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A New Synthetic Approach to the C Ring of Known as Well as Novel Bryostatin Analogues

Paul A. Wender,* Michael F. T. Koehler,[†] and Martin Sendzik[‡]

Department of Chemistry, Stanford University, Stanford, California 94305-5080

wenderp@stanford.edu

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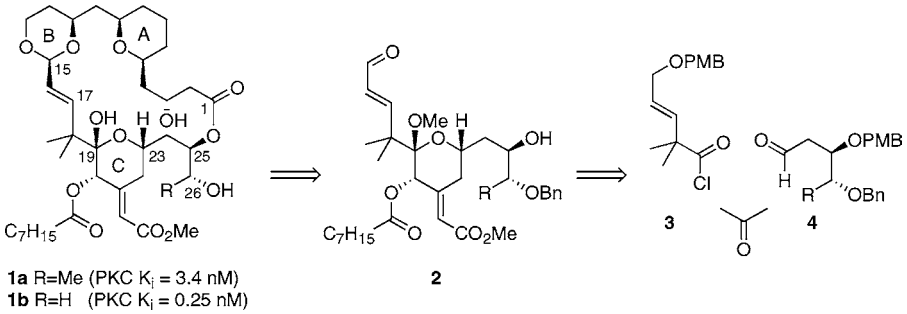
ABSTRACT



A new approach to the synthesis of the C ring subunit of known and potential bryostatin analogues is described. The convergent approach, illustrated above, requires fewer steps and offers greater flexibility in rapidly accessing diverse C ring analogues.

The bryostatins are a structurally novel class of macrocyclic lactones originally isolated from *Bugula neritina*, a marine bryozoan, on the basis of their potent antineoplastic activity.[1] Their unique mode of action has led to the entry of bryostatin 1 into human clinical trials as a single cancer chemotherapeutic agent and in combination with other therapies.[2] Unfortunately, the low natural abundance of bryostatin has limited its availability, thereby impeding further clinical trials, studies on its mode of action, and the identification of clinically superior analogues. Total synthesis and aquaculture have been explored to address this supply problem.[3,4] Our own approach to this problem is directed at the design of clinically superior but structurally simpler analogues that can be supplied through total synthesis. Two such analogues (**1a**,**b**) have now been reported that meet or exceed the performance of bryostatin 1 (K_i = 1.4 nM)[5] in binding to protein kinase C (PKC) and in inhibiting human cancer cell growth.[6] Both are available through synthesis and are currently in pre-clinical development. Each possesses a partially modified C ring which we have proposed to play a critical role in receptor recognition.[7] In agreement with this proposal, this feature is only modestly varied in all natural and designed compounds possessing activity.[8,9] Given the apparent importance of the C ring, we have explored alternative strategies that allow for more efficient access to

[†] Current address: Genentech Inc., 1 DNA Way, South San Francisco, CA 94080.

[‡] Current address: Celera, 180 Kimball Way, South San Francisco, CA 94080.

(1) Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846−6848.

(2) Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841−1860.

(3) (a) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407−7408. (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2354−2359. (c) Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290−2294.

(4) Mendola, D. In *Drugs from the Sea*; Fusetani, N., Ed.; Karger: Basel, 2000; pp 120−133.

(5) Pettit, G. R. *J. Nat. Prod.* **1996**, *59*, 812−821.

(6) (a) Wender, P. A.; DeBrabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C. M.; Shiozaki, M.; Pettit, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 4534−4535. (b) Wender, P. A.; DeBrabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C. M.; Siedenbiedel, C.; Pettit, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 6624−6629.

(7) Wender, P. A.; Koehler, K. F.; Sharkey, N. A.; Dell'Aquila, M. L.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4214−4218.

