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A modular total synthesis of aculeatins A, B, E, F and 6-*epi*-aculeatins E, F

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ABSTRACT

The total synthesis of aculeatins A, B, E and F confirming the assigned absolute configuration of recently isolated aculeatins E and F is documented. A convergent approach has been designed by the addition of both the terminal units (phenol and side chain) at an advanced stage. The central 1,3,5-triol unit with the requisite stereochemistry was prepared from the commercially available α-D-glucoheptonic-γ-lactone. Selective *O*-debenzylation during the hydrogenolysis of the diyne intermediate and the one pot phenolic oxidation with concomitant spiroketalization highlight the accomplished total syntheses.

1. Introduction

Access to a collection of distinctive small molecules is an important aspect in the realm of chemical genetics and for identifying new therapeutic candidates.[1] Several philosophies addressing the target molecules ensemble either in a forward or the backward sense have been put forwarded, with an ultimate aim of providing flexible and diverse routes with the potential of addressing both the number and function with an ease.[2–4] Concepts funded upon the designing around, and of the synthesis of natural products and natural products like small molecules have provided a direct entry of 'total synthesis programs' into medicinal chemistry research.[3,4] Development of synthetic methods that are efficient and the design of strategies that are modular with a flexibility window was a prerequisite for the synthesis of natural product derived and inspired compound collections.[5] Herein we describe such a simple technology that addresses the synthesis of several of naturally occurring aculeatins and also of some of their C(6)-epimers.

Bio-activity guided isolation of herbaceous plants which traces their origin to folk medicine is one of the reliable approaches in identifying new drugs of natural origin. In 2000, Heilmann et al. reported the isolation of three biologically active metabolites aculeatins A–C from the petroleum ether extract of the rhizomes of *Amomum aculeatum* ROXB, a plant used in the folk medicine of Papua New Guinea against fever and malaria.[6] The aculeatins A–C were identified as potent inhibitors of the human tumor KB cell line and also displayed promising activity against the Plasmodium falciparum strains K1 and NF54.[7] With the help of extensive 2D-NMR experiments, the structures of aculeatins A–C were characterized by the presence of a fascinating 1,7-dioxadispiro[5.1.5.2]-pentadecane spirocyclic architecture. Soon afterward, the same group added aculeatin D (**4**) to this family and reported remarkably high cytotoxicity, *anti*-bacterial and *anti*-protozoal activities.[8] In 2007, Kinghorn et al. reported the isolation of related metabolites aculeatols A–D; the *C*(9) hydroxylated aculeatins A or B having either the same or two carbon truncated side chains.[9a] Subsequently, the isolation of truncated aculeatins A and D, named, respectively as aculeatins F (**6**) and E (**5**), were reported by the same group.[9b] In addition to their promising biological activities, because of the presence of unprecedented dioxadispirocyclic architecture, aculeatins A–D aroused substantial interest culminating in several total syntheses from various groups.[10–13] Wong and co-workers reported the first total synthesis of racemic aculeatin A (**1**) and its spiroepimer aculeatin B (**2**).[10a] The construction of the central tricyclic system was accomplished by using phenol oxidative spirocyclization. In 2005, Bulger and co-workers reported the first total synthesis of racemic aculeatin D confirming the structure and relative stereochemistry.[12a] The absolute configuration of aculeatins A, B and D were established by Falomir's group by employing repetitive asymmetric allylations[13a] and revealed the interchange in the assigned structures of aculeatins A and B. This has been further corroborated by the total synthesis of **1** and **2** by several other groups.[10,13]

The structural similarity present in aculeatins A, B and D–F and their promising biological activities provide an opportunity to explore a modular assembly of aculeatins and related derivatives. In this context, we have recently documented a concise total synthesis

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of the aculeatin D and its *C*(6)-epimer.[12b] Herein we document the complete details of our work including the synthesis of aculeatins A, B and the first total synthesis of E and F confirming their absolute configurations and also report the synthesis of 6-*epi*-aculeatins E–F.

2. Results and discussion

Our retrosynthetic disconnections are outlined in Figure 1. The construction of the central tricyclic core was the final event which was planned through the global deprotection of a differentially protected keto 3,5-diol unit and subsequent phenol oxidative spiroketalization. To allow for maximum flexibility, the key disconnection of the aculeatins carbon-frame was made at two places resulting in two simple appending units and an epimeric pair of functionalized building blocks. Considering the fact that several of the analogs of these two appending units are commercially available or that one can access their functionalized analogs very easily, the additions were planned at an advanced stage. As given in Figure 2, the diastereomeric alkyne epoxides **9** and **10** were identified as the central chirons, respectively for the aculeatins A/B/F (**1**/**2**/**6**) and for the aculeatin D/E (**4**/**5**).

The synthesis of oxiranes **9** and **10** were planned from the alkynol **14**, which can be accessed from the lactone **15**. As part of our program for 1,3-polyol natural products synthesis, we have developed a simple six-step protocol for the preparation of **15** from commercially available D-glucoheptonolactone.[14] Following the Yamaguchi protocol,[15] the alkyl side chain can be incorporated at the oxirane end. A Sonogashira coupling[16] was opted for the addition of the phenol unit at the alkyne end. In keeping with our previous observation, we hypothesized a selective propargylic –OBn cleavage during the Raney Ni hydrogenolysis of the alkyne units.[17] Oxidation of the released free *C*(6)–OH should provide the advanced keto 3,5-diol unit (Scheme 1).

The synthesis started with the preparation of the γ-lactone **15** following the procedures developed in our laboratory.[14] The controlled DIBAL-H reduction of the γ-lactone **15** in CH_2Cl_2 at −78 °C gave the intermediate lactol in quantitative yields, which upon alkynylation using the Ohira–Bestmann reagent resulted in the formation of alkynol **14** in 72% yield.[12b,18] To access the oxirane **9** with the central *syn*,*syn*-1,3-polyol configuration the configuration at the C(4) center had to be inverted. The Mitsunobu inversion of

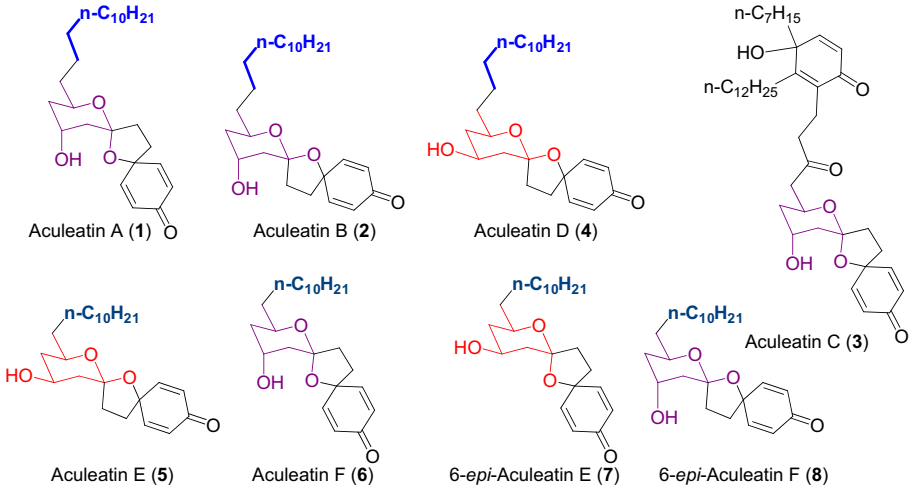


Figure 1. Natural aculeatins A–F (**1–6**) and the unnatural 6-*epi*-aculeatins E (**7**) and F (**8**).

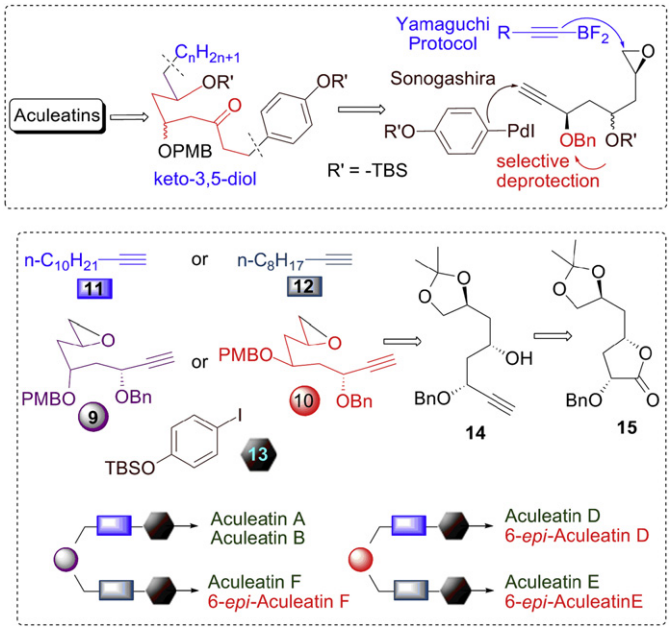
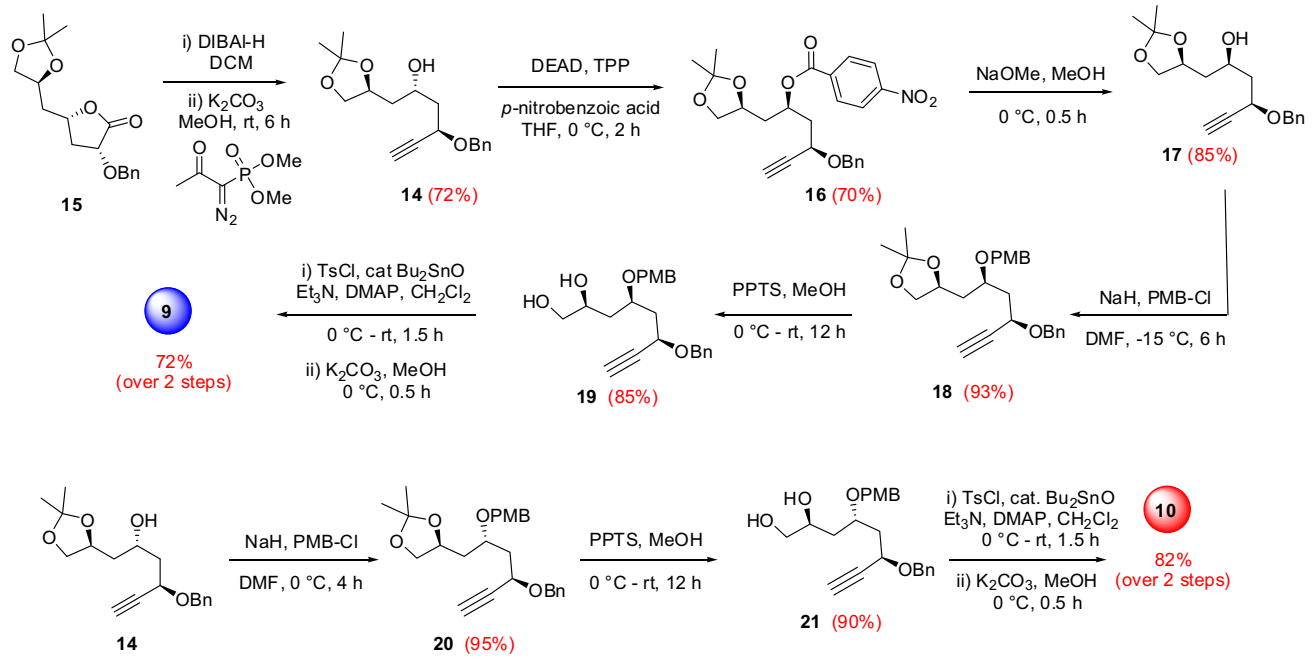


Figure 2. Key retrosynthetic disconnections and the modular building blocks.

