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Towards the Total Synthesis of the Norsesterterpene Diacarnoxide C

Marc-André Schneider[a] and Karlheinz Seifert*[a]

Abstract: The synthesis of the norsesterterpene diacarnoxide C was achieved. The endoperoxide moiety could be prepared in nine and the norsesquiterpene moiety in five steps starting from (*E*)-3-methyl-6-oxohex-2-en-1-yl acetate and dihydro-*β*-ionone. The peroxide aldehyde and the norsesquiterpene sulfone were coupled in an (*E*)-selective Julia-Kocienski reaction. The coupling product was transformed in three additional steps to an inseparable mixture of diacarnoxide C and three further isomers.

Introduction

The norsesterterpene endoperoxides diacarnoxide A–D have been isolated from the the marine sponge *Diacarnus levii*.[1a] These compounds, mainly diacarnoxide B, selectively act as bioreductive cytotoxins on hypoxic prostatic and breast tumour cells. Bioreductive cytotoxins are organic compounds which are chemically activated under the reducing conditions that exist within hypoxic tissues. The hypoxia-inducible factor-1 (HIF-1) is induced in hypoxic tumour cells and represents a transcription factor that regulates oxygen homeostasis. Diacarnoxides, aikupikoxides[1b], mycaperoxides[1c-g], and trunculins[1h] are examples of natural products containing the interesting 3,6,6-trisubstituted 1,2-dioxan ring in their structures (Fig. 1). For this reason diacarnoxide C (**1**) represents a synthetically challenging target.

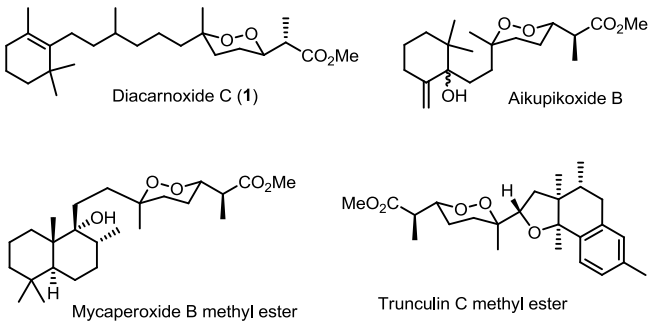
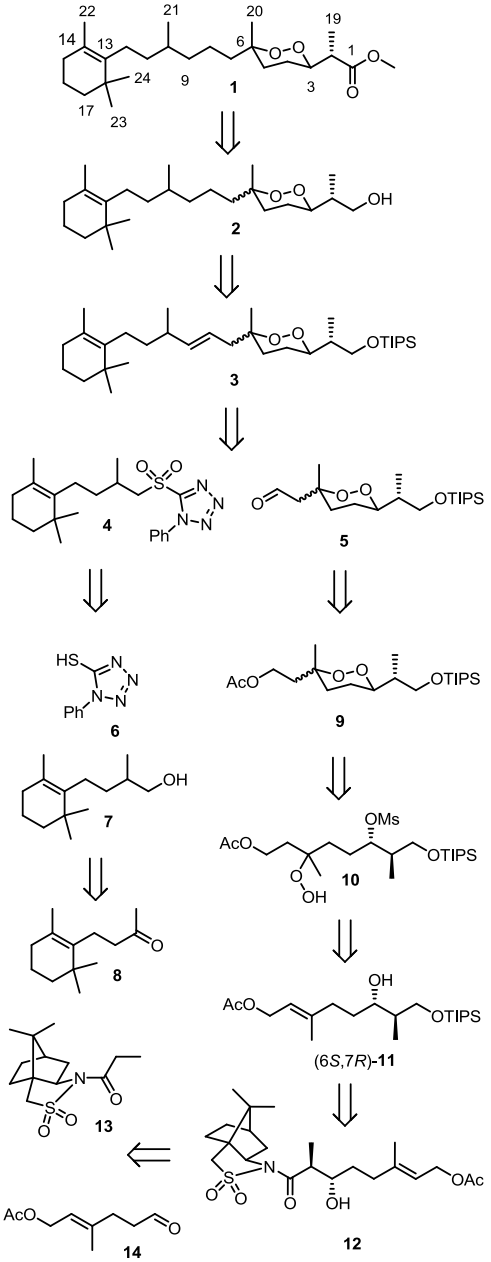


Fig. 1: Marine endoperoxides.

The first reported synthesis of a marine norsesterterpene endoperoxide is the total synthesis of mycaperoxide B methyl ester.[1i,j] The key step of this synthesis is the Michael cycloaddition of a hydroperoxide to an *α,β*-unsaturated ester leading to myca- peroxide B methyl ester and its diastereo-



Scheme 1. Retrosynthesis of diacarnoxide C (**1**).

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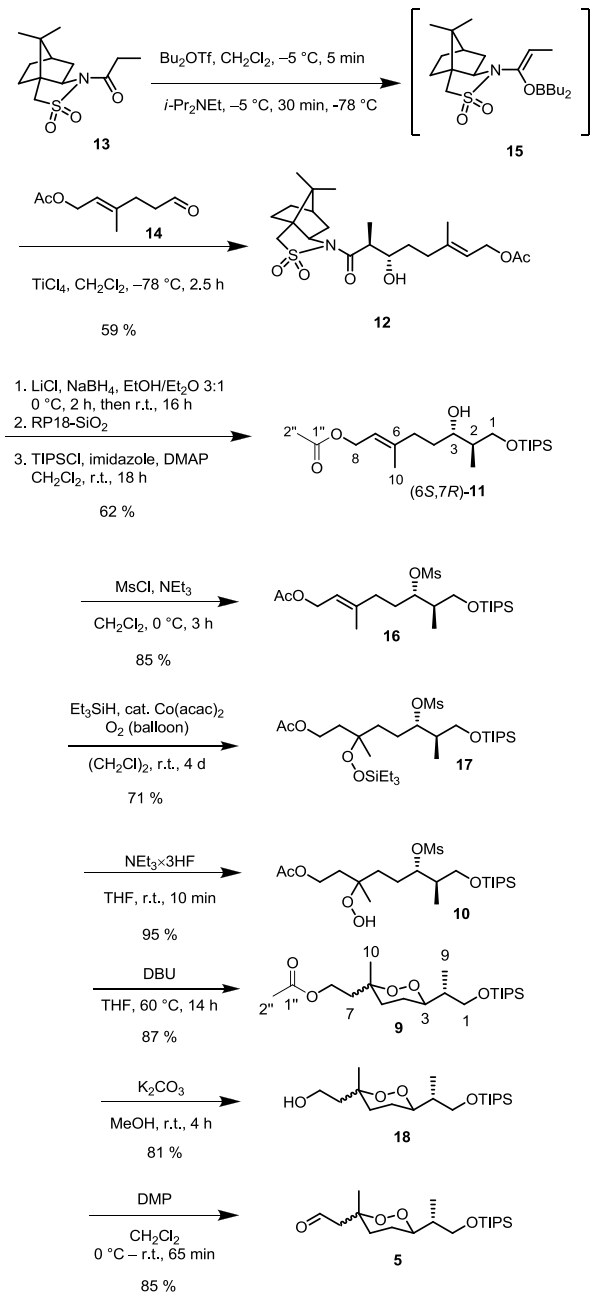
10.1002/ejoc.201700922

isomers (10 %) and tetrahydrofuran byproducts (43 %). To avoid the formation of tetrahydrofurans, diacarnoxide C (**1**) should be synthesized in a convergent fashion from a peroxide and a side-chain fragment.

The retrosynthesis of diacarnoxide C (**1**) leads via **2** and **3** to the norsesquiterpene sulfone **4** and the peroxide aldehyde **5** (Scheme 1). The connection of both fragments could be realized by a Julia-Kocienski reaction. The sulfone **4** can be obtained by oxidation of the thioether which can be prepared from the primary alcohol **7** and the thiol **6** in a Mitsunobu reaction. The alcohol **7** could be synthesized from dihydro-*β*-ionone (**8**) by chain elongation. The endoperoxide aldehyde

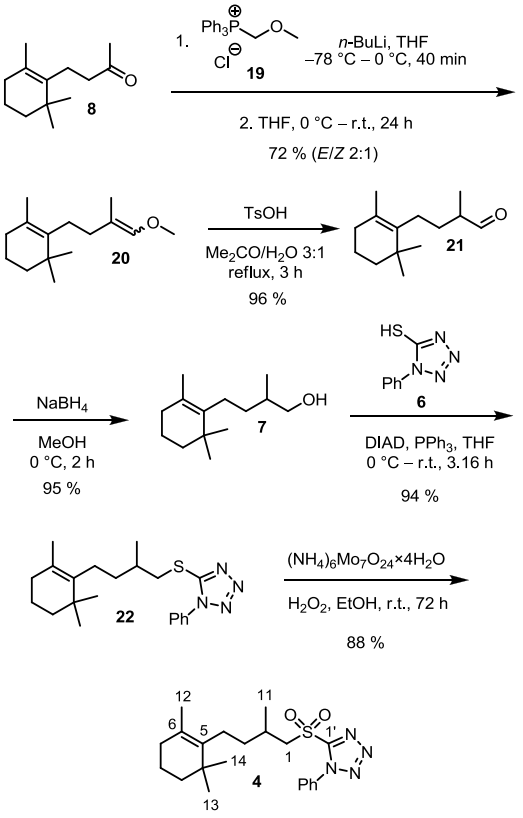


Scheme 2. Synthesis of the endoperoxide **5** via Oppolzer-aldol reaction.

