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Control of Olefin Geometry in the Bryostatin B-Ring through Exploitation of a C_2-Symmetry Breaking Tactic and a Smith–Tietze Coupling Reaction

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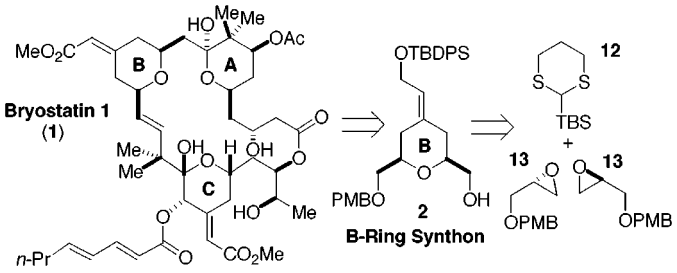
ABSTRACT



A completely stereocontrolled asymmetric synthesis of an advanced B-ring synthon for the bryostatin family of antitumor agents is reported. Noteworthy features of our synthesis include the Smith–Tietze bis-alkylation reaction between 12 and 13 en route to C_2-symmetrical ketone 10 and the totally stereoselective conversion of 10 into triol 18 via a Grignard addition tactic. Triol 18 was converted to epoxide 3 in nine steps, and an acid-catalyzed intramolecular Williamson etherification reaction completed the synthesis of 2.

The bryostatins are an architecturally intriguing family of antitumor macrolides[1] that have shown considerable clinical promise for the treatment of various human cancers.[2] Unfortunately, supply issues continue to overshadow the development of these agents as antitumor drugs, and this has led to substantial synthetic interest[3,4] in this class, not only from the perspective of increasing current clinical supply but also from the standpoint of identifying substantially simplified analogues with superior anticancer properties. Some time ago, we reported[5] an efficient asymmetric synthesis of a fully elaborated C-ring intermediate for bryostatin 1. We now describe our synthetic studies on the bryostatin B-ring, which have recently culminated in the development of a fully stereocontrolled asymmetric synthesis of pyran **2**.

Our retrosynthetic thinking for bryostatin 1 (**1**) (Scheme 1) called for the intermediacy of alcohol **2** as a subtarget and focused on the possible usage of an intramolecular Williamson etherification[6] strategy to assemble the pyran ring system. We envisaged creating pyran **2** from the internal epoxide ring-opening of epoxy-alcohol **3**, and further analysis of **3** duly suggested that it might be obtainable from the α,β-unsaturated lactone **4** by lactone reduction, selective *O*-silylation, *O*-isopropylidene cleavage, selective *O*-mesylation, and base treatment. Compound **4** appeared accessible from

