.7 Hz), 1.66 (1H, q, *J* = 11.0 Hz), 1.63−1.35 (6H, m); ^{13}C NMR (150 MHz, C_5D_5N) δ 139.79, 139.76, 129.1, 129.0, 128.5 (×2), 128.3, 128.2, 84.2, 83.6, 82.4, 82.2, 80.8, 78.0, 77.8, 73.8, 74.5, 71.2, 70.8, 67.9, 40.1, 39.6, 37.5, 37.3, 30.1, 26.1, 21.1; HREIMS *m*/*z* calcd for $C_{31}H_{40}O_6$ (M^+) 508.2825, found 508.2816. The stereochemistry of **18** was determined based on the NOESY experiments (600 MHz, C_5D_5N) as shown in Figure 3.

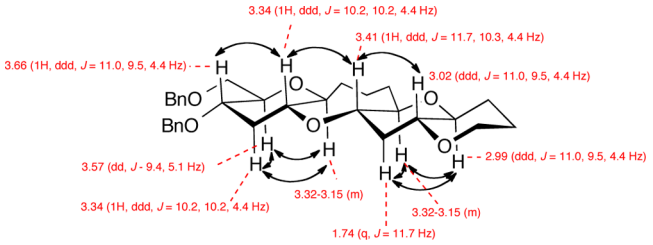

Figure 3. NOESY correlation between axial protons of **18**.

(2*S*,3*R*,4a*S*,7a*R*,8a*S*,12a*R*,13a*R*,14a*R*)-2-(Benzyloxy)-3-((benzyloxy)methyl)hexadecahydropyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*g*]oxocine (13a-*epi*-18). To a suspension of ketone **9** (39.1 mg, 0.063 mmol) and powdered 4 Å molecular sieves (196 mg) in CH_2Cl_2 (2.5 mL) at −40 °C were added $BF_3{\cdot}OEt_2$ (0.038 mL, 0.312 mmol) and trimethylsilyldiazomethane (0.314 mL of a 2.0 M solution in hexanes, 0.628 mmol), and the reaction mixture was stirred at −40 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The reaction mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure to afford the crude α-silyl ketone **16**, which was immediately used in the next reaction without further purification.

To a solution of the above silyl ketone **16** in THF (2 mL) was added TBAF (0.324 mL of a 1 M solution in THF, 0.324 mmol), and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (60% EtOAc in hexane) to afford hemiacetal **19** (21.4 mg, 65%).

To a solution of hemiacetal **19** (19.3 mg, 0.037 mmol, mixture of diastereomers) in CH_2Cl_2 (1 mL) at 0 °C were added Et_3SiH (0.059 mL, 0.369 mmol) and TMSOTf (0.330 mL, 0.182 mmol), and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (30→40% EtOAc in hexane) gave the tetracyclic polyethers **18** (7.1 mg, 36%) and 13a-*epi*-**18** (7.1 mg, 38%).

13a-epi-18. $[\alpha]^{28}_D$ +29.7 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 1454, 1094 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.34−7.06 (10H, m, Ar), 4.52 and 4.56 (each 1H, d, *J* = 12.5 Hz), 4.38 and 4.17 (each 1H, d, *J* = 11.7 Hz), 3.87 (1H, br d, *J* = 11.0 Hz), 3.74 (1H, m), 3.71 (1H, dd, *J* = 10.3, 5.1 Hz), 3.61 (1H, ddd, *J* = 11.7, 8.8, 3.7 Hz), 3.49−3.44 (2H, m), 3.35 (1H, ddd, *J* = 10.3, 10.3, 5.1 Hz), 3.30 (1H, br s), 3.22−3.15 (2H, m), 3.06 (1H, br t, *J* = 5.1 Hz), 2.99 (1H, ddd, *J* = 9.5, 9.5, 4.4

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Hz), 2.29 (1H, ddd, J = 11.7, 3.7, 3.7 Hz), 2.24 (1H, m), 2.05 (1H, ddd, J = 13.2, 3.7, 3.7 Hz), 2.02−1.94 (3H, m), 1.65 (1H, m), 1.55−1.49 (3H, m), 1.48 (1H, q, J = 11.0 Hz), 1.38−1.16 (3H, m); ^{13}C NMR (150 MHz, C_6D_6) δ 139.7, 139.5, 128.92, 128.87, 128.3, 128.2, 128.1, 127.9, 81.6, 79.0, 78.2 (×2), 76.8, 75.3, 74.0, 73.9, 71.3, 70.8, 69.4, 68.3, 39.0, 35.5, 35.7, 31.9, 30.4, 26.6, 19.1; HREIMS m/z calcd for $C_{31}H_{40}O_6$ (M^+) 508.2825, found 508.2844. The stereochemistry was determined based on the value of the coupling constant as shown in Figure 4.

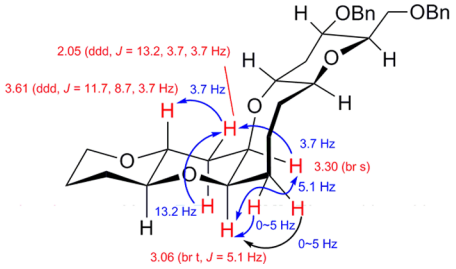

Figure 4. Coupling constants of 13a-*epi*-**18**..

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,10a*S*,11a*R*,13a*S*)-2-(Hydroxymethyl)-tetradecahydro-2*H*-pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepin-3-ol (26). A mixture of benzyl ether **10** (302 mg, 0.611 mmol) and $Pd(OH)_2/C$ (60.4 mg) in EtOAc (12 mL) was stirred vigorously under a hydrogen atmosphere at room temperature for 18 h. The reaction mixture was diluted with MeOH (12 mL) to dissolve the precipitated product. The catalyst was removed by filtration through a short pad of Celite, and the pad was washed thoroughly with MeOH. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by flash chromatography (6→10% MeOH in EtOAc) to afford diol **26** (183 mg, 95%) as a colorless solid. Mp 212−213 °C; $[\alpha]^{29}_D$ +3.6 (c 1.02, $CHCl_3$); IR ($CHCl_3$) 3442, 1456, 1345, 1280, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.90 (1H, br d, J = 11.7 Hz), 3.83 (1H. ddd, J = 11.4, 6.0, 4.2 Hz), 3.75 (1H, ddd, J = 11.4, 6.0, 4.8 Hz), 3.63 (1H, m), 3.36 (1H, m), 3.32 (1H, ddd, J = 11.0, 11.0, 3.7 Hz), 3.27 (1H, ddd, J = 11.0, 11.0, 4.4 Hz), 3.21 (2H, m), 3.15 (1H, ddd, J = 8.4, 4.2, 4.2 Hz), 2.96 (2H, m), 2.60 (1H, d, J = 5.4 Hz, OH), 2.40 (1H, ddd, J = 12.0, 4.2, 4.2 Hz), 2.36 (1H, t, J = 6.0 Hz, OH), 2.30 (1H, ddd, J = 11.4, 3.3, 3.3 Hz), 2.06−1.98 (3H, m), 1.91−1.84 (2H, m), 1.75−1.68 (2H, m), 1.52 (2H, q, J = 12.0 Hz), 1.40 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 82.0, 81.5, 81.1, 79.5, 78.8, 77.9, 77.2, 67.8, 66.8, 63.0, 40.2, 37.4, 29.2, 29.16, 29.1, 25.4; HREIMS m/z calcd for $C_{16}H_{26}O_6$ (M^+) 314.1729, found 314.1754.

((2*R*,3*S*,4a*R*,5a*S*,6a*R*,10a*S*,11a*R*,13a*S*)-3-((Triethylsilyl)oxy)-tetradecahydro-2*H*-pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepin-2-yl)methyl Trifluoromethanesulfonate (2). To a solution of diol **26** (183 mg, 0.583 mmol) and 2,6-lutidine (0.405 mL, 3.498 mmol) in THF (12 mL) at −80 °C was added Tf_2O (0.100 mL, 0.595 mmol). After the reaction mixture was stirred at −80 °C for 30 min, TESOTf (0.158 mL, 0.699 mmol) was added and the reaction mixture was stirred for another 40 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (10→20% EtOAc in hexane) gave triflate **2** (249 mg, 76%) as a pale yellow oil. $[\alpha]^{26}_D$ +32.0 (c 1.28, $CHCl_3$); IR ($CHCl_3$) 1456, 1415, 1245, 1145, 1090, 945, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (1H, dd, J = 10.7, 1.5 Hz), 4.52 (1H, dd, J = 10.7, 5.9 Hz), 3.90 (1H, br d, J = 11.2 Hz), 3.57 (1H, ddd, J = 10.7, 9.9, 4.9 Hz), 3.40−3.28 (3H, m), 3.27−3.16 (3H, m), 3.00−2.92 (2H, m), 2.35 (1H, ddd, J = 11.7, 4.4, 4.4 Hz), 2.30 (1H, ddd, J = 11.7, 3.9, 3.9 Hz), 2.08−1.97 (3H, m), 1.92−1.82 (2H, m), 1.75−1.67 (1H, m), 1.55 (1H, q, J = 11.7 Hz), 1.51 (1H, q, J = 11.2 Hz), 1.40 (1H, m), 0.96 (9H, t, J = 7.8 Hz), 0.61 (6H, q, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.6 (q, J_{C-F} = 319 Hz, CF_3), 82.0, 81.6, 79.6, 79.1, 78.1, 77.9, 77.2, 75.5, 67.9, 66.1, 40.8, 37.4, 29.2, 29.1, 28.9, 25.4, 6.7, 4.9; HREIMS m/z calcd for $C_{23}H_{39}F_3O_8SSi$ (M^+) 560.2087, found 560.2103.

