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Synthesis of a Ring-Expanded Bryostatin Analogue

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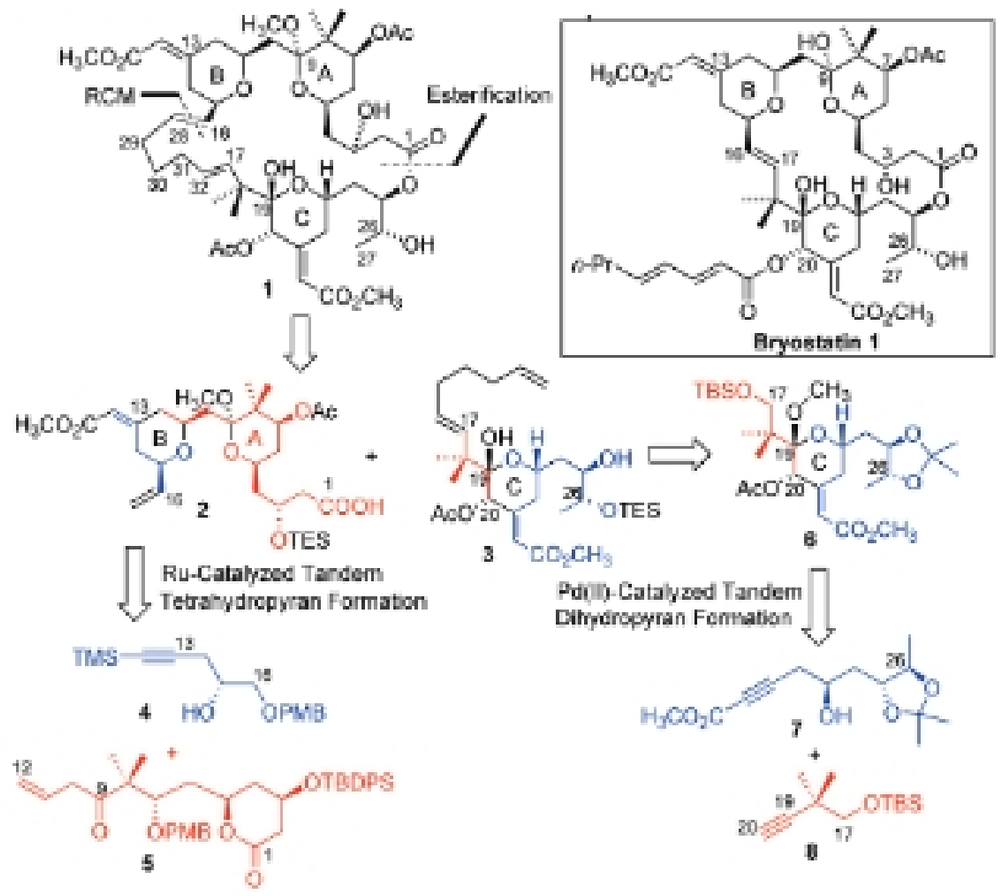
The bryostatins are a family of marine natural products that display a wide range of biological activities, most notably their anticancer activity in vivo.[1] This effect is attributed to their ability to modulate the functions of protein kinase C isozymes within cells. One of the members of this family, 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 analogues[8] 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.

