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Enantioselective Total Synthesis and Absolute Configuration of Apiosporic Acid

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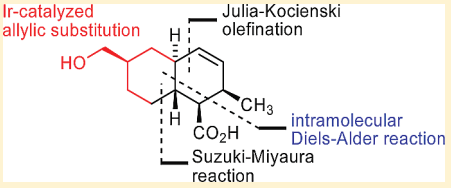
Supporting Information

ABSTRACT: The first total synthesis of the polyketide apiosporic acid is presented. Key steps are a Julia–Kocienski olefination, a Suzuki–Miyaura cross-coupling, and an intramolecular Diels–Alder reaction. The absolute configuration of the natural product was determined.



Endophytic microorganisms have proven to be a rich source of biologically active compounds.[1] Some secondary metabolites containing a *trans*-decalin moiety were isolated from the marine endophytic fungus *Apiospora montagnei* Saccardo (Figure 1).[2,3] Apiosporamide (**2**) exhibits potent

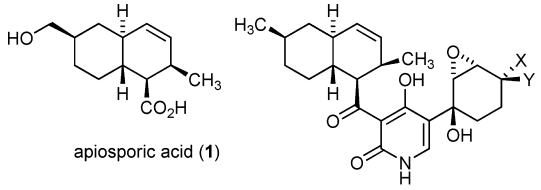


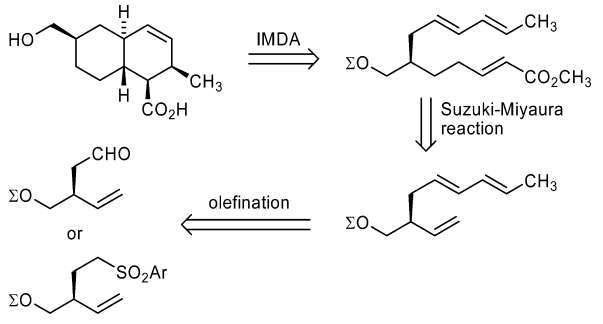
Figure 1. Polyketides isolated from *Apiospora montagnei* Saccardo.

antifungal and antibacterial activity, and the ketone **3** shows cytotoxicity against HeLa S3 cell cultures.[4] The related apiosporic acid (**1**) was found to be inactive in antibacterial, antifungal, and antialgal assays; cytotoxic properties were not evaluated.[3]

The relative configurations displayed in Figure 1 were determined by NMR spectroscopy. Compounds **2** and **3** have been synthesized by Williams et al. using an ex chiral pool approach, which allowed assignment of the absolute configurations.[5] Here, we report the first enantioselective total synthesis of apiosporic acid (**1**). By our synthesis, the anticipated structure is confirmed, and the absolute configuration is established. The substitution pattern of the cyclohexene ring suggests a synthetic strategy with an intramolecular Diels–Alder reaction (IMDA)[6] as key step (Scheme 1).[7] This has been discussed as possibility for the biosynthesis of apiosporamide (**2**)[2] and has also been applied in the synthesis of apiosporamide.[5]

The precursor was anticipated to be accessible via hydroboration/Suzuki coupling at the vinyl group of the triene described in Scheme 1. The 1,3-diene moiety was planned to be introduced by olefination of an aldehyde, which has been

Scheme 1. Retrosynthetic Analysis (Σ = Protecting Group)



prepared in our group via a regio- and enantioselective iridium-catalyzed allylic alkylation.[8] Alternatively, a chiral sulfone could be employed for olefination. An issue of concern was the *Z*/*E* selectivity of the olefination step; however, as the *E*,*E*-diene is expected to react much faster in the Diels–Alder reaction than any of the isomers, a marked kinetic preference for the correct bicyclic product was foreseen. As a protecting group, trityl was chosen as this was expected to be cleaved in situ during a Lewis acid catalyzed Diels–Alder reaction.

The aldehyde **5**, required for the Wittig-based route (Scheme 2), was prepared from ester **4** (enantiomeric purity of 97% ee) according to our previously published procedure starting with an iridium-catalyzed enantioselective allylic substitution.[9] The absolute configuration of ester **4** has been firmly established by chemical correlation with quinine.[10] The sulfone needed for the Julia-based route was prepared as follows. Reduction of **4** with DIBAL-H in THF furnished alcohol **6**. This was transformed by Mitsunobu reaction into the sulfide **7**, which was subjected to molybdenum-catalyzed oxidation with H_2O_2 to furnish the phenyltetrazolylsulfone **8**.

