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Enantioselective total synthesis of 13-*O*-brefeldin A

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ABSTRACT

An enantioselective route to the title compound, a heteroatom substituted close analogue of natural brefeldin A, is described. As a key step in the whole synthesis, concatenation of the lower chain and the cyclopentanone-upper chain moiety was achieved using a Rh-catalyzed Michael addition of a vinyl boronic acid to an enone, which effectively eliminated the problems encountered with the corresponding cuprate protocol and exemplified the potential of the strategy in synthesizing similar analogues.

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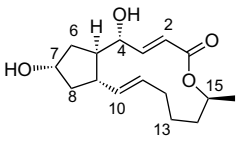
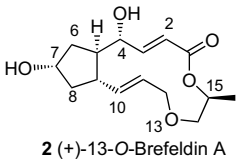
1. Introduction

(+)-Brefeldin A[1] (**1**, BFA) is one of the natural products that have attracted considerable attention in the synthetic community since the late 1970s. To date, some 30 total/formal syntheses have already been documented in the literature.[2] Apart from its interesting molecular architecture BFA's significant antitumor, antiviral, antifungal, and antimitotic activities are also important factors that stimulated researchers to enter the area. Several investigations devoted to BFA's derivatives and analogues have already appeared.[3] In a recent paper we reported[3i] the 15-demethyl analogue of **1**. Here we wish to describe synthesis of 13-*O*-substituted BFA (**2**), a novel analogue that is not accessible from natural BFA through partial structural modification.



1 (+)-Brefeldin A



2 (+)-13-*O*-Brefeldin A

2. Results and discussion

Inspection of the BFA's structure revealed that insertion of a heteroatom at position 13 would make it possible to use lactate and propargyl bromide as the precursors for the lower chain. Besides, as O- or S-alkylation, especially when using a reactive halide, is remarkably more facile than alkylation of a carbon atom, replacement of the C-13 with an oxygen or sulfur atom, therefore, may facilitate the synthesis without causing drastic changes in molecular size and shape of the end product. Should not this change affect the bioactivities, such a more readily accessible lower chain may be also used as a substitute for the all-carbon chain to facilitate the synthesis of analogues modified in other positions. These considerations urged us to synthesize **2**.

In a recent paper,[2m] we described the first application of the Rh-catalyzed[4] Michael addition of vinyl boronic acids to enones in total synthesis of natural products, where the union of the lower chain (**3a**) of BFA and the enone **4** was achieved in 95% yield using only 0.03 mol % of $[RhCl(COD)]_2$ (COD=cycloocta-1,5-diene) as the catalyst. As far as the synthesis of BFA is concerned, this Rh catalyst-boronic acid approach enjoys a number of advantages over the traditional cuprate protocol, including simple operations, low sensitivity toward air and moisture, no need for the use of a large excess of the optically active lower chain, and high reproducibility. Indeed, when using the conventional cuprate protocol we were frustrated at times by complete failure in obtaining the anticipated Michael adduct while the optically active starting materials accumulated through many steps of reactions were fully destroyed. Such a problem appeared to be even more serious with the oxygen-substituted lower chain (the cuprates closely related to **3b**), perhaps the presence of an alkoxy group at the allylic position had some adverse effects. Encouraged by the success with

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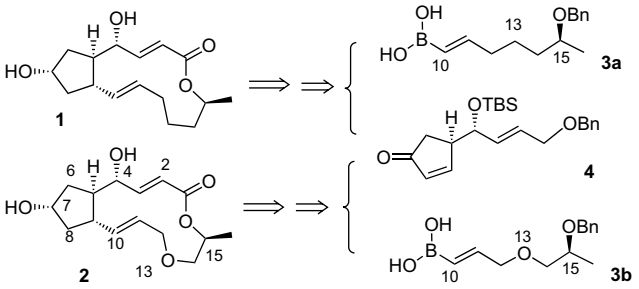
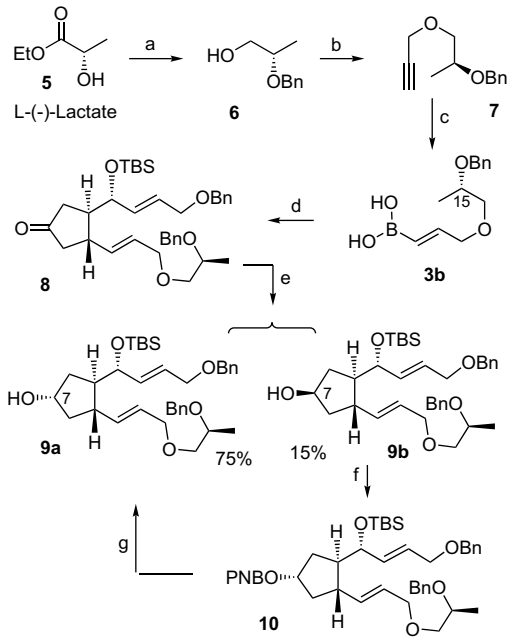
the all-carbon lower chain addition in total synthesis of **1**, we decided to examine the Rh-boronic acid approach (Scheme 1) in the present investigation.



