Application of Photoinduced Biomimetic Cascade Cyclizations of Terpenoid Polyalkenes for the Synthesis of (±)-Stypoldione

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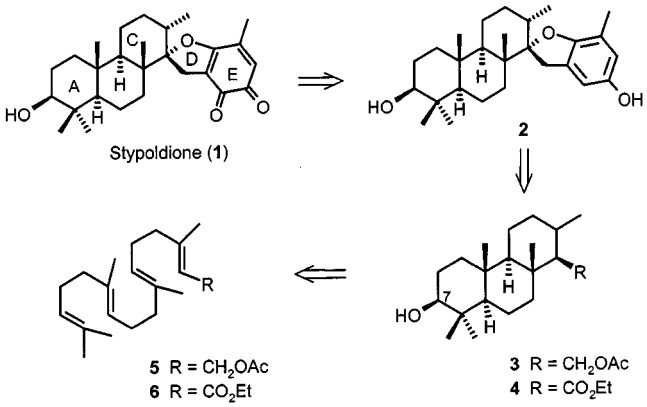
An efficient formal total synthesis of (±)-stypoldione (**1**) has been accomplished, using photochemically triggered electron transfer to initiate biomimetic-type cascade cyclizations of terpenoid polyalkenes as the key step. (–)-Stypoldione (**1**) is an antitumoral marine toxin produced by the tropical brown alga *Stypopodium zonale*.

Introduction

(−)-Stypoldione (**1**), an ichthyotoxic and cytotoxic metabolite of the tropical brown alga *Stypopodium zonale* (Lamouroux) Papenfuss was originally isolated in 1979 by Fenical and Gerwick.[1,2] This marine toxin inhibits cells division of marine embryos and mammalian cell cultures in a concentration-dependent manner.[3,4] At low concentrations (i.e. 5−10 μM), stypoldione selectively inhibits cytokinesis through a mechanism that does not appear to involve disassembly of microtubules, while at higher concentrations (i.e. 80 μM and above), both cytokinesis and mitosis are inhibited. Furthermore, stypoldione reacts covalently with the sulfhydryl groups of a number of proteins, peptides, and small molecules; therefore, it could potentially react with a large number of cellular targets. This compound has also been found to display antitumor properties.[3]

The broad biological activity of **1** and its novel structure make it an attractive target for total synthesis and for structure-activity studies.[5,6] Three successful syntheses of the title compound have been reported.[7−9] However, the lengthy and laborious construction of the tricyclic diterpene portion of **1** is a problem common to the total syntheses so far achieved. As found in our earlier work concerning photoinduced polyalkene cyclizations via radical cations,[10−13] a *trans-anti-trans*-fused 6,6,6-membered tricyclic diterpenoid can be assembled stereoselectively in one step from readily available acyclic terpenoid polyalkene precursors. These cyclizations involve biomimetic-style reaction cascades, the yields of which are very reasonable (20−30%) − e.g. **5** → **3** and **6** → **4** (Scheme 1) − in view of the creation of seven new stereogenic centers in a single operational step. Furthermore, these transformations offer a unique opportunity for a short and stereocontrolled synthesis of the tricyclic diterpene portion of stypoldione. Accordingly, application of this cyclization reaction to the total synthesis of **1**, via stypoldiol (**2**), would probably allow a straightforward approach (Scheme 1). This paper describes in detail our new synthesis of (±)-**1** (for a preliminary communication, see ref.[13]).



Scheme 1. Retrosynthetic analysis of stypoldione (**1**)

Results and Discussion

The first step of this synthesis involves the preparation of an appropriate intermediate from the photoproducts **3** or **4** for further introduction of the spirobenzofuranyl unit (DE rings) of the target **1**. Thus, aldehyde **8** was prepared first, as shown in Scheme 2. As mentioned before, **3** and **4** are derived from **5** and **6**, respectively, in one step by photoinduced electron transfer (PET) triggered cyclizations.[10−13] Both **3** and **4** can be converted into **8** via the alcohol **7**. After the hydroxy groups at C-7 in **3** and **4** had been protected as MEM ethers, alcohol **7** was obtained either by saponification of the acetate moiety with a 0.5 M solution of KOH in methanol at room temperature (71% overall yield), or by reduction of the ester group with $LiAlH_4/AlCl_3$ in dry Et_2O at 0 °C (70% overall yield). The 2α/2β (1:3) epimers of **7** can easily be separated by chromatography on silica gel, and their stereochemistry was confirmed by ^1H NMR NOESY measurements (for the NMR connectivities of 2α-**7**, see bottom of Scheme 2) and chemical interconversions.[10] Pyridinium dichromate (PDC) was initially used for the oxidation of alcohol **7** to aldehyde **8**, but the yield was only 50−60%. After attempts at optimization, it was

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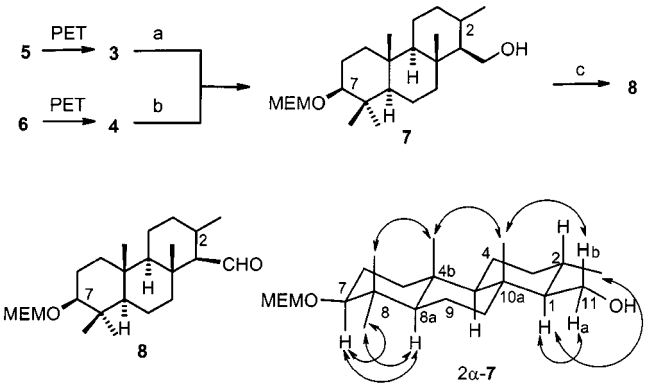
found that the oxidation of **7** with tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO)[14] in CH_2Cl_2 in the presence of 4-Å molecular sieves takes place smoothly, to give the desired aldehyde **8** in 85% yield.

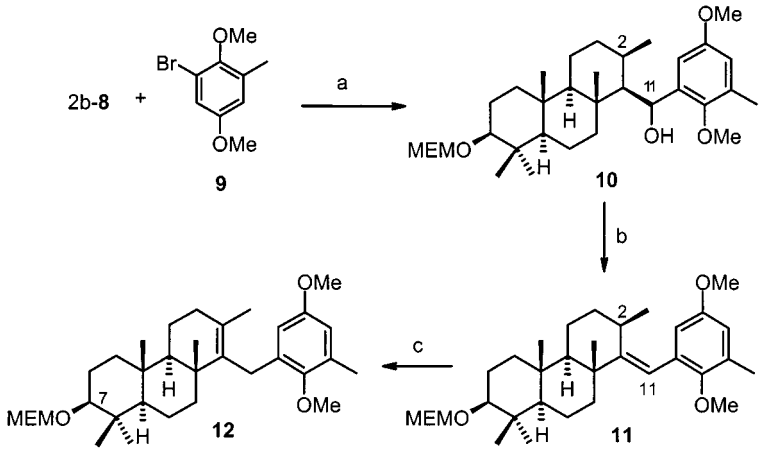


Scheme 2. Synthesis of the aldehyde **8**; reagents and conditions: a: 1. MEMCl, *i*Pr_2NEt, CH_2Cl_2, room temp., 2. 0.5 M KOH, MeOH, room temp. (71% overall); b: 1. MEMCl, *i*Pr_2NEt, CH_2Cl_2, room temp., 2. $LiAlH_4$, $AlCl_3$, Et_2O, 0 °C (70% overall); c: TPAP, NMO, CH_2Cl_2, room temp. (85%)

With **8** readily at hand, attention was then focussed on its coupling with bromide **9**[15] and subsequent elaboration to the pivotal intermediate **12** (Scheme 3). Although both the 2α and 2β epimers of **8** might be converted into **12**, only the major epimer 2β-**8** was used for this total synthesis – solely for the purposes of clean spectral identification of **10** and **11** en route to **12**. Of course, a mixture of both epimers of **8** may in future be employed for these transformations, offering practical simplicity and avoiding laborious separation. The preparation of **12** commenced with the coupling of aldehyde 2β-**8** with an organocopper reagent derived from bromide **9** in THF at −40 °C to give the desired alcohol **10** in 80% yield. The alcohol **10** was a mixture of two epimers at C-11, which could easily be separated by column chromatography on silica gel. However, the separation was not necessary for preparative purposes, because both epimers could again be converted into olefin **11** after dehydration.

