First Total Synthesis of Aspinolide B, a New Pentaketide Produced by *Aspergillus ochraceus*

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The first asymmetric total synthesis of Aspinolide B (**1**), a new 10-membered lactone discovered by chemical screening methods in the cultures of *Aspergillus ochraceus*, has been accomplished. The key steps included a selective Felkin-type addition of TMS-acetylene to aldehyde **3a** and a Nozaki−Hiyama−Kishi coupling reaction to build the required 10-membered ring. This synthesis confirmed the absolute stereochemistry of aspinolide B, established through Helmchen's method and corrected its previously reported specific optical rotation.

Introduction

Aspinolide B (**1**) is a new decanolide produced from cultures of *Aspergillus ochraceus*,[1] a class of lactones that has received special attention over the last years.[2] While the relative stereochemistry was established by X-ray analysis,[1] its absolute stereochemistry was assigned after establishing its 4*S* configuration by Helmchen's method.[3] Other representative members of the 10-membered lactones are decarestrictine D,[4] phoracantolide I,[5] and achaetolide (Figure 1).[6]

The synthesis of medium-sized lactones may be a difficult challenge particularly in cases in which destabilizing nonbonded, transannular interactions, and unfavorable entropic factors must be overcome.[7] Taking into account that the previous approaches to 10-membered lactones have generally relied on esterification/lactonization strategy to construct the macrolide core, we considered a novel strategy to 10-membered lactones based on the formation of a C−C bond as the final maneuver in the formation of the macrolide.[8] Recent success in the simultaneous formation of the C6−C7 bond and installation of the correct configuration at C7 in the total synthesis of decarestrictine D[9] prompted the decision to employ the intramolecular Nozaki−Hiyama−Kishi reaction in the formation of the C7−C8 bond in the synthesis of aspinolide **1**. Vinylic iodide **2** was conceived

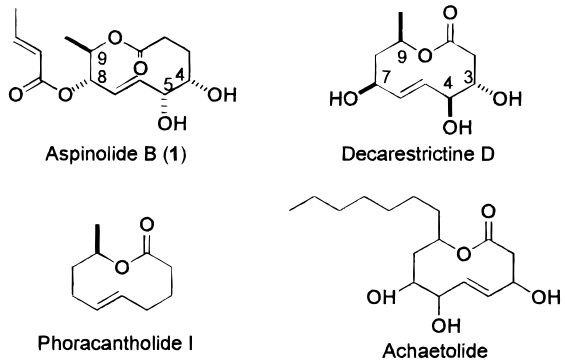

Figure 1. Some ten-membered lactone natural products.

to undergo an intramolecular Nozaki−Hiyama−Kishi reaction to provide the decanolide moiety of aspinolide B (**1**). Access to this intermediate would be secured by esterification of the corresponding carboxylic acid and a secondary alcohol derived from (*R*)-lactic acid. The C1−C7 fragment was planned to be prepared from aldehyde **3a** or **3b** by a stereocontrolled addition of a two-carbon fragment in order to set the proper configuration at C5. Finally, aldehydes **3a** and **3b** would be obtained from optically pure lactone **4** (Scheme 1).

Results and Discussion

The synthesis of the C1−C7 carboxylic acid fragment of **1** requires the preparation of a glycol, which may be approached through the Felkin-type addition of lithiated TMS-acetylene or an equivalent vinylic species to an α-hydroxy aldehyde under nonchelation control.[10]

Protection of lactone **4**[11] as its *p*-methoxybenzyl (PMB) ether[12] was performed in Et_2O with triflic acid (TfOH) as a catalyst (81% yield). Reduction of PMB ether **5** with $LiAlH_4$ afforded the monoprotected triol **6a** in 93% yield

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(2) For recent reviews see: (a) Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365. (b) Collins, I. *J. Chem. Soc., Perkin. Trans. 1* **1999**, 1377.
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(11) Obtained from (*S*)−(+)-glutamic acid in two steps: (i) $NaNO_2$, HCl, H_2O; (ii) $Me_2S{\cdot}BH_3$, THF. Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449.
(12) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

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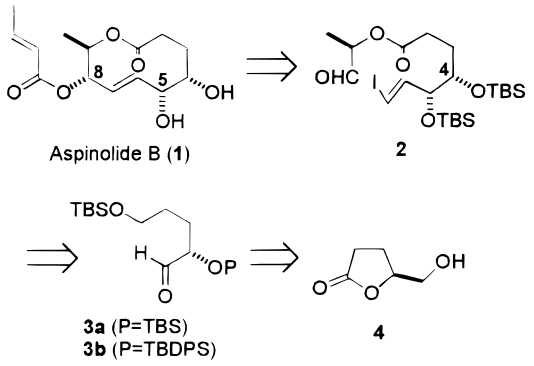
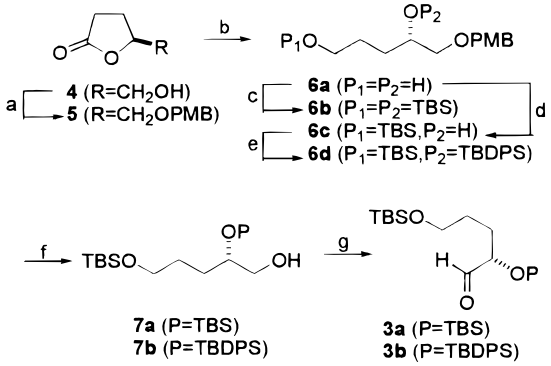
Scheme 1



Scheme 2[a]



[a] (a) PMB-acetimidate, Et_2O, TfOH (cat.) (81%); (b) $LiAlH_4$, THF (93%); (c) TBSCl, DMF, imidazole (99%); (d) TBSCl, DMAP, Et_3N, CH_2Cl_2 (93%); (e) TBDPSCl, DMF, imidazole (93%); (f) DDQ, CH_2Cl_2:H_2O (20:1), 0 °C (92% for **6b**; 94% for **6d**); (g) TPAP, NMO, 4A MS, CH_2Cl_2 (90% for **7a**; 85% for **7b**).

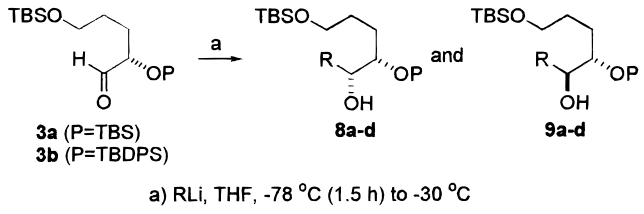


Figure 2. Nucleophilic addition to aldehydes **3a**,**b**.

which was converted to the corresponding bis-TBS ether **6b** in DMF and imidazole (99% yield). The *p*-methoxybenzyl group in **6b** was removed with DDQ to give alcohol **7a** in 92% yield. Oxidation with tetrapropylammonium perruthenate (TPAP)[13] afforded aldehyde **3a** in 90% yield. Alternatively, **6a** was protected as its mono-TBS ether **6c** in 93% yield when the reaction was carried out in CH_2Cl_2. The fully protected triol **6d** was obtained in 93% yield from **6c** after protection of the secondary hydroxyl group with TBDPSCl in DMF and converted to **3b** (two steps, 80% overall yield) through the same reaction sequence described for **3a** (Scheme 2).