Scheme 1.

As we have already developed a highly efficient route to the enone **4**,[2m] the main task before executing the Michael addition depicted in Scheme 1 was to prepare the boronic acid **3b**. To this end, L-ethyl lactate was protected[5] with benzyl group and reduced[6] to the corresponding alcohol using the literature procedures (Scheme 2). The resultant **6** was alkylated with propargyl bromide/NaH in DMF, giving alkyne **7**.[7]



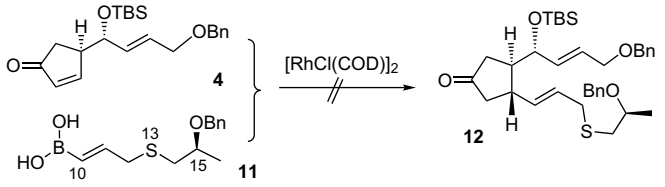
Scheme 2. (a) Refs. 5,6; (b) NaH/propargyl bromide/DMF, 86% (Ref. 7); (c) (i) catecholborane (neat)/70 °C, (ii) H_2O/rt, 89% from **7**; (d) enone **4**/$[RhCl(COD)]_2$/MeOH/H_2O (6:1)/LiOH/rt/1 h, 92%; (e) SmI_2/*i*-PrOH/THF/0 °C/3 h; (f) DEAD/Ph_3P/*p*-nitrobenzoic acid/THF/rt/2 days, 89%; (g) NaOH/MeOH/rt/2 h, 91%.

Conversion of the terminal alkyne to corresponding vinyl boronic acid was achieved by the addition of catecholborane followed by hydrolysis. As mention in the previous work, complete removal of catechol at the work-up is of critical importance. Contamination of **3b** by traces of catechol may lead to complete failure in the subsequent Rh-catalyzed Michael addition. Besides, compared with the boronic acid involved in the synthesis of **1**, the one in this work (**3b**) is remarkably more unstable and thus should be used in the next step immediately after its preparation.

In sharp contrast to the difficulty repeatedly encountered with the corresponding cuprated-mediated Michael addition, the addition of **3b** to **4** proceeded smoothly when using $[RhCl(COD)]_2$ as the catalyst, affording the adduct **8** in 92% yield. The C-7 ketone was then reduced with SmI_2/*i*-PrOH, which proved[2m] to be the best reducing agent for the corresponding reduction in the synthesis of **1**. In the present case, the desired **9a** was also formed as the major product as expected. The minor isomer **9b** was readily separated from **9a** and could be converted into **9a** through Mitsunobu inversion using DEAD (diethyl azodicarboxylate)/Ph_3P/*p*-nitrobenzoic acid followed by alkaline hydrolysis.

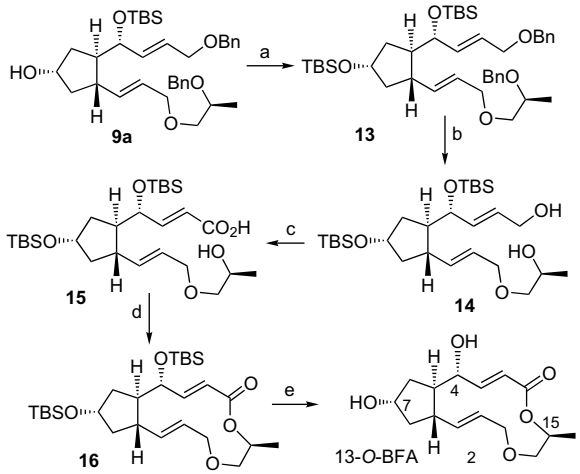
Use of the 'ate' compounds prepared[8] in situ from DIBAL-H/*n*-BuLi and DIBAL-H/*t*-BuLi, respectively, to reduce **8** was also examined. As observed[2m] previously with the similar substrate in the synthesis of **1**, reduction under such conditions also afforded the β-OH isomer **9b** as the main product. When using DIBAL-H/*n*-BuLi as reducing agent, the ratio of **9a**/**9b** was ca. 1:5. With DIBAL-H/*t*-BuLi, **9b** was formed as the only detectable product in quantitative yield after reaction in THF at −78 °C for 30 min.