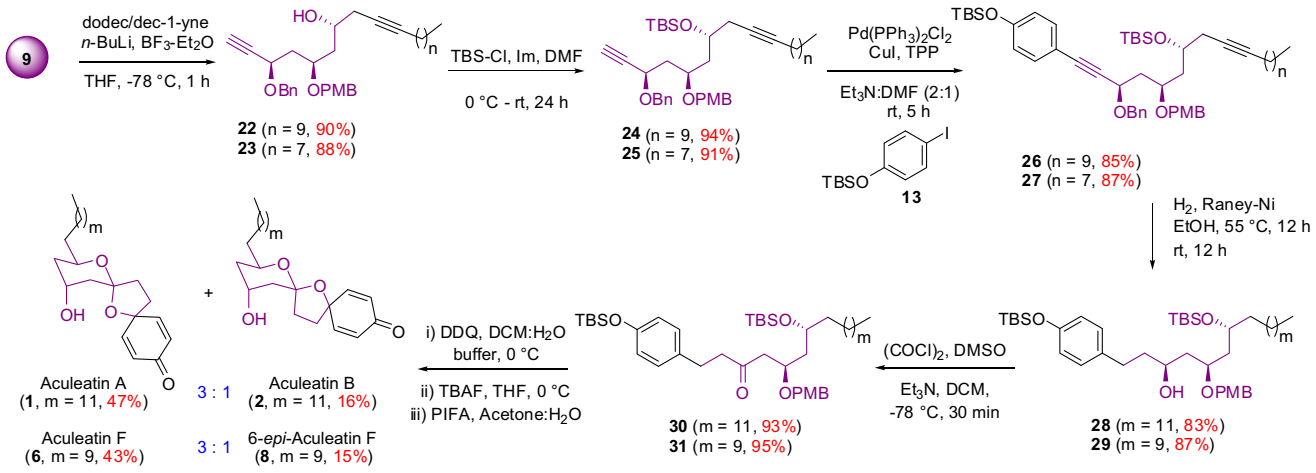
alkynol **14** by using DEAD, TPP could be conducted in good yields by employing the *p*-nitrobenzoic acid as the nucleophile to afford the corresponding nitrobenzoate **16**.[19] Saponification of nitrobenzoate ester **16** with NaOMe in MeOH secured the required *syn*,*syn*-alkynol **17** having physical data different from that of the starting alkynol **14** (Scheme 1).

The free hydroxyl group of alkynol **17** was protected as its PMB ether by employing NaH and PMB-Cl in DMF at −15 °C. Subsequently, the isopropylidene group of the resulting compound **18** was deprotected by employing PPTS in methanol to afford the diol **19**. The primary hydroxyl group of diol **19** was selectively tosylated by treatment with *p*-TsCl, catalytic Bu_2SnO, DMAP and triethylamine in CH_2Cl_2 and the resulting tosylate was employed without any purification for oxirane formation using K_2CO_3 in methanol to furnish epoxide **9**. The synthesis of the *anti*,*anti*-configured oxirane **10** commenced with the PMB protection of free hydroxyl group present in **14** by using NaH, PMB-Cl in DMF at 0 °C to secure **20**. The isopropylidene group of **20** was hydrolyzed in the presence of PPTS in methanol and the resulting diol **21** was converted to the corresponding oxirane **10** following the established conditions[12b] for selective 1-OH tosylation and the subsequent treatment of the intermediate tosylate with K_2CO_3 in methanol (Scheme 1).

We next proceeded for the synthesis of aculeatins A, B and F by selecting the *syn*,*syn*-oxirane **9** as the common starting point (Scheme 2). The regioselective opening of epoxide **9** with either



Scheme 1. Synthesis of the oxiranes **9** and **10**.



Scheme 2. Synthesis of the Aculeatin A (**1**), B (**2**), F (**6**) and 6-*epi*-F (**8**).

dodec-1-yne **11** or dec-1-yne **12** was examined under the Yamaguchi conditions. The successful conditions involved the treatment of the alkyne (4.5 equiv) with *n*-BuLi (4.5 equiv) at −78 °C and then the addition of $BF_3{\cdot}Et_2O$ (4 equiv) followed by the introduction of the oxirane **9** (1 equiv) after a short interval. Under these conditions, the diynes **22** and **23** were obtained in 90% and 88% yields, respectively and converted to the corresponding TBS-ethers **24** and **25** by treatment with TBS-Cl/imidazole in DMF. Our next concern was the extension of the alkyne end in **24** and **25** through the Sonogashira coupling with a *p*-iodophenol derivative. Keeping our experience with the synthesis of aculeatin D in mind, we have employed the TBS protected *p*-iodophenol **13**, as it gave better yields in coupling reactions and also as phenol protection is essential for the selective propargylic debenzylation during the hydrogenolysis of the alkyne units. Thus the Sonogashira coupling of **24** or **25** with **13** was best effected by a thorough degassing of the reaction mixture prior to the addition of CuI and gave the coupled products **26** (85%) and **27** (87%). After this extension at both the ends, the remaining exercise is the synthesis of advanced keto 3,5-diols **30** and **31** and their one pot sequential TBS and PMB ethers deprotection followed by key phenol oxidative spiroketalization, to complete the synthesis of aculeatins A and F and their spiro-epimers aculeatin B and 6-*epi*-aculeatin F, the latter being unnatural. To this end, the hydrogenolysis of both the alkyne groups and selective debenzylation of compounds **26** and **27** was carried out by using Raney Ni/H_2 (20 psi) at 55 °C in good yields.[17] The free C(6)–OH of the resulting products **28** and **29** was oxidized under Swern conditions (oxalyl chloride, DMSO and Et_3N in DCM at −78 °C) to afford the protected keto 3,5-diols **30** and **31**.

After having the well functionalized **30** and **31** in hand, our next concern was their global deprotection and subsequent oxidative phenol cyclization to complete the total synthesis of aculeatins A, B and F. Our optimized conditions involving a sequential deprotection of PMB ether by employing DDQ (CH_2Cl_2, pH 7.0 phosphate

buffer, 0 °C) followed by TBS-ether deprotection using TBAF (THF at 0 °C) produced the completely deprotected keto 3,5-diol which, upon the oxidative spiroketalization using PIFA (10:1, v/v acetone:water, rt, under dark) afforded the corresponding epimeric aculeatins mixture. Thus, following this protocol, aculeatins A and B (3:1) were prepared in 63% overall yield from the keto 3,5-diol **30**. Our scale-up syntheses involve proceeding with the alcohol via oxidation, two sequential deprotections and oxidative cyclization without the purification of any of the intermediates and isolation of the corresponding natural products without any compromise on the final yields. The spectral and the analytical data of **1** and **2** were in good agreement with data reported for natural aculeatins A and B (Tables 1 and 2, Electronic Supplementary data). Similarly, the keto 3,5-diol **31**, upon one pot sequential deprotections and oxidative phenol cyclization, afforded a 3:1 mixture of aculeatin F (**6**) and its *C*(6)-epimer **8**. The spectral data of **6** was in agreement with the data reported for the natural aculeatin F (Table 1, Supplementary data) and the specific rotation measured ($[\alpha]_D^{25}=-4.7$ (*c* 2.0, $CHCl_3$), natural aculeatin F lit.[9b] $[\alpha]_D^{23}=-5.3$ (*c* 0.9, $CHCl_3$)) confirmed its assigned absolute configuration. The stereochemical outcome of these oxidative cyclizations is in accordance with the observations of Wong and co-workers.[13b] In general shorter reaction times allowed the isolation of reasonable amounts of less stable β-anomer (aculeatin B/6-*epi*-aculeatin F). Earlier, Marco co-workers have reported the isolation of a 5.5:1 ratio of aculeatins A:B, when the reaction was prolonged for 24 h.[13a] Even it has been noticed that on standing, aculeatin B slowly converts to more stable aculeatin A.[10b]

Next, we focused on the synthesis of truncated analog aculeatin E (**5**) from the oxirane **10** (Scheme 3).[12b] The opening of the oxirane

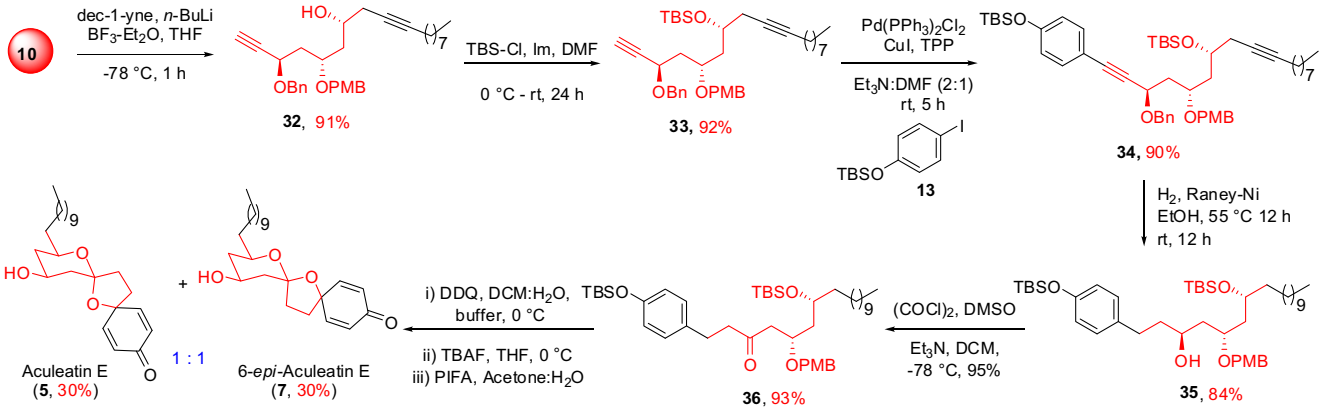
3. Conclusion

A flexible approach for the total synthesis of aculeatins has been documented. Central to the success of our approach is a dual-end disconnection of the aculeatins core leading to three segments in which the two terminal segments are easily available and are amicable toward alterations for the synthesis of aculeatin like small molecule libraries. The middle fragment that forms the key bicyclic spirocyclic core present in the aculeatins has been simplified to differentially protected *syn*,*syn* or *anti*,*anti*-1,3,5-triol units having an oxirane and an alkyne as the terminal functional units to couple the remaining two fragments at an advanced stage. The key 1,3,5-*anti*,*anti*-triol lactone **15** was derived from commercially available D-glucoheptono-γ-lactone which was transformed to the two key diastereomeric coupling units **9** and **10** by simple synthetic transformations. We hypothesized a selective propargylic –OBn cleavage during the Raney Ni hydrogenolysis of the alkyne units which could be executed by protecting the phenol oxygen as its TBS-ether. After verifying the viability of this convergent strategy taking the total synthesis of the aculeatin D, in this paper we documented the flexibility of our approach to synthesize the natural aculeatins A, B, E, and F along with the unnatural 6-*epi*-aculeatins E and F.

4. Experimental

4.1. General methods

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried



Scheme 3. Synthesis of the E (**5**) and 6-*epi*-E (**7**).