Of the two envisaged approaches to a conjugated diene, olefination of aldehyde **5** (Table 1) constitutes the shorter

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Scheme 2. Syntheses of the Chiral Building Blocks 5 and 8 (Σ = CPh_3)

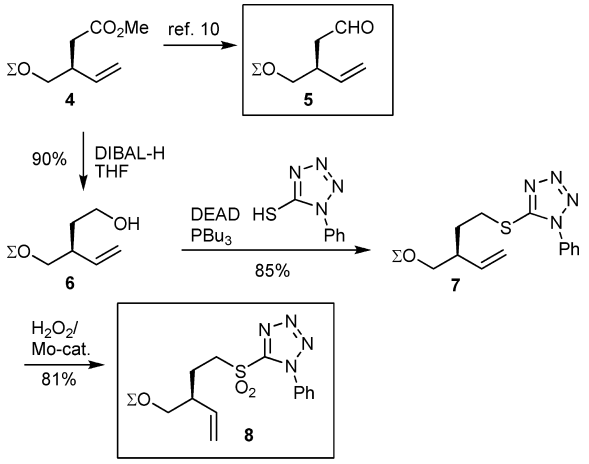
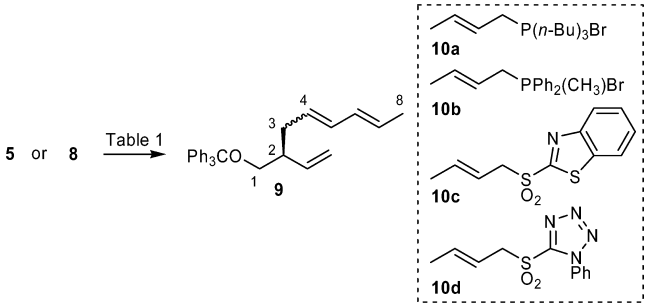


Table 1. Olefination Reactions[17]



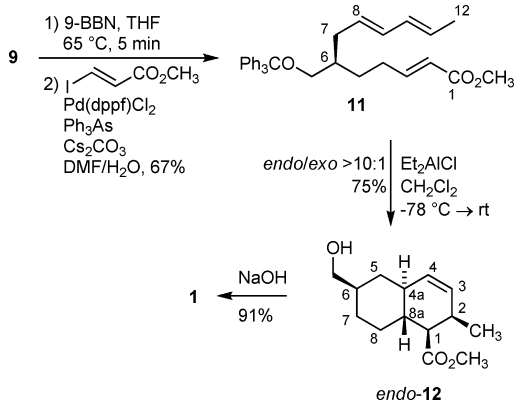
entry	conditions	yield[a] (%)	E/Z[b]
1	**5** + **10a**, KO-*t*-Bu, toluene, 0 °C[c]	83	64:36
2	**5** + **10b**, KO-*t*-Bu, THF, −20 °C[c]	77	57:43
3	**10c**, KHMDS, DME, then **5**, −78 °C → rt	90	50:50
4	**10c**, LiHMDS, DME, then **5**, −78 °C → rt	quant.	31:69
5	**5** + **10d**, KHMDS, DME, −78 °C → rt[c]	81	63:37
6	**10d**, LiHMDS, DME, then **5**, −78 °C → rt	62	60:40
7	**8**, LiHMDS, DME, then crotonaldehyde, −78 °C → rt	81	80:20
8	**8** + crotonaldehyde, KHMDS, DME, −78 °C → rt[c]	69[d]	94:6

[a]Isolated yield. [b]Determined by ^{1}H NMR. [c]The base was added to a solution of the other reactants. [d]83% based on recovered **8**.

route, and this was investigated first. As a rule, the Wittig olefination[11] of aldehydes with ylides derived from allylic triphenylphosphonium salts proceeds with low *Z*/*E* selectivity. Tamura et al. reported *E*-selective olefinations with allyltributylphosphonium salts;[12] this method gave excellent results in the preparation of *E*,*Z*-dienes.[13] In our hands, this procedure gave a 2:1 mixture of *E*/*Z*-isomers, which we could not separate (entry 1). The Wittig reaction starting with phosphonium salt **10b**[14] proceeded with even lower *E*/*Z* selectivity (entry 2). Julia−Kocienski olefinations[15] applying heteroarylsulfones **10c** and **10d**[16] also failed to give a useful level of selectivity (entries 3−6). The alternative route starting with tetrazole **8**, i.e., reaction of metalated sulfone **8** with crotonaldehyde under Barbier-type conditions, gave an excellent selectivity upon use of KHMDS as base (entry 8).

The enoate moiety was introduced via Suzuki coupling as follows (Scheme 3).[18] Hydroboration of **9** with 9-BBN and