When using boronic acid **11** as the lower chain, which contained a sulfur instead of an oxygen atom at the allylic position, no Michael adduct (**12**) was formed at all under otherwise identical conditions (Scheme 3). The starting materials were essentially quantitatively recovered. Increasing the amount of the added rhodium catalyst did not lead to any changes.



Scheme 3.

Compound **9a** was then further elaborated into the end product 13-*O*-BFA **2** as shown in Scheme 4. The hydroxyl group was first masked as a TBS ether with TBSCl (*t*-butyl-dimethyl-silyl chloride) in DMF (*N*,*N*′-dimethylformamide) in the presence of 2,6-lutidine. The two benzyl protecting groups were removed under the conditions[9] of Liu, giving diol **14**. The allylic hydroxyl group was selectively oxidized into the corresponding aldehyde with activated MnO_2 in CH_2Cl_2,[10] which on further treatment with $NaClO_2$ in the presence of NaH_2PO_4/methyl-2-butene[11] afforded the hydroxyl acid **15**.



Scheme 4. (a) 2,6-Lutidine/TBSCl/DMF/rt/24 h, 91%; (b) Li/naphthalene/THF/−30 °C/3 h, 85%; (c) (i) MnO_2/CH_2Cl_2/rt/4 h, (ii) *t*-BuOH/$NaClO_2$/NaH_2PO_4/$Me_2C{=}CHMe$/rt/2 h, 70%; (d) MNBA/DMAP/4 Å MS/toluene/rt/20 h, 81%; (e) 2 N HCl/THF/H_2O (1:1)/rt/48 h, 94%.

The macrolactonization was realized using the MNBA (2-methyl-6-nitrobenzoic anhydride) protocol[12] of Shiina, which in

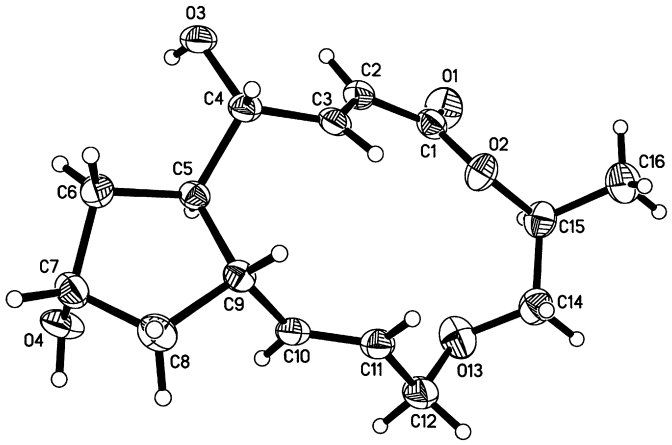


Figure 1. The ORTEP plot of 13-*O*-BFA (**2**).

our hands gave the most satisfactory results[2m,13] in synthesis of **1** and antimycin A_{3b}. Finally, the TBS protecting groups were hydrolyzed with 2 N HCl in THF/H_2O to afford the end product 13-*O*-BFA **2**.

Although initially compound **2** was obtained as an oil after chromatography, it could be crystallized from MeOH. This property made it possible to perform a single crystal X-ray crystallographic analysis[14] (Fig. 1).

3. Conclusions

As part of our efforts to develop new analogues of natural brefeldin A for future study of the structure–activity relationships (SAR), 13-*O*-BFA has been synthesized. Its single crystal X-ray structure has also been determined. Unlike many derivatives/analogues of BFA so far known, this novel heteroatom substituted congener is not accessible from structural modification of the natural BFA and thus might offer relevant SAR information not attainable otherwise. The synthesis exploits the general strategy recently developed by us for the natural product **1** itself, with the key concatenation step achieved using the Rh-catalyzed[4] Michael addition of a vinyl boronic acid to an enone. Use of this protocol here effectively eliminated the problems associated with the conventional cuprate Michael addition and thus greatly facilitated the whole synthesis. However, when the vinyl boronic acid contained a sulfur instead of an oxygen atom at the allylic position the Michael addition could not occur under otherwise the same conditions.

4. Experimental

4.1. General

The ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature using a Varian Mercury 300 or a Bruker Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR spectrometer. The ESIMS and ESIHRMS/MALDIHRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 T) FTMS mass spectrometer, respectively. The melting points were uncorrected. Optical rotations were recorded on a Jasco P-1030 polarimeter. Dry THF and Et_2O were distilled from Na/Ph_2CO under N_2 prior to use. Dry DMF and CH_2Cl_2 were distilled over CaH_2 under N_2 prior to use. PE (chromatography eluent) stands for petroleum ether (bp 60–90°C).