(2*R*,4a*R*,5a*S*,7a*R*,8a*S*,12a*R*,13a*S*,14a*R*,15a*S*)-2-(((2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-(Benzyloxy)-6-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)octahydropyrano[3,2-*b*]pyran-2-yl)methyl)hexadecahydropyrano[2′,3′:5,6]pyrano[3,2-*b*]-pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepin-3(2*H*)-one (28) from triflate 2 and epoxy sulfone 3. *i. Coupling Reaction.* To a solution of triflate **2** (249 mg, 0.445 mmol) and epoxy sulfone **3**[26] (618 mg, 0.890 mmol, 29:19:40:12 mixture of diastereomers) in THF (12 mL) and HMPA (0.310 mL, 1.782 mmol), at −100 °C, was added *n*-BuLi (0.584 mL of a 1.6 M solution in hexane, 0.935 mmol) in a dropwise fashion. After being stirred at −100 °C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification of the residue by flash chromatography (6→20% EtOAc in CH_2Cl_2) afforded the coupling product **27** (468 mg, 95%) as a pale yellow oil, as well as the recovered epoxy sulfone **3** (255 mg).

ii. Removal of the Triethylsilyl Group. A solution of the coupling product **27** (468 mg, 0.418 mmol) and $TsOH·H_2O$ (8 mg, 0.042 mmol) in CH_2Cl_2 (4 mL) and MeOH (4 mL) was stirred at room temperature for 1 h. The reaction was quenched with Et_3N, and the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (70% EtOAc in *n*-hexane) gave hydroxy epoxy sulfone (428 mg, 100%) as a colorless oil.

iii. Preparation of Bromo Ketone. To a suspension of hydroxy epoxy sulfone (428 mg, 0.432 mmol) and LiBr (75 mg, 0.864 mmol) in CH_2Cl_2 (5 mL) at −15 °C was added $MgBr_2·OEt_2$ (223 mg, 0.864 mmol). The reaction mixture was stirred at −15 °C for 30 min and then at −5 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification of the residue by flash chromatography (60% EtOAc in hexane) afforded the bromo ketone (389 mg, 97%) as a colorless oil.

iv. Cyclization with DBU. To a solution of bromo ketone (389 mg, 0.418 mmol) in CH_2Cl_2 (5 mL) was added DBU (0.066 mL, 0.439 mmol) at room temperature, and the solution was stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water, dried, and concentrated under reduced pressure. Purification by flash chromatography (40% EtOAc in hexane) gave ketone **28** (290 mg, 82%) as a colorless oil. $[\alpha]^{22}_D$ −9.2 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1723, 1455, 1344, 1256, 1087, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.19 (10H, m, Ar), 4.61 and 4.54 (each 1H, d, J = 12.2 Hz), 4.53 and 4.40 (each 1H, d, J = 11.7 Hz), 3.99 (1H, dd, J = 5.4, 4.4 Hz), 3.91 (1H, br d, J = 11.2 Hz), 3.74 (1H, dd, J = 10.7, 1.5 Hz), 3.64 (1H, dd, J = 10.7, 5.4 Hz), 3.52−3.20 (11H, m), 3.04−2.91 (4H, m), 2.88 (1H, dd, J = 16.1, 4.9 Hz), 2.45 (1H, ddd, J = 11.7, 4.4, 4.4 Hz), 2.40−2.28 (5H, m), 2.11−2.00 (3H, m), 1.94−1.86 (2H, m), 1.78 (1H, ddd, J = 14.2, 8.8, 4.4 Hz), 1.75−1.68 (2H, m), 1.58 (1H, q, J = 10.7 Hz), 1.53 (1H, q, J = 11.7 Hz), 1.50 (1H, q, J = 11.2 Hz), 1.41 (1H, m), 1.40 (1H, q, J = 11.2 Hz), 0.86 (9H, s), 0.54 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 138.2, 138.0, 128.4, 128.3, 127.9, 127.8 (×2), 127.6, 82.0, 81.5, 80.1, 79.8, 79.6, 79.0, 78.2, 78.0, 77.2, 76.1, 75.9, 75.7, 75.1, 73.5, 72.6, 71.2, 70.9, 69.3, 67.9, 44.5, 39.2, 37.4, 37.0, 35.0, 32.7, 29.2 (×2), 29.1, 25.7, 25.4, 17.9, −4.1, −4.7; HRFABMS m/z calcd for $C_{48}H_{69}O_{11}Si$ (MH^+) 849.4604, found 849.4624.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a-*S*,18a*R*,19a*S*,20a*R*,21a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-19a-methoxyhexacosahydro-2*H*-pyrano[2‴′,3‴′:5‴,6‴]-pyrano[2‴,3‴:5″,6″]pyrano[2″,3″:5′,6′]pyrano[2′,3′:5,6]-pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepine (29). A solution of ketone **28** (10.0 mg, 0.012 mmol) and $TsOH·H_2O$ (2.3 mg, 0.012 mmol) in 1,2-dichloroethane (2 mL) and MeOH (1 mL) was stirred at 80 °C for 15 h. Trimethyl orthoformate (0.130 mL, 1.19 mmol) was then added, and the reaction mixture was stirred at

