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A Short Synthetic Pathway to a Fully-Functionalized Southern Hemisphere of the Antitumor Macrolide Bryostatin 1

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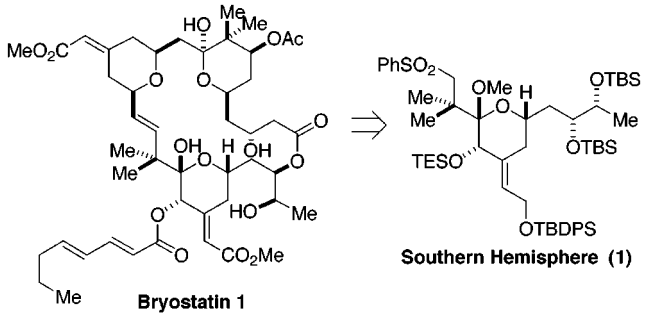
ABSTRACT



An 18-step asymmetric synthesis of the bryostatin 1 "southern hemisphere" fragment (1) has been developed. Key steps include an aldol reaction between 6 and 7 and a dehydration to establish the (*E*)-exocyclic alkene in 2 and a stereoselective Luche reduction and protection with TESOTf to access 1.

The recent cure of a 41-year old woman with advanced non-Hodgkin's lymphoma[1] has heightened medical and synthetic interest in bryostatin 1[2] and has brought to the fore the issue of scarcity of supply. A large number of synthetic groups have already attempted to address this problem, with a number (Masamune,[3] Evans,[4] and Nishiyama/Yamamura[5]) having accomplished impressive total syntheses of various family members. Wender and associates[6] have also recently reported the first simplified bryostatin analogues with powerful antitumor effects and potent PKC-binding activity. Our own synthetic efforts in this area have resulted in a fully stereocontrolled asymmetric synthesis of the bryostatin B-ring (via a novel C_2-symmetry-breaking olefination tactic)[7] and an advanced C-ring model study.[8] In continuation of these endeavors, we now report a fully stereocontrolled 18-step asymmetric synthesis of the "Southern Hemisphere" intermediate **1**, which has introduced all the functionality

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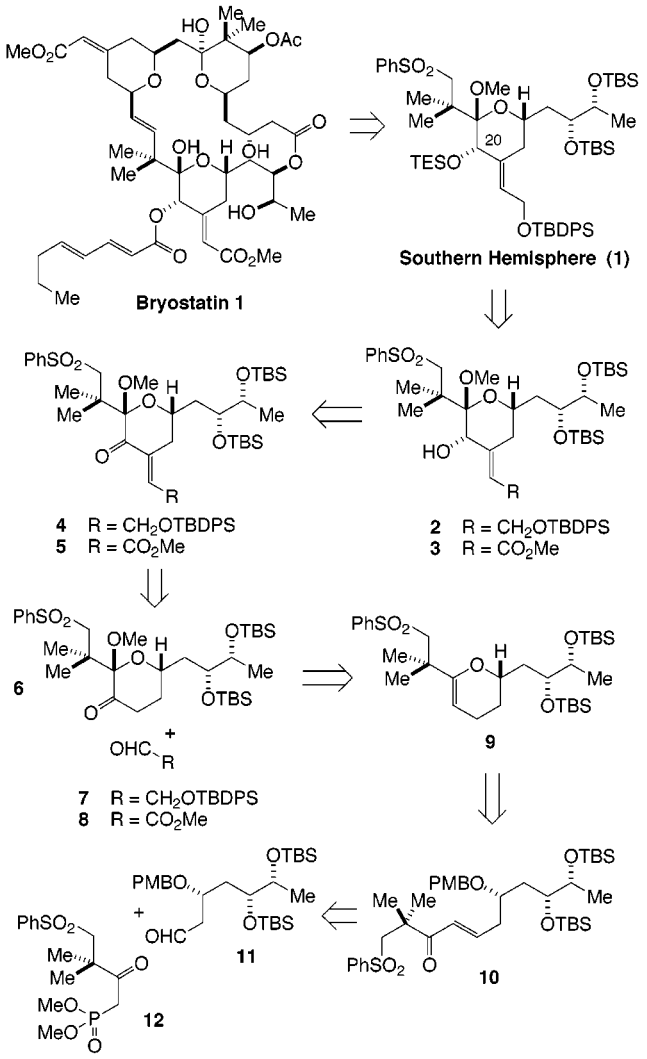
needed for a future convergent total synthesis of bryostatin 1.