4.2. Synthesis of ketone 8 via Rh-mediated Michael addition of 3b to enone 4

A solution of alcohol **6** (3.32 g, 20 mmol) in dry DMF (10 mL) was added dropwise to a suspension of NaH (0.96 g, 60% suspension in mineral oil, 24 mmol, washed with hexane) in dry DMF (70 mL) stirred at 0 °C. The mixture was stirred at the same temperature for 1 h before propargyl bromide (1.32 mL, 24 mmol) was added dropwise. The stirring was continued at ambient temperature for 24 h (giving a dark mixture). Water (100 mL) was then introduced. The mixture was extracted with Et_2O (4×50 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (1:10 EtOAc/PE) gave **7** as yellowish oil (3.50 g, 17.1 mmol, 86%). $[\alpha]_D^{24}$ −4.3 (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.25 (m, 5H), 4.62 (s, 2H), 4.20 (d, *J*=2.1 Hz, 2H), 3.80–3.70 (m, 1H), 3.62–3.53 (m, 2H), 2.43 (t, *J*=2.3 Hz, 1H), 1.22 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.4, 127.7, 127.5, 74.4, 73.8, 71.1, 58.6, 17.2.

A mixture of the above prepared **7** (774 mg, 3.79 mmol) and catecholborane (neat, 0.43 mL, 3.98 mmol) was stirred at 70 °C (bath) under argon until TLC showed completion of the reaction (ca. 24 h). The mixture was cooled down to ambient temperature. Water (10 mL) was then added. The mixture was vigorously stirred for 5 min. The upper layer (aqueous) was then removed using a pipette. This procedure was repeated for five times (until TLC showed no catechol remained in the organic layer). The organic phase was diluted with Et_2O (25 mL), washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (1:3 EtOAc/PE) gave the unstable **3b** as a colorless oil (843 mg, 3.37 mmol, 89%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 6.54 (dt, *J*=18.2, 4.6 Hz, 1H), 5.69 (dt, *J*=18.3, 1.8 Hz, 1H), 4.63 (s, 1H), 4.62 (s, 1H), 4.11 (dd, *J*=4.1, 2.7 Hz, 2H), 3.82–3.70 (m, 1H), 3.60–3.40 (m, 2H), 1.22 (d, *J*=6.1 Hz, 3H); FTIR (film) 3291, 2927, 2871, 1643, 1603, 1512, 1472, 1373, 1259, 1236, 1097, 1057, 745, 698 cm^{-1}, which was utilized immediately in the following step.

LiOH (7.3 mg, 0.174 mmol, 0.5 equiv) was added to a mixture of the above prepared boronic acid **3b** (104 mg, 0.416 mmol), $[RhCl(COD)]_2$ (5.1 mg, 0.01 mmol), and enone **4** (129 mg, 0.347 mmol) in MeOH/H_2O (6:1, 2.1 mL). The mixture was stirred at ambient temperature for 1 h before being concentrated on a rotary evaporator. The residue was chromatographed on silica gel (1:12 EtOAc/PE) to afford **8** as a colorless oil (185 mg, 0.309 mmol, 92%). $[\alpha]_D^{28}$ −49.3 (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.26 (m, 10H), 5.78–5.60 (m, 4H), 4.63 (s, 2H), 4.50 (s, 2H), 4.32 (d, *J*=6.6 Hz, 1H), 4.04–3.98 (m, 4H), 3.75 (quintet, *J*=6.0 Hz, 1H), 3.52 (dd, *J*=10.0, 6.0 Hz, 1H), 3.42 (dd, *J*=10.0, 4.6 Hz, 1H), 2.89–2.75 (m, 1H), 2.54–2.33 (m, 2H), 2.25–1.90 (m, 3H), 1.18 (d, *J*=6.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.1, 138.9, 138.2, 135.0, 134.2, 128.4, 128.3, 127.6, 127.5, 127.3, 74.4, 74.0, 72.1, 71.5, 71.1, 70.7, 69.9, 49.3, 45.3, 40.9, 37.8, 25.9, 18.2, 17.2, −3.7, −4.7; FTIR (film) 2928, 2856, 1744, 1716, 1451, 1361, 1253, 1108, 972, 836 cm^{-1}; ESIMS *m*/*z* 601.3 ($[M+Na]^+$). MALDIHRMS calcd for $C_{35}H_{50}O_5SiNa$ ($[M+Na]^+$): 601.3320; found: 601.3321.

