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Synthesis of Chiral *trans-syn-cis* and *trans-anti-trans* [6.6.6] Tricycles by Transannular Diels-Alder Reaction

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Abstract

Stereocontrolled asymmetric synthesis and transannular Diels-Alder (TADA) reaction of a 14-membered *trans-cis-cis* (TCC) macrocyclic trienone with an activated dienophile leading to an A.B.C [6.6.6] tricycle having one angular methyl group is reported. The results of thermal and Lewis acid catalyzed TADA reaction are discussed.
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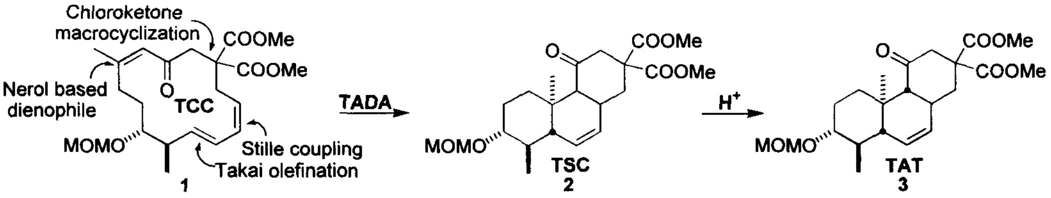
1. Introduction

Our fundamental investigation on the transannular Diels-Alder (TADA) reaction has proved that this strategy is a powerful tool in constructing polycyclic frameworks[1]. Recently, we have reported[2] the diastereoselective transformation of a TCC macrocyclic trienone with an activated dienophile into a *trans-syn-cis* (TSC) tricycle having two angular methyl groups thus so making the quassinoid family available. Since the diastereoselectivity highly depends on the neighboring functionalities of the strategic event, it was desirable to examine the generality and



Scheme 1

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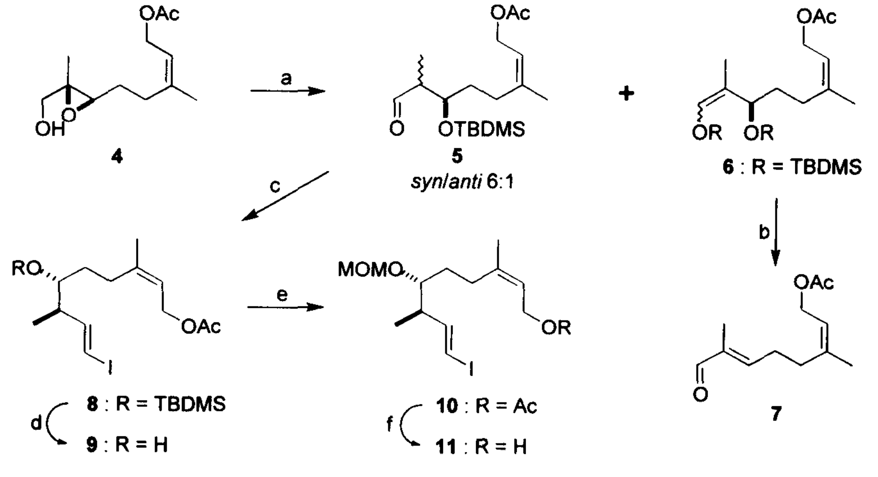
limitations of this transformation by decreasing the number of angular methyl groups. Now, we report the synthesis of TCC macrocyclic trienone **1** (Scheme 1), its TADA reaction which generates TSC tricycle **2** and its subsequent isomerization to produce TAT tricycle **3**. Having the angular methyl group only at C-10, these optically active tricycles can serve as key intermediates for the asymmetric synthesis of a number of natural di- and triterpenes.

2. Results and discussion

2.1. Synthesis of macrocycle 1

The synthesis of macrocycle **1** follows the general strategy reported recently[2]. However, several important modifications were carried out to simplify the synthetic route. Nerol was used again as starting material to build the activated dienophile although in a different manner. The rearrangement of epoxysilylethers into *syn*-aldols[3] offers a simple access to the necessary chiral groups. The diene system was also built differently using a Takai olefination[4] followed by Stille coupling[5]. Finally, two successive malonate alkylations, first with an allylic chloride and then with a chloroketone were applied again to construct the macrocycle (Scheme 1).

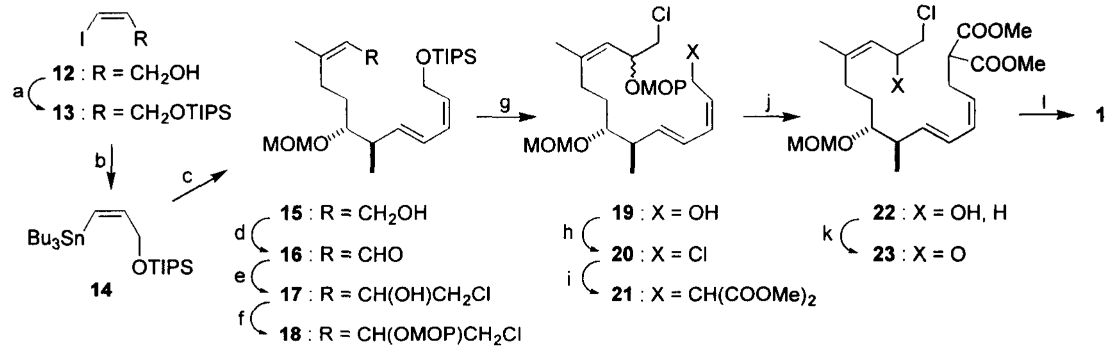
The synthesis was started with the (+)-enantiomer of the known epoxyalcohol **4** available from nerol in three steps[6] (Scheme 2). Following Jung's protocol,[3] adding *tert*-butyldimethylsilyl triflate (TBDMSOTf) to chiral epoxide **4** at –40°C did indeed catalyze the rearrangement of epoxide **4** to aldehyde **5** obtained with an excellent yield. Unfortunately, the diastereoselectivity did not reach the reported high value, our de was only 71%. A small amount (2%) of silyl enol ether **6** was also isolated, *in situ* hydrolysis of which could be responsible for



Scheme 2: a) TBDMSOTf, *s*-collidine, mol. sieve, CH_2Cl_2, -40°C, 48 h, 91% (**5**/**6**=91:2); b) HCl (1N), THF, rt, 1 h, 100%: c) $CrCl_2$, CHI_3, THF, 60°C, 20 min, 70%; d) TBAF, THF, rt, 2 h, 98%, then separation; e) MOMCl, DIPEA, CH_2Cl_2, 0°C-rt, 4h, 91%; f) DIBALH, CH_2Cl_2, -78°C, 1 h, 97%.

the scrambling at the methyl center in **5**. Moreover, the structure of the very unstable **6** was further established by hydrolyzing this compound to enal **7**. The inseparable mixture of aldehyde **5** was then used for the subsequent Takai olefination[4]. Thus, applying chromium(II) chloride and iodoform in a THF/DMF mixture, aldehyde **5** was transformed in 70% yield to the very sensitive *trans*-vinyl iodide **8**. Immediate desilylation with tetrabutylammonium fluoride (TBAF) gave alcohol **9** as a mixture of stereoisomers in 98% yield. Gratifyingly, at this stage, the isomers could be easily separated by silica gel chromatography. The major alcohol *syn*-**9** was protected as MOM ether **10**, then acetate deprotection with diisobutylaluminum hydride (DIBALH) provided alcohol **11**.

