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Enantioselective synthesis and absolute configurations of aculeatins A, B, D, and 6-*epi*-aculeatin D

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Abstract—The three naturally occurring, bioactive spiroacetals aculeatins A, B, and D, as well as the non-natural 6-*epi*-aculeatin D have been synthesized for the first time in enantiopure form using an asymmetric allylation as the only chirality source. A further key step was a stereoselective aldol reaction with remote induction. The absolute configurations of the natural products have been established and an erroneous structural assignment has been corrected.

1. Introduction

The aculeatins A and B are two epimeric spiroacetals isolated six years ago from the terrestrial plant species *Amomum aculeatum* Roxb. (fam. Zingiberaceae). They were assigned structures (*relative* configurations) **1** and **2**, respectively. A more complex variant, aculeatin C-**3**, was also isolated from the same plant (Fig. 1). Later, the same authors reported the isolation of a fourth member of this compound family, named aculeatin D and assigned structure and relative configuration **4**.[1,2] These compounds were found to display antiprotozoal activity against some *Plasmodium* and *Trypanosoma* species. In addition, they showed antibacterial activity and were cytotoxic against the KB cell line.

The aculeatins A–D represent a novel type of natural compounds displaying the unusual, previously unreported 1,7-dioxadispiro[5.1.5.2]pentadecane system. The observed biological activity of the aculeatins may be related to the presence of a Michael acceptor moiety.[3] Spiroacetals themselves are also interesting molecular fragments, which are present in many pharmacologically relevant substances such as macrolide or polyether antibiotics.[4] In view of this and of the aforementioned biological activities, it is not surprising that the aculeatins have already aroused interest in the synthetic community. As a matter of fact, two papers have recently appeared, which deal with the synthesis of aculeatins A, B, and D in racemic form.[5] Both syntheses relied upon the same type of phenolic oxidation to form the 1,7-dioxadispiro[5.1.5.2]pentadecane system (see below). In this paper, we present with full detail the first synthesis of **1**, **2**, and **4** in enantiopure form.[6] Another product generated in our synthesis was optically pure 6-*epi*-aculeatin D, previously synthesized in racemic form[5b] but not reported as a natural product so far.

The retrosynthetic concept for aculeatins A and B is depicted in Scheme 1. The dispirocyclic system is generated via

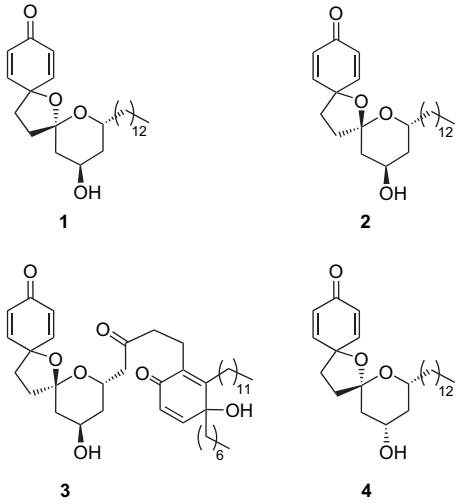

Figure 1. Published structures and relative configurations of the aculeatins A–D (**1**–**4**).

Keywords: Aculeatins; Absolute configuration; Asymmetric allylation; Aldol reaction; Remote induction; Spiroacetals; Hypervalent iodine; Oxidative spiroacetalization.
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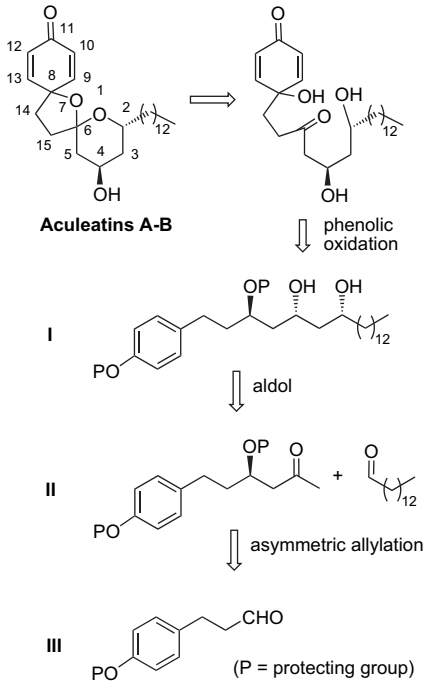
phenolic oxidation of an appropriately substituted intermediate ketone, related in turn to the protected triol **I**. The latter is derived from the aldol reaction of ketone **II** with *n*-tetradecanal. Intermediate **II** should be obtained from a suitably protected dihydro-*p*-coumaraldehyde **III** by means of asymmetric allylation and further functional manipulation.

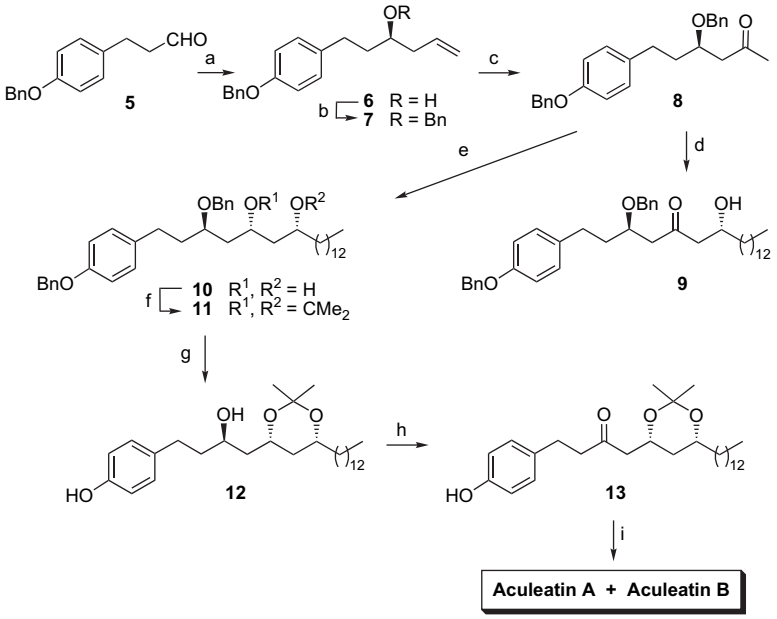


Scheme 1. Retrosynthetic analysis of aculeatins A and B.