80 °C for another 3 h. The solution was cooled to room temperature and the reaction was quenched with Et_3N (0.10 mL). The resulting mixture was concentrated under reduced pressure to afford 29.8 mg of a white solid. Purification by flash chromatography (25% EtOAc in CH_2Cl_2) afforded **29** (6.3 mg, 71%) as a colorless solid. Mp 253−254 °C; $[\alpha]_D^{23}$ +48.3 (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3010, 2947, 2873, 1455, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.19 (10H, m), 4.62 and 4.54 (each 1H, d, *J* = 12.2 Hz), 4.56 and 4.38 (each 1H, d, *J* = 11.7 Hz), 3.90 (1H, d, *J* = 10.7 Hz), 3.75 (1H, dd, *J* = 10.7, 1.5 Hz), 3.66 (1H, d, *J* = 10.7, 4.9 Hz), 3.54 (1H, ddd, *J* = 10.7, 9.8, 4.4 Hz), 3.77−3.02 (12H, m), 3.24 (3H, s), 2.96 (2H, m), 2.56 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 2.48 (1H, dd, *J* = 12.9, 3.9 Hz), 2.38−2.29 (3H, m), 2.08−1.83 (7H, m), 1.73−1.34 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.8, 128.4, 128.3, 127.9, 127.8 (×2), 127.6, 96.3, 82.2, 81.9, 80.5, 79.7, 79.5, 78.6, 78.1, 77.9, 77.3, 77.1, 76.9, 76.3, 75.4, 73.4, 72.3, 71.0, 69.1, 68.6, 67.8, 47.2, 37.4, 37.4, 36.7, 35.1, 34.7, 34.6, 29.7, 29.2, 29.1, 25.4; MS (FAB) 749 (M + H), 717 (M − OMe); HRFABMS *m*/*z* calcd for $C_{43}H_{57}O_{11}$ (MH^+) 749.3895, found 749.3876.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a-*S*,18a*R*,19a*S*,20a*R*,21a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-hexacosahydro-2*H*-pyrano[2‴′,3‴′:5‴,6‴]pyrano-[2‴,3‴:5″,6″]pyrano[2″,3″:5′,6′]pyrano[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepine (30). To a solution of methyl acetal **29** (6.3 mg, 0.0084 mmol) and Et_3SiH (0.030 mL, 0.19 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C was added TMSOTf (0.010 mL, 0.055 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with $CHCl_3$, and the extract was washed brine, dried, and concentrated under reduced pressure to afford 7.2 mg of a white solid. Flash chromatography (2% MeOH in $CHCl_3$) provided 6.8 mg of a white solid. Further purification by flash chromatography (0→4% MeOH in $CHCl_3$) afforded **30** (6.0 mg, 99%) as a colorless solid. Mp 356−357 °C; $[\alpha]_D^{22}$ +24.5 (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) 3009, 2935, 2873, 1455, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.19 (10H, m), 4.62 and 4.55 (each 1H, d, *J* = 12.2 Hz), 4.56 and 4.39 (each 1H, d, *J* = 11.2 Hz), 3.90 (1H, d, *J* = 11.2 Hz), 3.75 (1H, d, *J* = 10.7, 1.5 Hz), 3.66 (1H, d, *J* = 10.7, 4.9 Hz), 3.53 (1H, ddd, *J* = 10.7, 9.8, 4.9 Hz), 3.43 (1H, ddd, *J* = 9.8, 4.9, 1.5 Hz), 3.39−3.30 (3H, m), 3.24−3.17 (2H, m), 3.14−2.93 (10H, m), 2.56 (1H, ddd, *J* = 11.2, 4.4, 4.4 Hz), 2.41−2.28 (5H, m), 2.04−1.99 (3H, m), 1.93−1.88 (2H, m), 1.70−1.68 (2H, m), 1.55−1.38 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.9, 128.4, 128.3, 127.9, 127.79, 127.76, 127.6, 82.1, 82.0, 80.5, 79.7, 79.3, 77.9, 77.3, 77.1 (×3), 76.9, 76.8, 76.69, 76.66, 76.3, 73.5, 72.3, 71.0, 69.1, 67.9, 37.4, 37.0, 35.1 (×4), 29.3 (×2), 29.2, 25.5; MS (FAB) 719 (M + H); HRFABMS calcd for $C_{42}H_{54}O_{10}$ (MH^+) 719.3790, found 719.3792.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a-*S*,18a*R*,19a*R*,20a*R*,21a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-19a-(ethylthio)hexacosahydro-2*H*-pyrano[2‴′,3‴′:5‴,6‴]-pyrano[2‴,3‴:5″,6″]pyrano[2″,3″:5′,6′]pyrano[2′,3′:5,6]-pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepine (31). *i. Hemiacetalization of Ketone **28**.* A solution of ketone **28** (10 mg, 0.012 mmol) and $TsOH·H_2O$ (2.3 mg, 0.012 mmol) in THF (1 mL) and water (0.1 mL) was stirred at 65 °C for 7 h. The solution was cooled to room temperature, and the reaction was quenched with Et_3N (1 mL). The resulting mixture was concentrated under reduced pressure. Purification by flash chromatography (0→10% MeOH in $CHCl_3$) provided 6.0 mg of a colorless solid. Further purification by flash chromatography (0→4% MeOH in $CHCl_3$) afforded hemiacetal 19a-OH-**31** (5.2 mg, 60%) as a colorless solid. (2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a*S*,18a*R*,19a*S*,20a*R*,21a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)hexacosahydro-2*H*-pyrano[2‴′,3‴′:5‴,6‴]pyrano[2‴,3‴:5″,6″]pyrano[2″,3″:5′,6′]pyrano[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepin-19a-ol (19a−OH-**31**): mp 290−295 °C (decomp); $[\alpha]_D^{28}$ +32.7 (*c* 0.38, $CHCl_3$); IR ($CHCl_3$) 3691, 3585, 3010, 2947, 2873, 1455, 1080 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35−7.19 (10H, m), 4.62 and 4.54 (each 1H, d, *J* = 12.1 Hz), 4.56 and 4.39 (each 1H, d, *J* = 11.3 Hz), 3.90 (1H, d, *J* = 10.7 Hz) 3.78−3.74 (2H, m), 3.66 (1H, dd, *J* = 10.8, 4.7 Hz), 3.54 (1H, ddd, *J* = 10.9, 9.5, 4.7 Hz), 3.42 (1H, ddd, *J* = 9.5, 4.7, 1.5 Hz), 3.38−3.26 (5H, m), 3.23−3.19 (2H, m), 3.14−3.08 (3H, m), 3.05 (1H, ddd, *J* = 11.4, 9.1, 4.0 Hz), 2.98−2.93 (2H, m), 2.55 (1H, ddd, *J* = 11.3, 4.7, 4.0 Hz), 2.37 (1H, ddd, *J* = 11.4, 4.1, 4.1 Hz), 2.31 (1H, brs), 2.30−2.28 (2H, m), 2.19 (1H, dd, *J* = 12.4, 4.8 Hz), 2.12 (1H, ddd, *J* = 11.3, 4.0, 4.0 Hz), 2.05−1.99 (3H, m), 1.90−1.85 (2H, m), 1.81 (1H, ddd, *J* = 11.7, 11.7, 11.7 Hz), 1.72−1.68 (2H, m), 1.65−1.45 (5H, m), 1.40 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.2, 137.9, 128.40, 128.35, 127.9, 127.79, 127.76, 127.6, 94.0, 82.3, 81.9, 80.5, 79.7, 79.4, 78.2, 77.9, 77.8, 77.3, 77.0, 76.8, 76.4, 76.3, 73.5, 72.3, 71.0, 69.1, 68.6, 67.9, 41.4, 37.5, 36.8, 35.1, 34.8, 29.9, 29.3 (×2), 29.1, 25.5; MS (FAB) 735 (M + H), 717 (M − OH); HRFABMS calcd for $C_{42}H_{55}O_{11}$ (MH^+) 735.3744, found 735.3784.

*ii. Thioacetalization of Hemiacetal 19a-OH-**31**.* To a solution of 19a-OH-**31** (16.5 mg, 0.0225 mmol) in CH_2Cl_2 (1 mL) and nitromethane (1 mL) were added EtSH (0.40 mL, 5.4 mmol) and $Zn(OTf)_2$ (11 mg, 0.03 mmol), and the reaction mixture was stirred at room temperature for 2 h. An additional 66 mg of $Zn(OTf)_2$ (0.18 mmol) was added, and stirring was continued for another 10 h. The reaction was quenched with water (2 mL), and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with 10% aqueous NaOH solution and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (0→4% MeOH in $CHCl_3$) afforded thioacetal **31** (17.4 mg, 94%) as a colorless solid. Mp 210−212 °C; $[\alpha]_D^{29}$ +63.3 (*c* 1.45, $CHCl_3$); 3010, 2938, 2872, 1455, 1075 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.19 (10H, m), 4.62 and 4.55 (each 1H, d, *J* = 12.4 Hz), 4.56 and 4.39 (each 1H, d, *J* = 11.5 Hz), 4.04 (1H, ddd, *J* = 12.4, 8.7, 3.7 Hz), 3.90 (1H, d, *J* = 11.5 Hz), 3.76−3.70 (2H, m), 3.65 (1H, dd, *J* = 11.0, 4.8 Hz), 3.53 (1H, ddd, *J* = 10.8, 9.2, 4.3 Hz), 3.44 (1H, dd, *J* = 9.2, 4.3 Hz), 3.37−3.29 (4H, m), 3.25−3.11 (5H, m), 3.05 (1H, ddd, *J* = 11.9, 8.3, 3.9 Hz), 2.97−2.95 (2H, m), 2.58−2.27 (7H, m), 2.10−1.97 (5H, m), 1.90−1.84 (2H, m), 1.72−1.38 (8H, m), 1.25 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.2, 137.9, 128.4, 128.3, 127.9, 127.8 (×2), 127.6, 88.2, 82.3, 81.8, 80.7, 80.5, 79.6, 79.5, 79.2, 77.9, 77.5, 77.2, 76.9, 76.40, 76.37, 73.4, 72.3, 71.0, 69.1, 68.9, 67.8, 40.0, 37.4, 36.9, 35.1, 34.8, 31.0, 29.30, 29.26, 29.2, 25.4, 20.2, 14.5; MS (FAB) 779 (M + H), 717 (M − SEt); HRFABMS calcd for $C_{44}H_{59}O_{10}S$ (MH^+) 779.3829, found 779.3843.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a-*S*,18a*R*,19a*S*,20a*R*,21a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-19a-methylhexacosahydro-2*H*-pyrano[2‴′,3‴′:5‴,6‴]pyrano-[2‴,3‴:5″,6″]pyrano[2″,3″:5′,6′]pyrano[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepine (32). To a solution of thioacetal **31** (4.5 mg, 0.0058 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added *m*-chloroperbenzoic acid (2.0 mg, 0.0116 mmol). The reaction mixture was stirred at room temperature for 2 h and then recooled to 0 °C. A 2.0 M solution of $AlMe_3$ in heptane (0.029 mL, 0.058 mmol) was added, and the reaction mixture was stirred at room temperature for 0.5 h. An additional 0.10 mL of a 2.0 M solution of $AlMe_3$ in heptane (0.20 mmol) was added, and stirring was continued for another 3 h. The reaction was quenched with saturated aqueous potassium sodium tartrate solution (2 mL), and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (0→4% MeOH in $CHCl_3$) afforded **32** (3.1 mg, 73%) as a colorless solid. Mp 209−211 °C; $[\alpha]_D^{28}$ +36.8 (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) 3010, 2949, 2873, 1456, 1082 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.20 (10H, m), 4.62 and 4.54 (each 1H, d, *J* = 12.4 Hz), 4.56 and 4.39 (each 1H, d, *J* = 11.3 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.75 (1H, dd, *J* = 10.6, 1.4 Hz), 3.66 (1H, dd, *J* = 10.6, 4.8 Hz), 3.54 (1H, ddd, *J* = 10.6, 9.5, 4.8 Hz), 3.44−3.40 (2H, m), 3.38−3.30 (3H, m), 3.22−3.03 (8H, m), 2.96−2.95 (2H, m), 2.56 (1H, ddd, *J* = 11.4, 4.4, 4.4 Hz), 2.37 (1H, ddd, *J* = 11.7, 4.0, 4.0 Hz), 2.30−2.26 (2H, m), 2.13−2.10 (2H, m), 2.05−1.99 (3H, m), 1.91−1.85 (2H, m), 1.72−1.69 (2H, m), 1.63 (1H, ddd, *J* = 11.7, 11.7, 11.7 Hz), 1.55−1.36 (6H, m), 1.27 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.2, 137.9, 128.4, 128.3, 127.9, 127.8 (×2), 127.6, 82.4, 81.9, 80.5, 79.9, 79.7, 79.5, 78.9, 78.4, 77.9, 77.3, 77.0, 76.8, 76.5, 73.7, 73.5, 72.4,