Here the stage was set to build the *cis*-olefin of the diene system by Stille coupling. Synthesis of the required vinylstannane was accomplished in two steps starting from the known (*Z*)-iodopropenol **12** (Scheme 3) available in two steps from commercial ethyl propiolate[7]. Accordingly, after protection, iodosilylether **13** was transmetallated with tributyltin chloride to vinylstannane **14** *via* a vinyllithium intermediate with an overall yield of 68%. The Stille cross coupling was performed under standard conditions with bis(acetonitrile)dichloropalladium(II) to yield triene **15**. It was elongated, *via* aldehyde **16** obtained by Swern oxidation[8], with *in situ* generated chloromethyllithium[9] to an epimeric mixture of chlorohydrin **17** in 85% yield. The alcohol formed was temporaly masked as methoxyisopropyl (MOP) ether **18**. After desilylation, alcohol **19** was chlorinated by Schreiber's method[10] then chloride **20** was subjected to a nucleophilic displacement with the sodium salt of the connector to obtain malonate **21** with an overall yield of 61% for the last four steps. Finally, deprotection of the MOP ether to chlorohydrin **22** and oxidation with Dess-Martin periodinane[11] provided chloroketone **23**, the substrate for macrocyclization. This last step was performed by a five-hour syringe pump

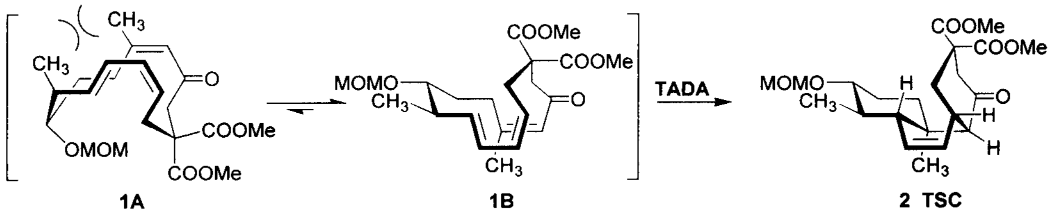


Scheme 3: a) TIPSOTf, 2,6-lutidine, THF, 0°C, 1 h, 90%; b) *n*-BuLi, THF, -78°C then Bu_3SnCl -78°C→rt, 1.5 h, 76%; c) $(MeCN)_2PdCl_2$, THF/DMF, **11**, rt, 2 h, 85%; d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 1 h then Et_3N, rt, 85%; e) ICH_2Cl, *n*-BuLi, THF, -78°C, 1 h, 85%; f) 2-methoxypropene, PPTS, CH_2Cl_2, rt, 30 min; g) TBAF, THF, 0°C→rt, 2 h, 80% over 2 steps; h) hexachloroacetone, PPh_3, THF, -20°C, 1 h; i) $CH_2(COOMe)_2$, NaH, THF/DMF, rt, then **20**, 1 h; j) HCl (0.1N), THF, rt, 10 min, 77% over 3 steps; k) Dess-Martin periodinane, CH_2Cl_2, rt, 30 min, 90%; l) Cs_2CO_3, MeCN, syringe pump addition of **23** over 5 h, c_{final}: 0.9mM, 83%.

addition of the substrate to a Cs_2CO_3 suspension in acetonitrile at 45°C with a final concentration of 1.7 mM to afford macrocycle **1** in an excellent yield of 83%.[2]

2.2. TADA studies of macrocycle 1

Interestingly, heating macrocyclic trienone **1** at 230°C for 24 h led to a clean transformation into tricycle **2**. Consequently, TADA reaction of macrocycle **1** shows the same high diastereoselectivity as our precedent[2], in spite of the fact that the forming tricycle **2** has only one angular methyl group. The TSC stereochemistry of the product was confirmed by single crystal X-ray analysis. This result can be explained by considering the fact that, with TCC macrocyclic trienone **1**, the only way to reach the *chair-boat-chair* conformation required in the transition state for the TADA reaction, the enone system must be severely twisted, thus deconjugated. This factor requires further activation, thus so, has a negative effect on the reaction rate, as a result, this TADA reaction can only be performed at high temperature. However, even at this high temperature, the diastereoselectivity is perfect, the only operative rotamer being **1B**, which has the two substituents in the pseudo equatorial orientation (Scheme 4).



Scheme 4

In principle, the addition of a Lewis acid should reduce the energy barrier associated with the TADA reaction when an activated dienophile is involved. However, similarly to our previous study[2], we have found that this is not the case here. We could not induce TADA reaction with Lewis acids. Even heating, with a variety of Lewis acids produced only unidentified decomposition products. Since Lewis acids should further increase the inherent conjugation, they have a detrimental effect on the reaction.

Finally, when TSC tricycle **2** was heated in the presence of potassium carbonate in metanol, it was completely epimerized to the thermodynamically more stable TAT tricycle **3** (Scheme 1).

3. Conclusion

Investigation of the TADA reaction of chiral 14-membered TCC macrocyclic trienone **1** having an activated dienophile revealed its clean transformation to TSC tricycle **2**. This product could easily be isomerized to the thermodynamically more stable TAT tricycle **3** under acid or base catalyzed conditions. It was also found that, having an enone dienophile in this series of TCC macrocycles, the conjugation, in fact, deactivated the dienophile due to conformational restrictions, rather than activating it as it might have been expected. On the other hand, enolization of the very same ketone functionality makes the thermodynamically favored TAT tricycle **3** available, which is impossible directly by the TADA reaction.[1]

Finally, since epoxyalcohol **4** is available in both enantiomeric forms, tricycles **2** or **3** can serve as a respective TSC or TAT key intermediate in the asymmetric total synthesis of natural diterpenes having related frameworks.

4. Experimental

All reactions were performed under nitrogen atmosphere with oven (150°C) or flame-dried glasswares. All solvents were distilled prior to use; diethyl ether and tetrahydrofuran were dried by distilling over sodium benzophenone ketyl. Toluene, acetonitrile, dichloromethane and dimethylformamide were distilled over calcium hydride. Cesium carbonate was flame-dried under reduced pressure before use. Analytical and preparative thin-layer chromatography were carried out on precoated glass plates (0.25 mm) with 60 F-250 silica gel (Merck). Material were visualized with an ultraviolet lamp and/or by spraying with a solution of phosphomolybdic acid (10% in ethanol) followed by heating on a hot plate. Column chromatography was performed with silica gel 60 (230-400 mesh, Merck). Infrared (IR) spectra were taken on a Perkin-Elmer 1600 FT-IR spectrometer. The optical rotation ($[\alpha]_D$) measurement were obtained with a Perkin-Elmer 141 polarimeter with 1dm length of cellpath. Concentration are given in g/100 mL. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-300 instrument. The following abbreviations were used: s: singulet, d: doublet, t: triplet, q: quartet, dd: doublet of doublet, m: multiplet, br: broad. Chemical shifts are reported in δ values relative to chloroform (7.26 ppm) for ^{1}H-NMR and (77 ppm) for ^{13}C-NMR as internal standard. Where necessary COSY and NOESY and J-resolved experiments were performed. Mass spectra (MS) and high resolution mass spectra (HR-MS) were obtained on a VG Micromass ZAB-2F instrument (70 eV). Melting points (uncorrected) were determined on a Büchi M-50 or a Reichert apparatus. X-ray crystallographic analyses were performed on an Enraf-Nonius CAD-4 diffractometer.