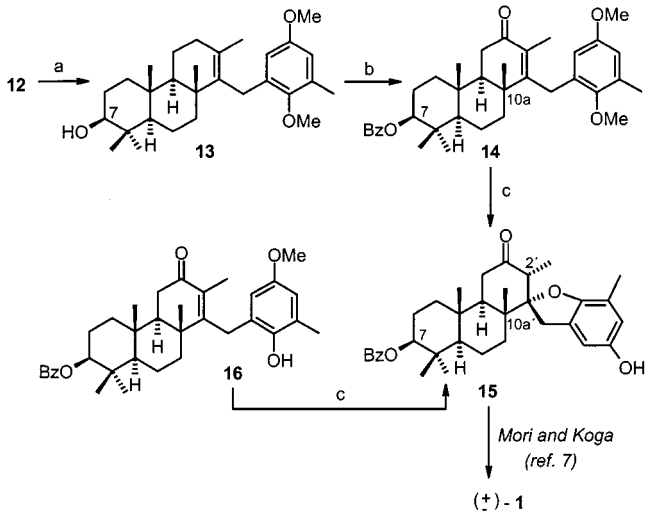
The dehydration of **10** proved to be problematic. A variety of dehydration reagents was tested, including $SOCl_2$/pyridine, TsOH, TsCl/4-DMAP (Et_3N), and DCC/CuCl.[16] Only DCC/CuCl in benzene at reflux brought about smooth dehydration of **10** to give **11** in 85% yield. Gratifyingly, treatment of **11** with a 1 M potassium *tert*-butoxide solution in DMSO at 110 °C resulted in rapid and complete conversion into its isomer **12** in 90% yield. In this procedure, the *exo* double bond shifted to the *endo* position – apparently because of the dominance of the more stable benzyl secondary anion at C-11 over the resonance tertiary anion at C-2 prior to protonation. The key intermediate **12** represents an important skeleton, which may be very useful for studies of biosynthetic aspects and biomimetic synthesis of stypoldione (**1**) or other metabolites of *S. zonale*.[5,6]

With the pivotal olefin **12** securely established, attention was next focused on the spiroannulation. After some unsuccessful attempts to induce cyclization,[17] an intramolecular Michael addition strategy, via the enone **14** (Scheme 4), was finally employed successfully for the construction of the spirobenzofuranyl unit, following an analogous literature example.[7] To this end, the MEM protecting group at C-7 in **12** was first cleaved by treatment with HCl (2 N)/ethylene glycol/THF (3:1:4) at room temperature to give the alcohol **13** in 80% yield. Protection of the liberated hydroxy group of **13** as a benzyl ether was followed by oxidation with an excess of chromium trioxide/3,5-dimethylpyrazole complex (CrO_3/3,5-DMP) in CH_2Cl_2 at −20 °C, affording **14** in 65% overall yield from **13**. For inducing the spiroannulation, it is necessary to render the alkene site electron-deficient by transforming it into an enone. The crucial stage in this synthetic sequence had accordingly been reached. Removal of the methyl protecting groups of the aryl moiety and the subsequent intramolecular Michael addition should then form the spirobenzofuranyl unit. Thus, treatment of **14** with BBr_3 in CH_2Cl_2 at −78 °C for 1 h, warming the solution to −10 °C over 3 h, and subsequent hydrolysis with water finally furnished the ketone **15** in 28% isolated yield, together with some side products including **16**. An additional quantity of **15** (14%) was obtained by treatment of the side prod-



Scheme 3. Synthesis of intermediate **12**; reagents and conditions: a: *n*BuLi, CuI, THF, −40 °C (80%); b: DCC, CuCl, PhH, reflux (85%); c: *t*BuOK, DMSO, 110 °C (90%)

ucts with BBr_3 once more. The combined total yield of **15** finally amounted to 42%.

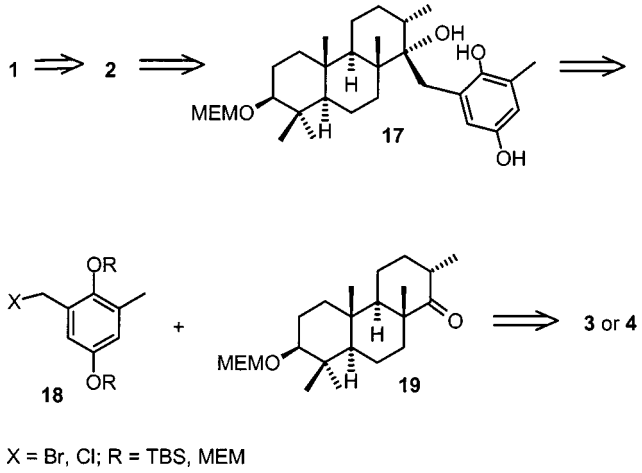


Scheme 4. Synthesis of ketone **15** and (±)-stypoldione (**1**); reagents and conditions: a: HCl (2 N)/ethylene glycol/THF, room temp. (80%); b: 1. BzCl, pyridine, CH_2Cl_2, room temp., 2. CrO_3/3,5-DMP, CH_2Cl_2, −20 °C (65% overall); c: BBr_3, CH_2Cl_2, −78 °C → −10 °C (42%)

The analytical data (i.e., 400 MHz ^{1}H NMR, IR, MS) are identical with the literature data for this compound.[7] The exclusive, stereoselective formation of **15** is probably due to preferential axial Michael addition by the phenolic oxygen atom to the enone of **14**, along with the avoidance of steric interaction with the axial C-10a methyl group (Scheme 5). Similarly, the 2′-methyl group in **15** exclusively adopts the equatorial position to avoid 1,3-interaction between the 2′- and 10a′-methyl groups.

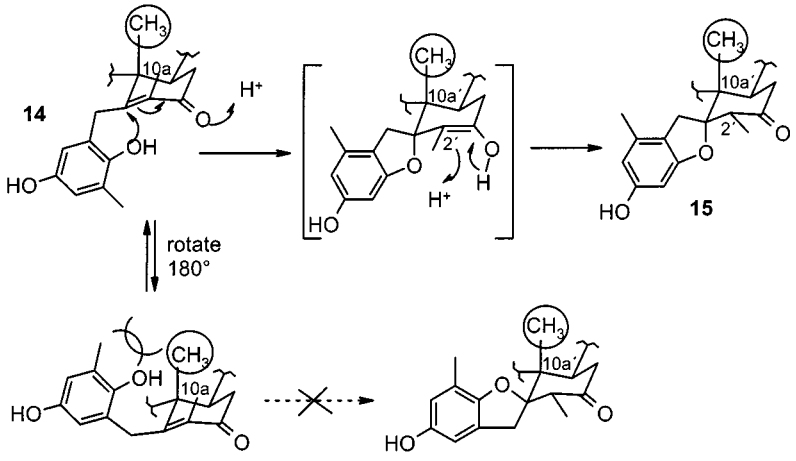
Ketone **15** possesses all seven stereogenic centers, including the spiro ring junction, of (±)-stypoldione (**1**). According to Mori and Koga,[7] **15** can be readily transformed into (±)-**1** in three steps, and hence an efficient formal total synthesis of the title compound has been accomplished by our route.