5 could be traced back to the acetyl-protected primary alcohol **9** which could be synthesized by the intramolecular nucleophilic substitution of the mesylate group by the hydroperoxide of **10**. Compound **10** can be generated by mesylation of the secondary OH-group of the mono-protected 1,3-diol (6*S*,7*R*)-**11** and hydroperoxysilylation of its double bond. The TIPS-protected 1,3-diol-motive of (6*S*,7*R*)-**11** can be established via **12** by an Oppolzer-aldol reaction (**13** + **14**).

Results and Discussion

The carbon skeleton of the 1,2-dioxane moiety of diacarnoxide C (**1**) was established by an Oppolzer-aldol reaction[2a] (Scheme 2). We have used this aldol reaction of the *N*-propanoyl sultam **13** with aldehyde **14** for the synthesis of (2*S*,2'*S*,5'*S*)-lilac aldehyde before.[2b] The aldol product **12** was reduced with $NaBH_4$ in the presence of LiCl[2c] to the primary alcohol which could be purified by RP-18-SiO_2-chromatography and protected with TIPSCl (triisopropyl silyl chloride) to the TIPS-ether (6*S*,7*R*)-**11**. This compound was transformed with methanesulfonyl chloride and triethylamine to the mesylate **16**.[2d] The Isayama-Mukaiyama-hydroperoxysilylation[2e] of the double bond of **16** gave the triethylsilylhydroperoxide **17** and this TES-ether was deprotected with NEt_3×3HF[2f] to the hydroperoxide **10**. Cyclization of the mesylate **10** with DBU led to the endoperoxide **9** in a very good yield of 87 %. The acetyl group of **9** was removed by transesterification with K_2CO_3 in MeOH. Oxidation of the primary alcohol function of **18** with Dess-Martin-periodinane[2g] led to the endoperoxide aldehyde **5**. Starting from the Oppolzer-aldol product **12** the yield of the endoperoxide synthon **9** was 30.9 % over 6 steps. The 1,2-dioxane moiety **9** can also be prepared by an Evans-aldol route over 6 steps with a yield of only 7.6 % starting from the Evans-aldol product (see supporting information).

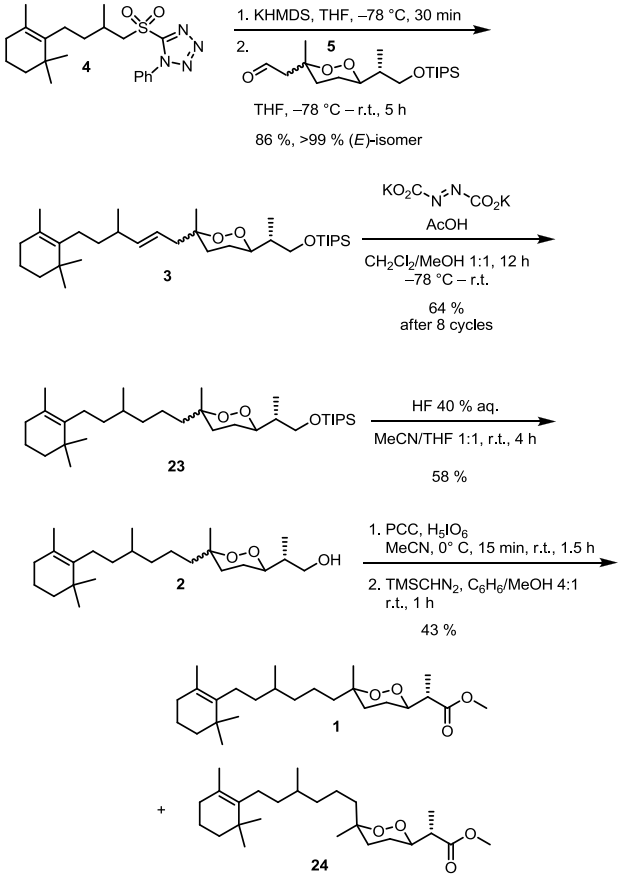


Scheme 3. Synthesis of the sulfone **4**.

10.1002/ejoc.201700922

The synthesis of the side chain of diacarnoxide C (**1**) started with the deprotonation of methoxymethyltriphenylphosphonium chloride (Levines reagent, **19**)[3a] with *n*-BuLi to the ylide which gave with dihydro-*β*-ionone (**8**) in a Wittig-reaction[3b] the enolether **20** as a 2:1 mixture of (*E*)- and (*Z*)-isomer (Scheme 3). Compound **20** was converted with TsOH (*p*-toluenesulfonic acid) in Me_2CO/H_2O under release of methanol to the aldehyde **21**.[3b] Reduction of the carbonyl group of **21** with $NaBH_4$ in MeOH led to the alcohol **7**. The thioether **22** was prepared in a Mitsunobu reaction of **7** with 1-phenyl-1*H*-tetrazol-5-thiol (**6**) in the presence of PPh_3 and DIAD (diisopropyl azodicarboxylate).[3c] Oxidation of **22** with H_2O_2 in the presence of catalytic amounts of $(NH_4)_6Mo_7O_{24}\times4H_2O$ (10 mol-%) gave the sulfone **4**.[3c]

The C-C-bond formation between the norsesquiterpene sulfone **4** and the endoperoxide aldehyde **5** could be achieved by a Julia-Kocienski reaction[3c] (Scheme 4). The (*E*)-selective Julia-Kocienski reaction[4a] of the sulfone **4** and aldehyde **5** with KHMDS (potassium hexamethyldisilazide) as base gave the coupling product **3** as a mixture of four isomers. The reaction was carried out under premetallation conditions. After addition of the aldehyde **5** to the sulfone **4**, an unsatisfyingly slow rate of product formation was indicated by TLC of the reaction mixture. Thereupon the entry was kept under Barbier-conditions and KHMDS was added so long until complete conversion could be detected by TLC. The 8,9-double bond of **3** was hydrogenated with diimide which was obtained *in situ* from freshly prepared dipotassium azodicarboxylate[4b] with AcOH.[4c] Due to the stagnating rates of product formation, the hydrogenation of **3** to **23** had to be repeated 8 times. The TIPS-ether **23** was cleaved with HF 40% aq.[4d] to yield the primary alcohol **2** which was oxidized to the carboxylic acid with catalytic amounts of PCC and H_5IO_6 as co-oxidant in MeCN.[4e] Treatment of the acid with $TMSCHN_2$ (trimethylsilyl diazomethane) in a C_6H_6/MeOH-mixture[4f] gave an inseparable mixture of diacarnoxide C (**1**) with (2*S*,3*R*,6*S*,10*RS*)- and **24** with (2*S*,3*R*,6*R*,10*RS*)-configuration. Natural diacarnoxide C possesses the relative configuration (2*S'*,3*R'*,6*S'*,10*R'S'*). The ^{1}H-, ^{13}C NMR (Table S3 and Table S4), and HRESI-MS data of the synthesized compound **1** are in good agreement with those of natural diacarnoxide C.



Scheme 4. Synthesis of diacarnoxide C (**1**).

Conclusions

A short and efficient synthesis of diacarnoxide C (**1**) is described. Starting from the aldehyde **14** the endoperoxide aldehyde **5** was prepared in nine steps via an Oppolzer-aldol route (Scheme 2). The cyclization of the hydroperoxide **10** to the endoperoxide **9** was achieved with DBU as base. Dihydro-*β*-ionone (**8**) was transformed in five steps to the norsesquiterpene sulfone **4** (Scheme 3). The endoperoxide aldehyde **5** could be coupled with the sulfone **4** in an (*E*)-selective Julia-Kocienski-reaction to the desired olefine **3** which was transformed in three additional steps to an inseparable mixture of diacarnoxide C (**1**) and its diastereomer **24**, both with (10*RS*)-configuration (Scheme 4). The ^{1}H-, ^{13}C NMR, and HRESI-MS data of the synthesized compound **1** are in good agreement with those of natural diacarnoxide C.

Experimental Section

General: All reactions were performed in oven-dried glassware and the moisture sensitive reactions under an argon atmosphere using standard Schlenk techniques. THF and Et_2O were distilled from sodium diphenyl ketyl, benzene from $LiAlH_4$, CH_2Cl_2, pyridine from CaH_2, and MeOH from molecular sieve 3 Å. Triethylamine and diisopropylethylamine were distilled and stored under argon for a maximum of 24 h prior to use. Solvents for chromatography were purchased technical grade and distilled prior to use. Thin-layer chromatography (TLC) was carried out on precoated Alugram® SIL G/UV_{254} plates from Macherey–Nagel. TLC spots were visualized by dipping the plate into potassium permanganate, molybdophosphoric acid (5 % in ethanol) or cerium ammonium molybdate solution with subsequent heating. Preparative LC separations were conducted on silica 60 (40 – 63 µm) from Macherey–Nagel. GC analyses were carried out with a ThermoScientific Trace GC Ultra on a TR-5MS column. IR spectra were recorded with a Perkin–Elmer FTIR spectrophotometer equipped with an ATR (attenuated total reflectance) sampling unit. Mass spectra were recorded using a Finnigan MAT 95 (EI, 70 eV) and a Bruker APEX IV (HRMS, ESI) fourier transformation ion cyclotron resonance mass spectrometer. NMR spectroscopic data were recorded under conditions as indicated with a Bruker Avance 300 and a Bruker Avance-III-HD 500 spectrometer. Solvent signals were used as internal standard (^{1}H = 7.26 ppm and ^{13}C = 77.1 ppm for $CDCl_3$). All starting compounds were purchased from commercial sources and used as received. Reactions were monitored by TLC or gas chromatography.

