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Concise Formal Synthesis of the Bryostatin Southern Hemisphere (C17−C27)

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Abstract: An efficient synthesis of Hale and co-workers' C17−C27 bryostatin southern hemisphere intermediate has been accomplished in six steps and 33% overall yield from (*R*)-2-(benzyloxy)propanal. The synthesis features a one-pot DIBALH/HWE ester homologation as well as a novel acetonide rearrangement/glycal formation cascade.

The bryostatins constitute a family of polyacetate-derived natural products originally isolated from the bryozoan *Bugula neritina* by Pettit and co-workers.[1] Their potent antineoplastic activity, low toxicity, and unique mode of action have led to numerous human clinical trials investigating bryostatin 1 (Figure 1) alone or in combination with other chemotherapies.[2,3] Detailed studies by Wender have shown that simplified analogues are capable of maintaining enzyme-binding capability and even exhibiting increased biological activity.[4]

The majority of the naturally occurring bryostatins have the general structure shown in Figure 1, differing only in the ester functionalities at C7 and C20. Bryostatin 3 contains further oxidation at C22, and bryostatins 10, 11, and 13 are deoxygenated at C20. Total syntheses of bryostatins 7, 2, and 3 by Masamune,[5] Evans,[6] and Yamamura,[7] respectively, have provided important benchmarks for further synthetic efforts toward these important targets. However, the lengths of these routes, each requiring at least 40 linear steps (about 80 total steps), have encouraged many other groups to explore potentially more practical routes.[8] An efficient, highly convergent, and relatively brief synthetic route to the bryostatins remains an important goal.

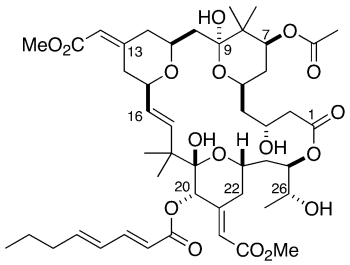

FIGURE 1. Bryostatin **1**.

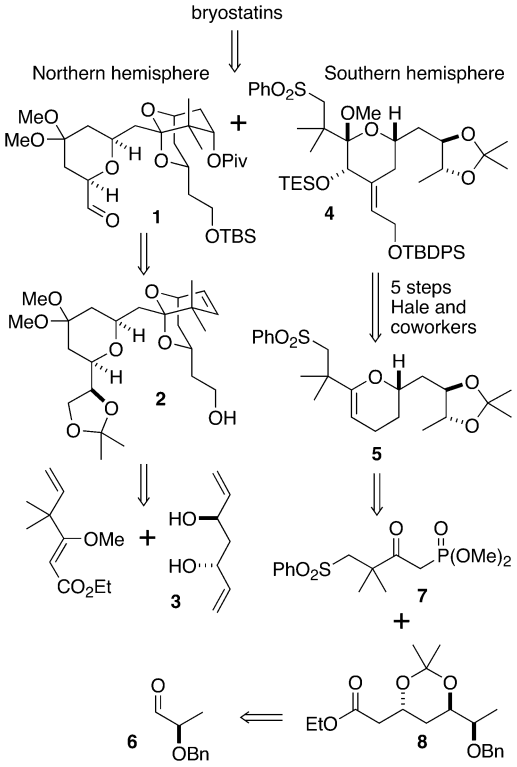

FIGURE 2. Bryostatin retrosynthesis.

Our interest in the bryostatins was stimulated by a realization that the northern hemisphere (C1−C16) fragment (**1**, Figure 2) could be obtained via our recently developed C_2-symmetric diene-diol ketalization/ring-closing metathesis desymmetrization strategy.[9] Compound **2**, containing the complete northern fragment skeleton, has indeed been realized in only seven steps from diene diol **3**.[10] This account details our completion of a brief southern hemisphere (C17−C27) formal synthesis, targeting Masamune's phenyl sulfone **4**, which was used to complete a bryostatin 7 total synthesis.[5] Our route

(1) Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846.

(2) (a) The Bryostatins. Pettit, G. R. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Ed.; Springer-Verlag: New York, 1991; pp 153−195. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (c) Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841. (d) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, *19*, 413.

