A Biomimetic Synthesis of Sacculatane Diterpenoids

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The biomimetic synthesis of sacculatane-type epimeric compounds **14a** and **14b** is reported. The key synthetic step is the low-temperature superacidic cyclization of (all-*E*)-*ω*-acetoxygeranylgeraniol **12** obtained in nine steps from geranyllinalool (**13**). The 19-acetoxysacculata-7,17-dien-11-ol (**14a**) could be an important and convenient starting compound for the synthesis of other sacculatane diterpenoids.

1. Introduction. – Diterpenoids constitute one of the largest group of isoprenoids found both in terrestrial and marine organisms [1]. Their structural and stereochemical diversity along with the biological activity have continued to present challenges to synthetic organic chemists. One of the interesting structural moiety found in natural diterpenoids is the bicyclic core prenylated at the geminal dimethyl group of ring A. This pattern of ring-A functionalization is found in sacculatanes, a family of diterpenoids mainly isolated from liverworts [2][3]. The continuous search for new sacculatanes is due to the biological activity exhibited by the representative members of this compound class, including piscicidal, antimicrobial, anti-HIV-1, and cytotoxic activities [2]. Further investigations of the biological activity of other sacculatanes is hampered by the limited availability of these compounds from natural sources. As a solution of this problem, interesting examples of growing liverworts in axenic culture have been recently reported [4]. On the other hand, chemical synthesis could provide sufficient quantities of sacculatanes for biological-activity and SAR studies. We report here the first example of a synthetic path to sacculatane skeleton based on the biomimetic direct superacidic cyclization of the open-chain diterpenic substrate.

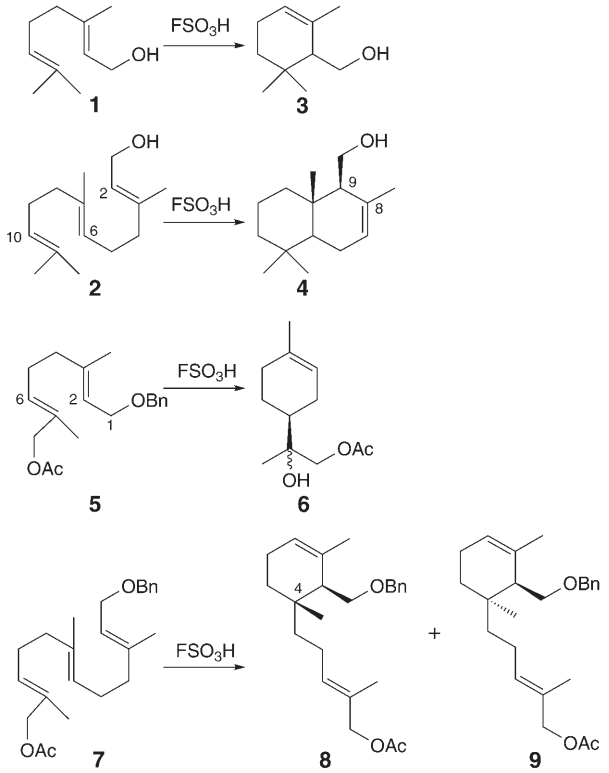
2. Results and Discussion. – Previous reports on the synthesis of sacculatanes and related compounds are rather scarce [5–7]. The synthetic strategy that provided access to the sacculatane skeleton was based on the use of optically active *Wieland–Miescher* ketone analogs and employed a long sequence of steps for attaching the proper functional groups to the bicyclic system of the starting material [6]. This approach provided optically active sacculatanes, but included too many steps that affected its attractivity.

Our systematic studies on superacid-induced cyclization of terpenoids led to some interesting results. We have shown in previous communications [8–11] that the behavior of *α*,*ω*-bifunctionalized open-chain terpenic substrates under the action of

a superacid is different from that observed for substrates with no ω-functionalization.

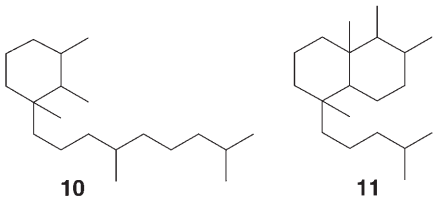
It has been demonstrated that the superacidic cyclization of geraniol (**1**) and (*E,E*)-farnesol (**2**) gives cyclogeraniol (**3**) and drimenol (**4**), respectively (*Scheme 1*) [12]. On the other side, the α,ω-bifunctionalized monoterpenic derivative **5** provided a mixture of epimeric *p*-menthane compound **6** on superacidic treatment. This was the single example of an aliphatic monoterpene superacidic cyclization affording compounds with *p*-menthane skeleton. Due to the presence of the terminal AcO group, in this case the cyclization process started with the solvolysis of the functional group at C(1) instead of the protonation of the terminal C=C bond [10]. The superacidic treatment of the sesquiterpenic analog **7** of compound **5** afforded a mixture of epimeric α-cyclogeraniol derivatives **8** and **9**, prenylated at the geminal dimethyl groups at C(4) [11].

Scheme 1



A plausible explanation of these results may be the fact that the superacid protonated first the terminal oxygenated functional group to form the corresponding oxonium ions, impeding the subsequent protonation of the terminal C=C bond leading to thermodynamically unfavorable 1,3-dicationic systems. Consequently, in the sesquiterpenic substrate **7**, the cyclization process was initiated by protonation of the internal C=C bond.