4.3. SmI_2 reduction of cyclopetanone 8 leading to alcohols 9a/9b

A freshly prepared solution of SmI_2 (0.1 M, 13 mL) in anhydrous THF was added dropwise to a solution of ketone **8** (150 mg, 0.259 mmol) in anhydrous THF (2.0 mL) and *i*-PrOH (0.4 mL) stirred to 0 °C. The resulting blue solution was stirred at 0 °C until TLC showed completion of the reaction (ca. 3 h). Et_2O (20 mL) and 1% aq HCl (5.0 mL) were added. The mixture was stirred for another 15 min before the phases were separated. The aqueous layer was

back extracted with Et_2O. The combined organic layers were washed successively with aq satd $Na_2S_2O_3$, water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (1:10 EtOAc/PE) afforded **9a** (the more polar component, 113 mg, 0.194 mmol, 75%) and **9b** (the less polar component, 23 mg, 0.0396 mmol, 15%) as colorless oils.

Data for **9a**: $[\alpha]_D^{28}$ −14.7 (*c* 3.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.21 (m, 10H), 5.75–5.60 (m, 3H), 5.51 (dt, *J*=15.4, 6.0 Hz, 1H), 4.63 (s, 2H), 4.49 (s, 2H), 4.30–4.22 (m, 1H), 4.02–3.95 (m, 4H), 3.79–3.67 (m, 1H), 3.50 (dd, *J*=9.8, 6.0 Hz, 1H), 3.39 (dd, *J*=10.0, 5.5 Hz, 1H), 2.39–2.53 (m, 1H), 2.22–2.10 (m, 1H), 2.03–1.86 (m, 2H), 1.65–1.37 (m, 2H), 1.20 (d, *J*=6.8 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.4, 138.1, 136.2, 128.4, 128.3, 127.7, 127.6, 127.5, 126.4, 126.1, 74.1, 74.0, 72.8, 72.2, 72.0, 71.9, 71.1, 70.2, 50.3, 42.7, 42.6, 35.2, 26.0, 18.2, 17.4, −3.7, −4.7; FTIR (film) 3364, 2927, 2855, 1454, 1373, 1257, 1093, 972, 835, 697 cm^{-1}; ESIMS *m*/*z* 603.5 ($[M+Na]^+$). ESIHRMS calcd for $C_{35}H_{52}O_5SiNa$ ($[M+Na]^+$): 603.3476; found: 603.3466.

Data for **9b**: $[\alpha]_D^{28}$ −8.9 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 10H), 5.70–5.43 (m, 4H), 4.54 (s, 2H), 4.42 (s, 2H), 4.20–4.04 (m, 2H), 3.40–3.85 (m, 4H), 3.73–3.60 (m, 1H), 3.45 (dd, *J*=10.0, 5.9 Hz, 1H), 3.33 (dd, *J*=10.1, 4.7 Hz, 1H), 2.80 (br s, OH), 2.70–2.60 (m, 1H), 1.90–1.75 (m, 3H), 1.70–1.56 (m, 2H), 1.43–1.35 (m, 1H), 1.15 (d, *J*=6.4 Hz, 3H), 0.93 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.2, 137.1, 135.6, 128.4, 128.3, 127.6, 127.4, 126.9, 126.2, 74.1, 73.9, 72.9, 72.4, 72.0, 71.8, 71.0, 69.9, 50.3, 43.3, 42.1, 34.8, 25.9, 18.2, 17.3, −3.8, −4.5; FTIR (film) 3466, 2929, 2856, 1454, 1362, 1255, 1100, 972, 836, 697 cm^{-1}; ESIMS *m*/*z* 603.4 ($[M+Na]^+$). ESIHRMS calcd for $C_{35}H_{52}O_5SiNa$ ($[M+Na]^+$): 603.3476; found: 603.3468.

4.4. LiAl(*i*-Bu)$_2$(*t*-Bu)H reduction of 8 leading to 9b

t-BuLi (1.7 M in pentane, 2.1 mL, 3.6 mmol) was slowly added to DIBAL-H (1.0 M in toluene, 3.6 mL, 3.6 mmol) stirred at 0 °C under argon to generate LiAl(*i*-Bu)$_2$(*t*-Bu)H (0.63 M). The resultant clear solution (0.63 M, 1.1 mL, 0.67 mmol) was then added to a solution of **8** (95 mg, 0.165 mmol) in anhydrous THF (4.0 mL) stirred at −78 °C under argon. The solution was stirred at −78 °C for 30 min before being diluted with EtOAc (30 mL), washed with 5% aq HCl, aq satd $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent on a rotary evaporator left **9b** (the only product) as a colorless oil (96 mg, 0.165 mmol, 100%). Data for **9b**: see above.