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71.1, 69.1, 69.0, 67.9, 43.0, 37.5, 37.1, 35.5, 35.2, 30.6, 29.35, 29.28, 29.2, 25.5, 16.2; MS (FAB) 733 (M + H); HRFABMS calcd for $C_{43}H_{57}O_{10}$ (MH^+) 733.3952, found 733.3919.

(4a*S*,5a*R*,7a*S*,8a*R*,12*R*,13a*S*,14a*R*,15a*S*,16a*R*)-12-(((2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-(Benzyloxy)-6-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)octahydropyrano[3,2-*b*]pyran-2-yl)methyl)hexadecahydro-2*H*-pyrano[2′,3′:5,6]pyrano[2,3-*f*]-pyrano[3,2-*b*:5,6-*b*′]bis(oxepine)-11(12*H*)-one (33). To a suspension of ketone **28** (50.0 mg, 0.0589 mmol) and powdered 4 Å molecular sieves (287 mg) in CH_2Cl_2 (6 mL) were added trimethylsilyldiazomethane ($TMSCHN_2$) (0.148 mL of a 2.0 M solution in hexanes, 0.295 mmol) and $BF_3{\cdot}OEt_2$ (0.036 mL, 0.30 mmol) at −80 °C, and the reaction mixture was stirred at −80 °C for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was allowed to warm to room temperature and extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated under reduced pressure to afford the crude α-TMS ketone, which was immediately used in the next step without further purification.

A solution of the above α-TMS ketone and PPTS (14.8 mg, 0.0589 mmol) in MeOH (1 mL) and CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h. Additional PPTS (50.0 mg, 0.199 mmol) was added, and the reaction mixture was stirred at room temperature for another 2.5 h. The reaction was quenched with Et_3N (0.1 mL). The reaction mixture was concentrated under reduced pressure to give 131 mg of colorless oil. Purification by flash chromatography (30% EtOAc in *n*-hexane) afforded the seven-membered ketone **33** (44.0 mg, 87%) as a colorless oil. $[\alpha]^{22}_D$ +15.1 (*c* 0.58, $CHCl_3$); IR ($CHCl_3$) 3009, 2933, 2860, 1712, 1455, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.18 (10H, m), 4.50 and 4.537 (each 1H, d, *J* = 12.5 Hz), 4.540 and 4.37 (1H, d, *J* = 11.4 Hz), 3.98 (1H, dd, *J* = 4.4, 6.6 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.74 (1H, dd, *J* = 10.6, 1.5 Hz), 3.63 (1H, dd, *J* = 10.6, 5.1 Hz), 3.48 (1H, ddd, *J* = 10.6, 9.5, 4.4 Hz), 3.42−3.16 (9H, m), 3.05−2.93 (5H, m), 2.85 (1H, ddd, *J* = 13.7, 11.9, 1.8 Hz), 2.42−2.27 (5H, m), 2.21−2.11 (2H, m), 2.05−1.98 (3H, m), 1.91−1.82 (2H, m), 1.78−1.37 (9H, m), 0.85 (9H, s), 0.05 (6H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 215.8, 138.2, 138.0, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 84.0, 82.1, 81.5, 81.0, 80.7, 80.2, 79.7, 79.2, 78.0, 77.7, 77.3, 76.0, 75.6, 73.5, 72.6, 71.2, 70.3, 69.4, 67.9, 39.2, 38.8, 37.4, 36.6, 35.6, 34.9, 29.4, 29.3 (×2), 29.2, 25.7, 25.5, 17.9, −4.0, −4.7; HRFABMS calcd for $C_{49}H_{71}O_{11}Si$ (MH^+) 863.4760, found 863.4734.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a-*S*,18a*R*,20a*S*,21a*R*,22a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-octacosahydropyrano[3,2-*b*]pyrano[2,3-*j*:6,5-*j*′]bis(pyrano-[2′,3′:5,6]pyrano[3,2-*b*]oxepine) (34). *i. Acetalization of Ketone* ***33***. A solution of **33** (7.0 mg, 0.0081 mmol) and $TsOH{\cdot}H_2O$ (1.7 mg, 0.0089 mmol) in 1,2-dichloroethane (2 mL) and MeOH (1 mL) was stirred at 80 °C for 2 h. An additional 3.4 mg of $TsOH{\cdot}H_2O$ (0.0179 mmol) was added, and stirring was continued at 80 °C for another 15 h. Trimethyl orthoformate (0.13 mL) was added, and heating was continued for 4 h. The reaction mixture was cooled to room temperature, and the reaction was quenched with Et_3N (0.1 mL). The resulting mixture was concentrated under reduced pressure to give 10.5 mg of a white solid. Purification by flash chromatography (30→50% EtOAc in benzene) afforded methyl acetal 20a-OMe-**34** (4.4 mg, 71%) as a colorless solid. (2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a*S*,18a*R*,20a*S*,21a*R*,22a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-20a-methoxyoctacosahydropyrano[3,2-*b*]pyrano-[2,3-*j*:6,5-*j*′]bis(pyrano[2′,3′:5,6]pyrano[3,2-*b*]oxepine) (20a-OMe-**34**): mp 266−272 °C (decomp); $[\alpha]^{22}_D$ +30.2 (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 3009, 2946, 2872, 1455, 1081 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.19 (10H, m), 4.62 and 4.54 (each 1H, d, *J* = 12.5 Hz), 4.56 and 4.39 (each 1H, d, *J* = 11.4 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.75 (1H, dd, *J* = 11.0, 1.8 Hz), 3.66 (1H, dd, *J* = 11.0, 4.8 Hz), 3.53 (1H, ddd, *J* = 11.0, 9.2, 4.4 Hz), 3.43 (1H, ddd, *J* = 9.5, 4.8, 1.8 Hz), 3.40−3.33 (2H, m), 3.31−3.18 (6H, m), 3.23 (3H, s), 3.15−3.11 (2H, m), 3.07−3.02 (2H, m), 2.96−2.94 (2H, m), 2.55 (1H, ddd, *J* = 11.4, 4.4, 4.4 Hz), 2.35 (1H, ddd, *J* = 12.1, 4.0, 4.0 Hz), 2.30−2.25 (2H, m), 2.08−1.99 (7H, m), 1.93−1.83 (4H, m), 1.71−1.68 (2H, m), 1.62−1.40 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.2, 137.9, 128.4, 128.3, 127.9, 127.81, 127.78, 127.6, 99.9, 82.1, 82.0, 81.5, 80.8, 80.5, 79.7, 79.6, 79.4, 77.9, 77.3, 77.2, 76.9, 76.2, 73.4, 72.4, 71.0, 69.1, 68.8, 67.9, 47.4, 38.8, 37.4, 35.1, 34.7, 31.9, 30.8, 29.31, 29.28, 29.2, 27.6, 25.5; MS(FAB) 763 (M + H), 731 (M − OMe); HRFABMS calcd for $C_{44}H_{59}O_{11}$ (MH^+) 763.4052, found 763.4080.