Scheme 3. Suzuki−Miyaura and Intramolecular Diels−Alder Reactions

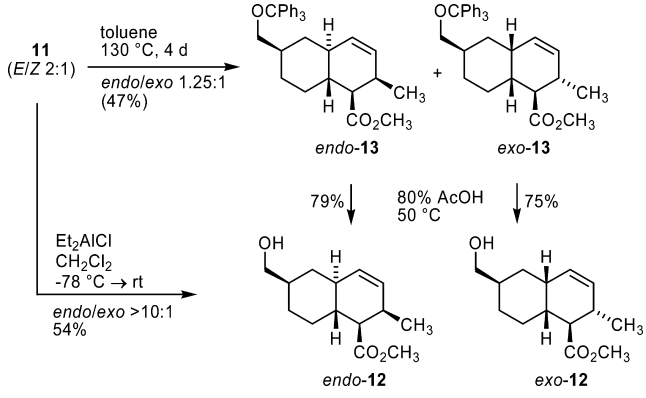


subsequent Suzuki coupling with methyl (2*E*)-3-iodoacrylate applying Pd(dppf)Cl_2/Ph_3As[19] as catalyst furnished ester **11** in good yield. A short reaction time (5 min) in the hydroboration step was crucial for success in this reaction. When a solution of **11** in CH_2Cl_2 at −78 °C was treated with Et_2AlCl, the mixture turned yellow immediately, which indicated formation of the trityl cation. Upon warming to rt, the Diels−Alder products **12** were formed slowly. ^{1}H NMR analysis showed that the diastereoselectivity of the reaction was excellent (*endo*-**12**/*exo*-**12** >10:1). Finally, saponification with NaOH gave apiosporic acid (**1**). Spectral data of synthetic **1** were identical to those of the natural product, thus confirming the assigned structure. The optical rotation of the synthetic material ($[\alpha]^{20}_D$ −96.8 (*c* 0.92, MeOH)) agreed with that reported for the natural product ($[\alpha]^{28}_D$ −103.6 (*c* 0.50, MeOH)).[3] The overall yield of **1** from **4** was 23%.

Cytotoxic properties of **1** against a standard set of human cancer cell lines were evaluated at the National Cancer Institute, Bethesda, MD; no significant activity was found (mean growth: 102%).

The cyclization was also carried out with a mixture of (8*E*)-**11** and (8*Z*)-**11** obtained by the Wittig olefination according to entry 1 of Table 1 and Suzuki coupling. Under Lewis acid catalyzed conditions, only (8*E*)-**11** underwent an intramolecular Diels−Alder reaction (Scheme 4). Thus, a chemical separation of the geometric isomers is possible in the cyclization step. A yield of 54% was achieved in the IMDA reaction, and the overall yield of **1** from **4** via this route was 26%. Thus, this route is shorter and proceeds in slightly higher

Scheme 4. Preparation of Reference Compounds



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overall yield than the route via **8**. In the thermal Diels–Alder reaction (Scheme 4), a low diastereoselectivity was observed (*endo*/*exo* 1.25:1). Cleavage of the trityl group under acidic conditions furnished *endo*-**12** and *exo*-**12** required for the characterization of the compounds of the *exo* series and determination of *endo*/*exo* selectivity.

In summary, we have presented the first enantioselective synthesis of the polyketide apiosporic acid. Key steps were a Julia–Kocienski olefination, a Suzuki–Miyaura reaction, and an intramolecular Diels–Alder reaction. The chiral starting material of known absolute configuration was prepared by iridium-catalyzed allylic alkylation. Thus, the absolute configuration of the natural product has been established.

EXPERIMENTAL SECTION

(3*S*)-3-[(Trityloxy)methyl]pent-4-en-1-ol (6). DIBAL-H (1 M in hexanes, 3.2 mL, 3.2 mmol) was added dropwise to a solution of **4** (497 mg, 1.29 mmol) in dry THF (10 mL) at −55 °C. Complete conversion was reached after 1 h [TLC: R_f(**4**) = 0.54, R_f(**6**) = 0.27, PE/EtOAc 3:1]. MeOH (0.5 mL) was added, and the solution was allowed to warm to rt. Saturated aqueous sodium potassium tartrate solution (10 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/EtOAc 3:1) yielded **6** (415 mg, 90%) as colorless oil: $[\alpha]^{20}_D$ +23.5 (*c* 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52–1.65 (2 H, m), 1.72–1.84 (1 H, m), 2.37–2.50 (1 H, m), 3.00–3.14 (2 H, m), 3.54–3.69 (2 H, m), 5.03–5.13 (2 H, m), 5.73 (1 H, ddd, *J* = 17.3, 10.1, 8.7 Hz), 7.18–7.33 (9 H, m), 7.40–7.47 (6 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.8 (CH_2), 41.9 (CH), 61.2 (CH_2), 67.1 (CH_2), 86.7 (C_q), 116.1 (CH_2), 127.1 (CH), 127.9 (CH), 128.8 (CH), 140.1 (CH), 144.3 (C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{25}H_{26}NaO_2$ [M + Na]$^+$ 381.18250, found 381.18217.

