Formal Synthesis of the Bryostatin Northern Hemisphere: Asymmetric Synthesis of the B Ring and C1–C9 Fragment

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Received 7 December 2010

Abstract: A formal synthesis of the top half fragment of bryostatin 11 has been developed. Stereoselective construction of the B ring was achieved by using a ring-closing metathesis reaction in conjunction with asymmetric glycolate alkylation. Furthermore, the C1–C9 fragment was synthesized by Brown allylation, chelation-controlled aldol condensation, and Saksena–Evans reduction to construct all stereogenic centers.

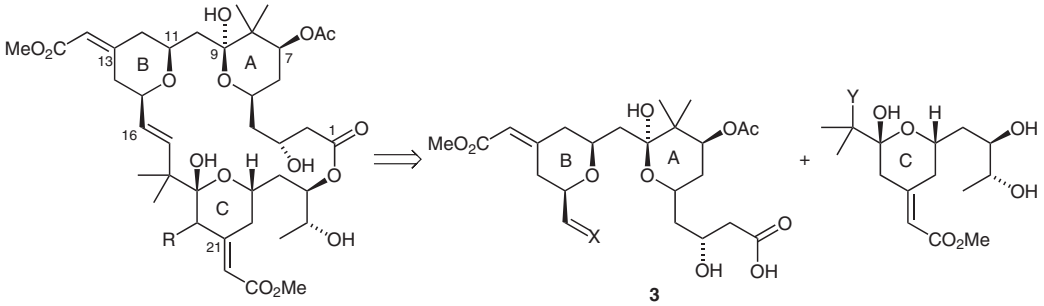
Key words: bryostatin 11, asymmetric glycolate alkylation, ring-closing metathesis

We previously reported a unified approach to the enantioselective synthesis of 2,6-*cis*- and 2,6-*trans*-disubstituted tetrahydropyranones using asymmetric glycolate alkylation–ring closing metathesis reaction.[2] To expand the utility of our strategy for the total synthesis of natural products, we describe herein the asymmetric synthesis of the B ring and C1–C9 fragment of bryostatin 11, a marine macrolide.

Bryostatins were originally isolated from the marine bryozoan *Bugula neritina* by Pettit and co-workers[3] and 20 kinds of bryostatins have been isolated to date.[4,5c] Bryostatins exhibit potent biological activities through a unique mode of action against protein kinase C.[5] Especially, bryostatin 1 (**1**, Scheme 1) is currently under investigation in human clinical trials as a single agent or in combination with other chemotherapies.[6] The limited supply of bryostatins from natural sources demands that it be provided by total synthesis for biological activity studies. Nevertheless, only four total syntheses of bryostatins have been completed until 2010,[7–11] although many related preparations of analogues[4b,5e,12] and fragments[5,13] have been reported. The interesting biological activity as well as unique structure of bryostatins led us to focus on the effective total synthesis of bryostatin 11 (**2**).

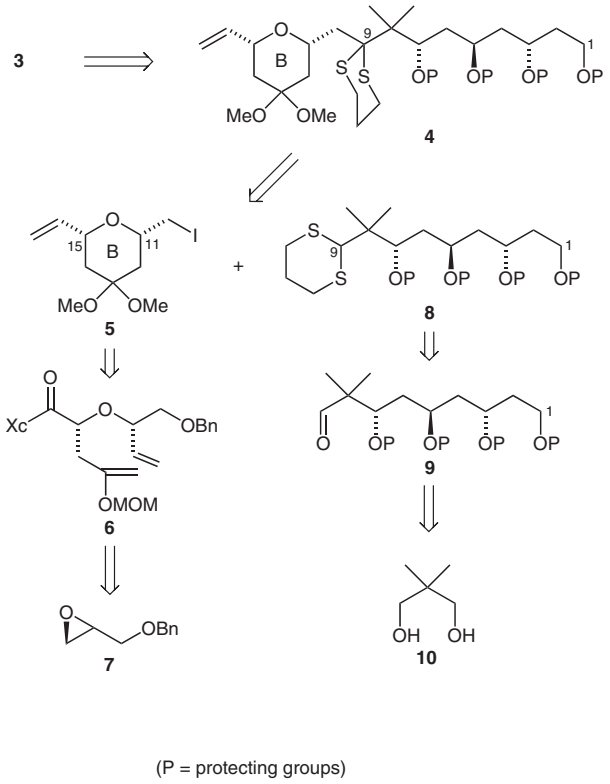
In our synthetic strategy toward **2**, we planned to connect the top C1–C16 and bottom C17–C27 half fragments by employing Yamaguchi coupling to form the ester linkage and ring-closing olefin metathesis (RCM) or Julia olefination[4b,5a–e,7–13] to construct the C16–C17 double bond. We first planned a RCM approach, although Thomas and Trost have recently reported a lack of success in their synthesis.[14] As shown in Scheme 2, our retrosynthetic analysis of the top half fragment began with opening of the A ring (**3** → **4**) followed by disconnection of the B ring and C1–C9 fragment (**4** → **5** + **8**[15]). We could obtain the B ring stereoselectively by using our established 2,6-disubstituted tetrahydropyranone synthetic methodology.[2] The C1–C9 linear subunit would be prepared by constructing all stereocenters, starting from 2,2-dimethyl propanediol **10**. Finally, we would couple the B ring precursor **5** with thioketal **8** according to Yamamura's[9] or Hoffman's[15] method.