The next step included the diastereoselective addition of a two-carbon nucleophile to aldehydes **3a** and **3b** (Figure 2). According to Guanti et al.,[10] under nonchelation control (TBDPS as the protecting group of the α-hydroxy group) stereoselective anti addition (83:17 ratio) of lithium trimethylsilylacetylide to (*R*)-O-*tert*-butyldiphenylsilyl lactaldehyde was achieved. We decided

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Table 1. Selectivity in the Addition of Nucleophile to Aldehyde

entry	aldehyde	P	R	Yield (%)	Ratio **8**:**9**[a]
1	**3a**	TBS	TMS—	81	**8a**:**9a** (11.5:1)
2	**3a**	TBS	Bu_3Sn	44	**8b**:**9b** (2.2:1)
3	**3b**	TBDPS	TMS—	67	**8c**:**9c** (2:1)[b]
4	**3b**	TBDPS	Bu_3Sn	62	**8d**:**9d** (1.5:1)[b]

[a] Determined by GC analysis. [b] Determined after protection with TBDPSCl.

to evaluate the addition of the lithium anions of trimethylsilylacetylene and *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene[14] to the TBS- and TBDPS-protected dihydroxy aldehydes **3a** and **3b**. Our results are summarized above (Table 1).

Our results indicated that the addition of the lithium derivatives of 1-tri-*n*-butyl vinylstannane and trimethylsilylacetylene to **3b** (Table 1, entries 3 and 4) can be used to homologate the carbon chain, but with low diastereoselection (up to 2:1). Moreover, scrambling of the TBDPS-silyl protecting group leading to mixtures of silyl ethers at C3 and C4 was observed, which required conversion to the corresponding bis-silyl ethers prior to the determination of the diastereoisomeric ratio. When the addition was performed to **3a**, the lithium derivative of 1-tri-*n*-butyl vinylstannane surprisingly gave low anti selectivity (Table 1, entry 2) while lithium trimethylsilylacetylide (Table 1, entry 1) assured both good yield and anti selectivity. The reason for the higher selectivity observed for **3a** in comparison with the results described for lactaldehyde may result from the bulkier nature of the $(CH_2)_3OTBS$ group in **3a** when compared with the methyl group in (*R*)-*O*-*tert*-butyldiphenylsilyl lactaldehyde. However, the origin of the higher selectivity in the addition of lithium trimethylsilylacetylide to **3a** when compared to the addition to **3b** is not clear at this moment. The assignment of anti stereochemistry to the major isomer required the transformation[15] of the crude mixture of diastereoisomers **8a/9a** to the corresponding mixture of ketal **10a** and its C5 epimer: a 2.2% increment in the H4 signal of **10a** was observed upon irradiation of H5 and supported the anti stereochemistry assigned for the major stereoisomer **8a** (Figure 3).The anti relative stereochemistry of the majors isomers **8b**−**d** was tentatively assigned after **8a**.

(14) Obtained in two steps from acetylene and tributyltin chloride: (i) acetylene, THF, −78 °C, then *n*-BuLi and *n*-Bu_3SnCl 78% (Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432); (ii) ethynyl(tributyl)-tin, *n*-BuSnH, AIBN 96% (Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581).

(15) (i) TBSCl, imidazole, DMF; (ii) $AgNO_3$, THF, EtOH, H_2O, KCN; (iii) Ac_2O, DMAP, Et_3N, CH_2Cl_2; (iv) TBAF, THF; (v) 2,2-dimethoxypropane, DMF, TsOH; (vi) K_2CO_3, MeOH.

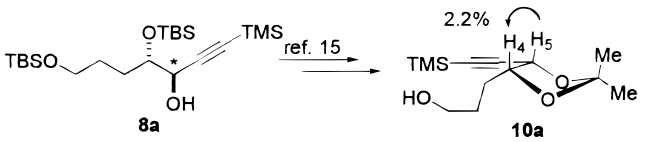


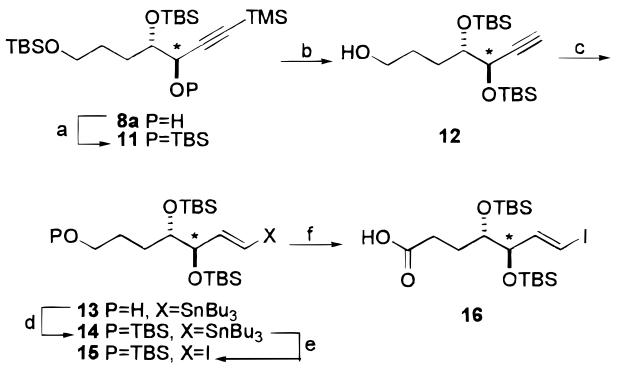
Figure 3.

Having selected an attractive methodology to set the proper configuration at C5 in **8a**, protection of the hydroxyl group with TBSCl afforded the fully silylated triol **11** in quantitative yield. Treatment of **11** with $AgNO_3$ in THF/H_2O/EtOH, conditions adapted from those described by Nicolaou and Webber,[16] selectively removed the acetylenic TMS as well as the primary TBS protecting group. This transformation occurred in 93% yield to provide acetylenic alcohol **12**. The required transformation of the terminal acetylenic moiety to the corresponding (*E*)-vinyl iodide was initially carried out under palladium catalysis [$Cl_2Pd(PPh_3)_2$],[17] as described by Guibé et al.,[18] followed by iodide exchange to afford the product in 69% yield. Unfortunately, the desired (*E*)-vinyl iodide was obtained along with its regioisomer and the corresponding terminal olefin in a 81:10:9 ratio, respectively. The desired transformation was successfully carried out by radical stannylation with $^nBu_3SnH$ and AIBN as catalyst, which afforded vinyl stannane **13** in 78% yield as a single isomer. Attempts to convert **13** directly to the corresponding iodide proved difficult. Initially tin−iodide exchange (I_2, CCl_4) was performed in low yields (up to 38%) when **13** was employed, and the separation of tin-containing side-products was tedious. These problems were circumvented by protection of the free hydroxyl group with TBSCl (89% yield) which led to nonpolar silylated compound **14** and allowed us to employ the tin-removal protocol with 1 M aqueous NaOH solution.[19] Tin−iodide exchange was performed in 86% yield when **14** was employed to give iodide **15**, which was converted to the required carboxylic acid **16** in 89% yield after an one-pot desilylation−oxidation sequence.[20] The conversion of **8a** to **16** was carried out with mixtures containing less than 10% of the minor isomer at the assigned position (Scheme 3).

The synthesis of lactate derivative **21** containing the C8−C10 fragment was readily accomplished starting from (*R*)-methyl lactate (**17**). Protection of **17** with TBSCl (90% yield) afforded silyl ether **18** which was reduced (DIBAL-H, CH_2Cl_2, 0 °C) to produce monoprotected diol **19** in 50% yield. Following protection as the *p*-methoxybenzyl **20** (69% yield), desilylation with TBAF in THF afforded C8−C10 fragment **21** in 91% yield (Scheme 4).