Our most recent plan for assembling the bryostatin 1 C-ring called for the intermediacy of phenyl sulfone **1** and the implementation of a combined aldol/dehydration tactic on aldehyde **7** and ketone **6** to obtain enone **4** (Scheme 1).

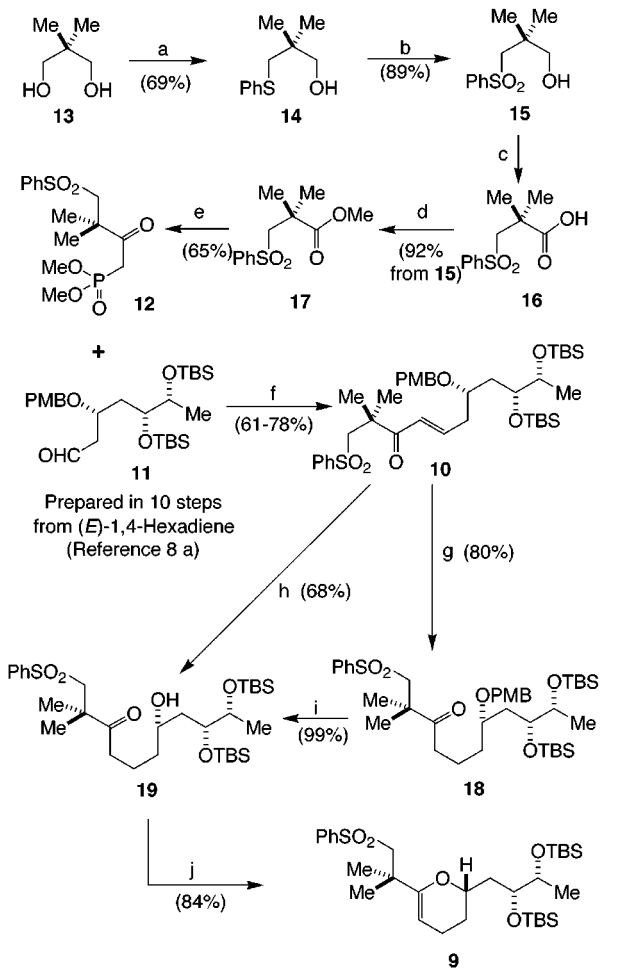
Scheme 1



The C(20)-alkoxy group was to be introduced by stereocontrolled 1,2-ketoreduction and protection. A priori, such a pathway appeared to offer considerable strategic advantages over an alternative we had already investigated, in which methyl glyoxalate **8**[4,6] and **6** were employed for the combined aldol-dehydration-reduction sequence (Scheme 1). The latter had afforded an unstable γ-hydroxy-enoate **3** (via enone **5**) that, disappointingly, had shown a distinct preference for undergoing hydroxyl-directed 1,4-reduction prior to ester reduction. Given these difficulties and the problems we encountered in O-silylating alcohol **3**, we concluded that the methyl glyoxalate pathway to **1** was fundamentally flawed. A successful union between **6** and **7** promised to overcome these difficulties and enhance the overall convergency of our final synthesis. With this as background, we now present details of our pathway to **1**.[9,10]