10 with dec-1-yne, gave **32**. The free *C*(5)-OH in **32** was protected as TBS-ether and then subjected to the Sonogashira coupling with **13** to afford the diynes **34**. Subsequently, the diynes **34** was advanced to the key ketone 1,5-diols **36**, by hydrogenolysis with Raney Ni/H_2 proceeding via a Swern oxidation. The final stage of the synthesis are sequential deprotection of the TBS and PMB ethers of **36** and oxidative phenol cyclization of the intermediate ketodiols, providing the aculeatin E (**5**), along with its spiroepimer **7**. The natural product and its epimer were obtained in almost equal ratio, which is similar to the Wong and co-workers observation with related aculeatin D synthesis.[13b] The comparison of the ^1H and ^{13}C NMR spectra with the natural aculeatines D and E (Table 3, Supplementary data) established their structure and the observed similar specific rotation of the synthetic aculeatin *E* values confirmed its assigned absolute configuration ($[\alpha]_D^{25}=+47.7$ (*c* 1, $CHCl_3$); lit.[9b] $[\alpha]_D^{23}=+46.5$ (*c* 1, $CHCl_3$)).

glassware. All anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel (100–200 mesh). Optical rotations were determined on a Jasco DIP-370 digital polarimeter. Specific optical rotations $[\alpha]_D$ are given in $10^{-1}\times deg\times cm^2\times g^{-1}$. ^1H and ^{13}C NMR spectroscopy measurements were carried out on Bruker AC 200 MHz or Bruker DRX 400 MHz spectrometers, and TMS was used as internal standard. ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. The Multiplicity of ^{13}C NMR signals was assigned with the help of DEPT spectra and the abbreviations used: s=singlet d=doublet t=triplet q=quartet, represent C (quaternary), CH, CH_2

and CH_3, respectively. Mass spectroscopy was carried out on an API QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) spectrometer. Elemental analysis data were obtained on a Thermo Finnigan Flash EA 1112 Series CHNS Analyzer.

4.2. (2*S*,4*S*,6*R*)-1,2-*O*-isopropylidene-4-*O*-(4-nitrobenzoyl)-6-*O*-benzyl-oct-7-yne-1,2,4,6-tetraol (16)

To a solution of alcohol **14**[12b] (500 mg, 1.64 mmol) in dry THF (5 mL), TPP (517 mg, 1.97 mmol) and DEAD (343 mg, 1.97 mmol) were added at 0 °C and stirred for 15 min, followed by *p*-nitrobenzoic acid (330 mg, 1.97 mmol). After stirring for additional 2 h at 0 °C, the reaction mixture was quenched by adding satd $NaHCO_3$, poured into water and extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried over (Na_2SO_4) and concentrated. Purification of the crude by column chromatography (13% ethyl acetate in petroleum ether) gave the **16** (520 mg, 70%) as colorless oil. R_f=0.50 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$=+23.9 (c 1, $CHCl_3$). IR ($CHCl_3$): ν 3291, 2931, 2852, 2110, 1724, 1528, 1455, 1350, 1274, 1102, 872, 839, 752, 699, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (dt, *J*=8.8, 2.0 Hz, 2H), 8.09 (dt, *J*=8.8, 2.0 Hz, 2H), 7.30–7.26 (m, 5H), 5.57–5.51 (m, 1H), 4.80 (d, *J*=11.6 Hz, 1H), 4.42 (d, *J*=11.6 Hz, 1H), 4.26 (ddd, *J*=8.5, 6.5, 2.0 Hz, 1H), 4.19 (ddd, *J*=12.8, 6.5, 5.8 Hz, 1H), 4.05 (dd, *J*=8.1, 5.8 Hz, 1H), 3.53 (t, *J*=7.7 Hz, 1H), 2.50 (d, *J*=2.0 Hz, 1H), 2.36 (ddd, *J*=14.4, 8.1, 7.0 Hz, 1H), 2.17 (ddd, *J*=14.4, 6.3, 4.6 Hz, 1H), 2.06 (dt, *J*=14.5, 7.3 Hz, 1H), 1.92 (dt, *J*=14.5, 5.8 Hz, 1H), 1.34 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5 (q), 26.8 (q), 37.9 (t), 39.8 (t), 65.6 (d), 69.3 (t), 70.6 (t), 70.9 (d), 72.7 (d), 74.9 (d), 81.5 (s), 109.0 (s), 123.3 (d, 2C), 127.7 (d), 128.0 (d, 2C), 128.2 (d, 2C), 130.6 (d, 2C), 135.7 (s), 137.2 (s), 150.3 (s), 164.0 (s) ppm. ESI-MS: *m*/*z* 476.1 (100%, $[M+Na]^+$), 492.1(28%, $[M+K]^+$), 454.2 (14%, $[M+1]^+$). Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00, N; 3.09. Found: C, 65.81; H, 5.94, N; 3.2.

4.3. (2*S*,4*S*,6*R*)-1,2-*O*-isopropylidene-6-*O*-benzyl-oct-7-yne-1,2,4,6-tetraol (17)

A solution of benzoate **16** (300 mg, 0.66 mmol) and NaOMe (35 mg, 0.66 mmol) in MeOH (5 mL) was stirred at 0 °C for 0.5 h. Several drops of CH_3COOH were added to the reaction mixture to adjust the pH to 7. The solution was diluted with water (20 mL) and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and evaporated. Purification of the crude by column chromatography (20% ethyl acetate in petroleum ether) yielded the alcohol **17** (171 mg, 85%) as colorless oil. R_f=0.50 (Petether/EtOAc 1:1), $[\alpha]_D^{25}$=–8.7 (*c* 2, $CHCl_3$). IR ($CHCl_3$): ν 3486, 3308, 2923, 2852, 2110, 1730, 1463, 1378, 1215, 1157, 1071, 760, 698, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 5H), 4.83 (d, *J*=11.6 Hz, 1H), 4.51 (d, *J*=11.6 Hz, 1H), 4.36 (dt, *J*=7.1, 1.9 Hz, 1H), 4.30–4.24 (m, 1H), 4.08 (dd, *J*=8.1, 6.0 Hz, 2H), 3.54 (t, *J*=7.7 Hz, 1H), 3.42 (s, 1H), 2.53 (d, *J*=2.0 Hz, 1H), 2.05 (ddd, *J*=13.8, 9.0, 7.3 Hz, 1H), 1.86 (ddd, *J*=13.8, 6.5, 3.2 Hz, 1H), 1.77–1.65 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7 (q), 26.8 (q), 40.4 (t), 42.7 (t), 67.1 (d), 68.4 (d), 69.6 (t), 70.8 (t), 74.5 (d), 75.0 (d), 82.1 (s), 109.2 (s), 127.9 (d), 128.1 (d, 2C), 128.5 (d, 2C), 137.3 (s) ppm. ESI-MS: *m*/*z* 327.1 (100%, $[M+Na]^+$), 343.1(19%, $[M+K]^+$), 305.2 (4%, $[M+1]^+$), 277.1 (15%, $[M+1-H_2O]^+$). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.85; H, 7.94.

4.4. (2*S*,4*S*,6*R*)-1,2-*O*-isopropylidene-4-*O*-benzyl-6-*O*-(4-methoxybenzyl)-oct-7-yne-1,2,4,6-tetraol (18)

To a solution of alcohol **17** (500 mg, 1.64 mmol) in dry DMF (2 mL), NaH (78 mg, 1.97 mmol) was added portion-wise at −15 °C and stirred for 15 min, followed by *p*-methoxybenzyl chloride (0.28 mL, 1.97 mmol). After stirring for additional 6 h at −15 °C, the reaction mixture was quenched by adding satd Na_2SO_4, poured into water and extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. Purification of the crude by column chromatography (15% ethyl acetate in petroleum ether) gave the PMB-derivative **18** (634 mg, 93%) as colorless oil. R_f=0.4 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$=+30.4 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): ν 3305, 3012, 2932, 2870, 2115, 1720, 1612, 1586, 1513, 1455, 1380, 1370, 1302, 1248, 1216, 1173, 1158, 1086, 1059, 823, 756, 699, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.27 (m, 5H), 7.19 (d, *J*=8.5 Hz, 2H), 6.84 (d, *J*=8.5 Hz, 2H), 4.79 (d, *J*=11.5 Hz, 1H), 4.47 (d, *J*=11.5 Hz, 1H), 4.41 (br s, 2H), 4.31 (dt, *J*=7.3, 1.8 Hz, 1H), 4.18 (q, *J*=7.0 Hz, 1H), 3.91 (dd, *J*=7.8, 5.9 Hz, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.43 (t, *J*=7.8 Hz, 1H), 2.50 (d, *J*=1.9 Hz, 1H), 2.18 (dt, *J*=13.9, 7.2 Hz, 1H), 1.98–1.90 (m, 2H), 1.73 (dt, *J*=13.4, 6.0 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7 (q), 26.9 (q), 37.5 (t), 40.1 (t), 55.2 (q), 66.0 (d), 69.6 (t), 70.7 (t, 2C), 72.8 (d), 73.0 (d), 74.5 (d), 82.5 (s), 108.5 (s), 113.7 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.4 (d, 2C), 130.4 (s), 137.6 (s), 137.6 (s), 159.2 (s) ppm. ESI-MS: *m*/*z* 463.2 (21%, $[M+K]^+$), 447.3 (100%, $[M+Na]^+$), 425.3 (8%, $[M+H]^+$). Anal. Calcd for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.45; H, 7.55.

4.5. (2*S*,4*S*,6*R*)-4-*O*-benzyl-6-*O*-(4-methoxybenzyl)-oct-7-yne-1,2,4,6-tetraol (19)

A solution of PMB-derivative **18** (500 mg, 1.17 mmol) in methanol (20 mL) was cooled to 0 °C, PPTS (44 mg, 0.17 mmol) was added in portions, and the reaction mixture was warmed to rt, stirred for 12 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue obtained was purified by column chromatography (60% ethyl acetate in petroleum ether) to afford the diol **19** (380 mg, 85%) as colorless oil. R_f=0.30 (Petether/EtOAc 2:3), $[\alpha]_D^{25}$=–16.0 (*c* 1, $CHCl_3$). IR ($CHCl_3$): ν 3423, 3291, 2919, 2850, 2112, 1717, 1612, 1514, 1463, 1451, 1305, 1249, 1069, 1028, 822, 752, 699, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.28 (m, 5H), 7.20 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 4.80 (d, *J*=11.7 Hz, 1H), 4.53 (d, *J*=10.9 Hz, 1H), 4.47 (d, *J*=11.7 Hz, 1H), 4.39 (d, *J*=10.9 Hz, 1H), 4.21 (dt, *J*=7.4, 1.8 Hz, 1H), 3.91 (br s, 1H), 3.78–3.77 (m, 4H), 3.55 (br s, 1H), 3.49 (dd, *J*=11.0, 2.5 Hz, 1H), 3.35 (dd, *J*=11.0, 6.4 Hz, 1H), 2.53 (s, 1H), 2.40 (br s, 1H), 2.24 (ddd, *J*=14.0, 7.4, 5.4 Hz, 1H), 1.92 (dd, *J*=14.0, 6.1 Hz, 1H), 1.68 (dt, *J*=14.6, 8.9 Hz, 1H), 1.55 (dt, *J*=14.5, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.3 (t), 39.9 (t), 55.2 (q), 65.3 (d), 66.7 (t), 70.6 (t, 2C), 71.0 (d), 74.5 (d), 75.5 (d), 82.3 (s), 113.9 (d, 2C), 127.9 (d), 128.2 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 129.7 (s), 137.3 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 423.4 (28%, $[M+K]^+$), 407.4 (100%, $[M+Na]^+$), 402.5 (14%, $[M+18]^+$) 385.4 (7%, $[M+1]^+$). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.96; H, 7.26.