(3) For current information on bryostatin 1 clinical trials, see: http://www.cancer.gov/search/clinical_trials/

(4) See ref 2d and (a) Wender, P. A.; Baryza, J. L.; Bennett, C. E.; Bi, C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; Lacôte, E.; Lippa, B.; Nell, P. G.; Turner, T. M. *J. Am. Chem. Soc.* **2002**, *124*, 13648. (b) Wender, P. A.; Mayweg, A. V. W.; VanDeusen, C. L. *Org. Lett.* **2003**, *5*, 277.

(5) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407.

(6) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540.

(7) Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290.

(8) (a) See ref 2d. (b) Hale, K. J.; Frigerio, M.; Manaviazar, S. *Org. Lett.* **2003**, *5*, 503.

(9) (a) Burke, S. D.; Müller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827. (b) Burke, S. D.; Voight, E. A. *Org. Lett.* **2001**, *3*, 237. (c) Voight, E. A.; Rein, C.; Burke, S. D. *Tetrahedron Lett.* **2001**, *42*, 8747. (d) Keller, V. A.; Martinelli, J. R.; Strieter, E. R.; Burke, S. D. *Org. Lett.* **2002**, *4*, 467. (e) Voight, E. A.; Rein, C.; Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489.

(10) Voight, E. A.; Roethle, P. A.; Burke, S. D. Unpublished results.

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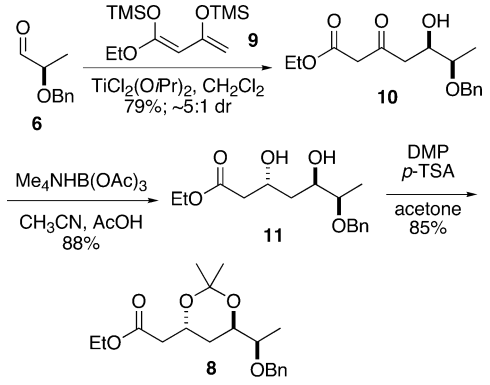
SCHEME 1. Synthesis of Ester 8

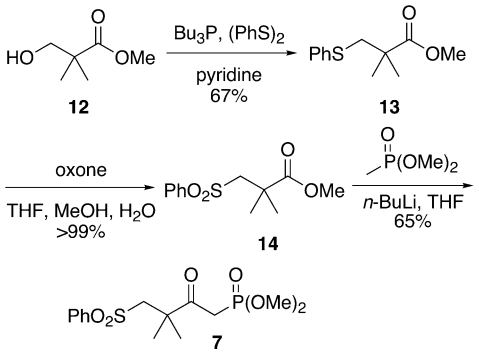


intersects Hale and co-workers' intermediate, glycal **5**,[8b] after only six steps from (*R*)-2-(benzyloxy)propanal (**6**), in favorable comparison to Hale's route, which required 15 steps from *trans*-1,4-hexadiene. This strategy was dependent on a proposed one-pot diisobutylaluminum hydride (DIBALH)/Horner−Wadsworth−Emmons (HWE) ester homologation between phosphonate **7**[11] and ester **8**. Hydrogenation and a novel acetonide rearrangement/glycal formation cascade would then yield **5**, completing an expeditious formal synthesis. We hoped to arrive at *β*-ketophosphonate **7** and ester **8** via modifications and improvements of previously reported routes.[11,12] If successfully executed, the route suggested in Figure 2 would constitute the shortest (11 step) approach to the completed southern fragment yet reported.