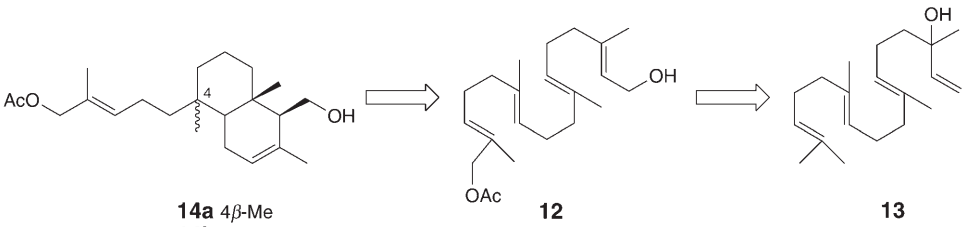
Accordingly, it was conceivable that an α,ω-bifunctionalized diterpenic substrate, under the action of the superacid, would also lead to the protonation of the internal C=C bonds to give either the monocyclic diterpenic compounds with C-skeleton **10** or/and bicyclic compounds with the sacculatane skeleton **11**.



10 **11**

Since the possibility of obtaining **11** in such a straightforward and biomimetic fashion was appealing, we investigated the superacidic cyclization of aliphatic α,ω-bifunctionalized diterpenoid substrate **12** obtained from commercially available geranyllinalool (**13**). This approach leading to sacculatanic compounds **14a** and **14b** is presented in the retrosynthetic *Scheme 2*.

Scheme 2



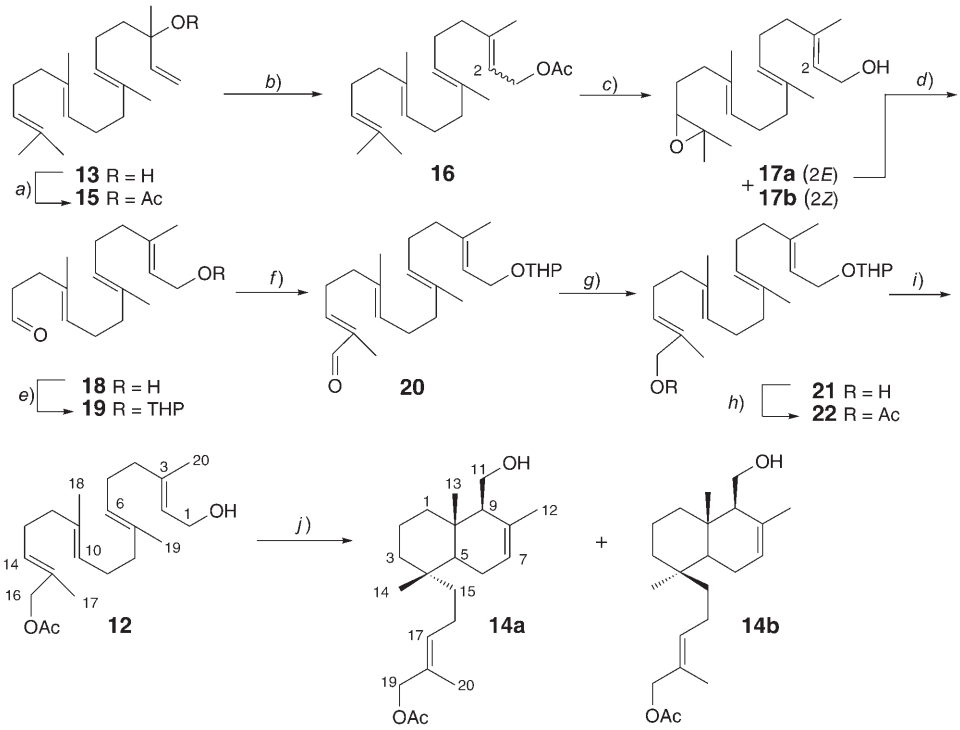
14a 4β-Me
14b 4α-Me
12
13

The geranyllinalool (**13**) was acetylated under standard conditions to geranyllinalyl acetate (**15**), which was isomerized with $[PdCl_2(MeCN)_2]$ to the mixture (*ca.* 85 : 15) of (2*E*)- and (2*Z*)-geranylgeranyl acetates **16** (*Scheme 3*) [13]. This mixture was treated with *N*-bromosuccinimide (NBS) followed by K_2CO_3 according to the procedure of *Van Tamelen* and *Curphey* [14] to provide the mixture of compounds **17a** and **17b**. This mixture was separated by column chromatography on silica gel. The spectral data of racemic **17a** were identical with those of known optically active product [15].

Periodate cleavage of the epoxy compound **17a** and protection of the free OH group in **18** as the 3,4,5,6-tetrahydro-2*H*-pyranyloxy (THPO) group provided the substrate **19** for the *Wittig* olefination. This reaction proceeded in a good yield and selectivity: the (*E*)-isomer of the aldehyde **20** was isolated in 68% yield. Reduction of **20** with $NaBH_4$, followed by standard protecting-group manipulations, afforded the desired α,ω-bifunctionalized substrate **12**. The structure of **12** was confirmed by the spectral data. It should be mentioned that our attempts to perform a direct allylic oxidation of the Me group at C(15) of **16** with SeO_2 led to a complex mixture of products.