*ii. Reductive Etherification of Acetal 20a-OMe-**34**.* To a solution of 20a-OMe-**34** (4.1 mg, 0.0054 mmol) and Et_3SiH (0.019 mL, 0.12 mmol) in CH_2Cl_2 (0.4 mL) at 0 °C was added TMSOTf (0.0063 mL, 0.035 mmol), and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) solution, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated under reduced pressure to give 4.1 mg of a white solid. Purification by flash chromatography (0→2% MeOH in $CHCl_3$) afforded 3.3 mg (84%) of **34** as a colorless solid. Mp 355−362 °C (decomp); $[\alpha]^{22}_D$ +23.7 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 3009, 2936, 2872, 1455, 1076 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.19 (10H, m), 4.61 and 4.54 (each 1H, d, *J* = 12.5 Hz), 4.56 and 4.39 (each 1H, d, *J* = 11.7 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.75 (1H, dd, *J* = 10.6, 1.8 Hz), 3.65 (1H, dd, *J* = 10.6, 5.1 Hz), 3.53 (1H, ddd, *J* = 11.0, 9.5, 4.4 Hz), 3.42 (1H, ddd, *J* = 9.5, 5.1, 1.8 Hz), 3.39−3.23 (5H, m), 3.21−3.15 (2H, m), 3.14−3.08 (3H, m), 3.06−2.93 (5H, m), 2.55 (1H, ddd, *J* = 11.0, 4.4, 4.4 Hz), 2.37−2.33 (2H, m), 2.31−2.26 (2H, m), 2.04−1.98 (5H, m), 1.89−1.83 (4H, m), 1.72−1.69 (2H, m), 1.57−1.39 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.2, 137.9, 128.40, 128.35, 127.9, 127.8 (×2), 127.6, 82.12, 82.09, 81.7, 81.6, 80.5, 79.6, 79.44, 79.39, 79.3, 77.9, 77.3, 76.8, 76.7 (×2), 76.1, 73.5, 72.3, 71.0, 69.1, 67.9, 38.9, 37.4, 37.0, 35.2, 35.1, 29.4, 29.3, 29.2 (×3), 25.5; MS (FAB) 733 (M + H); HRFABMS calcd for $C_{43}H_{57}O_{10}$ (MH^+) 733.3946, found 733.3939.

(4a*S*,5a*R*,7a*S*,8a*R*,13*R*,14a*S*,15a*R*,16a*S*,17a*R*)-13-(((2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-(Benzyloxy)-6-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)octahydropyrano[3,2-*b*]pyran-2-yl)methyl)octadecahydropyrano[2‴,3‴:5″,6″]pyrano-[2″,3″:6′,7′]oxepino[2′,3′:5,6]pyrano[3,2-*b*]oxocin-12(13*H*)-one (35). To a suspension of ketone **33** (35.0 mg, 0.0405 mmol) and powdered 4 Å molecular sieves (196 mg) in CH_2Cl_2 (4 mL) were added $BF_3{\cdot}OEt_2$ (0.050 mL, 0.41 mmol) and $TMSCHN_2$ (0.203 mL of a 2.0 M solution in hexanes, 0.406 mmol) at −40 °C, and the reaction mixture was stirred at −40 °C for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The reaction mixture was allowed to warm to room temperature and extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated under reduced pressure to afford the crude α-TMS ketone, which was immediately used in the next reaction without further purification.

A solution of the above α-TMS ketone and PPTS (30.5 mg, 0.121 mmol) in MeOH (1.0 mL) and $CHCl_3$ (1.0 mL) was stirred at room temperature for 7 h. Additional PPTS (100 mg, 0.398 mmol) was added, and the reaction mixture was stirred at room temperature for another 10 h and then at 60 °C for 6 h. The reaction mixture was cooled to room temperature, and the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2, and the extract was washed with brine, dried, and concentrated under reduced pressure. The residual pale yellow oil was purified by flash chromatography (15% EtOAc in benzene) to afford 19.1 mg of colorless oil. Further purification by flash chromatography (15% acetone in *n*-hexane), followed by preparative TLC (15% acetone in *n*-hexane), gave the eight-membered ketone **35** (13.4 mg, 38%) as a colorless amorphous solid. Mp 67−69 °C; $[\alpha]^{22}_D$ +32.8 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3008, 2933, 2859, 1709, 1455, 1083 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.19 (10H, m), 4.60 and 4.538 (each 1H, d, *J* = 12.5 Hz), 4.540 and 4.37 (each 1H, d, *J* = 11.0 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.80 (1H, dd, *J* = 7.3, 3.7 Hz), 3.74 (1H, dd, *J* = 11.0, 1.5 Hz), 3.62 (1H, dd, *J* = 11.0, 5.1 Hz), 3.48 (1H, ddd, *J* = 11.0, 9.5, 4.4 Hz), 3.41−3.14 (10H, m), 3.06−2.95 (5H, m), 2.41 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 2.35 (1H, ddd, *J* = 12.5, 4.4, 4.4 Hz), 2.31−2.29 (2H, m), 2.17 (1H, ddd, *J* = 13.9, 7.3, 2.9 Hz), 2.04−1.98 (4H, m), 1.93−1.83 (5H, m), 1.78 (1H, ddd, *J* = 13.9, 10.3, 3.7 Hz), 1.73−1.69 (2H, m), 1.64 (1H, ddd, *J* = 11.7, 11.7, 11.7 Hz), 1.57−1.34 (5H, m), 0.86 (9H, s), 0.05 (6H, s); ^{13}C NMR

(150 MHz, $CDCl_3$) δ 218.5, 138.2, 138.0, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 85.3, 82.7, 82.2, 81.6, 81.3, 80.1, 79.7, 79.0, 77.9, 77.6, 77.2, 76.1, 75.7, 73.5, 72.7, 71.2, 70.4, 69.4, 67.9, 39.3, 39.2, 37.4, 36.7, 36.1, 34.8, 32.9, 29.4, 29.3 (×2), 25.7, 25.5, 23.7, 17.9, −4.1, −4.7; MS (FAB) 877 (M + H), 819 (M − *t*-Bu); HRFABMS calcd for $C_{50}H_{73}O_{11}Si$ (MH^+) 877.4917, found 877.4940.

(2*S*,3*R*,4a*S*,5a*R*,6a*S*,9a*R*,10a*S*,12a*R*,13a*S*,17a*R*,18a*S*,19a*R*,20a*S*,21a*R*,22a*S*,23a*R*)-2-(Benzyloxy)-3-((benzyloxy)methyl)-octacosahydro-1*H*-pyrano[2‴,3‴:5″,6″]pyrano[2″,3″:6′,7′]-oxepino[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2″,3″:5′,6′]pyrano-[2′,3′:5,6]pyrano[2,3-*g*]oxocine (1: CDEFGHIJ-ring polycyclic skeleton of yessotoxin). *i. Acetalization of the Ketone* ***35****.* A solution of **35** (11.7 mg, 0.0133 mmol) and $TsOH·H_2O$ (5.0 mg, 0.0263 mmol) in MeOH (0.5 mL) and 1,2-dichloroethane (0.5 mL) was stirred at 55 °C for 5.5 h. Additional volumes of 1,2-dichloroethane (0.5 mL) and trimethyl orthoformate (0.20 mL, 1.8 mmol) were added, and the reaction mixture was stirred at 55 °C for another 2 h. The solution was cooled to room temperature, and the reaction was quenched with Et_3N. The resulting mixture was concentrated under reduced pressure to give 18.3 mg of a white solid. Purification by flash chromatography (30→70% EtOAc in *n*-hexane) afforded methyl acetal 6a-OMe-**1** (9.0 mg, 87%) as a colorless solid. (2*S*,3*R*,4a*S*,5a*R*,6a*S*,9a*R*,10a*S*,12a*R*,13a*S*,17a*R*,18a*S*,19a*R*,20a*S*,21a*R*,22a*S*,23a*R*)-2-(benzyloxy)-3-((benzyloxy)methyl)-6a-methoxyoctacosahydro-1*H*-pyrano[2‴,3‴:5″,6″]pyrano-[2″,3″:6′,7′]oxepino[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2″,3″:5′,6′]-pyrano[2′,3′:5,6]pyrano[2,3-*g*]oxocine (6a-OMe-**1**): mp 219−221 °C; $[\alpha]^{22}_D$ +31.6 (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 3009, 2947, 2871, 1455, 1341, 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.19 (10H, m), 4.62 and 4.54 (each 1H, d, *J* = 12.4 Hz), 4.57 and 4.39 (each 1H, d, *J* = 11.5 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.75 (1H, dd, *J* = 10.5, 1.4 Hz), 3.66 (1H, dd, *J* = 10.5, 5.0 Hz), 3.54 (1H, ddd, *J* = 11.0, 10.2, 4.4 Hz), 3.44−3.41 (2H, m), 3.38−3.25 (3H, m), 3.23−3.08 (6H, m), 3.17 (3H, s), 3.06−2.95 (4H, m), 2.55 (1H, ddd, *J* = 11.5, 4.4, 4.4 Hz), 2.31−2.26 (4H, m), 2.18 (1H, ddd, *J* = 13.7, 10.5, 3.2 Hz), 2.05−1.91 (5H, m), 1.88−1.81 (3H, m), 1.73−1.62 (4H, m), 1.55−1.44 (3H, m), 1.41−1.34 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.9, 128.4, 128.3, 127.9, 127.80, 127.77, 127.6, 98.8, 85.7, 85.6, 82.1, 81.3, 81.1, 80.5, 79.6, 79.5, 77.9, 77.3, 76.9, 76.8, 76.1, 73.4, 72.3, 71.0, 69.1, 68.1, 67.9, 47.6, 40.1, 37.5, 37.34, 37.25, 35.1, 34.8, 33.8, 29.3, 29.2 (×2), 25.5, 17.8; MS (FAB) 777 (M + H), 745 (M − OMe); HRFABMS calcd for $C_{45}H_{61}O_{11}$ (MH^+) 777.4208, found 777.4203.