(6*S*,7*R*,*E*)-6-Hydroxy-3,7-dimethyl-8-(triisopropylsilyloxy)oct-2-enyl acetate ((6*S*,7*R*)-11): To a suspension of LiCl (256 mg, 6.50 mmol) and $NaBH_4$ (246 mg, 6.50 mmol) in EtOH (15 mL) was added a solution of the amide **12** (574 mg, 1.30 mmol) in Et_2O (5 mL) at 0 °C. The resulting solution was stirred for 2 h at 0 °C and 16 h at room temp.. The reaction was quenched with saturated NH_4Cl solution (50 mL), the organic phase was evaporated, and the aqueous phase extracted with $CHCl_3$ (3 × 15 mL). The organic phase was evaporated and the crude product purified by column chromatography (RP18-silica gel, 12 µm, spheric; H_2O with 40, 45, and 50% MeOH). Extraction of the appropriate chromatographic fraction with $CHCl_3$/MeOH 9:1 and evaporation of the solvent gave a 1:1 mixture of 1,3-diol and auxiliary which was dissolved in CH_2Cl_2 (9 mL). To this solution imidazole (197 mg, 2.90 mmol), DMAP (14.7 mg, 120 µmol), and TIPSCl (501 mg, 552 µL, 2.60 mmol) were added at room temp.. After stirring for 18 h the white precipitate was filtered off and washed with CH_2Cl_2. The organic phase was washed with H_2O, dried with $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel; hexanes/EtOAc 9:1), to give (6*S*,7*R*)-**11** (313 mg, 0.81 mmol, 62%) as a colourless oil. R_f = 0.16 (hexanes/EtOAc 3:1). $[\alpha]_D^{23}$ = –17.9 (c = 1.0, CH_2Cl_2). FT-IR: $\tilde{\nu}$ = 3514, 2943, 2866, 1740, 1462, 1382, 1366, 1230, 1096, 1020, 881 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.37 (t, *J* = 7.1 Hz, 1 H, 7-H), 4.58 (d, *J* = 7.1 Hz, 2 H, 8-H), 4.13 (s, 1 H, 3-OH), 3.89 (dd, *J* = 9.9, 3.8 Hz, 1 H, 1-H_A), 3.66 (dd, *J* = 9.9, 8.1 Hz, 1 H, 1-H_B), 3.52 (m, 1 H, 3-H), 2.29 (m, 1 H, 5-H_A), 2.11 (m, 1 H, 5-H_B), 2.05 (s, 3 H, 2''-H), 1.73 (m, 1 H, 2-H), 1.71 (s, 3 H, 10-H), 1.65 (m, 1 H, 4-H_A), 1.55 (m, 1 H, 4-H_B), 1.12 (m, 3 H, 1'-H), 1.06 (d, *J* = 6.2 Hz, 18 H, 2'-H), 0.85 (d, *J* = 7.0 Hz, 3 H, 9-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.4 (C-1''), 143.0 (C-6), 118.0 (C-7), 76.8 (C-3), 69.5 (C-1), 61.6 (C-8), 39.7 (C-2), 35.3 (C-5), 33.4 (C-4), 21.3 (C-2''), 18.1 (C-2'), 16.8 (C-10), 13.8 (C-9), 11.8 (C-1') ppm. HRMS (ESI): calcd. for $C_{21}H_{43}O_4Si$ $[M + H]^+$ 387.2925; found 387.2921.

(6*S*,7*R*,*E*)-3,7-Dimethyl-6-(methansulfonyloxy)-8-(triisopropylsilyloxy)-oct-2-enyl acetate (16): To a solution of the secondary alcohol (6*S*,7*R*)-**11** (170 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) was added under argon at 0 °C NEt_3 (54 mg, 74 µL, 0.53 mmol) and MsCl (60 mg, 40 µL, 0.53 mmol). The mixture was stirred at 0 °C for 3 h. The solution was diluted with CH_2Cl_2 (5 mL), the organic phase was washed with saturated NH_4Cl- (5 mL) and saturated NaCl-solution (5 mL) and was dried with $MgSO_4$. The residue was purified by column chromatography (silica gel; hexanes/EtOAc 9:1), to give **16** (139 mg, 0.30 mmol, 85%) as colourless oil. R_f = 0.39 (hexanes/Et OAc 4:1). $[\alpha]_D^{23}$ = –6.5 (*c* = 1.0, CH_2Cl_2). FT-IR: $\tilde{\nu}$ = 2944, 2865, 1738, 1463, 1359, 1234, 1176, 1101, 1022, 904, 790, 682 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.35 (t, *J* = 7.0 Hz, 1 H, 7-H), 4.85 (m, 1 H, 3-H), 4.55 (d, *J* = 7.0 Hz, 2 H, 8-H), 3.63 (dd, *J* = 10.0, 5.7 Hz, 1 H, 1-H_A), 3.59 (dd, *J* = 10.0, 7.0 Hz, 1 H, 1-H_B), 2.99 (s, 3 H, 1'''-H), 2.21 (m, 2 H, 2-H, 5-H_A), 2.09 (m, 1 H, 5-H_B), 2.03 (s, 3 H, 2''-H), 1.82 (m, 1 H, 4-H_A) 1.75 (m, 1 H, 4-H_B), 1.69 (s, 3 H, 10-H), 1.03 (m, 3 H, 1'-H), 1.02 (m, overlapped, 18 H, 2'-H), 0.94 (d, *J* = 7.0 Hz, 3 H, 9-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.2 (C-1''), 141.1 (C-6), 119.1 (C-7), 85.0 (C-3), 65.0 (C-1), 61.3 (C-8), 39.7 (C-2), 38.7 (C-1'''), 35.2 (C-5), 28.2 (C-4), 21.1 (C-2''), 18.1 (C-2'), 16.6 (C-10), 11.9 (C-1'), 11.6 (C-9) ppm. HRMS (ESI): calcd. for $C_{22}H_{44}$ NaO_6SSi $[M + Na]^+$ 487.2520; found 487.2511.

(6*S*,7*R*)-3,7-Dimethyl-6-(methylsulfonyloxy)-3-(triethylsilylperoxy)-8-(triisopropylsilyloxy)octyl acetate (17): Et_3SiH (66 mg, 0.57 mmol) and $Co(acac)_2$ (8 mg, 0.03 mmol) was added at room temp. to a solution of mesylate **16** (132 mg, 0.28 mmol) in $(CH_2Cl)_2$ (6 mL). The mixture was stirred under O_2-atmosphere (balloon) at room temp. for 1 d. After addition of the same amounts of Et_3SiH and $Co(acac)_2$ the mixture was stirred under O_2-atmosphere at room temp. for further 3 d. The deep green solution was evaporated and the residue was purified by column chromatography (silica gel with Florisil® column head; hexanes/EtOAc 6:1) to give **17** (122 mg, 0.20 mmol, 71%) as a 2:3 mixture of C-3 epimers. R_f = 0.31 (hexanes/EtOAc 4:1). FT-IR: $\tilde{\nu}$ = 2941, 2869, 1742, 1463, 1362, 1237, 1176, 1104, 1015, 904, 800 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.81 (m, 1 H, 3-H), 4.13 (m, 2 H, 8-H), 3.62 (m, 2 H, 1-H), 2.98 (s, 3 H, 1'''-H), 2.16 (m, 1 H, 2-H), 2.02 (s, 3 H, 2''-H), 1.88 (m, 2 H, 7-H), 1.78 (m, 1 H, 5-H_A), 1.77 (m, 1 H, 4-H_A), 1.73 (m, 1 H, 4-H_B), 1.61 (m, 1 H, 5-H_B), 1.16, 1.15 (s, 3 H, 10-H), 1.06 (m, 3 H, 1'-H), 1.03 (m, overlapped, 18 H, 2'-H), 0.96 (m, overlapped, 3 H, 9-H), 0.94 (t, *J* = 7.9 Hz, 9 H, 2''''-H) 0.63 (q, *J* = 7.9 Hz, 6 H, 1''''-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.3 (C-1''), 171.2 (C-1''), 85.5, (C-3), 85.4 (C-3), 82.6 (C-6), 82.5 (C-6), 65.0 (C-1), 61.0 (C-8), 39.9 (C-2), 39.7 (C-2), 38.6 (C-1'''), 35.8 (C-7), 35.6 (C-7), 32.9 (C-5), 32.7 (C-5), 24.4 (C-4), 24.2 (C-4), 22.0 (C-10), 21.8 (C-10), 21.1 (C-2''), 18.1 (C-2'), 12.0 (C-1', C-9), 6.8 (C-2''''), 6.7 (C-2''''), 3.8 (C-1'''') ppm. HRMS (ESI): calcd. for $C_{28}H_{60}NaO_8SSi_2$ $[M + Na]^+$ 635.3440; found 635.3431.