Superacidic cyclization of **12** was carried out by treatment with 5 equiv. of FSO_3H ($-78°$, 15 min) to afford a mixture (*ca.* 3 : 1) of racemic compounds **14a** and **14b** (total

Scheme 3



a) Ac_2O, CH_2Cl_2, 4-(dimethylamino)pyridine (DMAP), 0°, 1 h, r.t. 24 h; 63%. *b*) $[PdCl_2(MeCN)_2]$, THF, r.t, 18 h, 90%. *c*) 1. *N*-Bromosuccinimide (NBS), THF/H_2O, 0°, 1.5 h, r.t. 2 h; 2. K_2CO_3, MeOH, r.t. 20 h; overall 34%. *d*) $NaIO_4$, HIO_4, THF, r.t. 5 h; 35%. *e*) 3,4-Dihydro-2*H*-pyran (DHP), CH_2Cl_2, pyridinium *p*-toluenesulfonate (PPTS), 12 h; 46%. *f*) $Ph_3P{=}C(Me)CHO$, THF, reflux, 18 h; 79%. *g*) $NaBH_4$, EtOH, 0°, 1 h; 66%. *h*) Ac_2O, Py, r.t., 1 h; 96%. *i*) TsOH, MeOH, r.t. 12 h; 53%. *j*) FSO_3H (5 equiv.), i-$PrNO_2$, −78°, then Et_3N, 15 min; 25%.

yield 25%). The reaction mixture was purified by reversed-phase (RP) HPLC to give individual pure compounds **14a** and **14b**. Analysis of the spectral data of both reaction products suggested a close structural similarity between them, indicating the presence of the same C-skeleton. Compounds **14a** and **14b** are isomers with the molecular formula $C_{22}H_{36}O_3$ as deduced from HR-MS, containing the molecular peak at *m*/*z* 348 and implying five degrees of unsaturation. The ^{1}H-NMR spectra of both molecules displayed signals of two vinylic Me groups (Me(12) and Me(20)) and two olefinic H-atoms (H−C(7) and H−C(17)), indicating the presence of two trisubstituted C=C bonds. In addition to the signal attributed to the terminal CH_2(19) group, two 3-H *singlet*s due to the Me groups, Me(13) and Me(14), linked to quaternary sp^3-C-atoms, were also observed in both ^{1}H-NMR spectra that were completed by the presence of an *ABX* system attributed to a OH-bearing CH_2 methylene group (CH_2(11)) and further connected with an allylic CH moiety (H−C(9)). These data indicated that both cyclization products retained two of the four C=C bonds of the starting compound **12**,

and that the two remaining unsaturation degrees required by the molecular formula were due to two rings. A detailed analysis of NMR data allowed us to assign to both compounds **14a** and **14b** a bicyclic structure with an angular Me group (Me(13)) at C(10), and homo-AcO-prenyl chain and a geminal Me group at C(4). These data are consistent with the presence of the sacculatane skeleton in compounds **14a** and **14b**. In particular, comparison of the NMR data of the major reaction product **14a** with those reported in the literature for model sacculatane diterpenes [4] showed a good agreement of the δ(C) values of the C-atoms of the bicyclic core of the molecules, implying the same relative configuration.

NMR Data of the isomer **14b** (see *Exper. Part*) were substantially similar to those of **14a**, the main differences being in the ^{13}C-NMR resonances of C(5) (δ 47.6 in **14a**, 52.1 in **14b**), C(14) (δ 20.8 in **14a**, 29.0 in **14b**), and C(15) (δ 43.6 in **14a**, 32.2 in **14b**). These data indicated that compound **14b** had a different relative configuration at C(4), with the equatorial Me(14) group and, consequently, axially oriented the homoprenyl chain. So, compound **14b** was the 4-epimer of **14a**.

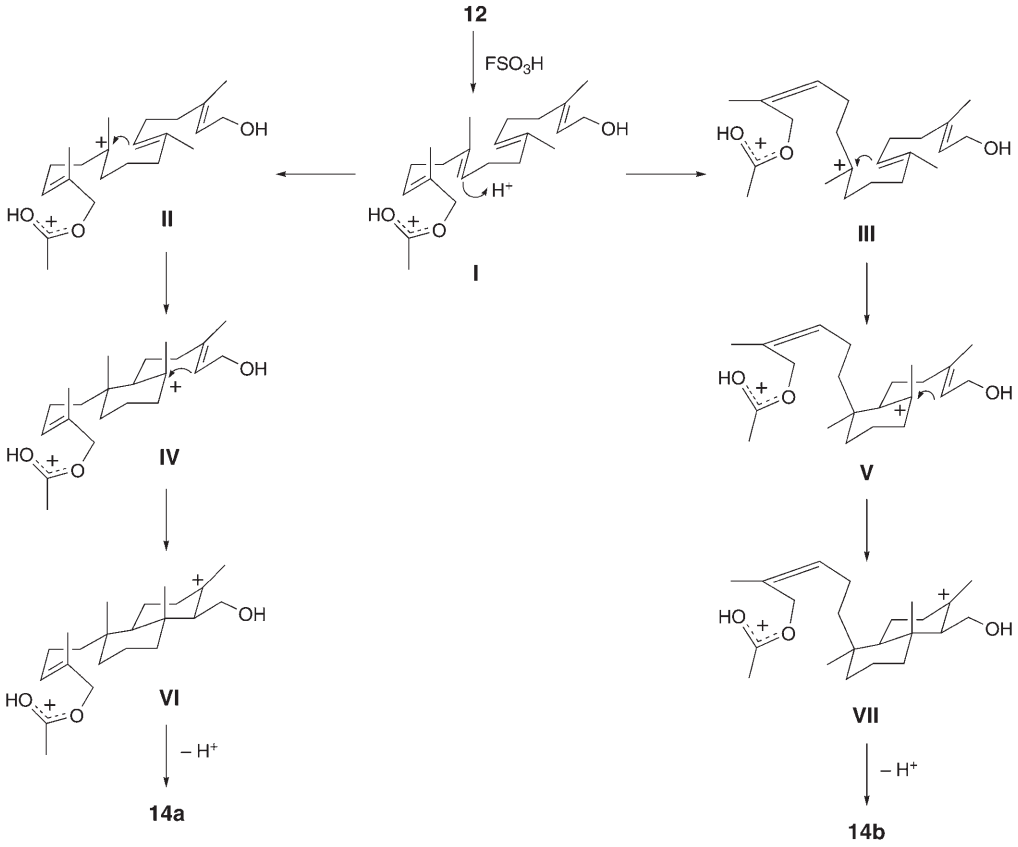
It is interesting to note that the natural sacculatanes so far reported have the same configuration as the epimer **14a**, which is formed as the major product of the cyclization reaction.