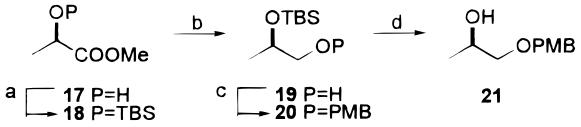
The coupling of the C1−C7 fragment **16** and the C8−C10 fragment **21** was initially performed employing diisopropylcarbodiimide (DIC) in CH_2Cl_2 which afforded ester **22** in 61%. However, better results were achieved under Yamaguchi conditions[21] to give crude ester **22**, which required careful purification by flash chromatography on silica gel to furnish isomerically pure ester **22** in 71% yield along with the C5 epimer as a minor component (4% yield). Deprotection of the PMB ether in **22** upon treatment with DDQ afforded alcohol **23** in 84% yield. At this point we were ready to carry out the key step in the synthetic plan: Dess−Martin periodinane oxidation of **23** gave aldehyde **2**, which was treated without prior purification with excess $CrCl_2$ (15 equiv)[22] containing 0.5% of $NiCl_2$ in DMF (0.005 M). A smooth reaction ensued to afford a 1.5:1 mixture of diastereoisomeric allylic alcohols **24a/24b** in 49% yield over two steps.[23] The lack of facial selectivity in the Nozaki−Hiyama−Kishi reaction was circumvented as the chromatographic separation of the 8*R*-epimer **24b** allowed its conversion to the 8*S*-epimer **24a** by Mitsunobu inversion[24] (*p*-nitrobenzoic acid, triphenylphosphine, and diethyl azodicarboxylate) to give a *p*-nitrobenzoate ester, which was hydrolyzed with potassium carbonate in methanol in 56% overall yield. Esterification of **24a** with crotonic acid (diisopropylcarbodiimide in CH_2Cl_2) afforded the corresponding ester **25** in 89% yield. Synthetic (−)-aspinolide B (**1**) was obtained after desilylation of **25** upon treatment with HF·pyridine complex in THF at room temperature in 46% yield (Scheme 5). The synthetic material proved to be spectroscopically identical (^1H and ^{13}C NMR and IR) with an authentic sample kindly provided by Prof. Zeeck. However, the specific optical rotation of the synthetic sample ($[\alpha]_D$ −44.0 (*c* 1.0,

Scheme 3[a]



[a] (a) TBSCl, DMF, imidazole (100%); (b) $AgNO_3$, EtOH, THF, H_2O, then KCN (93%); (c) $HSnBu_3$, AIBN (cat.), 90 °C (78%); (d) TBSCl, Et_3N, DMAP (cat.), CH_2Cl_2 (89%); (e) I_2, CCl_4 then CH_2Cl_2, NaOH (86%); (f) Jones reagents, acetone, 0 °C (89%).

Scheme 4[a]



[a] (a) TBSCl, DMF, imidazole (90%); (b) DIBAL-H, CH_2Cl_2, 0 [a]C (50%); (c) PMB-trichloroacetimidate, Et_2O, TfOH (cat.) (69%); (d) TBAF, THF (91%).

(16) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.
(17) Miyaura, N.; Suzuki, A. *Org. Synth.* **1990**, *68*, 130.
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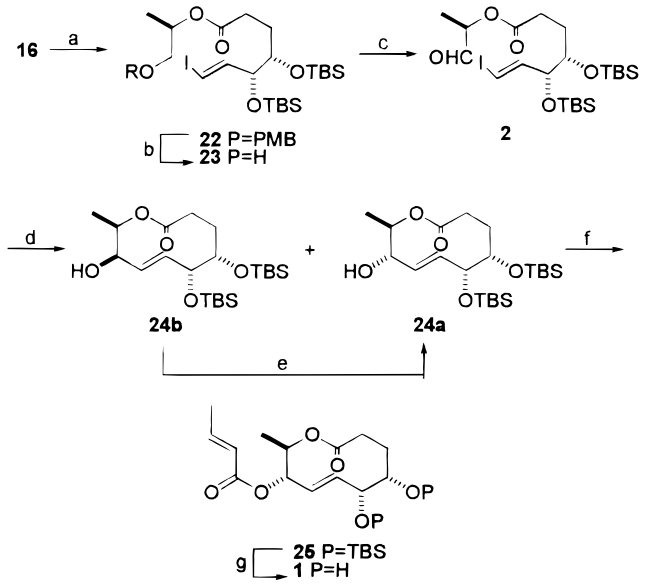
(21) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(22) The Nozaki−Hiyama−Kishi coupling experiments were carried out with $CrCl_2$ purchased from Merck Schuchardt or Aldrich (>99.9%) and dried at 1 mmHg and 250 °C for 4 h immediately prior to use.
(23) The stereochemistry at C8 was assigned on basis of ^1H NMR data of aspinolide B which displays H8 at 4.94 ppm as a double dublet (J = 9.0, 8.0 Hz), characteristic of trans diaxial orientation. In comparison, H8 in **24a** (δ 3.83 ppm) appears as double triplet (J = 8.5, 8.5, 5.0 Hz) while in **24b** (δ 4.30 ppm) as a singlet.
(24) Mitsunobu reaction carried out with crotonic acid instead of *p*-NBA was unsucessfull.

Scheme 5[a]



[a] (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then **21**, DMAP, benzene (71%); (b) DDQ, CH_2Cl_2:H_2O (20:1), 0 °C (84%); (c) Dess−Martin periodinane, CH_2Cl_2, H_2O (cat.); (d) $CrCl_2$/$NiCl_2$ (0.5%), DMF, 0.005 M (49% for two steps); (e) (i) *p*-NBA, DEAD, PPh_3, benzene; (ii) K_2CO_3, MeOH (56% over two steps); (f) crotonic acid, DIC, CH_2Cl_2 (89%); (g) HF·pyridine complex, pyridine, THF (46%).

MeOH)) differed from the previously reported value for natural aspinolide B ($[\alpha]_D$ −19.1 (*c* 1.0, MeOH)).[1,25]

In conclusion, the first asymmetric total synthesis of (−)-aspinolide B was achieved in 19 steps and 2.4% overall yield from **4**. Homologation of aldehyde **3a** was performed in good yield and selectivity, efficiently providing *anti*-diol **8a**. The Nozaki−Hiyama−Kishi coupling reaction proved to be useful for the construction of 10-membered ring lactones **24a** and **24b**, despite the low facial selectivity. Studies are underway aimed to control the stereochemical outcome of this reaction when applied to the formation of medium- and large-ring lactones.

Experimental Section

General. Melting points are uncorrected. Unless otherwise stated, all reactions were run under a nitrogen atmosphere. Anhydrous solvents were freshly distilled before use: diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from sodium and stored over 4A molecular sieve. Methylene chloride and triethylamine were distilled from CaH_2. Dimethylformamide was treated with P_2O_5, distilled from CaH_2, and stored over 4A molecular sieve. $CrCl_2$ containing 0.5 mol % $NiCl_2$ was activated 4 h at 250 °C under vacuum (1 mmHg) and weighed under argon atmosphere in a glovebox. The remaining reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 250, 300, or 500 MHz; ^{13}C NMR spectra were recorded at 62.5, 75, or 125 MHz. $CHCl_3$ (δ 7.26) was used as an internal standard in ^{1}H NMR spectra. ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.0 ppm. Optical rotations were measured at 25 °C at 589 nm or at 546 nm (mercury line). Combustion analyses were conducted at the Mikroanalytisches Laboratorium des Institut für Organische Chemie der Universität, Göttingen. Column chromatography was performed using silica gel (70−230 mesh), except when stated otherwise.