4.5. Conversion of 9b into 10

With cooling (ice-water bath) and stirring, DEAD (216 μL, 1.383 mmol) was added dropwise to a solution of **9b** (196 mg, 0.337 mmol), Ph_3P (345 mg, 1.316 mmol), and *p*-nitrobenzoic acid (212 mg, 2.282 mmol) in dry THF (6.7 mL). After completion of the addition, the clear yellow solution was stirred at ambient temperature until TLC showed completion of the reaction (ca. 2 days). Solvent was removed by rotary evaporation. The residue was chromatographed on silica gel (1:50 EtOAc/PE) to give **10** as a yellow sticky oil (219 mg, 0.300 mmol, 89%). $[\alpha]_D^{27}$ −12.6 (*c* 2.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J*=8.9 Hz, 2H), 8.15 (d, *J*=9.1 Hz, 2H), 7.40–7.20 (m, 10H), 5.75–5.53 (m, 4H), 5.43–5.35 (m, 1H), 4.61 (s, 2H), 4.48 (s, 2H), 4.25–4.19 (m, 1H), 4.05–3.95 (m, 4H), 3.80–3.65 (m, 1H), 3.50 (dd, *J*=9.8, 5.8 Hz, 1H), 3.39 (dd, *J*=9.8, 4.7 Hz, 1H), 2.66–2.53 (m, 1H), 2.48−2.35 (m, 1H), 2.23–2.10 (m, 1H), 2.07–1.93 (m, 1H), 1.92–1.80 (m, 1H), 1.80–1.67 (m, 2H), 1.20 (d, *J*=6.4 Hz, 3H), 0.93 (s, 9H), 0.06 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 138.1, 136.4, 135.9, 135.6, 130.5, 128.3, 128.2, 127.6, 127.5, 127.4, 126.8, 126.6, 123.4, 76.6, 74.1, 73.8, 72.0, 71.7, 71.6, 71.0, 70.0, 50.6, 42.3, 39.3, 32.1, 25.9, 18.1, 17.2, −3.7, −4.8; FTIR (film) 2927, 2855, 1723, 1607, 1496, 1453, 1350, 1274, 1118, 969, 837, 721, 697 cm^{-1}; ESIMS *m*/*z* 752.5 ($[M+Na]^+$). ESIHRMS calcd for $C_{42}H_{55}NO_8SiNa$ ($[M+Na]^+$): 752.3589; found: 752.3577.

4.6. Conversion of 10 into 9a

A solution of NaOH (1.012 g, 2.525 mmol) in MeOH (4 mL) was added to a solution of **10** (219 mg, 0.300 mmol) in MeOH (2 mL). After completion of the addition, the mixture was stirred at ambient temperature until TLC showed completion of the reaction (ca. 2 h). Water (5 mL) was added. The mixture was concentrated on a rotary evaporator. The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine before being dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation and column chromatography on silica gel (1:8 EtOAc/PE) gave **9a** as a colorless oil (159 mg, 0.273 mmol, 91%). Data for **9a**: see above.

4.7. TBS protection of 9a leading to 13

A solution of **9a** (120 mg, 0.207 mmol), 2,6-lutidine (0.05 mL, 0.414 mmol), and TBSCl (62 mg, 0.414 mmol) in anhydrous DMF (1.0 mL) was stirred at ambient temperature for 24 h. Ice-water (5.0 mL) was introduced. The mixture was extracted with Et_2O (3×25 mL). The combined ethereal phases were washed with aq satd $CuSO_4$, water and brine, dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left a residue, which was purified by flash column chromatography (1:25 EtOAc/PE) to afford **13** as a colorless oil (131 mg, 0.188 mmol, 91%). $[\alpha]_D^{28}$ −15.8 (*c* 6.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.22 (m, 10H), 5.73–5.60 (m, 3H), 5.48 (dt, *J*=15.1, 6.2 Hz, 1H), 4.62 (s, 2H), 4.49 (s, 2H), 4.25–4.16 (m, 1H), 4.15–4.10 (m, 1H), 4.03–3.93 (m, 4H), 3.78–3.67 (m, 1H), 3.50 (dt, *J*=10.2, 6.1 Hz, 1H), 3.39 (dt, *J*=10.1, 4.8 Hz, 1H), 2.46–2.34 (m, 1H), 2.09–1.73 (m, 3H), 1.56–1.39 (m, 2H), 1.21 (d, *J*=6.5 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 6H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.5, 138.3, 136.5, 128.4, 128.3, 127.6, 127.5, 127.4, 126.1, 125.6, 73.9, 73.3, 72.3, 72.0, 71.7, 71.1, 70.1, 49.9, 43.1, 42.3, 35.0, 25.9, 18.1, 17.3, −3.7, −4.8; FTIR (film) 2928, 2855, 1736, 1471, 1361, 1251, 1110, 835, 774, 696 cm^{-1}; ESIMS *m*/*z* 717.7 ($[M+Na]^+$). ESIHRMS calcd for $C_{41}H_{66}O_5Si_2Na$ ($[M+Na]^+$): 717.4341; found: 717.4322.

