Bryostatins

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Catalysis in the Total Synthesis of Bryostatin 16**

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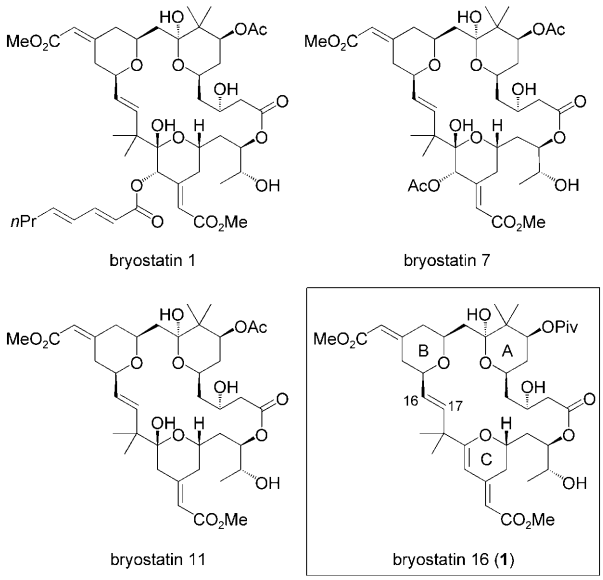
bryostatins · homogeneous catalysis · lactones · macrocycles · total synthesis

Macrocyclic secondary metabolites, perhaps best exemplified by the polyketide macrolactones, hold a special place in the history of natural product total synthesis. The exquisite biological potency and novel modes of action that many of these natural products possess, coupled with the fact that they often cannot be obtained in sufficient quantities for complete testing, has provided a clear need to develop efficient syntheses from robust chemical feedstocks. Notwithstanding the medicinal importance of these natural products, synthetic chemists have been awed by their intricate and imposing beauty, and inspired to recreate these compounds in the laboratory.

Virtually all conceivable syntheses of a polyketide macrolactone require a macrocyclization step. In spite of the numerous methods that exist to close macrocycles, relatively few of these reactions are used in total synthesis. This can be attributed to the highly functionalized and often sensitive nature of macrocyclization precursors in synthesis campaigns; in other words, only mild and chemoselective methods can be used. As a result, the field has traditionally been dominated by macrolactonizations[1] with ring-closing metathesis (RCM)[2] more recently sharing the spotlight.[3] In November 2008, however, Trost and Dong reported an elegant total synthesis of bryostatin 16 that is highlighted by a rare palladium-catalyzed alkyne–ynoate coupling macrocyclization step.[4] Their synthesis establishes this reaction as a powerful macrocyclization method that could have broad applicability in total synthesis.

The target molecule of Trost's synthesis, bryostatin 16 (**1**), belongs to a family of related macrolactones known collectively as the bryostatins.[5] First isolated by Pettit and coworkers from the marine bryozoan *Bugula neritina*,[6] these compounds, particularly bryostatin 1, have been shown to be highly potent antitumor agents.[5] Indeed, bryostatin 1 has been tested in numerous phase I and II anticancer clinical trials.[7] More recently it has also been shown to positively affect cognition and memory in animals,[8] and has entered phase II clinical trials for treatment of Alzheimer's disease.[7]



From a structural viewpoint, the bryostatins are extraordinarily beautiful and dauntingly complex 26-membered lactones. They are typified by three highly substituted pyran rings (A, B, and C), two sensitive exocyclic trisubstituted enoates, and a sterically crowded C16–C17 *trans* double bond. They primarily differ in the degree of oxygenation that decorates the C ring and in the acylation pattern found on both the A and C rings. The bryostatins have been challenging chemists since their discovery more than 25 years ago, and until Trost's recent synthesis, only three total syntheses had been reported.[9] These syntheses, each regarded as a landmark achievement in its own right, all relied on a Julia olefination to form the C16–C17 double bond and a late-stage Yamaguchi lactonization to close the macrocycle.[10]

Trost's retrosynthetic analysis of bryostatin 16 was perhaps influenced by a general desire to close the bryostatin macrocycle in a novel manner and also to incorporate synthetic methods developed within his own group. Recent results from both the Trost[11] and Thomas[12] research groups highlighted the difficulties in using RCM to close the macrocycle at the C16–C17 double bond. This prompted Trost and Dong to attempt an unprecedented alkyne–ynoate coupling reaction as the macrocyclization step (Scheme 1). This reaction,[13] which the authors had used in earlier bryostatin studies to forge the C ring intermolecularly,[11] would not only close the macrocycle (**3**→**2**) but immediately set the stage for formation of the C ring (**2**→**1**).