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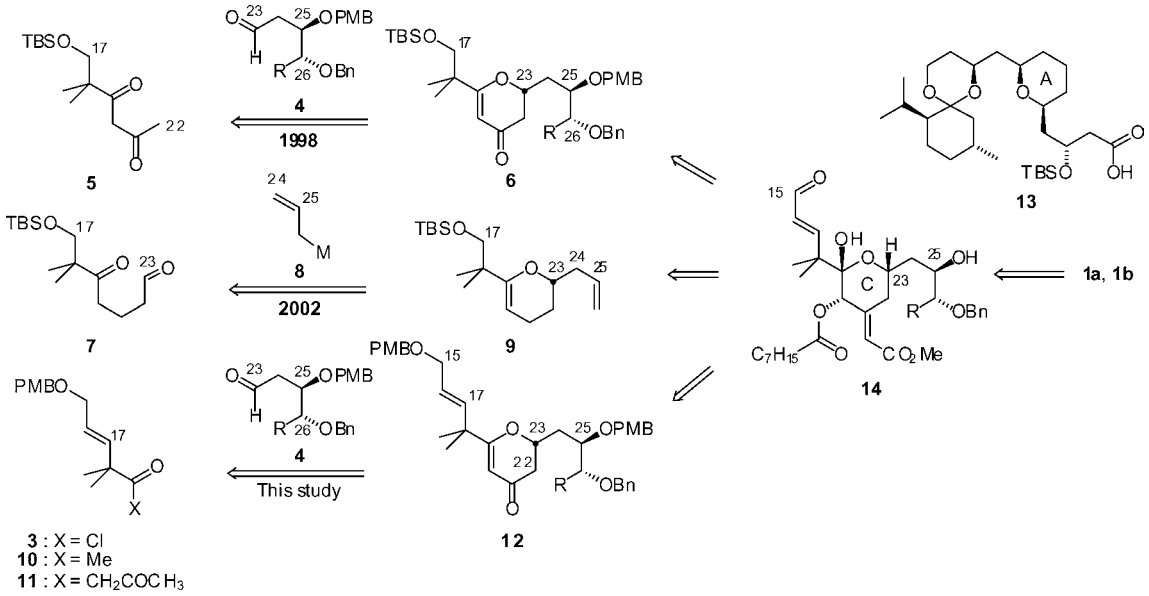


Figure 1. Approaches to the synthesis of the C ring in the preparation of bryostatin analogues **1a** and **1b**.[6a,8b]

known analogues and for more flexible access to new C ring analogues (Figure 1).

Our previous approaches to bryostatin analogues are based on the late-stage convergent coupling of the C ring **14** to a spacer domain **13** through esterification at C25 followed by a novel macrotransacetalization that establishes a dioxolane B ring with thermodynamic control of the C15 stereocenter. The C ring **14** is derived from precursors **6** and **9** through either C22−C23 or C23−C24 bond formation, allowing for differences in the timing of introduction of stereochemistry at C25 and C26. Both approaches require late stage homologation of C17 to introduce C15 and C16. Initially, this process required four steps. More recent work involving the use of an alkoxyvinyl zincate has reduced this homologation to a single step, although it still requires the use of a densely and delicately appointed advanced stage intermediate.[8b] The strategies reported herein were motivated by the view that this C15−C17 fragment could be introduced early in the synthesis thereby avoiding this late stage manipulation. A further consequence of this approach is increased flexibility in the C22−C23 bond formation and consequent control of stereochemistry. Finally, when coupled with our macrotransacetalization strategy, this early introduction of the C15−C17 fragment allows for the conversion of many intermediates along the synthetic path into macrocycles with varied C rings.

Three strategies are reported herein, each benefiting from the early introduction of the C15−C17 fragment and differing by the timing and selectivity of stereogenesis at C23.

The first subgoal of this effort was the preparation of hydropyranone **12** (Scheme 1). Three separate routes were examined based on fragments **3**, **10**, and **11**. The preparation of these fragments started with the alkylation of methyl isobutyrate with allyl bromide to give ester **15**. Free radical bromination with *N*-bromosuccinimide provided the allylic bromide,[10] which was treated with *p*-methoxybenzyl (PMB) alcohol under basic conditions, to give a mixture of PMB and methyl esters **16a**,**b** upon quenching with NH_4OH. Weinreb amide **17** is obtained through treatment of this mixture with the magnesium anion of *N*,*O*-dimethylhydroxylamine. Reaction of **17** with MeLi gave methyl ketone **10** in excellent yield. The formation of acid chloride **3** entailed hydrolysis of **16a**,**b** to acid **16c** and subsequent reaction with NaH and oxalyl chloride. Diketone **11** was obtained from **3** by reaction of the latter with the enolate of acetone.

The individual conversion of fragments **3**, **10**, and **11** to hydropyranone **12** was next examined. Condensation of the dianion of diketone **11** with aldehyde **4a**[11] at −78 °C gave compound **19** with a modest 58% diastereoselectivity (ds) at C23. Similar selectivity was observed in earlier work using **5**, the lower homologue of **11** (Figure 1).[6a] In an effort to improve this selectivity, the sequence of bond-forming events was changed and the enolate of acetone was condensed with aldehyde **4a** to give **18** which was then condensed as its dianion with acid chloride **3** to give **19** now with an improved 81% ds.[12] In a third approach, aldehyde **4a** was allylated following Brown's protocol[13] to give alcohol **20** in 83% ds. The major isomer was then protected as the TBS ether and

(8) (a) Wender, P. A.; Hinkle, K. W. *Tetrahedron Lett.* **2000**, *41*, 6725−6729. (b) Wender, P. A.; Baryza, J. L.; Bennett, C. E.; Bi, F. C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; LaCote, E.; Lippa, B. S.; Nell, P. G.; Turner, T. M. *J. Am. Chem. Soc.* **2002**, *124*, 13648−13649.