The proposed reaction mechanism for cyclization of **12** is shown in *Scheme 4*. On treatment with superacid, the ω-AcO group of **12** is protonated to give the carboxonium ion **I**, which does not allow the protonation of the terminal C=C bond, as it was mentioned above, whereas the protonation of C(10)=C(11) bond occurs with the formation of the dications **II** or **III**, which are transformed into dications **IV** and **V**, respectively. Their further cyclization and deprotonation lead to the final compounds **14a** and **14b**, respectively. The prevalence of isomer **14a** in the reaction products was explained by the fact that the pre-reactive conformation **II** with the bulky group in quasi-equatorial position is energetically more favorable then the conformation **III**, which leads to compound **14b** with the bulky group in axial configuration. The proposed reaction mechanism mimics the biosynthetic pathway that leads to sacculatane skeleton [16]. Based on biogenetic considerations, it is reasonable to hypothesize that the formation of the prenylated bicyclic core of sacculatanes could take place by a selective cyclization process of the open chain diterpenic precursor, as shown in *Scheme 5*. The alternative direct attachment of the C_5 moiety to the bicyclic core leading to sacculatane framework should be unlikely to occur.

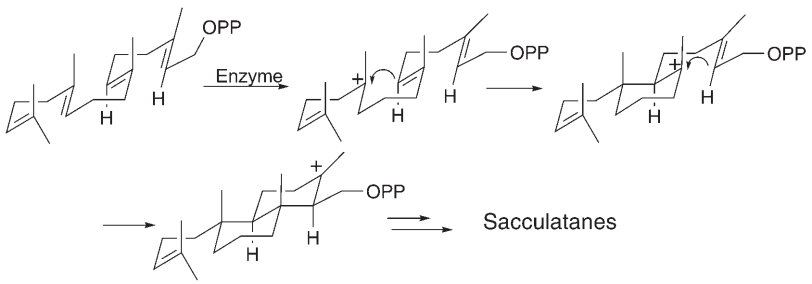
3. Conclusions. – In summary, a biomimetic synthetic route has been developed to compounds of sacculatane structure, based on a selective initiation of the cyclization process in the α,ω-bifunctionalized open-chain diterpenic substrate by protonation of the internal C=C bond. This selectivity was due to the deactivation of the terminal C=C bond in the geranylgeraniol skeleton by the ω-allylic AcO group. The proposed synthesis of sacculatane compounds involves ten steps starting from geranyllinalool (**13**), and could be used in the synthesis of further members of the sacculatane family.

Thanks are due to Mr. *C. Iodice* for spectrophotometric measurements. NMR Spectra were recorded at the *ICB NMR Service*, the staff of which is acknowledged. *V. K.* thanks *NATO-CNR Outreach Fellowship Program* for a senior fellowship. *N. U.* is grateful to *Short-Term Mobility CNR Program* for financial support.

Scheme 4. *Proposed Reaction Mechanism for Cyclization of* **12**



Scheme 5. *The Hypothetical Mechanism of Sacculatane Biosynthesis*



Experimental Part

1. *General.* All air- and water-sensitive reactions were performed in flame-dried glass ware, which was cooled to r.t. under a constant flow of Ar. These reactions were subsequently conducted under an inert atmosphere. Et_2O and THF were distilled from sodium-benzophenone, CH_2Cl_2 was distilled from

P_2O_5. All reagents were purchased from *Aldrich* and used as received. The workup of the reaction mixtures included exhaustive extraction with Et_2O, washing with H_2O up to neutral, drying over anh. Na_2SO_4, filtration, and removal of the solvent *in vacuo*. Semiprep. HPLC: *Shimadzu* liquid-chromatographic system. Column chromatography (CC): commercial *Merck* silica gel *60* (70–230 mesh ASTM). TLC: *Merck* pre-coated silica-gel plates. The chromatograms were sprayed with 0.1% $Ce(SO_4)_2$ in 2N H_2SO_4 and heated at 80° for 5 min to detect the spots. IR Spectra: *Bio-Rad FTS 7* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$ on *Bruker AM 400* and *Bruker WM 300* spectrometers; chemical shifts (δ) in ppm, referred to $CHCl_3$ as internal standard (^{1}H: δ 7.26 and ^{13}C: δ 77.0). EI-MS: *Carlo Erba TRIO 2000* spectrometer.