(6*S*,7*R*)-3-Hydroperoxy-3,7-dimethyl-6-(methylsulfonyloxy)-8-(triisopropylsilyloxy)octyl acetate (10): To a solution of silylperoxide **17** (111 mg, 0.18 mmol) in THF (3 mL) was added NEt_3×3HF (29 mg, 30 µl, 0.18 mmol). The mixture was stirred for 10 min at room temp.. The reaction was quenched with saturated $NaHCO_3$-solution. The mixture was extracted with EtOAc (2 × 5 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated to give **10** (86 mg, 0.17 mmol, 95%) as a 2:3 mixture of C-3 epimers. R_f = 0.17 (hexanes/EtOAc 4:1). FT-IR: $\tilde{\nu}$ = 3422, 2942, 2867, 1738, 1464, 1332, 1241, 1173, 1035, 904, 786 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.67 (s, 1 H, 6-OOH), 4.86 (m, 1 H, 3-H), 4.20 (m, 2 H, 8-H), 3.64 (m, 2 H, 1-H), 3.01 (s, 3 H, 1'''-H), 2.14 (m, 1 H, 2-H), 2.04 (s, 3 H, 2''-H), 1.98 (m, 1 H, 7-H_A), 1.88 (m, 1 H, 4-H_A), 1.85 (m, 1 H, 7-H_B), 1.82 (m, 1 H, 4-H_B), 1.81 (m, 1 H, 5-H_A), 1.61 (m, 1 H, 5-H_B), 1.16, 1.12 (s, 3 H, 10-H), 1.04 (m, 3 H, 1'-H), 1.03 (m, overlapped, 18 H, 2'-H), 0.96, 0.95 (d, *J* = 7.0 Hz, 3 H, 9-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.6 (C-1''), 85.2 (C-3), 82.5 (C-6), 64.9 (C-1), 60.8 (C-8), 60.7 (C-8), 39.4 (C-2), 38.7 (C-1'''), 38.6 (C-1'''), 35.7 (C-7), 35.3 (C-7), 32.0 (C-5), 31.8 (C-5), 24.2 (C-4), 21.3 (C-10), 21.2 (C-10), 20.9 (C-2''), 18.1 (C-2'), 12.1 (C-9), 11.9 (C-1') ppm. HRMS (ESI): calcd. for $C_{22}H_{47}O_8SSi$ $[M + H]^+$ 499.2755; found 499.2754.

2-((6*R*)-3-Methyl-6-((*R*)-1-(triisopropylsilyloxy)propan-2-yl)-1,2-dioxan-3-yl) ethyl acetate (9): To a solution of the hydroperoxide **10** (302 mg, 0.61 mmol) in THF (20 mL) in a Schlenk flask was added DBU (304 mg, 300 µL, 2.00 mmol) and the mixture was heated at 60 °C for 14 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 6:1→4:1), to give a 2:3 mixture of the C-3 epimeric endoperoxides **9** (207 mg, 0.53 mmol, 87%) as a colourless oil. **9a**, Me-10 axial; **9b**, Me-10 equatorial. R_f = 0.38 (hexanes/EtOAc 4:1). FT-IR: $\tilde{\nu}$ = 2943, 2866, 1742, 1463, 1366, 1233, 1099, 1067, 1034, 882, 794 cm^{-1}. **9a**, ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.15 (m, 2 H, 8-H), 4.03 (m, 1 H, 3-H), 3.65 (m, 2 H, 1-H), 2.03 or 2.02 (s, 3H, 2''-H), 1.82 (m, 2 H, 7-H), 1.70 (m, 1 H, 2-H), 1.67 (m, 4 H, 4-H, 5-H), 1.35 (s, 3 H, 10-H), 1.06 (m, overlapped, 18 H, 2'-H) 1.05 (m, 3 H, 1'-H), 1.00 or 0.99 (d, *J* = 6.9 Hz, 3 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.2 or 171.1 (C-1''), 82.3 (C-3), 79.0 (C-6), 65.3 (C-1), 60.2 (C-8), 38.9 (C-7), 39.7 (C-2), 32.9 (C-5), 23.5 (C-

4), 21.2 or 21.1 (C-2''), 20.9 (C-10), 18.1 (C-2'), 12.7 (C-9), 12.1 (C-1') ppm. **9b**, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.17 (m, 2 H, 8-H), 4.03 (m, 1 H, 3-H), 3.65 (m, 2 H, 1-H), 2.28 (m, 1 H, 7-H_A), 2.03 or 2.02 (s, 3 H, 2''-H), 1.90 (m, 1 H, 7-H_B), 1.80 (m, 2 H, 4-H), 1.76 (m, 2 H, 5-H), 1.70 (m, 1 H, 2-H), 1.14 (s, 3 H, 10-H), 1.06 (m, overlapped, 18 H, 2'-H), 1.05 m, 3 H, 1'-H), 1.00 or 0.99 (d, J = 6.9 Hz, 3 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.2 or 171.1 (C-1''), 82.0 (C-3), 78.6 (C-6), 65.3 (C-1), 61.1 (C-8), 39.7 (C-2), 33.7 (C-5), 33.2 (C-7), 24.8 (C-10), 23.7 (C-4), 21.2 or 21.1 (C-2''), 18.1 (C-2'), 12.8 (C-9), 12.1 (C-1') ppm. HRMS (ESI): calcd. for $C_{21}H_{43}O_5Si$ $[M + H]^+$ 403.2874; found 403.2867.

2-{(6*R*)-3-Methyl-6-[(*R*)-1-(triisopropylsilyloxy)propan-2-yl]-1,2-dioxan-3-yl}ethanol (18): To a solution of endoperoxide acetate **9** (51.5 mg, 133 µmol) in MeOH (130 mL) was added K_2CO_3 (1.83 mg, 13 µmol). After stirring at room temp. for 4 h MeOH was removed under vacuum. The residue was partitioned between CH_2Cl_2 (70 mL) and H_2O (70 mL). The organic phase was dried with $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 4:1), to give a 2:3 mixture of the C-3 epimeric endoperoxide alcohol **18** (39 mg, 108 µmol, 81%) as a colourless oil. **18a**, Me-10 axial; **18b**, Me-10 equatorial. R_f = 0.25 (hexanes/EtOAc 4:1). FT-IR: $\tilde{\nu}$ = 3388, 2940, 2865, 1462, 1381, 1246, 1099, 1068, 1031, 1012, 881. **18a**, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.05 (m, 1 H, 3-H), 3.73 (m, 2 H, 8-H), 3.66 (dd, J = 9.8, 5.4 Hz, 1 H, 1-H_A), 3.63 (dd, J = 9.8, 5.1 Hz, 1 H, 1-H_B), 1.78 (m, 2 H, 7-H), 1.69 (m, 1 H, 2-H), 1.67 (m, 2 H, 5-H), 1.66 (m, 2 H, 4-H), 1.38 (s, 3 H, 10-H), 1.05 (m, 3 H, 1'-H), 1.04 (m, overlapped, 18 H, 2'-H), 1.00 (d, J = 6.9 Hz, 3 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 82.3 (C-3), 80.8 (C-6), 65.3 (C-1), 58.6 (C-8), 43.1 (C-7), 39.7 (C-2), 33.1 (C-5), 23.5 (C-4), 20.9 (C-10), 18.1 (C-2'), 12.6 (C-9), 12.1 (C-1') ppm. **18b**, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.05 (m, 1 H, 3-H), 3.88 (m, 2 H, 8-H), 3.66 (dd, J = 9.8, 5.4 Hz, 1 H, 1-H_A), 3.63 (dd, J = 9.8, 5.1 Hz, 1 H, 1-H_B), 2.38 (m, 1 H, 7-H_A), 1.82 (m, 2 H, 4-H), 1.70 (m, 2 H, 5-H), 1.69 (m, 1 H, 2-H), 1.65 (m, 1 H, 7-H_B) 1.16 (s, 3 H, 10-H), 1.05 (m, 3 H, 1'-H), 1.04 (m, overlapped, 18 H, 2'-H), 1.00 (d, J = 6.9 Hz, 3 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 82.3 (C-3), 79.7 (C-6), 65.3 (C-1), 59.1 (C-8), 39.7 (C-2), 36.9 (C-7), 34.1 (C-5), 24.7 (C-10), 23.7 (C-4), 18.1 (C-2'), 12.8 (C-9), 12.1 (C-1') ppm. HRMS (ESI): calcd. for $C_{19}H_{41}O_4Si$ $[M + H]^+$ 361.2769; found 361.2763.