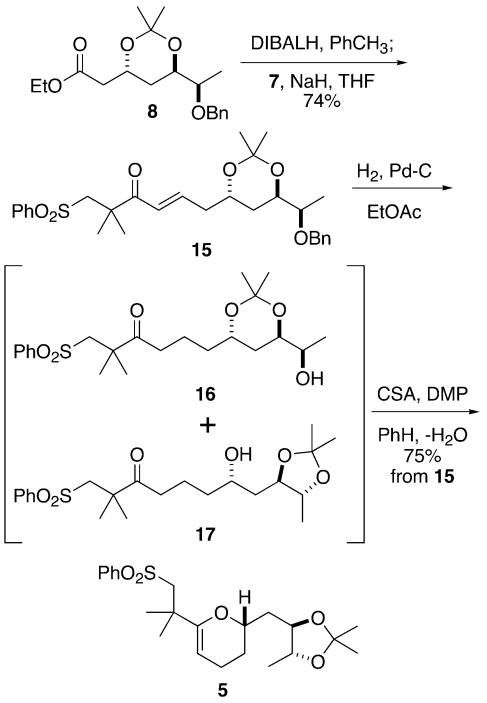
To begin the synthesis (Scheme 1), the bis(trimethylsilyl)enol ether **9** derived from ethyl acetoacetate[13] was added to a cooled (−78 °C) solution of (*R*)-2-(benzyloxy)propanal (**6**)[14] and $TiCl_2(OiPr)_2$ according to Evans' procedure,[15] affording *β*-hydroxy ketone **10** with ~5:1 diastereoselectivity in 79% yield. An *anti*-selective reduction of this mixture using tetramethylammonium triacetoxyborohydride[16] over 40 h from −30 to −15 °C delivered diol **11** in 88% yield, still as a 5:1 ratio of diastereomers. Although **11** was difficult to purify at this stage, acetonide formation using 2,2-dimethoxypropane (DMP) and catalytic *p*-TSA in acetone facilitated diastereomer separation, providing access to the desired intermediate **8** in 85% isolated yield as a single diastereomer.[12]

Although a preparation of *β*-ketophosphonate **7** has been reported previously,[11] we sought an abbreviated route, which is detailed in Scheme 2. Commercially available methyl 2,2-dimethyl-3-hydroxypropionate (**12**) was converted to phenyl sulfide **13**[17] in 67% yield using tributylphosphine, phenyl disulfide, and pyridine.[18] Oxi-

SCHEME 2. Synthesis of *β*-Ketophosphonate 7



SCHEME 3. Completion of the Formal Synthesis



dation with oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)[11] provided phenyl sulfone **14**[19] in quantitative yield without the need for purification. The known conversion of **14** to **7** was then carried out as reported[11] in preparation for the one-pot DIBALH/HWE reaction with intermediate **8**.

Ester **8** was reduced with DIBALH (1.1 equiv) at −78 °C in toluene (Scheme 3). In a separate flask, *β*-ketophosphonate **7** (1.2 equiv) was deprotonated with sodium hydride in THF, and the resulting anion was added via cannula to the first flask. After warming to room temperature, α,*β*-unsaturated ketone **15** was obtained in 74% yield from **8**. Hydrogenation of the double bond in **15** was accompanied by hydrogenolysis of the benzyl ether, yielding hydroxyketone **16**. Varying amounts of five-membered ring acetonide (**17**) were always observed in this reaction, presumably due to the more thermodynamically stable nature of this ring in comparison with

(11) Hale, K. J.; Frigerio, M.; Manaviazar, S. *Org. Lett.* **2001**, *3*, 3791.
(12) Baxter, J.; Mata, E. G.; Thomas, E. J. *Tetrahedron* **1998**, *54*, 14359. This three-step sequence is closely related to a strategy reported by Thomas and co-workers; however, a completed southern hemisphere synthesis was not realized by this route.
(13) (a) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688. (b) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.
(14) Prepared via a modification of Heathcock's procedure: Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247. See Supporting Information for details.
(15) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816.
(16) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(17) Gracia, J.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2865.
(18) Shibuya, H.; Tsujii, S.; Yamamoto, Y.; Miura, H.; Kitagawa, I. *Chem. Pharm. Bull.* **1984**, *32*, 3417.
(19) See ref 11 and Parham, W. E.; McKown, W. D.; Nelson, V.; Kajigaeshi, S.; Ishikawa, N. *J. Org. Chem.* **1973**, *38*, 1361.