A central intermediate in the route to ketone **6** was glycal **9**; its synthesis is shown in Scheme 2. Our original proposal for **9** had envisaged constructing its carbon backbone through a Wadsworth−Horner−Emmons reaction between the β-ketophosphonate **12** and the aldehyde **11**[8] (see Scheme 1). It

Scheme 2[a]



[a] Reagents and conditions: (a) $(PhS)_2$ (0.55 equiv), Bu_3P (0.6 equiv), DMF (0.2 M), 70 °C, 3 h. (b) Oxone (2.8 equiv), THF/MeOH/H_2O rt, 2 h. (c) $RuCl_3 \cdot xH_2O$ (0.1 equiv), $NaIO_4$ (2.2 equiv), MeCN/CCl_4/H_2O (2:2:3) (0.06 M), 0 °C to rt, 2 h. (d) K_2CO_3 (5 equiv), MeI (10 equiv), DMF (0.4 M), rt, 12 h. (e) $(MeO)_2P(O)Me$ (2.5 equiv), THF (0.3 M), add *n*-BuLi in hexanes (2.5 equiv) over 40 min, then stir at −78 °C for 1 h 40 min, then add ester **17** over 20 min, then warm to rt for 3−4 h. (f) **11** (1 equiv) and **12** (1.05 equiv), LiCl (2 equiv), *i*-Pr_2NEt (5 equiv), MeCN (0.16 M), rt, 16 h. (g) 20% $Pd(OH)_2$/C (1 g per 5.3 g of **10**), H_2, EtOAc ([**10**] = 0.1 M), rt, 12 h. (h) 20% $Pd(OH)_2$/C (0.2 g per 1 g of **10**), H_2, MeOH ([**10**] = 0.1 M), rt, 2 h. (i) DDQ (1.5 equiv), CH_2Cl_2/H_2O (18:1) (0.08 M), 0 °C, 0.5 h. (j) CSA (0.05 equiv), C_6H_6 ([**19**] = 0.03 M), Δ, 2 h.

