ORGANIC LETTERS

2005
Vol. 7, No. 11
2149−2152

Synthetic Studies on the Bryostatins: Preparation of a Truncated BC-Ring Intermediate by Pyran Annulation

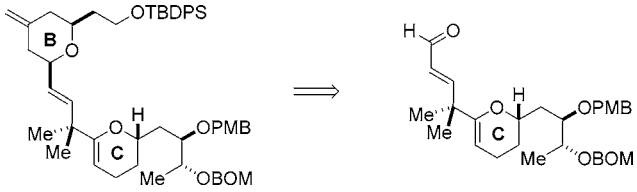
Gary E. Keck* and Anh P. Truong

Department of Chemistry, University of Utah, 315 South 1400 East RM 2020, Salt Lake City, Utah 84112-0850

keck@chemistry.utah.edu

Received March 9, 2005

ABSTRACT



A synthesis of a potential BC-ring subunit (C_9–C_{27}) for bryostatin 1, a remarkably potent anticancer agent, has been developed in 16 steps and 18% overall yield. The key features of this route include a BITIP-catalyzed asymmetric allylation reaction, chelation-controlled allylations, a hydroformylation reaction, and a pyran annulation reaction.

The bryostatins were originally isolated by Pettit and co-workers in 1968 and fully characterized in 1982.[1] Their unique biological effects have led to the entry of bryostatin 1 into human clinical trials as a single-agent cancer chemotherapeutic, as well as in studies of combination therapies.[2] Due to the impressive biological profile of this agent coupled with its remarkable molecular structure, bryostatin 1 has been an attractive target to the synthetic, biological, and medical communities.[3]

Since the initial elucidation of the bryostatin structures, three successful syntheses have been accomplished by Masamune, Evans, and Yamamura, which provide important precedent for further synthetic efforts.[4,5] For example, both Evans and Yamamura have demonstrated that the exocyclic enoate on the B-ring can be installed with a high degree of stereoselectivity by means of a Horner−Emmons reaction using a BINOL-based reagent developed by Fuji.[6] Moreover, in an important series of papers, Wender and co-workers have reported the first simplified bryostatin analogues that retain activity against human cancer cell lines.[7] The scarcity of bryostatin 1 from natural sources and difficulties in the isolation of these materials impact negatively upon further clinical trials and detailed studies of its mode of action. This situation has prompted us to set up a program aimed at the development of a convergent and efficient synthesis of bryostatin 1 and structurally simplified bryostatin analogues, which hopefully will exhibit biological activity similar to

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

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

(3) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep* **2002**, *19*, 413 and references therein.

(4) (a) Evans, D. A.; Carter, P. H.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540. (b) Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290. (c) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407.

(5) For additional recent synthetic work in this area, see: (a) Voight, E. A.; Seradj, H.; Roethle, P. A.; Burke, S. D. *Org. Lett.* **2004**, *6*, 4045. (b) Voight, E. A.; Roethle, P. A.; Burke, S. D. *J. Org. Chem.* **2004**, *69*, 4534. (c) Hale, K. J.; Frigerio, M.; Hummersone, M. G.; Manaviazar, S. *Org. Lett.* **2003**, *5*, 503. (d) 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. (e) Ball, M.; Baron, A.; Bradshaw, B.; Omori, H.; MacCormick, S.; Thomas, E. J. *Tetrahedron Lett.* **2004**, *45*, 8747.

(6) (a) Tanaka, K.; Ohta, Y.; Fuji, K.; Taga, T. *Tetrahedron Lett.* **1993**, *34*, 4071. (b) Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1996**, *37*, 3735.