(9) (a) Hale, K. J.; Frigerio, M.; Manaviazar, S.; Hummersone, M. G.; Fillingham, I. J.; Barsukov, I. G.; Damblon, C. F.; Gescher, A.; Roberts, G. C. K. *Org. Lett.* **2003**, *5*, 499−502. (b) Hale, K. J.; Frigero, M.; Manaviazar, S. *Org. Lett.* **2003**, *5*, 503−505.

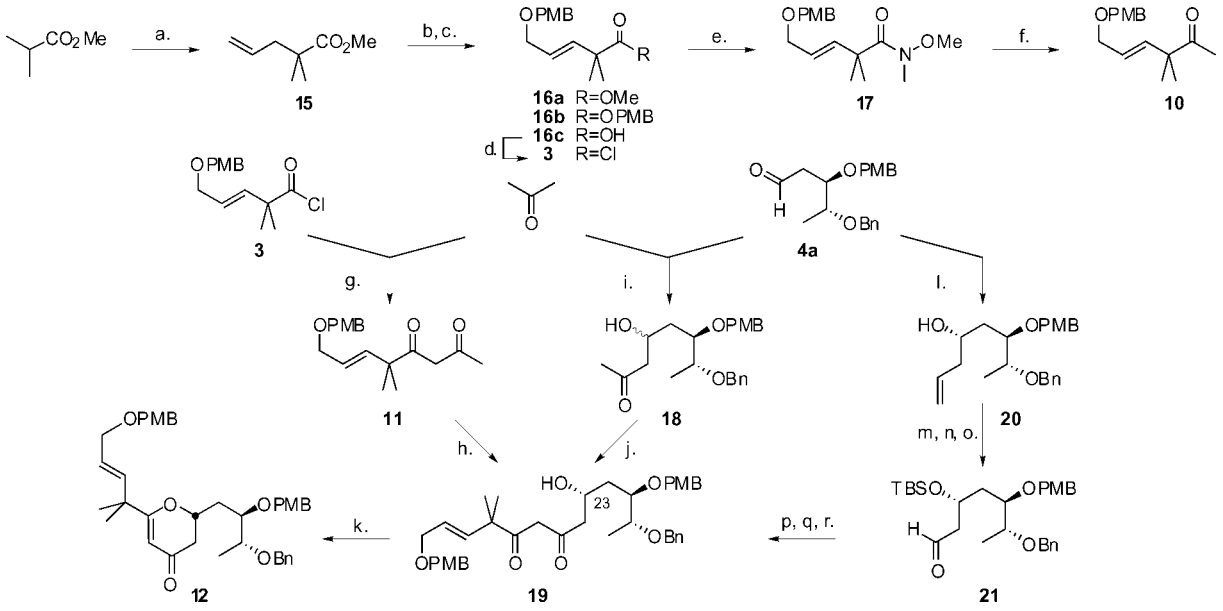
(10) Greenwood, F. L.; Kellert, M. D.; Sedlak, J. In *Organic Syntheses*; Rabjohn, N., Ed.; John Wiley & Sons: New York, 1963; Collect. Vol. IV, pp 108−110.

(11) Prepared in five steps from (*R*)-(+)-methyl lactate. See ref 6a.

(12) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646−7647.

(13) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092−2093.

Scheme 1. Synthesis of the C Ring Precursor **12**[a]