(5*S*)-5-(4-Methoxybenzyloxymethyl)tetrahydro-2-furanone (5). To a stirred solution of (5*S*)-5-hydroxymethyltetrahydro-2-furanone **4**[11] (233 mg, 2.01 mmol) and *p*-methoxybenzyl trichloroacetimidate (702 mg, 2.48 mmol) in Et_2O (4 mL) was added one drop of a solution of TfOH (0.05 mL) in Et_2O (10 mL). After 1 h the reaction was quenched by the addition of saturated $NaHCO_3$. The aqueous phase was extracted twice with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (AcOEt:hexane 4:6) afforded ether **5** (385 mg, 81%) as a white solid. Mp: 42.5−44 °C; $[\alpha]_D$ +10.6 (*c* 1.0, $CHCl_3$); IR 1779 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.68−4.64 (m, 1H), 4.51(s, 2H), 3.81 (s, 3H), 3.66 (dd, J = 10.7, 3.3 Hz, 1H), 3.56 (d, J = 10.7, 4.2 Hz, 1H), 2.70−2.40 (m, 2H), 2.40−2.30 (m, 1H), 2.30−2.20 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.3, 159.2, 129.6, 129.2, 113.8, 79.0, 73.1, 71.1, 55.2, 28.3, 24.1. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.07%; H, 6.83%. Found: C, 65.91%; H, 6.72%.

(4*S*)-5-(4-Methoxybenzyloxy)pentane-1,4-diol (6a). To a suspension of $LiAlH_4$ (1.06 g, 27.9 mmol) in THF (110 mL) at 0 °C was added a solution of PMB ether **5** (2.64 g, 11.2 mmol) in THF (30 mL). The reaction mixture was stirred for 2 h and successively treated at 0 °C with water (1.05 mL), 10% aqueous NaOH (1.05 mL), and water (3.15 mL). The inorganic solids were filtered and washed with AcOEt. The organic extracts were dried over $MgSO_4$ and concentrated to afford **6a** (2.49 g, 93%) as a colorless oil. $[\alpha]_D$ −8.6 (*c* 1.0, EtOH); IR 3317 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.47 (s, 2H), 3.84−3.79 (m, 1H), 3.80 (s, 3H), 3.66−3.60 (m, 2H), 3.45 (dd, J = 9.3, 3.4 Hz, 1H), 3.31 (dd, J = 9.3, 7.9 Hz, 1H), 2.86 (br, 2H), 1.70−1.60 (m, 2H), 1.60−1.50 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.2, 129.9, 129.4, 113.8, 74.1, 73.0, 70.3, 62.7, 55.2, 30.1, 29.4. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.96%; H, 8.39%. Found: C, 64.65%; H, 8.56%.

(2*S*)-2,5-Bis(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pentane (6b). To a solution of diol **6a** (7.15 g, 29.8 mmol) in DMF (14.3 mL) were added imidazole (10.72 g, 157.6 mmol) and TBSCl (10.76 g, 71.3 mmol). The mixture was stirred for 7.5 h and diluted with Et_2O, and the reaction was quenched by the addition of 70 mL of brine. After phase separation the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Silica gel chromatography (AcOEt:hexane 5:95) furnished **6b** (13.80 g, 99%) as a colorless oil. $[\alpha]_D$ −8.0 (*c* 1.0, $CHCl_3$); IR 1250 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 3.90−3.78 (m, 1H), 3.61 (t, J = 5.7 Hz, 2H), 3.37 (δAB, Δ = 12.7 Hz, J = 12.7, 5.5 Hz, 2H), 1.66−1.41 (m, 4H), 0.90 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.0, 130.6, 129.2, 113.6, 74.4, 72.9, 71.3, 63.4, 55.2, 31.0, 28.6, 26.0, 25.9, 18.3, 18.2, −4.4, −4.8, −5.3 (×2). Anal. Calcd for $C_{25}H_{48}O_4Si_2$: C, 64.05%; H, 10.32%. Found: C, 64.01%; H, 10.14%.

(2*S*)-2,5-Bis(*tert*-butyldimethylsilyloxy)-1-pentanol (7a). To a stirred solution of **6b** (13.8 g, 29.5 mmol) in CH_2Cl_2 (157 mL) containing water (7.8 mL) at 5 °C was added DDQ (8.69 g, 38.3 mmol). After 2 h the reaction mixture was filtered and washed with CH_2Cl_2. The extract was successively washed with saturated $NaHCO_3$ and brine and then dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on a silica gel column (AcOEt:hexane 1:4) to give alcohol **7a** (9.47 g, 92%) as a colorless oil. $[\alpha]_D$ +8.5 (*c* 1.3, $CHCl_3$); IR 3400 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.80−3.72 (m, 1H), 3.62−3.53 (m, 3H), 3.45 (ddd, J = 11.0, 6.3, 5.5 Hz, 1H), 1.95 (t, J = 6.3 Hz, 1H), 1.60−1.45 (m, 4H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 72.7, 66.2, 63.1, 30.3, 28.5, 25.9, 25.8, 18.3, 18.1, −4.5, −4.6, −5.3 (×2). Anal. Calcd for $C_{17}H_{40}O_3Si_2$: C, 58.56%; H, 11.56%. Found: C, 58.58%; H, 11.32%.

(2*S*)-2,5-Bis(*tert*-butyldimethylsilyloxy)pentanal (3a). Solid tetrapropylammonium perruthenate (3.2 mg, 0.0091

(25) After completion of this work, a personal communication from Prof. A. Zeeck confirmed the specific optical rotation of natural aspinolide B to be identical to the one found for the synthetic material ($[\alpha]_D$ = −44.0 (*c* 1.0, MeOH)) and not the one reported in his original paper ($[\alpha]_D$ −19.1 (*c* 1.0, MeOH)).

mmol) was added in one portion to a stirred mixture of alcohol **7a** (85 mg, 0.24 mmol), 4-methylmorpholine *N*-oxide (32 mg, 0.27 mmol), and powdered 4A molecular sieve (90 mg) in CH_2Cl_2 (0.36 mL). After 1 h the reaction mixture was filtered through a short pad of silica gel, eluted with AcOEt:hexane 1:4 and concentrated, furnishing the crude aldehyde **3a** (75 mg, 90%) as a colorless oil. $[\alpha]_D$ −15.8 (*c* 1.0, $CHCl_3$); IR 2799, 1738 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.60 (d, J = 1.6 Hz, 1H), 4.00 (ddd, J = 6.8, 5.1, 1.6 Hz, 1H), 3.62 (t, J = 5.9 Hz, 2H), 1.80−1.53 (m, 4H), 0.92 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 204.1, 77.5, 62.7, 29.1, 27.9, 25.9, 25.7, 18.3, 18.2, −4.6, −4.9, −5.3 (×2).

(4*S*,5*R*)-7-Trimethylsilyl-1,4-bis(*tert*-butyldimethylsilyloxy)-6-heptyn-5-ol (8a). *n*-BuLi (31.2 mL, 2.3 M in hexane, 71.6 mmol) was diluted at 0 °C in THF (92 mL), and trimethylsilylacetylene (10.1 mL, 7.04 g, 71.7 mmol) was added. After 30 min, the solution was cooled to −78 °C, and a solution of the aldehyde **3a** (8.28 g, 23.9 mmol) in THF (10 mL) was added via cannula. After the mixture had been stirred for 1.5 h, the cooling bath was removed and the reaction quenched at −30 °C by the addition of saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography (AcOEt:hexane 1:19) afforded the addition products **8a** and **8b** (8.48 g, 81%) as an 11.5:1 inseparable mixture (determined by GC). $[\alpha]_D$ −3.0 (*c* 1.0, $CHCl_3$); IR 3429, 2175 cm^{-1}. **8a**: ^1H NMR (250 MHz, $CDCl_3$) δ 4.31 (dd, J = 5.6, 3.9 Hz, 1H), 3.80−3.74 (m, 1H), 3.61 (t, J = 5.6 Hz, 2H), 2.38 (d, J = 5.6 Hz, 1H), 1.80−1.40 (m, 4H), 0.90 (s, 9H), 0.89 (s, 9H), 0.16 (s, 9H), 0.09 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 103.6, 90.9, 74.8, 66.4, 63.2, 28.8, 28.6, 25.9, 25.8, 18.3, 18.1, −0.2, −4.4, −4.5, −5.3 (×2). Anal. Calcd for $C_{22}H_{48}O_3Si_3$: C, 59.40%; H, 10.88%. Found: C, 59.10%; H, 10.79%.