2. Results and discussion

Scheme 2 shows the details of the synthesis of spiroacetals **1** and **2**. Thus, the known 3-(*p*-benzyloxyphenyl)propanal **5**[7] was subjected to asymmetric allylation using the chiral allylborane prepared from allylmagnesium bromide and (−)-DIP–Cl [(−)-diisopinocampheylchloroborane].[8] In this way, homoallyl alcohol **6** was obtained in over 96% ee as judged by NMR examination of the Mosher ester.[9] Benzylation of the hydroxyl group followed by Wacker oxidation[10] provided methyl ketone **8**. Boron aldol reaction[11] of this ketone with *n*-tetradecanal afforded the desired aldol **9** in 70% yield as a single diastereomer. The aldol can be then reduced to the monobenzylated *anti*,*syn*-1,3,5-triol **10** but it was much more expedient to perform the aldol reduction in situ with $LiBH_4$ to stereoselectively yield **10**.[12] Protection of the two free hydroxyl groups as an acetonide followed by hydrogenolytic debenzylation afforded **12**. Swern oxidation of the latter compound furnished ketone **13**, which was then submitted to hydrolytic cleavage of the acetonide moiety. However, while the expected β,δ-dihydroxy ketone was formed, the yield was low (<35%). Fortunately, treatment of acetonide **12** with phenyliodonium bis(trifluoroacetate) not only caused the desired phenolic oxidation[5,13,14] but also acetonide hydrolysis and subsequent spiroacetalization. This cleanly yielded a 5.5:1 mixture of two optically active products with spectral properties identical to those reported for aculeatins A and B.[1] Intermediates or by-products of 4-hydroxycyclohexa-2,5-dienone type[5b] (see Scheme 1) were not detected.

A closer examination of the respective NMR spectral properties revealed, however, an important issue. The major product exhibited in fact the optical rotation and spectral



Scheme 2. Synthesis of aculeatins A and B. Reaction conditions: (a) allylBIpc$_2$ from (−)-Ipc$_2$BCl and allylmagnesium bromide, Et_2O, 3 h, −90 °C; (b) NaH; THF, then BnBr, rt, overnight, 85% overall from **5**; (c) $PdCl_2$, $CuCl_2$, aq DMF, O_2, 2 d, 75%; (d) Bu_2BOTf, $EtNiPr_2$, CH_2Cl_2, −78 °C, 1 h, followed by addition of *n*-tetradecanal, 3 h, −78 °C, 70%; (e) Bu_2BOTf, $EtNiPr_2$, CH_2Cl_2, −78 °C, 1 h, followed by addition of *n*-tetradecanal, 3 h, −78 °C, then $LiBH_4$, 2 h, −78 °C, 65% overall; (f) 2,2-dimethoxypropane, CSA (cat.), Me_2CO, rt, 1 d, 72%; (g) H_2 (1 atm), 10% Pd–C, EtOAc, rt, 6 h, 70%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C→0 °C, 87% and (i) $PhI(OOCCF_3)_2$, Me_2CO–H_2O (9:1), rt, 24 h, 65% overall, 5.5:1 mixture of aculeatins A and B. Acronyms: Ipc, isopinocampheyl; CSA, camphorsulfonic acid.

properties associated with aculeatin A.[1] It was stable and showed no noticeable tendency to isomerize to the minor stereoisomer. NOE measurements pointed out the absence of dipolar correlations between the methine proton H-2 and one methylene proton at C-15 (for numbering, see Scheme 1). This strongly suggests that its configuration corresponds to **2** (Fig. 2), not to **1** as proposed.[1] In addition,

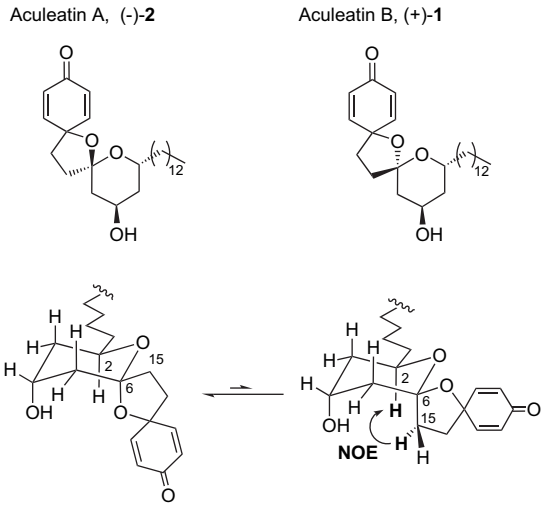
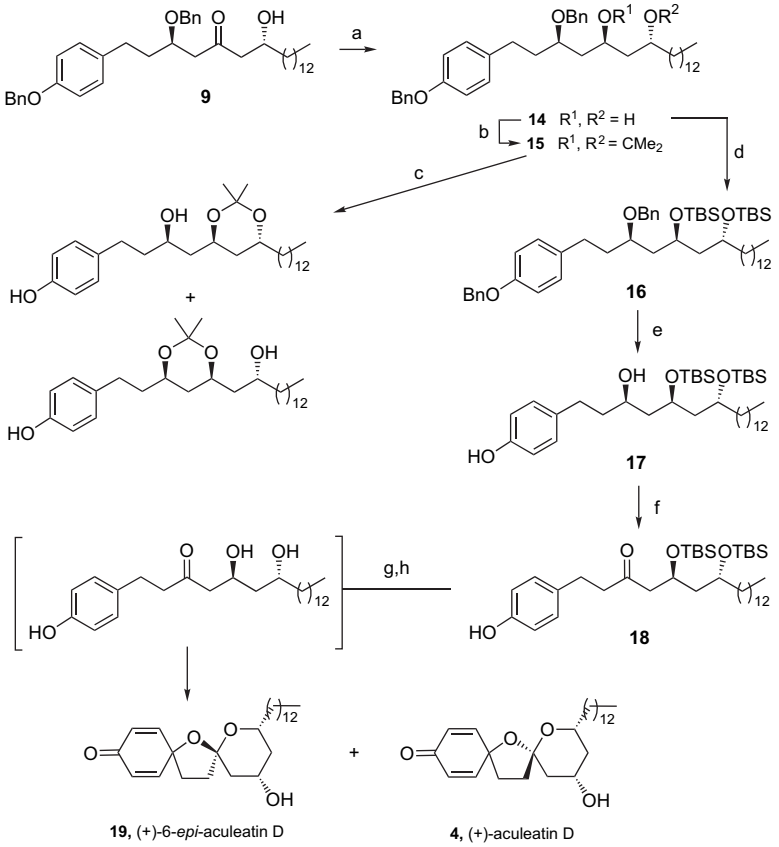


Figure 2. Corrected structures and absolute configurations of aculeatins A and B.

structure **2** benefits from a favorable anomeric effect,[15] in agreement with the higher stability of aculeatin A. In support of this reasoning, the minor isomer, which was unstable and isomerized slowly to the major one, showed a marked NOE between the methine proton H-2 and one methylene proton at C-15. These properties, which are associated to aculeatin B,[1a] are only compatible with stereostructure **1** (Fig. 2), which does not exhibit a favorable anomeric effect. A further support is given by the markedly higher δ value of H-2 in aculeatin A (δ 4.10 vs δ 3.86 ppm in aculeatin B), which points to its 1,3-diaxial relation with the anomeric oxygen atom. In summary, the Swiss workers[1] erroneously interchanged the relative stereostructures of the aculeatins A and B, *which are therefore **2** and **1**, respectively.*[16] The optical rotation values of the synthetic compounds were very similar to those of the natural compounds and the signs are the same. Our synthesis therefore has led to the natural enantiomers of both aculeatins and permitted the establishment of their absolute configurations (Fig. 2).