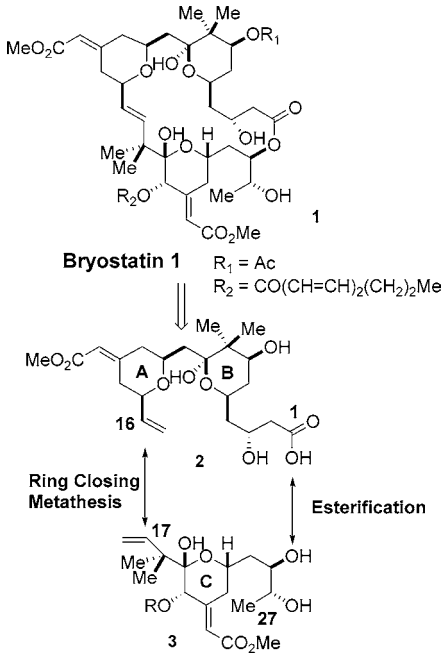
(7) Wender, P. A.; Baryza, J. L.; Bennett, C. E.; Bi, F. C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; Lacote, E.; Lippa, B.; Nell, P. G.; Turner, T. M. *J. Am. Chem. Soc.* **2002**, *124*, 13648.

10.1021/ol050511w CCC: $30.25
Published on Web 04/28/2005

that of bryostatin 1. Toward the goal of developing a practical synthetic route to these materials, we describe herein a concise and efficient synthesis of the BC-ring portion (C_9-C_{27}) of bryostatin 1.

Our initial retrosynthetic analysis of bryostatin 1 is shown in Scheme 1. Disconnections of the macrolactone ester

Scheme 1. Initial Retrosynthetic Analysis of Bryostatin 1

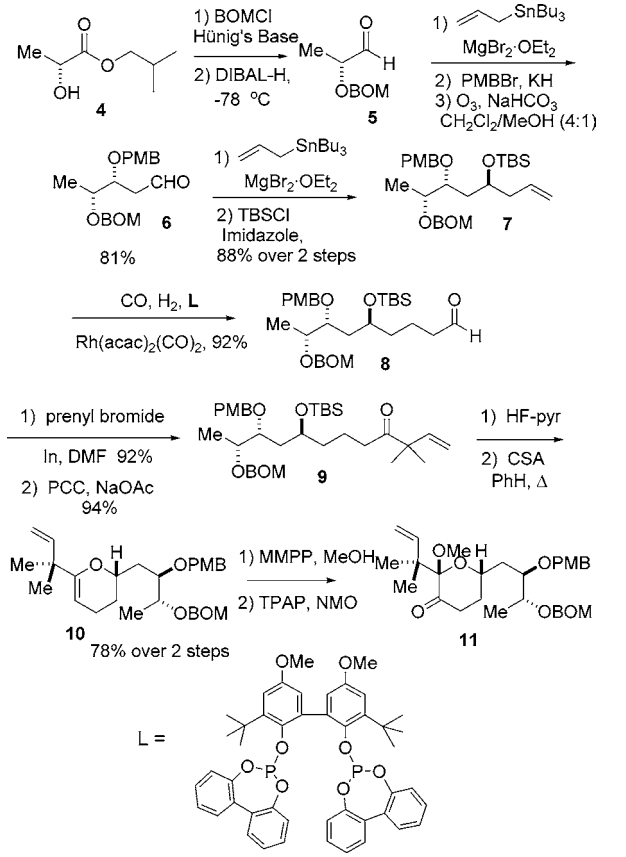


linkage and the $C_{16}-C_{17}$ trans olefinic bond provide an AB-ring fragment and a C-ring fragment. It was initially envisioned that the olefinic unit might be constructed via olefin metathesis, with the Julia coupling utilized in all other approaches to date available as a backup alternative from the same advanced intermediates. Given the apparent importance of the C-ring to the biological activity of bryostatin, we sought a strategy that would allow for systematic modifications in this region to provide for efficient access to new C-ring analogues. Moreover, for our purposes, differential protection of the C_{26} and C_{27} hydroxyl groups was essential. Since this requirement adds additional steps over approaches where both hydroxyls of this diol can be masked simultaneously, for example, as an acetonide, a high degree of efficiency in the construction of this segment was necessary.

Synthesis of the $C_{17}-C_{27}$ Fragment. We anticipated that the C-ring exocyclic enoate could be incorporated from a ketone via an aldol condensation with methyl glyoxylate, as previously documented in the Wender and Evans studies. Due to the potential instability of the enoate at C_{21}, we decided to install this α,β-unsaturated subunit at a late stage in the synthesis.