(2*R*,3*R*)-, (2*S*,3*R*)-(*Z*)-8-Acetoxy-3-(*tert*-butyldimethylsilyloxy)-2,6-dimethyl-6-octenal (5) and (1*E*,6*Z*)-(3*R*)-8-acetoxy-1,3-bis(*tert*-butyldimethylsilyloxy)-2,6-dimethyl-1,6-octa-diene (6): To a mixture of alcohol (+)-**4** ($[\alpha]_D^{25}$:+10.7° (c: 2, CH_2Cl_2), (for (-)-**4**)[6], $[\alpha]_D^{25}$:-11°) (2.0 g, 8.85 mmol), molecular sieves (4Å, 1 g) and 2,4,6-collidine (2.1 mL, 15.93 mmol) in CH_2Cl_2 (5 mL), TBMSOTf (3.56 mL, 15.48 mmol) was added rapidly at –40°C. The reaction mixture was stirred for 48 h at -40°C then 2,4,6-collidine (2.1 mL) and TBMSOTf (3.56 mL) were added again rapidly. It was stirred for an additional 30 min, quenched with NH_4Cl (10 mL, sat.) and extracted with CH_2Cl_2 and ether (2x20 mL). The extracts were dried over $MgSO_4$, filtered and evaporated. Chromatography (hexane/ethyl acetate, 95:5) of the residual material gave enolether **6** (100 mg, 2%) and a mixture of two diastereomers of **5** (2.75 g, 91%, *syn*/*anti* 6:1 by ^{1}H-NMR) as colorless oils. **6:** IR (neat, cm^{-1}, ν): 2931, 2857, 1729, 1669, 1463, 1257, 1056 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.21, (1H, s, $SiOC\underline{H}=C(CH_3)$), 5.33 (1H, t, J: 7.0 Hz, $C(CH_3)=C\underline{H}CH_2$), 4.54 (2H, d, J: 7.0 Hz, $C\underline{H}_2OAc$), 3.89 (1H, t, J: 6.5 Hz, $C\underline{H}OSi$), 2.15-2.05 (1H, m, $C\underline{H}HCH_2C(CH_3)=CH$), 2.04 (3H, s, $C\underline{H}_3CO_2$), 1.95-1.85 (1H, m, $CH\underline{H}CH_2C\text{-}(CH_3)=CH$), 1.75 (3H, s, $C(C\underline{H}_3)=CH$), 1.65-1.45 (5H, m, $SiOCH=C(C\underline{H}_3)$, $C\underline{H}_2C(CH_3)=CH$), 0.95-0.85 (18H, m, $(SiC(C\underline{H}_3)_3)_2$), 0.15-0.05 (12H, m, $(Si(C\underline{H}_3)_2)_2$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 170.9, 143.2, 136.1, 119.4, 118.6, 109.5, 74.8, 73.9, 62.7, 60.9, 35.2, 28.6, 28.1, 25.8, 25.6, 23.5, 21.0, 18.2, 8.0, -4.6, -4.8, -5.0, -5.3, -5.5. MS (m/e): 457 (MH$^+$); HR-MS: calcd. for $C_{24}H_{49}O_4Si_2$: 457.3169; found: 457.3159. aldehydes **5:** IR (neat, cm^{-1}, ν): 2956, 2886, 1732, 1463, 1252, 1024. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 9.77, (1H, s, $C\underline{H}O$), 5.36 (1H, t, J: 7.5 Hz, $C(CH_3)=C\underline{H}$), 4.54 (2H, d, J: 7.5 Hz, $C\underline{H}_2OAc$), 4.09 (1H, dt, J: 4.0 and 6.5 Hz, $C\underline{H}OSi$), 2.49 (1H, m, $C\underline{H}CH_3$), 2.25-2.15 (1H, m, $C\underline{H}HCHOSi$), 2.04 (3H, s, $C\underline{H}_3CO_2$), 2.05-1.90 (1H, m, $CH\underline{H}CHOSi$), 1.76 (3H, s, $C(C\underline{H}_3)=CH$), 1.72-1.45 (2H, m, $C\underline{H}_2C(CH_3)=CH$), 1.08 (3H, d, J: 7.0 Hz, $CHC\underline{H}_3$), 0.87 (9H, m, $SiC(C\underline{H}_3)_3$), 0.07 (6H, 2s, $Si(C\underline{H}_3)_2$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 204.6, 170.7, 142.0, 119.2, 73.0, 71.9, 60.6, 51.0, 33.1, 28.3, 25.6, 23.3, 17.8, 7.7, -3.7, -4.4, -4.8. MS (m/e): 360 $(M+NH_4)^+$; HR-MS: calcd. for $C_{18}H_{38}NO_4Si$: 360,2570; found: 360.2564.

(2*E*,6*Z*)-8-Acetoxy-2,6-dimethyl-2,6-octadienal (7): To a solution of enol ether **6** (830 mg, 1.8 mmol) in THF (25 mL), HCl (1.0 N, 15 mL) was added at 23°C. It was stirred for 1 h, neutralized with $NaHCO_3$ (25 mL, sat.) and extracted with ether. The extract was dried over $MgSO_4$ and concentrated. Chromatography (hexane/ethyl acetate, 7:3) afforded compound **7** (375 mg, 100 %) as a colorless oil. IR (neat, cm^{-1}, ν): 3014, 2976, 1732, 1682, 1644, 1445, 1240 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 9.39 (1H, s, $C\underline{H}O$), 6.45 (1H, t, J: 7.5 Hz, $CHOC(CH_3)=C\underline{H}$), 5.43, (1H, t, J: 7.5 Hz, $C(CH_3)=C\underline{H}CH_2$), 4.56 (2H, d, J: 7.5 Hz, $C\underline{H}_2OAc$), 2.47 (2H, q, J: 7.5 Hz, $C\underline{H}_2CH_2C(CH_3)=CH$), 2.31 (2H, t, J: 7.5 Hz, $C\underline{H}_2C(CH_3)=CH$), 2.04 (3H, s, $C\underline{H}_3CO_2$), 1.79 (3H, s, $CHOC(C\underline{H}_3)$), 1.75 (3H, s, $C(C\underline{H}_3)=CH$); ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 195.0, 170.9, 153.0, 140.8, 139.7, 120.5, 60.6, 30.4, 27.2, 23.1, 20.9, 9.1. MS (m/e): 228 (MNH_4^+), 211 (MH$^+$); HR-MS: calcd. for $C_{12}H_{19}O_3$: 211.1334; found: 211.1331.

(1*E*,7*Z*)-(3*R*,4*R*)-9-Acetoxy-3,7-dimethyl-1-iodo-1,7-nonadien-4-ol (*syn*-9) and (1*E*,7*Z*)-(3*S*,4*R*)-9-acetoxy-3,7-dimethyl-1-iodo-1,7-nonadien-6-ol (*anti*-9): To $CrCl_2$ (15.05 g, 122.5