The same retrosynthetic concept depicted in Scheme 1 was applied to aculeatin D with only a change, related to the inverted configuration at C-4. Thus, aldol **9** was reduced with TABH[17] to stereoselectively afford the expected *anti*-1,3-diol **14** (minor isomer not detected by means of NMR), subsequently transformed into its acetonide **15** (Scheme 3). Problems arose, however, during hydrogenolytic cleavage of the two benzyl groups. Under all conditions we tried,



Scheme 3. Synthesis of aculeatin D and 6-*epi*-aculeatin D. Reaction conditions: (a) TABH, AcOH–MeCN, −30 °C, 12 h, 86%; (b) 2,2-dimethoxypropane, CSA (cat.), Me_2CO, rt, 12 h, 89%; (c) H_2 (1 atm), 10% Pd–C, EtOAc, rt, 6 h, 40%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, Δ, 91%; (e) H_2 (1 atm), 10% Pd–C, EtOAc, rt, 15 min, 74%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C→0 °C, 81%; (g) TASF, DMF, 0 °C, 90 min, then rt, 4 h and (h) $PhI(OOCCF_3)_2$, Me_2CO–H_2O (9:1), rt, 30 min, 77% overall for the two steps, 2.7:1 mixture of aculeatin D (minor) and 6-*epi*-aculeatin D (major). Acronyms: TABH, tetramethylammonium triacetoxyborohydride; TASF, tris(dimethylamino)sulfonium difluoro-trimethylsilicate; TBSOTf, *tert*-butyldimethylsilyl triflate.

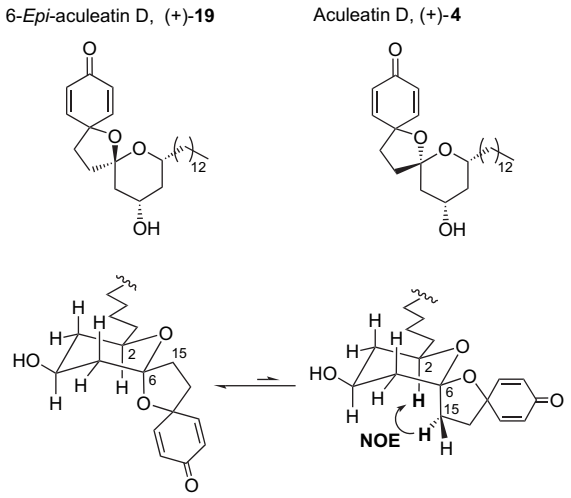


Figure 3. Structures and absolute configurations of aculeatin D **4** and 6-*epi*-aculeatin D **19**.

partial migration (transacetalization) of the acetonide group took place with formation in low yield of two isomeric acetonides, the undesired one being the major compound. We then replaced the acetonide moiety by other protecting groups such as MOM, MEM or TES (triethylsilyl), all cleavable under mild conditions.[18] However, no success was achieved with these groups, either. The acetal-like MOM or MEM groups were introduced with unsatisfactory yields and showed a marked tendency to form six-membered formaldehyde acetals with the proximal hydroxy group.[19] The TES group behaved better in this aspect but was partially cleaved under hydrogenolytic conditions. Eventually, the TBS group proved appropriate. Double silylation of diol **14** worked well, as did the subsequent hydrogenolysis and oxidation steps, which finally yielded ketone **18**. The latter was desilylated under mild conditions with TASF.[20] Without purification, the intermediate diol was subjected as above to oxidative spiroacetalization with $PhI(OCOCF_3)_2$ to yield a 2.7:1 mixture of compounds **4** (minor) and **19** (major), again with no 4-hydroxycyclohexa-2,5-dienone being isolated. Compounds **4** and **19** displayed physical and spectral features identical to those reported for natural aculeatin D[1b] and synthetic 6-*epi*-aculeatin D,[5b] respectively. NOE measurements were consistent with the published structures (Fig. 3). The absolute configuration of natural aculeatin D turns out to be as depicted in the figure.

3. Conclusions

The naturally occurring, bioactive spiroacetals aculeatins A, B, and D, as well as the hitherto non-natural 6-*epi*-aculeatin D, have been synthesized for the first time in enantiopure form. Their absolute configurations have been established, and a previous structural misassignment has been corrected.

4. Experimental

4.1. General

$^1H/^{13}C$ NMR spectra were measured at 500/125 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Carbon atom types (C, CH, CH_2, and CH_3) were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV), the CIMS (CH_4 as the gas carrier) or the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR data are given only for compounds with relevant functions (OH, C=O, and C≡C–H) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions, which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium–benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic (basic), an additional washing with 5% aq $NaHCO_3$ (aq NH_4Cl) was performed. Drying over anhydrous Na_2SO_4 and elimination of the solvent under reduced pressure were followed by chromatography of the residue on a silica gel column (60–200 μm) with the indicated eluent. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer. Reagent acronyms are explained in the captions of Schemes 2 and 3.

4.1.1. (*R*)-1-(4-Benzyloxyphenyl)hex-5-en-3-ol (6). Allylmagnesium bromide (commercial 1 M solution in Et_2O, 2.5 mL, 2.5 mmol) was added dropwise under N_2 via syringe to a solution of (−)-DIP–Cl (0.97 g, 3 mmol) in dry Et_2O (12 mL) cooled in a dry ice-acetone bath. After replacing the latter by an ice bath, the mixture was stirred for 1 h. The solution was allowed to stand, whereby precipitation of magnesium chloride took place. The supernatant solution was carefully transferred to another flask via cannula. After cooling this flask at −90 °C, a solution of freshly prepared[7] 3-(4-benzyloxyphenyl)-propanal (480 mg, ca. 2 mmol) in dry Et_2O (5 mL) was added dropwise via syringe. The resulting solution was further stirred at −90 °C for 3 h. The reaction mixture was quenched through addition of phosphate pH 7 buffer solution (12 mL), MeOH (12 mL), and 30% H_2O_2 (6 mL). After stirring for 30 min, the mixture was poured onto satd aq $NaHCO_3$ and worked-up (extraction with Et_2O). For synthetic purposes, the oily residue was used directly in the next step. For analytical characterization, an aliquot of the residue was subjected to a careful column chromatography on silica gel (hexane, then hexane–EtOAc, 19:1 and 9:1) yielding pure **6** (>98:2 mixture of enantiomers as estimated via the Mosher ester): colorless solid, mp 61–63 °C; $[\alpha]_D$ +12.7 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (5H, m), 7.14 (2H, d, *J*=8.5 Hz), 6.93 (2H, d, *J*=8.5 Hz), 5.85 (1H, m), 5.20–5.15 (2H, m), 5.06 (2H, s), 3.70 (1H, m), 2.78 (1H, m), 2.67 (1H, m), 2.33 (1H, m), 2.22 (1H, m), 1.80–1.75 (2H, m) (hydroxyl proton not detected); ^{13}C NMR (125 MHz) δ 157.1, 137.2, 134.4 (C), 134.6, 129.3 (×2), 128.5 (×2), 127.8, 127.4 (×2), 114.8 (×2), 69.9 (CH), 118.2, 70.1, 42.0, 38.6, 31.1 (CH_2); IR ν_{max} 3370 (br, OH), 3076, 1513, 1453, 1254,

913 cm^{-1}; HR EIMS *m/z* (rel int.) 282.1619 (M^+, 20), 197 (10), 91 (100). Calcd for $C_{19}H_{22}O_2$, 282.1620. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.89; H, 7.83.