Our synthesis (Scheme 2) commenced with BOM protection of the hydroxyl group of (*R*)-isobutyl lactate (**4**) using BOMCl and Hünig's base. DIBAL-H half-reduction of the

Scheme 2. Synthesis of the $C_{17}-C_{27}$ Fragment



BOM-protected ester afforded aldehyde **5**. Chelation-controlled allylation by reaction with allyltri-*n*-butylstannane and $MgBr_2 \cdot Et_2O$ provided the C_{25} alcohol as a single diastereomer. After protection of the resulting alcohol as a PMB ether using PMBBr and KH in THF, oxidative cleavage of the olefin using ozonolysis in CH_2Cl_2/MeOH (4:1) at −78 °C in the presence of $NaHCO_3$ (to prevent the formation of the dimethylacetal) furnished aldehyde **6** in good yield. A second allylstannane addition to aldehyde **6**, again with $MgBr_2 \cdot Et_2O$ as the Lewis acid, gave rise to a new stereocenter at C_{21} with essentially complete selectivity (>95:5).[8] The hydroxyl group was then protected as a TBS ether using TBSCl and imidazole in DMF to give alkene **7** in 97% yield.

Initial attempts at hydroformylation of the terminal alkene using dicarbonylacetylacetonato rhodium(I) and $P(OPh)_3$ in toluene resulted in decomposition. However, it was found that when the reaction conditions and ligand developed by Buchwald were employed, hydroformylation of alkene **7** proceeded smoothly to give an 11:1 (linear:branched) mixture, which could be separated to give the desired aldehyde **8** in 92% yield.[9] Treatment of aldehyde **8** with a prenyl indium reagent generated in situ in DMF at ambient temperature afforded the desired alcohol as a mixture of

(8) (a) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *5*, 5478. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

(9) Cuny, G. D.; Buchwald, S. L. *J. Am. Soc. Chem.* **1993**, *115*, 2066.

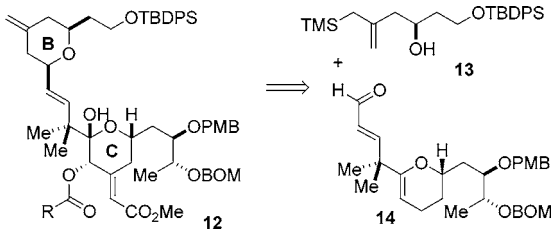
diastereomers in excellent yield (92%). This hindered alcohol was then oxidized with a combination of PCC, 4 Å MS, and NaOAc in CH_2Cl_2 to afford ketone **9** (94%). Multigram quantities of analytically pure ketone **9** (>20 g) have been prepared using this reaction sequence in 57% overall yield from the starting aldehyde **5**. Thus, this overall sequence is remarkably efficient.

With ketone **9** in hand, we set out to close the C-ring. Removal of the TBS ether using HF·py or TBAF in THF at room temperature provided the corresponding hydroxy ketone in good yield (87%). This hydroxy ketone was then cyclized with concomitant dehydration under acidic conditions (CSA, PhH, azeotropic removal of water at 85 °C) to give glycal **10** in 90% yield. Epoxidation of this glycal with MMPP proceeded with methanolysis to give an intermediate methoxyketal-alcohol that was immediately oxidized with TPAP to furnish ketone **11** (67% over two steps). It is at this stage that the exocylic ester at C_{21} can be installed using a known three-step protocol that was reported by Evans and co-workers or a one-step procedure that was published by both Wender and Hale.[3,4,10,11]

We have recently reported the development of methodology that allows for a very concise asymmetric construction of 4-methylene dihydropyrans, which we termed the pyran annulation reaction.[12] This process was developed specifically to provide access to the B-ring of the bryostatins. To investigate the viability of such a strategy, in the present case, we would require access to a C-ring enal such as **14**. This could then potentially be employed in a pyran annulation reaction with a β-hydroxy allylsilane to incorporate a functionalized B-ring subunit in just one additional linear step.