4.6. (*S*)-2-((2*S*,4*R*)-4-(Benzyloxy)-2-(4-methoxy-benzyloxy)-hex-5-ynyl)oxirane (9)

To a solution of diol **19** (600 mg, 1.56 mmol) in dry CH_2Cl_2 (15 mL) were added Bu_2SnO (7 mg) and *p*-TsCl (327 mg, 1.71 mmol) followed by triethylamine (435 μL, 3.12 mmol) and DMAP (20 mg) at 0 °C. The reaction mixture was slowly warmed to rt and stirred for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and extracted. The combined organic phases were washed with water and brine, dried over (Na_2SO_4), and concentrated. The crude tosylate (840 mg) was dissolved in methanol (20 mL) and stirred with anhydrous K_2CO_3 (270 mg) for 30 min at 0 °C and concentrated. The crude was dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4), and concentrated. Purification of the crude by column chromatography (18% ethyl acetate in petroleum ether) gave the epoxide **9** (410 mg, 72% for two steps) as a colorless oil.

R_f=0.50 (Petether/EtOAc 1:1), $[\alpha]_D^{25}$=−13.2 (*c* 1, $CHCl_3$). IR ($CHCl_3$): *ν* 3304, 3010, 2923, 2110, 1720, 1612, 1586, 1514, 1248, 1070, 822, 757, 698, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.35–7.28 (m, 5H), 7.21 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 4.80 (d, *J*=11.5 Hz, 1H), 4.48 (d, *J*=10.9 Hz, 1H), 4.47 (d, *J*=10.8 Hz, 1H), 4.42 (d, *J*=10.9 Hz, 1H), 4.33 (ddd, *J*=8.3, 6.5, 2.0 Hz, 1H), 3.87 (ddd, *J*=10.5, 8.3, 5.5 Hz, 1H), 3.80 (s, 3H), 3.03–2.99 (m, 1H), 2.72 (br t, *J*≈4.7 Hz, 1H), 2.50 (d, *J*=1.8 Hz, 1H), 2.42 (dd, *J*=4.9, 2.5 Hz, 1H), 2.22 (ddd, *J*=14.2, 8.3, 6.3 Hz, 1H), 1.98 (ddd, *J*=13.2, 8.2, 4.7 Hz, 1H), 1.77 (t, *J*=5.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 36.9 (t), 40.4 (t), 46.8 (t), 49.2 (d), 55.3 (q), 66.1 (d), 70.7 (t), 70.9 (t), 73.7 (d), 74.5 (d), 82.5 (s), 113.8 (d, 2C), 127.8 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.4 (d, 2C), 130.4 (s), 137.6 (s), 159.2 (s) ppm. ESI-MS: *m*/*z* 405.3 (28%, $[M+K]^+$), 389.3 (100%, $[M+Na]^+$), 384.3 (14%$^+$). Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.30; H, 7.28.

4.7. (3*R*,5*R*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)icosa-1,9-diyn-7-ol (22)

Dodec-1-yne (816 mg, 4.91 mmol) was taken in a flame-dried two-necked round-bottom flask (50 mL) and dissolved in anhydrous THF (15 mL). The reaction mixture was cooled to −78 °C, treated with *n*-BuLi (2.1 mL, 4.91 mmol, 2.34 M in hexane) drop wise and stirred for 15 min, to this $BF_3\cdot Et_2O$ (0.55 mL, 4.36 mmol) was added and stirring was continued for an additional 15 min. A solution of epoxide **9** (400 g, 1.09 mmol) in anhydrous THF (10 mL) was added and stirred for 30 min at −78 °C. The reaction mixture was quenched at −78 °C by addition of satd Na_2SO_4 (20 mL), diluted with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude residue by column chromatography (20% ethyl acetate in petroleum ether) afforded **22** (512 mg, 90%) as colorless oil. R_f=0.40 (Petether/EtOAc 3:2), $[\alpha]_D^{25}$=−19.8 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): *ν* 3469, 3308, 2922, 2851, 2111, 1738, 1612, 1588, 1514, 1463, 1248, 1089, 1031, 823, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.35–7.28 (m, 5H), 7.20 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.81 (d, *J*=11.6 Hz, 1H), 4.50 (d, *J*=11.6 Hz, 1H), 4.50 (d, *J*=10.8 Hz, 1H), 4.41 (d, *J*=10.8 Hz, 1H), 4.26 (br ddd, 7.3, 6.3, 1.9 Hz, 1H), 3.94–3.88 (m, 1H), 3.83–3.81 (m, 1H), 3.78 (s, 3H), 3.19 (br s, 1H), 2.51 (d, *J*=2.0 Hz, 1H), 2.29–2.26 (m, 2H), 2.22 (ddd, *J*=14.1, 7.2, 5.9 Hz, 1H), 2.14–2.09 (m, 2H), 1.96 (dt, *J*=14.0, 6.2 Hz, 1H), 1.82 (ddd, *J*=14.4, 4.5, 3.2 Hz, 1H), 1.73 (br dt, *J*=14.6, 8.5 Hz, 1H), 1.46 (br dt, *J*=14.6, 7.2 Hz, 2H), 1.35–1.25 (br s, 14H), 0.88 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.1 (q), 18.7 (t), 22.6 (t), 27.8 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 40.1 (t), 40.2 (t), 55.2 (q), 65.7 (d), 69.3 (d), 70.6 (t), 70.7 (t), 74.4 (d), 75.5 (d), 76.1 (s), 82.4 (s), 82.8 (s), 113.9 (d, 2C), 127.8 (d), 128.0 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 129.9 (s), 137.5 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 571.6 (26%, $[M+K]^+$), 555.6 (100%, $[M+Na]^+$), 533.6 (7%, $[M+1]^+$). Anal. Calcd for $C_{35}H_{48}O_4$: C, 78.91; H, 9.08; Found: C, 78.67; H, 9.22.

4.8. (3*R*,5*R*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)octadeca-1,9-diyn-7-ol (23)

The similar procedure as in the preparation of **22** was used to open epoxide **9** (400 mg, 1.09 mmol) with the dec-1-yne (680 mg, 4.91 mmol) affording **23** (484 mg, 88%) as colorless oil. R_f=0.45 (Petether/EtOAc 3:2) $[\alpha]_D^{25}$=−101.4 (*c* 1.6, $CHCl_3$). IR ($CHCl_3$): *ν* 3439, 3152, 2917, 2857, 2111, 1613, 1403, 1216, 1085, 1039, 757, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.35–7.28 (m, 5H), 7.20 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.82 (d, *J*=11.6 Hz, 1H), 4.51 (d, *J*=11.0 Hz, 1H), 4.48 (d, *J*=11.6 Hz, 1H), 4.42 (d, *J*=10.7 Hz, 1H), 4.26 (dd, *J*=6.3, 2.0 Hz 1H), 3.87 (ddd, *J*=14.0, 10.8, 5.8 Hz, 1H), 3.85–3.81 (m, 1H), 3.80 (s, 3H), 3.21 (d, *J*=2.5 Hz, 1H), 2.52 (d, *J*=2.0 Hz, 1H), 2.28 (ddd, *J*=8.0, 4.7, 2.0 Hz, 2H), 2.23 (ddd, *J*=13.9, 7.2, 5.9 Hz, 1H), 2.12 (tt, *J*=7.2, 2.3 Hz, 2H), 1.96 (dt, *J*=14.0, 6.2 Hz, 1H), 1.81 (ddd, *J*=14.5, 4.7, 3.2 Hz, 1H), 1.73 (dt, *J*=14.5, 8.8 Hz, 1H), 1.46 (br dt, *J*≈14.5, 6.9 Hz, 2H), 1.37–1.31 (m, 3H), 1.26 (br s, 7H), 0.88 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.1 (q), 18.8 (t), 22.6 (t), 27.8 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 31.8 (t), 40.1 (t), 40.2 (t), 55.2 (q), 65.7 (d), 69.4 (d), 70.7 (t), 70.7 (t), 74.4 (d), 75.5 (d), 76.1 (s), 82.4 (s), 82.8 (s), 113.9 (d, 2C), 127.8 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 129.9 (s), 137.5 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 527.6 (100%, $[M+Na]^+$), 543.6 (37%, $[M+K]^+$), 505.7(8%, $[M+1]^+$). Anal. Calcd for $C_{33}H_{44}O_4$: C, 78.53; H, 8.79. Found: C, 78.80; H, 9.04.

4.9. ((3*R*,5*S*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)icosa-1,9-diyn-7-yloxy)(*tert*-butyl)-dimethylsilane (24)

A solution of alcohol **22** (1 g, 1.87 mmol) in dry DMF (4 mL) was cooled to 0 °C, imidazole (766 mg, 11.26 mmol) followed by TBS-Cl (848 mg, 5.63 mmol) were added and stirring was continued at rt for 24 h. The reaction mixture was partitioned between ethyl acetate and water, organic layer was separated and aqueous layer was extracted with ethyl acetate. Combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) afforded TBS-derivative **24** (1.14 g, 94%) as colorless oil. R_f=0.45 (Petether/EtOAc 4:1), $[\alpha]_D^{25}$=+11.0 (*c* 2, $CHCl_3$). IR ($CHCl_3$): *ν* 3308, 2926, 2855, 2110, 1614, 1514, 1463, 1249, 1095, 836, 776, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.35–7.28 (m, 5H), 7.19 (d, *J*=8.7 Hz, 2H), 6.83 (d, *J*=8.7 Hz, 2H), 4.80 (d, *J*=11.5 Hz, 1H), 4.49 (d, *J*=11.5 Hz, 1H), 4.48 (d, *J*=10.8 Hz, 1H), 4.39 (br ddd, *J*=8.7, 5.9, 2.0 Hz, 1H), 4.35 (d, *J*=10.8 Hz, 1H), 3.84–3.81 (m, 2H), 3.80 (s, 3H), 2.47 (d, *J*=2.0 Hz, 1H), 2.29–2.27 (m, 2H), 2.13–2.10 (m, 2H), 2.04 (br s, 1H), 1.58 (br s, 1H), 1.49–1.42 (m, 3H), 1.27–1.25 (m, 15H), 0.89 (s, 9H), 0.87 (t, *J*=4.0 Hz, 3H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −4.5 (q), −4.3 (q), 14.1 (q), 14.2 (q), 18.0 (s), 18.8 (t), 22.7 (t), 25.9 (q, 2C), 28.1 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 40.8 (t), 41.3 (t), 55.3 (q), 66.5 (d), 68.7 (d), 70.6 (t), 70.7 (t), 73.1 (d), 74.5 (d), 76.9 (s), 82.4 (s), 82.8 (s), 113.7 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.4 (d, 2C), 130.8 (s), 137.8 (s), 159.1 (s) ppm. ESI-MS: *m*/*z* 669.7 (100%, $[M+Na]^+$), 685 (29%, $[M+K]^+$), 647.7 (26%, $[M+1]^+$). Anal. Calcd for $C_{41}H_{62}O_4Si$: C, 76.11; H, 9.66. Found: C, 76.32; H, 9.85.