Trimethyl[(3*R*,4*S*)-3,4,7-tris(*tert*-butyldimethylsilyloxy)-1-heptynyl]silane (11). To a solution of alcohol **8a** (4.2 g, 9.4 mmol, 11.5:1 mixture) in DMF (10.2 mL) were added imidazole (2.06 g, 30.3 mmol) and TBSCl (2.06 g, 13.7 mmol). The mixture was stirred for 48 h and diluted with CH_2Cl_2, and the reaction was quenched by the addition of brine. After phase separation the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Silica gel chromatography (AcOEt:hexane 1:99) furnished the fully protected silane **11** (5.25 g) as a colorless oil in a 11.5:1 mixture with its C3 epimer in quantitative yield. $[\alpha]_D$ −20.3 (*c* 1.0, $CHCl_3$); IR 2175 cm^{-1}. **11**: ^1H NMR (250 MHz, $CDCl_3$) δ 4.15 (d, J = 6.2 Hz, 1H), 3.75−3.68 (m, 1H), 3.59 (t, J = 5.5 Hz, 2H), 1.74−1.52 (m, 4H), 0.89 (s, 18H), 0.88 (s, 9H), 0.14 (s, 9H), 0.07 (s, 6H), 0.03 (s, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 107.0, 89.6, 75.3, 67.0, 63.5, 29.4, 27.5, 26.0 (×2), 25.8, 18.3, 18.2, 18.2, −0.2, −4.1, −4.3, −4.4, −5.0, −5.3 (×2); LRMS (EI) *m*/*z* (relative intensity) 501 (35%, $[M - C_4H_9]^+$), M^+ 185 (100%). HRMS calcd for $C_{24}H_{53}O_3Si_4$ $[M - C_4H_9]^+$: 501.3072. Found: 501.3072.

(4*S*,5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6-heptyn-1-ol (12). Compound **11** (5.18 g, 9.26 mmol, 11.5:1 mixture) was dissolved in ethanol (74 mL) and THF (45 mL) and cooled to 0 °C. To this magnetically stirred solution was added dropwise a solution of silver nitrate (6.30 g, 37.1 mmol) in ethanol (103 mL) and water (103 mL) over a period of 2 h. After the addition was complete, this mixture was stirred at room-temperature overnight. After 16 h a solution of potassium cyanide (17.4 g, 267 mmol) in water (56 mL) was added, and the mixture was extracted with Et_2O, and the extracts were dried over $MgSO_4$ and concentrated. Purification by column chromatography (AcOEt:hexane 1:4) gave the deprotected alcohol **12** (3.20 g, 93%) as a colorless oil in a 11.5:1 mixture with its C5 epimer. $[\alpha]_D$ −29.9 (*c* 1.0, $CHCl_3$); IR 3312, 2362 cm^{-1}. **12**: ^1H NMR (250 MHz, $CDCl_3$) δ 4.25 (dd, J = 5.3, 2.2 Hz, 1H), 3.80−3.72 (m, 1H), 3.70−3.58 (m, 2H), 2.35 (d, J = 2.1 Hz, 1H), 1.80−1.55 (m, 5H), 0.90 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 84.2, 75.4, 73.5, 66.5, 63.2, 29.2, 27.9, 25.9, 25.8, 18.2 (×2), −4.2, −4.4, −4.5, −5.1; LRMS (EI) *m*/*z* (relative intensity) 315 (10%, $[M - C_4H_9]^+$), M^+ 73 (100%). HRMS calcd for $C_{15}H_{31}O_3Si_2$ $[M - C_4H_9]^+$: 315.1812. Found: 315.1811.

(4*S*,5*R*,6*E*)-7-Tributyltin-4,5-bis(*tert*-butyldimethylsilyloxy)-6-hepten-1-ol (13). The terminal acetylene **12** (59 mg, 0.16 mmol, 11.5:1 mixture) in $HSnBu_3$ (0.10 mL, 0.11 g, 0.32 mmol) in the presence of a catalytic amount of AIBN (1 mg) was heated at 90−100 °C for 48 h. Column chromatography (hexane) furnished stannane **13** (82 mg, 78%) as a colorless liquid in a 11.5:1 mixture with its C5 epimer. $[\alpha]_{546}$ −15.4 (*c* 1.3, $CHCl_3$); IR 3334, 1601 cm^{-1}. **13**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.10 (dd, J = 19.3, 1.0 Hz, 1H), 5.94 (dd, J = 19.1, 6.6 Hz, 1H), 3.94 (ddd, J = 6.6, 4.9, 1.0 Hz, 1H), 3.66−3.57 (m, 4H), 1.68−1.60 (m, 4H), 1.54−1.45 (m, 6H), 1.30 (sex., J = 7.3 Hz, 6H), 0.91−0.86 (m, 33H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 130.1, 80.0, 75.9, 63.3, 29.7, 29.1, 28.4, 27.3, 26.0 (×2), 18.3, 18.2, 13.7, 9.4, −4.0 (×2), −4.5, −4.7; LRMS (EI) *m*/*z* (relative intensity) 607 (55%, $[M - C_4H_9]^+$), 73 (100%). HRMS calcd for $C_{27}H_{59}O_3Si_2Sn$ $[M - C_4H_9]^+$: 607.3025. Found: 607.3027.

Tributyl[(*E*,3*R*,4*S*)-3,4,7-tris(*tert*-butyldimethylsilyloxy)-1-heptenyl]stannane (14). To a solution of **13** (1.69 g, 2.55 mmol, 11.5:1 mixture) in CH_2Cl_2 (10 mL) were added at room-temperature triethylamine (0.43 mL, 3.1 mmol), DMAP (38 mg, 0.31 mmol), and TBSCl (462 mg, 3.06 mmol). After 16 h the solution was diluted with Et_2O and washed with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography (AcOEt:hexane 1:99) gave the fully protected stannane **14** (1.77 g, 89%) as a colorless liquid in a 11.5:1 mixture with its C3 epimer. $[\alpha]_{546}$ −20.0 (*c* 1.0, $CHCl_3$); IR 1601 cm^{-1}. **14**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (dd, J = 19.0, 0.7 Hz, 1H), 5.96 (dd, J = 19.1, 6.3 Hz, 1H), 3.91 (ddd, J = 6.3, 4.1, 0.7 Hz, 1H), 3.63−3.55 (m, 3H), 1.65−1.40 (m, 10H), 1.31 (sex., J = 7.3 Hz, 6H), 0.92−0.86 (m, 48H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 129.4, 80.3, 76.2, 63.6, 29.7, 29.2, 28.5, 27.3, 26.0 (×2), 26.0, 18.4, 18.3, 18.2, 13.7, 9.4, −3.9, −4.0, −4.5, −4.6, −5.3 (×2); LRMS (EI) *m*/*z* (relative intensity) 721 (10%, $[M - C_4H_9]^+$), 185 (100%). HRMS calcd for $C_{33}H_{73}O_3Si_3Sn$ $[M - C_4H_9]^+$: 721.3890. Found: 721.3890.