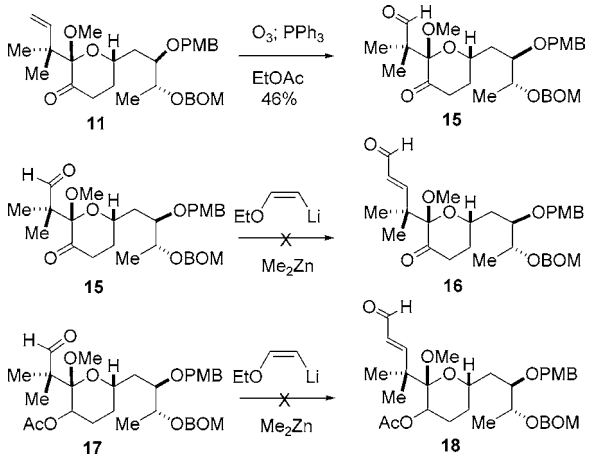
We initially attempted to access this enal intermediate via homologation of the aldehyde that arose from an oxidative cleavage of the alkene moiety in **11** (Scheme 4).

Scheme 3. Potential New Approach



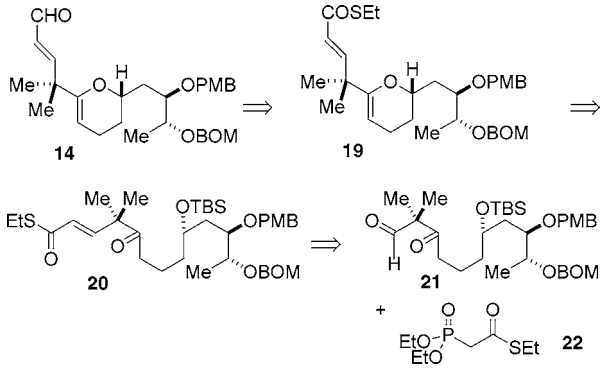
Conditions similar to those that were employed by Wender and co-workers did not afford the 2-carbon homologated product.[5] As shown in Scheme 4, even the vinyl zincate used successfully by the Wender group failed to add into this hindered aldehyde. Thus, we were led to explore a different approach that elaborated a less sterically encumbered aldehyde.

Scheme 4. Attempted Homologation



We envisioned that the α,β-unsaturated aldehyde could come from an α,β-unsaturated thiol ester (Scheme 5). Thus,

Scheme 5. Retrosynthetic Analysis of the C-Ring Enal



we decided to reorder two independent operations: instead of forming the C-ring first and then extending the chain at C_{17}, we decided to elaborate at C_{17} prior to closing the C-ring. This timing of the sequence would permit the homologation to be performed on a less sterically hindered substrate. In addition, this approach would provide for a more convergent route to the α,β-unsaturated aldehyde utilizing intermediates that were already in hand.

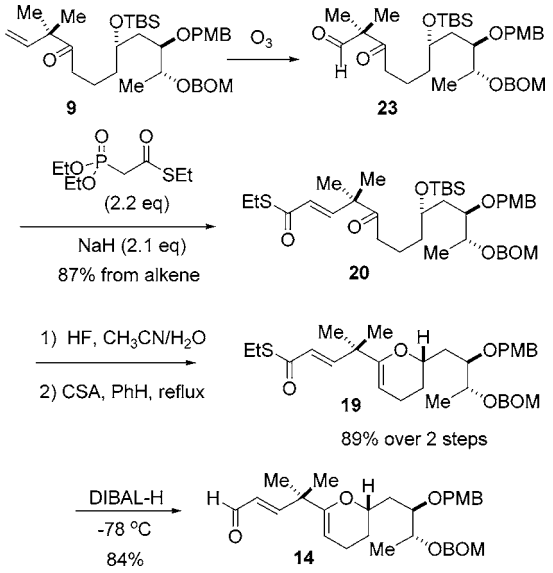
The investigation of this alternative approach began with the ozonolysis of alkene **9** (Scheme 6). The resulting aldehyde **23** was immediately subjected to a Horner−Emmons reaction to give the desired α,β-unsaturated thiol ester **20** with both excellent stereoselectivity and yield (92%). Deprotection of the TBS ether using HF/py buffer was followed by cyclization to give the desired glycal **19** in 89% yield over two steps. Half-reduction of the thiol ester with DIBAL-H at −78 °C then provided the desired α,β-unsaturated aldehyde **14** in 84% yield. Utilizing the sequence

(10) Wender, P. A.; De Brabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C.-M.; Shiozaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4534.