mmol) in THF (30 mL), a solution of iodoform (14.46 g, 36.75 mmol) and aldehyde **5** (4.19 g, 12.25 mmol) in dioxane (180 mL) was added at 0°C by canula. The resulting mixture was heated for 20 min at 60°C and quenched with NaCl (200 mL, sat.). The chromium salts were removed by filtration over a medium porosity paper filter and the filtrate was extracted with a mixture of ether/ethyl acetate (1:1). The extract was filtered over a silica pad (10 cm) and evaporated. The temperature of the water bath on the rotary evaporator should not exceed 25°C to avoid thermal decomposition of the product. Chromatography (hexane/ethyl acetate, 95:5) of the crude material afforded a mixture of diasteromers of **8** (4.00 g, 70 %) as a pale yellow oil. This sensitive material was used immediately in the next step without characterization. Thus, to a solution of iodide **8** (4.0 g, 8.58 mmol) in THF (50 mL), TBAF (18.9 mL, 18.9 mmol, 1.0 M in THF) was added at 23°C. It was stirred for 2 h, neutralized with NH_4Cl (sat.) and extracted with ether. The extract was dried over $MgSO_4$, filtered and evaporated. The crude material was purified by chromatography (hexane/ethyl acetate, 95:5) to provide both isomers as colorless oils. Less polar diasteromer was *anti*-**9** (450 mg, 15.0 %): $[\alpha]_D^{25}$: -20.0° (c: 2.0 in CH_2Cl_2). IR (neat, cm^{-1}, ν): 3599, 3528, 2970, 2875, 1730, 1452, 1240, 1022. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.51 (1H, dd, J: 14.5 8.5 Hz, C$\underline{H}$=CHI), 6.09 (1H, d, J: 14.5 Hz, CH=C$\underline{H}$I), 5.37 (1H, t, J: 7.5 Hz, $C(CH_3)=C\underline{H}$), 4.65-4.50 (2H, m, $C\underline{H}_2OAc$), 3.40-3.35 (1H, m, C$\underline{H}$OH), 2.35-2.10 (3H, m, $C\underline{H}(CH_3)CH=CHI$, $C\underline{H}_2C(CH_3)=CH$), 2.05 (3H, s, $C\underline{H}_3CO_2$), 1.75 (3H, s, $C(C\underline{H}_3)=CH$), 1.60-1.40 (2H, m, $C\underline{H}_2CH_2C(CH_3)=CH$), 1.05 (3H, d, J: 7.0 Hz, $CH(C\underline{H}_3)$-CH=CH). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 171.1, 147.8, 142.2, 119.7, 75.9, 73.4, 61.0, 46.8, 32.4, 28.0, 23.2, 21.1, 16.0. MS (m/e): 370 (MNH_4^+); HR-MS: calcd. for $C_{13}H_{25}NO_3I$: 370.0879; found: 370.0874. More polar diasteromer was *syn*-**9** (2.50 g, 83 %): $[\alpha]_D^{25}$: +22.8° (c: 2.0 in CH_2Cl_2). IR (neat, cm^{-1}, ν): 3526, 3018, 2971, 2876, 1731, 1240, 1021. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.49 (1H, dd, J: 14.5 and 8.5 Hz, C$\underline{H}$=CHI), 6.09 (1H, d, J: 14.5 Hz, CH=C$\underline{H}$I), 5.37 (1H, t, J: 7.5 Hz, $C(CH_3)=C\underline{H}$), 4.70-4.50 (2H, m, $C\underline{H}_2OAc$), 3.45-3.30 (1H, m, C$\underline{H}$OH), 2.35-2.05 (3H, m, $C\underline{H}(CH_3)CH=CH$, $C\underline{H}_2C(CH_3)=CH$), 2.05 (3H, s, $C\underline{H}_3CO_2$), 1.74 (3H, s, $C(C\underline{H}_3)=CH$), 1.65-1.35 (2H, m, $C\underline{H}_2CH_2C(CH_3)=CH$), 1.03 (3H , d, J: 7.0 Hz, $CH(C\underline{H}_3)CH=CH$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 171.1, 148.6, 142.1, 119.7, 75.5, 73.2, 61.0, 46.7, 32.0, 28.1, 23.2, 21.0, 14.3. MS (m/e): 370 (MNH_4^+); HR-MS: calcd. for $C_{13}H_{25}NO_3I$: 370.0879; found: 370.0874.

(2*Z*,8*E*)-(6*R*,7*R*)-3,7-Dimethyl-9-iodo-6-(methoxymethoxy)-2,8-nonadien-1-ol (11): To a solution of alcohol *syn*-**9** (4.24 g, 12.03 mmol) in CH_2Cl_2 (30 mL), diisopropylethylamine (DIPEA) (6.30 mL, 36.09 mmol) and chloromethyl methyl ether (MOMCl) (3.65 mL, 48.13 mmol) were added sequentially at 0°C. It was stirred for 4 h at 23°C, quenched with NH_4Cl (sat.) and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, filtered and concentrated. Chromatography (hexane/ethyl acetate, 4:1) of the residue afforded acetate **10** (4.58 g, 96 %) as a colorless oil to be used immediately in the next step. To a solution of acetate **10** (4.53 g, 11.44 mmol) in CH_2Cl_2, DIBALH (17.2 mL, 17.2 mmol, 1.0 M in CH_2Cl_2) was added dropwise over 15 min at -78°C. After 1 h stirring at -78°C, it was neutralized with a Na,K-tartrate solution (200 mL, 1.0 M), stirred for another hour at 23°C then extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, filtered and concentrated. Chromatography (hexane/ethyl acetate, 3:2) of the residue afforded alcohol **11** (3.92 g, 97%) as a colorless oil. $[\alpha]_D^{25}$: +41.4° (c: 2.0 in CH_2Cl_2). IR (neat, cm^{-1}, ν): 3410, 2934, 2883, 1449, 1377, 1100. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.54 (1H, dd, J: 14.5 and 7.5 Hz, $C\underline{H}=CHI$), 6.07 (1H, d, J: 14.5 Hz, $CH=C\underline{H}I$), 5.44 (1H, t, J: 7.0 Hz, $C(CH_3)=C\underline{H}$), 4.65 (2H, s, $OC\underline{H}_2OCH_3$), 4.10 (2H, m, $C\underline{H}_2OAc$), 3.40-3.35 (4H, m, $OCH_2OC\underline{H}_3$, $C\underline{H}OMOM$), 2.55-2.45 (1H, m, $C\underline{H}(CH_3)CH=CH$), 2.13 (2H, t, J: 8.0 Hz, $C\underline{H}_2C(CH_3)=CH$), 1.73 (3H, s, $C\underline{H}_3CO_2$), 1.65-1.45 (2H, m, $C\underline{H}_2CH_2C(CH_3)=CH$), 1.02 (3H, d, J: 7.0 Hz, $CH(C\underline{H}_3)CH=CH$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 147.9, 139.0, 124.6, 96.0, 80.6, 75.3, 58.5, 55.7, 43.5, 29.4, 27.5, 23.2, 14.6. MS (m/e): 337 (M^+-OH); HR-MS: calcd. for $C_{13}H_{22}O_2I$: 337.0664; found: 337.0656.

(*Z*)-1-Iodo-3-triisopropylsilyloxypropene (13): To a solution of iodopropenol **12**[7] (15 g, 81.5 mmol) in THF (100 mL), 2,6-lutidine (12 mL, 106 mmol) and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) (32 mL, 97.8 mmol) were added at 0°C. It was stirred for 1 h at 0°C, quenched with NH_4Cl (100 mL, sat.) and extracted with ether. The extract was dried over $MgSO_4$, filtered and concentrated. Chromatography (hexane) of the crude product afforded **13** (24.9 g, 90%) as a colorless oil. IR (neat, cm^{-1}, ν): 2865, 1463, 1278, 1105. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.46 (1H, dt, J: 7.5 and 5.0 Hz, $ICH=C\underline{H}$), 6.21 (1H, dt, J: 7.5 and 2.0 Hz, $IC\underline{H}=CH$), 4.31 (2H, dd, J: 5.0 and 2.0 Hz, $C\underline{H}_2OTIPS$), 1.08 (21H, m, $Si(C\underline{H}(C\underline{H}_3)_2)_3$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 141.6, 79.5, 67.2, 17.9, 11.9. MS (m/e): 297 (M^+-C_3H_7); HR-MS: calcd. for $C_9H_{18}OSiI$: 297.0172; found: 297.0180.

(*Z*)-1-Tributylstannyl-3-triisopropylsilyloxypropene (14): To a solution of **13** (1.0 g, 2.94 mmol) in THF (25 mL), *n*-butyllithium (2.0 mL, 3.23 mmol, 1.6 M in hexane) was added slowly at -78°C. After 1 h stirring at -78°C, tributyltin chloride (1.75 mL, 6.47 mmol) was added. It was stirred for an additional 30 min at –78 °C and 1 h at 23°C, neutralized with NH_4Cl (50 mL, sat.) and extracted with ether. The extract was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography (hexane 100 %) to afford stannane **14** (1.11 g, 76 %) as a colorless oil. IR (neat, cm^{-1}, ν): 2927, 2865, 1462, 1373, 1253, 1097, 1013, 881, 808, 681. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.63 (1H, dt, J: 13.0 and 6.0 Hz, $CH=C\underline{H}CH_2$), 5.94 (1H, d, J: 13.0 Hz, $SnC\underline{H}=CH$), 4.18 (2H, d, J: 6.0 Hz, $C\underline{H}_2OTIPS$), 1.60-1.45 (6H, m, $Sn(CH_2C\underline{H}_2CH_2CH_3)_3$), 1.36-1.25 (6H, m, $Sn(CH_2CH_2C\underline{H}_2$-$CH_3)_3$), 1.08 (21H, m,

$Si(C\underline{H}(C\underline{H}_3)_2)_3)$, 0.95-0.85 (15H, m, $Sn(C\underline{H}_2CH_2CH_2C\underline{H}_3)_3$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 148.4, 128.8, 67.2, 29.2, 27.3, 18.0, 13.6, 12.1, 10.3. MS (m/e): 447 (M^+-C_4H_9). HR-MS: calcd. for $C_{20}H_{43}OSiSn$: 447.2105; found: 447.2099.