Compound **11** was derived in two steps from (*S*)-(+)-benzyl glycidyl ether (**7**) in 66% overall yield (Scheme 3).[16] It was converted into the desired oxazolidinone glycolate **13**[17] via a one-pot reaction from an intermediate alkoxyglycolic acid through the in situ formation of a mixed pivalic anhydride. Exposure of **13** to iodide **14**[2] and $NaH(SiMe_3)_2$ produced *syn*-diene **6**[18] in 74% yield with



Scheme 1

SYNLETT 2011, No. 10, pp 1413–1418
Advanced online publication: 26.05.2011
DOI: 10.1055/s-0030-1260586; Art ID: S09310ST

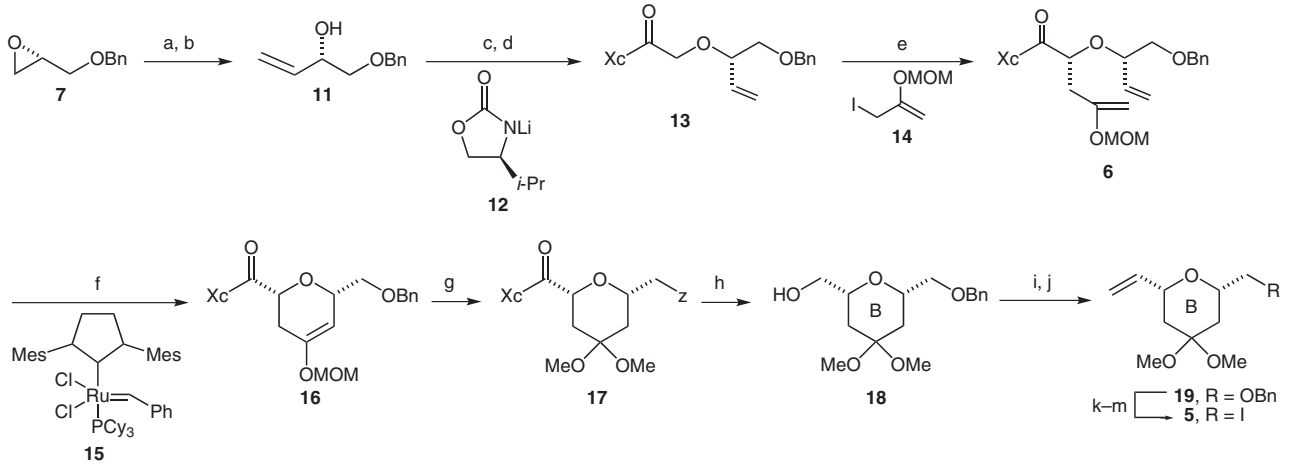


Scheme 2 Retrosynthetic analysis of top fragment

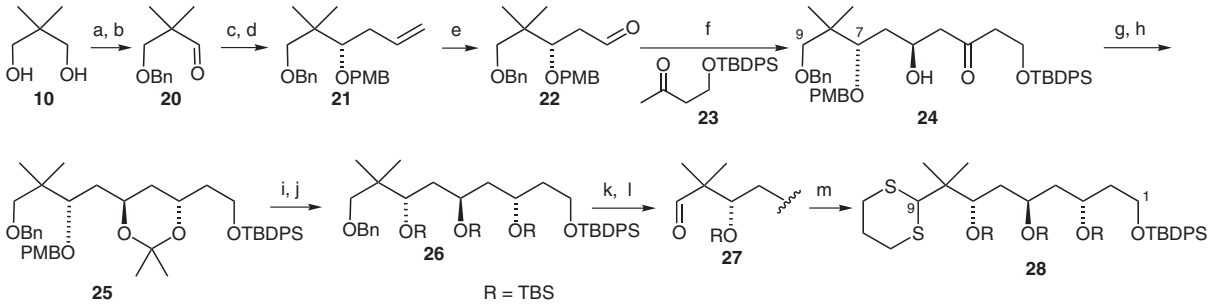
excellent diastereoselectivity. Ring-closing metathesis of diene **6** with 10 mol% of Grubbs second-generation ruthenium carbine **15**[19] as a catalyst led to **16**[20] in 89% yield, along with 6% of recovered starting material. The MOM enol ether was converted directly into methyl ketal **17**[21] in 82% yield by treatment with methyl orthoformate in the presence of catalytic acid (PPTS–PTSA = 1:1) in THF–MeOH (3:1, v/v) solution.

