Accepted Manuscript

Formal synthesis of actinoranone using a one-pot semipinacol rearrangement/wittig reaction

Martina Menger, Mathias Christmann

PII: S0040-4020(18)31330-9

DOI: https://doi.org/10.1016/j.tet.2018.11.003

Reference: TET 29914

To appear in: *Tetrahedron*

Received Date: 18 September 2018

Revised Date: 1 November 2018

Accepted Date: 3 November 2018

Please cite this article as: Menger M, Christmann M, Formal synthesis of actinoranone using a one-pot semipinacol rearrangement/wittig reaction, *Tetrahedron* (2018), doi: https://doi.org/10.1016/j.tet.2018.11.003.

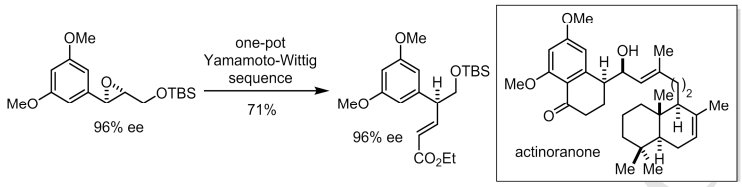
Graphical Abstract

Formal Synthesis of Actinoranone Using a One-Pot Semipinacol Rearrangement/Wittig Reaction

Leave this area blank for abstract info.

Martina Menger, Mathias Christmann*

Freie Universität Berlin, Institute of Chemistry and Biochemistry, Takustr. 3, 14195 Berlin, Germany



Tetrahedron
journal homepage: www.elsevier.com

Formal Synthesis of Actinoranone Using a One-Pot Semipinacol Rearrangement/Wittig Reaction

Martina Menger, Mathias Christmann*

Freie Universität Berlin, Institute of Chemistry and Biochemistry, Takustr. 3, 14195 Berlin, Germany

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Actinoranone, Sclareolide
Semipinacol Rearrangement
Terpenes, Chiral Pool

ABSTRACT

Here, we report a formal synthesis of the marine cytotoxic meroterpenoid actinoranone. Key steps include a semipinacol rearrangement/Wittig reaction sequence and a chiral pool approach for the syntheses of the tetralone and the ocatalin fragments, respectively. The presented route provides access to the natural product in 14 steps in the longest linear sequence.

* Corresponding author. Tel.: +49-30-838-60182; fax: +49-30-838-460182; e-mail: mathias.christmann@fu-berlin.de

1. Introduction

The marine environment is becoming an increasingly important source for the discovery of new potentially bioactive molecules and drug leads.[1] While the diversity of life in the terrestrial habitat is extraordinary, the greatest biodiversity and chemical novelty occurs in the oceans.[2-4] Marine actinomycetes are a prolific source of secondary metabolites. In general, the Actinobacteria subclass is comprising half of the discovered secondary metabolites, in particular, antibiotics,[5] antitumor agents,[6] immunosuppressive agents,[7] and enzymes.[8] A large number of terrestrial actinomycetes have been screened and isolated but their distribution in the sea is largely unexplored. The vast majority of the marine actinomycetes are derived from the genus *Streptomyces*. This is the largest genus of Actinobacteria and is widely spread in marine and terrestrial ecosystems.[9] Interestingly, the genus *Streptomyces* alone accounts for the majority the antibiotics used today.[10-11]

Studies of marine actinomycetes have yielded a large number of structurally diverse bioactive molecules.[12] In 2013, Fenical and co-workers isolated the cytotoxic meroterpenoid actinoranone (**1**) from the marine actinomycetes strain CNQ-027.[13] This strain shares only 97.6% 16S rRNA gene sequence identity with the genus *Streptomyces marinus*, hence might represent new species adapted to live in the sea.[14] Actinoranone constitutes of a tetralone fragment of polyketidic origin (C1'–C10') and a bicyclic diterpenoid fragment (C1–C20) connected by a C–C single bond between C15 and C8´. Its promising LD_{50} value of 2.0 µg/mL against HCT-116 human colon carcinoma prompted the initiation of several synthesis programs.[13] The first total synthesis of actinoranone was achieved by Ye[15] in 2017 and led to a revision of the initially proposed configuration of **1** (Figure 1). Later that year a formal synthesis was realized by the group of Pastre.[16-17]

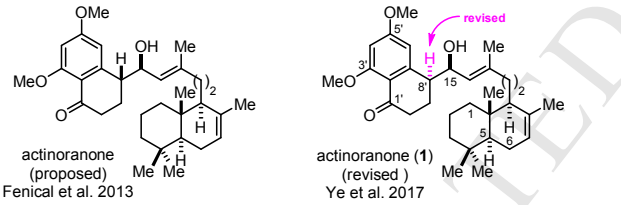
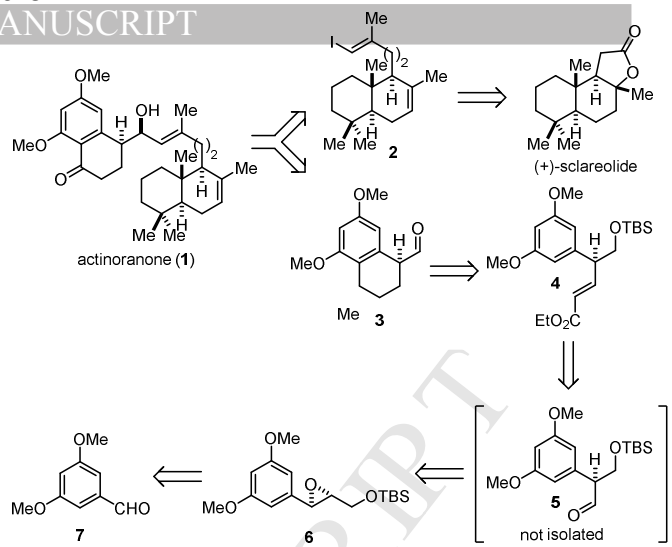


Figure 1: Originally proposed (left) and revised structure (right) of actinoranone **1**.

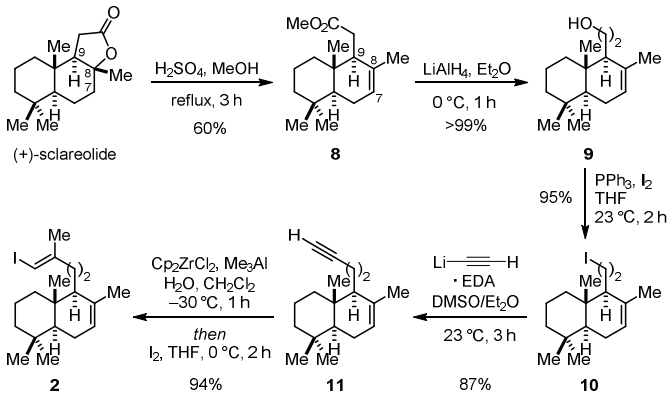
Similar to the previously reported approaches, our retro-synthetic analysis exploits a polar disconnection between C14 and C15 leading to vinyl iodide **2** and the bicyclic aldehyde **3** as the key fragments (Scheme 1). Likewise, we envisioned that **2** could be obtained from the sesquiterpenoid sclareolide.[18-27] In contrast to Ye and Pastre, we anticipated aldehyde **3** to be accessible from ester **4**. For the synthesis of this intermediate, a semipinacol rearrangement/Wittig reaction sequence starting from silyl ether **6** was considered. Such a one-pot strategy avoids the isolation of the configurationally labile aldehyde **5**. The chiral silylated epoxyalcohol **6** can be obtained from 3,5-dimethoxy-benzaldehyde **7** using standard transformations.