(11) For a different route to a similar intermediate (with a different protecting group at C_{26}), see: Keck, G. E.; Yu, T.; McLaws, M. *J. Org. Chem.* **2005**, *70*, 2543.

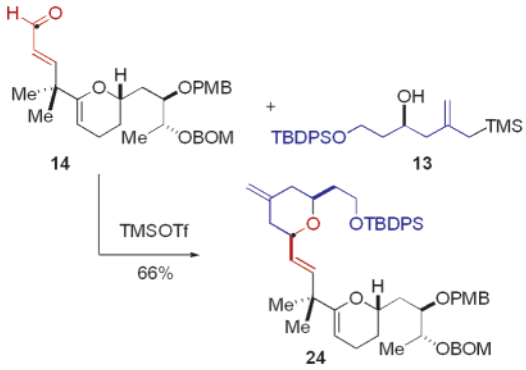
(12) Keck, G. E.; Covel, J. A.; Schiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189.

Scheme 6. Completion of the C-Ring Enal (C_{15}−C_{27})



outlined above and shown in Scheme 6 allowed the C_{15}−C_{27} fragment **14** to be assembled in 15 steps (27% overall yield) from (*R*)-isobutyl lactate.

Scheme 7. Pyran Annulation with Enal **14**



Having accomplished the synthesis of the desired C-ring enal, we next attempted to couple this fragment with a simple hydroxy allylsilane to incorporate the B-ring using the pyran annulation reaction. The requisite allylsilane **13** was prepared enantioselectively via the BITIP-catalyzed CAA protocol as previously described.[12]

Several aspects of the annulation reaction were potentially of concern. First of all, we had not examined any cases of this reaction using α,β-unsaturated aldehydes. Although we had no reason to suspect a problem with this sort of substrate, the compatibility of such unsaturation with the pyran annulation process was not known. Of more concern was the presence of the highly reactive glycal moiety in the substrate, as well as the PMB and BOM protecting groups, which are also reasonably labile under acidic conditions. In the event, reaction of enal **14** with the hydroxy allylsilane **13** in ether at −78 °C, under the influence of TMS triflate as previously described, was found to afford the desired bicyclic product **24** in 66% isolated yield. Although this is a lower yield than typically obtained for this process with less complex substrates, it is reasonable given the nature of the C-ring glycal substrate.[13]

It should be noted that this annulation reaction is very reminiscent of the Diels−Alder reaction in terms of the structural changes accomplished. Thus, in structural terms, one can consider that the pyran is constructed by a four-carbon annulation across the π-bond of an aldehyde, leading to incorporation of the B-ring pyran in a single step.[14]

In summary, a short (15 steps), efficient (27% overall yield), and practical synthesis of the C-ring enal intermediate **14** has been established. One additional step incorporates a functionalized B-ring fragment. The resulting BC-ring subunit is suitably functionalized to serve as an advanced intermediate in the synthesis of bryostatin 1. In addition, as the following letter describes,[15] a number of highly convergent approaches to tricylic macrocyclic analogues of bryostatin are made possible utilizing this C-ring intermediate with the pyran annulation reaction as a key strategic element.

Supporting Information Available: Spectral (^{1}H and ^{13}C NMR) data for compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgment. Financial assistance provided by the National Institutes of Health (through Grant GM-28961) is gratefully acknowledged.

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(13) The somewhat lower yield seems to be associated with the use of this unsaturated aldehyde as a substrate. In a similar case containing the glycal and the same protecting groups, but a saturated aldehyde, a yield of 80% was obtained. (See following paper in this issue.)

(14) Mechanistically, this is incorrect, as the pyran oxygen originates from the hydroxyl group in the hydroxy allylsilane component; however, for purposes of analysis of target structures, it is convenient to think of the reaction in these terms.

(15) Keck, G. E.; Truong, A. P. *Org. Lett.* **2005**, *7*, 2153.