The oxazolidinone was reductively cleaved to give alcohol **18**, plus inseparable oxazolidinone. The mixture was oxidized under Swern conditions, and a methylene Wittig reaction with the resulting aldehyde gave olefin **19**[22] in good yield. The desired B ring precursor **5** was obtained by reductive removal of the benzyl ether under Birch conditions, followed by standard two-step iodination (1. TsCl, 2. NaI, acetone). The terminal olefin could be potentially transformed to an aldehyde for Julia coupling, if RCM failed.

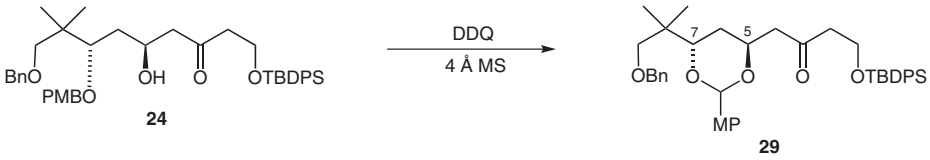
With the stereoselective synthesis of B ring completed successfully, assembly of the C1–C9 linear unit was performed. Protection of 2,2-dimethyl-1,3-propanediol (**10**) with benzyl chloride (1 mol equiv) in the presence of KO*t*-Bu gave the monobenzyl ether in 74% yield (Scheme 4). The remaining alcohol was oxidized under Swern conditions to the aldehyde **20**, which was exposed to Brown's asymmetric alkylation[23] to construct the C7 stereogenic center. The resulting mixture of the inseparable desired allylic alcohol and 4-isocaranol was treated with PMBCl in the presence of KH in THF to furnish PMB ether **21**[24] in 66% overall yield. The terminal olefin was oxidatively cleaved to the aldehyde, which was condensed with ketone **23** according to Vandewall's procedure[25] to afford *anti*-hydroxy ketone **24**.[26] After various attempts, the 3,5-*anti*-diol was constructed in good yield and selectivity (*anti*/*syn* = 7.6:1) by using Evans–Saksena reduction [$Me_4NHB(OAc)_3$, MeCN, AcOH].[27] At this point, the use of Li(O*t*-Bu)$_3$AlH as a reduction reagent gave lower selectivity, although Vandewall reported a satisfactory result with a similar compound with OBn at C7 and OPMB at C9. Because Evans–Saksena reduction of the related hydroxy ketone with OPMB at C7 and OMOM at C9 also provided better selectivity[28] than Vandewall's procedure, a methoxy group on PMB might affect the selectivity of Li(O*t*-Bu)$_3$AlH reduction. The resulting diol was protected as the acetonide, and then *anti*-acetonide **25**[29] was separated from *syn*-acetonide by column chromatography on silica gel. Both the PMB group and the acetonide were



Scheme 3 *Reagents and conditions*: (a) NaH, DMSO, 70 °C, 70 min then **7**, DMSO, r.t., 30 min; (b) $CaCO_3$, 1,2-dichlorobenzene, heat, overnight (66% from **7**); (c) NaH, THF, r.t., 10 min, then **11**, r.t., overnight; (d) PivCl, Et_3N, Et_2O, 0 °C, 1 h, then **12**, THF, –78 °C to 0 °C, 3 h (45% from **11**); (e) $NaN(SiMe_3)_2$, THF, –78 °C, 30 min, then **14**, –78 °C to –45 °C, 1 h (74%); (f) **15** (10 mol%), CH_2Cl_2, reflux, overnight (89%); (g) PTSA–PPTS (1:1), $CH(OMe)_3$, THF–MeOH (3:1), reflux, 1 h (82%); (h) $LiBH_4$, Et_2O, MeOH, 0 °C, 1 h (80%); (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N (80%); (j) PPh_3CH_3Br, toluene, KO*t*-Bu, THF, r.t., overnight, (92%); (k) Na, NH_3 (l), THF, –78 °C, 4 h (74%); (l) TsCl, pyridine, 0 °C to r.t., overnight, (91%); (m) NaI, acetone, reflux, overnight (85%).