4.10. ((3*R*,5*S*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)octadeca-1,9-diyn-7-yloxy)(*tert*-butyl)-dimethylsilane (25)

The same procedure as in the preparation of **24** was used with the alcohol **23** (500 mg, 1.0 mmol) affording TBS-derivative **25** (554 mg, 91%) as colorless oil. R_f=0.50 (Petether/EtOAc 4:1), $[\alpha]_D^{25}$=+53.6 (*c* 1, $CHCl_3$). IR ($CHCl_3$): *ν* 3308, 2929, 2856, 2110, 1613, 1514, 1463, 1361, 1248, 1091, 1039, 835, 775, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.35–7.29 (m, 5H), 7.20 (d, *J*=8.5 Hz, 2H), 6.84 (d, *J*=8.5 Hz, 2H), 4.80 (d, *J*=11.5 Hz, 1H), 4.49 (d, *J*=11.5 Hz, 1H), 4.48 (d, *J*=10.9 Hz, 1H), 4.41–4.37 (m, 1H), 4.35 (d, *J*=10.9 Hz, 1H), 3.86–3.82 (m, 1H), 3.80 (s, 3H), 2.46 (d, *J*=1.9 Hz, 1H), 2.28 (dd, *J*=4.7, 2.2 Hz, 2H), 2.12 (tt, *J*=7.0, 2.4 Hz, 2H), 2.06–1.90 (m, 3H), 1.85–1.78 (m, 1H), 1.49–1.42 (m, 2H), 1.37–1.33 (m, 3H), 1.26 (s, 8H), 0.89 (s, 9H), 0.87 (t, *J*=4.0 Hz, 3H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −4.5 (q), −4.2 (q), 14.1 (q), 18.0 (s), 18.8 (t), 22.6 (t), 25.9 (q, 3C), 28.1 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 29.7 (t), 31.9 (t), 40.8 (t), 41.3 (t), 55.3 (q), 66.5 (d), 68.6 (d), 70.6 (t), 70.8 (t), 73.1 (d), 74.6 (s), 82.4 (s), 82.7 (s), 113.7 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.4 (d, 2C), 130.7 (s), 137.8 (s), 159.1 (s) ppm. ESI-MS: *m*/*z* 641.9 (100%, $[M+Na]^+$), 657.9(66%, $[M+K]^+$), 619.9 (25%, $[M+1]^+$). Anal. Calcd for $C_{39}H_{58}O_4Si$: C, 75.68; H, 9.44. Found: C, 75.52; H, 9.51.

4.11. ((3*R*,5*S*,7*R*)-3-(Benzyloxy)-1-(4-(*tert*-butyl-dimethyl-silyloxy)phenyl)-5-(4-methoxy-benzyloxy)icosa-1,9-diyn-7-yloxy)(*tert*-butyl)dimethylsilane (26)

To a solution of alkyne **24** (300 mg, 0.46 mmol), TBS-iodophenol **13** (310 mg, (0.)93 mmol) in Et_3N (8 mL) and DMF (4 mL), TPP (12 mg, 0.046 mmol) and $Pd(PPh_3)_2Cl_2$ (32 mg, 0.046 mmol), were added and degassed with argon for 30 min. CuI (9 mg, 0.046 mmol) was added and degassed with argon for 10 min and stirred at rt for 5 h. The reaction mixture was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried (Na_2SO_4), concentrated and the residue obtained was purified by column chromatography (5%→10% ethyl acetate in petroleum ether) to afford **26** (340 mg, 85%) as colorless oil. R_f=0.45 (Petether/EtOAc 4:1), $[\alpha]_D^{25}$=+49.2 (*c* 1, $CHCl_3$). IR ($CHCl_3$): ν 3436, 2928, 2224, 1603, 1507, 1251, 1096, 911, 837, 778, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.31 (m, 5H), 7.30 (d, *J*=8.5 Hz, 2H), 7.22 (d, *J*=8.5 Hz, 2H), 6.83 (d, *J*=8.5 Hz, 2H), 6.77 (d, *J*=8.5 Hz, 2H), 4.85 (d, *J*=11.6 Hz, 1H), 4.56 (d, *J*=11.6 Hz, 1H), 4.50 (d, *J*=10.9 Hz, 1H), 4.39 (d, *J*=10.9 Hz, 1H), 3.89–3.82 (m, 2H), 3.78 (s, 3H), 2.29–2.27 (m, 2H), 2.16–2.09 (m, 3H), 2.05 (ddd, *J*=13.3, 9.2, 4.2 Hz, 1H), 1.96 (ddd, *J*=14.0, 4.2, 5.0 Hz, 1H), 1.85 (ddd, *J*=14.0, 7.4, 4.6 Hz, 1H), 1.45 (dd, *J*=14.8, 7.4 Hz, 2H), 1.36–1.30 (m, 2H), 1.25 (m, 10H), 0.98 (s, 9H), 0.87 (t, *J*=6.8 Hz, 3H), 0.83 (s, 9H), 0.20 (s, 6H), 0.06 (s, 6H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5 (q), −4.4 (q, 2C), −4.3 (q), 14.1 (q), 17.9 (s), 18.2 (s), 18.8 (t), 22.7 (t), 25.6 (q, 3C), 25.8 (q, 3C), 28.1 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.6 (t), 29.7 (t), 31.9 (t), 41.1 (t), 41.4 (t), 55.2 (q), 67.2 (d), 68.7 (d), 70.6 (t), 70.7 (t), 73.2 (d), 76.7 (s), 82.3 (s), 86.6 (s), 86.7 (s), 113.7 (d, 2C), 115.6 (s) 120.1 (d, 2C), 128.1 (d, 2C), 128.3 (d, 2C), 129.5 (d, 2C), 130.8 (s), 133.2 (d, 2C), 138.1 (s), 155.9 (s), 159.1 (s) ppm. ESI-MS: *m*/*z* 876.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{53}H_{80}O_5Si_2$: C, 74.59; H, 9.45. Found: C, 74.82; H, 9.31.

4.12. ((3*R*,5*S*,7*R*)-3-(Benzyloxy)-1-(4-(*tert*-butyl-dimethyl-silyloxy)phenyl)-5-(4-methoxy-benzyloxy)octadeca-1,9-diyn-7-yloxy)(*tert*-butyl)dimethylsilane (27)

The similar procedure as in the preparation of **26** was used with the alkyne **25** (400 mg, 0.65 mmol). The crude was purified by column chromatography (5%→10% ethyl acetate in petroleum ether) to afford **27** (465 mg, 87% yield) as colorless oil. R_f=0.40 (Petether/EtOAc 4:1), $[\alpha]_D^{25}$=+49.2 (*c* 1, $CHCl_3$). IR ($CHCl_3$): ν 3436, 2929, 2857, 2224, 1603, 1507, 1463, 1251, 1096, 911, 837, 777, 665 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.30 (m, 7H), 7.22 (d, *J*7.2 Hz, 2H), 6.83 (d, *J*=7.4 Hz, 2H), 6.78 (d, *J*=7.2 Hz, 2H), 4.86 (d, *J*=11.6 Hz, 1H), 4.57 (d, *J*=11.6 Hz, 1H), 4.51 (d, *J*=10.7 Hz, 1H), 4.41 (d, *J*=10.7 Hz, 1H), 3.89–3.81 (br s, 2H), 3.79 (s, 3H), 2.29 (s, 2H), 2.12 (s, 3H), 2.05 (br s, 1H), 1.98–1.90 (m, 1H), 1.89–1.86 (m, 1H), 1.46 (t, *J*=6.4 Hz, 2H), 1.35 (br s, 2H), 1.30–1.22 (br s, 9H), 0.99 (s, 9H), 0.87 (t, *J*=6.85 Hz, 3H), 0.83 (s, 9H), 0.21 (s, 6H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.5 (q), −4.4 (q, 2C), −4.3 (q), 14.1 (q), 17.9 (s), 18.2 (s), 18.8 (t), 22.6 (t), 25.6 (q, 3C), 25.8 (q, 3C), 25.9 (s), 28.1 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 31.9 (t), 41.1 (t), 41.4 (t), 55.2 (q), 67.2 (d), 68.7 (d), 70.6 (t), 70.7 (t), 73.2 (d), 82.3 (s), 86.6 (s), 86.7 (s), 113.7 (d, 2C), 115.6 (s) 120.1 (d, 2C), 127.6 (d), 128.1 (d, 2C), 128.3 (d, 2C), 129.5 (d, 2C), 130.8 (s), 133.2 (d, 2C), 138.1 (s), 155.9 (s), 159.1 (s) ppm. ESI-MS: *m*/*z* 848.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{51}H_{76}O_5Si_2$: C, 74.22; H, 9.28. Found: C, 74.38; H, 9.16.

4.13. (3*S*,5*S*,7*R*)-5-*O*-(4-Methoxybenzyl)-7-*O*-*tert*-butyldimethylsilyl-1-(4-*tert*-butyldimethyl-silyloxyphenyl)icosane-3,5,7-triol (28)

A suspension of di-TBS-derivative **26** (150 mg, 0.174 mmol) and Raney-Ni (300 mg) in ethanol (10 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere at 55 °C for 12 h and then stirred at rt for 12 h. The reaction mixture was filtered through a plug of filter aid, washed with ethyl acetate thoroughly (3×20 mL), and concentrated. Purification of crude product by column chromatography (10% ethyl acetate in petroleum ether) yielded hydrogenated product **28** (100 mg, 83%) as a colorless oil. R_f=0.45 (Petether/EtOAc 8:2), $[\alpha]_D^{25}$=−5.1 (*c* 1, $CHCl_3$). IR ($CHCl_3$): ν 3480, 2855, 1611, 1510, 1252, 1039, 836, 758, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J*≈8.5 Hz, 2H), 7.06 (d, *J*=8.3 Hz, 2H), 6.89 (d, *J*=8.5 Hz, 2H), 6.76 (d, *J*=8.3 Hz, 2H), 4.59 (d, *J*=10.9 Hz, 1H), 4.36 (d, *J*=10.9 Hz, 1H), 3.84 (br s, 1H), 3.82 (s, 3H), 3.80–3.76 (m, 1H), 3.72–3.66 (m, 1H), 2.71 (ddd, *J*=13.8, 10.2, 5.5 Hz, 1H), 2.60 (ddd, *J*=13.8, 10.0, 6.5 Hz, 1H), 1.94 (ddd, *J*=13.8, 8.2, 3.5 Hz, 1H), 1.78–1.74 (m, 2H), 1.68–1.63 (m, 5H), 1.51–1.41 (m, 3H), 1.25 (br s, 20H), 0.96 (s, 9H), 0.87 (s, 12H), 0.170 (s, 6H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5 (q), −4.4 (q, 2C), −4.1 (q), 14.1 (q), 18.0 (s), 18.2 (s), 22.7 (t), 25.0 (t), 25.7 (q, 3C), 25.9 (q, 3C) 29.4 (t), 29.7 (t, 6C), 29.8 (t), 30.9 (t), 31.9 (t), 37.9 (t), 39.7 (t), 41.0 (t), 41.3 (t), 55.3 (q), 69.5 (d), 71.1 (t), 71.2 (d), 77.7 (d), 113.9 (d, 2C), 119.8 (d, 2C), 129.2 (d, 2C), 129.6 (d, 2C), 129.9 (s), 135.0 (s), 153.5 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 793.98 (100, $[M+Na]^+$). Anal. Calcd for $C_{46}H_{82}O_5Si_2$: C, 71.63; H, 10.72. Found: C, 71.79; H, 10.91.