the six-membered ring acetonide.[20] Therefore, instead of separating **16** and **17**, the crude mixture, after filtration of the hydrogenation catalyst and concentration, was dissolved in benzene (PhH) and treated with 5 mol % camphorsulfonic acid (CSA) in the presence of DMP as a dehydrating agent.[21] After 5 h at room temperature, the desired glycal (**5**) was obtained in 75% overall yield for the two steps.[22] The ^{1}H and ^{13}C NMR data for **5** matched that reported by Hale and co-workers,[8b] and X-ray crystallographic analysis of recrystallized **5** (Et_2O/hexanes) confirmed this structural assignment.[23]

In conclusion, a convenient and highly convergent formal synthesis of the bryostatin southern hemisphere (**4**, Figure 2) has been carried out in six steps and 33% overall yield from (*R*)-2-(benzyloxy)propanal. This accomplishment brings a practical route to natural and nonnatural bryostatins closer within reach. Efforts toward the bryostatin northern hemisphere (**1**, Figure 2) from intermediate **2** continue and will be reported in due course.

Experimental Section

Preparation of β-Hydroxy Ketone 10. A solution of Ti(O*i*Pr)$_4$ (1.83 mL, 6.19 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C, and $TiCl_4$ (0.646 mL, 5.89 mmol) was added. After 15 min, cooling to −78 °C was followed by addition of a cooled (−78 °C) solution of (*R*)-2-(benzyloxy)propanal (**6**, 1.24 g, 7.55 mmol) in CH_2Cl_2 (6 mL) via cannula. The resulting yellow solution was stirred 15 min before a cooled (−78 °C) solution of bis(trimethylsilyl)enol ether **9** (3.73 g, 13.6 mmol) in CH_2Cl_2 (6 mL) was added over 10 min via cannula. The yellow-orange reaction mixture was stirred for 20 min at −78 °C, followed by warming to 0 °C and addition of pH 7 phosphate buffer (70 mL). CH_2Cl_2 (30 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified via FCC (10−12% acetone/hexanes) to give β-hydroxy ketone **10** (1.75 g, 79%) as a slightly yellow oil in ∼5:1 dr. For the major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.4−7.2 (m, 5H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.19 (q, *J* = 7 Hz, 2H), 4.04 (tdd, *J* = 6.5, 5, 4.5 Hz, 1H), 3.51 (qd, *J* = 6.5, 5 Hz, 1H), 3.49 (s, 2H), 2.74 (d, *J* = 4.5 Hz, 1H), 2.73 (d, *J* = 6.5 Hz, 2H), 1.27 (t, *J* = 7 Hz, 3H), 1.22 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 202.6 (C), 167.1 (C), 138.2 (C), 128.4 (CH × 2), 127.8 (CH × 2), 127.7 (CH), 76.6 (CH), 70.9 (CH_2), 70.3 (CH), 61.3 (CH_2), 49.9 (CH_2), 45.7 (CH_2), 14.9 (CH_3), 14.1 (CH_3); IR (thin film) 3499, 3030, 2979, 1742, 1712 cm^{-1}; $[\alpha]^{24}_D$ −14 (*c* 1.3, $CHCl_3$); HRMS (FAB) calcd for $C_{16}H_{22}O_5Na$ (M + Na^+) 317.1365, found 317.1379.

Preparation of Diol 11. $Me_4NHB(OAc)_3$ (10.9 g, 40.0 mmol) was dissolved in CH_3CN (41 mL) at room temperature, and AcOH (13 mL) was added slowly. After 20 min, cooling to −40 °C was followed by addition of β-hydroxy ketone **10** (1.18 g, 4.00 mmol) in CH_3CN (13 mL) via cannula. The clear solution was stirred at −30 °C for 24 h and −15 °C for 16 h and then poured into saturated Rochelle's salt (50 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 20 mL), dried (Na_2SO_4), and concentrated. Purification by FCC (40−70% Et_2O/hexanes) gave diol **11** (1.04 g, 88%) as a clear semisolid with one minor diastereomer (from starting material mixture, dr ∼5:1). For the major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.2−7.4 (m, 5H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.4−4.2 (m, 1H), 4.17 (q, *J* = 7 Hz, 2H), 3.9−3.7 (m, 1H), 3.46 (apquint, *J* = 6.5 Hz, 1H), 3.44 (d, *J* = 4 Hz, 1H), 2.83 (d, *J* = 3 Hz, 1H), 2.52 (d, *J* = 6.5 Hz, 2H), 1.8−1.5 (m, 2H), 1.27 (t, *J* = 7 Hz, 3H), 1.21 (d, *J* = 6 Hz, 3H); ^{13}C ($CDCl_3$) δ 172.8 (C), 138.4 (C), 128.7 (CH), 128.0 (CH × 2), 127.9 (CH × 2), 78.5 (CH), 72.3 (CH), 71.2 (CH_2), 65.7 (CH), 60.8 (CH_2), 41.9 (CH_2), 38.8 (CH_2), 15.6 (CH_3), 14.4 (CH_3); IR (thin film) 3446, 2978, 2924, 1733 cm^{-1}; $[\alpha]^{24}_D$ −35 (*c* 1.0, $CHCl_3$); HRMS (FAB) calcd for $C_{16}H_{24}O_5Na$ (M + Na^+) 319.1521, found 319.1526.