(*E*,3*R*,4*S*)-1-Iodo-3,4,7-tris(*tert*-butyldimethylsilyloxy)-1-heptene (15). To a stirred solution of the stannane **14** (1.69 g, 2.17 mmol, 11.5:1 mixture) in CCl_4 (25 mL) was added I_2 (1.38 g, 5.43 mmol). After 2 h the mixture was diluted with Et_2O and washed with 10% aqueous $NaHSO_3$. The aqueous layer was extracted with Et_2O, and the organic layer was concentrated. The crude product mixture was redissolved in CH_2Cl_2 (10 mL), aqueous 1 M NaOH (10 mL) was added, and the mixture was vigorously stirred for 1 h. The organic phase was separated, washed successively with aqueous 1 M NaOH and brine, and dried over $MgSO_4$. Column chromatography (hexane) afforded the iodide **15** (1.14 g, 86%) as a colorless viscous oil in a 11.5:1 mixture with its C3 epimer. $[\alpha]_{546}$ −20.0 (*c* 1.0, $CHCl_3$); IR 1608 cm^{-1}. **15**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.50 (dd, J = 14.5, 7.2 Hz, 1H), 6.20 (dd, J = 14.6, 1.0 Hz, 1H), 3.91 (ddd, J = 7.1, 5.4, 1.0 Hz, 1H), 3.62−3.54 (m, 3H), 1.58−1.50 (m, 4H), 0.89 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 78.5, 77.6, 75.3, 63.4, 29.8, 27.9, 26.0, 25.9, 25.9, 18.3, 18.2, 18.1, −4.1, −4.3, −4.5, −4.7, −5.3 (×2); LRMS (EI) *m*/*z* (relative intensity) 557 (8%, $[M - C_4H_9]^+$), 73 (100%). HRMS calcd for $C_{21}H_{46}O_3Si_3I$ $[M - C_4H_9]^+$: 557.1800. Found: 557.1801.

(4*S*,5*R*,6*E*)-7-Iodo-4,5-bis(*tert*-butyldimethylsilyloxy)-6-heptenoic Acid (16). A stirred ice-cold acetone solution (66 mL) of iodide **15** (1.06 g, 1.72 mmol, 11.5:1 mixture) was treated dropwise with 8 M Jones reagent (ca. 1.5 mL). The excess of the Jones reagent was quenched by the addition of 2-propanol, and the mixture was allowed to reach room temperature. The clear greenish solution was decanted, and the remaining chromium salts were extracted four times with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo, and the

remaining crude product was purified by column chromatography (AcOEt:hexane 5:95) to give the carboxylic acid **16** (791 mg, 89%) as a white solid in a 11.5:1 mixture with its C5 epimer. Mp: 91−93 °C; $[\alpha]_{546}$ −30.0 (*c* 1.0, $CHCl_3$); IR 3300−2600, 1705, 1610 cm^{-1}. **16**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (dd, J = 14.4, 7.1 Hz, 1H), 6.24 (dd, J = 14.5, 0.9 Hz, 1H), 3.88 (ddd, J = 7.1, 5.4, 1.0 Hz, 1H), 3.61 (q, J = 5.3 Hz, 1H), 2.43−2.37 (m, 2H), 1.90−1.80 (m, 2H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 146.8, 78.3, 78.2, 74.0, 29.1, 27.9, 25.9, 25.8, 18.1, 18.0, −4.1, −4.3, −4.7, −4.9; LRMS (EI) *m*/*z* (relative intensity) 457 (16%, $[M - C_4H_9]^+$), 73 (100%). HRMS calcd for $C_{15}H_{30}O_3Si_3I$ $[M - C_4H_9]^+$: 457.0727. Found: 457.0728.

Methyl (2*R*)-2-(*tert*-Butyldimethylsilyloxy)propanoate (18). Using the conditions described for the conversion of **6a** to **6b**, the silylated compound **18** was obtained from (*R*)-methyl lactate **17** in 90% as a colorless liquid. $[\alpha]_D$ +27.2 (*c* 1.89, CCl_4); lit.[26] (2*S*)-**18** $[\alpha]_D$ −26.9 (*c* 1.89, CCl_4); IR 1760, 1740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.27 (q, J = 6.7 Hz, 1H), 3.66 (s, 3H); 1.33 (d, J = 6.8 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.4, 68.2, 51.7, 25.6, 21.2, 18.2, −5.1, −5.4.

(2*R*)-2-(*tert*-Butyldimethylsilyloxy)propan-1-ol (19). A toluene solution (4.8 mL) of ester **18** (1.04 g, 4.8 mmol) was cooled to −78 °C, treated with DIBAL (11.9 mL, 1.0 M in hexane, 11.9 mmol), stirred at −78 °C for 40 min, and then allowed to reach room temperature. After 2 h the reaction was quenched by the addition of AcOEt. Then, a saturated solution of sodium potassium tartrate was added, and the mixture was stirred overnight. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford the alcohol **19** (457 mg, 50%) as a colorless oil. $[\alpha]_D$ −23.1 (*c* 1.18, $CHCl_3$); IR 3394 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.90 (quintd, J = 6.3, 3.7 Hz, 1H), 3.49 (ddd, J = 11.0, 7.4, 3.7 Hz, 1H), 3.35 (ddd, J = 10.9, 6.4, 5.0 Hz, 1H), 2.01 (dd, J = 7.4, 5.2 Hz, 1H); 1.10 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 69.0, 68.1, 25.8, 19.8, 18.0, −4.4, −4.8. LRMS (EI) *m*/*z* (relative intensity) 133 (7%, $[M - C_4H_9]^+$), 75 (100%). HRMS calcd for $C_5H_{13}O_2Si$ $[M - C_4H_9]^+$: 133.0685. Found: 133.0684.

(2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-(4-metoxybenzyloxy)propane (20). Using the conditions described for the conversion of **4** to **5,** PMB ether **20** was obtained from alcohol **19** in 69% as a colorless oil. $[\alpha]_{546}$ +5.0 (*c* 2.0, $CHCl_3$); IR 1614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.24 (m, 2H), 6.90−6.85 (m, 2H), 4.47 (s, 2H), 3.97 (sex., J = 6.0 Hz, 1H), 3.80 (s, 3H), 3.38 (dd, J = 9.5, 5.9 Hz, 1H), 3.28 (dd, J = 9.5, 5.5 Hz, 1H), 1.16 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 130.6, 129.1, 113.6, 75.9, 72.9, 67.7, 55.2, 25.8, 20.9, 18.2, −4.7, −4.8.