Scheme 4 *Reagents and conditions*: (a) BnCl, KO*t*-Bu, dioxane, reflux, overnight (74%); (b) $(COCl)_2$, DMSO, –78 °C then Et_3N (92%); (c) 4-ICr_2B-allyl, Et_2O, –78 °C, 3 h, warmed to r.t. over 2 h; 30% H_2O_2, NaOH, reflux, overnight; (d) PMBCl, KH, THF, r.t., overnight (81% from **20**); (e) OsO_4, NMO, THF, r.t., overnight, then $NaIO_4$, THF, H_2O (85%); (f) **23**, LDA, THF, –78 °C, 2 h then **22**, THF, –78 °C, 15 min (70%); (g) $Me_4NHB(OAc)_3$, MeCN–AcOH, –30 °C, 22 h (98%, *anti*/*syn* = 7.6:1); (h) $Me_2C(OMe)_2$, PPTS, THF, r.t., overnight (96%) then separation; (i) DDQ, CH_2Cl_2–H_2O, then 70% AcOH, r.t., 1.5 h (78%); (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, –15 °C to 0 °C, 2.5 h (92%); (k) $Pd(OH)_2$/C, H_2, EtOAc, r.t., 24 h (69%); (l) $(COCl)_2$, DMSO, –78 °C then Et_3N (89%); (m) $HS(CH_2)_3SH$, $MgBr_2{\cdot}OEt_2$, Et_2O, r.t., 4 h (76%).



Scheme 5

removed in a one-pot reaction to supply the trialcohol, which was then reprotected as the TBS triether **26**. Subsequently, reductive cleavage of the benzyl ether and oxidation of the resulting alcohol afforded aldehyde **27**. Treatment of **27** with 1,3-propanedithiol in the presence of $MgBr_2{\cdot}OEt_2$ provided thioketal **28** in 75% yield. Meanwhile, hydrogenation of **25** with Raney nickel accomplished the selective removal of the benzyl ether to provide the primary alcohol, which was converted into the aldehyde under Swern conditions. Unfortunately, the thioketalization of the resulting aldehyde yielded unknown products without the desired compound.

The relative stereochemistry of C5 and C7 was confirmed from the NOESY spectrum of the corresponding *p*-methoxybenzylidene acetal **29** derived from β-hydroxy ketone **24** (Scheme 5). An NOE effect was observed between the C5 equatorial proton and C6 protons, as well as between the C7 axial proton and the benzyl protons (Figure 1). Further support for the relative stereochemical assignment of C5 and C7 was obtained by inspection of the ^{13}C NMR spectrum of acetonide **25** with regards to Rychnovsky and Evans theory.[30] In the ^{13}C NMR spectrum of *anti*-isomer **25** the gem-dimethyl groups on the acetonide carbon were present at δ = 25.98 and 25.71 ppm, due to a twist-boat conformation. In comparison, the dimethyl carbons on the corresponding *syn*-isomer were observed at δ = 30.83 and 20.52 ppm, due to a chair conformation.

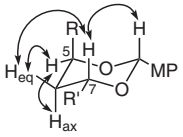


Figure 1 NOE observation of **29**

With the B ring and C1–C9 linear unit in hand, the coupling[31] of iodide **5** with thioketal **28** as well as further progress on the completion of the total synthesis of bryostatin 11 will be reported in due course.