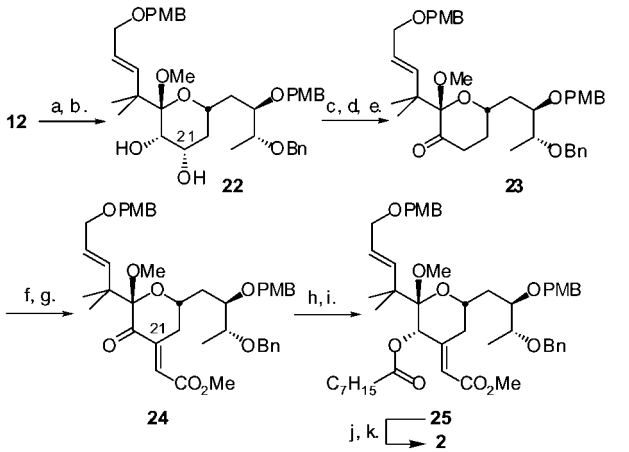


[a] Reagents and conditions: (a) LDA, THF, allyl Br, −78 °C, 90%; (b) NBS, benzoyl peroxide, CCl_4, reflux, 72%; (c) NaH, PMBOH, THF, 35 °C, NH_4OH quench gives **16a**,**b**, 74%; aq quench gives **16c**, 74%; (d) NaH, $(COCl)_2$, Et_2O; (e) (MeO)NHMe·HCl, PhMgBr, −20 °C, then **16a**,**b**, 90%; (f) MeLi, THF, −20 °C, 99%; (g) acetone, LDA (3 equiv), THF, −78 °C, 77%; (h) LDA, THF, −78 °C then **4a**, 65%, 58% ds; (i) acetone, LDA (3 equiv), THF, −78 °C, 87%, 81% ds; (j) LDA, THF, −78 °C then **3**, 61%; (k) TsOH, 4 Å sieves, $PhCH_3$, 83%; (l) (−)-MeOB(Ipc)$_2$, allyl MgBr, Et_2O, −78 °C, 66%, 83% ds; (m) NaH, TBSCl, DMAP, CH_2Cl_2, reflux, 86%; (n) OsO_4, NMO, 2:1 THF/H_2O; (o) $NaIO_4$, 2:1 THF/H_2O, 85% over two steps; (p) **10**, LDA, THF, −78 °C, 96%; (q) TPAP, NMO, CH_2Cl_2, 4 Å sieves, 55%; (r) HF·pyridine, pyridine, THF, 70%.

the terminal olefin was cleaved to the aldehyde **21**. The latter was condensed with the enolate of ketone **10** to give **19** after oxidation of the initially formed alcohols with tetrapropylammonium perruthenate (TPAP)[14] and deprotection with tetrabutylammonium fluoride (TBAF). Diketone **19** was readily cyclized to hydropyranone **12**, which was spectroscopically identical to the major diastereomer produced by the other two routes.

Scheme 2 depicts the completion of the revised synthesis of **2**, the C ring portion of analogue **1a**. This was accomplished in a fashion inspired by our first generation synthesis but now with the C15−C16 fragment in place. Beginning with the critical hydropyranone intermediate **12**, which provides a point of divergence for accessing a variety of analogues, Luche reduction gave selectively the equatorial alcohol[15] which in turn directed subsequent epoxidation and methanolysis to give **22**. Treatment of **22** with benzoyl chloride resulted in selective protection of the equatorial C21 alcohol, allowing oxidation of the C20 alcohol with the Dess−Martin periodinane.[16] Samarium diiodide mediated elimination of the C21 benzyl ester gave **23**. An aldol reaction with methyl glyoxalate followed by mesylation and elimination of the resulting β-keto alcohol gave selectively the *E*-olefin at C21 in **24**. The C20 ketone was then reduced under Luche conditions and acylated to give **25**. Following

Scheme 2. Completion of C Ring Portion[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3$·7 H_2O, MeOH, −20 °C; (b) *m*-CPBA, $NaHCO_3$, MeOH, 0 °C, 71% for two steps; (c) BzCl, DMAP, CH_2Cl_2, 0 °C; (d) Dess−Martin periodinane, CH_2Cl_2, 89% for two steps; (e) SmI_2, −78 °C, THF/MeOH, 87%; (f) LDA, $OHCCO_2Me$, THF, −78 °C, 88%; (g) $ClSO_2Me$, Et_3N, CH_2Cl_2, −10 °C, then DBU, THF, 81%; (h) $NaBH_4$, $CeCl_3$·7H_2O, MeOH, −20 °C; (i) $C_7H_{15}CO_2H$, 2,4,6-trichlorobenzoyl chloride, NEt_3, $PhCH_3$, 86% for two steps; (j) DDQ, wet CH_2Cl_2; (k) MnO_2, CH_2Cl_2, 42% for two steps.

(14) Lenz, R.; Ley, S. V. *J. Chem. Soc., Perkins Trans. 1* **1997**, 3291−3292.

(15) Luche, J. L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601−602.

(16) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

deprotection of the C15 and C25 alcohols with DDQ and selective oxidation to the C15 aldehyde using manganese dioxide, the completed C ring subunit **2** was obtained.