(2*R*)-1-(4-Metoxybenzyloxy)propan-2-ol (21). To a stirred solution of **20** (717 mg, 2.31 mmol) in THF (6 mL) was added TBAF (906 mg, 3.47 mmol). After 5 h the mixture was diluted with Et_2O and successively washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography (AcOEt:hexane 1:3) afforded alcohol **21** (412 mg, 91%) as a colorless liquid. $[\alpha]_{546}$ −12.8 (*c* 1.28, $CHCl_3$); IR 3440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27−7.25 (m, 2H), 6.90−6.86 (m, 2H), 4.48 (s, 2H), 3.97 (dqd, J = 8.2, 6.4, 3.0 Hz, 1H), 3.80 (s, 3H), 3.43 (dd, J = 9.4, 3.1 Hz, 1H), 3.25 (dd, J = 9.2, 8.4 Hz, 1H), 2.25 (br, 1H), 1.13 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 130.0, 129.3, 113.8, 75.5, 72.9, 66.4, 55.2, 18.6; LRMS (EI) *m*/*z* (relative intensity) 196 (10%, M^+), 121 (100%). HRMS calcd for $C_{11}H_{16}O_3$ (M^+): 196.1099. Found: 196.1100.

(1*R*,4*S*,5*R*,6*E*)-2-(4-Methoxybenzyloxy)-1-methylethyl 7-Iodo-4,5-bis(*tert*-butyldimethylsilyloxy)-6-heptenoate (22). 2,4,6-Trichlorobenzoyl chloride (10 μL, 0.06 mmol) was added to a stirred THF (1 mL) solution of acid **16** (29 mg, 0.056 mmol) and Et_3N (9 μL, 0.06 mmol) at room temperature. After 16 h, the precipitate was filtered off, and the filtrate was evaporated in vacuo to leave a solid, which was taken up in benzene (1.4 mL). A solution of alcohol **21** (12 mg, 0.062 mmol) and DMAP (15 mg, 0.12 mmol) in benzene (0.6 mL) was added to the above solution, and stirring was continued for 2 h at room temperature. The reaction mixture was diluted with Et_2O and washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to leave an oil, which was flash chromatographed on silica gel (AcOEt:hexane 1:24) to give ester **22** (27.6 mg, 71%) as a colorless viscous oil. $[\alpha]_{546}$ −16.1 (*c* 0.93, $CHCl_3$); IR 1738, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.22 (m, 2H), 6.90−6.85 (m, 2H), 6.49 (dd, J = 14.5, 7.2 Hz, 1H), 6.23 (d, J = 14.6 Hz, 1H), 5.16−5.04 (m, 1H), 4.47 (δAB, Δ = 17.2 Hz, J = 11.7 Hz, 2H), 3.88 (t, J = 6.0 Hz, 1H), 3.80 (s, 3H), 3.61 (q, J = 5.1 Hz, 1H), 3.48 (dd, J = 10.3, 5.8 Hz, 1H), 3.41 (dd, J = 10.4, 4.6 Hz, 1H), 2.40−2.35 (m,2H), 1.88−1.78 (m, 2H), 1.22 (d, J = 6.6 Hz, 3H), 0.88 (s, 18H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 159.2, 146.8, 130.1, 129.2, 113.8, 78.5, 78.1, 74.3, 72.8, 72.1, 69.3, 55.2, 29.7, 28.3, 25.9, 25.8, 18.2, 18.1, 16.8, −4.1, −4.3, −4.6, −4.9; LRMS (EI) *m*/*z* (relative intensity) 635 (0.3%, $[M - C_4H_9]^+$), 121 (100%). HRMS calcd for $C_{26}H_{44}O_6Si_2I$ $[M - C_4H_9]^+$: 635.1721. Found: 635.1721.

(1*R*,4*S*,5*R*,6*E*)-2-Hydroxy)-1-methylethyl 7-Iodo-4,5-bis(*tert*-butyldimethylsilyloxy)-6-heptenoate (23). Using the conditions described for the conversion of **6b** to **7a**, ester **23** was obtained from PMB ether **22** in 84% as a colorless viscous oil. $[\alpha]_{546}$ −30.8 (*c* 1.3, $CHCl_3$); IR 3460, 1732, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, J = 14.4, 6.9 Hz, 1H), 6.24 (d, J = 14.4 Hz, 1H), 4.99 (quintd, J = 6.6, 3.6 Hz, 1H), 3.89 (dd, J = 6.9, 5.5 Hz, 1H), 3.70−3.66 (m, 3H), 2.44−2.35 (m, 2H), 1.83 (td, J = 7.9, 5.2 Hz, 2H), 1.90−1.80 (br, 1H), 1.23 (d, J = 6.5 Hz, 3H), 0.88 (s, 18H), 0.06 (s, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 146.8, 78.4, 78.2, 74.1, 72.0, 66.1, 29.6, 28.3, 25.9, 25.8, 18.2, 18.1, 16.2, −4.1, −4.3, −4.6, −4.9; LRMS (EI) *m*/*z* (relative intensity) 515 (23%, $[M - C_4H_9]^+$), 73 (100%). HRMS calcd for $C_{18}H_{36}O_5Si_2I$ $[M - C_4H_9]^+$: 515.1146. Found: 515.1146.

(5*S*,6*R*,9*R*/*S*,10*R*)-9-Hydroxy-5,6-bis(*tert*-butyldimethylsilyloxy)-10-methyl-3,4,5,6,9,10-hexahydro-2*H*-2-oxecinone (24a and 24b). To a suspension of Dess−Martin periodinane (201 mg, 0.474 mmol) in CH_2Cl_2 (5.2 mL) was added a solution of alcohol **23** (136 mg, 0.237 mmol) in CH_2Cl_2 (1.4 mL). To this suspension was added water (8.5 μL, 0.47 mmol). The reaction mixture was stirred for 25 min, and it was diluted with AcOEt. After the addition of saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted twice with AcOEt. The combined organic layers were washed successively with aqueous 1 M $NaHSO_3$ and brine and dried over $MgSO_4$. Concentration produced crude aldehyde **2** (135 mg, quantitative) which was used in the next step without further purification.

To a suspension of $CrCl_2$ (347 mg, 2.82 mmol) containing 0.5 mol % of $NiCl_2$ in degassed DMF (40 mL) was added via cannula, under cooling with an ice bath, a solution of the aldehyde above (135 mg, azeotroped with 2 × 0.5 mL of benzene in vacuum) in degassed DMF (7.5 mL). The reaction mixture was stirred overnight at room temperature, and the solvent was distilled off under vacuum (0.1 mmHg). The residue was taken up in saturated NH_4Cl and extracted with Et_2O and AcOEt. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by flash chromatography (AcOEt:hexane 1:19) to yield a 1.5:1 mixture of **24a** and **24b** (51.9 mg, 49% for two steps). Apolar isomer **24a** (white solid): R_f 0.40 (AcOEt:hexane 1:4); mp: 137−140 °C; $[\alpha]_{546}$ −31.6 (*c* 0.95, $CHCl_3$); IR 3504, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.64 (ddd, J = 15.4, 8.8, 2.2 Hz, 1H), 5.48 (dd, J = 15.4, 1.7 Hz, 1H), 4.83 (dq, J = 8.5, 4.9 Hz, 1H), 4.36 (s, 1H), 3.83 (td, J = 8.5, 4.9 Hz, 1H), 3.54 (d, J = 10.0 Hz, 1H), 2.60 (dtd, J = 14.9, 10.3, 0.9 Hz, 1H), 2.41 (ddd, J = 14.6, 10.5, 1.0 Hz, 1H), 1.97 (dd, J = 14.4, 11.2 Hz, 1H), 1.71 (d, J = 5.1 Hz, 1H), 1.46−1.40 (m, 1H), 1.38 (d, J = 6.4 Hz, 3H), 0.95 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.06 (s,