1-Phenyl-5-[[(3*S*)-3-[(trityloxy)methyl]pent-4-en-1-yl]thio]-1*H*-tetrazole (7). DEAD (40 wt % in toluene, 1.3 mL, 2.9 mmol) and PBu_3 (0.71 mL, 2.9 mmol) were added to a solution of **6** (415 mg, 1.16 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (405 mg, 2.3 mmol) in dry THF (15 mL) at 0 °C. Complete conversion was reached after 2 h [TLC: R_f(**6**) = 0.27, R_f(**7**) = 0.51, PE/EtOAc 3:1]. Water (20 mL) was added, and the solution was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/EtOAc 10:1) yielded **7** (512 mg, 85%) as colorless needles (mp 109–112 °C (EtOAc/PE)): $[\alpha]^{20}_D$ +17.8 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.75–1.84 (1 H, m), 2.10 (1 H, dddd, *J* = 13.5, 8.7, 7.4, 4.6 Hz), 2.39–2.48 (1 H, m), 3.04 (1 H, dd, *J* = 8.9, 6.5 Hz), 3.10 (1 H, dd, *J* = 9.0, 5.8 Hz), 3.23 (1 H, ddd, *J* = 13.0, 8.5, 7.5 Hz), 3.42 (1 H, ddd, *J* = 13.0, 8.9, 5.1 Hz), 5.08–5.15 (2 H, m), 5.69 (1 H, ddd, *J* = 17.1, 10.3, 8.7 Hz), 7.19–7.24 (3 H, m), 7.24–7.30 (6 H, m), 7.39–7.43 (6 H, m), 7.51–7.58 (5 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.7 (CH_2), 31.3 (CH_2), 43.9 (CH), 66.5 (CH_2), 86.6 (C_q), 117.3 (CH_2), 124.0 (CH), 127.1 (CH), 127.9 (CH), 128.8 (CH), 129.9 (CH), 130.2 (CH), 133.9 (C_q), 138.7 (CH), 144.2 (C_q), 154.4 (C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{32}H_{30}N_4NaOS$ [M + Na]$^+$ 541.20325, found 541.20317.

1-Phenyl-5-[[(3*S*)-3-[(trityloxy)methyl]pent-4-en-1-yl]-sulfonyl]-1*H*-tetrazole (8). Aqueous H_2O_2 (35 wt %, 1.2 mL, 14 mmol) was added to a suspension of **7** (511 mg, 985 μmol) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (241 mg, 195 μmol) in EtOH (10 mL) and EtOAc (2 mL). The mixture was stirred for 1 d at rt [TLC: R_f(**8**) = R_f(**7**) = 0.51, PE/EtOAc 3:1]. Water (30 mL) was added, and the solution was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/EtOAc 5:1) yielded **8** (440 mg, 81%) as colorless oil: $[\alpha]^{20}_D$ +10.1 (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88–1.97 (1 H, m), 2.20–2.28 (1 H, m), 2.40–2.48 (1 H, m), 3.04 (1 H, dd, *J* = 9.2, 6.9 Hz), 3.16 (1 H, dd, *J* = 9.2, 5.3 Hz), 3.61 (1 H, ddd, *J* = 14.6, 11.1, 6.3 Hz), 3.69 (1 H, ddd, *J* = 14.8, 11.2, 4.9 Hz), 5.13 (1 H, br d, *J* = 17.3 Hz), 5.17 (1 H, br d, *J* = 10.5 Hz), 5.66 (1 H, ddd, *J* = 17.3, 10.2, 8.6 Hz), 7.20–7.25 (3 H, m), 7.26–7.31 (6 H, m), 7.39–7.43 (6 H, m), 7.55–7.64 (3 H, m), 7.65–7.70 (2 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.8 (CH_2), 43.4 (CH), 54.4 (CH_2), 66.1 (CH_2), 86.8 (C_q), 118.2 (CH_2), 125.2 (CH), 127.2 (CH), 128.0 (CH), 128.8 (CH), 129.8 (CH), 131.6 (CH), 133.2 (C_q), 137.6 (CH), 144.0 (C_q), 153.6 (C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{32}H_{30}N_4NaO_3S$ [M + Na]$^+$ 573.19308, found 573.19301.

Trityl (2*S*,4*E*,6*E*)-2-Vinylocta-4,6-dien-1-yl Ether (9). Under an atmosphere of argon, KHMDS (0.5 M in toluene, 0.48 mL, 0.24 mmol) was added dropwise to a solution of **8** (101 mg, 184 μmol) and crotonaldehyde (23 μL, 0.28 mmol) in dry DME (2 mL) at −78 °C. The solution was allowed to warm to rt within 16 h when no further conversion was detected [TLC: R_f(**8**) = 0.34, R_f(**9**) = 0.80, PE/EtOAc 5:1]. Water (5 mL) was added, and the aqueous layer was separated and extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/EtOAc 20:1) yielded **9** (49.6 mg, 69%, 83% based on recovered **8**) as a colorless oil in addition to recovered **8** (17.1 mg, 17%). The ratio *E*/*Z* = 94:6 was determined by ^{1}H NMR: $[\alpha]^{20}_D$ +1.5 (*c* 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.71 (3 H, d, *J* = 6.4 Hz), 2.13 (1 H, dt, *J* = 14.3, 7.2 Hz), 2.28–2.40 (2 H, m), 2.99–3.08 (2 H, m), 4.99–5.06 (2 H, m), 5.35–5.45 (1 H, m), 5.48–5.59 (1 H, m), 5.72 (1 H, ddd, *J* = 17.4, 10.5, 7.9 Hz), 5.90–5.99 (2 H, m), 7.18–7.32 (9 H, m), 7.40–7.47 (6 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.2 (CH_3), 34.7 (CH_2), 44.7 (CH), 66.2 (CH_2), 86.4 (C_q), 115.6 (CH_2), 127.0 (CH), 127.2 (CH), 127.8 (CH), 128.9 (CH), 129.5 (CH), 131.7 (CH), 131.9 (CH), 140.1 (CH), 144.5 (C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{29}H_{30}NaO$ [M + Na]$^+$ 417.21889, found 417.21861.