2. *Geranyllinalyl Acetate* (**15**) [13]. *Geranyllinalool* (**13**; 138 mg, 0.476 mmol) and DMAP (116 mg, 0.952 mmol) were dissolved in dry CH_2Cl_2 (1 ml) under N_2. Ac_2O (0.09 ml, 0.952 mmol) was added, and the mixture was stirred at 0° for 1 h and then at r.t. for 24 h. The mixture was diluted with CH_2Cl_2 (12 ml) and washed successively with sat. aq. $CuSO_4$ (4 × 5 ml), sat. aq. $NaHCO_3$ (2 × 5 ml) and brine (5 ml), dried and evaporated *in vacuo*. The residue was purified by flash chromatography (FC) on (silica gel (3.3 g); hexane/AcOEt 99:1) to yield **15** (100 mg, 63%). Colorless oil. ^{1}H-NMR (300 MHz): 1.52 (*s*, Me); 1.57 (*s*, 3 Me); 1.65 (*s*, Me); 1.98 (*s*, MeCO); 1.90–2.20 (*m*, 6 CH_2); 5.04–5.07 (*m*, 5 CH); 5.95 (*dd*, J = 10.9, 17.5, 1 H, CH=C).

3. *(2Z,6E,10E)- and (2E,6E,10E)-Geranylgeranyl Acetates* (**16**) [13]. Compound **15** (677 mg, 2.039 mmol) was dissolved in dry THF (23 ml), $[PdCl_2(CH_3CN)_2]$ (26 mg, 0.101 mmol) was added, and the mixture was stirred under N_2 for 18 h. An additional portion of $[PdCl_2(CH_3CN)_2]$ (26 mg, 0.101 mmol) was added, and stiring was continued for another 12 h. The mixture was evaporated *in vacuo*, and the residue was purified by FC (silica gel (4.5 g); hexane/AcOEt 20:1) to yield the mixture of acetates **16** (609 mg, 90%) as a pale yellow oil. HPLC analysis showed an (*E*)/(*Z*) ratio of *ca.* 85:15. ^{1}H-NMR (300 MHz): 1.63 (*s*, 3 Me); 1.68 (*s*, Me); 1.73 (*s*, Me); 1.90–2.20 (*m*, 6 CH_2, AcO); 4.56 (*d*, J = 7.1, CH_2); 5.10 (*m*, 3 CH), 5.32 (*t*, J = 7.1, CH).

4. (*all*-E)-*14,15-Epoxygeranylgeraniol* (**17a**) [15]. To a solution of the mixture **16** (606 mg, 1.825 mmol) in THF (8.7 ml)/H_2O (2.9 ml), *N*-bromosuccinimide (NBS; 357 mg, 1.825 mmol) was added at 0° under stirring. The mixture was stirred for 1.5 h at 0° and 2 h at r.t. Then, it was diluted with H_2O (20 ml) and worked up as usual. The residue (846 mg) obtained after evaporation of the solvent was dissolved in MeOH (11.5 ml) and treated with K_2CO_3 (756 mg, 5.48 mmol). The suspension obtained was stirred for 20 h at r.t., filtered, and the solvent was evaporated *in vacuo*. The crude product (627 mg) was submitted to FC (silica gel (25 g); increasing gradient of AcOEt in petroleum ether) gave racemic **17a** (192 mg, 34% after two steps). IR (film): 3413, 2923, 2854, 1667, 1448, 1379, 1249, 1120, 1010. ^{1}H-NMR (300 MHz): 1.25 (*s*, 3 H); 1.29 (*s*, 3 H); 1.59 (*s*, 3 H); 1.61 (*s*, 3 H); 1.67 (*d*, J = 1, 3 H); 1.94–2.23 (*m*, 11 H); 2.70 (*t*, J = 6, 1 H); 4.14 (*d*, J = 7, 2 H); 5.12–5.19 (*m*, 2 H); 5.41–5.45 (*m*, 1 H). ^{13}C-NMR (75 MHz): 16.4; 16.6; 19.1; 25.3; 26.7; 26.9; 27.8; 36.7; 39.9; 40.0; 58.5; 59.8; 64.6; 123.8; 124.3; 125.2; 134.4; 135.6; 140.0. ESI-MS: 307 (12, $[M+H]^+$), 289 (52), 271 (32), 259 (20), 221 (20), 203 (33), 191 (19), 161 (32), 153 (84), 135 (100), 121 (61), 109 (84). HR-EI-MS: 306.2549 ($C_{20}H_{34}O_2^+$; calc. 306.2559).

5. *Periodate Cleavage of* **17a**. To a soln. of **17a** (182 mg, 0.597 mmol) in THF (4.5 ml) and H_2O (1 ml) were added successively $NaIO_4$ (75 mg, 0.35 mmol) and HIO_4 (149 mg, 0.66 mmol). After 4 h of stirring at r.t. another portion of $NaIO_4$ (75 mg, 0.33 mmol) was added, and stirring was continued for an additional h. The mixture was diluted with H_2O (10 ml) and extracted with $CHCl_3$ (3 × 20 ml). The combined org. phase was washed with brine to neutral and dried. After removal the solvent, the crude residue (198 mg) was used in the next step without purification. An aliquot of the crude product was subjected to FC to provide a pure sample of *(12E)-14-hydroxy-4,8,12-trimethyltetradeca-4,8,12-trienal* (**18**). IR (film): 3406, 2925, 1723, 1668, 1446, 1382, 1108, 1016, 756. ^{1}H-NMR (300 MHz): 1.59 (*s*, 3 H); 1.60 (*s*, 3 H); 1.67 (*s*, 3 H); 1.70–1.74 (*m*, 8 H); 2.24 (*t*, J = 7, 1 H); 2.40–2.48 (*m*, 1 H); 4.15 (*d*, J = 7, 2 H); 5.06–5.15 (*m*, 2 H); 5.37–5.44 (*m*, 1 H); 9.74 (*t*, J = 2, 1 H). ^{13}C-NMR (75 MHz): 16.3; 16.4; 16.6; 26.6; 26.8; 32.2; 38.9; 39.8; 42.4; 59.7; 123.7; 124.3; 125.7; 133.2; 135.4; 140.0; 203.2. ESI-MS: 265 (37, $[M+H]^+$), 247 (45), 229 (43), 217 (12), 203 (16), 189 (14), 177 (18), 161 (66), 149 (55), 135 (64), 121 (69), 111 (100). HR-EI-MS: 264.2077 ($C_{17}H_{28}O_2^+$; calc. 264.2089).