Scheme 1: Retrosynthetic analysis of actinoranone **1**.

2. Results and Discussion

The synthesis of vinyl iodide **2** started with the preparation of trisubstituted $\Delta^{7,8}$-alkene **8** from commercially available (+)-sclareolide (Scheme 2). Treatment with sulfuric acid in methanol resulted in a one-pot methanolysis of the lactone followed by elimination of the resulting tertiary alcohol at C8.[27-28] Subsequently, the ratio of $\Delta^{7,8}$-alkene, $\Delta^{8,9}$-alkene, and exocyclic $\Delta^{8,19}$-alkene was optimized by screening different reaction temperatures and times. After three days at 23 °C, a mixture of alkene-isomers ($\Delta^{7,8}$, $\Delta^{8,9}$, $\Delta^{8,19}$ = 1.0:0.2:0.7) with $\Delta^{7,8}$-alkene **8** as the major product was obtained. Heating the reaction mixture to reflux for 24 h afforded two endocyclic alkene isomers, i.e. the thermodynamically most stable tetrasubstituted $\Delta^{8,9}$-alkene and the $\Delta^{7,8}$-alkene in a 1:1 ratio. Reducing the reaction time to 3 h gave the best result for the desired $\Delta^{7,8}$-alkene **8** (60% yield). Other acids such as HCl, AcOH, or H_3PO_4 led to no improvement. Nevertheless, the optimized selectivity and yield for **8** constitute an improvement over those reported literature.[28]

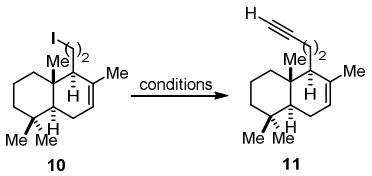


Scheme 2: Synthesis of fragment **2**.

Next, ester **8** was reduced to primary alcohol **9** using $LiAlH_4$ followed by the conversion into iodide **10** under Appel conditions. The subsequent two-carbon extension to alkyne **4** required some optimization. Using lithium acetylide ethylenediamine complex (LAEDA) in DMSO[29-30] at ambient temperature gave the desired product **11** in only moderate yield of 42% (Table 1, entry 1). Changing the solvent to DMF (entry 2) slightly increased the yield of **11**, whereas using HMPA[31] lowered the yield to 7% (entry 3). Other methods such as the

reaction with *in situ* generated lithium trimethylsilylacetylide[32] or Sonogashira coupling[33] with trimethylsilylacetylene did not provide any of the desired product (not displayed). Treatment of **10** with sodium acetylide[34] in DMF slightly improved the yield to 58% (entry 4). Finally, treatment of iodide **10** with LAEDA in a 1:1 solvent mixture of DMSO/Et_2O gave alkyne **11** in 87% (entry 5).

Table 1: Two-carbon homologation of **10**.



Entry	Conditions	Solvent	t(h)	**11** (%)[a]
1	LAEDA (2.0 equiv) at 23 °C	DMSO	72	42
2	LAEDA (3.0 equiv) at 50 °C	DMF	16	45
3	LAEDA (2.0 equiv) at 23 °C	HMPA	18	7
4	Na–≡ (2.0 equiv) at 0 °C	DMF	2	58
5	LAEDA (3.0 equiv) at 23 °C	DMSO/Et_2O[b]	3	87

[a] Isolated yield. [b] 1:1 *v*/*v* was used.

With alkyne **11** in hand, we turned our focus to Negishi's[35-36] zirconium-catalyzed carboalumination-iodination sequence.[37-38] Application of Wipf's protocol[39] afforded *E*-vinyl iodide **2** in 94% yield. Precise temperature control and slow addition of the reactants were crucial to avoid premature proto-demetallation, as reported by Ye and co-workers.[15] In summary, intermediate **2** was obtained from (+)-sclareolide in five steps and 47% overall yield (Figure 2). While our approach shares some of the synthetic transformations used by Ye (15 steps) and Pastre (9 steps), we have been able to shorten the previous sequences to just 5 steps and raise the overall yield fragment **2** to 47%. This optimized route should also be useful for future SAR studies.[16]

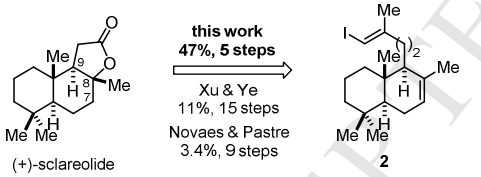
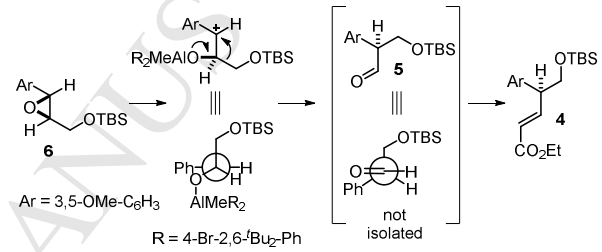


Figure 2: Comparison of the synthetic approaches to fragment **2**.

Our route to the tetralone fragment was based on the chirality transfer from epoxyalcohol **6** to the stereogenic center in the benzyl position of aldehyde **5**. Such transformation belongs to the semipinacol rearrangements (type III: epoxides).[40-41] It is also known under the name Meinwald rearrangement[42] and Yamamoto epoxide rearrangement. The required silylated epoxyalcohol was prepared starting from the readily available allylic alcohol **12** (Scheme 3).[43] A catalytic Sharpless epoxidation[44] followed by treatment with TBSOTf permitted stereoselective preparation of the epoxy silyl ether required for the rearrangement in good yield and excellent enantiomeric excess (**10**, Scheme 3). At this point, we investigated the antiperiplanar migration of the vicinal C–C bond to benzylic position using a Yamamoto rearrangement.[44-47] Therefore, we applied the original reaction conditions using stoichiometric amounts of the *in situ* formed aluminum-based Lewis acid MABR (methylaluminum bis-(4-bromo-2,6-di-*tert*-butylphenoxide)).[48-52] The originally described work-up with NaF·H_2O gave aldehyde **11** in 33% yield and a decreased enantiomeric excess (*ee*) of 60% (Table 1, entry 1). Therefore, we investigated various work-up methods that were aimed to avoid undesired racemization (entries 2–6). Pouring the crude reaction mixture into diluted aqueous hydrochloric acid enhanced the yield to 65% yet with a strongly reduced enantiomeric excess of 33% (entry 2). Addition of saturated aqueous NH_4Cl or H_2O did not give better results in terms of yield and enantioselectivity (entries 3 and 4). Removal of the reaction solvent yielded 36% of **5** (57% *ee*, entry 5). As the newly formed stereogenic center in the benzylic position and α to the aldehyde **5** proved to be very sensitive to the applied work-up conditions, we decided to directly submit the reaction mixture to the subsequent Wittig olefination. Direct addition of freshly prepared Wittig reagent gave a poor 3% yield of **4** (entry 6). Thus, the reaction mixture was concentrated and re-dissolved in THF prior to the ylide addition. To our delight, unsaturated ester **4** was obtained in 44% yield whilst completely suppressing the undesired racemization (entry 7). After extensive screening, we found out that addition of THF followed by careful removal of CH_2Cl_2 gave the best result. Under these conditions, ester **4** was finally obtained in 71% yield and 96% *ee* (entry 8).