Methyl (2*E*,6*R*,8*E*,10*E*)-6-[[(Triphenylmethyl)oxy]methyl]-dodeca-2,8,10-trienoate (11). Under an atmosphere of argon, a solution of **9** (391 mg, 991 μmol) and 9-BBN (247 mg, 2.03 mmol) in dry THF (8 mL) was heated at 65 °C. Complete conversion was reached after 5 min [TLC: R_f(**9**) = 0.80, R_f(**11**) = 0.59, PE/EtOAc 5:1]. After being cooled to rt, the solution was added to a suspension of Pd(dppf)Cl_2 (37 mg, 51 μmol), Ph_3As (30.9 mg, 101 μmol), Cs_2CO_3 (593 mg, 1.82 mmol), and methyl (2*E*)-3-iodoacrylate (238 mg, 1.11 mmol) in DMF/H_2O 15:1 (3 mL). The suspension was vigorously stirred at rt overnight. Then, water (10 mL) was added, and the solution was extracted with Et_2O (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/Et_2O 50:1) yielded **11** (315 mg, 66%) as a colorless oil: $[\alpha]^{20}_D$ +5.5 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.41–1.55 (2 H, m), 1.61–1.68 (1 H, m), 1.73 (3 H, d, *J* = 6.5 Hz), 1.95–2.08 (2 H, m), 2.13 (1 H, dt, *J* = 13.8, 6.9 Hz), 2.25 (1 H, dt, *J* = 13.8, 6.9 Hz), 2.96 (1 H, dd, *J* = 9.1, 5.5 Hz), 3.05 (1 H, dd, *J* = 9.0, 4.7 Hz), 3.71 (3 H, s), 5.38 (1 H, dt, *J* = 14.1, 7.0 Hz), 5.55 (1 H, dq, *J* = 13.3, 6.6 Hz), 5.71 (1 H, d, *J* = 15.6 Hz), 5.88–6.03 (2 H, m), 6.88 (1 H, dt, *J* = 15.6, 6.9 Hz), 7.20–7.34 (9 H, m), 7.40–7.49 (6 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.2 (CH_3), 29.6 (CH_2), 29.7 (CH_2), 35.0 (CH_2), 38.9 (CH), 51.5 (CH_3), 64.5 (CH_2), 86.4 (C_q), 121.0 (CH), 127.0 (CH), 127.3 (CH), 127.9 (CH), 128.9 (CH), 129.5 (CH), 131.7 (CH), 132.3 (CH), 144.4 (C_q), 149.7 (CH), 167.2 (C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{33}H_{36}NaO_3$ [M + Na]$^+$ 503.25567, found 503.25533.

Methyl (1*R*,2*R*,4a*S*,6*R*,8a*R*)-6-Hydroxy-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (*endo*-12). Et_2AlCl (1.8 M in toluene, 0.18 mL, 0.32 mmol) was added dropwise to a solution of **11** (50 mg, 104 μmol) in dry CH_2Cl_2 (1.5 mL) at −78 °C. The solution was allowed to warm to rt. Complete conversion was reached after 22 h [TLC: R_f(**11**) = 0.77, R_f(*endo*-**12**) = 0.39, PE/EtOAc 1:1]. Water (5 mL) was added dropwise; the aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/EtOAc 1:1) yielded *endo*-**12** (18.7 mg, 75%) as a colorless oil. The ratio *endo*/*exo* > 10:1 was determined by ^{1}H NMR: $[\alpha]^{20}_D$ −70.2 (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (1 H, q, *J* = 12.4 Hz), 0.90 (3 H, d, *J* = 6.9 Hz), 0.92–0.99 (1 H, m), 1.09 (1 H, qd, *J* = 12.9, 3.7 Hz), 1.41 (1 H,

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qd, J = 11.2, 2.8 Hz), 1.56−1.68 (2 H, m), 1.71−1.81 (1 H, m), 1.81−1.88 (2 H, m), 2.01 (1 H, dq, J = 12.4, 3.0 Hz), 2.52−2.61 (2 H, m), 3.44−3.52 (2 H, m), 3.68 (3 H, s), 5.41 (1 H, d, J = 9.9 Hz), 5.58 (1 H, ddd, J = 9.8, 3.9, 2.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.0 (CH_3), 29.65 (CH_2), 29.68 (CH_2), 32.7 (CH), 36.1 (CH_2), 36.8 (CH), 41.0 (CH), 41.6 (CH), 49.7 (CH), 51.4 (CH_3), 68.7 (CH_2), 130.9 (CH), 131.4 (CH), 174.6 (C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{14}H_{22}NaO_3$ $[M + Na]^+$ 261.14612, found 261.14613.