(2*Z*,8*E*,10*Z*)-(6*R*,7*R*)-3,7-Dimethyl-6-(methoxymethoxy)-12-triisopropylsilyloxydodeca-2,8,10-trienol (15): To a solution of iodide **11** (2.62 g, 7.41 mmol) and stannane **14** (4.84 g, 9.63 mmol) in THF/DMF (100 mL, 1:4, degased with 5 freeze-thaw cycles), bis(acetonitrile) dichloropalladium(II) (96 mg, 0.370 mmol) was added. The mixture was stirred for 2 h at 23°C, quenched with NH_4OH (100 mL, 10 %) and extracted with ether. The extract was dried over $MgSO_4$, filtered and concentrated. Chromatography (hexane/ethyl acetate 7:3) of the crude product afforded trienol **15** (2.78 g, 85 %) as a yellow oil. $[\alpha]_D^{25}$: +19.2° (c: 2.0, CH_2Cl_2). IR (neat, cm^{-1}, ν): 3417, 2841, 2866, 1657, 1461 1250, 1097. ^{1}H-NMR (300 MHz, $CDCl_3$,δ): 6.31 (1H, dd, J: 15.0 and 11.0 Hz, $CH{=}C\underline{H}CH{=}CHCH_2$), 5.99 (1H, t, J: 11.0 Hz, $CH{=}CHC\underline{H}{=}CH$-$CH_2$), 5.66 (1H, dd, J: 15.5 and 7.5 Hz, $C\underline{H}{=}CHCH{=}CHCH_2$), 5.50-5.40 (2H, m, $C(CH_3){=}C\underline{H}$, $CH{=}CHCH{=}C\underline{H}CH_2$), 4.66 (2H, s, $OC\underline{H}_2OCH_3$), 4.42 (2H, d, J: 6.5 Hz, $C\underline{H}_2OTIPS$), 4.45-4.05 (2H, m, $C\underline{H}_2OH$), 3.40-3.35 (4H, m, $OCH_2OC\underline{H}_3$, $C\underline{H}OMOM$), 2.55-2.45 (1H, m, $C\underline{H}(CH_3)$-$CH{=}CH$), 2.20-2.10 (2H, m, $C\underline{H}_2C(CH_3){=}CH$), 1,72 (3H, s, $C(C\underline{H}_3){=}CH$), 1.65-1.45 (3H, m, $C\underline{H}_2CH_2C(CH_3){=}CH$, $CH_2O\underline{H}$), 1.08 (24H, m, $Si(C\underline{H}(C\underline{H}_3)_2)_3$, $CH(C\underline{H}_3)$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 139.4, 137.2, 129.3, 128.8, 125.3, 124.5, 96.1, 81.6, 59.8, 58.6, 55.7, 40.3, 29.8, 27.4, 23.2, 17.9, 15.9, 11.9. MS (m/e): 422 (M^+-H_2O). HR-MS: calcd. for $C_{25}H_{46}O_3Si$: 422.3216, found: 422.3213.

(2*Z*,8*E*,10*Z*)-(6*R*,7*R*)-3,7-Dimethyl-6-(methoxymethoxy)-12-triisopropylsilyloxydodeca-2,8,10-trienal (16): To a solution of oxalyl chloride (0.980 mL, 11.22 mmol) in CH_2Cl_2 (75 mL), dimethyl sulfoxide (DMSO) (1.60 mL, 22.45 mmol) was added over 15 min at -78°C. After 30 min stirring, alcohol **15** (3.80 g, 8.64 mmol) in CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred for 1 h then triethylamine (5.30 mL, 37.99 mmol) was added. It was allowed to warm to 23°C over 90 min. Water (100 mL) was added then the mixture was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography (hexane/ethyl acetate, 4:1) to give the trienal **16** (3.21 g, 85 %) as a yellow oil. $[\alpha]_D^{25}$: +11.6° (c: 2.0, CH_2Cl_2). IR (neat, cm^{-1}, ν): 2942, 2866, 1676, 1462, 1379, 1147, 1098, 1035. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 9.95 (1H, d, J: 8.0 Hz, $C\underline{H}O$), 6.31 (1H, dd, J: 15.0 and 11.0 Hz, $CH{=}C\underline{H}CH{=}CHCH_2$), 5.98 (1H, t, J: 11.0 Hz, $CH{=}CH$-$C\underline{H}{=}CHCH_2$), 5.85 (1H, d, J: 8.0 Hz, $C(CH_3){=}C\underline{H}$), 5.66 (1H, dd, J: 15.0 and 7.0 Hz, $C\underline{H}{=}CH$-$CH{=}CHCH_2$), 5.49 (1H, dt, J: 11.0 and 6.0 Hz, $CH{=}CHCH{=}C\underline{H}CH_2$), 4.67 (2H, dd, J: 7.0 and 4.0 Hz, $OC\underline{H}_2OCH_3$), 4.41 (2H, d, J: 6.0 Hz, $C\underline{H}_2OTIPS$), 3.43 (1H, m, $C\underline{H}OMOM$), 3.40 (3H, s, $OCH_2OC\underline{H}_3$), 2.64 (2H, dd, J: 9.5 and 2.0 Hz, $C\underline{H}_2C(CH_3)=CH$), 2.54 (1H, q, J: 7.0 Hz, $C\underline{H}(CH_3)CH=CH$), 1.96 (3H, s, $C(C\underline{H}_3)=CH$), 1.70-1.60 (2H, m, $C\underline{H}_2CH_2C(CH_3)=CH$), 1.07 (24H, m, $CH(C\underline{H}_3)$, $Si(C\underline{H}(C\underline{H}_3)_2)_3$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 190.4, 164.0, 136.5, 129.7, 128.5, 128.2, 125.6, 96.4, 81.6, 59.9, 55.7, 40.2, 30.6, 28.4, 24.8, 17.9, 16.0, 11.8. MS (m/e): 395 ($M^+-C_3H_7$); HR-MS: calcd. for $C_{22}H_{39}O_4Si$: 395.2617, found: 395.2612.

(2*Z*,4*E*,10*Z*)-(6*R*,7*R*,12ξ)-13-Chloro-6,10-dimethyl-7-(methoxymethoxy)-1-triisopropylsilyloxytrideca-2,4,10-trien-12-ol (17): To a solution of aldehyde **16** (100 mg, 0.228 mmol) in THF, chloroiodomethane (25 μL, 0.342 mmol) and *n*-butyllithium (185 μL, 0.296 mmol, 1.6 M in hexane) was added sequentially at -78°C. It was stirred for 1 h at -78°C, quenched with NH_4Cl (sat.) and extracted with ether. The extract was dried over $MgSO_4$, and concentrated. Chromatography (toluene/ethyl acetate 9:1) of the residue afforded **17** (94 mg, 85%) as a colorless oil. $[\alpha]_D^{25}$: +21.5° (c: 2.0, CH_2Cl_2). IR (neat, cm^{-1}, ν): 3441, 2943, 2866, 1664, 1461, 1379, 1252, 1097. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.35-6.20 (1H, m, $CH=C\underline{H}CH=CH-CH_2OTIPS$), 5.98 (1H, dt, J: 11.0 and 4.0 Hz, $CH=CHC\underline{H}=CHCH_2OTIPS$), 5.70-5.60 (1H, m, $C\underline{H}=CHCH=CHCH_2OTIPS$), 5.52-5.43 (1H, dt, J: 11.0 and 6.0 Hz, $CH=CHCH=C\underline{H}-CH_2OTIPS$), 5.18 (1H, t, J: 8.0 Hz, $C(CH_3)=C\underline{H}$), 4.66 (2H, d, J: 3.0 Hz, $OC\underline{H}_2OCH_3$), 4.51 (1H, m, $C\underline{H}OH$), 4.42 (2H, d, J: 6.0 Hz, $C\underline{H}_2OTIPS$), 3.50-3.46 (2H, m, $C\underline{H}_2Cl$), 3.43-3.36 (4H, m, $OCH_2OC\underline{H}_3$, $C\underline{H}OMOM$), 2.53-2.46 (1H, m, $C\underline{H}CHOMOM$), 2.26-2.06 (2H, m, $C\underline{H}_2C(CH_3)=CH$), 1.72 (3H, d, J: 3.5 Hz, $C(C\underline{H}_3)=CH$), 1.60-1.44 (2H, m, $C\underline{H}_2CH_2-C(CH_3)=CH$), 1.15-1.01 (24H, m, $Si(C\underline{H}(C\underline{H}_3)_2)_3$, $CH(C\underline{H}_3)$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 137.2, 135.0, 131.3, 129.7, 129.5, 128.8, 128.7, 125.5, 124.3, 123.7, 96.2, 81.7, 81.5, 68.3, 67.9, 63.5, 59.9, 55.8, 49.7, 49.6, 40.5, 40.4, 30.1, 29.8, 28.4, 27.8, 23.4, 23.3, 18.0, 16.2, 16.1, 12.0. MS (m/e): 471 $(M-OH)^+$; HR-MS: calcd. for $C_{26}H_{48}O_3SiCl$: 471.3061; found: 471.3055.