Table 2: Optimization of the Yamamoto rearrangement.

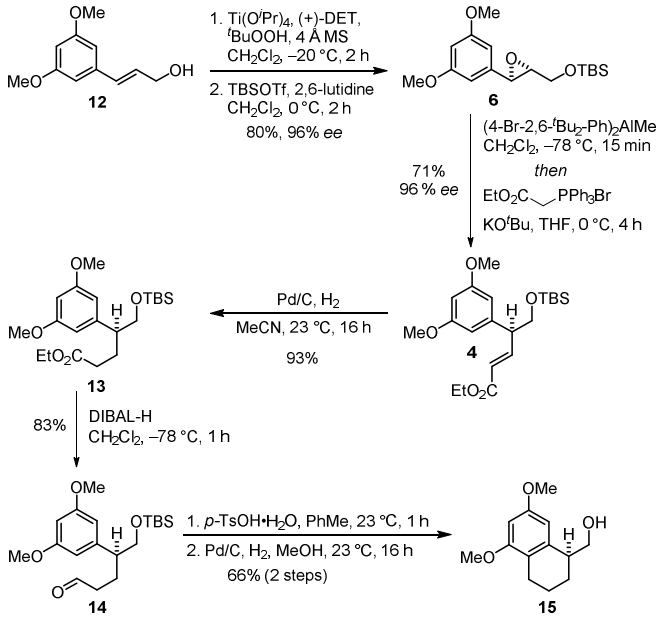


Entry	Conditions Work-up[a]	Product	Yield[b] (%)	*ee* (%)
1	NaF (6.0 equiv), H_2O (8.0 equiv) addition, stirring at 23 °C for 30 min, filtration over Celite®	**5**	33	60
2	Poured into diluted HCl solution, extraction with CH_2Cl_2	**5**	65	33
3	Addition of saturated NH_4Cl solution, extraction with CH_2Cl_2	**5**	38	7
4	Addition of H_2O (excess), extraction with CH_2Cl_2	**5**	61	14
5	Removal of CH_2Cl_2 under HV	**5**	36	57
6[c]	Addition to Wittig reagent	**4**	3	–
7	Removal of CH_2Cl_2 under HV, redissolved in THF and addition to Wittig reagent	**4**	44	96
8	Addition of THF, removal of CH_2Cl_2 under HV, addition to Wittig reagent	**4**	71	96

[a] After the described work-up, flash column chromatography (10:1 = pentane: Et_2O) was performed. [b]Isolated yield. [c]*ee* was not measured.

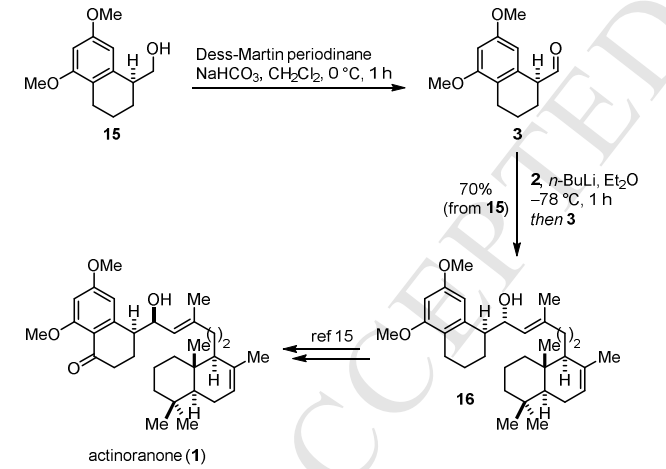
The route toward aldehyde fragment **3** (and its stable alcohol precursor **15**) continued with the hydrogenation of the double bond of **4** using Pd/C (10 w%) under H_2-atmosphere. Using MeOH as solvent led to an undesired cleavage of the silyl group.[53] This problem was solved by changing the solvent to MeCN which afforded ester **13** in 93% yield. Ester **13** was then transformed into aldehyde **14** in 83% yield *via* DIBAL-H reduction. At this point, our synthesis towards the bicyclic alcohol **3** converged into Pastre´s and Ye's route.[16] Following their conditions, acid catalyzed cyclization and silyl ether cleavage using *p*-TsOH was followed by hydrogenation

employing Pd/C in MeOH (10 w%, slightly acidic) to give bicyclic alcohol **15** in 66% yield.



Scheme 3: Synthesis of fragment **15**.

Finally, the coupling of fragments **2** and **3** was carried out following Ye's[15] and Pastre's[16] procedure. The aldehyde fragment was prepared by Dess-Martin oxidation of **15** to give **3**, which was directly added to a solution of *in situ* lithiated vinyl iodide **2**. The allylic alcohol **16** was obtained in 70% yield thereby completing the formal synthesis of actinoranone (Figure 4).



Scheme 4: Completion of the formal synthesis of actinoranone **1**.[15]

According to Xu's and Ye's work,[15] actinoranone **1** can be obtained from **16** in three additional steps inverting the configuration at C-15 under Mitsunobu conditions followed by benzylic C–H oxidation using DDQ, and basic hydrolysis of the Mitsunobu ester.

3. Conclusion

In summary, we have achieved a formal synthesis of actinoranone starting from commercially available (+)-sclareolide and 3,5-dimethoxybenzaldehyde. The synthesis of the terpenoid fragment **2** was completed in 5 steps and 47% yield using a streamlined synthesis involving a two-carbon homologation and a subsequent zirconium-catalyzed carboalumination. The polyketide fragment **3** was obtained in nine steps with 17% overall yield from 3,5-dimethoxybenzaldehyde. Complementary to the previously reported syntheses, the single stereogenic center in **3** was generated from silylated epoxyalcohol **6** using a semipinacol rearrangement.