2-((6*R*)-3-Methyl-6-((*R*)-1-(triisopropylsilyloxy)propan-2-yl)-1,2-dioxan-3-yl) acetaldehyde (5): The primary alcohol **18** (72.3 mg, 0.20 mmol) was diisolved under argon in abs. CH_2Cl_2 and cooled to 0 °C. Dess-Martin-periodinane (93.3 mg, 0.22 mmol) was added and after 65 min the reaction was quenched by addition of a 1:1 mixture of saturated $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried with $MgSO_4$ and evaporated under vacuum to dryness. The residue was purified by column chromatography (silica gel; hexanes/EtOAc 4:1), to give a 2:3 mixture of the C-3 epimeric endoperoxide aldehydes **5** (60.7 mg, 0.17 mol, 85%) as a colourless liquid. **5a**, Me-10 axial; **5b**, Me-10 equatorial. R_f = 0.65 (hexanes/EtOAc 4:1). FT-IR: $\tilde{\nu}$ = 2942, 2867, 1725, 1463, 1377, 1103, 1064, 1012, 883, 793, 682. **5a**, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.78 (dd, J = 2.8 Hz, 1H, 8-H), 4.09 (m, 1 H, 3-H), 3.66 (dd, J = 9.9, 5.4 Hz, 1 H, 1-H_A), 3.63 (dd, J = 9.9, 5.5 Hz, 1 H, 1-H_B), 2.56 (dd, J = 15.2, 3.7 Hz, 1 H, 7-H_A), 2.50 (dd, J = 15.2, 3.0 Hz, 1 H, 7-H_B), 1.84 (m, 2H, 4-H), 1.76 (m, 2 H, 5-H), 1.74 (m, 1 H, 2-H), 1.43 (s, 3 H, 10-H), 1.04 (m, 3 H, 1'-H), 1.03 (m, overlapped, 18 H, 2'-H), 1.01 or 1.00 (d, J = 7.0 Hz, 3 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 200.6 (C-8), 82.4 (C-3), 79.1 (C-6), 65.2 (C-1), 53.2 (C-7), 39.4 (C-2), 32.7 (C-5), 23.2 (C-4), 21.7 (C-10), 18.1 (C-2'), 12.8 (C-9), 12.0 (C-1') ppm. **5b**, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.83 (dd, J = 3.7, 1.8 Hz, 1H, 8-H), 4.09 (m, 1 H, 3-H), 3.66 (dd, J = 9.9, 5.4 Hz, 1 H, 1-H_A), 3.63 (dd, J = 9.9, 5.5 Hz, 1 H, 1-H_B), 3.08 (d, J = 14.6 Hz, 1 H, 7-H_A), 2.52 (d, J = 14.6 Hz, 1 H, 7-H_B), 1.82 (m, 1 H, 5-H_A), 1.76 (m, 1 H, 4-H_A), 1.73 (m, 1 H, 5-H_B), 1.70 (m, 1 H, 4-H_B), 1.67 (m, 1 H, 2-H), 1.23 (s, 3 H, 10-H), 1.04 (m, 3 H, 1'-H), 1.03 (m, overlapped, 18 H, 2'-H), 1.01 or 1.00 (d, J = 7.0 Hz, 3 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 202.3 (C-8), 82.3 (C-3), 78.7 (C-6), 65.1 (C-1), 48.2 (C-7), 39.7 (C-2), 33.7 (C-5), 25.2 (C-10), 23.8 (C-4), 18.1 (C-2'), 12.7 (C-9), 12.0 (C-1') ppm. HRMS (ESI): calcd. for $C_{19}H_{39}O_4Si$ $[M + H]^+$ 359.2612; found 359.2610.

2-(4-Methoxy-3-methylbut-3-enyl)-1,3,3-trimethylcyclohex-1-ene (20): Phosphonium chloride **19** (12.2 g, 35.5 mmol) was suspended under argon atmosphere in THF (150 mL). After cooling to –78 °C *n*-BuLi (2.5 M in hexane, 14.2 mL, 35.5 mmol) was added during a period of 10 min. The deep red solution of the ylide which was formed from **19** was stirred at –78 °C for 30 min and warmed to 0 °C To this solution was added dropwise during a period of 5 min dihydro-*β*-ionone (**8,** 5.31 g, 5.75 mL, 27.3 mmol) whereupon decolourisation occurred. The reaction mixture was warmed to room temp., stirred for 24 h, and quenched with saturated NH_4Cl solution (100 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried with $MgSO_4$ and evaporated. The crude product was purified by column chromatography (silica gel; hexanes/CH_2Cl_2 19:1 → 17:3), to give **20** (4.36 g, 19.6 mmol, 72%) as a colourless oil and an (*E*/*Z*)-mixture of 2:1. R_f = 0.54 (*Z*)-isomer, 0.42 (*E*)-isomer (hexanes/CH_2Cl_2 3:1). FT-IR: $\tilde{\nu}$ = 2959, 2928, 2868, 2829, 1682, 1456, 1381, 1358, 1207, 1128, 1061, 928, 924. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.80, 5.72 (m, 1 H, 1-H_E, 1-H_Z), 3.54, 3.51 (s, 3 H 1'-H_E, 1'-H_Z), 2.04 (m, 2 H, 4-H), 1.90 (m, 2 H, 3-H), 1.90 (t, J = 6.1 Hz, 2 H, 7-H), 1.64 (d, J = 1.4 Hz, 11-H_E), 1.61 (s, 3 H, 12-H), 1.58 (d, J = 1.5 Hz, 11-H_Z), 1.57 (m, 2 H, 8-H), 1.42 (m, 2 H, 9-H), 1.02 (s 6 H, 13-H_Z, 14-H_Z), 0.99 (s, 6 H, 13-H_E, 14-H_E) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 141.6 (C-1), 137.2 (C-5), 127.1 (C-6), 114.9 (C-2), 59.2 (C-1'), 40.1 (C-9), 40.0 (C-9), 35.0 (C-10), 34.8 (C-3), 32.9 (C-7), 28.7 (C-13, C-14), 28.3 (C-4), 27.1 (C-4), 20.0 (C-12), 19.7 (C-8), 17.4 (C_Z-11), 12.9 (C_E-11) ppm. MS (EI, 70 eV): *m*/*z* (%) = 222 (6) $[M]^+$, 190 (3), 137 (12), 121 (4); 107 (4), 95 (20), 85 (100), 67 (7), 55 (23).

2-Methyl-4-(2,6,6-trimethylcyclohex-1-enyl)butanal (21): To the enolether **20** (7.15 g, 32.2 mmol) in Me_2CO/H_2O 3:1 was added TsOH×H_2O (6.73 g, 35.4 mmol). The reaction mixture was stirred under reflux for 3 h, cooled to 0 °C, and the pH-value was adjusted to 7 with 0.2 N NaOH. The solvent was removed under vacuum and the aqueous phase was extracted with MTBE (2 × 250 mL). The combined organic phases were dried with MgSO4, filtered, and evaporated to dryness to give the aldehyde **21** (6.41 g, 30.8 mmol, 96%) as colourless liquid. R_f = 0.25 (hexanes/CH_2Cl_2 3:1). FT-IR: $\tilde{\nu}$ = 2960, 2928, 2869, 2829, 2702, 1726, 1472, 1457, 1377, 1362, 1208, 1117, 919. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.60 (d, J = 2.0 Hz, 1 H, 1-H), 2.30 (m, 1 H, 2-H), 1.96 (m, 2 H, 4-H), 1.86 (t, J = 6.3 Hz, 2 H, 7-H), 1.72 (m, 1 H, 3-H_A), 1.54 (s, 3 H, 12-H), 1.51 (m, 2 H, 8-H), 1.38 (m, 1 H, 3-H_B), 1.37 (m, 2 H, 9-H), 1.09 (d, J = 6.9 Hz, 11-H), 0.94 (s, 3 H, 13-H or 14-H), 0.93 (s, 3 H, 13-H or 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 204.8 (C-1), 136.7 (C-5), 127.5 (C-6), 47.2 (C-2), 39.8 (C-9), 34.9 (C-10), 32.8 (C-7), 31.1 (C-3), 28.6 (C-13, C-14), 26.1 (C-4), 19.9 (C-12), 19.5 (C-8), 13.2 (C-

11) ppm. MS (EI, 70 eV): 208 (24, $[M]^+$), 193 (20), 175 (35), 150 (38), 135 (69), 123 (100), 107 (51), 95 (40), 81 (81), 69 (37), 55 (41).

2-Methyl-4-(2,6,6-trimethylcyclohex-1-enyl)butan-1-ol (7): To aldehyde **21** (1.01 g, 4.83 mmol) in MeOH (10 mL) was added at 0 °C $NaBH_4$ (201 mg, 5.31 mmol). After 2 h the reaction mixture was warmed to room temp., H_2O (30 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$, filtered, and evaporated to dryness to give the alcohol **7** (968 mg, 4.60 mmol, 95%). R_f = 0.47 (hexanes/Me_2CO 4:1). FT-IR: $\tilde{\nu}$ = 3312, 2960, 2928, 2869, 1473, 1457, 1378, 1362, 1038, 990. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.50 (dd, J = 10.3, 5.7 Hz, 1 H, 1-H_A), 3.38 (dd, J = 10.3, 6.7 Hz, 1 H, 1-H_B), 2.09 (s, 1 H, 1-OH), 2.06 – 1.86 (m, 2 H, 4-H), 1.87 (t, J = 6.3 Hz, 2 H, 7-H), 1.59 (m, 1 H, 2-H), 1.56 (s, 3 H, 12-H), 1.53 (m, 2 H, 8-H), 1.43 (m, 1 H, 3-H_A), 1.39 (m, 2 H, 9-H), 1.18 (m, 1 H, 3-H_B), 0.96 (s, 6 H, 13-H, 14-H), 0.94 (d, J = 6.7 Hz, 11-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 137.5 (C-5), 126.7 (C-6), 68.2 (C-1), 40.0 (C-9), 36.9 (C-2), 35.0 (C-10), 33.9 (C-3), 32.8 (C-7), 28.7 (C-13, C-14), 26.3 (C-4), 19.9 (C-12), 19.6 (C-8), 16.6 (C-11) ppm. MS (EI, 70 eV): 210 (25, $[M]^+$), 195 (20), 177 (25), 137 (8), 123 (100), 107 (34), 95 (60), 81 (57), 69 (22), 55 (27). HRMS (ESI): calcd. for $C_{14}H_{27}O$ $[M + H]^+$ 211.2056; found 211.2053.