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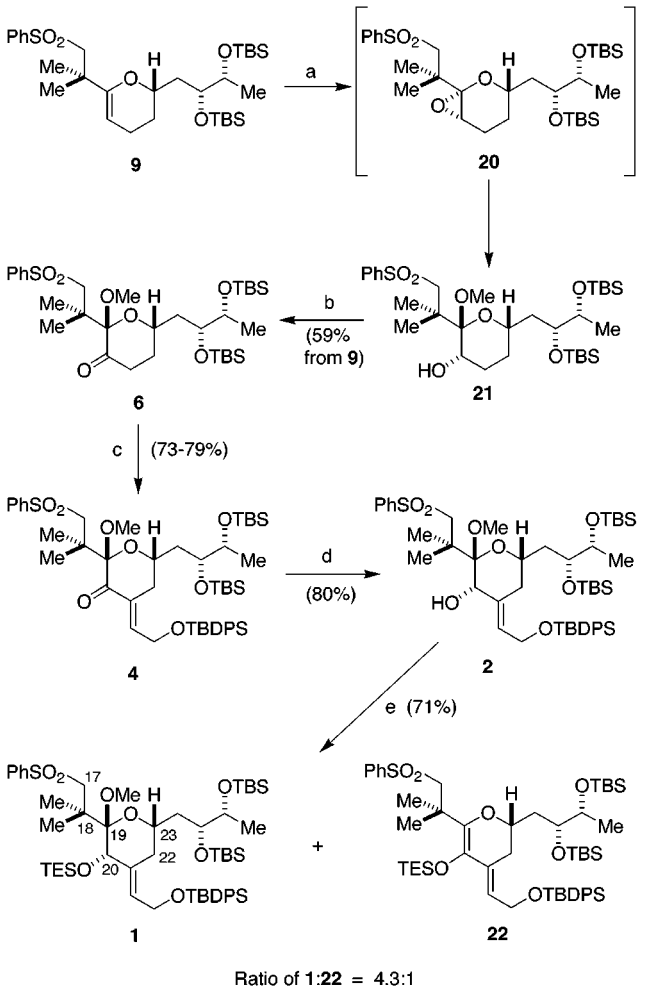
transpired that the requisite β-ketophosphonate **12** could be readily prepared from **13** in five steps as detailed in Scheme 2. 2,2-Dimethylpropane-1,3-diol **13** was selectively thioetherified with tri-*n*-butylphosphine and phenyl disulfide in DMF[11] at 70 °C for 3 h, and the product thioether **14** was oxidized with oxone in THF/MeOH/H_2O[11] to access the phenyl sulfone **15**. The primary alcohol group in **15** was then oxidized with in situ generated ruthenium tetraoxide, and the acid **16** was esterified with potassium carbonate and iodomethane in DMF.[12] Methyl ester **17** condensed readily with an excess of the lithio-anion of methyl dimethylphosphonate[13,9bb] at low temperature to give the desired β-ketophosphonate **12** in 37% overall yield from **13**. Aldehyde **11** had previously been prepared in 10 steps from (*E*)-1,4-hexadiene during our earlier model work on the C-ring of bryostatin 1.[8] It reacted cleanly with **12** under the Roush−Masamune coupling conditions[14] to produce enone **10** as essentially a single geometrical isomer in 61−78% yield. Although compound **10** could be converted directly into alcohol **19** by catalytic hydrogenation over $Pd(OH)_2$ in MeOH, higher yields were usually obtained if the alkene in **10** was selectively hydrogenated and the PMB group of **18** was removed with DDQ.[15] By following this two-step protocol, δ-hydroxyketone **19** could typically be isolated in 79% overall yield. The hydrogenolytic route to **19** normally furnished it in 68% yield. Hydroxy-ketone **19** underwent rapid ring closure to glycal **9** when heated with camphorsulfonic acid in benzene at reflux under Dean−Stark conditions.[4] A three-step sequence was needed to arrive at ketone **6**, and glycal epoxidation was a key step (Scheme 3). The most satisfactory protocol for forming the labile glycal epoxide **20** reacted **9** with redistilled dimethyldioxirane in acetone and anhydrous methanol in the presence of 4Å molecular sieves at 0 °C for 12 min. Under these conditions a very clean and almost totally stereospecific epoxidation took place on the α-face of the alkene to provide **20**. After a catalytic quantity of PPTS was added to the reaction

Scheme 3[a]



[a] Reagents and conditions: (a) DMDO (0.07 M in Me_2CO) (1.4 equiv), MeOH ([**9**] = 0.02 M), 4Å MS, 0 °C, 12 min, then add PPTS (0.2 equiv), warm to rt, stir 10 min. (b) PDC (2 equiv), DMF (0.1 M), rt, 12 h. (c) *n*-BuLi in hexanes (2.5 M, 1.5 equiv), THF ([**6**] = 0.015 M), −78 °C, 5 min, then add aldehyde **7** (5 equiv) in THF (0.5 M) in one portion, stir 5 min at −78 °C, then warm to rt for 20 min. (d) $CeCl_3 \cdot 7H_2O$ (10 equiv), $NaBH_4$ (5 equiv), MeOH ([**4**] = 0.05 M), −78 °C for 1 h, then 0 °C for 5 min. (e) Et_3SiOTf (5 equiv), 2,6-lutidine (10 equiv), CH_2Cl_2 (0.014 M), −78 °C to rt, then stir for 0.5 h.