4.1.2. (*R*)-4-Benzyloxy-6-(4-benzyloxyphenyl)hex-1-ene (7). Solid sodium hydride 95% (125 mg, ca. 5 mmol) was suspended under N_2 in dry THF (5 mL). A solution of the crude residue of the previous reaction in dry THF (5 mL) was added. The mixture was stirred at room temperature for 45 min and treated with tetra-*n*-butyl ammonium iodide (18 mg, 0.05 mmol) and benzyl bromide (0.6 mL, ca. 5 mmol). The mixture was stirred overnight at room temperature. Work-up (extraction with Et_2O) and column chromatography on silica gel (hexane–EtOAc, 99:1) furnished **7** (630 mg, 85% overall from **5**): oil; $[\alpha]_D$ +21.7 (*c* 2.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.13 (2H, d, *J*=8.5 Hz), 6.94 (2H, d, *J*=8.5 Hz), 5.90 (1H, m), 5.15–5.10 (2H, m), 5.08 (2H, s), 4.65 (1H, d, *J*=11.5 Hz), 4.53 (1H, d, *J*=11.5 Hz), 3.53 (1H, m), 2.78 (1H, m), 2.66 (1H, m), 2.50–2.40 (2H, m), 1.95–1.85 (2H, m); ^{13}C NMR (125 MHz) δ 157.0, 138.8, 137.3, 134.7 (C), 134.8, 129.3 (×2), 128.5 (×2), 128.3 (×2), 127.8, 127.7 (×2), 127.5, 127.4 (×2), 114.8 (×2), 77.7 (CH), 117.1, 70.9, 70.1, 38.2, 35.9, 30.8 (CH_2); IR ν_{max} 3065, 3031, 1511, 1454, 1239, 736 cm^{-1}; HR EIMS *m/z* (rel int.) 372.2101 (M^+, 10), 287 (13), 119 (37), 91 (100). Calcd for $C_{26}H_{28}O_2$, 372.2089. Anal. Calcd for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.89; H, 7.50.

4.1.3. (*R*)-4-Benzyloxy-6-(4-benzyloxyphenyl)hexan-2-one (8). Olefin **7** (615 mg, 1.65 mmol) was dissolved in DMF containing 10% water (40 mL) and treated with $PdCl_2$ (90 mg, ca. 0.5 mmol) and CuCl (500 mg, ca. 5 mmol). The mixture was stirred at room temperature under O_2 for 48 h, then poured onto satd aq NH_4Cl and worked-up (extraction with Et_2O). Column chromatography on silica gel (hexane–EtOAc, 9:1) provided **8** (480 mg, 75%): oil; $[\alpha]_D$ +3.5 (*c* 1.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.12 (2H, d, *J*=8.5 Hz), 6.94 (2H, d, *J*=8.5 Hz), 5.07 (2H, s), 4.57 (2H, s), 4.00 (1H, br quintuplet, $J\approx6$ Hz), 2.82 (1H, dd, *J*=15.5, 7 Hz), 2.75–2.65 (2H, m), 2.59 (1H, dd, *J*=15.5, 5 Hz), 2.18 (3H, s), 1.95–1.85 (2H, m); ^{13}C NMR (125 MHz) δ 207.3, 157.0, 138.4, 137.2, 134.1 (C), 129.2 (×2), 128.5 (×2), 128.3 (×2), 127.8, 127.7 (×2), 127.5, 127.4 (×2), 114.8 (×2), 74.9 (CH), 71.5, 70.0, 48.4, 36.3, 30.5 (CH_2), 31.0 (CH_3); IR ν_{max} 3063, 3031, 1714 (C=O), 1610, 1511, 1454, 1239, 1074, 1027, 738 cm^{-1}; HR FABMS *m/z* 388.2037 (M^+). Calcd for $C_{26}H_{28}O_3$, 388.2038. Anal. Calcd for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26. Found: C, 80.49; H, 7.33.

4.1.4. (*R*)-4-Benzyloxy-6-(4-benzyloxyphenyl)hexan-2-one (8). Olefin **7** (615 mg, 1.65 mmol) was dissolved in DMF containing 10% water (40 mL) and treated with $PdCl_2$ (90 mg, ca. 0.5 mmol) and CuCl (500 mg, ca. 5 mmol). The mixture was stirred at room temperature under O_2 for 48 h, poured onto satd aq NH_4Cl and worked-up (extraction with Et_2O). Column chromatography on silica gel (hexane–EtOAc, 9:1) provided **8** (480 mg, 75%): oil; $[\alpha]_D$ +3.5 (*c* 1.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.12 (2H, d, *J*=8.5 Hz), 6.94 (2H, d, *J*=8.5 Hz), 5.07 (2H, s), 4.57 (2H, s), 4.00 (1H, br quintuplet, $J\approx6$ Hz), 2.82 (1H, dd, *J*=15.5, 7 Hz), 2.75–2.65 (2H, m), 2.59 (1H, dd, *J*=15.5, 5 Hz), 2.18 (3H, s), 1.95–1.85 (2H, m); ^{13}C NMR (125 MHz) δ 207.3, 157.0, 138.4, 137.2, 134.1 (C), 129.2 (×2), 128.5 (×2), 128.3 (×2), 127.8, 127.7 (×2), 127.5, 127.4 (×2), 114.8 (×2), 74.9 (CH), 71.5, 70.0, 48.4, 36.3, 30.5 (CH_2), 31.0 (CH_3); IR ν_{max} 3063, 3031, 1714 (C=O), 1610, 1511, 1454, 1239, 1074, 1027, 738 cm^{-1}; HR FABMS *m/z* 388.2037 (M^+). Calcd for $C_{26}H_{28}O_3$, 388.2038. Anal. Calcd for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26. Found: C, 80.49; H, 7.33.