In order to improve the synthetic route to stypoldione (**1**) further, another strategy, as shown in Scheme 6, was devised and tested in parallel. It was hoped that ketone **19,** derived from **3** or **4,** would couple with the aryl bromide **18** to give **17** and the subsequent quinol-to-tertiary-alcohol cyclization would form the spirobenzofuranyl unit en route to **1** via **2**.



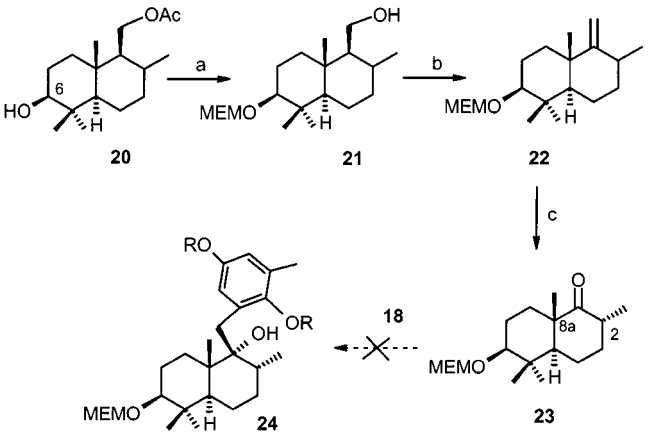
Scheme 6. Retrosynthetic analysis of stypoldione (**1**)

To check the feasibility of this second strategy, model studies (Scheme 7) were conducted, starting from the bicyclic compound **20**, obtained as a PET product from commercially available all-*trans*-farnesyl acetate.[18,19] Thus, protection of the 6-OH group of **20** as a MEM ether, followed by saponification of the acetate moiety of MEM-protected **20**, readily afforded alcohol **21** in 86% overall yield from **20**. The olefin **22** was then obtained in 80% overall yield by means of Grieco's *ortho*-nitrophenylselenenylation[20] of **21** in the presence of Bu_3P, followed by oxidation of the formed selenide with a 30% aqueous solution of H_2O_2. Oxidative cleavage of the double bond of **22** with RuO_4 provided a mixture of 2α/2β epimeric ketones, which was transformed into the pure 2α epimer **23** by sodium methoxide induced equilibration. At this point, a crucial stage in these model studies was reached. Unfortunately, despite many attempts, we have been unable to produce the desired tertiary alcohol **24** using **23** and **18**. Neither the Barbier method,[21] nor the Grignard reaction,[22] were able to effect the formation of **24** by the use of magnesium or lithium. Other alter-



Scheme 5. Stereoselective intramolecular course of the Michael addition

native procedures employing organocerium reagents,[23] a charge-transfer complex [Mg(anthracene)THF_3],[24] or sonochemical Barbier reaction[25] also failed to give any coupling product. The failure of these attempted coupling reactions is probably due to strong shielding of the carbonyl position by the methyl groups at C-2 and C-8a, not allowing the required approach of the metallated benzyl reagents at C-1.



Scheme 7. Synthesis of ketone **23** and model studies; reagents and conditions: a: 1. MEMCl, *i*Pr_2NEt, CH_2Cl_2, room temp., 2. 0.5 M KOH in MeOH, room temp. (86% overall); b: 1. *o*-$O_2NC_6H_4SeCN$, Bu_3P, THF, room temp., 2. 30% H_2O_2, 0 °C (80% overall); c: RuO_4, CCl_4, room temp. (70%)

Conclusion

The pivotal cyclizations of terpenoid polyalkenes, such as **5** → **3** and **6** → **4,** triggered by photochemical radical cation formation, allow a novel and efficient means of access to (±)-stypoldione in a formal total synthesis. The construction of the essential ABC ring core is based upon application of PET methodology and is much shorter than previous literature approaches. The title marine antitumor toxin has to date been synthesized three times. In comparison with these former total syntheses, the present approach is more concise in that access to the tricyclic diterpene core (ABC rings) of **1** is facilitated through the key photochemical steps to **3** and **4**. Formation of the structurally characteristic spirobenzofuranyl unit (CDE rings) in **1** is best achieved by intramolecular Michael addition, i.e. **14** → **15**. In parallel with these findings, a model study aiming at a still shorter access to the title compound was undertaken. However, severe steric interactions on the pathway to the spiro precurser (**23** → **24**) blocked this second approach.

Experimental Section

General: All melting points were determined using a Reichert or a Kofler apparatus and are uncorrected. − IR spectra were measured as KBr pellets or liquid films using a Perkin−Elmer 200 or a Bruker IFS 66 spectrometer. − NMR spectra were recorded with the following Bruker instruments: a WM-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C), an AC-270 (270 MHz for ^{1}H, 67.9 MHz for ^{13}C), or an AM-400 (400 MHz for ^{1}H, 100.6 MHz for ^{13}C) with dilute solutions in deuteriochloroform ($CDCl_3$) at 300 K unless stated otherwise. The chemical shift values are given in δ units (ppm) with trimethylsilane as internal standard. All coupling constants, *J*, are reported in Hz. A combination of COSY, DEPT, and INV4GS long range measurements was used for complete assignment of most of the products. − Mass spectra were recorded with a Finnigan MAT 311A instrument at 70 eV ionization energy. Data are presented in *m*/*z* (%) values. When required, molecular ion peaks were ascertained by chemical ionization (CI) or fast atom bombardment (FAB) techniques. − Column chromatography was performed on Merck silica gel 60 (0.063−0.20 mm or 0.04−0.063 mm). All reactions were monitored by TLC on Merck silica gel 60 F_{254} precoated aluminum plates, which were developed with UV light followed by spraying with acidic vanillin solution. − Oxygen- or moisture-sensitive reactions were performed under an argon flow in glassware dried either by oven or heat gun, and equipped with rubber septa. Air- or moisture-sensitive liquids and solutions were transferred by syringe; solids were transferred through a funnel under argon. Solvents were purchased from Merck or Aldrich and used directly or purified by standard procedures.[26] "Concentration" involved drying of the combined organic layers with anhydrous sodium sulfate, filtration, and solvent removal under reduced pressure. Compounds have been named according to standard nomenclature (IUPAC) by means of the program AUTONOM.