(1*R*,2*R*,4a*S*,6*R*,8a*R*)-6-(Hydroxymethyl)-2-methyl-1,2,4a,5,6,7,8,8a-octahydro-1-naphthalenecarboxylic Acid (Apiosporic Acid, 1). Aqueous NaOH (1 M, 5 mL) was added to a solution of *endo*-**12** (84 mg, 0.35 mmol) in MeOH (2 mL). Complete conversion was reached after 27 h at rt [TLC: R_f(*endo*-**12**) = 0.39, R_f(**1**) = 0.22, PE/EtOAc 1:1]. The solution was acidified with HCl (1 M, 1 mL) until pH 2 was reached. The solution was extracted with ethyl acetate (5 × 15 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/EtOAc 1:1) yielded **1** (72.5 mg, 91%) as colorless needles: $[\alpha]^{20}_D$ −96.8 (*c* 0.92, MeOH) [lit.[3] $[\alpha]^{28}_D$ −103.6 (*c* 0.50, MeOH)]; ^{1}H NMR (acetone-d_6, 500 MHz) δ 0.79 (1 H, q, J = 12.5 Hz), 0.94 (3 H, d, J = 6.9 Hz), 0.90−1.00 (1 H, m), 1.04 (1 H, qd, J = 12.4, 3.4 Hz), 1.28−1.37 (1 H, m), 1.52−1.63 (1 H, m), 1.72−1.79 (1 H, m), 1.82−1.89 (2 H, m), 2.11 (1 H, dd, J = 12.1, 3.1 Hz), 2.53 (1 H, dd, J = 11.4, 6.0 Hz), 2.55−2.60 (1 H, m), 2.60−3.90 (1 H, br s), 3.38 (2 H, dd, J = 6.2, 1.9 Hz), 5.41 (1 H, d, J = 9.9 Hz), 5.59 (1 H, ddd, J = 9.8, 4.2, 2.8 Hz), 9.60−11.50 (1 H, br s); ^{13}C NMR (acetone-d_6, 125 MHz) δ 18.0 (CH_3), 30.1 (CH_2), 30.2 (CH_2), 33.0 (CH), 37.0 (CH_2), 37.5 (CH), 41.9 (CH), 42.2 (CH), 49.7 (CH), 68.1 (CH_2), 131.7 (CH), 131.8 (CH), 174.7 (C_q); HR-MS (FT-ICR-ESI-) calcd for $C_{13}H_{19}O_3$ $[M - H]^-$ 223.13397, found 223.13413.

Methyl (1*R*,2*R*,4a*S*,6*R*,8a*R*)-2-Methyl-6-[[(triphenylmethyl)oxy]methyl]-1,2,4a,5,6,7,8, 8a-octahydronaphthalene-1-carboxylate (*endo*-13) and Methyl (1*R*,2*S*,4a*R*,6*R*,8a*R*)-2-Methyl-6-[[(triphenylmethyl)oxy]methyl]-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (*exo*-13).

Thermal Intramolecular Diels−Alder Reaction. A solution of **11** (349 mg, 727 μmol, (8*E*)-**11**/(8*Z*)-**11** = 2:1) and di-*tert*-butylhydroquinone (0.5 mg) in dry and degassed toluene (8 mL) was heated at 130 °C in a sealed tube. No further conversion was detected after 4 d [TLC: R_f(**11**) = 0.25, R_f(*endo*-**13**) = R_f(*exo*-**13**) = 0.31, PE/EtOAc 20:1]. The solvent was removed in vacuo, and the residue was subjected to flash chromatography (silica, PE/EtOAc 50:1) to yield a mixture of *endo*-**13** and *exo*-**13** (164 mg, 47%). The ratio *endo*-**13**/*exo*-**13** = 1.25:1 was determined by ^{1}H NMR. Further purification by preparative HPLC (silica, PE/Et_2O 50:1) yielded *endo*-**13** (92 mg, 26%) as colorless needles (mp 126−129 °C (Et_2O/PE)) and *exo*-**13** (61 mg, 17%) as a colorless oil.