4.1.5. (3*R*,5*R*,7*R*)-3-Benzyloxy-1-(4-benzyloxyphenyl)-eicosane-5,7-diol (10). A solution of ketone **8** (466 mg, 1.2 mmol) in dry CH_2Cl_2 (8 mL) was cooled under N_2 to −78 °C and treated sequentially with diisopropyl ethyl amine (260 μL, 1.5 mmol) and a 1 M solution of Bu_2BOTf in CH_2Cl_2 (1.35 mL, 1.35 mmol). The mixture was stirred for 1 h at the same temp, followed by addition of a solution of *n*-tetradecanal (287 mg, 1.35 mmol)[21] in dry CH_2Cl_2 (5 mL). The mixture was stirred at −78 °C for further 3 h, treated with a 2 M solution of $LiBH_4$ in THF (1.2 mL, 2.4 mmol), and further stirred at −78 °C for 2 h. The reaction was quenched by addition of phosphate pH 7 buffer solution (7 mL) and MeOH (7 mL), followed by 30% aq H_2O_2 solution (3.5 mL). After stirring for 30 min at room temperature, the mixture was worked-up (extraction with CH_2Cl_2). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexane–EtOAc, 9:1) yielded diol **10** (470 mg, 65%): amorphous solid; $[\alpha]_D$ −10.2 (*c* 0.75, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.08 (2H, d, *J*=8.5 Hz), 6.91 (2H, d, *J*=8.5 Hz), 5.05 (2H, s), 4.56 (1H, d, *J*=11.5 Hz), 4.54 (1H, d, *J*=11.5 Hz), 4.18 (1H, m), 3.85 (1H, m), 3.75 (1H, m), 2.70–2.60 (2H, m), 2.00 (1H, m), 1.85–1.75 (2H, m), 1.65 (1H, ddd, *J*=14.5, 7, 2.5 Hz), 1.55–1.45 (2H, m), 1.40–1.25 (24H, br m), 0.90 (3H, t, *J*=7 Hz) (hydroxyl protons not detected); ^{13}C NMR (125 MHz) δ 157.2, 138.1, 137.2, 134.2 (C), 129.3 (×2), 128.6 (×2), 128.5 (×2), 128.1 (×2), 127.9 (×2), 127.4 (×2), 114.9 (×2), 76.3, 72.7 (CH), 70.7 (CH+CH_2), 71.3, 43.4, 40.5, 38.0, 35.5, 31.9, 30.8, 29.6 (several overlapped signals), 29.5 (several overlapped signals), 29.4, 25.4, 22.7 (CH_2), 14.1 (CH_3); IR ν_{max} 3420 (br, OH), 3032, 1511, 1455, 1240, 736 cm^{-1}; HR FABMS *m/z* 603.4363 (M+H^+). Calcd for $C_{40}H_{59}O_4$, 603.4413. Anal. Calcd for $C_{40}H_{58}O_4$: C, 79.69; H, 9.70. Found: C, 79.79; H, 9.53.

4.1.6. (4*S*,6*R*)-4-[(*R*)-2-Benzyloxy-4-(4-benzyloxyphenyl) butyl]-2,2-dimethyl-6-*n*-tridecyl-[1,3]dioxane (11). Diol **10** (452 mg, 0.75 mmol) was dissolved in dry acetone (15 mL) and treated with camphorsulfonic acid (10 mg, ca. 0.05 mmol) and 2,2-dimethoxypropane (3 mL). After adding activated 3 Å molecular sieves (0.5 g), the mixture was stirred overnight at room temperature. The mixture was then poured onto satd aq $NaHCO_3$ and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexane–EtOAc, 99:1) furnished **11** (347 mg, 72%): amorphous solid; $[\alpha]_D$ −12.7 (*c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.10 (2H, d, *J*=8.5 Hz), 6.91 (2H, d, *J*=8.5 Hz), 5.06 (2H, s), 4.58 (1H, d, *J*=11.5 Hz), 4.50 (1H, d, *J*=11.5 Hz), 4.10 (1H, m), 3.81 (1H, m), 3.75 (1H, m), 2.66 (2H, m), 1.90–1.85 (2H, m),

1.70–1.65 (2H, m), 1.50 (1H, m), 1.41 (6H, s), 1.40–1.25 (24H, br m), 1.16 (1H, q, J=11.5 Hz), 0.91 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 157.0, 138.9, 137.3, 134.8, 98.4 (C), 129.3 (×2), 128.6 (×2), 128.4 (×2), 127.9 (×2), 127.8, 127.5, 127.4 (×2), 114.8 (×2), 74.7, 69.1, 65.8 (CH), 71.6, 70.1, 42.1, 37.7, 36.6, 36.5, 31.9, 30.3, 29.6 (several overlapped signals), 29.5 (several overlapped signals), 29.4, 25.0, 22.7 (CH_2), 30.4, 20.0, 14.1 (CH_3); IR ν_{max} 3031, 1511, 1455, 1379, 1241, 736 cm^{-1}; HR EIMS *m/z* (rel int.) 642.4664 (M^+, 1), 627 (14), 584 (5), 476 (59), 197 (33), 91 (100). Calcd for $C_{43}H_{62}O_4$, 642.4648. Anal. Calcd for $C_{43}H_{62}O_4$: C, 80.33; H, 9.72. Found: C, 80.22; H, 9.84.

4.1.7. (4*S*,6*R*)-4-[(*R*)-2-Hydroxy-4-(4-hydroxyphenyl) butyl]-2,2-dimethyl-6-*n*-tridecyl-[1,3]dioxane (12). Pd–C 10% (50 mg) was suspended in EtOAc (5 mL) and stirred under an H_2 atmosphere for 15 min. Compound **11** (321 mg, 0.5 mmol) dissolved in EtOAc (10 mL) was added via syringe. The mixture was stirred at room temperature and ambient pressure for 6 h, and filtered through Celite. Solvent removal in vacuo and column chromatography on silica gel (hexane–EtOAc, 4:1) gave **12** (162 mg, 70%): colorless solid, mp 80–82 °C; $[\alpha]_D$ −1.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 5.40 (1H, br s, OH), 4.20 (1H, m), 3.94 (1H, m), 3.82 (1H, m), 3.10 (1H, br s, OH), 2.73 (1H, m), 2.59 (1H, m), 1.80–1.50 (6H, br m), 1.45 (3H, s), 1.40 (3H, s), 1.40–1.25 (24H, br m), 0.88 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 153.9, 134.2, 98.7 (C), 129.5 (×2), 115.3 (×2), 69.2, 68.3, 67.5 (CH), 41.9, 39.3, 36.4, 36.3, 31.9, 31.2, 29.6 (several overlapped signals), 29.5 (several overlapped signals), 29.4, 25.0, 22.7 (CH_2), 30.3, 19.7, 14.1 (CH_3); IR ν_{max} 3370 (br, OH), 1514, 1459, 1262, 828 cm^{-1}; HR EIMS *m/z* (rel int.) 462.3732 (M^+, 1), 447 (14), 386 (16), 107 (100). Calcd for $C_{29}H_{50}O_4$, 462.3709. Anal. Calcd for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.22; H, 10.84.