Preparation of Acetonide 8. Diol **11** (1.01 g, 3.40 mmol) was dissolved in 2:1 acetone/DMP (33 mL), and *p*-TSA·H_2O (65 mg, 0.34 mmol) was added. After 30 min at room temperature, the clear reaction mixture was quenched with Et_3N (3.4 mL) and concentrated. Purification by FCC (10−15% Et_2O/hexanes) gave acetonide **8** (975 mg, 85%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.4−7.2 (m, 5H), 4.63 (ABq, J_{AB} = 11.5, $\Delta\nu_{AB}$ = 7 Hz, 2H), 4.26 (dddd, *J* = 10, 8, 6, 5.5 Hz, 1H), 4.15 (ABX$_3$, J_{AB} = 11 Hz, $J_{AX} = J_{BX}$ = 7 Hz, $\Delta\nu_{AB}$ = 6 Hz, 2H), 3.88 (dt, *J* = 10, 6.5 Hz, 1H) 3.54 (apquint, *J* = 6.5 Hz, 1H), 2.52 (*A*B*X*, J_{AB} = 15.5 Hz, J_{AX} = 8 Hz, 1H), 2.44 (A*B*X, J_{AB} = 15.5 Hz, J_{BX} = 5.5 Hz, 1H), 1.86 (ddd, *J* = 12.5, 10, 6 Hz, 1H), 1.50 (ddd, *J* = 12.5, 10, 6.5 Hz, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.26 (t, *J* = 7 Hz, 3H), 1.15 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9 (C), 139.1 (C), 128.3 (CH × 2), 127.7 (CH × 2), 127.5 (CH), 100.8 (C), 76.3 (CH), 71.8 (CH_2), 69.9 (CH), 63.8 (CH), 60.5 (CH_2), 40.9 (CH_2), 33.6 (CH_2), 24.8 (CH_3), 24.4 (CH_3), 15.3 (CH_3), 14.3 (CH_3); IR (thin film) 2986, 2936, 1737 cm^{-1}; $[\alpha]^{24}_D$ +40 (*c* 1.1, $CHCl_3$); HRMS (FAB) calcd for $C_{19}H_{28}O_5Na$ (M + Na^+) 359.1834, found 359.1837.

Preparation of Sulfide 13. Methyl 2,2-dimethyl-3-hydroxypropionate (6.40 mL, 50.0 mmol), pyridine (100 mL), phenyl disulfide (12.0 g, 55.0 mmol), and tributylphosphine (15.0 mL, 60.0 mmol) were heated to 60 °C and stirred 20 h. After cooling to room temperature, Et_2O (200 mL) was added and the mixture was washed with 1N HCl (3 × 100 mL), saturated aq $NaHCO_3$ (2 × 100 mL), dried (Na_2SO_4), and concentrated. Purification by FCC (0−10% Et_2O/hexanes × 2) gave phenyl sulfide **13** (7.47 g, 67%) as a clear oil. Characterization data were consistent with the previously reported data.[17]