(2*Z*,4*E*,10*Z*)-(6*R*,7*R*,12ξ)-13-Chloro-6,10-dimethyl-7-(methoxymethoxy)-12-(methoxyisopropoxy)-1-triisopropylsilyloxytrideca-2,4,10-triene (18): To a solution of alcohol **17** (65 mg, 0.133 mmol) in CH_2Cl_2 (15 mL), 2-methoxypropene (64 μL, 0.665 mmol) and PPTS (3.5 mg, 13.3 μmol) were added at 23°C. It was stirred for 30 min, neutralized with NH_4Cl (sat.) and extracted with CH_2Cl_2. Removal of the solvents from the dried extracts ($MgSO_4$) afforded an oil which was purified by chromatography (hexane/ethyl acetate 9:1) to afford chloride **18** as a colorless oil. $[\alpha]_D^{25}$: +16.4° (c: 2.0 in CH_2Cl_2). IR (neat, cm^{-1}, ν): 2943, 2866, 1660, 1461, 1258, 1209, 1096. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.29 (1H, dd, J: 15.0 and 11.0 Hz, $CH=C\underline{H}-CH=CHCH_2$), 5.98 (1H, t, J: 11.0 Hz, $CH=CHC\underline{H}=CHCH_2$), 5.69 (1H, dd, J: 15.0 and 8.0 Hz, $C\underline{H}=CHCH=CHCH_2$), 5.47 (1H, dt, J: 11.0 and 6.0 Hz, $CH=CHCH=C\underline{H}CH_2$), 5.11 (1H, d, J: 9.0 Hz, $C(CH_3)=C\underline{H}$), 4.67 (2H, s, $OC\underline{H}_2OCH_3$), 4.60-4.50 (1H, m, $C\underline{H}OMOP$), 4.41 (2H, d, J:

6.5 Hz, $C\underline{H}_2OTIPS$), 3.53-3.31 (6H, m, $C\underline{H}OMOM$, $C\underline{H}_2Cl$, $OCH_2OC\underline{H}_3$), 3.18 (3H, d, J: 2.0 Hz, $C\underline{H}_3OC(CH_3)_2$), 2.54-2.47 (1H, m, $C\underline{H}CHOMOM$), 2.30-1.95 (2H, m, $C\underline{H}_2C$-(CH_3)=CH), 1.71 (3H, s, $C(C\underline{H}_3)$=CH), 1.70-1.40 (2H, m, $C\underline{H}_2CH_2C(CH_3)$=CH), 1.37 (3H, s, $CH_3OC(C\underline{H}_3)_2$), 1.31 (3H, s, $CH_3OC(C\underline{H}_3)_2$), 1.15-1.00 (24H, m, $Si(C\underline{H}(C\underline{H}_3)_2)_3$, $CH(C\underline{H}_3)$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 139.0, 138.6, 137.4, 131.2, 129.6, 128.7, 125.3, 100.9, 96.1, 81.8, 67.9, 60.0, 55.8, 49.2, 47.8, 47.6, 40.2, 39.9, 29.5, 28.5, 25.4, 23.3, 18.0, 15.8, 12.0. MS (m/e): 471 $(M-C_4H_9O_2)^+$; HR-MS: calcd. for $C_{26}H_{48}O_3SiCl$: 471.3061, found: 471.3064.

(2*Z*,4*E*,10*Z*)-(6*R*,7*R*,12ξ)-13-Chloro-6,10-dimethyl-7-(methoxymethoxy)-12-(methoxy-isopropoxy)trideca-2,4,10-trienol (19): To a solution of **18** (40 mg, 0.0714 mmol) in THF (5 mL), TBAF (214 µL, 0.214 mmol, 1.0 M in THF) was added at 0°C. It was stirred for 30 min at 23°C, quenched with $NaHCO_3$ (sat.) and extracted with ether. The extract was dried over $MgSO_4$ and concentrated. Chromatography (hexane/ethyl acetate 7:3) of the residue gave **19** (23 mg, 80%) as a colorless oil. $[\alpha]_D^{25}$: +29.1° (c: 1.0, CH_2Cl_2). IR (neat, cm^{-1}, ν): 3449, 2938, 1662, 1455, 1147. ^1H-NMR (300 MHz, C_6D_6, δ) 6.45-6.33 (1H, m, CH=$C\underline{H}CH$=$CHCH_2$), 6.02 (1H, t, J: 11.0 Hz, CH=$CHC\underline{H}$=$CHCH_2$), 5.62 (1H, dd, J: 15.0 and 8.0 Hz, $C\underline{H}$=CHCH=CH-CH_2), 5.48 (1H, dt, J: 11.0 and 7.0 Hz, CH=CHCH=$C\underline{H}CH_2$), 5.18 (1H, d, J: 9.0 Hz, $C(CH_3)$=$C\underline{H}$), 4.78-4.65 (1H, m, $C\underline{H}OMOP$), 4.60-4.52 (2H, m, $OC\underline{H}_2OCH_3$), 4.16-4.11 (2H, m, $C\underline{H}_2OH$), 3.52-3.43 (1H, m, $C\underline{H}OMOM$), 3.35-3.25 (5H, m, $C\underline{H}_2Cl$, $OCH_2OC\underline{H}_3$), 3.09 (3H, d, J: 3.0 Hz, $C\underline{H}_3OC(CH_3)_2$), 2.50-2.00 (4H, m, $C\underline{H}CHOMOM$, $C\underline{H}_2C(CH_3)$=CH, $CH_2O\underline{H}$), 1.60 (3H, s, $C(C\underline{H}_3)$=CH), 1.50-1.25 (8H, m, $C\underline{H}_2CH_2C(CH_3)$=CH, $CH_3OC(C\underline{H}_3)_2$), 1.03 (3H, dd, J: 7.0 and 2.5 Hz, $CH(C\underline{H}_3)$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 138.7, 138.4, 138.3, 136.5, 131.5, 131.2, 130.4, 129.5, 126.2, 125.5, 101.1, 96.4, 81.8, 81.7, 68.3, 58.8, 55.6, 54.0, 49.1, 48.2, 48.0, 40.8, 40.7, 40.6 30.2, 30.0, 28.3, 28.2, 25.7, 25.4, 23.4, 21.0, 16.5, 16.3, 14.3. MS (m/e): 332 $(M-C_4H_{10}O_2)NH_4^+$; HR-MS: calcd. for $C_{17}H_{31}NO_3Cl$: 332.1992; found: 332.1996.