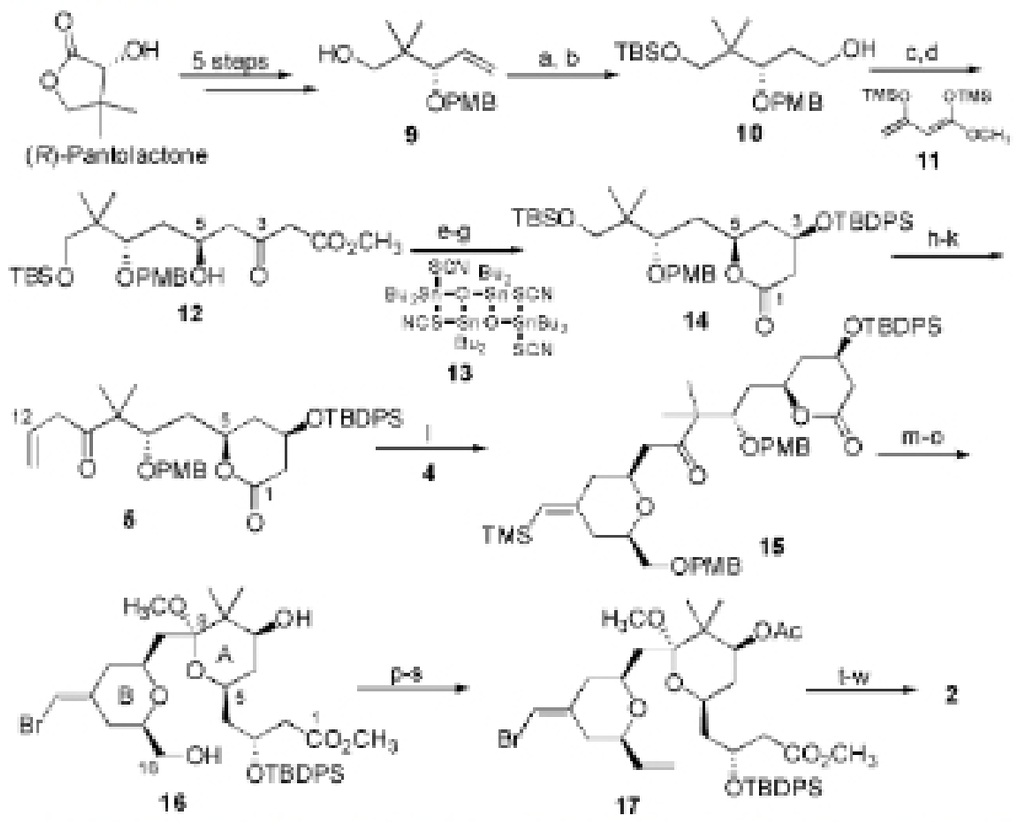
Scheme 1



Shown in Scheme 1 is our retrosynthetic analysis. Inspired by the B-ring and C-ring segments, we developed a Ru-catalyzed tandem process[9] for the synthesis of 4-methylene-*cis*-2,6-tetrahydropyran and a Pd(II)-catalyzed tandem reaction[10] 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 macrocycle.[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 **9**[14] was converted to the hydroxyketone **12** following a procedure[5] from Evans. Subsequent hydroxyl-directed *anti*-reduction,[15] lactonization,[16] and protection gave lactone **14**. At this

Scheme 2 [a]



[a] Reagents and conditions: (a) TBSOTf, Et_3N, −78 °C, 94%; (b) 9-BBN, then H_2O_2, NaOAc, 93%; (c) TEMPO, KBr, NaOCl, CH_2Cl_2/H_2O; (d) Ti(O-*i*-Pr)$_2Cl_2$, **11**, toluene, −78 °C, 69% over two steps, ~10:1 dr at C(5); (e) $Me_4NBH(OAc)_3$, AcOH/CH_3CN, −35 °C, 96%, 15:1 dr at C(3); (f) 10 mol % of Otera's catalyst **13**, hexane, reflux; (g) TBDPSCl, imidazole, DMF, 50 °C, quantitative; (h) AcOH/H_2O (4:1), 69%; (i) Dess−Martin oxidation; (j) allyl iodide, In, DMF, rt, 66% over two steps; (k) Dess−Martin oxidation, 85%; (l) 10 mol % of [CpRu($CH_3CN)_3$]PF_6, acetone, rt, 56% yield, dr 9:1; (m) NBS, DMF, 93%; (n) BF_3·OEt_2, 1,3-propanedithiol, CH_2Cl_2, 0 °C, 98%; (o) PPTS, CH_3OH, $CH(OCH_3)_3$, reflux, 71%; (p) TESCl, DMAP, then pyridine, Ac_2O, 92%; (q) PPTS, MeOH, rt, 85%; (r) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt; (s) Ph_3PCH_3Br, *n*-BuLi, 63% over two steps; (t) TBAF, THF, rt, 82%; (u) Me_3SnOH, DCE, 140 °C, microwave, 82%; (v) $Pd(PPh_3)_4$, CO, DMF/CH_3OH, 85 °C, 94%; (w) TESOTf, 2,6-lutidine, CH_2Cl_2, 68%.

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 **16** 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 **18**[17] with methyl propionate delivered methyl ynoate **19**, which was coupled with alkyne **20**[18] 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 oxidation[20]/Luche reduction[21] sequence. After intro-