Acknowledgment

K. Nakagawa-Goto acknowledges support from a research fellowship from Uehara Memorial Foundation in Japan.

References and Notes

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(17) ***N*-Acyloxazolidinone 13**
A round-bottom flask was charged with NaH (60% on mineral oil, 1.52 g, 39.3 mmol) and washed with hexanes to remove the mineral oil. The NaH was then dissolved in THF (15 mL) and cooled to 0 °C. Allylic alcohol **11** (2.27 g, 12.6 mmol) in THF (10 mL) was added and stirred at r.t. for 10 min. The mixture was cooled to 0 °C, and bromoacetic acid (1.84 g, 13.5 mmol) in THF (5 mL) was added dropwise via an addition funnel over 10 min with evolution of hydrogen gas. The reaction mixture was warmed to r.t. and stirred overnight. The cloudy reaction mixture was quenched slowly with H_2O at 0 °C. The organic layer was separated. The aqueous layer was adjusted to pH 4 with 1 N HCl aq solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to obtain the crude glycolic acid (2.8 g) as an orange oil, which was dissolved in dry Et_2O (40 mL). Et_3N (2.0 mL, 14.4 mmol) was added slowly, and the mixture was cooled to –78 °C. Pivaloyl chloride (1.6 mL, 13.0 mmol) was added dropwisee. After 5 min, the mixture was warmed to 0 °C, where it was stirred for 1 h and subsequently recooled to –78 °C. In a separate flask, (*S*)-(+)-4-isopropyloxazolidin-2-one (1.70 g, 13.1 mmol) was dissolved in THF (20 mL) and cooled to –78 °C. *n*-BuLi (1.3 M in hexanes, 11.5 mL, 14.9 mmol) was added dropwise via syringe, and the mixture was stirred for 10 min. The lithiated oxazolidinone **12** was added via cannula to the mixed anhydride, and the reaction was stirred for an additional 10 min before being warmed to 0 °C, where stirring continued for 3 h. The reaction was quenched by the addition of H_2O and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography gave acyl oxazolidinone **13** (1.98 g, 45% from **11**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 3 H), 7.30–7.24 (m, 2 H), 5.85–5.74 (m, 1 H), 5.39–5.26 (m, 2 H), 4.78 (AB, *J* = 17.9 Hz, 2 H), 4.73 (AB, *J* = 11.5 Hz, 2 H), 4.59 (s, 2 H), 4.40–4.33 (m, 1 H), 4.24–4.18 (m, 2 H), 4.18–4.10 (m, 1 H), 3.67 (dd, *J* = 10.2, 6.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 4.2 Hz, 1 H), 2.48–2.37 (m, 1 H), 0.90 (d, *J* = 7.0 Hz, 3 H) 0.85 (d, *J* = 7.0 Hz, 3 H). HRMS: *m/z* calcd for $C_{19}H_{25}NO_5Na$ [M^+ + Na]: 370.1625; found: 370.1607.
(18) **Diene 6**
Into a flask equipped with an addition funnel was added sodium bis(trimethylsilyl)amide (0.75 M in toluene, 15 mL, 11.3 mmol). THF (30 mL) was added, and the solution was cooled to –78 °C. Acyl oxazolidinone **13** (2.42 g, 7.0 mmol) in THF (10 mL) was added dropwise via an addition funnel. After stirring for 30 min at –78 °C, allyl iodide **14** (5.05 g, 22.1 mmol) in THF (10 mL) was added via syringe. After 10 min, the reaction was warmed to –45 °C and stirred at that temperature for 1 h. The reaction was quenched by the addition of sat. NH_4Cl and warmed to r.t. The aqueous layer was extracted twice with 50% EtOAc–hexanes. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided diene **6** (2.29 g, 74%) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.40–7.22 (m, 5 H), 5.83–5.71 (m, 1 H), 5.57–5.50 (m, 1 H), 5.37 (d, *J* = 17.2 Hz, 1 H), 5.22 (d, *J* = 10.5 Hz, 1 H), 4.96–4.90 (m, 2 H), 4.54–4.43 (m, 2 H), 4.28–4.07 (m, 3 H), 3.97 (dd, *J* = 9.0, 3.1 Hz, 1 H), 3.64–3.50 (m, 3 H), 3.41 (s, 3 H), 2.66 (dd, *J* = 14.2, 3.8 Hz, 1 H), 2.46 (dd, *J* = 14.2, 8.5 Hz, 1 H), 2.34–2.21 (m, 1 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.80 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.8, 156.5, 153.7, 138.7, 128.6, 128.5, 127.7, 127.6, 127.0, 118.0, 93.9, 87.7, 81.2, 75.8, 74.5, 72.9, 63.6, 58.3, 56.3, 39.2, 28.3, 18.0, 14.8. $[\alpha]_D^{23}$ +68.9 (*c* 3.14, CH_2Cl_2). HRMS: *m/z* calcd for $C_{24}H_{33}NO_7Na$ [M^+ + Na]: 470.2155; found: 470.2192.
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(20) **Pyrane 16**
Into a flask equipped with a reflux condenser was added diene **6** (2.09 g, 4.68 mmol) in CH_2Cl_2 (1 L). Argon was bubbled through the stirring solution for 1 h. The solution was heated to reflux and Grubbs second-generation catalyst (0.411 g, 0.49 mmol) was added in one portion. The reaction was refluxed for 24 h and cooled to r.t. The air was bubbled into the reaction mixture and stirred for 3 h at r.t. Concentration in vacuo and purification by flash chromatography provided pyrane **16** (1.72 g, 88%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 3 H), 7.30–7.26 (m, 2 H), 5.30 (dd, *J* = 10.7, 3.9 Hz, 1 H), 4.98 (d, *J* = 6.2 Hz, 1 H), 4.91 (d, *J* = 6.2 Hz, 1 H), 4.90–4.88 (m, 1 H), 4.62 (d, *J* = 12.1 Hz, 1 H), 4.57 (d, *J* = 12.1 Hz, 1 H), 4.56–4.50 (m, 1 H), 4.50–4.44 (m, 1 H), 4.32 (t, *J* = 9.2 Hz, 1 H), 4.23 (dd, *J* = 9.2, 2.9 Hz, 1 H), 3.60 (dd, *J* = 10.2, 6.5 Hz, 1 H), 3.48 (dd, *J* = 10.2, 4.8 Hz, 1 H), 3.42 (s, 3 H), 2.57–2.47 (m, 1 H), 2.45–2.32 (m, 2 H), 0.92 (d, *J* = 7.0 Hz, 3 H),