Preparation of Sulfone 14. To a vigorously stirred solution of sulfide **13** (7.47 g, 33.3 mmol) in THF (22 mL), MeOH (22 mL), and H_2O (22 mL) at 0 °C was added oxone (57.3 g, 93.2 mmol) portionwise. After 5 min at 0 °C, the white suspension was warmed to room temperature and stirred for 30 min. The reaction was poured into H_2O (500 mL) and extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to give sulfone **14** (8.54 g, >99%) as a white solid. Characterization data were consistent with the previously reported data.[19]

Preparation of β-Ketophosphonate 7. Methyl dimethyl phosphonate (1.37 mL, 12.3 mmol) and THF (12 mL) were cooled to −78 °C, and *n*-BuLi (2.5 M in hexanes, 4.92 mL, 12.3 mmol) was added. After 15 min, ester **14** (1.26 g, 4.92 mmol) in THF (4 mL) was added dropwise via cannula, and the reaction warmed to room temperature and stirred for 4 h. The reaction mixture was poured into saturated aqueous NH_4Cl (80 mL), extracted with Et_2O (3 × 50 mL) and EtOAc (50 mL), dried (Na_2SO_4), and concentrated. Purification by FCC (80−100% EtOAc/hexanes) gave β-ketophosphonate **7** (1.12 g, 65%) as a clear, viscous oil: ^{1}H NMR ($CDCl_3$) δ 8.0−7.8 (m, 2H), 7.7−7.5 (m, 3H), 3.82 (d, *J* = 11 Hz, 6H), 3.49 (s, 2H), 3.38 (d, *J* = 21.5 Hz, 2H), 1.49 (s, 6H); ^{13}C ($CDCl_3$) δ 204.9 (C, d, J_{PC} = 7 Hz), 141.0 (C), 133.7 (CH), 129.3 (CH × 2), 127.5 (CH × 2), 65.2 (CH_2), 53.1 (CH_3 × 2, d, J_{PC} = 6 Hz), 47.5 (C, d, J_{PC} = 4 Hz), 36.1 (CH_2, d, J_{PC} = 134 Hz), 24.8 (CH_3 × 2); IR (thin film) 3065, 2956, 1710 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{21}O_6PSNa$ (M + Na^+) 371.0694, found 371.0689.

Preparation of Enone 15. A solution of β-ketophosphonate **7** (575 mg, 1.65 mmol) in THF (8 mL) was cooled to 0 °C, and

(20) See, for example: (a) Tius, M. A.; Fauq, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035. (b) Toshima, H.; Yoshida, S.; Suzuki, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6721. (c) Sánches-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209. (d) Solladié, G.; Colobert, F.; Denni, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3081.

(21) The reaction could also be carried out under Dean−Stark conditions without DMP; however, the yield was lowered to 56% as a result of acetonide hydrolysis side reactions.

(22) Purified **16** (69% from **15**) could be converted to **5** in 84% yield; however, the overall yield from **15** was higher when **16** was not isolated.

(23) See Supporting Information for X-ray crystallographic data.