4.8. Removal of the benzyl groups in 13 leading to 14

A solution of **13** (129 mg, 0.186 mmol) in anhydrous THF (4.0 mL) was added to a freshly prepared solution of Li-naphthalene in anhydrous THF (0.23 M, 12 mL) stirred at −30 °C under argon. The dark-green mixture was stirred at the same temperature for 3 h, when TLC showed completion of the reaction. Water was added carefully, followed by Et_2O (50 mL). The phases were separated. The organic phase was washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (1:3 EtOAc/PE) afforded **14** as a colorless oil (81 mg, 0.157 mmol, 85%). $[\alpha]_D^{27}$ −16.4 (*c* 3.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.74–5.54 (m, 3H), 5.42 (dt, *J*=15.5, 6.4 Hz, 1H), 4.18 (quintet, *J*=5.3 Hz, 1H), 4.08 (d, *J*=4.4 Hz, 2H), 4.02–3.85 (m, 4H), 3.41 (dd, *J*=9.2, 2.6 Hz, 1H), 3.23 (t, *J*=8.9 Hz, 1H), 2.28 (quintet, *J*=8.4 Hz, 1H), 2.07–1.93 (m, 2H), 1.70 (dd, *J*=8.6, 5.2 Hz, 2H), 1.44 (ddd, *J*=13.3, 8.4, 5.5 Hz, 1H), 1.15 (d, *J*=6.4 Hz, 3H), 0.87 (s, 18H), 0.03 (m, 6H), −0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 134.7, 129.1, 125.0, 76.4, 75.5, 73.1, 72.2, 66.4, 62.8, 50.1, 43.4, 42.9, 38.0, 25.9, 18.6, 18.1, −3.7, −4.7; FTIR (film) 3404, 2928, 2855, 1472, 1361, 1254, 1107, 836, 775 cm^{-1}; ESIMS *m*/*z* 537.5 ($[M+Na]^+$). ESIHRMS calcd for $C_{27}H_{54}O_5Si_2Na$ ($[M+Na]^+$): 537.3402; found: 537.3414.

4.9. Oxidation of the allylic alcohol in 14 leading to 15

A suspension of activated MnO_2 (170 mg, 1.955 mmol) and **14** (60 mg, 0.117 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was stirred at ambient temperature until TLC showed completion of the reaction (ca. 4 h). The solids were filtered off (washing with CH_2Cl_2). The filtrate and washings were combined and concentrated on a rotary evaporator to give the crude intermediate aldehyde, which was directly dissolved in *t*-BuOH (4.0 mL). To this solution were added 2-methyl-2-butene (0.26 mL) and a solution of $NaH_2PO_4 \cdot H_2O$ (468 mg, 3.39 mmol) in water (1.2 mL). A solution of $NaClO_2$ (97 mg, 1.07 mmol) in water (1.2 mL) was then added dropwise. After completion of the addition, the mixture was stirred at ambient temperature until TLC showed completion of the reaction (ca. 24 h). The mixture was acidified with 2 N HCl to pH 2, extracted with Et_2O (3×25 mL). The combined organic layers were washed in turn with water (10 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (1:2 EtOAc/PE) afforded **15** as a colorless oil (43 mg, 0.0813 mmol, 70%). $[\alpha]_D^{25}$ −9.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (dd, *J*=15.7, 5.4 Hz, 1H), 5.95 (d, *J*=15.8 Hz, 1H), 5.67 (dd, *J*=15.2, 8.4 Hz, 1H), 5.49 (dt, *J*=15.7, 6.0 Hz, 1H), 4.30–4.23 (m, 1H), 4.23–4.15 (m, 1H), 4.04–3.90 (m, 3H), 3.42 (dd, *J*=9.5, 2.9 Hz, 1H), 3.27–3.17 (m, 1H), 2.38 (quintet, *J*=8.3 Hz, 1H), 2.10–1.95 (m, 2H), 1.85–1.72 (m, 1H), 1.60–1.40 (m, 2H), 1.15 (d, *J*=6.5 Hz, 3H), 0.92 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 6H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 153.2, 138.6, 125.6, 119.4, 75.5, 73.0, 71.8, 66.5, 49.2, 43.1, 42.5, 35.6, 25.9, 25.8, 18.5, 18.1, −4.0, −4.8, −4.9; FTIR (film) 3445, 2930, 2857, 1699, 1659, 1472, 1256, 1105, 979, 837, 776 cm^{-1}; ESIMS *m*/*z* 551.5 ([M+Na]$^+$). MALDIHRMS calcd for $C_{27}H_{52}O_6Si_2Na$ ([M+Na]$^+$): 551.3244; found: 551.3243.