4. Experimental section

4.1 General procedures

All reactions sensitive to moisture and/or air were performed under an argon atmosphere using Schlenk techniques. Reagents and solvents were obtained from commercial sources and used as received unless otherwise noted. Anhydrous solvents (THF, CH_2Cl_2, Et_2O, PhMe) were purified using the solvent purification system MB-SPS-800 (Braun). The solvents (EtOAc, Et_2O, *n*-pentane) used for column chromatography and work up were purified from commercially available technical grade solvents by distillation under reduced pressure. Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded at the following frequencies: ^{1}H NMR at 400, 500, and 700 MHz, ^{13}C NMR at 100, 125, and 175 MHz with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet), coupling constant (Hz), and integration. High resolution mass spectra were measured with a TOF mass spectrometer. TLC visualization was accomplished using UV light and/or staining in a Cer(IV)-sulfate solution (5.0 g phosphomolybdic acid, 16 mL conc. H_2SO_4, 200 mL H_2O, 4.0 g cerium(IV) sulfate) or acidic *p*-anisaldehyde solution (450 mL EtOH, 25 mL anisaldehyde, 25 mL conc. H_2SO_4, 8 mL AcOH) and subsequent charring. Yields refer to isolated yields after flash column chromatography.

*4.2 Synthesis of Methyl 2-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate (**8**)*[28, 54]

(3a*R*)-(+)-Sclareolide (1.00 g, 4.00 mmol) was dissolved in MeOH (19 mL) and then treated with conc. H_2SO_4 (0.7 mL). After refluxing for 3 h, MeOH was distilled off and the residue dissolved in Et_2O (100 mL), washed with H_2O (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), and brine (20 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude alkenes were separated by column chromatography (*n*-pentane/Et_2O = 120:1 to 80:1) giving $\Delta^{7,8}$-**8** (636 mg, 2.4 mmol, 60%) and $\Delta^{8,9}$ (424 mg, 1.60 mmol, 40%) alkenes as colorless oils.

8: R_f = 0.46 (*n*-pentane/Et_2O = 40:1); ^{1}H (500 MHz, $CDCl_3$): δ = 5.47 – 5.39 (m, 1H), 3.68 (s, 3H), 2.49 (d, *J* = 9.5 Hz, 1H), 2.42 – 2.35 (m, 1H), 2.17 (dd, *J* = 16.5, 9.7 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.84 (dddt, *J* = 17.5, 12.0, 4.5, 2.4 Hz, 1H), 1.75 – 1.65 (m, 1H), 1.56 – 1.53 (m, 3H), 1.53 – 1.37 (m, 3H), 1.28 (dd, *J* = 12.2, 4.7 Hz, 1H), 1.18 (td, *J* = 13.1, 3.6 Hz, 1H), 1.09 (td, *J* = 13.0, 3.9 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 175.5, 133.8, 122.9, 51.9, 50.7, 49.9, 42.2, 39.2, 36.1 33.3, 33.1, 23.8, 22.0, 21.5, 18.9, 14.1 (2C) ppm.

The analytical data were identical with those published.[28]

*4.3 Synthesis of 2-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethan-1-ol (**9**)*

To a suspension of $LiAlH_4$ (0.230 g, 6.05 mmol, 1.5 equiv) in anhydrous Et_2O (20 mL), a solution of ester **8** (1.07 g, 4.04 mmol, 1.0 equiv) in anhydrous Et_2O (40 mL) was added slowly at 0 °C. The mixture was stirred for 1 h before it was quenched by the addition of aqueous HCl (1M; 50 mL). Afterwards, the mixture was extracted with Et_2O (4 x 50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. After purification by column chromatography (*n*-pentane/EtOAc = 5:1), alcohol **9** (0.954 g, 4.04 mmol, >99%) was obtained as colorless oil.

9: R_f = 0.39 (*n*-pentane/EtOAc = 5:1); ^{1}H (400 MHz, $CDCl_3$): δ = 5.41 (brs, 1H), 3.78 (dt, *J* = 9.5, 5.2 Hz, 1H), 3.66–3.47 (m, 1H), 2.04–1.91 (m, 1H), 1.92–1.78 (m, 1H), 1.72 (dd, *J* = 14.2, 7.2 Hz, 2H), 1.66 (s, 3H), 1.66–1.64 (m, 1H), 1.57–1.45 (m, 4H), 1.40 (d, *J* = 13.9 Hz, 1H), 1.18 (dd, *J* = 11.9, 5.1 Hz, 1H), 1.13 (dd, *J* = 13.1, 3.9 Hz, 1H), 0.95 (dt, *J* = 13.1, 3.9 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C (100 MHz, $CDCl_3$): δ = 134.7, 122.8, 64.5, 50.8, 50.2, 42.4, 39.3, 36.6, 32.3, 33.1, 30.6, 23.9, 22.2, 22.0, 18.9, 13.7 ppm.

*4.4 Synthesis of (4aS,5S,8aS)-5-(2-iodoethyl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (**10**)*

To a solution of alcohol **9** (500 mg, 2.12 mmol, 1.0 equiv) in anhydrous THF (35 mL), PPh_3 (666 mg, 2.54 mmol, 1.2 equiv), imidazole (288 mg, 4.23 mmol, 2.0 equiv), and I_2 (644 mg, 2.54 mmol, 1.2 equiv) were subsequently added and the mixture was stirred for 2 h at 23 °C. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane) giving alkyl iodide **10** (693 mg, 2.00 mmol, 95%) as colorless oil.

10: R_f = 0.98 (*n*-pentane); ^{1}H (400 MHz, $CDCl_3$): δ = 5.42 (brs, 1H), 3.38 (ddd, *J* = 10.3, 9.4, 4.7 Hz, 1H), 3.14 (td, *J* = 9.4, 7.5 Hz, 1H), 2.05 (dddd, *J* = 14.7, 10.3, 7.5, 1.8 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.89 – 1.72 (m, 3H), 1.67 (s, 3H), 1.65 – 1.60 (m, 1H), 1.56 – 1.51 (m, 1H), 1.47 (tq, *J* = 10.2, 3.4 Hz, 1H), 1.41 (dtd, *J* = 13.1, 3.2, 1.7 Hz, 1H), 1.19 (dd, *J* = 12.0, 4.9 Hz, 1H), 1.15 (dd, *J* = 13.2, 3.9 Hz, 1H), 1.04 (td, *J* = 13.1, 4.1 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.74 (s, 3H) ppm; ^{13}C (100 MHz, $CDCl_3$): δ = 133.7, 123.4, 56.6, 50.1, 42.3, 39.3, 36.8, 33.3, 33.1, 32.7, 23.9, 22.2, 22.0, 18.8, 13.9, 8.5 ppm.

*4.5 Synthesis of (4aS,5S,8aS)-5-(but-3-yn-1-yl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (**11**)*

To a suspension of LAEDA (40.0 mg, 0.434 mmol, 1.5 equiv) in anhydrous DMSO/Et_2O (1:1 *v*/*v*; 0.6 mL), was added a solution of iodide **10** (100 mg, 0.289 mmol, 1.0 equiv) in anhydrous Et_2O (0.3 mL) at 0 °C. The reaction was stirred for 1 h and then another portion of LAEDA (40.0 mg, 0.434 mmol, 1.5 equiv) was added. After 3 h the reaction was quenched by the addition of H_2O (2.0 mL) and extracted with Et_2O (3 x 30 mL). The combined organic phases were washed with H_2O (2 x 10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane) giving the alkyne **11** (61.7 mmol, 0.252 mmol, 87%) as colorless oil.