*ii. Reductive Etherification of Acetal 6a-OMe-****1****.* To a solution of 6a-OMe-**1** (7.9 mg, 0.010 mmol) and Et_3SiH (0.036 mL, 0.22 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C was added TMSOTf (0.012 mL, 0.066 mmol), and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated under reduced pressure to give 7.6 mg of a pale yellow solid. Purification by flash chromatography (CH_2Cl_2→2% MeOH in CH_2Cl_2) afforded the CDEFGHIJ-ring polycyclic ether **1** (6.8 mg, 89%) as a colorless solid. Mp 308−310 °C; $[\alpha]^{27}_D$ +14.7 (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3066, 3007, 2935, 1455, 1341, 1084 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.19 (10H, m), 4.61 and 4.54 (each 1H, d, *J* = 12.4 Hz), 4.56 and 4.39 (each 1H, d, *J* = 11.0 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.75 (1H, dd, *J* = 11.0, 1.4 Hz), 3.65 (1H, dd, *J* = 11.0, 5.2 Hz), 3.53 (1H, ddd, *J* = 11.0, 9.5, 4.4 Hz), 3.42 (1H, ddd, *J* = 9.5, 5.2, 1.4 Hz), 3.37−3.19 (6H, m), 3.12−2.95 (9H, m), 2.54 (1H, ddd, *J* = 11.0, 4.4, 4.4 Hz), 2.35−2.27 (4H, m), 2.19−2.12 (2H, m), 2.04−1.95 (4H, m), 1.88−1.81 (2H, m), 1.72−1.69 (2H, m), 1.57−1.38 (9H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.2, 138.0, 128.4, 128.3, 128.0, 127.79, 127.76, 127.6, 84.2, 83.9, 82.2, 81.9, 81.4, 81.3, 80.5, 79.6, 79.2, 77.9, 77.3, 76.61, 76.56, 76.2, 76.0, 73.5, 72.5, 71.0, 69.1, 67.9, 40.4, 38.5, 37.5, 36.9, 36.7, 35.2, 35.1, 29.3 (×3), 25.5, 20.6; HRFABMS calcd for $C_{44}H_{58}O_{10}$ (MH^+) 747.4103, found 747.4112.

(2*R*,3*S*,4a*R*,5a*S*,7a*R*,8a*S*,12a*R*,13a*S*,14a*R*,15a*S*)-2-(((2*S*,4a*S*,6*R*,7*S*,8a*R*)-7-(Benzyloxy)-6-((benzyloxy)methyl)-3-oxooctahydropyrano[3,2-*b*]pyran-2-yl)methyl)-octadecahydropyrano[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2′,3′:5,6]-pyrano[2,3-*f*]oxepin-3-yl acetate (36). *i. Reduction of Ketone* ***28****.* To a solution of **28** (20.0 mg, 0.0236 mmol) in MeOH (1 mL) and THF (1 mL) was added $NaBH_4$ (5.0 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 80 min. The reaction was quenched with saturated aqueous NH_4Cl solution (2 mL), and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated under reduced pressure to give 27.4 mg of a pale yellow oil. Purification by flash chromatography (50% EtOAc in *n*-hexane) afforded an 87:13 diastereomixture of alcohol (19.6 mg, 98%) of as a colorless oil. (2*R*,3*S*,4a*R*,5a*S*,7a*R*,8a*S*,12a*R*,13a*S*,14a*R*,15a*S*)-2-(((2*S*,3*R*,4a*S*,6*R*,7-*S*,8a*R*)-7-(benzyloxy)-6-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)octahydropyrano[3,2-*b*]pyran-2-yl)methyl)-octadecahydropyrano[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano-[2,3-*f*]oxepin-3-ol (alcohol **i**): $[\alpha]^{29}_D$ +2.5 (*c* 1.63, $CHCl_3$); IR ($CHCl_3$) 3410, 3009, 2952, 2860, 1455, 1083 cm^{-1}; MS (FAB) 851 (M + H), 719 (M − OTBS); ^1H NMR for the major isomer (600 MHz, $CDCl_3$) δ 7.33−7.17 (10H, m), 4.60 and 4.54 (each 1H, d, *J* = 12.1 Hz), 4.56 and 4.54 (each 1H, d, *J* = 11.3 Hz), 3.90 (1H, dd, *J* = 11.0 Hz), 3.74 (1H, dd, *J* = 10.6, 1.5 Hz), 3.63 (1H, dd, *J* = 10.6, 5.1 Hz), 3.62 (1H, d, *J* = 3.3 Hz), 3.53−3.30 (8H, m), 3.25−3.18 (3H, m), 3.12−2.95 (6H, m), 2.55 (1H, ddd, *J* = 11.3, 4.4, 4.4 Hz), 2.90−2.26 (4H, m), 2.08 (1H, ddd, *J* = 15.4, 5.2, 1.9 Hz), 2.05−2.00 (3H, m), 1.97 (1H, ddd, *J* = 15.4, 7.0, 3.7 Hz), 1.92−1.86 (2H, m), 1.72−1.69 (2H, m), 1.60−1.40 (6H, m), 0.87 (9H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR for the major isomer (150 MHz, $CDCl_3$) δ 138.1, 137.8, 128.4, 128.3, 127.9, 127.7 (×2), 127.6, 82.00, 81.97, 80.2, 79.63, 79.57, 79.3, 79.2, 77.9, 77.3, 76.8, 76.7, 75.9, 75.8, 73.5, 72.3, 71.0, 69.31, 69.25, 68.9, 67.8, 39.1, 37.5, 37.4, 37.0, 35.0, 34.4, 29.28, 29.26, 29.2, 25.7, 25.5, 17.9, −3.9, −4.9. HRFABMS calcd for $C_{48}H_{71}O_{11}Si$ (MH^+) 851.4687, found 851.4729.