This new synthetic route to **2** offers a number of advantages, including a reduction in step count as well as an increase in selectivity in generating the C23 stereocenter. The number of steps required has been reduced from 23 steps in the longest linear sequence to 19. The C23 stereocenter can now be produced with higher stereoselectivity (81% ds).

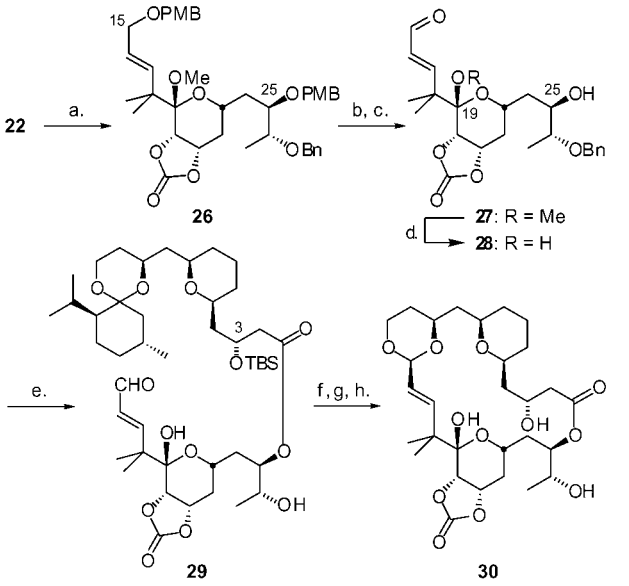
In addition to the synthetic improvements this route provides an important strategic advantage in accessing diverse analogues since all compounds with a closed C ring (i.e., from **12** forward and their derivatives) could potentially be converted into analogues for biological testing by performing the deprotection (C15, C25) and oxidation (C15) steps and then coupling the resulting C ring subunit to the AB ring portion **13** as illustrated for the preparation of **1a**,**b**.

To evaluate this more flexible access to possible analogues, an early intermediate was taken forward to the macrocycle analogue stage. Intermediate **22** was selected for this purpose, as it is produced early in the synthesis, and its vicinal diol provides a site for end stage diversification.

Toward this end, diol **22** was treated with triphosgene to give the carbonate **26** in excellent yield (Scheme 3). This compound was readily deprotected at the C15 and C25 positions through treatment with DDQ and the allylic C15 alcohol was then chemoselectively oxidized with manganese dioxide to give the corresponding unsaturated aldehyde **27**. Hydrolysis of the C19 mixed ketal, although challenging for this densely functionalized system and initially problematic, was finally accomplished through treatment with 48% aqueous HF in acetonitrile/water at 45 °C, producing the C19 hemiketal. This was then converted to the completed analogue **30** using our previously introduced macrotransacetalization strategy.[6a] Thus, the AB ring portion **13** was joined to the new C ring **28** through esterification at C25 using Yamaguchi's conditions.[17] Treatment with buffered HF·pyridine in THF removed the C3 TBS protecting group. This was followed by acetalization using Amberlyst-15 and 4 Å molecular sieves. Finally, the C26 benzyl protecting group was removed under standard conditions to give the completed macrocycle **30**.

This new synthetic approach to the C ring subunit **14** of the bryostatin analogues provides for greater efficiency and selectivity and, more significantly, it offers greater flexibility in accessing novel C ring analogues. Synthesis of analogue **30** demonstrates that substantially varied C ring subunits are now readily incorporated into our macrotransacetalization strategy, allowing access to new macrocycles. Whereas much of our earlier work addressed the biological activity resulting from changes in the spacer domain, this new strategy allows for a broader exploration of activities associated with changes in the putative recognition domain encompassing the C ring.

Scheme 3. Completion of the Macrocyclic Analogue **30**[a]



[a] Reagents and conditions: (a) triphosgene, pyridine, CH_2Cl_2, 93%; (b) DDQ, wet CH_2Cl_2, 66%; (c) MnO_2, CH_2Cl_2, 80%; (d) 48% aq HF, CH_3CN/H_2O (9:1), 45 °C, 79%; (e) **13**, 2,4,6-trichlorobenzoyl chloride, Et_3N, $PhCH_3$, then **28**, DMAP, 62%; (f) HF·pyridine, pyridine, THF; (g) Amberlyst-15, 4 Å sieves, CH_2Cl_2, 62% for two steps; (h) H_2, $Pd(OH)_2/C$, EtOAc, 88%.

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

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(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.