11: R_f = 0.76 (*n*-pentane); ^{1}H (500 MHz, $CDCl_3$): δ = 5.41 (brs, 1H), 2.37 (dddd, *J* = 16.7, 9.1, 5.0, 2.6 Hz, 1H), 2.18 (dtd, *J* = 16.7, 8.3, 2.6 Hz, 1H), 2.02 – 1.97 (m, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.89 – 1.83 (m, 2H), 1.76 – 1.70 (m, 2H), 1.68 (s, 3H), 1.59 – 1.48 (m, 1H), 1.48 – 1.37 (m, 3H), 1.22 – 1.17 (m, 1H), 1.15 (dd, *J* = 13.1, 3.8 Hz, 1H), 1.01 (td, *J* = 13.1, 3.8 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 134.7, 122.9, 85.0, 68.4, 53.8, 50.2, 42.4, 39.2, 36.7, 33.3, 33.2, 26.4, 23.9, 22.3, 22.0, 20.5, 18.9, 13.8 ppm.

*4.6 Synthesis of (4aS,5S,8aS)-5-((E)-4-iodo-3-methylbut-3-en-1-yl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (**2**)*[38]

To a solution of Cp_2ZrCl_2 (24.0 mg, 0.0820 mmol, 0.5 equiv) in anhydrous CH_2Cl_2 (6.0 mL), Me_3Al (2 M in PhMe; 0.24 mL, 0.489 mmol, 3.0 equiv) was added slowly at –30 °C. The pale-yellow mixture was stirred for 30 min at 23 °C and cooled to –30 °C again. At this point, H_2O (4.40 µL, 0.245 mmol, 1.5 equiv) was added and the mixture stirred for additional 30 min, and then a solution of alkyne **11** (40.0 mg, 0.163 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (0.30 mL) was added. After 1 h, I_2 (54.0 mg, 2.12 mmol, 1.3 equiv) dissolved in anhydrous THF (0.60 mL) was added and the yellow solution was stirred for 4 h at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) followed by extraction with *n*-pentane (3 x 30 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane) yielding vinyl iodide **2** (44.0 mg, 0.154 mmol, 94%) as colorless solid.

2: R_f = 0.94 (*n*-pentane); ^{1}H (500 MHz, $CDCl_3$): δ = 5.89 (q, *J* = 1.1 Hz, 1H), 5.40 (brs, 1H), 2.46 – 2.33 (m, 1H), 2.16 (dddd, *J* = 13.7, 10.3, 6.2, 0.8 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.89 – 1.86 (m, 1H), 1.85 (d, *J* = 1.1 Hz, 3H), 1.83 – 1.78 (m, 1H), 1.68 (brs, 3H), 1.62 – 1.47 (m, 3H), 1.47 – 1.38 (m, 2H), 1.34 – 1.26 (m, 1H), 1.20 – 1.12 (m, 2H), 0.93 (td, *J* = 13.1, 3.9 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 148.7, 135.0, 122.8, 75.0, 54.4, 50.3, 42.4, 42.2, 39.3, 36.9, 33.3, 33.1, 25.7, 24.2, 24.0, 22.3, 22.0, 18.9, 13.7 ppm.

*4.7 Synthesis of (E)-3-(3´,5´-dimethoxyphenyl)prop-2-en-1-ol (**12**)*[43, 55]

Triethyl phosphonoacetate (6.05 mL, 14.1 mmol, 1.8 equiv) was added to a suspension of NaH (60 w% mineral oil; 0.580 g, 24.0 mmol, 1.8 equiv) in anhydrous THF (71 mL) at 0 °C. The suspension cleared after stirring for 30 min, and then a solution of the 3,5-dimethoxybenzaldehyde (**7**, 2.00 g, 12.0 mmol, 1.0 equiv) in anhydrous THF (4.0 mL) was added. Stirring was continued for additional 16 h during gradual warming to 23 °C. The mixture was then quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (4 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude ester was dissolved in anhydrous CH_2Cl_2 (50 mL) and DIBAL-H (1M in CH_2Cl_2; 36.0 mL, 36.1 mmol, 3.0 equiv) was slowly added at 0 °C. The reaction mixture was stirred for 1 h and then quenched by careful addition of aqueous HCl (1M; 30 mL). The mixture was stirred for 30 min and then extracted with Et_2O (4 x 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (Et_2O/*n*- pentane = 2:1) giving allylic alcohol **12** (2.01 g, 10.4 mmol, 86%) as colorless oil.

12: R_f = 0.66 (*n*-pentane/Et_2O = 1:3); ^{1}H (500 MHz, $CDCl_3$): δ = 6.56 – 6.55 (m, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 6.53 – 6.51 (m, 1H), 6.38 – 6.36 (m, 1H), 6.34 (dd, *J* = 15.9, 5.7 Hz, 1H), 4.63 (brs, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 6H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 161.0 (2C), 138.9, 131.1, 129.2, 104.7 (2C), 100.0, 63.7, 55.4 (2C) ppm.

*4.8 Synthesis of tert-butyl(((2R,3R)-3-(3´,5´-dimethoxyphenyl) oxiran-2-yl)methoxy)dimethylsilane (**6**)[44]*

To a suspension of (+)-DET (0.240 mL, 1.41 mmol, 0.18 equiv) and powdered (or grinded) 4 Å MS in anhydrous CH_2Cl_2 (25 mL), $Ti(O^iPr)_4$ (0.350 mL, 1.17 mmol, 0.15 equiv) was added at –20 °C. The mixture was stirred for 30 min and then ^{t}BuOOH (5.5M in decane; 2.85 mL, 15.7 mmol, 2.0 equiv,) was added. After stirring for additional 30 min at –20 °C, a solution of allylic alcohol **12** (1.52 g, 7.83 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (3.5 mL) was added. The reaction mixture was stirred for 2 h at –20 °C and then quenched by the addition of aqueous NaOH (10% *w*/*w*; 10 mL) and brine (10 mL). The mixture was filtered through a pad of Celite and the filtrate was then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude epoxide was dissolved in anhydrous CH_2Cl_2 (77 mL) and treated with 2,6-lutidine (1.09 mL, 9.40 mmol, 1.2 equiv) and TBSOTf (1.98 mL, 8.61 mmol, 1.1 equiv) at 0 °C. The solution was stirred for 2 h at this temperature before quenching with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (*n*-pentane/Et_2O = 11:1), TBS-protected epoxide **6** (2.03 g, 6.26 mmol, 80%, 96% *ee*) was obtained as colorless oil.