ii. Acetylation of the Secondary Alcohol. A solution of a 87:13 diastereomixture of alcohol **i** (19.0 mg, 0.0223 mmol) and DMAP (1.0 mg, 0.0082 mmol) in pyridine (0.5 mL) and acetic anhydride (0.1 mL) was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (2 mL), and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (25% EtOAc in *n*-hexane) afforded acetate (15.3 mg, 77%) and its epimer (3.6 mg, 18%, ca. 80% purity based on NMR analysis) as colorless oils. (2*R*,3*S*,4a*R*,5a*S*,7a*R*,8a*S*,12a*R*,13a*S*,14a*R*,15a*S*)-2-(((2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-(Benzyloxy)-6-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-octahydropyrano[3,2-*b*]pyran-2-yl)methyl)octadecahydropyrano-[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepin-3-yl acetate (acetate **ii**): $[\alpha]^{29}_D$ +15.8 (*c* 1.28, $CHCl_3$); IR ($CHCl_3$) 3008, 2952, 2860, 1735, 1456, 1248, 1087, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.19 (10H, m), 4.60 and 4.55 (each 1H, d, *J* = 12.4 Hz), 4.59 (1H, m), 4.58 and 4.37 (each 1H, d, *J* = 11.5 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.75 (1H, dd, *J* = 10.6, 1.4 Hz), 3.63 (1H, dd, *J* = 10.6, 5.1 Hz), 3.53 (1H, ddd, *J* = 9.7, 6.4, 4.1 Hz), 3.47−3.41 (3H, m), 3.39−2.29 (3H, m), 3.26−3.17 (3H, m), 3.07−2.94 (6H, m), 2.56 (1H, ddd, *J* = 11.5, 4.1, 4.1 Hz), 2.46 (1H, ddd, *J* = 11.0, 4.1, 4.1 Hz), 2.35−2.28 (3H, m), 2.05−1.99 (4H, m), 2.01 (3H, s), 1.90−1.84 (2H, m), 1.73−1.68 (2H, m), 1.60−1.46 (4H, m), 1.39 (3H, q, *J* = ca. 11.0 Hz, three axial protons), 0.86 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 138.2, 138.0, 128.4, 128.3, 127.9, 127.71, 127.68, 127.6, 82.0 (×2), 80.1, 79.7, 79.5, 79.2, 77.9, 77.2, 77.0, 76.8, 76.1, 75.9, 75.6, 73.5, 72.6, 71.4, 71.0, 70.6, 69.4, 67.8, 39.4, 37.5, 37.0, 35.3, 35.1, 34.4, 29.3 (×2), 29.1, 25.8, 25.4, 21.1, 17.9, −4.0, −4.7; MS (FAB) 893 (M + H), 835 (M − *t*-Bu), 761 (M − OTBS); HRFABMS calcd for $C_{50}H_{73}O_{12}Si$ (MH^+) 893.4871, found 893.4849.

iii. Deprotection of the TBS Group. To a solution of acetate **ii** (15.0 mg, 0.0168 mmol) and AcOH (0.003 mL, 0.05 mmol) in THF (0.5 mL) was added Bu_4NF (0.034 mL of a 1.0 M solution in THF, 0.034 mmol), and the reaction mixture was stirred at room temperature. An additional two portions of 0.034 mL of a 1.0 M solution Bu_4NF in THF (0.034 mmol, 2.0 equiv for each portion) were added after 2 and 7 h. The reaction mixture was stirred for a

total of 24 h. After addition of brine (2 mL), the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (70% EtOAc in *n*-hexane) afforded the secondary alcohol (13.0 mg, 99%) as a colorless solid. (2*R*,3*S*,4a*R*,5a*S*,7a*R*,8a*S*,12a*R*,13a*S*,14a*R*,15a*S*)-2-(((2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-(benzyloxy)-6-((benzyloxy)methyl)-3-hydroxyoctahydropyrano[3,2-*b*]-pyran-2-yl)methyl)octadecahydropyrano[2′,3′:5,6]pyrano[3,2-*b*]-pyrano[2′,3′:5,6]pyrano[2,3-*f*]oxepin-3-yl acetate (hydroxy acetate **iii**): mp 145−147 °C; $[\alpha]^{28}_{D}$ +43.4 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3515, 3010, 2948, 2872, 1736, 1456, 1244, 1085, 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.20 (10H, m), 4.63 (1H, m), 4.61 and 4.55 (1H, d, *J* = 12.4 Hz), 4.58 and 4.38 (1H, d, *J* = 11.5 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.76 (1H, dd, *J* = 11.0, 1.8 Hz), 3.65 (1H, dd, *J* = 11.0, 5.1 Hz), 3.58 (1H, ddd, *J* = 9.6, 7.8, 1.8 Hz), 3.54−3.49 (2H, m), 3.42 (1H, ddd, *J* = 9.2, 5.1, 1.8 Hz), 3.38−3.28 (3H, m), 3.25 (1H, ddd, *J* = 9.2, 4.4, 4.4 Hz), 3.22−3.18 (2H, m), 3.13−2.93 (6H, m), 2.72 (1H, brs), 2.53 (1H, ddd, *J* = 11.5, 4.1, 4.1 Hz), 2.45 (1H, ddd, *J* = 11.5, 4.1, 4.1 Hz), 2.40 (1H, ddd, *J* = 11.5, 4.1, 4.1 Hz), 2.36 (1H, ddd, *J* = 11.5, 4.1, 4.1 Hz), 2.28 (1H, ddd, *J* = 11.5, 3.7, 3.7 Hz), 2.05 (3H, s), 2.04−1.99 (3H, m), 1.95−1.81 (4H, m), 1.73−1.68 (2H, m), 1.54−1.39 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 138.2, 138.0, 128.4, 128.3, 127.9, 127.74, 127.70, 127.6, 81.94, 81.91, 80.3, 79.7, 79.2, 79.0, 77.9, 77.2, 76.69, 76.66, 76.13, 76.11, 75.5, 73.5, 72.5, 71.0, 70.0, 69.3, 68.6, 67.8, 37.6, 37.4, 36.9, 35.2, 35.1, 33.5, 29.2 (×2), 29.1, 25.4, 21.1; MS (FAB) 779 (M + H), 687 (M − Bn); HRFABMS calcd for $C_{44}H_{59}O_{12}$ (MH^+) 779.4007, found 779.3998.

iv. Dess−Martin Oxidation. A mixture of hydroxy acetate **iii** (12.5 mg, 0.0160 mmol) and Dess−Martin periodinane (10 mg, 0.0236 mmol) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 1 h. An additional 30 mg of Dess−Martin periodinane (0.071 mmol) was added, and stirring was continued for another 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and 10% aqueous $Na_2S_2O_3$ solution (2 mL), and the resulting mixture was extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (50% EtOAc−*n*-hexane) afforded ketone **36** (10.7 mg, 86%) as a colorless solid. Mp 123−124 °C; $[\alpha]^{28}_{D}$ +46.4 (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) 3010, 2947, 2871, 1732, 1455, 1240, 1089, 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.21 (10H, m), 4.62 and 4.55 (each 1H, d, *J* = 12.4 Hz), 4.61 and 4.42 (each 1H, d, *J* = 11.5 Hz), 4.60 (1H, m), 3.96 (1H, dd, *J* = 6.4, 3.7 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.76 (1H, dd, *J* = 10.6, 1.4 Hz), 3.67 (1H, dd, *J* = 10.6, 5.1 Hz), 3.62−3.56 (2H, m), 3.48 (1H, ddd, *J* = 9.2, 5.1, 1.4 Hz), 3.42−3.28 (5H, m), 3.22−3.16 (2H, m), 3.03−2.93 (5H, m), 2.66 (1H, ddd, *J* = 11.5, 4.1, 4.1 Hz), 2.46 (1H, dd, *J* = 16.5, 10.6 Hz), 2.43 (1H, ddd, *J* = 11.5, 4.1, 4.1 Hz), 2.31 (1H, ddd, *J* = 11.5, 3.7, 3.7 Hz), 2.26 (1H, ddd, *J* = 11.5, 4.1, 4.1 Hz), 2.18 (1H, ddd, *J* = 14.7, 6.4, 3.2 Hz), 2.03 (3H, s), 2.02−1.99 (3H, m), 1.89−1.81 (3H, m), 1.73−1.69 (2H, m), 1.55−1.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 169.8, 138.0, 137.8, 128.41, 128.36, 127.9, 127.80, 127.76, 127.7, 82.0, 81.9, 79.9, 79.7, 79.2, 78.7, 77.9, 77.2, 76.8, 76.0, 75.7, 75.5, 74.4, 73.5, 72.0, 71.1, 70.8, 69.0, 67.8, 44.6, 37.4, 36.8, 35.1, 35.0, 32.1, 29.24, 29.23, 29.1, 25.4, 21.0; MS (FAB) 777 (M + H), 685 (M − Bn); HRFABMS calcd for $C_{44}H_{57}O_{12}$ (MH^+) 777.3850, found 777.3828.

(2*R*,3*S*,4a*R*,5a*S*,7a*R*,8a*S*,12a*R*,13a*S*,14a*R*,15a*S*)-2-(((2*R*,3*S*,4a*R*,6*S*,9a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-7-oxooctahydro-2*H*-pyrano[3,2-*b*]oxepin-6-yl)methyl)-octadecahydropyrano[2′,3′:5,6]pyrano[3,2-*b*]pyrano[2′,3′:5,6]-pyrano[2,3-*f*]oxepin-3-yl Acetate (37). To a suspension of ketone **36** (10.4 mg, 0.0134 mmol) and powdered 4 Å molecular sieves (42 mg) in CH_2Cl_2 (1 mL) at −80 °C were added $BF_3{\cdot}OEt_2$ (0.0083 mL, 0.067 mmol) and trimethylsilyldiazomethane (0.0335 mL of a 2.0 M solution in hexanes, 0.067 mmol), and the reaction mixture was stirred at −80 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (2 mL). The resulting mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure to afford the crude α-TMS ketone, which was immediately used in the next reaction without further purification.