endo-**13**: $[\alpha]^{20}_D$ +20.5 (*c* 1.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.82−1.00 (2 H, m), 0.90 (3 H, dd, J = 6.8, 0.8 Hz), 1.12 (1 H, qd, J = 12.6, 2.9 Hz), 1.39 (1 H, q, J = 10.9 Hz), 1.71−1.85 (2 H, m), 1.85−1.94 (2 H, m), 1.98 (1 H, d, J = 12.4 Hz), 2.52−2.62 (2 H, m), 2.83−2.96 (2 H, m), 3.68 (3 H, d, J = 0.6 Hz), 5.42 (1 H, d, J = 9.9 Hz), 5.53−5.57 (1 H, m), 7.23 (3 H, t, J = 7.3 Hz), 7.29 (6 H, t, J = 7.7 Hz), 7.44 (6 H, dd, J = 8.4, 0.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.9 (CH_3), 29.6 (CH_2), 30.2 (CH_2), 32.5 (CH), 36.58 (CH), 36.62 (CH_2), 39.0 (CH), 41.6 (CH), 49.5 (CH), 51.2 (CH_3), 68.6 (CH_2), 86.2 (C_q), 126.9 (CH), 127.8 (CH), 128.9 (CH), 130.9 (CH), 131.1 (CH), 144.6 (C_q), 174.5 (C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{33}H_{36}NaO_3$ $[M + Na]^+$ 503.25567, found 503.25558.

exo-**13**: $[\alpha]^{20}_D$ +14.6 (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.98 (3 H, d, J = 7.1 Hz), 1.21−1.27 (1 H, m), 1.30−1.35 (1 H, m), 1.35−1.40 (1 H, m), 1.41−1.47 (1 H, m), 1.53−1.69 (2 H, m), 1.90−1.97 (2 H, m), 1.99−2.05 (1 H, m), 2.39 (1 H, t, J = 9.0 Hz), 2.46−2.53 (1 H, m), 3.05−3.09 (2 H, m), 3.69 (3 H, s), 5.41 (1 H, dt, J = 10.0, 1.5 Hz), 5.47 (1 H, ddd, J = 9.9, 3.7, 2.8 Hz), 7.23 (3 H, tt, J = 7.1, 1.1 Hz), 7.27−7.31 (6 H, m), 7.43−7.47 (6 H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.7 (CH_3), 23.7 (CH_2), 24.7 (CH_2), 31.4 (CH), 31.6 (CH_2), 33.5 (CH), 34.1 (CH), 36.1 (CH), 47.9 (CH), 51.6 (CH_3), 64.7 (CH_2), 86.2 (C_q), 127.0 (CH), 127.8 (CH), 128.9 (CH), 130.8 (CH), 131.1 (CH), 144.5 (C_q), 176.8 (C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{33}H_{36}NaO_3$ $[M + Na]^+$ 503.25567, found 503.25558.

Methyl (1*R*,2*R*,4a*S*,6*R*,8a*R*)-6-Hydroxy-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (*endo*-12).

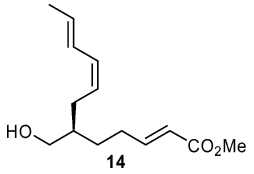
Removal of Trityl Group. A solution of *endo*-**13** (107.0 mg, 223 μmol) in 80% aqueous acetic acid (3 mL) was heated at 50 °C. Complete conversion was reached after 45 min [TLC: R_f(*endo*-**13**) = 0.81, R_f(*endo*-**12**) = 0.39, PE/EtOAc 1:1]. The solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O (4 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/EtOAc 5:1) yielded *endo*-**12** (42.1 mg, 79%) as a colorless oil.

Methyl (1*R*,2*S*,4a*R*,6*R*,8a*R*)-6-Hydroxy-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (*exo*-12).

Removal of Trityl Group. A solution of *exo*-**13** (154 mg, 320 μmol) in 80% aqueous acetic acid (4 mL) was heated at 50 °C. Complete conversion was reached after 1 h [TLC: R_f(*exo*-**13**) = 0.76, R_f(*exo*-**12**) = 0.22, PE/EtOAc 3:1]. The solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, PE/EtOAc 3:1) yielded *exo*-**12** (57.6 mg, 75%) as colorless needles (mp 94−96 °C (EtOAc/PE)): $[\alpha]^{20}_D$ −11.1 (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (3 H, d, J = 7.2 Hz), 1.29−1.44 (3 H, m), 1.52−1.60 (3 H, m), 1.61−1.69 (1 H, m), 1.78−1.86 (1 H, m), 2.06 (1 H, dq, J = 9.4, 4.7 Hz), 2.19−2.26 (1 H, m), 2.39 (1 H, dd, J = 9.4, 8.6 Hz), 2.48−2.56 (1 H, m), 3.58−3.63 (2 H, m), 3.69 (3 H, s), 5.44 (1 H, dt, J = 9.9, 1.8 Hz), 5.53 (1 H, ddd, J = 9.9, 4.0, 2.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.7 (CH_3), 23.3 (CH_2), 24.7 (CH_2), 31.0 (CH_2), 31.3 (CH), 33.9 (CH), 35.7 (CH), 36.2 (CH), 48.1 (CH), 51.6 (CH_3), 64.8 (CH_2), 130.8 (CH), 131.0 (CH), 176.7(C_q); HR-MS (FT-ICR-ESI+) calcd for $C_{14}H_{22}NaO_3$ $[M + Na]^+$ 261.14612, found 261.14613.

Methyl (1*R*,2*R*,4a*S*,6*R*,8a*R*)-6-Hydroxy-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (*endo*-12).