6. *THP Protection of* **18**. To the solution of crude hydroxy aldehyde obtained in the previous step in CH_2Cl_2 (1.2 ml) were added successively pyridinium *p*-toluenesulfonate (PPTS; 68 mg, 0.271 mmol) and

3,4-dihydro-2*H*-pyran (0.09 ml, 0.934 mmol). The mixture was stirred overnight at r.t. and worked up as usual. Removal of the solvent and FC (silica gel (6 g); 4% AcOEt in petroleum ether) gave 93 mg (46% after two steps) of *(12*E*)-4,8,12-trimethyl-14-(tetrahydro-2*H*-pyran-2-yloxy)tetradeca-4,8,12-trienal* (**19**). IR (film): 3432, 2927, 2719, 1726, 1668, 1442, 1384, 1199, 1117, 1023, 905, 869, 814. ^{1}H-NMR (300 MHz): 1.58 (*s*, 3 H); 1.60 (*s*, 3 H); 1.67 (*s*, 3 H); 1.94–2.14 (*m*, 8 H); 2.30 (*t*, *J* = 7, 1 H); 2.53–2.47 (*m*, 1 H); 3.47–3.54 (*m*, 1 H); 3.85–3.92 (*m*, 1 H); 3.99–4.05 (*m*, 1 H); 4.20–4.26 (*m*, 1 H); 4.61–4.63 (*m*, 1 H); 5.07–5.15 (*m*, 2 H); 5.33–5.37 (*m*, 1 H); 9.74 (*t*, *J* = 2, 1 H). ^{13}C-NMR (75 MHz): 16.3; 16.4; 16.8; 20.0; 25.8; 26.6; 26.8; 31.0; 32.2; 39.8; 39.9; 42.5; 62.6; 64.0; 98.1; 120.9; 124.5; 125.7; 133.2; 135.3; 140.6; 203.1. ESI-MS: 349 (4, $[M+H]^+$), 331 (10), 307 (12), 289 (11), 263 (23), 247 (27), 229 (27), 219 (10), 201 (10), 177 (12), 161 (34), 154 (100), 136 (77), 121 (24). HR-EI-MS: 348.2603 ($C_{22}H_{36}O_3^+$; calc. 348.2664).

7. *Olefination of* **19**. To the soln. of **19** (71 mg, 0.204 mmol) in dry THF (1.1 ml), the soln. of $Ph_3P{=}C(CH_3){-}CHO$ (81 mg, 0.255 mmol) in benzene/CH_2Cl_2 1:1 (0.8 ml) was added. The mixture was refluxed for 18 h under Ar. Dilution with H_2O (5 ml) was followed by usual workup to provide, after the evaporation of the solvent, the crude product (170 mg), which was submitted to FC (silica gel (15 g); 3% AcOEt in petroleum ether) to give *(14*E*)-2,6,10,14-tetramethyl-16-(tetrahydro-2*H*-pyranyloxy)hexadeca-2,4,10,14-tetraenal* (**20**; 54 mg, 79%), along with the unreacted aldehyde **19** (10 mg).

8. *Data of* **20**. Colorless viscous oil. IR (film): 3430, 2925, 2710, 1726, 1689, 1442, 1383, 1260, 1199, 1117, 1023, 905, 814. ^{1}H-NMR (300 MHz): 1.53 (*s*, 3 H); 1.56 (*s*, 3 H); 1.61 (*s*, 3 H); 1.68 (*d*, *J* = 1, 3 H); 1.88–2.12 (*m*, 8 H); 2.34–2.44 (*m*, 2 H); 3.40–3.48 (*m*, 1 H); 3.79–3.85 (*m*, 1 H); 3.92–3.99 (*m*, 1 H); 4.14–4.20 (*m*, 1 H); 4.54–4.57 (*m*, 1 H); 5.02–5.10 (*m*, 2 H); 5.32–5.27 (*m*, 1 H); 6.38–6.43 (*m*, 1 H); 9.31 (*s*, 1 H). ^{13}C-NMR (75 MHz): 16.2; 16.3; 16.4; 16.8; 20.0; 25.8; 26.6; 26.9; 27.8; 32.2; 38.3; 39.9; 40.0; 62.6; 64.0; 99.2; 120.9; 124.4; 125.9; 133.7; 135.9; 140.5; 154.9; 195.7. ESI-MS: 389 (16, $[M+H]^+$), 305 (18), 303 (12), 287 (100), 263 (23), 247 (25), 229 (30), 203 (22), 177 (24), 161 (57), 149 (72), 135 (77). HR-EI-MS: 388.2889 ($C_{25}H_{40}O_3^+$; calc. 388.2977).