[*c*-7-(2-Methoxyethoxymethoxy)-*c*-2,*c*-4b,8,8,*c*-10a-pentamethyl-1,2,3,4,*t*-4a,4b,5,6,7,8,*t*-8a,9,10,10a-tetradecahydrophenanthren-*r*-1-yl]methanol (2β-7)

(a) To a solution of **3** (600 mg, 1.71 mmol) in CH_2Cl_2 (15 mL) at room temp. under argon were added MEMCl (1.37 mL, 12.0 mmol) and *i*Pr_2NEt (2.09 mL, 12.0 mmol). After stirring at room temp. for 1 h, sat. Na_2CO_3 solution was added and the mixture was extracted with Et_2O. The extracts were washed with water and brine. After concentration, the residue was purified by chromatography on silica gel (*n*-pentane/Et_2O, 1:1) to give the MEM-protected **3** (670 mg) as an inseparable mixture of isomers, which was used directly for the next step. This mixture was dissolved in methanol (50 mL) containing KOH (1.4 g, 25.0 mmol) and stirred at room temp. until the saponification was complete (4 h) by TLC (*n*-pentane/ethyl acetate, 5:2). The reaction mixture was slowly diluted with water and extracted with Et_2O. The combined extracts were washed successively with 5% HCl, sat. $NaHCO_3$, water, and brine. After concentration, the residue was purified by chromatography on silica gel (*n*-pentane/ethyl acetate, 5:2) to give 2α-**7** (162 mg) and 2β-**7** (318 mg), both of them as white flakes after crystallization from *n*-pentane.

(b) A mixture of $LiAlH_4$ (38 mg, 1.0 mmol) and $AlCl_3$ (54 mg, 0.4 mmol) in 3 mL of Et_2O was stirred at 0 °C under argon for 1 h, after which a solution of the MEM-protected **4** (0.17 mmol) in 1.5 mL of Et_2O was added. This mixture was then stirred at 0 °C for 2 h. TLC (*n*-pentane/Et_2O, 1:1) and GC analysis showed complete conversion of the esters. The final reaction mixture was diluted with Et_2O, poured into a separating funnel containing 5% HCl, shaken, and partitioned. The aqueous phase was extracted again with Et_2O. After concentration of the organic layers, the residue was carefully chromatographed on silica gel, using *n*-pentane/Et_2O (1:1) as eluent, to afford the two epimeric alcohols 2α- and 2β-**7** (α/β = 1:3) in 71% overall yield from **4**; m.p. 88−90 °C. −IR (KBr): $\tilde{\nu}$ = 3377m (br.), 2961 s, 2939 s, 2871 s, 2847 s, 1449 m, 1384 m, 1361 w, 1202 w, 1168 m, 1136 m, 1113 m, 1096 m, 1045 s, 999 m, 848 w cm^{-1}. − ^{1}H NMR (400 MHz): δ = 4.79 [d, *J* = 7, 1 H, OC*H*HO (MEM)], 4.65 [d, *J* = 7, 1 H, OCH*H*O (MEM)],

3.80−3.40 [br. m, 2 H, H−C(11)], 3.69 [m, CH_2 (MEM)], 3.51 [m, CH_2 (MEM)], 3.35 [s, Me (MEM)], 3.07 [m, H−C(7)], 2.10−0.60 (br. m, 17 H), 0.90 [d, *J* = 7, Me−C-2], 0.89 (s, Me), 0.81 (s, Me), 0.79 (s, Me), 0.73 (s, Me). − ^{13}C NMR (100.6 MHz): δ = 94.8 [O*C*H_2O (MEM)], 85.0 [C(7)], 71.8 [CH_2 (MEM)], 66.9 [CH_2 (MEM)], 60.9 (CH), 60.7 [C(11)], 58.9 [Me (MEM)], 56.0 (CH), 55.6 (CH), 41.8 (CH_2), 38.6 (C), 38.2 (CH_2), 37.6 (C), 37.1 (C), 34.3 (CH_2), 28.3 (C-2), 27.9 (Me), 24.0 (CH_2), 18.1 (Me), 17.7 (CH_2), 16.4 (CH_2), 16.3 (Me), 16.1 (Me), 15.4 (Me). − MS: 396 (0.2) [M^+], 366 (1.7), 320 (9.6), 307 (21.8), 306 (27.3), 290 (22.5), 275 (11.2), 251 (41.4), 233 (46.0), 207 (25.0), 189 (36.7), 177 (19.5), 123 (38.2), 109 (51.9), 89 (96.6), 69 (39.5), 59 (100.0). − $C_{24}H_{44}O_4$ (396): calcd. C 72.68, H, 11.18; found C 72.60, H 11.10.

***c*-7-(2-Methoxyethoxymethoxy)-*c*-2,*c*-4b,8,8,*c*-10a-pentamethyl-1,2,3,4,*t*-4a,4b,5,6,7,8,*t*-8a,9,10,10a-tetradecahydrophenanthren-*r*-1-carbaldehyde (2β-8):** Alcohol 2β-**7** (272 mg, 0.69 mmol) was dissolved in dry CH_2Cl_2 (10 mL) containing both molecular sieves (4 Å) and NMO (0.2 g, 1.5 mmol) under argon. After the mixture had been stirred for 5 min, TPAP (0.05 mmol) was added and stirring was continued at room temp. under argon for 1 h. The initial green mixture darkened as the reaction proceeded. TLC (*n*-pentane/Et_2O, 1:1) analysis showed complete conversion of 2β-**7**. The reaction mixture was then poured directly onto a silica gel column and eluted with *n*-pentane/Et_2O (1:1) to give aldehyde 2β-**8** (230 mg, 85%) as a white foam. −IR (KBr): $\tilde{\nu}$ = 2937 s, 2853 m, 1698 s, 1452 m, 1387 m, 1240 m, 1208 m, 1168 s, 1113 s, 1051 s, 973 m, 856 w cm^{-1}. − ^{1}H NMR (250 MHz): δ = 9.80 (d, *J* = 1.5, C*H*O), 4.77 [d, *J* = 7, 1 H, OC*H*HO (MEM)], 4.63 [d, *J* = 7, 1 H, OCH*H*O (MEM)], 3.66 (m, CH_2), 3.48 (m, CH_2), 3.32 [s, Me (MEM)], 3.07 (dd, *J* = 4, 11, H−C-7), 2.40−0.60 (br. m, 16 H), 1.10 (s, Me), 0.96 (d, *J* = 7, Me−C-2), 0.88 (s, Me), 0.81 (s, Me), 0.73 (s, Me). − ^{13}C NMR (63 MHz): δ = 206.0 (*CH*O), 94.8 [O*C*H_2O (MEM)], 84.7 (C-7), 71.7 [CH_2 (MEM)], 66.8 [CH_2 (MEM)], 65.8 (CH), 59.9 (CH), 58.9 [Me (MEM)], 55.7 (CH), 41.3 (CH_2), 38.6 (C), 38.0 (CH_2), 37.24 (C), 37.1 (C), 33.9 (CH_2), 29.4 (C-2), 27.9 (Me), 23.84 (CH_2), 19.0 (Me), 17.3 (CH_2), 16.9 (Me), 16.3 (Me), 16.1 (Me), 16.0 (CH_2). − MS: 394 [M^+], 305 (5.8), 264 (22.1), 221 (22.3), 89 (100.0), 69 (22.4), 59 (74.3), 29 (8.2). − $C_{24}H_{42}O_4$ (394): calcd. C 73.05, H 10.73; found C 72.93, H 10.81.