6: R_f = 0.74 (*n*-pentane/Et_2O = 8:1); $[\alpha]_D^{25}$ = –28.7 ($CHCl_3$, c = 1.0); IR: $\tilde{\nu}$ = 833, 1152, 1252, 1347, 1461, 1470, 1597, 2360, 1856, 2929, 2953 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$): δ = 6.44 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 3.96 (dd, *J* = 12.1, 3.0 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.78 (s, 6H), 3.76 (d, *J* = 2.1 Hz, 1H), 3.12 – 3.07 (m, 1H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 161.2 (2C), 140.0, 103.5 (2C), 100.5, 63.0, 62.7, 56.0, 55.5 (2C), 26.0 (3C), 18.6, –5.1 (2C) ppm; HRMS (ESI): $[M+Na]^+$ calculated for $C_{17}H_{28}O_4SiNa^+$: 347.1649, found: 347.1640; $[M+K]^+$ calculated for $C_{17}H_{28}O_4SiK^+$: 363.1389, found: 363.1391.

*4.9 Synthesis of ethyl (S,E)-5-((tert-butyldimethylsilyl)oxy)-4-(3´,5´-dimethoxyphenyl)pent-2-enoate (**4**)[44]*

4-Bromo-2,6-di-*tert*-butylphenol (703 mg, 2.46 mmol, 4.0 equiv) was dissolved in anhydrous CH_2Cl_2 (14 mL) and the yellow solution was degassed (freeze-pump-thaw; three cycles). Subsequent addition of Me_3Al (2M in PhMe; 0.62 mL, 1.23 mmol, 2.0 equiv,) gave a colorless solution. Stirring was continued for 1 h till the gas development has ceased. After cooling to –78 °C, a solution of epoxide **6** (200 mg, 0.616 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was added to give a bright yellow solution. After 15 min stirring, anhydrous THF (3.0 mL) was added to the mixture and CH_2Cl_2 was carefully removed HV with the help of a cooling trap during warming to 23 °C (distillation was stopped after visual reduction of the 15.5 mL of CH_2Cl_2 and visual slowed or stopped distillation process). The resulting solution was then added to a suspension of the Wittig reagent (845 mg, 1.85 mmol, 3.0 equiv) and KO^{t}Bu (200 mg, 1.79 mmol, 2.9 equiv) in anhydrous THF (8.0 mL), which was previously reacted for 30 min at 0 °C. The reaction mixture was stirred for additional 4 h at 0 °C and quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with Et_2O (4 x 50 mL), the combined organic phases were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/Et_2O = 11:1) yielding ester **4** as pale-yellow oil (173 mg, 0.437 mmol, 71%, 96% *ee*).

4: R_f = 0.45 (*n*-pentane/Et_2O = 8:1); $[\alpha]_D^{25}$ = +12.8 ($CHCl_3$, c = 1.4); IR: $\tilde{\nu}$ = 833, 1152, 1428, 1461, 1594, 1717, 2856, 2929, 2953 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 15.8, 7.3 Hz, 1H), 6.39 – 6.26 (m, 3H), 5.85 (dd, *J* = 15.8, 1.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.85 (d, *J* = 6.7 Hz, 2H), 3.78 (s, 6H), 3.54 (q, *J* = 6.7 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), –0.01 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 166.4, 160.8 (2C), 148.4, 142.0, 122.5, 106.4 (2C), 98.7, 66.2, 60.1, 55.2 (2C), 51.2, 25.7 (3C), 18.1, 14.1, –5.6 (2C) ppm; HRMS (ESI): $[M+H]^+$ calculated for $C_{21}H_{34}O_5SiH^+$: 395.2249, found: 395.2230; $[M+Na]^+$ calculated for $C_{21}H_{34}O_5SiNa^+$: 417.2068, found: 417.2082.

*4.10 Synthesis of ethyl (S)-5-((tert-butyldimethylsilyl)oxy)-4-(3´,5´-dimethoxyphenyl)pentanoate (**13**)*

A mixture of alkene **4** (173 mg, 0.437 mmol, 1.0 equiv) and Pd/C (17.5 mg, 40 mg/mmol, 10% *w*/*w*) in MeCN (2.0 mL) was stirred under H_2 atmosphere for 16 h at 23 °C. The mixture was filtered through a pad of Celite® and the filter cake washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography (*n*-pentane/Et_2O = 9:1) giving ester **13** (161 mg, 0.406, 93%) as pale-yellow oil.

13: R_f = 0.44 (*n*-pentane/Et_2O = 8:1); $[\alpha]_D^{26}$ = +8.15 ($CHCl_3$, c = 0.75); IR: $\tilde{\nu}$ = 835, 1154, 1204, 1429, 1462, 1595, 1733, 2856, 2930, 2953 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 2.2 Hz, 2H), 6.32 (t, *J* = 2.6 Hz, 1H), 4.08 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.77 (s, 6H), 3.73 – 3.63 (m, 2H), 2.71 – 2.62 (m, 1H), 2.24 – 2.15 (m, 3H), 1.87 – 1.79 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), –0.01 (s, 3H), –0.03 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 173.8, 160.9 (2C), 144.8, 106.4 (2C), 98.5, 67.9, 60.3, 55.4 (2C), 48.5, 32.5, 27.3, 26.0 (3C), 18.4, 14.4, –5.3 (2C) ppm; HRMS (ESI): $[M+Na]^+$ calculated for $C_{21}H_{36}O_5SiNa^+$: 419.2224, found: 419.2218; $[M+K]^+$ calculated for $C_{21}H_{36}O_5SiK^+$: 435.1964, found: 435.1949.

*4.11 Synthesis of (S)-5-((tert-butyldimethylsilyl)oxy)-4-(3´,5´-dimethoxyphenyl)pentanal (**14**)*

To a solution of ester **13** (73.0 mg, 0.184 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1.8 mL), was added DIBAL-H (1.0M in CH_2Cl_2; 0.20 mL, 0.202 mmol, 1.1 equiv) at –78 °C. After stirring for 1 h, the reaction was quenched by the addition of saturated aqueous potassium sodium tartrate (5.0 mL), stirred for 30 min and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification of the crude by column chromatography (*n*-pentane/Et_2O = 5:1), aldehyde **14** (53.8 mg, 0.153 mmol, 83%) was obtained as colorless oil.

14: R_f = 0.42 (*n*-pentane/Et_2O = 6:1); $[\alpha]_D^{25}$ = +11.0 ($CHCl_3$, c = 1.05); IR: $\tilde{\nu}$ = 835, 1110, 1152, 1204, 1252, 1428, 1461, 1594, 1724, 2856, 2929, 2952 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$): δ = 9.70 (t, *J* = 1.6 Hz, 1H), 6.50 – 6.17 (m, 3H), 3.77 (s, 6H), 3.72 (dd, *J* = 9.9, 5.4 Hz, 1H), 3.66 (dd, *J* = 10.0, 7.4 Hz, 1H), 2.66 (ddt, *J* = 10.2, 7.4, 5.1 Hz, 1H), 2.36 (td, *J* = 7.8, 1.4 Hz, 2H), 2.29 – 2.07 (m, 1H), 1.91 – 1.74 (m, 1H), 0.87 (s, 9H), –0.01 (s, 3H), –0.02 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 202.5, 161.0 (2C), 144.6, 106.4 (2C), 98.6, 67.9, 55.4 (2C), 48.4, 42.2, 26.0 (3C), 24.5, 18.4, –5.3 (2C) ppm; HRMS (ESI): $[M+H]^+$ calculated for $C_{19}H_{32}O_5SiH^+$: 353.2143, found: 353.2161.