NaH (42 mg, 1.7 mmol) was added. The reaction was warmed to room temperature and stirred for 25 min, becoming a yellow solution. In a separate flask, ester **8** (428 mg, 1.27 mmol) and $PhCH_3$ (13 mL) were cooled to −78 °C, and DIBALH (1.5 M in $PhCH_3$, 1.02 mL, 1.53 mmol) was added slowly down the side of the flask. After 20 min, the phosphonate anion was added slowly down the side of the flask via cannula. The reaction was warmed to room temperature and stirred for 7 h, during which time a white precipitate was observed. Saturated aqueous Rochelle's salt (10 mL) was added carefully, stirring was continued for 10 min, and CH_2Cl_2 (50 mL) and H_2O (50 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by FCC (30−40% Et_2O/hexanes) gave enone **15** (482 mg, 74%) as a clear, viscous oil: ^{1}H NMR ($CDCl_3$) δ 8.0−7.8 (m, 2H), 7.7−7.5 (m, 3H), 7.4−7.2 (m, 5H), 6.96 (dt, J = 15.5, 7 Hz, 2H), 6.60 (dt, J = 15.5, 1.5 Hz, 2H), 4.63 (ABq, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 9.5 Hz, 2H), 3.91 (ddt, J = 9.5, 7.5, 6 Hz, 1H), 3.88 (dt, J = 9.5, 6 Hz, 1H), 3.52 (apquint, J = 6 Hz, 1H), 3.49 (s, 2H), 2.6−2.2 (m, 2H), 1.82 (ddd, J = 12.5, 9.5, 6 Hz, 1H), 1.49 (ddd, J = 12.5, 9.5, 6 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.37 (s, 6H), 1.15 (d, J = 6 Hz, 3H); ^{13}C ($CDCl_3$) δ 200.6 (C), 145.3 (CH), 141.7 (C), 139.2 (C), 133.7 (CH), 129.4 (CH × 2), 128.5 (CH × 2), 127.90 (CH × 2), 127.86 (CH × 2), 127.6 (CH), 125.2 (CH), 100.8 (C), 76.4 (CH), 71.9 (CH_2), 70.1 (CH), 65.8 (CH), 64.1 (CH_2), 46.1 (C), 38.8 (CH_2), 34.0 (CH_2), 25.1 (CH_3), 24.8 (CH_3 × 2), 24.7 (CH_3), 15.5 (CH_3); IR (thin film) 2982, 2934, 1691, 1625 cm^{-1}; $[\alpha]^{24}_D$ +35 (*c* 1.0, $CHCl_3$); HRMS (FAB) calcd for $C_{29}H_{38}O_6SNa$ (M + Na^+) 537.2287, found 537.2266.

Preparation of Compound Glycal 5. Enone **15** (252 mg, 0.490 mmol) was dissolved in EtOAc (5 mL), and Pd−C (10%, 245 mg) was added. After stirring under an atmosphere of H_2 overnight at room temperature, the catalyst was filtered and the filtrate was concentrated, giving crude **16** (containing some **17** by TLC), which was dissolved in PhH (3.7 mL) and DMP (1.2 mL). Camphorsulfonic acid (6 mg, 0.03 mmol) was added, and the reaction was stirred for 5 h at room temperature. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4), and concentrated. Purification by FCC (20−25% Et_2O/hexanes) gave glycal **5** (151 mg, 75%) as a white solid. A sample was recrystallized from Et_2O/hexanes for X-ray crystallographic analysis (see Supporting Information): ^{1}H NMR (C_6D_6) δ 7.9−7.8 (m, 2H), 7.0−6.9 (m, 3H), 4.46 (brt, J = 3.5, 1H), 3.74 (ddd, J = 10, 8.5, 2 Hz, 1H), 3.67 (tdd, J = 10, 3.5, 2.5 Hz, 1H), 3.53 (dq, J = 8.5, 6 Hz, 1H), 3.29 (d, J = 14 Hz, 1H), 3.16 (d, J = 14 Hz, 1H), 1.8−1.6 (m, 2H), 1.45 (ddd, J = 14, 9.5, 2.5 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.4−1.2 (m, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.2−1.0 (m, 1H), 1.09 (d, J = 6 Hz, 3H); 3.91 (s, 3H), 3.89 (s, 3H), 2.73 (ddd, J = 18, 2.5, 2 Hz, 1H), 2.47 (ddd, J = 18, 4, 2 Hz, 1H); ^{13}C NMR (C_6D_6) δ 156.5 (C), 143.0 (C), 133.0 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.3 (C), 108.4 (C), 95.1 (CH), 79.4 (CH), 77.6 (CH), 72.9 (CH), 64.2 (CH_2), 38.9 (CH_2), 38.7 (CH_2), 28.2 (CH_2), 28.02 (CH_3), 27.96 (CH_3), 27.3 (CH_3), 26.2 (CH_3), 20.7 (CH_2), 17.6 (CH_3); IR (thin film) 2981, 2930 cm^{-1}; $[\alpha]^{24}_D$ +40 (*c* 1.0, $CHCl_3$); mp 84−87 °C; HRMS (FAB) calcd for $C_{22}H_{32}O_5SNa$ (M + Na^+) 431.1868, found 431.1869.

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Supporting Information Available: Experimental procedure for (*R*)-2-(benzyloxy)propanal (**6**), ^{1}H and ^{13}C NMR spectra for **5** and **7**−**15**, and X-ray crystallographic data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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