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6H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 132.8, 130.4, 79.4, 78.2, 74.4, 72.9, 33.7, 28.0, 26.1, 25.9, 18.4, 18.3, 17.0, −4.4, −4.6−4.8, −4.9; LRMS (EI) *m/z* (relative intensity) 387 (0.5%, $[M - C_4H_9]^+$), 73 (100%). HRMS calcd for $C_{18}H_{35}O_5Si_2$ $[M - C_4H_9]^+$: 387.2023. Found: 387.2022. Polar isomer **24b** (viscous oil): R_f 0.35 (AcOEt:hexane 1:4); $[\alpha]_{546}$ −21.1 (*c* 0.71, $CHCl_3$); IR 3467, 1738, 1722, 1712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80−5.69 (m, 2H), 5.21−5.10 (m, 1H), 4.41 (s, 1H), 4.30 (s, 1H), 3.61 (d, J = 10.0 Hz, 1H), 2.58 (dt, J = 14.7, 10.8 Hz, 1H), 2.41 (dd, J = 14.7, 10.0 Hz, 1H), 2.04 (dd, J = 14.6, 10.4 Hz, 1H), 1.68 (br, 1H), 1.46−1.40 (m, 1H), 1.38 (d, J = 6.3 Hz, 3H), 0.94 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 6H), 0.01 (s, 3H); LRMS (EI) *m/z* (relative intensity) 387 (0.5%, $[M - C_4H_9]^+$), 73 (100%). HRMS calcd for $C_{18}H_{35}O_5Si_2$ $[M - C_4H_9]^+$: 387.2023. Found: 387.2023.

(5*S*,6*R*,9*R*,10*R*)-9-Hydroxy-5,6-bis(*tert*-butyldimethylsilyloxy)-10-methyl-3,4,5,6,9,10-hexahydro-2*H*-2-oxecinone (24a). To a solution of **24b** (11.2 mg, 0.0252 mmol), PPh_3 (33 mg, 0.13 mmol), and *p*-nitrobenzoic acid (18.4 mg, 0.110 mmol) in benzene (0.5 mL) was added at 0 °C diethyl azodicarboxylate (20 μL, 0.13 mmol). The ice-bath was removed, and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo, the crude *p*-nitrobenzoate derivative was dissolved in MeOH (0.2 mL) and water (30 μL), and K_2CO_3 (21 mg, 0.15 mmol) was added. The mixture was stirred for 2 h at room temperature, the solvent was removed, and the crude mixture diluted with Et_2O and water. The layers were separated, and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (AcOEt:hexane 1:19) of the crude product afforded **24a** (6.2 mg, 56%) as a white solid.

(5*S*,6*R*,9*S*,10*R*)-5,6-Bis(*tert*-butyldimethylsilyloxy)-10-methyl-2-oxo-3,4,5,6,9,10-hexahydro-2*H*-9-oxecinyl (*E*)-2-Butenoate (25). To a solution of crotonic acid (5.8 mg, 0.068 mmol) in CH_2Cl_2 (1 mL) were added DMAP (1.4 mg, 0.011 mmol) and diisopropylcarbodiimide (13 μL, 11 mg, 0.078 mmol). After 30 min, a solution of alcohol **24a** (25.1 mg, 0.0564 mmol) in CH_2Cl_2 (1.5 mL) was added via cannula. Within 30 min a precipitate was formed, and stirring was continued for 20 h. An additional solution of crotonic acid (5.8 mg, 0.068 mmol), DMAP (1.4 mg, 0.011 mmol), and DIC (13 μL, 11 mg, 0.078 mmol) in CH_2Cl_2 (1 mL) was stirred for 1 h and added to the reaction mixture via cannula. After 36 h the solvent was removed, and the crude product was purified by flash chromatography (AcOEt:hexane 1:99) to give TBS-protected Aspinolide **25** (25.4 mg, 89%) as a colorless oil. $[\alpha]_{546}$ −33.3 (*c* 0.45, $CHCl_3$); IR 1745, 1728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (dq, J = 15.5, 6.8 Hz, 1H), 5.85 (dd, J = 15.6, 1.7 Hz, 1H), 5.61 (dd, J = 15.4, 2.0 Hz, 1H), 5.54 (ddd, J = 15.4, 8.4, 2.1 Hz, 1H), 5.05 (dq, J = 9.1, 6.2 Hz, 1H), 4.95 (dd, J = 9.0, 8.5 Hz, 1H), 4.38 (s, 1H), 3.56 (d, J = 10.0 Hz, 1H), 2.60 (dt, J = 14.8, 10.6 Hz, 1H), 2.43 (dd, J = 14.7, 9.8 Hz, 1H), 2.00 (dd, J = 14.7, 11.2 Hz, 1H), 1.90 (dd, J = 6.8, 1.7 Hz, 3H), 1.43 (dd, J = 14.5, 10.4 Hz, 1H), 1.29 (d, J = 6.1 Hz, 3H), 0.93 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 6H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 165.6, 145.4, 133.8, 127.1, 122.3, 79.1, 78.1, 74.3, 70.4, 33.6, 28.0, 26.0, 25.9, 18.4, 18.3, 18.0, 16.9, −4.5, −4.6−4.9, −5.0; LRMS (EI) *m/z* (relative intensity) 455 (6%, $[M - C_4H_9]^+$), 69 (100%). HRMS calcd for $C_{22}H_{39}O_6Si_2$ $[M - C_4H_9]^+$: 455.2285. Found: 455.2284.

Aspinolide B (1). To a solution of **25** (14 mg, 0.027 mmol) in THF (0.40 mL) in a Nalgene tube was added freshly prepared buffered pyridinium hydrofluoride (stock solution prepared from 342 mg of Aldrich pyridinium hydrofluoride in 0.77 mL of pyridine). After 40 h at room temperature, the reaction mixture was diluted with Et_2O and neutralized by dropwise addition of saturated $NaHCO_3$. The layers were separated, the aqueous layer was extracted successively with Et_2O and AcOEt, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (AcOEt:hexane 1:1) afforded Aspinolide B **1** (3.5 mg, 46%) as a white solid. Mp: 102−3 °C; $[\alpha]_D$ −44.0 (*c* 1.0, MeOH); lit.:[1,25] mp = 106 °C; $[\alpha]_D$ −44.0 (*c* 1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (dq, J = 15.5, 6.9 Hz, 1H), 5.86 (dd, J = 15.6, 1.7 Hz, 1H), 5.67 (dd, J = 16.0, 1.9 Hz, 1H), 5.58 (ddd, J = 15.9, 8.3, 2.4 Hz, 1H), 5.10 (dq, J = 9.3, 6.4 Hz, 1H), 4.97 (dd, J = 9.0, 8.6 Hz, 1H), 4.55−4.50 (m, 1H), 3.68−3.62 (m, 1H), 2.47 (ddd, J = 15.6, 9.8, 1.0 Hz, 1H), 2.34−2.25 (m, 1H), 2.16 (d, J = 7.6 Hz, 1H), 2.09 (dd, J = 14.9, 11.7 Hz, 1H), 1.96 (d, J = 7.6 Hz, 1H), 1.90 (dd, J = 6.9, 1.6 Hz, 3H), 1.81−1.74 (m, 1H), 1.33 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 165.5, 145.9, 131.2, 127.8, 122.1, 78.6, 75.2, 72.9, 72.0, 32.5, 27.3, 18.0, 16.7.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **8a**, **15**, **22**, **23**, **24a**, **25**, and **1** and ^{1}H NMR spectra for compound **24b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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