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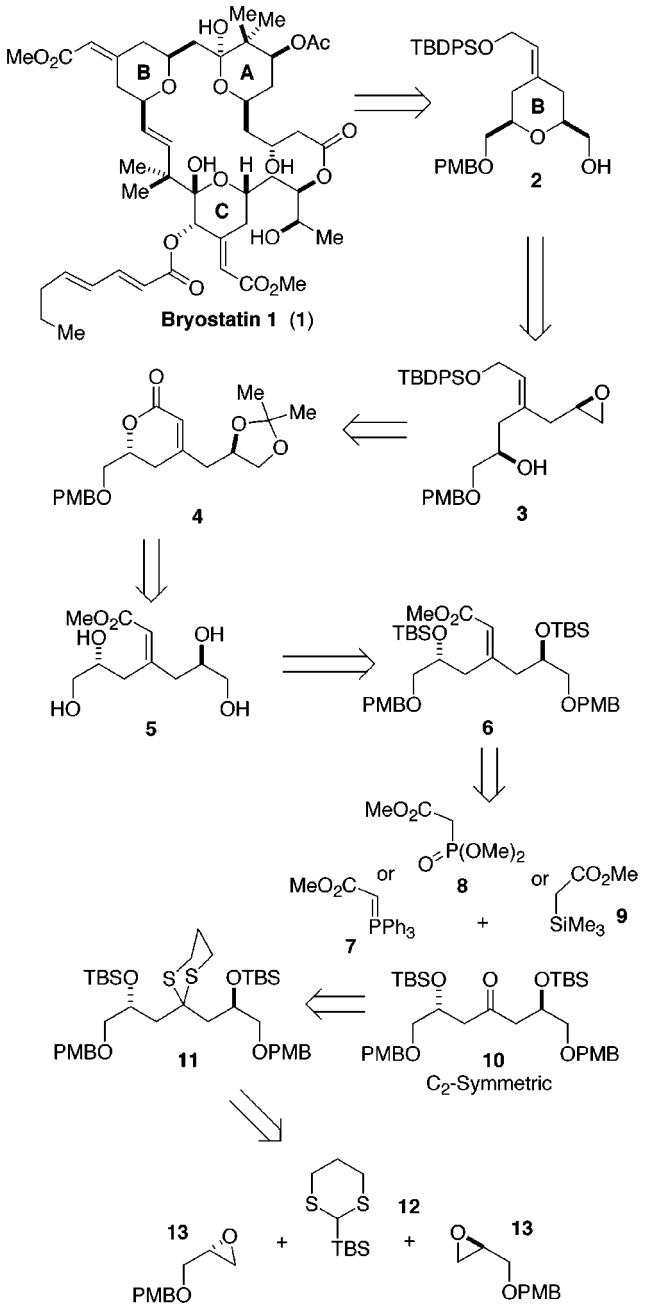
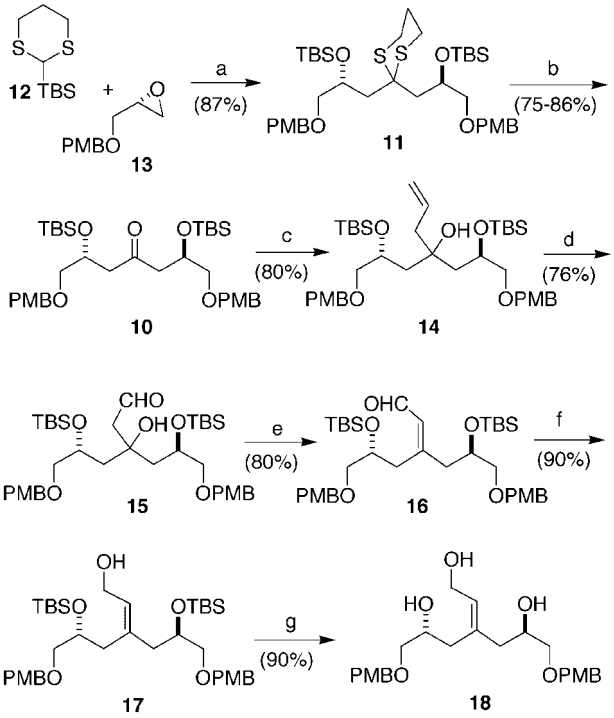
Scheme 1. Retrosynthetic Analysis of the Bryostatin 1 B-Ring



enoate **6** by mild acid hydrolysis and chemoselective protection. Retrosynthetic analysis of **6** suggested that it might be derived from a Wittig−Horner−Emmons[7] or Peterson[8] olefination reaction on ketone **10** with reagents **7**, **8**, or **9** respectively. The primary dividend that would arise from following this disconnective pathway would come from its implementation of the olefination process on a C_2-symmetrical ketone, which would guarantee that only one possible olefin isomer (**6**) could emerge. Ketone **10** was attractive as a synthetic intermediate, for it could potentially be assembled in two steps via a Smith−Tietze coupling reaction[9] between **12** and **13**.

With this in mind, we opened our synthetic campaign on **2** with the preparation of ketone **10**. This was synthesized through the aforementioned Smith−Tietze bis-alkylation reaction[9] between homochiral epoxide **13**[10] and the lithio anion of 2-TBS-1,3-dithiane (**12**) (Scheme 2). As found by

Scheme 2. Use of the Smith−Tietze Bisalkylation Reaction and a C_2-Symmetry Breaking Tactic To Prepare Triol **18**[a]