4.1.8. 1-[(4*R*,6*R*)-(2,2-Dimethyl-6-tridecyl-[1,3]dioxan-4-yl)]-4-(4-hydroxyphenyl)-butan-2-one (13). Oxalyl chloride (62 μL, ca. 0.7 mmol) was dissolved under N_2 in dry CH_2Cl_2 (3 mL). After cooling the solution to −78 °C, dry DMSO (56 μL, 0.8 mmol) was added dropwise with stirring for 5 min. A solution of alcohol **12** (162 mg, 0.35 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise, with additional stirring for 15 min. Addition of Et_3N (210 μL, 1.5 mmol) was followed by stirring for 15 min at −78 °C and for further 1 h at 0 °C. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc, 7:3) gave ketone **13** (140 mg, 87%): colorless solid, mp 53–55 °C; $[\alpha]_D$ −4.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 5.90 (1H, br s, OH), 4.32 (1H, m), 3.81 (1H, m), 2.85–2.70 (4H, br m), 2.67 (1H, dd, J=15.7, 7.2 Hz), 2.40 (1H, dd, J=15.7, 5.3 Hz), 1.50 (1H, m), 1.42 (3H, s), 1.37 (3H, s), 1.40–1.25 (24H, br m), 1.11 (1H, q, J=11.5 Hz), 0.88 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 209.0, 154.2, 132.7, 98.8 (C), 129.3 (×2), 115.4 (×2), 69.0, 65.9 (CH), 36.8, 36.3, 31.9, 29.6 (several overlapped signals), 29.5 (several overlapped signals), 29.3, 24.9, 22.7 (CH_2), 30.1, 19.7, 14.1 (CH_3); IR ν_{max} 3390 (br, OH), 1712 (C=O), 1614, 1515, 1379, 828 cm^{-1}; HR EIMS *m/z* (rel int.) 460.3568 (M^+, 1), 445 (8), 402 (18), 107 (100). Calcd for $C_{29}H_{48}O_4$, 460.3552. Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50. Found: C, 75.69; H, 10.63.

4.1.9. (2*R*,4*R*,6*S*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (aculeatin B) (1) and (2*R*,4*R*,6*R*)-4-hydroxy-2-tridecyl-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (aculeatin A) (2). Ketone **13** (140 mg, 0.3 mmol) was dissolved in a 9:1 acetone–water mixture (10 mL) and treated in four portions with $PhI(OCOCF_3)_2$ (430 mg, 1 mmol), each portion being added every hour. The reaction mixture was stirred overnight at room temperature in the dark. Work-up (extraction with EtOAc) and careful column chromatography on silica gel (hexane–EtOAc, 4:1, then 3:2) yielded **1** (12.5 mg) and **2** (69 mg).

*Aculeatin A (**2**):* oil; $[\alpha]_D$ −5.2 (*c* 0.9; $CHCl_3$), lit.[1a] $[\alpha]_D$ −5.3 (*c* 0.2, $CHCl_3$); IR ν_{max} 3550 (br, OH), 1673 (ketone C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (1H, dd, J=10, 3 Hz), 6.76 (1H, dd, J=10, 3 Hz), 6.14 (1H, dd, J=10, 1.7 Hz), 6.10 (1H, dd, J=10, 1.7 Hz), 4.15–4.10 (2H, m), 3.35 (1H, br d, J=10 Hz, OH), 2.38 (1H, m), 2.24 (1H, m), 2.05–2.00 (3H, m), 1.93 (1H, br d, J=14 Hz), 1.79 (1H, br dd, J=13.7, 2 Hz), 1.60–1.40 (5H, br m), 1.40–1.20 (20H, br m), 0.88 (3H, t, J=6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 109.2, 79.8 (C), 150.9, 148.7, 127.4, 127.2, 65.4, 64.9 (CH), 39.2, 38.0, 36.0, 34.2, 32.0, 29.7 (several overlapped signals), 29.4, 25.7, 22.7 (CH_2), 14.1 (CH_3); HR EIMS *m/z* (rel int.) 418.3117 (M^+, 2), 400 (M^+-H_2O, 6), 310 (6), 236 (25), 165 (100), 107 (73). Calcd for $C_{26}H_{42}O_4$, *M*=418.3083.

*Aculeatin B (**1**)*: oil; $[\alpha]_D$ +53.2 (*c* 0.4, $CHCl_3$), lit.[1a] $[\alpha]_D$ +50 (*c* 0.8, $CHCl_3$); IR ν_{max} 3460 (br, OH), 1670 (ketone C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, dd, J=10, 2.9 Hz), 6.77 (1H, dd, J=10, 2.9 Hz), 6.13 (1H, dd, J=10, 1.8 Hz), 6.10 (1H, dd, J=10, 1.8 Hz), 4.36 (1H, apparent quintuplet, J=3.2 Hz), 3.86 (1H, m), 2.68 (1H, br dd, J=12.8, 7.2 Hz), 2.30 (1H, td, J=12.3, 7.2), 2.10–2.00 (2H, m), 1.95–1.85 (2H, m), 1.60–1.40 (8H, br m), 1.40–1.20 (19H, br m), 0.88 (3H, t, J=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 108.6, 77.6 (C), 152.2, 149.2, 127.2, 127.1, 69.5, 65.2 (CH), 40.7, 38.0, 35.8, 35.4, 35.3, 31.9, 29.7 (several overlapped signals), 29.4, 29.3, 25.9, 22.7 (CH_2), 14.1 (CH_3); HR EIMS *m/z* (rel int.) 418.3108 (M^+, 9), 400 (M^+-H_2O, 24), 310 (16), 235 (85), 165 (100), 107 (23). Calcd for $C_{26}H_{42}O_4$, *M*=418.3083.