A mixture of the above α-TMS ketone and PPTS (10 mg, 0.040 mmol) in MeOH (0.3 mL) and CH_2Cl_2 (0.3 mL) was stirred at room temperature for 9.5 h. An additional 30 mg of PPTS (0.120 mmol) was added, and stirring was continued at room temperature for 7 h and then at 55 °C for 1 h. The reaction mixture was cooled to room temperature, and the reaction was quenched with Et_3N (0.5 mL). The resulting mixture was concentrated under reduced to give 57 mg of a pale yellow solid. Purification by flash chromatography (0→40% EtOAc in *n*-hexane) afforded **37** (6.0 mg, 57%) as a colorless solid. Mp 145−147 °C; $[\alpha]^{30}_{D}$ +23.5 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 2948, 2872, 1736, 1714, 1455, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.21 (10H, m), 4.60 and 4.53(each 1H, d, *J* = 12.1 Hz), 4.594 and 4.40 (each 1H, d, *J* = 11.5 Hz), 4.54 (1H, m), 3.95 (1H, dd, *J* = 6.6, 3.7 Hz), 3.90 (1H, d, *J* = 10.9 Hz), 3.75 (1H, d, *J* = 10.9 Hz), 3.63 (1H, dd, *J* = 10.9, 5.2 Hz), 3.53 (1H, ddd, *J* = 10.3, 10.3, 2.3 Hz), 3.50−3.29 (6H, m), 3.22−3.16 (2H, m), 3.08−2.95 (5H, m), 2.88 (1H, dd, *J* = 13.7, 12.1 Hz), 2.58 (1H, ddd, *J* = 12.1, 4.6, 4.6 Hz), 2.42 (1H, ddd, *J* = 11.5, 4.6, 4.6 Hz), 2.37 (1H, dd, *J* = 12.1, 6.9 Hz), 2.30−2.19 (3H, m), 2.04 (3H, s), 2.02−1.98 (4H, m), 1.88−1.83 (3H, m), 1.71−1.69 (2H, m), 1.61−1.38 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.1, 169.7, 138.2, 138.0, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 83.3, 82.0, 81.9, 80.8, 80.7, 80.0, 79.7, 79.3, 77.9, 77.2, 76.7, 75.6, 74.9, 73.5, 72.3, 71.1, 70.7, 69.2, 67.8, 37.4, 37.1, 36.8, 36.6, 35.5, 35.1, 29.24, 29.22, 29.1, 29.0, 25.4, 21.1; MS (FAB) 791 (M + H), 699 (M − Bn); HRFABMS calcd for $C_{45}H_{59}O_{12}$ (MH^+) 791.4007, found 791.4025.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a-*S*,18a*R*,19a*S*,20a*R*,22a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-octacosahydropyrano[2,3-*i*]pyrano[3,2-*b*:5,6-*b*′]bis(dipyrano-[3,2-*b*:2′,3′-*f*]oxepine) (38). *i. Acetalization of Ketone 37.* A solution of **37** (6.0 mg, 0.0076 mmol) and $TsOH{\cdot}H_2O$ (4.3 mg, 0.023 mmol) in MeOH (0.25 mL) and 1,2-dichloroethane (0.25 mL) was stirred at 75 °C for 24 h. An additional two portions of 0.5 mL of MeOH were added after 4 and 7 h to prevent the reaction mixture from drying up. The reaction mixture was cooled to room temperature. The reaction was quenched with Et_3N (0.1 mL), and the resulting mixture was concentrated under reduced pressure. Purification by flash chromatography (40→100% EtOAc in *n*-hexane) afforded methyl acetal 20a-OMe-**38** (4.7 mg, 81%) as a colorless solid. (2*R*,3*S*,4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,10a*R*,14a*S*,15a*R*,17a*S*,18a*R*,19a-*S*,20a*R*,22a*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-20a-methoxyoctacosahydropyrano[2,3-*i*]pyrano[3,2-*b*:5,6-*b*′]bis(dipyrano-[3,2-*b*:2′,3′-*f*]oxepine) (20a-OMe-**38**): mp 210−213 °C; $[\alpha]^{28}_{D}$ +3.8 (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) 3009, 2947, 2872, 1455, 1343, 1080 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.19 (10H, m), 4.60 and 4.54 (each 1H, d, *J* = 12.4 Hz), 4.57 and 4.37 (each 1H, d, *J* = 11.5 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.73 (1H, dd, *J* = 10.6, 1.4 Hz), 3.61 (1H, dd, *J* = 10.6, 5.2 Hz), 3.46 (1H, ddd, *J* = 11.7, 9.5, 4.5 Hz), 3.41 (1H, dd, *J* = 11.7, 4.0 Hz), 3.38−3.18 (9H, m), 3.23 (3H, s), 3.06−3.01 (3H, m), 2.97−2.95 (2H, m), 2.56 (1H, dt, *J* = 11.7, 4.5 Hz), 2.34 (1H, dt, *J* = 11.3, 4.0 Hz), 2.30 (1H, dt, *J* = 11.3, 3.7 Hz), 2.21 (1H, dt, *J* = 11.3, 3.7 Hz), 2.12 (1H, dddd, *J* = 14.6, 11.7, 6.2, 3.7 Hz), 2.06 (5H, m), 1.94 (1H, q, *J* = 11.7 Hz), 1.91−1.87 (3H, m), 1.79 (1H, dddd, *J* = 14.6, 7.7, 6.6, 3.7 Hz), 1.72−1.69 (2H, m), 1.58 (1H, q, *J* = 11.7 Hz), 1.520 (1H, q, *J* = 11.3 Hz), 1.516 (1H, q, *J* = 11.3 Hz), 1.43 (1H, q, *J* = 11.3 Hz), 1.40 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 138.1, 128.4, 128.3, 127.8, 127.74, 127.69, 127.6, 100.0, 82.1, 82.0, 81.9, 81.1, 80.1, 79.7, 79.4, 79.3, 78.0, 77.31, 77.28, 77.1, 77.0, 73.4, 72.5, 70.8, 69.3, 68.8, 67.8, 47.3, 37.5, 37.0, 36.9, 34.8, 31.9, 30.9, 29.3 (×2), 29.2, 27.6, 25.5; MS (FAB) 763 (M + H), 731 (M − OMe); HRFABMS calcd for $C_{44}H_{59}O_{11}$ (MH^+) 763.4057, found 763.4072.

ii. Reductive Etherification of Acetal 20a-OMe-38. To a solution of 20a-OMe-**38** (4.3 mg, 0.0056 mmol) and Et_3SiH (0.017 mL, 0.11 mmol) in CH_2Cl_2 (0.5 mL) was added TMSOTf (0.0051 mL, 0.028 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (2 mL), and the resulting mixture was extracted with CH_2Cl_2. The

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extract was washed with brine, dried, and concentrated under reduced pressure. Purification by flush chromatography (0→4% MeOH in $CHCl_3$) afforded **38** (3.9 mg, 95%) as a colorless solid. Mp 300−325 °C (decomp); $[\alpha]^{27}_D$ +19.7 (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 3009, 2936, 2872, 1456, 1342, 1076 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.20 (10H, m), 4.60 and 4.54 (each 1H, d, *J* = 12.5 Hz), 4.58 and 4.38 (each 1H, d, *J* = 11.4 Hz), 3.90 (1H, d, *J* = 11.0 Hz), 3.74 (1H, dd, *J* = 10.6, 1.5 Hz), 3.61 (1H, dd, *J* = 10.6, 5.2 Hz), 3.47 (1H, ddd, *J* = 10.6, 9.5, 4.8 Hz), 3.38−3.16 (10H, m), 3.05−2.95 (6H, m), 2.56 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 2.36−2.28 (4H, m), 2.04−2.00 (5H, m), 1.95−1.86 (4H, m), 1.73−1.69 (2H, m), 1.54−1.39 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 138.0, 128.4, 128.3, 127.9, 127.7 (×2), 127.6, 82.2, 82.1, 82.0, 81.7, 80.2, 79.7, 79.4, 79.3, 78.9, 77.9, 77.3, 77.0 (×2), 76.8 (×2), 73.5, 72.6, 70.9, 69.4, 67.9, 37.5, 37.1, 37.0 (×2), 35.2, 29.3 (×2), 29.21, 29.17 (×2), 25.5; MS (FAB) 733 (M + H); HRFABMS calcd for $C_{43}H_{57}O_{10}$ (MH^+) 733.3952, found 733.3955.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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