[a] Reagents and conditions: (a)**12**, *t*-BuLi (1 equiv), THF (0.3 M), HMPA (4 equiv), 0.5 h, −78 °C, add **13** (2 equiv), warm to 0 °C, stir 1.5 h, then add TBSCl (1.5 equiv) at −78 °C and warm to 20 °C; (b) $Hg(ClO_4)_2.xH_2O$ (2 equiv), $CaCO_3$ (4 equiv), THF−H_2O (4:1) (0.06 M), 0 °C, 0.3 h; (c) AllMgBr (1 M in THF, 1.2 equiv), THF (0.3 M), 0 °C, 0.3 h; (d) OsO_4 (0.04 M in H_2O, 0.015 equiv), $NaIO_4$ (6 equiv), THF (0.015 M); (e) $(CF_3CO)_2O$ (10 equiv), Et_3N (30 equiv), DMAP (0.1 equiv), CH_2Cl_2 (0.14 M), 45 °C, 16 h; (f) *i*-Bu_2AlH (1.2 equiv), CH_2Cl_2 (0.3 M), −78 °C, 5 h; (g) *n*-Bu_4NF (1 M in THF) (2.4 equiv), THF (0.3 M), 20 °C, 8 h.

Smith and Boldi[9a] in related systems, when HMPA was present in the reaction mixture, the *C*-TBS group of the initial monoalkylation product readily underwent a smooth *C*- to *O*-migration to generate a new 1,3-dithianyl anion. In the case at hand, this rearrangement led to the remaining equivalent of **13** being consumed fairly rapidly. After in situ trapping of the resulting alkoxide with TBSCl, the bis-*O*-silylated dithiane **11** was isolated in 87% yield. The keto group of **10** was liberated by reacting **11** with mercuric perchlorate[10] in THF and water at 0 °C.

Unfortunately, all our attempts at implementing the aforementioned Wittig or Peterson olefination chemistry on

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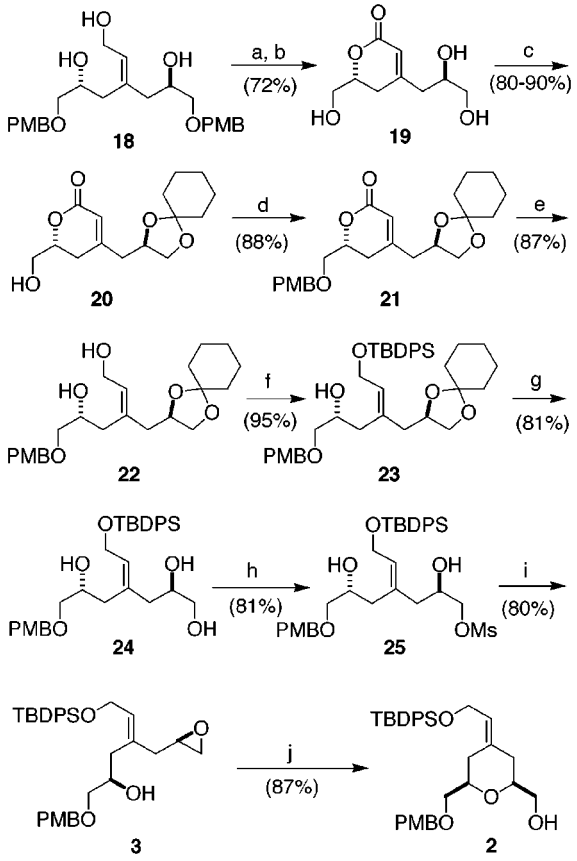
10 were unsuccessful (employing **7**, **8**, and **9** respectively). A Reformatsky reaction was therefore investigated between **10** and MeO_2CCH_2ZnBr in THF, but again this failed. It had been our intention to dehydrate the aldol addition product and obtain **6** as a single olefin isomer.[11]

In light of these difficulties, we modified our strategy to pyran **2**, and now made triol **18** (Scheme 2) our new subtarget. It was prepared efficiently from ketone **10** in five steps. Initially **10** was reacted with allylmagnesium bromide in THF at 0 °C to obtain alcohol **14** in 70−80% yield. The olefinic bond of **14** was then oxidatively degraded with osmium tetraoxide and sodium periodate[5] to furnish β-hydroxy aldehyde **15** in 76% yield. Dehydration was next effected with trifluoroacetic anhydride and triethylamine, in the presence of a catalytic quantity of 4-(dimethylamino)-pyridine; this procedure afforded the pure enal **16** in good yield (70−80%), along with a *trace quantity* of an as yet unidentified product. Reduction of the aldehyde in **16** with DIBAL next provided the desired allylic alcohol **17**, with excellent efficiency. Finally, the silyl groups were detached from **17** with TBAF to generate triol **18** as an oil in 81% yield from **16**.