4.1.10. (3*R*,5*S*,7*R*)-3-Benzyloxy-1-(4-benzyloxyphenyl) eicosane-5,7-diol (14). Tetramethylammonium triacetoxyborohydride (1.05 g, ca. 4 mmol) was dissolved under N_2 in an acetonitrile–acetic acid 1:1 mixture (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to −30 °C and treated dropwise with a solution of aldol **9** (300 mg, 0.5 mmol) in dry acetonitrile (3 mL). The solution was stirred at −30 °C for 12 h and at 0 °C for further 2 h. After quenching with aq 1 M sodium potassium tartrate (2 mL), the mixture was stirred for 1 h at room temperature. Work-up (extraction with CH_2Cl_2) and column chromatography of the residue on silica gel (hexane–EtOAc, 4:1) afforded diol **14** (260 mg, 86%): colorless solid, mp 57–59 °C; $[\alpha]_D$ −19.6 (*c* 1.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.45–7.30 (10H, m), 7.10 (2H, d, J=8.5 Hz), 6.92 (2H, d, J=8.5 Hz), 5.06 (2H, s), 4.63 (1H, d, J=11 Hz), 4.44 (1H, d, J=11 Hz), 4.18 (1H, m), 3.92 (1H, m), 3.78 (1H, m), 2.70–2.60 (2H, m), 2.00 (2H, br s, OH), 2.00–1.90 (2H, m), 1.70–1.40 (4H, m), 1.40–1.25 (24H, br m), 0.91 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 157.1, 137.8, 137.2, 134.2 (C), 129.3 (×2), 128.6 (×2), 128.5 (×2), 128.1 (×2), 127.9 (×2), 127.4 (×2), 114.9 (×2), 79.2, 69.4, 68.8 (CH), 70.6, 70.1, 43.0, 40.7, 37.6, 35.3, 31.9, 30.0, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 29.3, 25.7, 22.7 (CH_2), 14.1 (CH_3); IR ν_{max} 3420 (br, OH), 3063, 3031, 1511, 1455, 1240, 736 cm^{-1}; HR FABMS m/z 603.4401 (M+H$^+$). Calcd for $C_{40}H_{59}O_4$, 603.4413. Anal. Calcd for $C_{40}H_{58}O_4$: C, 79.69; H, 9.70. Found: C, 79.82; H, 9.82.

4.1.11. (4*R*,6*R*)-4-[(*R*)-2-Benzyloxy-4-(4-benzyloxyphenyl) butyl]-2,2-dimethyl-6-*n*-tridecyl-[1,3]dioxane (15). Diol **14** (45 mg, 0.075 mmol) was dissolved in dry acetone (1 mL) and treated with camphorsulfonic acid (1 mg, ca. 0.005 mmol) and 2,2-dimethoxypropane (0.5 mL). After adding activated 3 Å molecular sieves (50 mg), the mixture was stirred overnight at room temperature. The mixture was then poured onto satd aq $NaHCO_3$ and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexane–EtOAc, 99:1) furnished **15** (43 mg, 89%): oil; $[\alpha]_D$ −4 (*c* 2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.08 (2H, d, J=8.5 Hz), 6.91 (2H, d, J=8.5 Hz), 5.06 (2H, s), 4.53 (1H, d, J=11.5 Hz), 4.51 (1H, d, J=11.5 Hz), 3.94 (1H, m), 3.78 (1H, m), 3.55 (1H, br quintuplet, $J\approx$6 Hz), 2.75–2.65 (2H, m), 2.00 (1H, m), 1.95–1.85 (2H, m), 1.65–1.50 (3H, m), 1.40 (2H, m), 1.37 (3H, s), 1.40–1.25 (25H, br m), 0.92 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 157.0, 138.9, 137.3, 134.7, 100.1 (C), 129.3 (×2), 128.5 (×2), 128.3 (×2), 127.9, 127.8, 127.5, 127.4 (×2), 114.8 (×2), 74.7, 66.6, 63.7 (CH), 70.6, 70.1, 40.1, 39.0, 36.0, 35.9, 31.9, 30.5, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 29.5, 29.3, 25.4, 22.7 (CH_2), 24.8, 24.7, 14.1 (CH_3); IR ν_{max} 3031, 1511, 1455, 1378, 1224, 734 cm^{-1}; HR EIMS m/z (rel int.) 642.4645 (M$^+$, 1), 627 (1), 584 (25), 566 (5), 476 (9), 197 (13), 91 (100). Calcd for $C_{43}H_{62}O_4$, 642.4648. Anal. Calcd for $C_{43}H_{62}O_4$: C, 80.33; H, 9.72. Found: C, 80.41; H, 9.62.

4.1.12. 1-Benzyloxy-4-[(3*R*,5*R*,7*R*)-3-benzyloxy-5,7-bis-(*tert*-butyldimethylsilyloxy)eicosyl]benzene (16). Diol **14** (193 mg, 0.32 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and treated sequentially with 2,6-lutidine (350 μL, 3 mmol) and TBSOTf (550 μL, ca. 2.5 mmol). The reaction mixture was stirred at reflux for 6 h and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexane–EtOAc, 19:1) gave **16** (242 mg, 91%): oil; $[\alpha]_D$ +13.6 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.06 (2H, d, J=8.5 Hz), 6.88 (2H, d, J=8.5 Hz), 5.02 (2H, s), 4.54 (1H, d, J=11.5 Hz), 4.44 (1H, d, J=11.5 Hz), 3.84 (1H, br quintuplet, $J\approx$6 Hz), 3.72 (1H, br quintuplet, $J\approx$5.5 Hz), 3.57 (1H, br quintuplet, $J\approx$5.5 Hz), 2.70 (1H, m), 2.58 (1H, m), 1.90–1.75 (3H, br m), 1.60 (2H, m), 1.40 (1H, m), 1.40–1.25 (24H, br m), 0.86 (21H, br s), 0.05 (3H, s), 0.02 (6H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz) δ 157.1, 139.0, 137.3, 134.8, 18.1, 18.0 (C), 129.3 (×2), 128.6 (×2), 128.5 (×2), 128.1 (×2), 127.9 (×2), 127.4 (×2), 114.8 (×2), 75.7, 70.0, 67.7 (CH), 70.8, 70.1, 46.2, 42.7, 37.8, 36.3, 31.9, 30.7, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 25.0, 22.7 (CH_2), 26.0 (×6), 14.1, −3.9 (×2), −4.0 (×2) (CH_3); IR ν_{max} 3032, 1511, 1250, 1078, 835 cm^{-1}; HR EIMS m/z (rel int.) 773.5371 (M$^+$−*t*Bu, 1), 641 (4), 549 (6), 327 (58), 91 (100). Calcd for $C_{52}H_{86}O_4Si_2$–*t*Bu, 773.5360. Anal. Calcd for $C_{52}H_{86}O_4Si_2$: C, 75.12; H, 10.43. Found: C, 75.24; H, 10.54.

4.1.13. 4-[(3*R*,5*R*,7*R*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-3-hydroxyeicosyl]phenol (17). Pd–C 10%(250 mg) was suspended in EtOAc (8 mL) and stirred under H_2 atmosphere for 15 min. Compound **16** (233 mg, 0.28 mmol) dissolved in EtOAc (5 mL) was added via syringe. The mixture was stirred at room temperature and ambient pressure for 15 min and filtered through Celite *(caution: longer reaction times lead to partial desilylation!)*. Solvent removal in vacuo and column chromatography on silica gel (hexane–EtOAc, 4:1) furnished **17** (135 mg, 74%): oil; $[\alpha]_D$ +14 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 4.90 (1H, br s, OH), 3.89 (1H, br quintuplet, $J\approx$5 Hz), 3.78 (1H, m), 3.65 (1H, br quintuplet, $J\approx$5.5 Hz), 3.30 (1H, br s, OH), 2.70 (1H, m), 2.61 (1H, m), 1.80–1.55 (6H, m), 1.40–1.25 (24H, br m), 0.90 (21H, br s), 0.11 (6H, s), 0.05 (6H, s); ^{13}C NMR (125 MHz) δ 153.7, 134.4, 18.1, 17.9 (C), 129.5 (×2), 115.2 (×2), 71.7, 70.2, 70.1 (CH), 46.5, 44.3, 39.7, 37.4, 31.9, 30.8, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 29.4, 25.0, 22.7 (CH_2), 26.0 (×3), 25.9 (×3), 14.1, −3.9, −4.2 (×2), −4.3 (CH_3); IR ν_{max} 3380 (br, OH), 1515, 1471, 1463, 1255, 1078, 835 cm^{-1}; HR FABMS m/z 651.5209 (M+H$^+$). Calcd for $C_{38}H_{75}O_4Si_2$, 651.5204. Anal. Calcd for $C_{38}H_{74}O_4Si_2$: C, 70.09; H, 11.45. Found: C, 69.94; H, 11.54.