5-[2-Methyl-4-(2,6,6-trimethylcyclohex-1-enyl)butylthio]-1-phenyl-1*H*-tetrazol (22): The solution of alcohol **7** (1.00 g, 4.75 mmol), 1-phenyl-1*H*-tetrazolyl-5-thiol (**6**) (1.02 g, 5.70 mmol), and PPh_3 (1.50 g, 5.70 mmol) in THF (10 mL) was cooled to 0 °C under argon. Diisopropyl azodicarboxylate (1.25 g, 1.21 mL, 6.18 mmol) was added dropwise during a period of 10 min. The resulting pale yellow solution was stirred at 0 °C for 10 min, warmed up to romm temp., and stirred for further 3 h. The solution was evaporated and the residue was purified by column chromatography (silica gel, hexanes/CH_2Cl_2 4:1) to give **22** (1.66 g, 4.48 mmol, 94%) as a colourless oil. R_f = 0.37 (hexanes/CH_2Cl_2 4:1). FT-IR: $\tilde{\nu}$ = 2958, 2928, 2866, 1598, 1500, 1410, 1382, 1240, 1087, 1074, 1015, 750. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.55 (m, 5H, 2''H – 6''-H), 3.45 (dd, J = 12.5, 6.0 Hz, 1 H, 1-H_A), 3.30 (dd, J = 12.5, 7.3 Hz, 1 H, 1-H_B), 2.07 – 1.92 (m, 2 H, 4-H), 1.92 (m, 1 H, 2-H), 1.87 (t, J = 6.3 Hz, 2 H, 7-H), 1.54 (m, 3 H, 3-H_A, 8-H), 1.54 (s, 3 H, 12-H), 1.38 (m, 2 H, 9-H), 1.33 (m, 1 H, 3-H_B), 1.07 (d, J = 6.6 Hz, 3 H, 11-H), 0.95 (s, 6 H, 13-H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 154.8 (C-1'), 137.0 (C-5), 133.9 (C-1''), 130.1 (C-4''), 129.8 (C-3'', C-5''), 127.1 (C-6), 124.0 (C-2'', C-6''), 40.4 (C-1), 39.9 (C-9), 36.4 (C-3), 35.0 (C-10), 34.0 (C-2), 32.8 (C-7), 28.7 (C-13, C-14), 26.1 (C-4), 19.9 (C-12), 19.6 (C-8), 19.1 (C-11) ppm. HRMS (ESI): calcd. for $C_{21}H_{31}N_4S$ $[M + H]^+$ 371.2264; found 371.2263.

5-[2-Methyl-4-(2,6,6-trimethylcyclohex-1-enyl)butylsulfonyl]-1-phenyl-1*H*-tetrazol (4): To a solution of thioether **22** (1.31 g, 3.54 mmol) in EtOH (30 mL) was added under strong stirring $(NH_4)_8Mo_7O_{24}\times4H_2O$ (438 mg, 0.35 mmol) in 30% H_2O_2 (3.62 mL, 35.4 mmol). The yellow solution was stirred at room temp. for 72 h. After addition of H_2O (100 mL) and Et_2O (100 mL) the organic phase was separated and the aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic extracts were washed with H_2O (80 mL), saturated NaCl solution (80 mL), dried with MgSO4, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica gel; hexanes/Me_2CO 17:3), to give **4** (1.26 g, 3.13 mmol, 88%) as colourless, waxy substance. R_f = 0.41 (hexanes/Me_2CO 17:3). FT-IR: $\tilde{\nu}$ = 2932, 2866, 1596, 1498, 1460, 1335, 1267, 1151, 1013, 761.^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.70 (m, 2 H, 2''H, 6''-H), 7.67 (m, 3 H, 3''-H, 4''-H, 5''-H), 3.83 (dd, J = 14.5, 4.7 Hz, 1 H, 1-H_A), 3.61 (dd, J = 14.5, 7.8 Hz, 1 H, 1-H_B), 2.32 (m, 1 H, 2-H), 2.08 – 1.99 (m, 2 H, 4-H), 1.89 (t, J = 6.3 Hz, 2 H, 7-H), 1.63 (m, 1 H, 3-H_A) 1.56 (s, 3 H, 12-H), 1.54 (m, 2 H, 8-H), 1.47 (m, 1 H, 3-H_B), 1.41 (m, 2 H, 9-H), 1.20 (d, J = 6.9 Hz, 3 H, 11-H), 0.96 (s, 6 H, 13-H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 154.2 (C-1'), 136.4 (C-5), 133.2 (C-1''), 131.6 (C-4''), 129.8 (C-3'', C-5''), 127.6 (C-6), 125.3 (C-2'', C-6''), 62.0 (C-1), 39.9 (C-9), 37.1 (C-3), 35.0 (C-10), 32.9 (C-7), 29.4 (C-2), 28.7 (C-13, C-14), 25.8 (C-4), 19.9 (C-12), 19.7 (C-11), 19.6 (C-8) ppm. HRMS (ESI): calcd. for $C_{21}H_{31}O_2N_4S$ $[M + H]^+$ 403.2162; found 403.2154.

Triisopropyl-{(2*R*)-2-[(3*R*)-6-methyl-6-((*E*)-4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hex-2-enyl)-1,2-dioxan-3-yl]propoxy}silane (3): Under argon atmosphere the sulfone **4** (29 mg, 73.0 µmol) in THF (1 mL) was cooled to –78 °C and KHMDS (0.7 M in toluene, 105 µL, 73 µmol) was added dropwise. The resulting orange suspension was stirred at –78 °C for 30 min and aldehyde **5** (20 mg, 56.0 µmol) in absolute THF (1 mL) was added. After 2 h KHMDS (0.7 M in toluene, 5 × 50 µL, 175 µmol) was added over 3 h. When TLC showed complete consumption of starting aldehyde **5**, saturated NH_4Cl solution (5 mL) and Et_2O (2 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were dried with $MgSO_4$ and evaporated under vacuum to dryness. The residue was purified by column chromatography (silica gel; hexanes/EtOAc 19:1), to give a mixture of four isomers of **3** (25.7 mg, 48.0 µmol, 86%) as a colourless oil. **3a**, Me-20 axial; **3b**, Me-20 equatorial. R_f = 0.35 hexanes/CH_2Cl_2 9:2). FT-IR: $\tilde{\nu}$ = 2929, 2856, 1462, 1372, 1258, 1100, 1068, 1013, 973, 919, 882, 796, 681. **3a**, ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.36 (m, 2 H, 8-H, 9-H), 4.02 (m, 1 H, 3-H), 3.68 (dd, J = 9.7, 5.1 Hz, 1 H, 1-H_A), 3.64 (dd, J = 9.7, 5.7 Hz, 1 H, 1-H_B), 2.12 (m, 2 H, 7-H), 2.07 (m, 1 H, 10-H), 1.94, 1.88 (m, 2 H, 12-H), 1.88 (t, J = 6.1 Hz, 2 H, 15-H), 1.78 (m, 2 H, 4-H), 1.75 (m, 2 H, 5-H), 1.68 (m, 1 H, 2-H), 1.56 (s, 3 H, 22-H), 1.54 (m, 2 H, 16-H), 1.39 (m, 2 H, 17 H), 1.31 (m, 2 H, 11-H), 1.31 (s, 3 H 20-H), 1.05 (m, 3 H, 1'-H), 1.05 (m, overl.,18 H, 2'-H), 1.01 (d, J = 6.8 Hz, 3 H, 19-H), 0.96 (s, 6 H, 23-H, 24-H), 0.96 (m, overl., 3 H, 21-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 139.9 (C-9), 137.7 (C-13), 126.7 (C-14), 122.5 (C-8), 122.4 (C-8), 82.4 (C-3), 80.2 (C-6), 65.4 (C-1), 44.0 (C-7), 39.9 (C-17), 39.7 (C-2), 38.3 (C-10), 37.7 (C-11), 35.1 (C-18), 32.8 (C-15), 32.2 (C-5), 28.8 (C-23, C-24), 26.9 (C-12), 23.9 (C-4), 21.1 (C-20), 20.9 (C-21), 20.0 (C-22), 19.7 (C-16), 18.2 (C-2'), 12.8 (C-19), 12.1 (C-1') ppm. **3b**, ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.36 (m, 2 H, 8-H, 9-H), 4.02 (m, 1 H, 3-H), 3.68 (dd, J = 9.7, 5.1 Hz, 1 H, 1-H_A), 3.64 (dd, J = 9.7, 5.7 Hz, 1 H, 1-H_B), 2.45 (m, 2 H, 7-H), 2.07 (m, 1 H, 10-H), 1.94, 1.88 (m, 2 H, 12-H), 1.88 (t, J = 6.1 Hz, 2 H, 15-H), 1.68 (m, 1 H, 2-H), 1.62 (m, 2 H, 4-H), 1.58 (m, 2 H, 5-H), 1.56 (s, 3 H, 22-H), 1.54 (m, 2 H, 16-H), 1.39 (m, 2 H, 17 H), 1.31 (m, 2 H, 11-H), 1.08 (s, 3 H, 20-H), 1.05 (m, 3 H, 1'-H), 1.05 (m, overl.,18 H, 2'-H), 1.01 (d, J = 6.8 Hz, 3 H, 19-H), 0.96 (s, 6 H, 23-H, 24-H), 0.96 (m, overl., 3 H, 21-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 140.5 (C-9), 137.7 (C-13), 126.7 (C-14), 123.9 (C-8), 123.7 (C-8), 82.1 (C-3), 80.1 (C-6), 65.3 (C-1), 39.9 (C-17), 39.7 (C-2), 38.2 (C-7), 38.1 (C-10), 37.7 (C-11), 35.1 (C-18), 32.8 (C-15), 32.1 (C-5), 28.8 (C-23, C-24), 26.7 (C-12), 24.6 (C-20), 23.7 (C-4), 20.9 (C-21), 20.0 (C-22), 19.7 (C-16), 18.2 (C-2'), 12.9 (C-19), 12.1 (C-1') ppm. HRMS (ESI): calcd. for $C_{33}H_{63}O_3Si$ $[M + H]^+$ 535.4514; found 535.4538.