9. *Reduction of* **20**. The soln. of **20** (33 mg, 0.085 mmol) in EtOH (1 ml) was treated with $NaBH_4$ (6 mg, 0.145 mmol) at 0° under stirring. After 1 h at this temp., the reaction was quenched with a 10% soln. of H_2SO_4 (1 ml), and the mixture was worked up as usual. The crude product was submitted to FC (silica gel (1.7 g); increasing gradient of AcOEt in petroleum ether) to give *(14*E*)-2,6,10,14-tetramethyl-16-(tetrahydro-2*H*-yloxy)hexadeca-2,6,10,14-tetraen-1-ol* (**21**) (22 mg, 66%). Colorless viscous oil. IR (film): 3422, 2924, 2853, 1665, 1450, 1383, 1261, 1117, 1023. ^{1}H-NMR (300 MHz): 1.60 (*s*, 6 H); 1.67 (*s*, 3 H); 1.68 (*s*, 3 H); 2.16–1.96 (*m*, 12 H); 3.49–3.53 (*m*, 1 H); 3.86–3.92 (*m*, 1 H); 3.99 (*s*, 2 H); 3.89–4.14 (*m*, 3 H); 4.61–4.63 (*m*, 1 H); 5.09–5.23 (*m*, 2 H); 5.34–5.42 (*m*, 2 H). ^{13}C-NMR (75 MHz): 14.1; 16.3; 16.8; 20.0; 25.9; 26.6; 26.7; 26.9; 26.9; 31.1; 39.7; 40.0; 62.6; 64.0; 69.4; 98.1; 120.9; 124.3; 124.8; 126.4; 126.5; 134.2; 135.5; 140.6. ESI-MS: 391 (1, $[M+H]^+$), 373 (7), 361 (11), 309 (8), 289 (15), 271 (52), 259 (19), 203 (20), 177 (11), 161 (24), 154 (100), 147 (35), 137 (94), 109 (64). HR-EI-MS: 390.3099 ($C_{25}H_{42}O_3^+$; calc. 390.3134).

10. *Acetylation of* **21**. The soln. of **21** (10 mg, 0.026 mmol) in pyridine (0.05 ml) was treated with Ac_2O (5 µl, 0.053 mmol). The mixture was left overnight at r.t. and then worked up as usual. The crude product (14 mg) was submitted to FC (silica gel (0.7 g); increasing gradient of AcOEt in petroleum ether) to give *(14*E*)-2,6,10,14-tetramethyl-16-(tetrahydro-2*H*-yloxy)hexadeca-2,6,10,14-tetraen-1-yl acetate* (**22**; 12 mg, 96%). Colorless viscous oil. IR (film): 3416, 2934, 1741, 1671, 1443, 1379, 1237, 1118, 1024, 906, 814. ^{1}H-NMR (300 MHz): 1.60 (*s*, 6 H); 1.65 (*s*, 3 H); 1.68 (*s*, 3 H); 2.07 (*s*, 3 H); 3.49–3.53 (*m*, 1 H); 3.86–3.90 (*m*, 1 H); 4.00–4.06 (*m*, 1 H); 4.21–4.23 (*m*, 1 H); 4.45 (*s*, 2 H); 4.62–4.64 (*m*, 1 H); 5.11 (*td*, *J* = 7, 1, 2 H); 5.45 (*m*, 1 H); 5.36 (*m*, 1 H). ^{13}C-NMR (75 MHz): 14.3; 16.4; 16.8; 20.0; 21.4; 25.8; 26.5; 26.7; 27.0; 31.0; 39.4; 40.0; 62.6; 64.0; 70.7; 98.1; 120.9; 124.3; 125.0; 130.0; 130.2; 134.7; 135.6; 140.6; 171.4. ESI-MS: 433 (16, $[M+H]^+$), 347 (12), 331 (37), 313 (9), 287 (23), 271 (100), 238 (9), 203 (50), 189 (22), 161 (33), 135 (97), 121 (33). HR-EI-MS: 432.3179 ($C_{27}H_{44}O_4^+$; calc. 432.3240).

11. *THP Deprotection of* **22**. The soln. of **22** (509 mg, 1.18 mmol) in MeOH (10 ml) was treated with TsOH (7 mg) and left at r.t. overnight. Then, the mixture was diluted with sat. aq. $NaHCO_3$ (20 ml) and worked up as usual. The crude product (440 mg) was submitted to FC (silica gel (15 g); increasing gradient of AcOEt in petroleum ether) to give *(14*E*)-2,6,10,14-tetramethyl-16-hydroxyhexadeca-2,6,10,14-tetraen-1-yl acetate* (**12**; 217 mg, 53%). Colorless viscous oil. IR (film): 3423, 2925, 2855, 2361, 1740, 1668, 1447, 1379, 1235, 1023, 843. ^{1}H-NMR (300 MHz): 1.60 (*s*, 6 H); 1.65 (*s*, 3 H); 1.68 (*s*,

3 H); 2.07 (*s*, 3 H); 4.15 (*d*, *J* = 6.6, 2 H); 4.44 (*s*, 2 H); 5.11 (*m*, 1 H); 5.42 (*m*, 2 H). ^{13}C-NMR (75 MHz): 14.4; 16.4; 16.7; 21.5; 26.7; 26.8; 27.0; 39.5; 40.1; 59.8; 62.4; 69.8; 70.8; 123.7; 124.2; 125.1; 128.0; 128.4; 134.8; 135.7; 140.2; 170.0. ESI-MS: 331 (5, $[(M+H-H_2O]^+$), 282 (12), 271 (34), 203 (11), 189 (10), 175 (11), 147 (55), 135 (100), 133 (54), 109 (74). HR-EI-MS: 348.2652 ($C_{22}H_{32}O_3^+$; calc. 348.2664).