4.10. MNBA mediated lactonization of 15 leading to 16

A solution of hydroxyl acid **15** (18 mg, 0.034 mmol) in dry toluene (6.0 mL) was added slowly (with the aid of a syringe pump) over 4 h to a mixture of MNBA (18 mg, 0.051 mmol), DMAP (19 mg, 0.204 mmol) and activated 4 Å molecular sieves (405 mg) in dry toluene (12 mL) stirred at ambient temperature. After completion of the addition, the mixture was stirred at the same temperature for 20 h before being diluted with EtOAc (50 mL), washed in turn with aq satd $NaHCO_3$, water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel (1:50 EtOAc/PE) afforded **16** as a colorless oil (14 mg, 0.0274 mmol, 80%). $[\alpha]_D^{23}$ +17.3 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, *J*=15.8, 4.0 Hz, 1H), 5.90 (dd, *J*=15.8, 1.6 Hz, 1H), 5.63 (ddd, *J*=14.5, 9.7, 4.2 Hz, 1H), 5.43 (dd, *J*=15.2, 9.4 Hz, 1H), 5.20–5.08 (m, 1H), 4.24–4.17 (m, 1H), 4.04–3.74 (m, 3H), 3.60 (dd, *J*=11.2, 2.4 Hz, 1H), 3.46 (dd, *J*=11.3, 7.9 Hz, 1H), 2.30–1.87 (m, 4H), 1.22 (d, *J*=6.6 Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.07–0.01 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 152.5, 140.8, 126.2, 118.9, 76.3, 73.3, 72.5, 71.8, 69.6, 52.7, 44.0, 43.6, 42.0, 29.7, 25.8, 18.1, 16.0, −4.2, −4.8, −5.0; FTIR (film) 2955, 2928, 2856, 1718, 1664, 1647, 1496, 1256, 1122, 1078, 971, 837, 775 cm^{-1}; ESIMS *m*/*z* 533.5 ([M+Na]$^+$). ESIHRMS calcd for $C_{27}H_{50}O_5Si_2Na$ ([M+Na]$^+$): 533.3089; found: 533.3088.

4.11. Hydrolysis of TBS groups in 16 leading to 2 (13-*O*-BFA)

A solution of lactone **16** (27 mg, 0.0529 mmol) and aq HCl (2 N, 0.35 mL) in THF/H_2O (1:1 v/v, 4 mL) was stirred at ambient temperature for 48 h. Aq satd $NaHCO_3$ (2.0 mL) was then added. The mixture was extracted with Et_2O (3×25 mL). The combined organic phases were washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was recrystallized from MeOH to afford 13-*O*-BFA **2** as a white solid (14 mg, 0.0496 mmol, 91%). Mp 229–231 °C; $[\alpha]_D^{27}$ +31.5 (*c* 0.08, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.27 (dd, *J*=17.7, 4.0 Hz, 1H), 5.87 (dd, *J*=15.7, 1.7 Hz, 1H), 5.80 (ddd, *J*=14.8, 10.1, 4.2 Hz, 1H), 5.47 (dd, *J*=15.2, 9.5 Hz, 1H), 5.03 (ddd, *J*=8.7, 6.7, 2.1 Hz, 1H), 4.23 (quintet, *J*=5.1 Hz, 1H), 4.04 (ddd, *J*=9.6, 3.9, 1.5 Hz, 1H), 3.91 (dd, *J*=12.6, 4.3 Hz, 1H), 3.79 (dd, *J*=12.6, 10.1 Hz, 1H), 3.63 (dd, *J*=11.3, 2.1 Hz, 1H), 3.48 (dd, *J*=11.3, 8.7 Hz, 1H), 2.42 (quintet, *J*=8.9 Hz, 1H), 2.15 (ddd, *J*=13.9, 8.8, 5.7 Hz, 1H), 2.03 (ddd, *J*=12.5, 8.0, 4.0 Hz, 1H), 1.92 (quintet, *J*=8.9 Hz, 1H), 1.81 (ddd, *J*=14.0, 8.6, 6.3 Hz, 1H), 1.45 (ddd, *J*=13.5, 7.3, 5.3 Hz, 1H), 1.18 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.6, 155.0, 142.4, 128.3, 119.2, 76.9, 74.3, 73.0, 72.6, 71.6, 53.3, 45.9, 44.3, 42.3, 16.5; FTIR (KBr): 3239, 2929, 2878, 1710, 1646, 1456, 1258, 1116, 1070, 975 cm^{-1}; ESIMS *m*/*z* 305.2 ([M+Na]$^+$). MALDIHRMS calcd for $C_{15}H_{22}O_5Na$ ([M+Na]$^+$): 305.1359; found: 305.1360.

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