Synthesis of a Ring-Expanded Bryostatin Analogue

Barry M. Trost,* Hanbiao Yang, Oliver R. Thiel, Alison J. Frontier, and Cheyenne S. Brindle
Department of Chemistry, Stanford University, Stanford, California 94305

Received October 11, 2006; E-mail: bmtrost@stanford.edu

The bryostatins are a family of marine natural products that display a wide range of biological activities, most notably their anticancer activity in vivo.1 This effect is attributed to their ability to modulate the functions of protein kinase C isoforms within cells. One of the members of this family, bryostatin 1, is currently in several phase I and phase II clinical trials for the treatment of several cancers.2 The syntheses of bryostatins and their analogues have been an active research area since the structure elucidation of bryostatin 1 in 1982.3 To date, three total and one formal syntheses have been reported,4–7 and potent bryostatin analogues8 have been identified. In the analogue synthesis front, efforts have been centered on the simplification of the 26-membered macrolactone backbone. Herein, we report the synthesis of a ring-expanded analogue 1 (Scheme 1), which retains all the functionalities in the bryostatins, and their biological activities against several cancer cell lines.

Scheme 1

Shown in Scheme 1 is our retrosynthetic analysis. Inspired by the B-ring and C-ring segments, we developed a Ru-catalyzed tandem process9 for the synthesis of 4-methylene-cis-2,6-tetrahydropyran and a Pd(II)-catalyzed tandem reaction10 for the synthesis of dihydropyrans. Since our Pd(II) catalysis necessitates an early installation of the sensitive α,β-unsaturated methyl ester at C(13), we decided to evaluate a ring-closing metathesis (RCM) approach for the formation of the macrocyle.11,12 The steric hindrance of the C(16)–C(17) double bond (bryostatin numbering) made this approach risky, but we were encouraged by the potential to access ring-expanded analogues.13

Our synthesis of the northern hemisphere 2 is outlined in Scheme 2. The alcohol 94a was converted to the hydroxyketone 12 following a procedure5 from Evans. Subsequent hydroxyl-directed anti-reduction,14 lactonization,16 and protection gave lactone 14. At this stage, a β,γ-unsaturated ketone was introduced to give 5. The key Ru-catalyzed tandem coupling between enone 5 and homopropargylic alcohol 4 furnished tetrahydropyran 15 in 56% yield as a 9:1 cis:trans diastereomeric mixture, and no double bond isomer was observed. Although excess 5 (2.2 equiv) was used in the reaction, 1.2 equiv was recovered and recycled. Subsequent bromination and deprotection gave the corresponding diol, which was subjected to a tandem lactone methanolysis—ketalization to afford 16. Compound 16 was converted to vinyl bromide 17 and then the northern hemisphere 2 in eight steps.

Our synthesis of the southern hemisphere 3 commenced with d-glactonic acid 1,4-lactone (Scheme 3). Epoxide opening of 1817 with methyl propionate delivered methyl ynone 19, which was coupled with alkyne 20* under our tandem Pd(II) catalysis conditions to give dihydropyran 21 in 55% yield.19 At this stage, the vicinal oxygens at C(19) and C(20) were introduced via an epoxidation. Unfortunately, the stereochemistry of the newly introduced C(20) hydroxyl group was the opposite of that required for our synthesis. This undesired selectivity was overcome by a Dess–Martin oxidation30/Luche reduction21 sequence. After intro-

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Producing a terminal olefin via a Takai olefination and a Negishi cross-coupling, the resulting triene was then deprotected to give triols with 46% of 1, 46% of 2.

The compounds 1 and 27 were tested against several cancer cell lines. Particularly impressive and interesting is the ability of 1 to inhibit the growth of NCI-ADR-sensitive breast cancer cell line with added multi-drug-resistant pumps—with an IC50 of 123 nM.

In summary, a ring-expanded bryostatin analogue 1 with potent antitumor activity against the NCI-ADR cancer cell line was synthesized. Notable features include a Ru-catalyzed tandem tetrahydropyran formation, a Pd-catalyzed tandem dihydroxypropion formation, and a ring-closing metathesis. The chemistry reported herein should be applicable to future syntheses of the bryostatins and their analogues.

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References


The Julia olefination, a well-established method in the previous three total syntheses for the construction of the macrocycle, is unlikely to work for our system due to the basicity of this procedure; see ref 5b.


Our efforts to construct the bryostatin macrocycle via a RCA reaction met with no success; details will be reported in full account of our work. For another RCA approach by Thomas and co-workers, see ref 3f.


Synthesized in three steps from 3-methyl-2-butaneone. See Supporting Information for details.

This reaction is reproducible at 0.3 mmol scale. For large-scale reactions, a two-step procedure of Pd(OAc)2-catalyzed cross-coupling of 17 and 18 to form a one-yne adduct followed by PdCl2(CH2)2-catalyzed cyclocosimerization was performed. See Supporting Information for details.