*4.12 Synthesis of (S)-(5,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**15**)*

A solution of aldehyde **14** (53.8 mg, 0.153 mmol, 1.0 equiv) in anhydrous PhMe (5.2 mL) was treated with *p*TSA·H_2O (28.5 mg, 0.153 mmol, 1.0 equiv). The reaction was stirred for 1 h at 23 °C and quenched with saturated aqueous $NaHCO_3$ (5.0 mL). The mixture was extracted with EtOAc (3 x 20 mL), the combined organic phases were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/Et_2O = 8:1) giving the corresponding 3,4-alkene (45.1 mg, 0.135 mmol, 88%) as colorless oil.

R_f = 0.78 (*n*-pentane/Et_2O = 5:1); $[\alpha]_D^{25}$ = +1.77 ($CHCl_3$, c = 0.93); IR: $\tilde{\nu}$ = 833, 1092, 1148, 1207, 1319, 1425, 1463, 1576, 1603, 2856, 2928, 2952 cm^{-1}; ^1H (500 MHz, $CDCl_3$): δ = 6.71 (dd, *J* = 9.8, 2.9 Hz, 1H), 6.35 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 5.73 (ddd, *J* = 9.5, 5.9, 2.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.65 – 3.44 (m, 2H), 2.89 – 2.82 (m, 1H), 2.51 (ddd, *J* = 17.4, 6.0, 2.6 Hz, 1H), 2.42 – 2.29 (m, 1H), 0.89 (s, 9H), 0.00 (s, 6H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 159.5, 156.0, 138.5, 122.7, 120.7, 116.2, 105.8, 97.0, 64.5, 55.7, 55.5, 41.0, 26.1 (3C), 24.3, 18.5, –5.2, –5.3 ppm.; HRMS (ESI): $[M+H]^+$ calculated for $C_{19}H_{30}O_3SiH^+$: 335.2037, found: 335.2054; $[M+Na]^+$ calculated for $C_{19}H_{30}O_3SiNa^+$: 357.1856, found: 357.1869.

A mixture of the intermediate alkene (45.1 mg, 0.135 mmol, 1.0 equiv) and Pd/C (5.40 mg, 40 mg/mmol, 10% *w*/*w*) in MeOH (1.0 mL) was stirred under H_2 atmosphere for 16 h at 23 °C. To the mixture EtOAc (80 mL) was added and the suspension filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography (*n*-pentane/EtOAc = 3:1) giving alcohol **15** (22.5 mg, 0.101 mmol, 75%) as colorless oil.

15: R_f = 0.28 (*n*-pentane/EtOAc = 3:1); $[\alpha]_D^{25}$ = –2.2 ($CHCl_3$, c = 1.0); ^1H (500 MHz, $CDCl_3$): δ = 6.39 (d, *J* = 2.2 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 3.81 (d, *J* = 6.3 Hz, 2H), 3.79 (s, 6H), 2.92 (p, *J* = 5.4 Hz, 1H), 2.62 (dt, *J* = 16.9, 5.1 Hz, 1H), 2.53 – 2.42 (m, 1H), 1.95 – 1.86 (m, 1H), 1.81 (dd, *J* = 10.5, 3.6 Hz, 2H), 1.75 – 1.69 (m, 1H), 1.47 (brs, 1H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 158.3, 158.3, 138.4, 119.4, 104.2, 96.3, 67.0, 55.4, 55.3, 40.8, 24.9, 22.6, 19.1 ppm.

*4.13 Synthesis of (S,E)-1-((S)-5,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-3-methyl-5-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)pent-2-en-1-ol (**16**)*[16]

To a solution of alcohol **15** (23.0 mg, 0.103 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (1.0 mL), $NaHCO_3$ (13.0 mg, 0.152 mmol, 2.2 equiv) and DMP (44.0 mg, 0.104 mmol, 1.5 equiv) were added at 0 °C. The mixture was stirred for 1 h and then concentrated under reduced pressure. The obtained residue was purified by column chromatography (*n*-pentane/EtOAc = 3:1; R_f = 0.75 (*n*-pentane/EtOAc = 3:1)) to give aldehyde **3** which was immediately used in the following step.

^{n}BuLi (2.5M in hexane; 60 µL, 0.138 mmol, 2.0 equiv) was added to a solution of vinyl iodide **2** (27.0 mg, 0.0690 mmol, 1.0 equiv) in anhydrous Et_2O (1.2 mL) at –78 °C. After 1 h, the freshly prepared aldehyde **3** in Et_2O (1.2 mL) was added and the reaction was stirred for 16 h at the same temperature. The mixture was quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with EtOAc (4 x 15 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (*n*-pentane/EtOAc =10:1), allylic alcohol **16** (23.2 mg, 0.0483 mmol, 70%) was obtained as colorless oil.

16: R_f = 0.24 (*n*-pentane/EtOAc = 9:1); $[\alpha]_D^{25}$ = +20.6 ($CHCl_3$, c = 1.60); ^1H (500 MHz, $CDCl_3$): δ = 6.48 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* = 2.1 Hz, 1H), 5.39 (brs, 1H), 5.30 (d, *J* = 8.0 Hz, 1H), 4.76 (ddd, *J* = 7.8, 4.7, 2.8 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.88 – 2.79 (m, 1H), 2.62 (dt, *J* = 16.7, 6.4 Hz, 1H), 2.51 (dt, *J* = 17.0, 6.3 Hz, 1H), 2.21 (td, *J* = 13.2, 12.6, 4.5 Hz, 1H), 2.02 – 1.74 (m, 8H), 1.69 (s, 3H), 1.66 – 1.60 (m, 2H), 1.58 (s, 3H), 1.49 – 1.30 (m, 4H), 1.29 – 1.12 (m, 3H), 0.97 – 0.92 (m, 1H), 0.88 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 158.5 (2C), 139.3, 138.9, 135.7, 126.2, 122.7, 120.7, 105.0, 96.4, 72.0, 55.7 (2C), 55.0, 50.6, 44.6, 42.7, 42.6, 39.6, 37.2, 33.6, 33.4, 26.1, 24.2, 23.8, 23.0, 22.6, 22.3, 20.6, 19.2, 17.2, 13.9 ppm.

Acknowledgments

We thank Tommaso Pecchioli, Gregor Nagel, Robert Heinze, and Lisa Schneider (FU Berlin) for helpful discussions and Christiane Groneberg (FU Berlin) for analytical support.