(2,5-Dimethoxy-3-methylphenyl)-[*c*-7-(2-methoxyethoxymethoxy)-*c*-2,*c*-4b,8,8,*c*-10a-pentamethyl-1,2,3,4,*t*-4a,4b,5,6,7,8,*t*-8a,9,10,10a-tetradecahydrophenanthren-*r*-1-yl]methanol (10): A solution of *n*BuLi in *n*-hexane (15%, 0.5 mL, 0.82 mmol) was added dropwise to a stirred solution of **9** (138 mg, 0.6 mmol) in dry THF (2 mL) under argon at −40 °C. The brown mixture was stirred for 30 min and then CuI powder (57.5 mg, 0.3 mmol) was added in one portion. A brown/black color was observed. After an additional 30 min of stirring, a solution of 2β-**8** (118 mg, 0.3 mmol) in dry THF (2 mL) was added dropwise. The mixture was stirred at −40 °C for 2 h and then warmed to room temp., before being quenched with water and extracted with Et_2O. The combined extracts were washed with water and brine. After removal of the solvents, the residue was purified by chromatography on silica gel, using *n*-pentane/Et_2O (1:1) as eluent, to give the colorless, oily coupling product **10** (132 mg, 80%). − IR (film): 3479s (br.), 2935s (br.), 1603 w, 1467 s, 1454 s, 1386 m, 1318 m, 1199 s, 1169 s, 1110 s, 1049 s, 970 m, 931 w, 854 m cm^{-1}. − ^{1}H NMR (250 MHz): δ = 6.89 (d, *J* = 3, 1 H, H−Ar), 6.57 (d, *J* = 3, 1 H, H−Ar), 5.44 (br. s, H−C-11), 4.79 [d, *J* = 7, 1 H, OC*H*HO (MEM)], 4.66 [d, *J* = 7, 1 H, OCH*H*O (MEM)], 3.74 (s, *Me*OAr), 3.70 [m, CH_2 (MEM)], 3.68 (s, *Me*OAr), 3.53 [m, CH_2 (MEM)], 3.35 [s, Me (MEM)], 3.05 (dd, *J* = 4, 11, H−C-7), 2.24 (s, *Me*−Ar), 2.10−0.60 (br. m, 16 H), 1.24 (s, Me), 1.21 (d, *J* = 8, Me−C-2), 0.90 (s, Me), 0.83 (s, Me), 0.75 (s, Me). − ^{13}C NMR (63 MHz): δ = 155.4 (C), 148.5 (C), 140.0 (C), 131.7 (C), 114.8 [CH (Ar)], 110.2 [CH (Ar)], 94.9 [O*C*H_2O (MEM)], 85.0 (C-7), 71.8 [CH_2 (MEM)], 69.1 (C-11), 66.8 [CH_2 (MEM)], 61.6 (CH), 60.7 (*Me*OAr), 58.9 [Me (MEM)], 57.3 (CH), 55.42 (CH), 55.4 (*Me*OAr), 41.3 (CH_2), 39.4 (C), 38.6 (C), 38.3 (CH_2), 37.2 (C), 35.9 (CH_2), 28.3 (C-2), 27.9 (Me), 24.0 (CH_2), 19.0 (Me), 18.2 (Me), 17.9 (CH_2), 16.8 (CH_2), 16.3 (*Me*−Ar), 16.2 (Me), 16.1 (Me). − MS: 546 (5.2) [M^+], 544 (11.0), 438 (6.7), 260 (17.4), 221 (13.0), 181 (100.0), 89 (26.3), 59 (47.8), 43 (7.2).

(2,5-Dimethoxy-3-methylbenzylidene)-*c*-7-(2-methoxyethoxymethoxy)-*c*-2,*c*-4b,8,8,*c*-10a-pentamethyl-2,3,4,*t*-4a,4b,5,6,7,8,*t*-8a,9,10,10a-tridecahydrophenanthrene (11): A mixture of **10** (75 mg, 0.14 mmol), CuCl (30 mg, 0.3 mmol), DCC (164 mg, 0.8 mmol), and benzene (8 mL) was stirred at 80 °C under an argon flow for 5 h. During the reaction, a constant, small amount of solvent was maintained. TLC (*n*-pentane/Et_2O, 1:1) analysis showed complete conversion of **10**. The reaction mixture was cooled to room temp. and concentrated. The residue was purified by chromatography on silica gel, using *n*-pentane/Et_2O (1:1) as eluent, to give **11** (62 mg, 85%) as colorless, small bars after crystallization from *n*-pentane; m.p. 119−120 °C. − IR (KBr): $\tilde{\nu}$ = 2945 s, 2870 s, 1625 w, 1601 m, 1469 s, 1454 s, 1422 m, 1368 w, 1216 s, 1169 m, 1127 m, 1095 s, 1050 s, 1039 s, 971 m, 874 m, 671 w cm^{-1}. − ^{1}H NMR (250 MHz): δ = 6.56 (d, *J* = 3, 1 H, H−Ar), 6.50 (d, *J* = 3, 1 H, H−Ar), 6.21 (s, H−C-11), 4.82 [d, *J* = 7, 1 H, OC*H*HO (MEM)], 4.68 [d, *J* = 7, 1 H, OCH*H*O (MEM)], 3.72 (s, *Me*OAr), 3.71 [m, CH_2 (MEM)], 3.61 (s, *Me*OAr), 3.53 [m, CH_2 (MEM)], 3.37 [s, Me (MEM)], 3.08 (m, H−C-7), 2.23 (s, *Me*−Ar), 3.00−0.70 (br. m, 15 H), 1.20 (d, *J* = 7, Me−C-2), 1.18 (s, Me), 0.96 (s, Me), 0.92 (s, Me), 0.80 (s, Me). − ^{13}C NMR (63 MHz): δ = 156.7 (C), 154.8 (C), 150.5 (C), 133.3 (C), 131.5 (C), 116.0 (C-11), 114.2 [CH (Ar)], 112.9 [CH (Ar)], 94.8 [O*C*H_2O (MEM)], 84.9 (C-7), 71.8 [CH_2 (MEM)], 66.9 [CH_2 (MEM)], 60.1 (*Me*OAr), 59.3 (CH), 59.0 [*Me*O (MEM)], 55.8 (CH), 55.3 (*Me*OAr), 41.0 (C), 40.6 (CH_2), 38.7 (C), 38.3 (CH_2), 37.8 (C), 34.0 (CH_2), 30.8 (C-2), 28.0 (Me), 24.0 (Me), 23.8 (CH_2), 22.6 (Me), 18.3 (CH_2), 16.6 (CH_2), 16.4 (Me), 16.3 (Me), 16.2 (Me). − MS: 528 (53.4) [M^+], 287 (7.0), 257 (29.6), 218 (100.0), 201 (25.0), 187 (54.9), 165 (43.7), 135 (20.5), 89 (31.1), 59 (41.8). − $C_{33}H_{52}O_5$ (528): calcd. C 74.96, H 9.91; found C 74.78, 9.86.

(2,5-Dimethoxy-3-methylbenzyl)-*c*-7-(2-methoxyethoxymethoxy)-*c*-2,*c*-4b,8,8-*c*-10a-pentamethyl-3,4,*t*-4a,4b,5,6,7,8,*t*-8a,9,10,10a-dodecahydrophenanthrene (12): A solution of **11** (52 mg, 0.1 mmol) and *t*BuOK (672 mg, 6.0 mmol) in DMSO (6 mL) was stirred at 110 °C under argon for 1 h. TLC (*n*-pentane/Et_2O, 1:1) analysis indicated complete conversion of **11**. After cooling to room temp., water was added very slowly and the mixture was extracted with Et_2O. The extracts were washed with 5% HCl and sat. $NaHCO_3$. After separation and evaporation of the organic solvent, the residue was purified by chromatography on silica gel (*n*-pentane/Et_2O, 1:1) to give **12** (47 mg, 90%) as a light yellowish oil. − IR (film): $\tilde{\nu}$ = 2935 s (br.), 1693 w, 1603 m, 1466.8 s, 1386 m, 1314 m, 1215 m, 1171 s, 1111 s, 1052 s, 970 m, 856 m, 712 w cm^{-1}. − ^{1}H NMR (400 MHz): δ = 6.51 (d, *J* = 3, 1 H, H−Ar), 6.45 (d, *J* = 3, 1 H, H−Ar), 4.81 [d, *J* = 7, 1 H, OC*H*HO (MEM)], 4.66 [d, *J* = 7, 1 H, OCH*H*O (MEM)], 3.72 (s, *Me*OAr), 3.70 (s, *Me*OAr), 3.69 [m, CH_2 (MEM)], 3.53 [m, CH_2 (MEM)], 3.42 (d, *J* = 18, 1 H, H_a−C-11), 3.37 [s, *Me*O (MEM)], 3.30 (d, *J* = 18, 1 H, H_b−C-11), 3.06 (dd, *J* = 4, 11, H−C-7), 2.27 (s, *Me*−Ar), 2.20−0.70 (br. m, 14 H), 1.47 (s, Me−C-2), 0.98 (s, Me), 0.84 (s, Me), 0.83 (s, Me), 0.74 (s, Me). − ^{13}C NMR (100.6 MHz): δ = 155.3 (C), 150.2 (C), 137.0