4.14. (3*S*,5*S*,7*R*)-5-*O*-(4-Methoxybenzyl)-7-*O*-*tert*-butyldimethylsilyl-1-(4-*tert*-butyldimethyl-silyloxyphenyl)octadecane-3,5,7-triol (29)

The same procedure as in the preparation of **28** was used with the di-TBS-derivative **27** (180 mg, 0.22 mmol) to procure **29** as colorless oil (142 mg, 87% yield). R_f=0.40 (Petether/EtOAc 8:2), $[\alpha]_D^{25}$=−5.1 (*c* 1, $CHCl_3$). IR ($CHCl_3$): ν 3480, 2928, 2855, 1611, 1509, 1470, 1252, 1040, 836, 775, 692 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, *J*=8.2 Hz, 2H), 7.15 (d, *J*=7.7 Hz, 2H), 6.90 (d, *J*=8.2 Hz, 2H), 6.86 (d, *J*=7.7 Hz, 2H), 4.69 (d, *J*=10.7 Hz, 1H), 4.46 (d, *J*=10.7 Hz, 1H), 3.94 (br s, 1H), 3.91(s, 3H), 3.90–3.87 (m, 1H), 3.80 (br s, 1H), 2.80 (ddd, *J*=14.4, 9.9, 5.1 Hz, 1H), 2.70 (ddd, *J*=14.4, 9.9, 5.8 Hz, 1H), 2.04 (ddd, *J*=13.1, 8.3, 3.7 Hz, 1H), 1.85 (d, *J*=14.3 Hz, 2H), 1.80–1.62 (m, 4H), 1.57 (br s. 2H), 1.38 (br s, 18H), 1.09 (s, 9H), 1.00 (s, 12H), 0.30 (s, 6H), 0.17 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.5 (q), −4.5 (q, 2C), −4.1 (q), 14.1 (q), 18.0 (s), 18.2 (s), 22.7 (t), 25.0 (t), 25.7 (q, 3C), 25.9 (q, 3C) 29.3 (t), 29.6 (t, 4C), 29.8 (t), 30.9 (t), 31.9 (t), 37.9 (t), 39.6 (t), 40.9 (t), 41.3 (t), 55.2 (q), 69.4 (d), 70.1 (t), 71.2 (d), 77.7 (d), 113.9 (d, 2C), 119.8 (d, 2C), 129.2 (d, 2C), 129.6 (d, 2C), 130.0 (s), 135.0 (s), 153.5 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 766.2 (100%, $[M+Na]^+$), 782.4 (35%, $[M+K]^+$), 744.4 (35%, $[M+1]^+$). Anal. Calcd for $C_{44}H_{78}O_5Si_2$: C, 71.10; H, 10.58. Found: C, 71.06; H, 10.76.

4.15. (5*R*,7*R*)-5-(4-Methoxy-benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-1-(4-*tert*-butyldimethyl-silyloxyphenyl)icosan-3-one (30)

In a flame-dried, two-necked, round-bottom flask (25 mL) was dissolved oxalyl chloride (34 μL, 0.39 mmol) under N_2 atmosphere in dry CH_2Cl_2 (5 mL). After the solution was cooled to −78 °C, dry DMSO (50 μL, 0.71 mmol) was added drop wise with stirring for 15 min. A solution of alcohol **28** (100 mg, 0.12 mmol) in dry CH_2Cl_2 (5 mL) was added drop-wise and stirred for 30 min. To this was added Et_3N (108 μL, 0.78 mmol) and stirring continued for 15 min at −78 °C. The reaction mixture was partitioned between CH_2Cl_2 and water, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude by column chromatography (5% ethyl acetate in petroleum ether) afforded ketone **30** (93 mg, 93%) as a colorless oil. R_f=0.50 (Petether/EtOAc 8:2), $[\alpha]_D^{25}$=−4.5 (*c* 1, $CHCl_3$). IR ($CHCl_3$): ν 3432, 2927, 2955, 2854, 1718, 1611, 1510,

1252, 1081, 1040, 836, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, J=8.5 Hz, 2H), 6.99 (d, J=8.3 Hz, 2H), 6.84 (d, J=8.5, Hz, 2H), 6.72 (d, J=8.3 Hz, 2H), 4.40 (d, J=11.0 Hz, 1H), 4.36 (d, J=11.0 Hz, 1H), 4.05–3.99 (m, 1H), 3.79 (s, 3H), 3.70 (dd, J=11.2, 5.7 Hz, 1H), 2.80 (t, J=7.1 Hz, 2H), 2.70 (br d, $J\approx$7.1 Hz, 2H), 2.64 (d, J=7.8 Hz, 1H), 1.42 (br s, 4H), 1.29 (br s, 5H), 1.26 (s, 18H), 0.97 (s, 9H), 0.88 (s, 12H), 0.17 (s, 6H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5 (q, 3C), −4.3 (q), 14.1 (q), 18.0 (s), 18.2 (s), 22.7 (t, 2C) 25.2 (t), 25.8 (q, 3C), 25.9 (q, 3C), 28.7 (t), 29.4 (t, 2C), 29.7 (t, 3C), 29.8 (t), 31.9 (t, 2C), 37.2 (t), 41.9 (t), 45.8 (t), 48.3 (t), 55.2 (q), 69.4 (d), 71.1 (t), 72.8 (d), 113.7 (d, 2C), 120.0 (d, 2C), 129.1 (d, 2C), 129.5 (d, 2C), 130.6 (s), 133.7 (s), 153.8 (s), 159.1 (s), 208.9 (s) ppm. ESI-MS: m/z 792.3 (100, $[M+K]^+$). Anal. Calcd for $C_{46}H_{80}O_5Si_2$: C, 71.82; H, 10.48. Found: C, 71.99; H, 10.76.

4.16. (5*R*,7*R*)-5-(4-Methoxy-benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-1-(4-*tert*-butyldimethylsilyloxyphenyl)octadecan-3-one (31)

The same procedure as in the preparation of **28** was used with the alcohol **29** (120 mg, 0.49 mmol) affording **31** (114 mg, 95% yield) as colorless oil. R_f=0.45 (Petether/EtOAc 4:1), $[\alpha]_D^{25}$=−4.5 (c 1, $CHCl_3$). IR ($CHCl_3$): ν 3432, 2928, 2855, 1713, 1611, 1510, 1251, 1039, 916, 836, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, J=8.5 Hz, 2H), 6.99 (d, J=8.3 Hz, 2H), 6.84 (d, J=8.5, Hz, 2H), 6.73 (d, J=8.3 Hz, 2H), 4.40 (d, J=11.0 Hz, 1H), 4.37 (d, J=11.0 Hz, 1H), 4.01 (ddd, J=13.7, 6.7, 4.2 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, J=11.6, 5.8 Hz, 1H), 2.80 (t, $J\approx$7.4 Hz, 2H), 2.70 (t, $J\approx$7.4 Hz, 2H), 2.65 (d, J=7.9 Hz, 1H), 2.54 (dd, J=15.9, 4.4 Hz, 1H), 1.83–1.78 (m, 1H), 1.54–1.49 (m, 1H), 1.39 (br s, 2H), 1.29 (br s, 3H), 1.26 (s, 15H), 0.97 (s, 9H), 0.88 (s, 12H), 0.17 (s, 6H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5 (q, 3C), −4.3 (q), 14.1 (q), 18.0 (s), 18.2 (s), 22.7 (t) 25.2 (t), 25.7 (q, 3C), 25.9 (q, 3C), 28.7 (t), 29.4 (t), 29.7 (t, 4C), 29.8 (t), 31.9 (t), 37.2 (t), 41.9 (t), 45.8 (t), 48.3 (t), 55.2 (q), 69.4 (d), 71.1 (t), 72.8 (d), 113.7 (d, 2C), 119.9 (d, 2C), 129.1 (d, 2C), 129.5 (d, 2C), 130.6 (s), 133.7 (s), 153.8 (s), 159.1 (s), 208.9 (s) ppm. ESI-MS: m/z 764.4 (100%, $[M+Na]^+$), 780.6 (56%, $[M+K]^+$), 759.6 (20%, $[M+H_2O]^+$), 743.6 (15%, $[M+2]^+$), 741.6 (11%, $[M+1]^+$). Anal. Calcd for $C_{44}H_{76}O_5Si_2$: C, 71.30; H, 10.33. Found: C, 71.47; H, 10.35.

4.17. Aculeatins A (1) and B (2)

To a solution of PMB ether **30** (80 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) and buffer (2 mL) was added DDQ (26 mg, 0.11 mmol) portion-wise at 0 °C and stirring continued for another 30 min at the same temperature. The reaction mixture was filtered through a plug of filter aid. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The crude (72 mg) was dissolved in dry THF (5 mL) and treated with TBAF (222 μL of 1 M solution in THF, 0.22 mmol) at 0 °C. After the mixture was stirred for 15 min at the same temperature, solvent was evaporated under reduced pressure. The crude ketal (38 mg) was dissolved in acetone/H_2O (2.5 mL, 10:1 v/v solution), and PIFA (50 mg, 0.117 mmol) was added in single portion at room temperature. After the mixture was stirred for 15 min in darkness, a saturated aqueous solution of $NaHCO_3$ (4 mL) was added and the resulting mixture extracted with ethyl acetate (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (30% and 35% ethyl acetate in petroleum ether) to afford **1** (23 mg, 47%) and **2** (9 mg, 16%) as colorless oils.

*4.17.1. Aculeatin A (**1**).* R_f=0.25 (Petether/EtOAc 7:3) $[\alpha]_D^{25}$=−4.7 (c 2.0, $CHCl_3$); lit.[10] $[\alpha]_D^{23}$=−5.3 (c 0.9, $CHCl_3$). IR (neat): ν 3495, 2926, 2855, 1674, 1634, 1100, 1047, 999, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, J=10.0, 3.0 Hz, 1H), 6.76 (dd, J=10.0, 3.0 Hz, 1H), 6.15 (dd, J=10.0, 2.0 Hz, 1H), 6.12 (dd, J=10.0, 2.0 Hz, 1H) 4.16–4.07 (m, 2H), 3.37 (d, J=9.9 Hz, 1H), 2.43–2.33 (m, 1H), 2.24 (dd, J=10.4, 7.3 Hz, 1H), 2.05–1.98 (m, 3H), 1.96–1.90 (m, 1H), 1.80 (ddd, J=13.6, 5.4, 2.5 Hz, 1H), 1.50–1.39 (m, 4H), 1.30–1.23 (s, 21H), 0.88 (t, J=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.6 (t), 29.3 (t), 29.6 (t), 29.7 (t, 6C), 31.9 (t), 34.1 (t), 35.9 (t), 37.9 (t), 39.1 (t), 64.8 (d), 65.3 (d), 72.2 (t), 79.7 (s), 109.1 (s), 127.1 (d), 127.3 (d), 148.7 (d), 150.9 (d), 185.3 (s) ppm. ESI-MS: m/z 860 (47%, $[2M+Na]^+$), 441 (36%, $[M+Na]^+$), 419 (48%, $[M+1]^+$), 507.4 (100%). Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.47; H, 10.34.