Supplementary Information

Supplementary data related to this article can be found at

References

1. Martins A, Vieira H, Gaspar H, Santos S. *Mar. Drugs* 2014; 12: 1066.
2. Montaser R, Luesch H. *Future Med. Chem.* 2011; 3: 1475.
3. Haefner B. *Drug Discovery Today* 2003; 8: 536.
4. Donia M, Hamann MT. *Lancet Infect. Dis.* 2003; 3: 338.
5. Bérdy J. *J. Antibiot.* 2005; 58: 1.
6. Olano C, Méndez C, Salas J. *Mar. Drugs* 2009; 7: 210.
7. Mann J. *Nat. Prod. Rep.* 2001; 18: 417.
8. Oldfield C, Wood NT, Gilbert SC, Murray FD, Faure FR. *Antonie van Leeuwenhoek* 1998; 74: 119.
9. Dharmaraj S. *World J. Microbiol. Biotechnol.* 2010; 26: 2123.
10. Watve MG, Tickoo R, Jog MM, Bhole BD. *Arch. Microbiol.* 2001; 176: 386.
11. Chater KF. *Phil. Trans. R. Soc. B* 2006; 361: 761.
12. Fenical W, Jensen PR. *Nat. Chem. Biol.* 2006; 2: 666.
13. Nam S-J, Kauffman CA, Paul LA, Jensen PR, Fenical W. *Org. Lett.* 2013; 15: 5400.
14. Prieto-Davó A, Fenical W, Jensen PR. *Aquat. Microb. Ecol.* 2008; 52: 1.
15. Guo Y-A, Zhao M, Xu Z, Ye T. *Chem. Eur. J.* 2017; 23: 3572.
16. Novaes LFT, Pastre JC. *Org. Lett.* 2017; 19: 3163.
17. Novaes LFT, Gonçalves KdA, Trivella DBB, Pastre JC. *J. Org. Chem.* 2018; 83: 5160.
18. Fuzhuo L, Qian T, Sijia C, Lei Z, Yu L, Jianxian G, Zhen Y. *Angew. Chem. Int. Ed.* 2017; 56: 5844.
19. Oh S, Jeong IH, Shin W-S, Wang Q, Lee S. *Bioorg. Med. Chem. Lett.* 2006; 16: 1656.
20. Torre MCdl, García I, Sierra MA. *Chem. Eur. J.* 2005; 11: 3659.
21. Rosselli S, Bruno M, Pibiri I, Piozzi F. *Eur. J. Org. Chem.* 2002; 2002: 4169.
22. Wang H-S, Li H-J, Nan X, Luo Y-Y, Wu Y-C. *J. Org. Chem.* 2017; 82: 12914.
23. Zoretic PA, Fang H, Ribeiro AA, Dubay G. *J. Org. Chem.* 1998; 63: 1156.
24. Dixon DD, Lockner JW, Zhou Q, Baran PS. *J. Am. Chem. Soc.* 2012; 134: 8432.
25. Boukouvalas J, Wang J-X. *Org. Lett.* 2008; 10: 3397.
26. Kumar CNSSP, Chein R-J. *Org. Lett.* 2014; 16: 2990.
27. Menger M, Lentz D, Christmann M. *J. Org. Chem.* 2018; 83: 6793.

28. Koltsa MN, Mironov GN, Vlad PF. *Chem. Nat. Compd.* 1991; 27: 183.
29. Masuda Y, Mori K. *Biosci., Biotechnol., Biochem.* 2002; 66: 1032.
30. Asao K, Iio H, Tokoroyama T. *Tetrahedron Lett.* 1989; 30: 6401.
31. Dejarlais WJ, Emken EA. *Synth. Commun.* 1980; 10: 653.
32. Huang J, Wang H, Wu C, Wulff WD. *Org. Lett.* 2007; 9: 2799.
33. Tian P-P, Cai S-H, Liang Q-J, Zhou X-Y, Xu Y-H, Loh T-P. *Org. Lett.* 2015; 17: 1636.
34. Moody CJ, Shah P, Knowles P. *J. Chem. Soc., Perkin Trans. 1* 1988; 3249.
35. Negishi E, Van Horn DE, Yoshida T. *J. Am. Chem. Soc.* 1985; 107: 6639.
36. Negishi E-i. *Dalton Trans.* 2005; 827.
37. Valente C, Organ MG. *Chem. Eur. J.* 2008; 14: 8239.
38. Davoust M, Cantagrel F, Metzner P, Briere J-F. *Org. Biomol. Chem.* 2008; 6: 1981.
39. Wipf P, Lim S. *Angew. Chem., Int. Ed. Engl.* 1993; 32: 1068.
40. Gao, A.X.; Thomas, S.B.; Snyder, S.A. Snyder In *Pinacol and Semipinacol Rearrangements in Total Synthesis*; Rojas, C. M.,Ed.; John Wiley & Sons: Hoboken, 2015; Vol. 1, pp 3–33.
41. Song Z-L, Fan C-A, Tu Y-Q. *Chem. Rev.* 2011; 111: 7523.
42. Meinwald J, Labana SS, Chadra MS. *J. Am. Chem. Soc.* 1963; 85: 582.
43. Sauerberg P, Mogensen JP, Jeppesen L, Bury PS, Fleckner J, Olsen GS, Jeppesen CB, Wulff EM, Pihera P, Havranek M, Polivka Z, Pettersson I. *Bioorg. Med. Chem. Lett.* 2007; 17: 3198.
44. Gao S, Wang Q, Chen C. *J. Am. Chem. Soc.* 2009; 131: 1410.
45. Liu S-A, Trauner D. *J. Am. Chem. Soc.* 2017; 139: 9491.
46. Gao S, Wang Q, Huang LJ-S, Lum L, Chen C. *J. Am. Chem. Soc.* 2010; 132: 371.
47. Wilson MS, Woo JCS, Dake GR. *J. Org. Chem.* 2006; 71: 4237.
48. Maruoka K, Ooi T, Yamamoto H. *J. Am. Chem. Soc.* 1989; 111: 6431.
49. Maruoka K, Nagahara S, Ooi T, Yamamoto H. *Tetrahedron Lett.* 1989; 30: 5607.
50. Maruoka K, Ooi T, Nagahara S, Yamamoto H. *Tetrahedron* 1991; 47: 6983.
51. Maruoka K, Ooi T, Yamamoto H. *Tetrahedron* 1992; 48: 3303.
52. Maruoka K, Murase N, Bureau R, Ooi T, Yamamoto H. *Tetrahedron* 1994; 50: 3663.
53. Sajiki H, Ikawa T, Hattori K, Hirota K. *Chem. Commun.* 2003; 654.
54. Carman RW, Deeth HC. *Aust. J. Chem.* 1971; 24: 1099.
55. Bengtsson C, Nelander H, Almqvist F. *Chem. Eur. J.* 2013; 19: 9916.