Triisopropyl-{(2*R*)-2-[(3*R*)-6-methyl-6-(4-methyl-6-(2,2,6-trimethylcyclohex-1-enyl)hexyl)-1,2-dioxane-3-yl]propoxy}silane (23): The peroxide **3** (53 mg, 100 µmol) was dissolved in

CH_2Cl_2/MeOH 1:1 (2 mL) under argon atmosphere and dipotassium azodicarboxylate (97 mg, 500 µmol) was added. The yellow suspension was cooled to –78 °C and AcOH (90 mg, 86 µL in 1 mL CH_2Cl_2) was dropwise added. The mixture was slowly warmed to room temperature and stirred for 12 h. To the white suspension was added saturated NH_4Cl solution and the organic solvents were evaporated under vacuum. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried with $MgSO_4$ and evaporated under vacuum to dryness. The conversion was determined by ^{1}H NMR spectroscopy. The procedure described above was still repeated seven times and **23** (34.5 mg, 64.3 µmol, 64%) was obtained as colourless oil. **23a**, Me-20 axial; **23b**, Me-20 equatorial. R_f = 0.35 (hexanes/CH_2Cl_2 9:2). FT-IR: $\tilde{\nu}$ = 2929, 2856, 1462, 1372, 1258, 1100, 1068, 1013, 973, 919, 882, 796, 681. **23a**, ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.00 (m, 1 H, 3-H), 3.68 (dd, J = 9.7, 4.8 Hz, 1 H, 1-H_A), 3.63 (dd, J = 9.7, 5.7 Hz, 1 H, 1-H_B), 1.99, 1.88 (m, 2 H, 12-H), 1.88 (t, J = 6.3 Hz, 2 H, 15-H), 1.77 (m, 2 H, 4-H), 1.73 (m, 2 H, 5-H), 1.68 (m, 1 H, 2-H), 1.57 (s, 3 H, 22-H), 1.54 (m, 2 H, 16-H), 1.39 (m, 2 H, 17 H), 1.39 (m, 1 H, 10-H), 1.37 (m, 4 H, 7-H, 8-H), 1.33, 1.17 (m, 2 H, 9-H), 1.31 (s, 3 H, 20-H), 1.25 (m, 2 H, 11-H), 1.04 (m, 3 H, 1'-H), 1.04 (m, overl.,18 H, 2'-H), 1.01 (d, J = 6.9 Hz, 3 H, 19-H), 0.97 (s, 3 H, 23-H), 0.96 (s, 3 H, 24-H), 0.91 (d, J = 6.5 Hz, 3 H, 21-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 137.8 (C-13), 126.5 (C-14), 82.4 (C-3), 80.1 (C-6), 65.4 (C-1), 41.1 (C-7), 40.0 (C-17), 39.6 (C-2), 37.4 (C-9), 35.1 (C-18), 34.0 (C-10), 33.1 (C-5), 32.9 (C-15), 32.1 (C-11), 28.8 (C-23, C-24), 26.5 (C-12), 23.9 (C-4), 20.6 (C-8), 20.5 (C-8), 20.4 (C-20), 20.0 (C-22), 19.7 (C-16), 19.6 (C-21), 18.2 (C-2'), 12.9 (C-19), 12.0 (C-1') ppm. **23b**, ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.00 (m, 1 H, 3-H), 3.68 (dd, J = 9.7, 4.8 Hz, 1 H, 1-H_A), 3.63 (dd, J = 9.7, 5.7 Hz, 1 H, 1-H_B), 1.99, 1.88 (m, 2 H, 12-H), 1.88 (t, J = 6.3 Hz, 2 H, 15-H), 1.68 (m, 1 H, 2-H), 1.63 (m, 2 H, 5-H), 1.62 (m, 2 H, 4-H), 1.57 (s, 3 H, 22-H), 1.54 (m, 2 H, 16-H), 1.39 (m, 5 H, 7-H, 10-H, 17-H), 1.37 (m, 2 H, 8-H), 1.33, 1.17 (m, 2 H, 9-H), 1.25 (m, 2 H, 11-H), 1.08 (s, 3 H, 20-H), 1.04 (m, 3 H, 1'-H), 1.04 (m, overl.,18 H, 2'-H), 1.01 (d, J = 6.9 Hz, 3 H, 19-H), 0.97 (s, 3 H, 23-H), 0.96 (s, 3 H, 24-H), 0.91 (d, J = 6.5 Hz, 3 H, 21-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 137.8 (C-13), 126.5 (C-14), 82.1 (C-3), 80.0 (C-6), 65.3 (C-1), 44.1 (C-7), 40.0 (C-7, C-17), 39.8 (C-2), 37.6 (C-9), 35.1 (C-18), 33.8 (C-10), 32.9 (C-5, C-15), 32.1 (C-11), 28.8 (C-23, C-24), 26.4 (C-12), 24.4 (C-20), 23.6 (C-4), 21.3 (C-8), 21.2 (C-8), 20.0 (C-22), 19.7 (C-16), 19.6 (C-21), 18.2 (C-2'), 12.8 (C-19), 12.0 (C-1') ppm. HRMS (ESI): calcd. for $C_{33}H_{65}O_3Si$ $[M + H]^+$ 537.4697; found 537.4697.

(2*R*)-{(3*R*)-6-Methyl-6-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hexyl]-1,2-dioxane-3-yl}propan-1-ol (2): The TIPS-ether **23** (52 mg, 96.8 µmol) was dissolved in MeCN/THF 1:1 (3 mL) at room temp. and HF 40% aq. (100 µL) was added. After 4 h saturated $NaHCO_3$ solution (3 mL) was added and the organic solvents were evaporated under vacuum. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were dried with $MgSO_4$ and evaporated under vacuum to dryness to give **2** (21.3 mg, 56.1 µmol, 58%) as a colourless oil. **2a**, Me-20 axial; **2b**, Me-20 equatorial. R_f = 0.33 (hexanes/EtOAc 3:1). FT-IR: $\tilde{\nu}$ = 3409, 2924, 2854, 1438, 1376, 1260, 1089, 1018, 865, 798, 700. **2a**, ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.10 (m, 1 H, 3-H), 3.67 (m, 1 H, 1-H_A), 3.59 (m, 1 H, 1-H_B), 1.98, 1.88 (m, 2 H, 12-H), 1.88 (t, J = 6.3 Hz, 2 H, 15-H), 1.82 (m, 1 H, 2-H), 1.79 (m, 2 H, 4-H), 1.78 (m, 2 H, 5-H), 1.57 (s, 3 H, 22-H), 1.53 (m, 2 H, 16-H), 1.40 (m, 1 H, 10-H), 1.39 (m, 2 H, 7-H), 1.38 (m, 4 H, 8-H, 17-H), 1.33, 1.13 (m, 2 H, 9-H), 1.32 (s, 3 H, 20-H), 1.25 (m, 2 H, 11-H), 1.00 (d, J = 6.9 Hz, 3 H, 19-H), 0.98 (s, 6 H, 23-H, 24-H), 0.91 (d, J = 6.5 Hz, 3 H, 21-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 137.8 (C-13), 126.5 (C-14), 82.9 (C-3), 80.4 (C-6), 65.4 (C-1), 41.1 (C-7), 40.0 (C-17), 39.2 (C-2), 37.4 (C-9), 35.1 (C-18), 34.0 (C-10), 33.0 (C-5), 32.9 (C-15), 32.1 (C-11), 28.8 (C-23, C-24), 26.5 (C-12), 22.9 (C-4), 20.6 (C-8), 20.5 (C-8), 20.3 (C-20), 20.0 (C-22), 19.7 (C-16), 19.6 (C-21), 11.9 (C-19) ppm. **2b**, ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.10 (m, 1 H, 3-H), 3.67 (m, 1 H, 1-H_A), 3.59 (m, 1 H, 1-H_B), 1.98, 1.88 (m, 2 H, 12-H), 1.88 (t, J = 6.3 Hz, 2 H, 15-H), 1.82 (m, 1 H, 2-H), 1.66 (m, 2 H, 5-H), 1.62 (m, 2 H, 4-H), 1.57 (s, 3 H, 22-H), 1.53 (m, 2 H, 16-H), 1.40 (m, 1 H, 10-H), 1.39 (m, 2 H, 7-H), 1.38 (m, 4 H, 8-H, 17-H), 1.33, 1.13 (m, 2 H, 9-H), 1.25 (m, 2 H, 11-H), 1.08 (s, 3 H, 20-H), 1.00 (d, J = 6.9 Hz, 3 H, 19-H), 0.98 (s, 6 H, 23-H, 24-H), 0.91 (d, J = 6.5 Hz, 3 H, 21-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 137.8 (C-13), 126.5 (C-14), 82.5 (C-3), 80.3 (C-6), 65.4 (C-1), 40.0 (C-7, C-17), 39.3 (C-2), 37.6 (C-9), 35.1 (C-18), 33.8 (C-10), 32.9 (C-5, C-15), 32.1 (C-11), 28.8 (C-23, C-24), 26.3 (C-12), 24.5 (C-20), 22.8 (C-4), 21.3 (C-8), 21.0 (C-8), 20.0 (C-22), 19.7 (C-16), 19.6 (C-21), 11.8 (C-19) ppm. HRMS (ESI): calcd. for $C_{24}H_{45}O_3$ $[M + H]^+$ 381.3363; found 381.3355.