*4.17.2. Aculeatin B (**2**).* R_f=0.20 (Petether/EtOAc 7:3); $[\alpha]_D^{26}$=+46.8 (c 1.0, $CHCl_3$); lit.[10] $[\alpha]_D^{23}$=+50.0 (c 0.2, $CHCl_3$). IR (neat): ν 3521, 2916, 2849, 1665, 1621, 1068, 1020, 1005, 854 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J=10.0, 3.0 Hz, 1H), 6.78 (dd, J=10.0, 3.0 Hz, 1H), 6.14 (dd, J=10.0, 2.0 Hz, 1H), 6.11 (dd, J=10.0, 2.0 Hz, 1H), 4.39–4.35 (m, 1H), 3.91–3.82 (m, 1H), 2.69 (ddd, J=13.1, 7.4, 1.6 Hz, 1H), 2.31 (dt, J=12.3, 7.3 Hz, 1H), 2.11–2.02 (m, 2H), 1.98–1.86 (m, 2H), 1.65–1.53 (m, 2H), 1.49–1.42 (m, 4H), 1.23–1.33 (s, 21H), 0.88 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.9 (t), 29.4 (t, 2C), 29.6 (t, 3C), 29.7 (t, 3C), 31.9 (t), 35.3 (t), 35.4 (t), 35.7 (t), 37.9 (t), 40.6 (t), 65.2 (d), 69.4 (d), 77.6 (s), 108.5 (s), 127.1 (d), 149.1 (d), 152.2 (d), 185.7 (s). ESI-MS: m/z 441 (100% $[M+Na]^+$), 419 (44% $[M+1]^+$). Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.52; H, 10.31.

4.18. Aculeatin F (6) and 6-*epi*-aculeatin F (8)

The similar procedure as in the preparation of aculeatin A/B was used with the ketone **31** (100 mg, 0.13 mmol) to afford **6** (21 mg, 43%) and **8** (8 mg, 15%) as colorless oils.

*4.18.1. Aculeatin F (**6**).* R_f=0.24 (Petether/EtOAc 7:3). $[\alpha]_D^{26}$=−4.7 (c 2.0, $CHCl_3$); lit.[9b] $[\alpha]_D^{23}$=−5.3 (c 0.9, $CHCl_3$). IR (neat): ν 3494, 2927, 2854, 1677, 1633, 1100, 1046, 998, 852 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (dd, J=10.0, 2.8 Hz, 1H); 6.76 (dd, J=10.0, 2.8 Hz, 1H), 6.15 (dd, $J\approx$10.0, 1.8 Hz, 1H), 6.12 (dd, $J\approx$10.0, 1.8 Hz, 1H), 4.17–4.06 (m, 2H), 3.38 (d, J=10.0 Hz, 1H), 2.42–2.34 (m, 1H), 2.24 (dd, J=10.3, 8.1 Hz, 1H), 2.05–1.98 (m, 3H), 1.94 (br t, J=14.0 Hz, 1H), 1.80 (d, J=13.5 Hz, 1H), 1.54–1.39 (m, 4H), 1.29 (s, 17H), 0.88 (t, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.6 (t), 29.3 (t), 29.6 (t), 29.7 (t, 4C), 31.9 (t), 34.1 (t), 35.9 (t), 37.9 (t), 39.0 (t), 39.1 (t), 64.8 (d), 65.3 (d), 79.7 (s), 109.1 (s), 127.0 (d), 127.3 (d), 148.8 (d), 150.9 (d), 185.3 (s). ESI-MS: m/z 804.0 (47% $[2M+Na]^+$), 413.5 (36% $[M+Na]^+$), 491.5 (48% $[M+1]^+$), 507.4 (100%). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.69; H, 9.94.

*4.18.2. 6-epi-Aculeatin F (**8**).* R_f=0.18 (Petether/EtOAc 7:3). $[\alpha]_D^{26}$=+46.8 (c 1.0, $CHCl_3$), IR ($CHCl_3$): ν 3520, 2916, 2848, 1664, 1620, 1067, 1020, 1004, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J=10.0, 3.0 Hz, 1H), 6.78 (dd, J=10.0, 3.0 Hz, 1H), 6.14 (dd, J=10.0, 2.0 Hz, 1H), 6.11 (dd, J=10.0, 2.0 Hz, 1H), 4.39–4.35 (m, 1H), 3.91–3.83 (m, 1H), 2.69 (br dd, J=12.3, 7.4, Hz, 1H), 2.31 (dt, J=12.3, 7.4 Hz, 1H), 2.10–2.01 (m, 2H), 1.97–1.85 (m, 2H), 1.64–1.52 (m, 3H), 1.49–1.39 (m, 3H), 1.29 (s, 17H), 0.88 (t, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.9 (t), 29.3 (t), 29.4 (t), 29.6 (t, 4C), 31.9 (t), 35.3 (t, 2C), 35.7 (t), 37.9 (t), 40.5 (t), 65.2 (d), 69.4 (d), 77.6 (s), 108.5 (s), 127.1 (d, 2C), 149.2 (d), 152.3 (d), 185.7 (s). ESI-MS: m/z 413.5 (100% $[M+Na]^+$), 429.5 (22% $[M+K]^+$), 491 (24% $[M+1]^+$), 373.5 (22%, $[M+1-H_2O]^+$). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.97; H, 9.88.

4.19. (3*R*,5*S*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyloxy)octadeca-1,9-diyn-7-ol 32

The same procedure as in the preparation of **22** was used to couple the dec-1-yne (**12**) and oxirane **10** (400 mg, 1.1 mmol) to procure the diyne **32** (500 mg, 91%) as colorless oil. R_f=0.30

(Petether/EtOAc 8:2), $[\alpha]_D^{25}$=+79.7 (*c* 2.0, $CHCl_3$). IR ($CHCl_3$): *ν* 3469, 3305, 2930, 2857, 2111, 1612, 1586, 1513, 1455, 1249, 1216, 1069, 1034, 822, 756, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.34 (d, *J*=4H), 7.32–7.28 (m, 1H), 7.14 (ddd, *J*=8.6, 2.9, 2.0 Hz, 2H), 6.82 (ddd, *J*=8.6, 2.9, 2.0 Hz, 2H), 4.79 (d, *J*=11.6 Hz, 1H), 4.48 (d, *J*=10.8 Hz, 1H), 4.38 (d, *J*=11.6 Hz, 1H), 4.27 (d, *J*=10.8 Hz, 1H), 4.27–4.23 (m, 1H), 4.02–3.91 (m, 2H), 3.76 (s, 3H), 2.48 (d, *J*=2.0 Hz, 1H), 2.34–2.30 (m, 2H), 2.17–2.07 (m, 3H), 1.97 (ddd, *J*=14.5, 9.4, 3.9 Hz, 1H), 1.84 (ddd, *J*=14.5, 9.7, 3.9 Hz, 1H), 1.72 (ddd, *J*=14.5, 6.0, 2.7 Hz, 1H), 1.48 (dt, *J*=7.0, 1.2 Hz, 2H), 1.39–1.32 (m, 2H), 1.31–1.21 (br s, 9H), 0.86 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.1 (q), 18.7 (t), 22.6 (t), 27.8 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 31.8 (t), 39.2 (t), 41.1 (t), 55.2 (q), 65.0 (d), 67.4 (d), 70.6 (t), 71.5 (t), 73.1 (d), 74.0 (d), 76.0 (s), 82.8 (s), 83.0 (s), 113.8 (d, 2C), 127.8 (d), 128.2 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 130.1 (s), 137.6 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 527.6 (100%, $[M+Na]^+$), 543.6 (36%, $[M+K]^+$), 505.7(7%, $[M+1]^+$). 407.5 (46%, $[M-97]^+$), 383.4 (74%, $[M-115]^+$). Anal. Calcd for $C_{33}H_{44}O_4$: C, 78.53; H, 8.79. Found: C, 78.88; H, 9.02.

4.20. ((3*R*,5*R*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)-octadeca-1,9-diyn-7-yloxy)(*tert*-butyl)-dimethylsilane (33)

A solution of alcohol **32** (500 g, 0.99 mmol) in anhydrous DMF (3 mL) was cooled to 0 °C, imidazole (404 mg, 5.94 mmol) followed by TBS-Cl (447 mg, 2.97 mmol) were added and stirring was continued at rt for 24 h. The reaction mixture was portioned between ethyl acetate and water, organic layer was separated and aqueous layer was extracted with ethyl acetate. Combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) afforded TBS-derivative **33** (563 mg, 92%) as colorless oil. R_f=0.40 (Petether/EtOAc 7:3) $[\alpha]_D^{25}$=+24.2 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): *ν* 3308, 2928, 2856, 2110, 1613, 1514, 1463, 1248, 1091, 1039, 835, 775, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.37–7.28 (m, 5H), 7.16 (d, *J*=8.5 Hz, 2H), 6.83 (d, *J*=8.5 Hz, 2H), 4.79 (d, *J*=11.5 Hz, 1H), 4.43 (d, *J*=10.5 Hz, 1H), 4.40 (d, *J*=11.5 Hz, 1H), 4.30 (d, *J*=10.5 Hz, 1H), 4.27 (dt, *J*=6.9, 2.0 Hz, 1H), 3.99–3.92 (m, 1H), 3.90–3.83 (m, 1H), 3.76 (s, 3H), 2.47 (d, *J*=2.0 Hz, 1H), 2.33–2.30 (m, 2H), 2.13 (tt, *J*=7.0, 2.3 Hz, 2H), 2.05–1.97 (m, 3H), 1.64 (ddd, *J*=14.2, 8.0, 4.8 Hz, 1H), 1.50–1.43 (m, 2H), 1.38–1.34 (m, 2H), 1.246 (s, 8H), 0.89 (s, 9H), 0.86 (t, *J*=5.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −4.6 (q), −4.1 (q), 14.1 (q), 18.1 (s), 18.8 (t), 22.7 (t), 25.9 (q, 3C), 28.2 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 31.9 (t), 41.8 (t), 42.2 (t), 55.2 (q), 65.3 (d), 68.6 (d), 70.4 (t), 70.6 (t), 72.1 (d), 73.8 (d), 76.6 (s), 82.5 (s), 83.0 (s), 113.7 (d, 2C), 127.7 (d), 128.0 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 130.8 (s), 137.8 (s), 159.0 (s) ppm. ESI-MS: *m*/*z* 641.8 (23%, $[M+Na]^+$), 657.9 (14%, $[M+K]^+$), 429.5 (73%, $[M-189]^+$), 421.5 (100%, $[M-197]^+$). Anal. Calcd for $C_{39}H_{58}O_4Si$: C, 75.68; H, 9.44. Found: C, 75.51; H, 9.67.