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mixture, *trans*-diaxial epoxide ring opening was driven to completion, and **21** was isolated as essentially a single product. By way of contrast, when the epoxidation was conducted with redistilled dimethyldioxirane in acetone and dry CH_2Cl_2, a much less satisfactory outcome typically resulted. The trace amounts of water that were always present in our redistilled DMDO/acetone solutions invariably caused a significant amount of epoxide ring opening to give an unusable hemiketal mixture, even when 4Å sieves were added. Although ordinarily, this side reaction is not generally problematic with less-reactive aldose-type glycals, it can be seriously detrimental when the more reactive ketose-type glycals are being epoxidized. In our opinion, this new modification of the Danishefsky−Murray epoxidation method[16] offers distinct advantages for the preparation of "simple" ketose-type glycosides from "reactive" trisubstituted glycals bearing +I groups.

Continuing with our synthesis of **1**, alcohol **21** was oxidized to ketone **6** in good yield with pyridinium dichromate in DMF. Several sets of conditions were examined for effecting the key aldol addition/dehydration sequence. The most effective procedure enolized ketone **6** with *n*-butyllithium in THF at −78 °C and reacted the resulting enolate with the known aldehyde **7**;[17] elimination of the aldol adducts ensued shortly after the reaction was warmed to room temperature. The dehydration step delivered **4** as a single geometric isomer in 73−79% yield. The C(20)-hydroxyl was introduced stereospecifically via a Luche reduction with sodium borohydride and cerium trichloride in methanol.[18] Unstable **2** was isolated as the sole reaction product in 80% yield after SiO_2 flash chromatography. The final step in the sequence to **1** was *O*-triethylsilylation with TES-triflate and 2,6-lutidine. This proceeded rapidly at room temperature to deliver an inseparable 4.3:1 mixture of **1** and the elimination product tentatively assigned as **22**.

The NMR spectra of **1** were temperature-dependent, suggesting that the rate of internal rotation for the sterically congested C(18)−C(19) bond was slow on the NMR time scale. Thus, in the room temperature 500 MHz ^{1}H NMR spectrum of **1** in toluene-d_8 there were many broadened resonances. At 90 °C, however, the spectrum sharpened quite dramatically as a result of the rate of C(18)−C(19) bond rotation becoming fast on the NMR time scale. Under these conditions the rotationally averaged spectrum of **1** was observed. A NOESY experiment in toluene-d_8 at 90 °C revealed cross-peaks between the H(20) singlet at δ 4.38 and the C(18) geminal dimethyl singlets at δ 1.64 and 1.58, as one would expect. The same NOESY experiment also revealed an NOE between H(20) and the C(19)−OMe, which resonated at δ 3.27; this confirmed that both these groups were *cis* to one another. H(20) also gave rise to an NOE cross-peak with the exocyclic olefin multiplet at δ 5.68, while the exocyclic allylic methylenes of the CH_2OTBDPS group (at ca. δ 4.26 and 4.23) showed NOEs with the equatorial H(22), which appeared as a multiplet at δ 2.10. These combined results enabled the alkene and C(20)-alkoxy stereochemistry of **1** to be assigned with confidence. The *cis* relationship between H(23) and the C(19)−OMe was confirmed by NOE; the H(23) resonance appeared at δ 4.01. Interestingly, the C(20)-*O*-acetate derivative **23** obtained from **2** by O-acetylation (with Ac_2O/DMAP/pyridine) gave rise to a completely sharp, well-defined, 500 MHz ^{1}H NMR spectrum in toluene-d_8 (see Supporting Information), which indicated that the slow room temperature C(18)−C(19) bond rotation in **1** was a direct consequence of steric hindrance from the bulky OTES group at C(20).

In conclusion, a fully stereocontrolled 18-step asymmetric synthesis of the highly functionalized C-ring intermediate **1** has been developed from (*E*)-1,4-hexadiene. Our route, which proceeds in 2.57% overall yield, is considerably shorter than past synthetic pathways to southern hemisphere fragments with the exocyclic alkene in a form appropriate for further elaboration.[3,5] The great brevity of our route suggests that a 30-step (or less) total synthesis of bryostatin 1 might soon be possible.

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Supporting Information Available: High-resolution mass spectra, 500 MHz ^{1}H and 125 MHz ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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