12. *Superacidic Cyclization of* **12**. The soln. of **12** (137 mg, 0.39 mmol) in 2-nitropropane (1.8 ml) was chilled at $-78°$ and treated with a soln. of FSO_3H (117 mg, 1.17 mmol) in 2-nitropropane (0.4 ml), chilled at the same temp. After 15 min of stirring at the same temp., the reaction was quenched with a soln. of Et_3N in hexane (1:1, 1 ml). Dilution with H_2O (5 ml) and usual workup gave a crude product (154 mg), which was submitted to FC (silica gel (4 g); increasing gradient of AcOEt in petroleum ether) to give a mixture (3:1 according to ^{1}H-NMR) of sacculatane compounds **14a** and **14b** (34 mg, 25%). This mixture was separated by semiprep. HPLC on a normal-phase *Kromasil* silica (25 × 0.9 cm) column. Elution was performed with 1% i-PrOH in hexane.

13. *(2*E*)-5-[(1*S*,4a*S*,5*S*)-1,2,3,4,4a,5,8,8a-Octahydro-5-(hydroxymethyl)-1,4a,6-trimethylnaphthalen-1-yl]-2-methylpent-2-en-1-yl Acetate* (**14a**). Colorless viscous oil. IR (film): 3674, 2922, 2856, 1746, 1541, 1456, 1378, 1232, 1025. ^{1}H-NMR (400 MHz)[1]): 0.88 (*s*, Me(13) or Me(14)); 0.89 (*s*, Me(14) or Me(13)); 1.64 (br. *s*, Me(20)); 1.78 (br. *s*, Me(12)); 2.07 (*s*, AcO); 3.73 (*dd*, *J* = 11, 5, H−C(11b)); 3.86 (*dd*, *J* = 11, 3, H−C(11a)); 4.43 (*s*, CH_2(19); 5.41 (*t*, *J* = 7, H−C(17)); 5.51 (br. *s*, H−C(7)). ^{13}C-NMR (75.5 MHz)[1]): 13.9 (*q*, C(20)); 15.4 (*q*, C(13)); 18.5 (*t*, C(2)); 20.8 (*q*, C(14)); 21.0 (*q*, AcO); 21.6 (*t*, C(16)); 21.9 (*q*, C(12)); 23.3 (*t*, C(6)); 35.3 (*s*, C(4) or C(10)); 36.1 (*s*, C(10) or C(4)); 37.6 (*t*, C(3)); 39.6 (*t*, C(1)); 43.6 (*t*, C(15)); 47.6 (*d*, C(5)); 57.4 (*d*, C(9)); 60.9 (*t*, C(11)); 70.4 (*t*, C(19)); 123.9 (*d*, C(7)); 129.5 (*s*, C(18)); 130.5 (*d*, C(17)); 132.8 (*s*, C(8)); 171.1 (*s*, C=O). ESI-MS: 349 (29, $[M+H]^+$), 331 (32), 316 (8), 305 (5), 289 (100), 271 (73), 259 (28), 243 (7), 231 (7), 203 (16), 189 (27), 175 (26), 133 (47), 109 (64). HR-EI-MS: 348.2644 ($C_{22}H_{36}O_3^+$; calc. 348.2664).

14. *(2*E*)-5-[(1*R*,4a*S*,5*S*)-1,2,3,4,4a,5,8,8a-Octahydro-5-(hydroxymethyl)-1,4a,6-trimethylnaphthalen-1-yl]-2-methylpent-2-en-1-yl Acetate* (**14b**). Colorless viscous oil. IR (film): 3673, 2921, 2856, 1745, 1541, 1456, 1377, 1231, 1025, 845. ^{1}H-NMR (400 MHz)[1]): 0.88 (*s*, Me(13)); 0.87 (*s*, Me(14)); 1.65 (br. *s*, Me(20)); 1.78 (br. *s*, Me(12)); 2.08 (*s*, AcO); 3.73 (*dd*, *J* = 11, 5, H−C(11b)); 3.85 (*dd*, *J* = 11, 3, H−C(11a)); 4.45 (*s*, CH_2(19)); 5.45 (*t*, *J* = 7, H−C(17)); 5.53 (br. *s*, H−C(7)). ^{13}C-NMR (75.5 MHz)[1]): 13.8 (*q*, C(20)); 15.9 (*q*, C(13)); 18.5 (*t*, C(2)); 21.0 (*q*, AcO); 21.9 (*q*, C(12)); 22.8 (*t*, C(16)); 23.1 (*t*, C(6)); 29.0 (*q*, C(14)); 35.6 (*s*, C(4) or C(10)); 36.2 (*s*, C(10) or C(4)); 32.2 (*t*, C(15)); 37.0 (*t*, C(3)); 40.0 (*t*, C(1)); 52.1 (*d*, C(5)); 57.8 (*d*, C(9)); 60.9 (*t*, C(11)); 70.3 (*t*, C(19)); 124.2 (*d*, C(7)); 129.6 (*s*, C(18)); 130.8 (*d*, C(17)); 132.8 (*s*, C(8)); 171.1 (*s*, C=O). ESI-MS: 348 (2, M^+), 331 (3), 318 (3), 305 (2), 288 (10), 271 (5), 258 (29), 243 (6), 219 (12), 189 (22), 175 (30), 133 (46), 109 (100), 81 (74). HR-EI-MS: 348.2654 ($C_{22}H_{36}O_3^+$; calc. 348.2664).

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[1]) Assignments according to the C-atom numbering given in *Scheme 3*.

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