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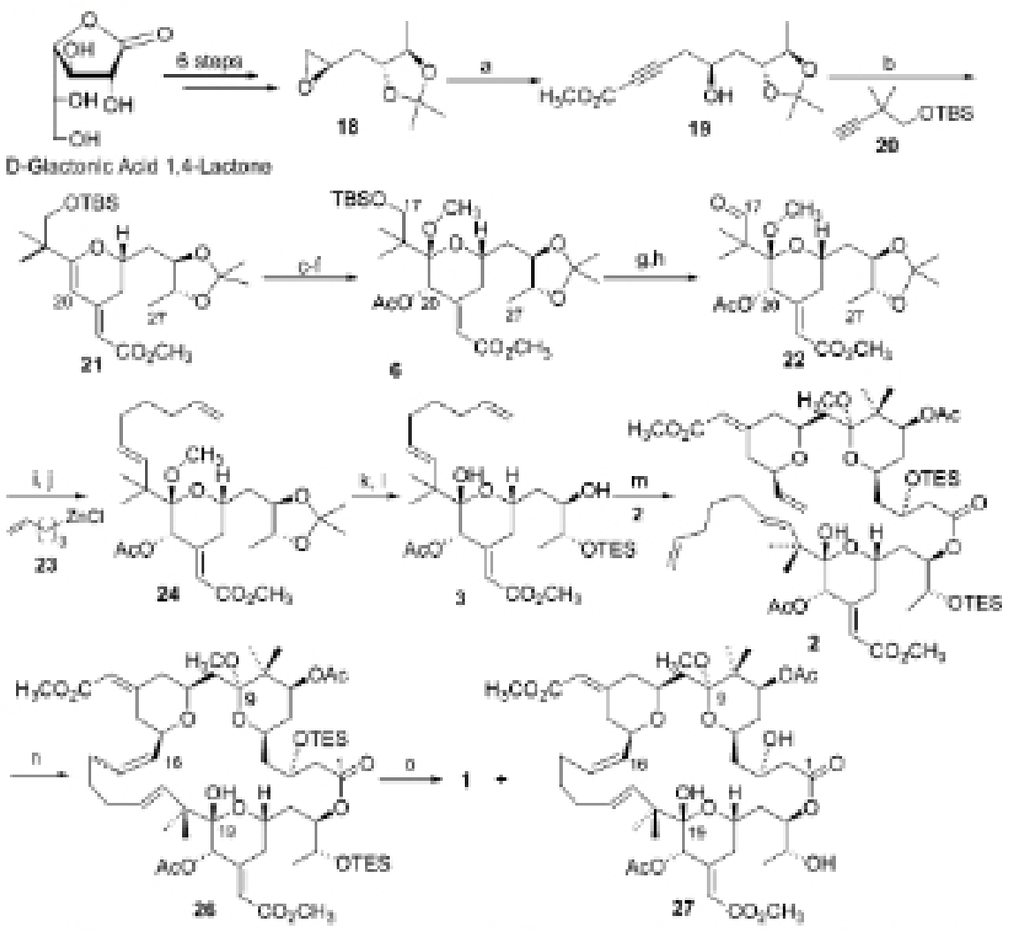
Scheme 3 [a]



[a] Reagents and conditions: (a) *n*-BuLi, methyl propionate, $BF_3{\cdot}OEt_2$, THF, −78 °C, 92%; (b) $Pd(OAc)_2$, tris(2,6-dimethoxyphenyl)phosphine, **20**, benzene, then $Pd(O_2CCF_3)_2$, rt, 55%; (c) trifluoroperacetic acid, Na_2HPO_4, $CH_2Cl_2/CH_3CN/CH_3OH$, 0 °C; (d) Dess−Martin oxidation; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, −30 °C; (f) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 45% over four steps; (g) $Et_3N{\cdot}3HF$, THF, rt, 54−77%; (h) Dess−Martin oxidation, 94%; (i) $CrCl_2$, CHI_3, THF, rt, 26% (47% BRSM); (j) $Pd(PPh_3)_4$, **22**, THF, rt, 68%; (k) $AcOH/H_2O$ (3:1); (l) TESCl, TEA, DMF, −35 to −15 °C, 60% over two steps; (m) Et_3N, DMAP, 2-methyl-6-nitrobenzoic acid anhydride, CH_2Cl_2, 51%; (n) benzene, 50−80 °C, 17 mol % of Grubbs−Hoveyda catalyst, 80%, 1:1 *E*:*Z* mixture; (o) PPTS, MeOH, rt, 36% of **1**, 46% of **27**.

ducing a terminal olefin via a Takai olefination[22] and a Negishi cross-coupling,[23] the resulting triene **24** was hydrolyzed and monosilylated to give the southern hemisphere **3**, which was then coupled with **2** in the presence of 2-methyl-6-nitrobenzoic acid anhydride[24] to give **25**. Gratifyingly, treatment of **25** with Grubbs−Hoveyda catalyst[25] gave 31-membered lactone **26** as an inseparable 1:1 *E*:*Z* mixture in 80% yield.[26] Final deprotection gave triols **1** and **27**, which were separated by preparative TLC.

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—a breast cancer cell line with added multi-drug-resistant pumps—with an IC_{50} of 123 nM.[27]

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 dihydropyran 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.

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