(C), 135.3 (C), 131.1 (C), 129.0 (C), 112.9 [CH (Ar)], 112.2 [CH (Ar)], 94.9 [O*CH*$_2$O (MEM)], 85.1 (C-7), 71.8 [CH_2 (MEM)], 66.9 [CH_2 (MEM)], 59.8 (*Me*OAr), 59.0 [Me (MEM)], 56.4 (CH), 55.4 (CH), 55.3 (*Me*OAr), 39.1 (C), 38.6 (C), 38.0 (CH_2), 37.7 (CH_2), 37.0 (C), 33.7 (CH_2), 27.9 (Me), 26.8 (CH_2), 24.1 (CH_2), 21.3 (Me), 20.2 (Me), 18.2 (CH_2), 18.1 (CH_2), 16.5 (Me), 16.3 (Me), 16.2 (Me). − MS: 528 (100.0) [M^+], 287 (13.6), 257 (58.2), 218 (13.3), 165 (92.6), 135 (31.4), 121 (14.0), 89 (34.7), 59 (35.2).

(2,5-Dimethoxy-3-methylbenzyl)-*c*-7-hydroxy-*c*-2,*c*-4b,8,8,*c*-10a-pentamethyl-3,4,*t*-4a,4b,5,6,7,8,*t*-8a,9,10,10a-dodecahydrophenanthrene (13): A mixture of **12** (40 mg, 0.08 mmol) in 8 mL of THF/ethylene glycol/HCl (2 N) (4:1:3) was stirred at room temp. until conversion was complete (2 d) as indicated by TLC (*n*-pentane/Et_2O, 1:1). Sat. $NaHCO_3$ solution was then added and the mixture was extracted with Et_2O. After separation and evaporation of the organic solvent, product **13** was isolated chromatographically (silica gel), using *n*-pentane/Et_2O (1:1) as eluent, as a colorless oil (27 mg, 80%). − ^{1}H NMR (250 MHz): δ = 6.51 (d, *J* = 3, 1 H, H−Ar), 6.45 (d, *J* = 3, 1 H, H−Ar), 3.72 (s, *Me*OAr), 3.70 (s, *Me*OAr), 3.43 (d, *J* = 17, 1 H, H_a−C-11), 3.29 (d, *J* = 17, 1 H, H_b−C-11), 3.16 (dd, *J* = 4, 11, H−C-7), 2.27 (s, *Me*−Ar), 2.26−0.70 (br. m, 15 H), 1.48 (s, Me−C-2), 0.98 (s, Me), 0.86 (s, Me), 0.82 (s, Me), 0.72 (s, Me). − ^{13}C NMR (63 MHz): δ = 155.3 (C), 150.2 (C), 136.9 (C), 135.3 (C), 131.1 (C), 129.0 (C), 113.1 [CH (Ar)], 111.9 [CH (Ar)], 78.9 (C-7), 59.8 (*Me*OAr), 56.4 (CH), 55.4 (*Me*OAr), 55.0 (CH), 39.1 (C), 38.8 (C), 38.1 (CH_2), 37.6 (CH_2), 37.1 (C), 33.7 (CH_2), 27.8 (Me), 27.3 (CH_2), 26.8 (C-11), 21.3 (Me−C-2), 20.2 (*Me*−Ar), 18.2 (CH_2), 18.1 (CH_2), 16.5 (Me), 16.3 (Me), 15.2 (Me).

***c*-7-(Benzoyloxy)-1-(2,5-dimethoxy-3-methylbenzyl)-2,*c*-4b,8,8,*c*-10a-pentamethyl-*t*-4a,4b,5,6,7,8,*t*-8a,9,10,10a-decahydrophenanthren-3-one (14):** To a solution of **13** (26 mg, 0.06 mmol) in dichloromethane (8 mL) at room temp. were added pyridine (0.6 mL) and benzoyl chloride (84 mg, 0.6 mmol). The mixture was stirred for 45 min, after which water was added, and extracted with Et_2O. The combined organic extracts were washed successively with 5% HCl, sat. $NaHCO_3$, H_2O, and brine. After concentration, the residue was passed through a short column (silica gel, 50fold), using *n*-pentane/Et_2O (1:1) as eluent. The obtained crude benzyl ether of **13** (42 mg) was used directly for the next − i.e., oxidation − step. − To a suspension of CrO_3 (600 mg, 6 mmol) in dry dichloromethane (4 mL) under argon at −20 °C was added 3,5-dimethylpyrazole (600 mg, 6.1 mmol) in one portion. After stirring at −20 °C for 20 min, a solution of the crude benzyl ether of **13** in dichloromethane (4 mL) was added at −20 °C. The mixture was stirred for 15 min, after which an aqueous solution of NaOH (5 N, 4 mL) was added in one portion at −20 °C. Stirring was continued for 20 min at −10 °C → 0 °C, and the mixture was extracted with Et_2O. The extracts were washed sequentially with 5% HCl, sat. $NaHCO_3$, and brine. After concentration, the residue was purified by chromatography on silica gel, using *n*-pentane/Et_2O (1:1) as eluent to give **14** (21 mg, 65% overall yield from **13**) as a white solid after crystallization from *n*-pentane/Et_2O (1:1); m.p. 224−226 °C. − IR (KBr): ṽ = 2943 s, 2875 m, 1716 s, 1664 s, 1602 m, 1479 s, 1451 m, 1339 m, 1275 s, 1215 m, 1174 m, 1114 s, 1063 s, 1012 s, 971 m, 948 w, 714 s cm^{-1}. − ^{1}H NMR (250 MHz): δ = 8.01 (m, 2 H, H−Ar), 7.53−7.38 (br. m, 3 H, H−Ar), 6.57 (d, *J* = 3, 1 H, H−Ar), 6.29 (d, *J* = 3, 1 H, H−Ar), 4.68 (dd, *J* = 5, 11, H−C-7), 3.74 (d, *J* = 16, 1 H, H_a−C-11), 3.72 (s, *Me*OAr), 3.71 (s, *Me*OAr), 3.52 (d, *J* = 16, 1 H, H_b−C-11), 2.51−0.85 (br. m, 12 H), 2.29 (s, *Me*−Ar), 1.72 (s, Me), 1.14 (s, Me), 0.98 (s, 2Me), 0.85 (s, Me). − ^{13}C NMR (63 MHz): δ = 199.9 (C-3), 166.2 (C), 164.6 (C), 155.6 (C), 150.0 (C), 132.8 [CH (Ar)], 132.6 (C), 131.9 (C), 131.8 (C), 130.8 (C), 129.5 [2 CH (Ar)], 128.3 [2 CH (Ar)], 113.3 [CH (Ar)], 111.9 [CH (Ar)], 80.9 (C-7), 60.0 (*Me*OAr), 55.4 (*Me*OAr), 54.9 (CH), 54.4 (CH), 41.0 (C), 38.1 (C), 37.2 (CH_2), 37.0 (C), 36.5 (CH_2), 34.4 (CH_2), 28.6 (CH_2), 27.9 (Me), 23.5 (CH_2), 19.5 (Me), 17.9 (CH_2), 16.7 (Me), 16.4 (Me), 15.9 (Me), 12.2 (Me). − MS: 558 (100.0) [M^+], 543 (8.2), 527 (3.5), 271 (4.6), 246 (4.9), 243 (2.4), 215 (4.4), 189 (7.6), 165 (53.2), 135 (33.6), 105 (64.4), 77 (9.3), 43 (5.0). − $C_{36}H_{46}O_5$ (558): calcd. C 77.39, H 8.30; found C 77.46, 8.32.