Dimethyl (3*Z*,5*E*,11*Z*)-(7*R*,8*R*,13ξ)-14-chloro-7,11-dimethyl-13-hydroxy-8-(methoxy-methoxy)tetradeca-3,5,11-trienedicarboxylate (22): To a solution of alcohol **19** (40 mg, 0.099 mmol) in THF (5 mL), triphenylphosphine (52 mg, 0.198 mmol), hexachloroacetone (17 µL, 0.108 mmol) and 2,4,6-collidine (65 µL, 0.495 mmol) were added sequentially at -20°C. After an hour stirring, it was quenched with $NaHCO_3$ (25 mL, sat.) and extracted with ether. The extract was dried over $MgSO_4$, filtered and concentrated to give sensitive dichloride **20**, which was used immediately in the next step without characterization: To a solution of sodium hydride (20 mg, 0.495 mmol, 60 % dispersion in oil) in a solvent mixture of THF (3 mL) and DMF (3 mL), dimethyl malonate (79 µL, 0.693 mmol) was added dropwise at 23°C. Once the evolution of hydrogen gas ceased, dichloride **20** (about 0.099 mmol) was added followed by NaI

(22 mg, 0.149 mmol). It was stirred for 1 h at 23°C, neutralized with NH_4Cl (sat.) and extracted with ether. The extract was dried over $MgSO_4$, filtered and concentrated. Crude **21** was dissolved in THF (10 mL) and HCl (10 mL, 0.1 N) was added. The mixture was stirred for 10 min at 23°C and extracted with ether. Removal of the solvents from the dried extract ($MgSO_4$) afforded an oil which was purified by chromatography (hexane/ethyl acetate 3:2) to give chlorohydrin **22** (34 mg, 77% over 3 steps) as a yellow oil. $[\alpha]_D^{25}$: +45.8° (c: 1.0, CH_2Cl_2). IR (neat, cm^{-1}, ν): 3438, 2955, 1738, 1438, 1233, 1033. ^1H-NMR (300 MHz, $CDCl_3$, δ): 6.34 (1H, dd, J: 15.0 and 11.0 Hz, $CH=C\underline{H}CH=CHCH_2$), 6.04 (1H, t, J: 11.0 Hz, $CH=CHC\underline{H}=CH-CH_2$), 5.67 (1H, dd, J: 15.0 and 8.0 Hz, $C\underline{H}=CHCH=CHCH_2$), 5.28-5.16 (2H, m, $CH=CH-CH=C\underline{H}CH_2$, $C(CH_3)=C\underline{H}$), 4.66 (2H, d, J: 3.0 Hz, $OC\underline{H}_2OCH_3$), 4.57-4.49 (1H, m, $C\underline{H}OH$), 3.76 (1H, m, $C\underline{H}(CO_2CH_3)_2$), 3.72 (6H, s, 2x$CO_2C\underline{H}_3$), 3.53-3.36 (6H, m, $C\underline{H}OMOM$, $C\underline{H}_2Cl$, $OCH_2OC\underline{H}_3$), 2.77 (2H, t, J: 7.5 Hz, $C\underline{H}_2CH(CO_2CH_3)_2$, 2.55-2.45 (1H, m, $CHC\underline{H}(CH_3)$, 2.30-2.00 (2H, m, $C\underline{H}_2C(CH_3)=CH$), 1.72 (3H, d, J: 4.0 Hz, $C(C\underline{H}_3)=CH$), 1.70-1.45 (2H, m, $C\underline{H}_2CH_2C(CH_3)=CH$), 1.24 (1H, s broad, $CHO\underline{H}$), 1.04 (3H, d, J: 7.0 Hz, $CH(C\underline{H}_3)$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 169.3, 167.4, 137.6, 137.4, 131.4, 125.1 124.5, 124.3, 123.8, 96.2, 81.6, 68.3, 67.9, 55.8, 53.1, 52.5, 51.6, 51.0, 49.7, 40.4, 30.0, 29.6, 28.3, 28.0, 27.1, 23.4, 23.3, 16.2, 16.1. MS (m/e): 464 (MNH_4^+); HR-MS: calcd. for $C_{22}H_{39}NO_7Cl$: 464.2415, found: 464.2425.

Dimethyl (3*Z*,5*E*,11*Z*)-(7*R*,8*R*)-14-chloro-7,11-dimethyl-8-(methoxymethoxy)-13-oxotetradeca-3,5,11-trienedicarboxylate (23): To a solution of alcohol **22** (20 mg, 44.8 μmol) in CH_2Cl_2 (5 mL), Dess-Martin periodinane (57 mg, 0.136 mmol) was added. It was stirred for 30 min, neutralized with $NaHCO_3$ (20 mL, sat.) and $Na_2S_2O_3$ (0.5 g) was added. After further 30 min stirring, it was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by chromatography (hexane/ethyl acetate 9:1) to afford chloroketone **23** (17.9 mg, 90 %) as a colorless oil. $[\alpha]_D^{25}$: -6.17° (c: 0.47, CH_2Cl_2). IR (neat, cm^{-1}, ν): 2951, 1740, 1704, 1616, 1440, 1234. ^1H-NMR (300 MHz, $CDCl_3$, δ): 6.34 (1H, dd, J: 15.0 and 11.0 Hz, ($CH=C\underline{H}CH=CHCH_2$), 6.22 (1H, s, $C(CH_3)=C\underline{H}$), 6.05 (1H, t, J: 11.0 Hz, $CH=CHC\underline{H}=CHCH_2$), 5.72 (1H, dd, J: 15.0 and 8.0 Hz, $C\underline{H}=CHCH=CHCH_2$), 5.24 (1H, dt, J: 11.0 and 8.0 Hz, $CH=CHCH=C\underline{H}CH_2$), 4.69 (2H, s, $OC\underline{H}_2OCH_3$), 4.06 (2H, s, $C\underline{H}_2Cl$), 3.73 (6H, s, 2 X $CO_2C\underline{H}_3$), 3.51-3.39 (5H, m, $OCH_2OC\underline{H}_3$, $C\underline{H}OMOM$ $C\underline{H}(CO_2CH_3)_2$), 2.80-2.51 (5H, m, $C\underline{H}_2CH$, $C\underline{H}_2C(CH_3)=CH$, $C\underline{H}(CH_3)$), 1.94 (3H, d, J: 1.0 Hz, $C(C\underline{H}_3)=CH$), 1.66-1.53 (2H, m, $C\underline{H}_2CH_2C(CH_3)=CH$), 1.07 (3H, d, J: 7.0 Hz, $CH(C\underline{H}_3)$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 190.7, 169.3, 164.2, 137.9, 131.5, 129.7, 124.9, 124.3, 119.8, 96.1, 81.8, 55.8, 52.5, 51.6, 49.2, 40.2, 39.9, 31.9, 30.5, 29.6, 29.4, 27.1, 25.8, 15.6. MS (m/e): 462 (MNH_4^+); HR-MS: calcd. for $C_{22}H_{37}NO_7Cl$: 462.2258, found: 462.2265.