0.88 (d, *J* = 7.0 Hz, 3 H). HRMS: *m/z* calcd for $C_{22}H_{29}NO_7Na$ [M^+ + Na]: 442.1842; found: 442.1860.

(21) **Acetal 17**

Pyrane **16** (61.2 mg, 0.15 mmol) was dissolved in THF (1.2 mL) and MeOH (0.4 mL). Methylorthoformate (0.25 mL, 2.29 mmol), PPTS (2.1 mg, 0.01 mmol), and PTSA (1.9 mg, 0.01 mmol) were added to the mixture, which was then refluxed for 1 h. The reaction mixture was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided acetal **17** (51.5 mg, 82%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 3 H), 7.30–7.26 (m, 2 H), 5.22 (dd, *J* = 11.7, 2.2 Hz, 1 H), 4.60 (d, *J* = 10.2 Hz, 1 H), 4.56 (d, *J* = 10.2 Hz, 1 H), 4.50–4.44 (m, 1 H), 4.31 (t, *J* = 8.7 Hz, 1 H), 4.23 (dd, *J* = 9.2, 3.1 Hz, 1 H), 3.92–3.85 (m 1 H), 3.60 (dd, *J* = 10.3, 5.9 Hz, 1 H), 3.50 (dd, *J* = 10.3, 4.5 Hz, 1 H), 3.29 (s, 3 H), 3.23 (s, 3 H), 2.40–2.30 (m, 2 H), 2.60–1.98 (m, 1 H), 1.62–1.54 (m, 1 H), 1.45 (t, *J* = 12.5 Hz, 1 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.87 (d, *J* = 7.0 Hz, 3 H). HRMS: *m/z* calcd for $C_{22}H_{31}NO_7Na$ [M^+ + Na]: 444.1998; found: 444.2040.

(22) **Olefin 19**

To a solution of **17** (1.23 g, 2.92 mmol) in Et_2O (15 mL) and MeOH (1.0 mL), lithium borohydride (2 M solution in THF, 7.0 mL, 14.0 mmol) was added at 0 °C. The reaction mixture was stirred for 1 h and then quenched with 3 N NaOH aq. The reaction mixture was allowed to warm to r.t. The organic layer was separated, and the organic layer was washed with 3 N NaOH aq. The combined aqueous layers were re-extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 891.2 mg of alcohol **18** including the removed oxazolidinone (the ratio was 3:2 calcd from ^{1}H NMR). It was found that the alcohol could be carried on without further purification. Into a flask equipped with a low-temperature thermometer was added CH_2Cl_2 (3.0 mL) and oxalyl chloride (2.0 M in CH_2Cl_2, 3.0 mL, 6.0 mmol). After cooling to –78 °C, DMSO (0.85 mL, 12.0 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise via syringe. After stirring for 10 min, the resulting primary alcohol in CH_2Cl_2 (3.0 mL) was added dropwise via syringe. After stirring for 15 min, Et_3N (2.1 mL, 15.1 mmol) was added slowly via syringe. The cooling bath was removed after 20 min, and the reaction was allowed to warm to 0 °C. The reaction mixture was quenched with H_2O. The organic layer was separated and washed with H_2O. The combined aqueous layers were re-extracted with CH_2Cl_2. The combined organic layers were washed with brine, and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 660.1 mg of aldehyde as colorless oil, which was a mixture with the cleaved oxazolidinone (the ratio was 21:10 calcd from ^{1}H NMR) and used in the next reaction without further purification.