***c*-7′-(Benzoyloxy)-*t*-4a′,4b′,5′,6′,7′,8′,*t*-8a′,9′,10′,10a′-decahydro-5-hydroxy-*t*-2′,*c*-4b′,7,8′,8′,*c*-10a′-hexamethylspiro[benzofuran-2(3*H*),1′(2′*H*)-phenanthren]-3′(4′*H*)-one (15):** To a solution of **14** (15 mg, 0.03 mmol) in dry CH_2Cl_2 (1.5 mL) at −78 °C under argon was added dropwise 1 M boron tribromide solution in CH_2Cl_2 (1.0 mL). The mixture was stirred at −78 °C for 1 h and then warmed to −10 °C over 3 h. It was subsequently hydrolyzed with H_2O (1 mL). After stirring at room temp. for 16 h, the mixture was extracted with Et_2O and the extracts were washed with H_2O and brine. After concentration, the residue was purified by chromatography on silica gel, using *n*-pentane/Et_2O (1:1 → 1:2) as eluent, to give the spirobenzofuranyl product **15** (4 mg, 28%) as a white solid, together with some side products including **16** (5 mg) as a white solid. The side products were treated once more with 1 M boron tribromide in CH_2Cl_2, worked up as before and the products were subjected to preparative thin layer chromatography (Merck silica 60 F_{254}, 10×20 cm glass plates, 0.25 mm, *n*-pentane/Et_2O, 1:2) to afford an additional quantity of **15** (2 mg, 14%). Hence the total yield of **15** amounted to 42%. − IR (KBr): ṽ = 3399 m (br.), 2924 s, 2849.6 s, 1714 s, 1466 s, 1273 s, 1113 m, 1070 s, 1025 s, 712 m cm^{-1}. − ^{1}H NMR (400 MHz): δ = 8.02 (d, *J* = 7, 2 H, H−Ar), 7.53 (t, *J* = 7, 1 H, H−Ar), 7.42 (t, *J* = 7, 2 H, H−Ar), 6.42 (s, 1 H, H−Ar), 6.39 (s, 1 H, H−Ar), 4.74 (dd, *J* = 5, 11, H−C-7′), 4.31 (s, 1 H), 3.36 (d, *J* = 17, 1 H, H_a−C-3), 2.92 (d, *J* = 17, 1 H, H_b−C-3), 2.10 (s, Me), 2.60−0.85 (br. m, 13 H), 1.17 (s, Me), 1.01 (s, Me), 0.97 (s, Me), 0.90 (d, *J* = 6.5, Me−C-2′), 0.88 (s, Me). − MS: 530 (88.4) [M^+], 271 (16.1), 135 (37.0), 105 (100.0), 77 (15.7).

Synthesis of 21: To a solution of **20** (2.3 g, 8.0 mmol) in CH_2Cl_2 (30 mL) at room temp. under argon were added MEMCl (6.0 g, 48 mmol) and *i*Pr_2NEt (7.2 g, 56.0 mmol). After stirring at room temp. for 1 h, sat. Na_2CO_3 solution was added to the reaction mixture. It was then extracted with Et_2O, the extracts washed with water and brine, and concentrated. The residue was purified by chromatography on silica gel (*n*-pentane/Et_2O, 1:1) to give the MEM ether of **20** (2.4 g) as a mixture of inseparable isomers, which was used directly for the next step. − The above mixture was dissolved in methanol (90 mL), containing KOH (2.52 g, 45.0 mmol), and stirred at room temp. until conversion into the alcohol was complete (4 h) by TLC (*n*-pentane/ethyl acetate, 5:2). The reaction mixture was then diluted with H_2O and extracted with Et_2O. The combined organic extracts were washed successively with 5% HCl, sat. $NaHCO_3$, water, and brine. After concentration, the residue was purified by chromatography on silica gel (*n*-pentane/ethyl acetate, 5:2) to give 2α-**21** (787 mg, 30%) as a colorless oil and 2β-**21** (997 mg, 38%) as long white needles after crystallization from *n*-pentane.

[*c*-6-(2-Methoxyethoxymethoxy)-*t*-2,5,5,*c*-8a-tetramethyl-1,2,3,4,*t*-4a,5,6,7,8,8a-decahydronaphthalen-*r*-1-yl]methanol (2α-21): IR (film): ṽ = 3447s (br.), 2938s (br.), 1457 m, 1387 m, 1366 m, 1199 w, 1169 m, 1110 s, 1049 s, 969 m, 849 w cm^{-1}. − ^{1}H NMR (270 MHz): δ = 4.79 [d, *J* = 7, 1 H, OC*H*HO (MEM)], 4.65 [d, *J* = 7, 1 H, OCH*H*O (MEM)], 3,76−3.54 (br. m, 2 H, H−C-9), 3.70 [m, CH_2 (MEM)], 3.50 [m, CH_2 (MEM)], 3.34 [s, Me (MEM)],

3.09 (dd, J = 4, 12, H−C-6), 1.90−0.50 (br. m, 12 H), 0.92 (d, J = 7, Me−C-2), 0.89 (s, Me), 0.84 (s, Me), 0.75 (s, Me). − ^{13}C NMR (67.9 MHz): δ = 94.8 [O*CH*$_2$O (MEM)], 84.9 (C-6), 71.7 [CH_2 (MEM)], 66.9 [CH_2 (MEM)], 61.6 (CH_2), 60.1 (CH), 58.9 [Me (MEM)], 54.4 (CH), 38.6 (C), 37.3 (CH_2), 37.1 (C), 36.7 (CH_2), 30.5 (C-2), 28.2 (Me), 24.0 (CH_2), 21.5 (CH_2), 20.8 (Me), 16.3 (Me), 15.5 (Me). − MS: 328 (< 0.1) [M^+], 298 (1.1), 252 (6.7), 239 (10.7), 222 (60.4), 205 (11.9), 183 (13.7), 165 (29.7), 123 (19.9), 109 (53.1), 89 (100.0), 69 (31.9), 59 (89.8).