4.21. ((3*R*,5*R*,7*R*)-3-(Benzyloxy)-1-(4-(*tert*-butyl-dimethyl-silyloxy)phenyl)-5-(4-methoxy-benzyloxy)octadeca-1,9-diyn-7-yloxy)(*tert*-butyl)dimethylsilane (34)

The coupling of alkyne **33** (200 mg, 0.32 mmol) and the iodo derivative **13** was carried out according to the procedure used for the preparation of **26**. Purification of the crude by column chromatography (5% ethyl acetate in petroleum ether) gave **34** (180 mg, 90%) as a colorless syrup. R_f=0.60 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$=+26.1 (*c* 1.5, $CHCl_3$). IR ($CHCl_3$): *ν* 3351, 2929, 2224, 1603, 1507, 1217, 1094, 838, 759, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.39–7.27 (m, 7H), 7.18 (d, *J*=8.6 Hz, 2H), 6.82 (d, *J*=8.6 Hz, 2H), 6.77 (d, *J*=8.6 Hz, 2H), 4.84 (d, *J*=11.6 Hz, 1H), 4.48 (d, *J*=11.6 Hz, 1H), 4.49–4.46 (m, 1H), 4.44 (d, *J*=10.8 Hz, 1H), 4.35 (d, *J*=10.8 Hz, 1H), 4.00–3.88 (m, 2H), 3.77 (s, 3H), 2.32 (ddd, *J*=5.3, 2.2 Hz, 2H), 2.17–2.05 (m, 4H), 2.01 (ddd, *J*=14.1, 7.7, 3.8 Hz, 1H), 1.68 (ddd, *J*=14.1, 8.0, 4.7 Hz, 1H), 1.64–1.57 (br s, 1H), 1.50–1.43 (m, 2H), 1.38–1.33 (m, 2H), 1.25 (s, 7H), 0.98 (s, 9H), 0.89 (s, 9H), 0.86 (t, *J*=5.0 Hz, 3H), 0.20 (s, 6H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −4.6 (q), −4.5 (q, 2C), −4.1 (q), 14.1 (q), 18.1 (s), 18.2 (s), 18.8 (t), 22.6 (t), 25.6 (q, 3C), 25.9 (q, 3C), 28.3 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 31.9 (t), 41.9 (t), 42.3 (t), 55.2 (q), 66.1 (d), 68.6 (d), 70.3 (t), 70.6 (t), 72.4 (d), 77.2 (s), 82.4 (s), 85.9 (s), 87.1 (s), 113.7 (d, 2C), 115.6 (s), 120.1 (d, 2C), 127.6 (d), 128.0 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 131.0 (s), 133.2 (d, 2C), 138.1 (s), 155.9 (s), 159.0 (s) ppm. ESI-MS: *m*/*z* 848.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{51}H_{76}O_5Si_2$: C, 74.22; H, 9.28. Found: C, 74.09; H, 9.15.

4.22. (3*S*,5*R*,7*R*)-5-*O*-(4-Methoxybenzyl)-7-*O*-*tert*-butyl-dimethylsilyl-1-(4-*tert*-butyldimethyl-silyloxyphenyl)-octadecane-3,5,7-triol (35)

The same procedure as in the preparation of **28** was used with the di-TBS-derivative **34** (140 mg, 0.17 mmol) affording **35** (105 mg, 84% yield) as colorless oil. R_f=0.30 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$=−5.1 (*c* 1, $CHCl_3$). IR ($CHCl_3$): *ν* 3480, 2855, 1611, 1510, 1252, 1039, 836, 758, 692 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.24 (d, *J*=8.5 Hz, 2H), 7.04 (dt, *J*=8.3 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 6.73 (d, *J*=8.3 Hz, 2H), 4.52 (d, *J*=10.9 Hz, 1H), 4.42 (d, *J*=10.9 Hz, 1H), 3.94–3.90 (br s, 1H), 3.84–3.81 (m, 2H), 3.80 (s, 3H), 3.13 (br s, 1H), 2.72 (ddd, *J*=14.6, 9.7, 5.4 Hz, 1H), 2.54 (ddd, *J*=15.8, 9.7, 6.3 Hz, 1H), 1.91–1.81 (m, 2H), 1.79–1.72 (m, 1H), 1.67–1.59 (m, 1H), 1.58–1.52 (m, 2H), 1.45–1.40 (m, 2H), 1.26 (s, 18H), 0.98 (s, 9H), 0.87 (s, 9H), 0.87 (t, *J*=5.0 Hz, 3H), 0.18 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* −4.5 (q, 2C), −4.4 (q), −4.1 (q), 14.1 (q), 18.1 (s), 18.2 (s), 22.7 (t, 2C), 24.7 (t), 25.7 (q, 3C), 25.9 (q, 3C), 29.3 (t), 31.1 (t, 2C), 31.9 (t), 37.7 (t, 2C), 39.5 (t, 2C), 39.8 (t), 41.5 (t), 55.2 (q), 68.1 (d), 69.7 (d), 70.7 (t, 2C), 74.9 (d), 113.9 (d, 2C), 119.8 (d, 2C), 129.2 (d, 2C), 129.4 (d, 2C), 130.2 (s), 134.9 (s), 153.6 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 766.1 (80%, $[M+Na]^+$), 779.1 (10%, $[M+K]^+$), 565.5 (100%). Anal. Calcd for $C_{44}H_{78}O_5Si_2$: C, 71.10; H, 10.58. Found: C, 71.25; H, 10.64.

4.23. (5*S*,7*R*)-5-(4-Methoxy-benzyloxy)-7-(*tert*-butyl-dimethylsilyloxy)-1-(4-*tert*-butyldimethyl-silyloxyphenyl)octadecan-3-one (36)

The Swern oxidation of the alcohol **35** (100 mg, 0.14 mmol) was carried out as described for the preparation of **30** and the ketone **36** (93 mg, 93%) was obtained as a colorless syrup after usual workup and purification by column chromatography (5% ethyl acetate in petroleum ether). R_f=0.50 (Petether/EtOAc 8:2), $[\alpha]_D^{25}$=−4.5 (*c* 1, $CHCl_3$). IR ($CHCl_3$): *ν* 3415, 2927, 1715, 1612, 1511, 1252, 1040, 836, 759, 686 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.19 (br.d, *J*=8.7 Hz, 2H), 6.99 (br.d, *J*=8.3 Hz, 2H), 6.85 (br.d, *J*=8.7 Hz, 2H), 6.73 (br.d, *J*=8.3 Hz, 2H), 4.43 (d, *J*=11.0 Hz, 1H), 4.39 (d, *J*=11.0 Hz, 1H), 4.08–4.02 (m, 1H), 3.84–3.73 (m, 1H), 3.79 (s, 3H), 2.80 (t, *J*=7.3 Hz, 2H), 2.71 (dd, *J*=15.5, 7.0 Hz, 1H), 2.69 (t, *J*=7.3 Hz, 2H), 2.49 (dd, *J*=15.6, 5.1 Hz, 1H), 1.76–1.69 (m, 1H), 1.52−1.41 (m, 3H), 1.25 (br s, 18H), 0.97 (s, 9H), 0.88 (s, 9H), 0.87 (t, *J*=7.2 Hz, 3H), 0.17 (s, 6H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −4.5 (q, 3C), −4.0 (q), 14.1 (q), 18.1 (s), 18.2 (s), 22.7 (t) 24.7 (t), 25.3 (t), 25.7 (q, 3C), 25.8 (q, 3C), 28.7 (t), 29.3 (t), 29.6 (t, 2C), 29.8 (t), 31.9 (t), 37.3 (t), 40.4 (t), 41.7 (t), 45.6 (t), 48.8 (t), 55.2 (q), 69.4 (d), 71.1 (t), 73.1 (d), 113.9 (d, 2C), 120.0 (d, 2C), 129.2 (d, 2C), 129.5 (d, 2C), 130.6 (s), 133.6 (s), 153.8 (s), 159.1 (s), 208.6 (s) ppm. ESI-MS: *m*/*z* 764.5 (100%, $[M+Na]^+$), 777.5 (56%, $[M+K]^+$), 742.5 (11%, $[M+1]^+$). Anal. Calcd for $C_{44}H_{76}O_5Si_2$: C, 71.30; H, 10.33. Found: C, 71.16; H, 10.52.

4.24. Aculeatin E (4) and 6-*epi*-Aculeatin E (7)

The same sequence of procedures as in the preparation of aculeatin A/B were used with the ketone **36** (90 mg, 0.122 mmol) affording an easily separable mixture of (flash column chromatography, 30–35% ethyl acetate in petroleum ether) aculeatin E (**5**) (16 mg, 30%) and 6-*epi*-aculeatin E **7** (15 mg, 30%) as colorless oils.

*4.24.1. Aculeatin E (**5**).* R_f=0.20 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$=+47.7 (*c* 1, $CHCl_3$); lit.[9b] $[\alpha]_D^{23}$=+46.5 (*c* 1, $CHCl_3$). IR (neat): ν 3410, 2916, 2849, 1665, 1628, 1057, 1009 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.99 (dd, *J*=10.3, 3.0 Hz, 1H), 6.78 (dd, *J*=10.3, 3.0 Hz, 1H), 6.14 (dd, *J*=10.0, 1.7 Hz, 1H), 6.12 (dd, *J*=10.0, 1.7 Hz, 1H), 3.85 (tt, *J*=11.2, 4.4 Hz, 1H), 3.40–3.34 (m, 1H), 2.39 (ddd, *J*=12.7, 7.5, 2.0 Hz, 1H), 2.27 (br ddd, *J*=12.5, 11.2, 7.5 Hz, 1H), 2.13 (ddd, *J*=12.3, 4.3, 1.8 Hz, 1H), 2.07 (ddd, *J*=12.5, 8.2, 1.9 Hz, 1H), 1.96 (br ddd, *J*=12.3, 4.4, 2.0 Hz, 1H), 1.84 (dt, *J*=12.5, 8.5 Hz, 2H), 1.67–1.57 (m, 3H), 1.50–1.48 (m, 2H), 1.26 (s, 17H), 0.88 (t, *J*=6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (q), 22.7 (t), 25.9 (t), 29.3 (t), 29.4 (t), 29.6 (t, 4C), 31.9 (t), 33.4 (t), 34.9 (t), 35.7 (t), 40.8 (t), 43.6 (t), 66.8 (d), 71.6 (d), 78.1 (s), 109.2 (s), 127.2 (d), 127.4 (d), 148.8 (d), 151.6 (d), 185.5 (s) ppm. ESI-MS: *m*/*z* 413.5 (100%, $[M+Na]^+$), 429.5 (33%, $[M+K]^+$), 391.5 (26%, $[M+1]^+$), 373.5 (18%, $[M+1\text{-}H_2O]^+$). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 74.08; H, 10.02.

*4.24.2. 6-epi-Aculeatin E (**7**).* R_f=0.25 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$=+14.6 (*c* 0.2, $CHCl_3$). IR (neat): ν 3412, 2915, 2848, 1662, 1627, 1052, 1004 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.82 (dd, *J*=10.2, 3.0 Hz, 1H), 6.76 (dd, *J*=10.2, 3.0 Hz, 1H), 6.12 (dd, *J*=10.1, 1.9 Hz, 1H), 6.10 (dd, *J*=10.1, 1.9 Hz, 1H), 4.10 (tt, *J*=12.2, 4.8 Hz, 1H), 3.83–3.77 (m, 1H), 2.43–2.35 (m, 1H), 2.25 (dd, $J\approx$10.9, 7.8 Hz, 1H), 2.10 (ddd, *J*=12.4, 4.8, 1.8 Hz, 1H), 2.06–2.00 (m, 2H), 1.97 (ddd, *J*=12.3, 4.4, 1.9 Hz, 1H), 1.65 (t, *J*=11.8 Hz, 1H), 1.57–1.51 (m, 1H), 1.49–1.41 (m, 2H), 1.32–1.22 (m, 18H), 1.18 (q, *J*=11.8 Hz, 1H), 0.88 (t, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.7 (t), 25.7 (t), 29.3 (t), 29.6 (t, 5C), 31.9 (t), 34.6 (t), 35.9 (t), 38.8 (t), 40.6 (t), 43.0 (t), 65.3 (d), 69.1 (d), 79.0 (s), 109.0 (s), 127.0 (d), 127.1 (d), 149.2 (d), 151.4 (d), 185.4 (s) ppm. ESI-MS: *m*/*z* 413.5 (100%, $[M+Na]^+$), 429.5 (22%, $[M+K]^+$), 391.5 (24%, $[M+1]^+$), 373.5 (22%, $[M+1\text{-}H_2O]^+$). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.77; H, 10.09.

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Supplementary data

Tables of the spectral data of natural and synthetic aculeatins, NMR and MS Spectra of aculeatins A, B, E, F and 6-*epi*-aculeatins E and F. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.058.

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