To a solution of Ph_3PCH_3Br (2.49 g, 7.0 mmol) in toluene (15.0 mL), KO*t*-Bu (520.0 mg, 4.6 mmol) in THF (3.0 mL) was added, and the mixture was stirred at r.t. for 1.5 h. To the resulting yellow suspension, aldehyde (660.1 mg) in toluene (7.0 mL) was added, and the mixture was stirred at r.t. overnight. The reaction was quenched by the addition of sat. NH_4Cl and warmed to r.t. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 498.9 mg (60%, 3 steps yields from **17**) of olefin **19** as colorless oil: Colorless oil. $[\alpha]_D^{23}$ +1.09 (*c* 1.83, CH_2Cl_2). IR (film): ν_{max} = 2938, 2861, 2828, 2361, 2339, 1458, 1358, 1314, 1075, 1049, 924, 737, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (4 H, m, ArH), 7.30–7.25 (1 H, m, ArH), 5.88 (1 H, ddd, *J* = 5.7, 10.5, 16.8 Hz, CH_2=C*H*), 5.27 (1 H, d, *J* = 16.8 Hz, C*H*H=CH), 5.12 (1 H, d, *J* = 10.5 Hz, CH*H*=CH), 4.56 (2 H, s, CH_2Ph), 4.06–4.00 (1 H, m, 6-H), 3.82–3.74 (1 H, m, 2-H), 3.56 (1 H, dd, *J* = 5.6, 10.2 Hz, CH_2OBn), 3.48 (1 H, dd, *J* = 4.6, 10.2 Hz, CH_2OBn), 3.22 (3 H, s, OCH_3), 3.19 (3 H, s, OCH_3), 2.06–1.96 (2 H, m, 3- and 5-H_{eq}), 1.38 (2 H, dd, *J* = 11.9, 12.3 Hz, 3- and 5-H_{ax}). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 138.5, 128.6, 127.9, 127.8, 115.6, 99.0, 75.2, 73.7, 73.6, 73.1, 47.9, 47.6, 38.7, 35.4. HRMS: *m/z* calcd for $C_{17}H_{24}O_4Na$ [M^+ + Na]: 315.1572; found: 315.1580.

(23) Brown, H. C.; Randa, R. S.; Bhat, K. S.; Zaidlewicz, M.; Rachela, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389..

(24) **PMB Ether 21**

To a solution of 4-ICr$_2$B-allyl in Et_2O (ca. 270 mmol), aldehyde **20** (8.25 g, 43.0 mmol), in Et_2O (15.0 mL) was added slowly via additional funnel at –78 °C. After stirring for 2 h, the mixture was allowed to warm to r.t. Then aq NaOH (3 M, 60 mL) was added carefully, followed by H_2O_2 (30% aq, 30 mL). The biphasic mixture was refluxed without condenser to evaporate Et_2O, and THF (60 mL) was added. The mixture was refluxed overnight, then diluted with H_2O and the phases separated. The aqueous layer was back extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided allylic alcohol (9.0 g) including a small amount of 4-ICr-OH. The resulting alcohol (9.0 g) in THF (10.0 mL) was added to a suspension of KH (30% in mineral oil, 7.96 g, 59.7 mmol) in THF (50.0 mL) at 0 °C. After stirring at r.t. for 15 min, the mixture was cooled to 0 °C. PMBCl (11.0 mL, 80.9 mmol) was added, and the mixture was stirred at r.t. overnight. The mixture was quenched with H_2O and extracted with EtOAc (3×). The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided PMB ether **21** (10.07 g, 70%, 2 steps yield from **20**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 4 H), 7.30–7.25 (m, 1 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 6.02–5.89 (m, 1 H), 5.14–5.06 (m, 1 H), 5.05–5.00 (m, 1 H), 4.55 (d, *J* = 10.7 Hz, 1 H), 4.49 (d, *J* = 12.3 Hz, 1 H), 4.45 (d, *J* = 12.3 Hz, 1 H), 4.39 (d, *J* = 10.7 Hz, 1 H), 3.79 (s, 3 H), 3.47 (dd, *J* = 8.6, 3.5 Hz, 1 H), 3.39 (d, *J* = 8.6 Hz, 1 H), 3.14 (d, *J* = 8.6 Hz, 1 H), 2.38–2.20 (m, 2 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 159.2, 139.1, 137.6, 131.7, 129.3, 128.5, 127.7, 127.6, 116.2, 113.8, 83.1, 77.61, 74.0, 73.3, 55.4, 40.2, 35.7, 22.3, 20.8. $[\alpha]_D^{23}$ +15.57 (*c* 4.74, CH_2Cl_2). HRMS: *m/z* calcd for $C_{23}H_{30}O_3Na$ [M^+ + Na]: 377.2087; found: 377.2081.

(25) Brabader, J. D.; Vandewalle, M. *Synthesis* **1994**, 855.