To chemically differentiate the two partially masked terminal 1,2-diol units in **18**, a chemoselective oxidation of the allylic hydroxyl was performed with activated manganese dioxide in chloroform (Scheme 3).[12] Initially, this reaction

Scheme 3. Conversion of Triol **18** into Pyran **2**[a]



[a] Reagents and conditions: (a) MnO_2 (30 equiv), $CHCl_3$ (0.15 M), 20 °C, 24 h; (b) CF_3CO_2H (40 equiv), anisole (30 equiv), CH_2Cl_2, −15 °C, 8 h; (c) cyclohexanone (20 equiv), EtOAc (0.3 M), *p*-TsOH (0.1 equiv), 6 h; (d) *p*-methoxybenzyl trichloroacetimidate (2 equiv), PPTS (0.5 equiv), CH_2Cl_2 (0.26 M), 20 °C, 8 h; (e) $NaBH_4$ (2.4 equiv), $CeCl_3 \cdot 7H_2O$ (2.4 equiv), MeOH (0.4 M), 0 °C, 1.5 h; (f) *t*-$BuPh_2SiCl$ (1 equiv), imidazole (1.5 equiv), DMF (0.17 M), 0 °C, 1 h; (g) 1,3-propanedithiol (10 equiv), $BF_3.Et_2O$ (0.1 equiv), CH_2Cl_2 (0.16 M), −78 to −10 °C, 1 h; (h) MsCl (1.1 equiv), collidine (10 equiv), CH_2Cl_2 (0.05 M), 0 °C, 4.5 h; (i) NaH (2 equiv), imidazole (2 equiv), THF (0.08 M), 0 °C, 0.3 h; (j) CSA (0.1 equiv), CH_2Cl_2 (0.06 M), 20 °C, 40 min.

afforded the desired enal with complete selectivity. Hemiacetal formation then ensued, allowing a second chemoselective oxidation to occur to fashion the desired α,β-unsaturated lactone. The two terminal PMB groups were detached from this product with TFA/anisole,[13] to access triol **19**. Regioselective *O*-isopropylidenation of the 1,2-diol unit in **19** was next attempted with catalytic iodine in acetone. The remaining hydroxyl was protected as a PMB ether using *p*-methoxybenzyltrichloroacetimidate[14] and PPTS; compound

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4 was obtained as an oil. Although the aforementioned *O*-isopropylidenation reaction worked reasonably well on small scale, considerable problems were encountered on scale-up. We therefore investigated the use of a cyclohexylidene acetal for the protection of this terminal 1,2-diol grouping in **19**. Fortunately, this ketalization process worked successfully on large scale, and as before, it proved a fairly simple matter to protect the remaining hydroxyl as a PMB-ether. Typically, this two-step protocol furnished compound **21** in 79% overall yield.

Our next objective was to selectively reduce the lactone in **21** to obtain diol **22**; this was accomplished with sodium borohydride and cerium trichloride in methanol.[15] The less sterically hindered allylic hydroxyl in **22** was then selectively *O*-silylated with TBDPSCl to gain access to **23**, and its cyclohexylidene group selectively cleaved with 1,3-propanedithiol and catalytic BF_3-etherate at low temperature;[16] this yielded triol **24**. A number of methods were evaluated for the selective *O*-sulfonylation of triol **24**. The mesyl chloride−collidine system of Burke and O'Donnell gave the best results.[17] Adherence to their recommended procedure typically led to the isolation of *O*-mesylate **25** in 81% yield.

We had hoped to convert compound **25** directly into pyran **2** by treatment with 2 equiv of sodium hydride and imidazole in THF. However, the only product formed under these reaction conditions was epoxy alcohol **3**, isolated in 80% yield. To bring about the desired 6-*exo*-*tet* ring-closure,[6b] epoxide **3** was treated with a catalytic quantity of camphorsulfonic acid in dichloromethane[6a] at room temperature for 40 min. This afforded pyran **2** as the sole reaction product in 87% yield.

In conclusion, we have developed a conceptually new synthetic strategy for the control of B-ring olefin geometry in the bryostatins. We anticipate that similar tactics will prove useful for the construction of advanced C-ring intermediates for molecules of the 20-deoxy-bryostatin class (e.g., bryostatin 11).

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Supporting Information Available: 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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