[*c*-6-(2-Methoxyethoxymethoxy)-*c*-2,5,5,*c*-8a-tetramethyl-1,2,3,4,*t*-4a,5,6,7,8,8a-decahydronaphthalen-*r*-1-yl]methanol (2β-21): M.p. 68−69 °C. − IR (KBr): ṽ = 3331s (br.), 2929 s, 2851 s, 1457 m, 1389 m, 1366 w, 1202 w, 1168 m, 113 s, 1091 s, 1048 s, 1028 s, 984 m, 966 m, 926 w, 853 w cm^{-1}. − ^{1}H NMR (270 MHz): δ = 4.80 [d, J = 7, 1 H, OC*H*HO (MEM)], 4.67 [d, J = 7, 1 H, OCH*H*O (MEM)], 3.85−3.50 (br. m, 2 H, H−C-9), 3.70 [m, CH_2 (MEM)], 3.53 [m, CH_2 (MEM)], 3.36 [s, Me (MEM)], 3.10 (dd, J = 4, 12, H−C-6), 2.20−0.70 (br. m, 12 H), 0.93 (s, Me), 0.92 (d, J = 8, Me−C-2), 0.83 (s, Me), 0.76 (s, Me). − ^{13}C NMR (67.9 MHz): δ = 94.9 [O*CH*$_2$O (MEM)], 84.8 (C-6), 71.8 [CH_2 (MEM)], 67.0 [CH_2 (MEM)], 60.8 (CH_2), 59.0 [Me (MEM)], 55.9 (CH), 55.5 (CH), 38.7 (C), 38.1 (CH_2), 37.0 (C), 34.4 (CH_2), 28.1 (C-2), 28.2 (Me), 23.8 (CH_2), 17.1 (CH_2), 17.0 (Me), 16.3 (Me), 15.5 (Me). − MS: 328 (< 0.1) [M^+], 298 (1.0), 252 (6.9), 239 (7.7), 222 (47.2), 205 (10.1), 165 (29.7), 123 (19.4), 109 (46.7), 89 (100.0), 69 (31.0), 59 (82.8). − $C_{19}H_{36}O_4$ (328): calcd. C 69.47, H 11.05; found C 69.55, H 11.09.

***c*-2-(2-Methoxyethoxymethoxy)-1,1,*c*-4a,*c*-6-tetramethyl-5-methylene-1,2,3,4,4a,5,6,7,8,*t*-8a-decahydronaphthalene (6α-22):** To a solution of 2α-**21** (203 mg, 0.62 mmol) in THF (3 mL) containing *o*-nitrophenylseleno cyanate (504 mg, 2.22 mmol) at room temp. under argon was added slowly tri-*n*-butylphosphane (450 mg, 2.22 mmol). The mixture was stirred at room temp. until the reaction was complete (4 h) by TLC (*n*-pentane/Et_2O, 1:1). After removal of the solvent, the residue was transferred to a silica gel column and chromatographed, using *n*-pentane/Et_2O (1:1) as eluent, to give a crude selenide derivative of 2α-**21** (identification by ^{1}H NMR) as a yellow oil. − To a solution of the selenide of 2α-**21** in THF (4 mL) was added dropwise an excess of 30% hydrogen peroxide (ca. 10 equiv., 6.2 mmol, 0.7 mL) at 0 °C. After addition was complete, the reaction mixture was warmed to room temp. and stirred for another 2.5 h, then diluted with water and extracted with Et_2O. The extracts were washed with brine and concentrated. The residue was purified by chromatography on silica gel (*n*-pentane/Et_2O, 1:1) to afford olefin 2α-**22** (155 mg) as a colorless oil in 80% overall yield from 2α-**21**. − ^{1}H NMR (400 MHz): δ = 4.81 [d, J = 7, 1 H, OC*H*HO (MEM)], 4.67 [d, J = 7, 1 H, OCH*H*O (MEM)], 4.58 (s, 1 H, H_a−C-9), 4.47 (s, 1 H, H_b−C-9), 3.70 [m, CH_2 (MEM)], 3.52 [m, CH_2 (MEM)], 3.35 [s, Me (MEM)], 3.08 (dd, J = 4, 11, H−C-6), 2.30−0.85 (br. m, 10 H), 1.01 (s, Me), 0.96 (d, J = 6, Me−C-2), 0.89 (s, Me), 0.80 (s, Me). − ^{13}C NMR (100.6 MHz): δ = 164.0 (C-1), 100.1 (C-9), 94.9 [O*CH*$_2$O (MEM)], 85.0 (C-6), 71.8 [CH_2 (MEM)], 66.9 [CH_2 (MEM)], 59.0 [Me (MEM)], 53.5 (C-4a), 39.8 (C), 39.1 (C), 37.3 (CH_2), 35.6 (CH_2), 33.1 (C-2), 28.1 (Me), 24.5 (CH_2), 21.9 (CH_2), 20.8 (Me), 19.1 (Me), 16.2 (Me).

***c*-6-(2-Methoxyethoxymethoxy)-*t*-2,5,5,*c*-8a-tetramethyl-1,2,3,4,*t*-4a,5,6,7,8,8a-decahydronaphthalen-1-one (2α-23):** A mixture of $RuO_2{\cdot}2H_2O$ (5 mg), $NaIO_4$ (336 mg, 1.56 mmol), and CCl_4/MeCN/H_2O (2:2:3) (3.5 mL) was stirred for 10 min at room temp.. The initial black color disappeared. Vinyl compound 2α-**22** (80 mg, 0.26 mmol) was then added, and the resulting black mixture was stirred at room temp. for 20 h. TLC (*n*-pentane/Et_2O, 1:1) analysis showed complete conversion of 2α-**22**. Water was added, and the mixture extracted with CH_2Cl_2. After concentration, the residue was purified by chromatography on silica gel (*n*-pentane/Et_2O, 1:1) to give ketone 2α-**23** (48 mg, 60%) as a colorless oil. − The same procedure as described for the preparation of 2α-**23** afforded 2β-**23** in 50% overall yield from 2β-**21**. Treatment of 2β-**23** with a 1 M solution of sodium methoxide in methanol at room temp. caused rapid (within 5 min) and complete conversion into 2α-**23**. − IR (film): ṽ = 2933 s, 2874 s, 1706 s, 1457 s, 1363 m, 1200 w, 1169 m, 1109 m, 1051 s, 987 s cm^{-1}. − ^{1}H NMR (400 MHz): δ = 4.80 [d, J = 7, 1 H, OC*H*HO (MEM)], 4.66 [d, J = 7, 1 H, OCH*H*O (MEM)], 3.69 [m, CH_2 (MEM)], 3.51 [m, CH_2 (MEM)], 3.35 [s, Me (MEM)], 3.06 (dd, J = 5, 11, H−C-6), 2.70−1.00 (br. m, 10 H), 1.11 (s, Me), 0.94 (s, Me), 0.93 (d, J = 6, Me−C-2), 0.87 (s, Me). − ^{13}C NMR (100.6 MHz): δ = 216.0 (C-1), 94.9 [O*CH*$_2$O (MEM)], 84.2 (C-6), 71.8 [CH_2 (MEM)], 67.1 [CH_2 (MEM)], 59.0 [Me (MEM)], 53.5 (CH), 48.2 (C), 39.8 (CH), 39.5 (C), 35.5 (CH_2), 31.2 (CH_2), 27.9 (Me), 23.7 (CH_2), 21.0 (CH_2), 18.8 (Me), 16.6 (Me), 14.8 (Me). − MS: 312 (6.1) [M^+], 236 (6.5), 230 (16.0), 223 (7.5), 207 (9.4), 180 (7.8), 124 (12.7), 89 (100.0), 69 (10.4), 59 (67.5).

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