Lewis Acid Catalyzed Intramolecular Diels−Alder Reaction Starting from a Mixture of (8E)-11 and (8Z)-11. Et_2AlCl (1.8 M in toluene, 1.1 mL, 1.98 mmol) was added dropwise to a solution of **11** (314.9 mg, 0.66 mmol, (8*E*)-**11**/(8*Z*)-**11** = 2:1) in dry CH_2Cl_2 (6 mL) at −78 °C. The solution was allowed to warm to rt. Complete conversion was reached after 65 h [TLC: R_f(**11**) = 0.77, R_f(**12**) = 0.44, R_f(**14**) = 0.47, PE/EtOAc 1:1]. Water (6 mL) and saturated aqueous potassium sodium tatrate (3 mL) were added, and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was subjected to flash chromatography on silica (PE/EtOAc 1:1) to yield a mixture of *endo*-**12** and **14**, which was dissolved in THF (4 mL). The solution was treated with aqueous LiOH (1 M, 10 mL). Complete consumption of **14** was reached after 45 min (TLC). The solution was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica (PE/EtOAc 3:1) yielded *endo*-**12** (83.5 mg, 54%) as a colorless oil. The ratio *endo*-**12**/*exo*-**12** >10:1 was determined by ^{1}H NMR.



14

■ ASSOCIATED CONTENT

Supporting Information

Determination of diastereoselectivities, ^{1}H and ^{13}C NMR spectra of all new compounds, and test results from the

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National Cancer Institute, Bethesda, MD, for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Review: Tan, R. X.; Zou, W. X. *Nat. Prod. Rep.* **2001**, *18*, 448−459.
(2) Alfatafta, A. A.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **1994**, *57*, 1696−1702.
(3) Klemke, C.; Kehraus, S.; Wright, A. D.; König, G. M. *J. Nat. Prod.* **2004**, *67*, 1058−1063.
(4) Shibazaki, M.; Taniguchi, M; Yokoi, T.; Nagai, K.; Watanabe, M.; Suzuki, K.; Yamamoto, T. *J. Antibiot.* **2004**, *57*, 379−382.
(5) Williams, D. R.; Kammler, D. C.; Donnell, A. F.; Goundry, W. R. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 6715−6718.
(6) Reviews: (a) Roush, W. R. In *Advances In Cycloadditions*; Curran, D. P., Ed.; JAI Press.: London, 1990; Vol. 2, pp 91−146. (b) Brocksom, T. J.; Nakamura, J.; Ferreira, M. L.; Brocksom, U. *J. Braz. Chem. Soc.* **2001**, *12*, 597−622. (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−4807. (d) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983−2992.
(7) For a related example, see: Witter, D. J.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 2613−2623.
(8) Reviews: (a) Takeuchi, R. *Synlett* **2002**, *12*, 1954−1965. (b) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, *20*, 3349−3366. (c) Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R.; Helmchen, G. *Chem. Commun.* **2007**, 675−691. (d) Helmchen, G. In *Iridium Complexes in Organic Synthesis*; Oro, L. A., Claver, C., Eds.; Wiley-VCH: Weinheim, 2009; pp 211−250. (e) Förster, S.; Helmchen, G.; Kazmaier, U. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; Wiley: Hoboken, 2010; pp 497−641. (f) Stanley, L. M.; Hartwig, J. F. *Acc. Chem. Res.* **2010**, *43*, 1461−1475. (g) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organomet. Chem.* **2012**, *38*, 155. (h) Catalyst preparation: Raskatov, J. A.; Spiess, S.; Gnamm, C.; Brödner, K.; Rominger, F.; Helmchen, G. *Chem.—Eur. J.* **2010**, *16*, 6601−6615.
(9) Franck, G.; Brödner, K.; Helmchen, G. *Org. Lett.* **2010**, *12*, 3886−3889.
(10) Gnamm, C.; Förster, S.; Miller, N.; Brödner, K.; Helmchen, G. *Synlett* **2007**, 790−794.
(11) Review: Vedejs, E.; Peterson, M. J. In *Topics In Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons, Inc.: New York, 1994; Vol. *21*, pp 1−157.
(12) (a) Tamura, R.; Kato, M.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1987**, *52*, 4121−4124. (b) Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723−2728.
(13) Brodmann, T.; Janssen, D.; Kalesse, M. *J. Am. Chem. Soc.* **2010**, *132*, 13610−13611.
(14) Wenfang, H.; Jun, Z.; Wenjing, J.; Yanneng, D. *Phosphorus, Sulfur, Silicon* **1989**, *46*, 99−104.
(15) Reviews: (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2553−2585. (b) Aissa, C. *Eur. J. Org. Chem.* **2008**, 1831−1844.
(16) Jervis, P. J.; Cox, L. R. *J. Org. Chem.* **2008**, *73*, 7616−7624.
(17) The olefination reagents **10** were prepared from crotyl bromide.
(18) Reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (c) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568.
(19) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015.