(26) **Hydroxy Ketone 24**

To a solution of (*i*-Pr)$_2$NH (1.5 mL, 10.7 mmol) in THF (3.0 mL), *n*-BuLi (1.4 M in hexane, 7.4 mL, 10.7 mmol) was added dropwise at –30 °C. After stirring for 10 min, the mixture was cooled to –78 °C, and a solution of **23** (3.54 g, 10.9 mmol) in THF (5.0 mL) was added slowly. The mixture was stirred for 2 h, and a solution of aldehyde **22** (1.74 g, 4.9 mmol) in THF (5.0 mL) was added slowly. After stirring for 15 min, the mixture was treated according to Vandewalle's procedure to provide hydroxy ketone **24** (2.33 g, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.60 (m, 4 H), 7.30–7.25 (m, 11 H), 7.23 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 4.62 (d, *J* = 10.9 Hz, 1 H), 4.56 (d, *J* = 10.9 Hz, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.46 (d, *J* = 12.1 Hz, 1 H), 4.29–4.20 (m, 1 H), 3.92 (t, *J* = 6.1 Hz, 2 H), 3.81–3.75

(m, 1 H), 3.77 (s, 3 H), 3.40 (d, *J* = 8.7 Hz, 1 H), 3.16 (d, *J* = 8.7 Hz, 1 H), 2.63–2.56 (m, 4 H), 1.66–1.56 (m, 1 H), 1.52–1.40 (m, 1 H), 1.03 (s, 9 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 211.2, 159.2, 138.9, 135.7, 133.5, 131.6, 130.0, 129.5, 128.5, 127.9, 127.7, 127.6, 113.9, 79.4, 74.8, 73.3, 64.9, 59.6, 55.5, 50.9, 46.3, 40.0, 37.6, 31.1, 27.0, 22.4, 20.8, 19.3. $[\alpha]_D^{23}$ –3.63 (*c* 3.55, CH_2Cl_2). HRMS: *m/z* calcd for $C_{42}H_{54}O_6SiNa$ [M^+ + Na]: 705.3587; found: 705.3588.

(27) (a) Saksena, A. K.; Mangiaraeina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Evans, D. A.; Dimare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476.

(28) Nakagawa-Goto, K.; Crimmins, M. T. *Synth. Commun.* **2011**, in press.

(29) **Acetonide 25**
A suspension of $Me_2NHB(OAc)_3$ (1.68 g, 6.39 mmol) in MeCN (5.0 mL) and AcOH (5.0 mL) was stirred at r.t. for 30 min under argon. The mixture was cooled to –45 °C, and hydroxy ketone **24** (773.7 mg, 1.14 mmol) in MeCN (5.0 mL) solution was then added. After stirring at –45 °C for 24 h, the mixture was quenched with 10% Rochelle's salts and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography afforded diol (760.8 mg, 98%, *anti*/*syn* = 7.6:1 mixture). To a solution of diol (614.0 mg, 0.9 mmol) in THF (5.0 mL), 2,2-dimethoxypropane (5.0 mL, excess) and PPTS (25.9 mg, 0.1 mmol) were added. After stirring at r.t. overnight, the mixture was quenched with sat. $NaHCO_3$. The whole was extracted with EtOAc (3×). The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided acetonide **25** (626.4 mg, 96%) as a colorless oil. Further purification by flash chromatography (CH_2Cl_2–hexane–Et_2O = 4:1:0.2 then 35% EtOAc–hexane) afforded *anti*-acetonide (553.6 mg) and *syn*-acetonide (72.8 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.63 (m, 4 H), 7.44–7.30 (m, 10 H), 7.30–7.24 (m, 1 H), 7.21 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 4.60–4.43 (m, 4 H), 4.15–4.02 (m, 2 H), 3.84–3.75 (m, 1 H), 3.79 (s, 3 H), 3.63–3.64 (m, 2 H), 3.38 (d, *J* = 8.6 Hz, 1 H), 3.16 (d, *J* = 8.6 Hz, 1 H), 1.79–1.50 (m, 4 H), 1.45–1.30 (m, 2 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.04 (s, 9 H), 0.95 (s, 6 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 159.2, 139.1, 135.8, 135.8, 134.2, 134.1, 131.8, 131.1, 129.8, 129.0, 128.5, 127.8, 127.8, 127.7, 127.6, 113.9, 100.36, 79.6, 77.6, 74.5, 73.3, 63.9, 63.5, 60.3, 55.5, 40.1, 39.3, 39.1, 38.9, 38.4, 30.6, 29.9, 29.1, 27.1, 25.8, 25.5, 23.9, 23.2, 22.3, 21.0, 19.4, 14.3, 11.2. $[\alpha]_D^{23}$ –3.82 (*c* 2.49, CH_2Cl_2). HRMS: *m/z* calcd for $C_{45}H_{60}O_6SiNa$ [M^+ + Na]: 747.4051; found: 747.4016.

(30) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

(31) Similar coupling was successfully performed by Hale, see ref. 12b.