4.1.14. (5*S*,7*R*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-1-(4-hydroxyphenyl)eicosan-3-one (18). Oxalyl chloride (34 μL, ca. 0.4 mmol) was dissolved under N_2 in dry CH_2Cl_2 (2 mL). After cooling the solution to −78 °C, dry DMSO (35 μL, ca. 0.5 mmol) was added dropwise with stirring for 5 min. A solution of alcohol **17** (130 mg, 0.2 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise, with additional stirring for 15 min. Addition of Et_3N (120 μL, 0.85 mmol) was followed by stirring for 10 min at −78 °C. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc, 7:3) gave **18** (105 mg, 81%): oil; $[\alpha]_D$ +10.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 5.50 (1H, br s, OH), 4.21 (1H, br quintuplet, $J\approx$6 Hz), 3.69 (1H, br quintuplet, $J\approx$6 Hz), 2.80 (2H, m), 2.72 (2H, m), 2.60 (1H, dd, J=15, 7.5 Hz), 2.60 (1H, dd, J=15, 4.7 Hz), 1.62 (1H, m), 1.58 (1H, m), 1.42 (2H, m), 1.40–1.25 (22H, br m), 0.89 (12H, br s, overlapping a methyl triplet), 0.86 (9H, s), 0.08 (3H, s), 0.05 (6H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 209.3, 154.0, 133.0, 18.1, 18.0 (C), 129.4 (×2), 115.4 (×2), 70.1, 67.5 (CH), 51.3, 46.4, 45.8, 37.7, 31.9, 30.8, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 29.4, 25.0, 22.7 (CH_2), 26.0 (×3), 25.9 (×3), 14.1, −4.1, −4.2 (×2), −4.4 (CH_3); IR ν_{max} 3400 (br, OH), 1704 (C=O), 1515, 1466, 1362, 1255, 1077, 835 cm^{-1}; HR FABMS m/z 649.5052 (M+H$^+$). Calcd for $C_{38}H_{73}O_4Si_2$, 649.5047. Anal. Calcd for $C_{38}H_{72}O_4Si_2$: C, 70.31; H, 11.18. Found, C, 70.44; H, 11.24.

4.1.15. (2*R*,4*S*,6*S*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (aculeatin D) (4) and (2*R*,4*S*,6*R*)-4-hydroxy-2-tridecyl-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (6-*epi*-aculeatin D) (19). Ketone **18** (65 mg, 0.1 mmol) was dissolved under N_2 in dry DMF (2 mL), cooled to 0 °C and treated with TASF (138 mg, 0.5 mmol). The mixture was stirred for 90 min at 0 °C, then for further 4 h at room temperature. Work-up (extraction with Et_2O) and solvent removal in vacuo gave an oily residue, which was directly used in the next step.

The crude material from above was dissolved in a 9:1 acetone–water mixture (10 mL) and treated with PhI-$(OCOCF_3)_2$ (86 mg, 0.2 mmol). The reaction mixture was stirred at room temperature in the dark until disappearance of the starting material (ca. 25 min, *monitoring with TLC!*). Work-up (extraction with EtOAc) and careful column chromatography on silica gel (hexane–EtOAc, 4:1, then 3:2) yielded **4** (9 mg) and **19** (24 mg).

*Aculeatin D (**4**)*: oil; $[\alpha]_D$ +43.5 (*c* 0.2, $CHCl_3$), lit.[1b] $[\alpha]_D$ +46.5 (*c* 1, $CHCl_3$); IR ν_{max} 3430 (br, OH), 1670 (ketone C=O) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.89 (1H, dd, *J*=10, 3 Hz), 6.21 (1H, dd, *J*=10, 2.8 Hz), 6.07 (1H, dd, *J*=10, 1.8 Hz), 6.04 (1H, dd, *J*=10, 1.8 Hz), 3.37 (1H, m), 2.95 (1H, m), 1.88 (1H, m), 1.79 (1H, m), 1.73 (1H, m), 1.55 (2H, m), 1.50–1.20 (26H, br m), 1.14 (1H, m), 1.01 (1H, m), 0.91 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 185.0, 109.6, 78.5 (C), 152.0, 149.0, 127.5, 127.3, 71.8, 66.9 (CH), 44.2, 41.5, 36.5, 35.4, 33.2, 32.5, 30.5 (br, several overlapped signals), 26.5, 23.5 (CH_2), 14.8 (CH_3); HR EIMS *m*/*z* (rel int.) 418.3059 (M^+, 2), 400 (M^+-H_2O, 16), 310 (5), 235 (35), 165 (80), 120 (94), 107 (100). Calcd for $C_{26}H_{42}O_4$, *M*=418.3083.

*6-Epi-aculeatin D (**19**)*: oil; $[\alpha]_D$ +5.7 (*c* 0.3, $CHCl_3$); IR ν_{max} 3430 (br, OH), 1671 (ketone C=O) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.68 (1H, dd, *J*=10, 3.2 Hz), 6.15–6.10 (2H, m), 6.01 (1H, dd, *J*=10, 2 Hz), 3.90 (1H, m), 3.70 (1H, m), 2.00 (1H, m), 1.87 (2H, m), 1.65 (1H, m), 1.55 (1H, m), 1.50–1.20 (27H, br m), 1.07 (1H, q, *J*=12 Hz), 0.90 (3H, t, *J*=6.9 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 185.2, 109.6, 79.7 (C), 151.4, 149.3, 127.5, 127.2, 69.7, 65.7 (CH), 44.3, 41.8, 39.4, 37.0, 35.5, 32.9, 30.5 (br, several overlapped signals), 26.6, 23.5 (CH_2), 14.8 (CH_3); HR EIMS *m*/*z* (rel int.) 418.3068 (M^+, 6), 400 (M^+-H_2O, 23), 310 (27), 235 (35), 165 (100), 107 (70). Calcd for $C_{26}H_{42}O_4$, *M*=418.3083.

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