Dimethyl (3*Z*,5*E*,11*Z*)-(7*R*,8*R*)-7,11-dimethyl-8-(methoxymethoxy)-13-oxocyclotetradeca-3,5,11-trienedicarboxylate (1): To a vigorously stirred suspension of Cs_2CO_3 (2.9 g, 9.0 mmol) in dry acetonitrile (700 mL), a solution of chloroketone **23** (280 mg, 0.63 mmol) in acetonitrile (5 mL) was added slowly with a syringe pump over a period of 5 h (c_{final}: 0.9 mM) at 45°C. After six additional hour of stirring at this temperature, the mixture was filtered over a silica pad (5 cm) then the solvent was evaporated. The residue was purified by chromatography (hexane/ether 9:1) to afford macrocycle **1** (214 mg, 83%) as a white solid. Mp: 98-100°C (hexane/ether). $[\alpha]_D^{25}$: -1.55° (c: 2.0, CH_2Cl_2). IR (neat, cm^{-1}, ν): 2953, 2881, 1736, 1688, 1627, 1437, 1378, 1286, 1210, 1145, 1035. ^1H-NMR (300 MHz, $CDCl_3$, δ): 6.28 (1H, dd, J: 15.0 and 11.0 Hz, $CH(CH_3)CH{=}C\underline{H}$), 6.06 (1H, t, J: 11.0 Hz, $CH(CH_3)CH{=}CHC\underline{H}{=}CH$), 5.90 (1H, s, $C(CH_3){=}C\underline{H}$), 5.24 (1H, dd, J: 15.0 and 10.5 Hz, $CH(CH_3)C\underline{H}{=}CH$), 5.10 (1H, m, $CH(CH_3)CH{=}CHCH{=}C\underline{H}$), 4.69 and 4.57 (2H, AB, J_{AB}: 7.0 Hz, $OC\underline{H}_2OCH_3$), 3.71 (3H, s, $CO_2C\underline{H}_3$), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.60 (1H, t, J: 14.0 Hz, $CH{=}CHC\underline{H}H$), 3.37 (3H, s, $OCH_2OC\underline{H}_3$), 3.30 (1H, m, $C\underline{H}OMOM$), 3.22 and 2.87 (2H, AB, J_{AB}: 19.5 Hz, $C\underline{H}_2C{:}\,O$), 3.13 (1H, dt, J: 13.0 and 2.5 Hz, $C\underline{H}HC(CH_3){=}CH$), 2.75 (1H, dd, J: 14.0 and 5.0 Hz, $CH{=}CHCH\underline{H}$), 2.40-2.30 (1H, m, $C\underline{H}(CH_3)$)), 2.05-1.95 (1H, m, $C\underline{H}HCHOMOM$), 1.90-1.75 (1H, m, $CH\underline{H}C(CH_3){=}CH$), 1.75 (3H, s, $C(C\underline{H}_3){=}CH$), 1.09 (1H, t, J: 13.5 Hz, $CH\underline{H}CHOMOM$), 1.03 (3H, d, J: 6.5 Hz, $CH(C\underline{H}_3)$)). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 199.6, 170.8, 170.7, 155.0, 136.3, 133.0, 126.4, 125.3, 124.3, 96.0, 80.6, 55.6, 54.5, 52.8, 44.3, 41.5, 30.8, 30.5, 24.4, 23.4, 18.2. MS (m/e): 408 (M^+); HR-MS: calcd. for $C_{22}H_{32}O_7$: 408.2148; found: 408.2150.

(4aα,4bα,7α,8β,8aβ,10aα) Dimethyl 4b,8-dimethyl-7-methoxymethoxy-4-oxo-3,4,4a,4b,5,6,7,8,8a,10a-decahydro-1H-phenanthrene-2,2-dicarboxylate (2): A solution of macrocyclic trienone **1** (15 mg, 36.8 μmol) in dry toluene (0.5 mL, previously degazed with 5 freeze-thaw cycles) was heated for 24 h at 230°C in a vacuum sealed quartz tube (washed with NH_4OH, water and acetone before use) in a temperature controlled oven. Upon cooling, the tube was opened and the content was evaporated. Chromatography (hexane-ethyl acetate, 4:1) of the residue afforded TSC tricycle **2** (14 mg, 93%) as a white solid. A small sample was recrystallized from (hexane/ether, 9:1) to give colorless crystals, which were submitted to X-ray diffraction analysis. Mp: 118-120°C. $[\alpha]_D^{25}$: +116.3° (c: 2.0, CH_2Cl_2). IR (neat, cm^{-1}, ν): 2950, 1739, 1444, 1253, 1209, 1150, 1106, 1039. ^1H-NMR (300 MHz, $CDCl_3$, δ): 5.73 (1H, dt, J: 10.5 and 2.0 Hz, $C_{10}\underline{H}$), 5.42 (1H, dt, J: 10.5 and 2.5 Hz, $C_9\underline{H}$), 4.76 and 4.62 (2H, AB, J_{AB}: 7.0 Hz, $OC\underline{H}_2OCH_3$), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.68 (3H, s, $CO_2C\underline{H}_3$), 3.39 (3H, s, $OCH_2OC\underline{H}_3$), 3.20-3.05 (2H, m, $C_7\underline{H}$, $C_{10a}\underline{H}$), 2.90 and 2.61 (2H, AB, J_{AB}: 15.0 Hz, $C_3\underline{H}_2$), 2.55-2.35 (3H, m, $C_1\underline{H}_a$, $C_{4a}\underline{H}$, $C_5\underline{H}$), 2.20-2.10 (1H, m, $C_{8a}\underline{H}$), 2.09 (1H, d, J: 7.0 Hz. $C_1\underline{H}_b$), 2.05-1.95 (1H, m, $C_6\underline{H}_a$), 1.73-1.60 (1H, m, $C_6\underline{H}_b$), 1.55-1.40 (1H, m, $C_8\underline{H}$), 1.25-1.15 (1H, m, $C_5\underline{H}$), 1.04 (3H, d, J: 6.5

Hz, $C_8C\underline{H}_3$), 0.90 (3H, s, $C_{4b}C\underline{H}_3$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 207.0, 171.3, 170.7, 129.5, 128.3, 95.8, 82.4, 55.7, 55.1, 53.1, 52.7, 46.5, 42.3, 36.0, 35.7, 34.4, 31.7, 29.6, 27.7, 18.9, 14.9. MS (m/e): 408 (M^+); HR-MS: calcd. for $C_{22}H_{32}O_7$: 408.2148; found: 408.2154.

(4aβ,4bα,7α,8β,8aβ,10aα) Dimethyl 7-methoxymethoxy-4b,8-dimethyl-4-oxo-3,4,4a,4b,5,6,7,8,8a,10a-decahydro-1H-phenanthrene-2,2-dicarboxylate (3): To a solution of TSC tricycle **2** (7 mg, 17.2 mmol) in methanol (5 mL), K_2CO_3 (24 mg, 172 mmol) was added at 23°C. The resulting mixture was stirred for 12 h at 60°C then $NaHCO_3$ (sat.) was added. It was extracted with CH_2Cl_2, the extract was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by chromatography (hexane/ethyl acetate, 4:1) to afford colorless crystals of TAT tricycle **3** (5 mg 71%). Mp: 118-119°C. $[\alpha]_D^{25}$: -9.3° (c: 0.15, CH_2Cl_2). IR (neat, cm^{-1}, ν): 2924, 2853, 1738, 1464, 1378, 1261, 1210, 1041. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 5.75 (1H, dt, J: 10 and 2 Hz, CH=C$\underline{H}$), 5.50 (1H, dt, J: 10 and 2 Hz, C$\underline{H}$=CH), 4.77 and 4.61 (2H, AB, J_{AB}: 7 Hz, $C\underline{H}_2OCH_3$), 3.76 (3H, s, $CO_2C\underline{H}_3$), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.40 (3H, s, CH_3O), 3.05-2.99 (1H, m), 2.92 (1H, dd, J: 13 and 2 Hz), 2.67 (1H, d), 2.58 (1H, dt, J: 14 and 2 Hz), 2.50 (1H, dt, J: 14 and 3 Hz), 2.42 (1H, t broad, 12 Hz), 2.10 (1H, d, 11 Hz), 2.00 (1H, d, 14 Hz), 1.97-1.93 (1H, m), 1.68-1.47 (4H, m), 1.04 (3H, d, J: 7 Hz, $CHC\underline{H}_3$), 0.97 (3H, s CH_3). ^{13}H-NMR (75 MHz, $CDCl_3$, δ): 207.1, 171.3, 170.7, 128.6, 128.3, 95.6, 82.2, 61.8, 57.4, 55.6, 53.2, 50.3, 46.7, 37.2, 36.6, 36.0, 35.1, 34.2, 33.3, 29.7, 27.3, 15.0, 12.0. MS (m/e): 408 (M^+). HR-MS: calcd. for $C_{22}H_{32}O_7$: 408.2148; found: 408.2154;

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