Diacarnoxide C (1) and (2*S*)-methyl-2-((3*R*,6*R*)-6-methyl-6-(4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hexyl)-1,2-dioxan-3-yl)propanoate (24): To a solution of **2** (21.3 mg, 56.1 µmol) in MeCN (1 mL) was added H_5IO_6 (25.4 mg, 112.2 µmol) under stirring. The resulting whitely suspension was cooled to 0 °C and PCC (2.7 mg, 12 µmol) was added. The yellow-orange suspension was stirred at 0 °C for 15 min and at room temp. for 1.5 h. The reaction was quenched with half saturated NaCl solution (5 mL). MTBE (15 mL) was added and the organic phase was separated. The aqueous phase was extracted with MTBE (3 × 5 mL). The combined organic phases were dried with $MgSO_4$ and evaporated under vacuum to dryness. The residue was dissolved in C_6H_6/MeOH 4:1 (1 mL) and $TMSCHN_2$ (2 M in hexane, 40 µL, 80.1 µmol) was added at room temp.. After 1 h the solvent was removed under vacuum and the residue was purified by column chromatography (silica gel; hexanes/EtOAc 3:1), to give an inseparable mixture of two isomers of **1** and two isomers of **24** with a yield of 9.9 mg, 24.2 µmol, 43% as a waxy oil. **1**, Me-20 axial; **24**, Me-20 equatorial. R_f = 0.66 (hexanes/EtOAc 3:1). **1**, ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.11 (m, 1 H, 3-H), 3.66 (s, 3 H, OMe), 2.62 (m, 1 H, 2-H), 1.99, 1.88 (m, 2 H, 12-H), 1.88 (t, J = 6.3 Hz, 2 H, 15-H), 1.66 (m, 2 H, 4-H), 1.63 (m, 2 H, 5-H), 1.57 (s, 3 H, 22-H), 1.53 (m, 2 H, 16-H), 1.46 (m, 2 H, 7-H), 1.39 (m, 3 H, 10-H, 17-H), 1.36 (m, 2 H, 8-H), 1.32 (s, 3 H, 20-H), 1.25 (m, 2 H, 11-H), 1.24 (d, J = 6.6 Hz, 3 H, 19-H), 1.24, 1.13 (m, 2 H, 9-H), 0.98 (s, 6 H, 23-H, 24-H), 0.88 (d, J = 6.5 Hz, 3 H 21-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 174.6 (C-1), 137.8 (C-13), 126.5 (C-14), 81.6 (C-3), 80.4 (C-6), 51.8 (OMe), 42.9 (C-2), 40.1 (C-7), 40.0 (C-17), 37.5 (C-9), 35.1 (C-18), 34.0 (C-10), 32.4 (C-5), 32.8 (C-15), 31.8 (C-11), 28.8 (C-23, C-24), 26.5 (C-12), 22.8 (C-4), 20.7 (C-8), 20.6 (C-8), 20.3 (C-20), 19.9 (C-22), 19.7 (C-16), 19.6 (C-21), 13.7 (C-19) ppm. **24**, ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.11 (m, 1 H, 3-H), 3.69 (s, 3 H, OMe), 2.62 (m, 1 H, 2-H), 1.99, 1.88 (m, 2 H, 12-H), 1.88 (t, J = 6.3 Hz, 2 H, 15-H), 1.66 (m 2 H, 4-H), 1.63 (m, 2 H, 5-H), 1.57 (s, 3 H, 22-H), 1.53 (m, 2 H, 16-H), 1.46 (m, 2 H, 7-H), 1.39 (m, 3 H, 10-H, 17-H), 1.36 (m, 2 H, 8-H), 1.25 (m, 2 H, 11-H), 1.24 (d, J = 6.6 Hz, 3 H, 19-H), 1.24, 1.13 (m, 2 H, 9-H), 1.13 (s, 3 H, 20-H), 0.98 (s, 6 H, 23-H, 24-H), 0.88 (d, J = 6.5 Hz, 3 H, 21-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 174.6 (C-1), 137.8 (C-13), 126.5 (C-14), 81.2 (C-3), 80.3 (C-6), 52.0 (OMe), 43.1 (C-2), 40.0 (C-17), 39.3 (C-7), 37.6 (C-9), 35.1 (C-18), 33.9 (C-10), 32.8 (C-15), 32.1 (C-5), 31.8 (C-11), 28.8 (C-23, C-24), 26.3 (C-12), 24.5 (C-20), 22.8 (C-4), 21.3 (C-8), 21.0 (C-8), 19.9 (C-22), 19.7 (C-16), 19.6 (C-21), 14.3 (C-19) ppm. HRMS (ESI): calcd. for $C_{25}H_{44}O_4Na$ $[M + Na]^+$ 431.3132; found 431.3125.

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Supporting Information (see footnote on the first page of this article): Synthesis of the endoperoxide **9** via Evans-aldol route; NMR-spectra of compounds (6*S*,7*R*)-**11**, **16**, **17**, **10**, **9**, **18**, **5**, **22**, **4**, **27, 28**, (6*R*,7*R*)-**11**, **29**, **31**; ^{1}H- and ^{13}C NMR data of compounds **3**, **23**, **2**, **1** and **24**.

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Keywords: Total Synthesis • Natural Products • Terpenoids • Peroxides • Julia-Kocienski-reaction • Oxygen heterocyles

[1] a) J. Dai, Y. Liu, Y.-D. Zhou, D. G. Nagle, *J. Nat. Prod.* **2007**, *70*, 130-133. b) D. T. A. Youssef, W. Y. Yoshida, M. Kelly, P. J. Scheuer, *J. Nat. Prod.* **2001**, *64*, 1332-1335. c) J. Tanaka, T. Higa, K. Suwanborirux, U. Kokpol, G. Bernardinelli, C. W. Jefford, *J. Org. Chem.* **1993**, *58*, 2999-3002. d) R. J. Capon, S. J. Rochfort, S. P. B. Ovenden, R. P. Metzger, *J. Nat. Prod.* **1997**, *60*, 1261-1264. e) R. J. Capon, S. J. Rochfort, S. P. B. Ovenden, *J. Nat. Prod.* **1998**, *61*, 525-528. f) P. Phuwapraissirisan, S. Matsunaga, N. Fusetani, N. Chaitanawisuti, S. Kritsanapunta, P. Menasveta, *J. Nat. Prod.* **2003**, *66*, 289-291. g) R. J. Capon, *J. Nat. Prod.* **1991**, *54*, 190-195. h) H. He, D. J. Faulkner, H. S. M. Lu, J. Clardy, *J. Org. Chem.* **1991**, *56*, 2112-2115. i) E. M. P. Silva, R. J. Pye, C. Cardin, L. M. Harwood, *Synlett* **2010**, 509-513. j) E. M. P. Silva, R. J. Pye, G. D. Brown, L. M. Harwood, *Eur. J. Org. Chem.* **2012**, 1209-1216.

[2] a) W. Oppolzer, P. Lienhard, *Tetrahedron Lett.* **1993**, *34*, 4321-4324. b) M.-A. Schneider, S. Dötterl, K. Seifert, *Chem. & Biodiv.* **2013**, 10, 1252-1259. c) Y. S. Yadav, V. Rajender, *Eur. J. Org. Chem.* **2010**, 2148-2156. d) C. Xu, C. Schwartz, J. Raible, P. H. Dussault, *Tetrahedron* **2009**, *65*, 9680-9685. e) P. M. O'Neill, S. Hindley, M. D. Pugh, J. Davies, P. G. Bray, B. K. Park, D. S. Kapu, S. A. Ward, P. A. Stocks, *Tetrahedron Lett.* **2003**, *44*, 8135-8138. f) E. Westman, R. Strömberg, *Nucleic Acids Research* **1994**, *22*, 2430-2431. g) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

[3] a) S. G. Levine, *J. Am. Chem. Soc.* **1958**, *80*, 6150-6151. b) H. Häuser, *Offenlegungsschrift DE 3900793 A1*, **1990**. b) S. Kojima, S. Maki, T. Hirano, Y. Ohmiya, H. Niwa, *Tetrahedron Lett.* **2000**, *41*, 4409-4413. c) P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563-2585.

[4] a) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26-28. b) J. Thiele, *Ann.* **1892**, *271*, 127-136. c) J. W. Hamersma, E. I. Snyder, *J. Org. Chem.* **1965**, *30*, 3985-3988. d) F. R. Newton, D. P. Reynolds, *Tetrahedron Lett.* **1979**, *20*, 3981-3982. e) M. Hunsen, *Synthesis* **2005**, 2487-2490. f) N. Hashimoto, T. Aoyama, T. Shiori, *Chem. Pharm. Bull.* **1981**, *29*, 1475-1478.

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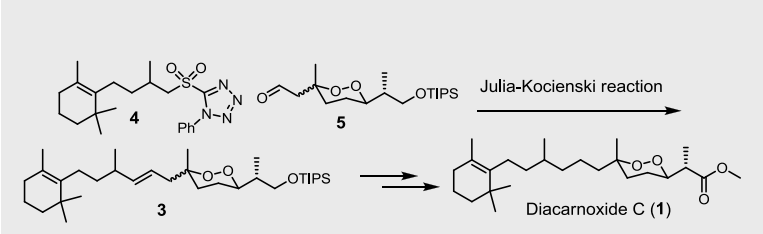

Key Topic*

Terpene Peroxides

*M.-A. Schneider, K. Seifert**

Page No. – Page No.

Towards the Total Synthesis of the Norsesterterpene Diacarnoxide C

The first total synthesis of diacarnoxide C (**1**) was achieved. The key step of the synthesis is the Julia-Kocienski reaction of the sulfone **4** with the the aldehyde **5**.

Supporting Information ((optional))

((Please insert the Supporting Information here if applicable.))