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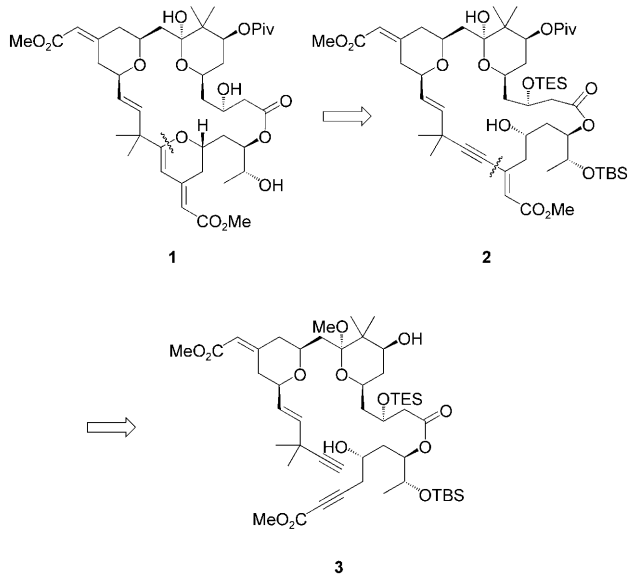
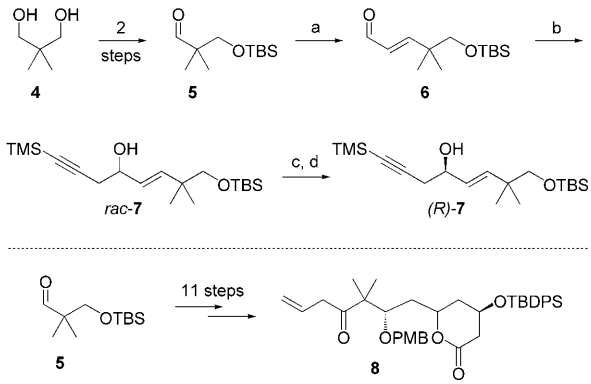


Scheme 1. Brief retrosynthetic analysis of bryostatin 16. Piv = pivaloyl, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl.

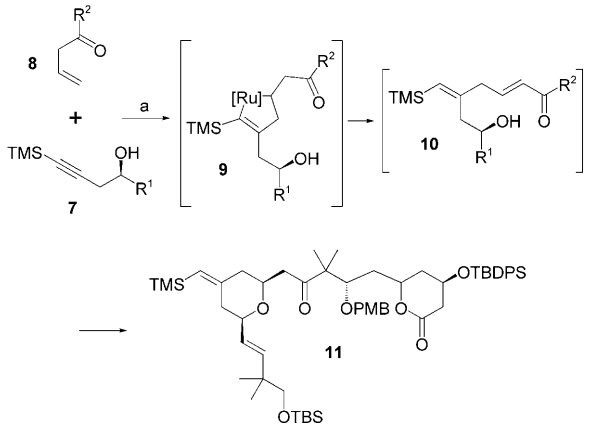
The starting point for the synthesis was inexpensive 2,2-dimethylpropane-1,3-diol (**4**), which was easily converted to aldehyde **5** in a known two-step sequence (Scheme 2).[14] An efficient homologation using a procedure established by Wender et al.[15] yielded aldehyde **6**, which could be converted by an indium-mediated propargylation to racemic alcohol **7**.[16] Dess–Martin oxidation and subsequent CBS reduction then provided enantiomerically enriched **7** (90% *ee*). A nice feature of this synthesis is that alkene **8** could also be obtained from aldehyde **5** in an 11-step sequence.[17]

With fragments **7** and **8** in hand, the synthesis shifted into high gear as Trost and Dong forged their union utilizing a method previously developed in the Trost lab.[18] A cationic ruthenium complex catalyzed the atom-economical coupling



Scheme 2. Synthesis of alkyne **7** and alkene **8**. a) (*Z*)-1-bromo-2-ethoxyethene, *t*BuLi, Me_2Zn, Et_2O, −78 °C, then **5**, then $NaHSO_4$, RT, 97%; b) (3-bromo-1-propynyl)trimethylsilane, In^0, InF_3 (10 mol%), THF, 65 °C, 68%; c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; d) (*S*)-2-methyl-CBS-oxazaborolidine (5 mol%), catecholborane, CH_2Cl_2, −78 °C, 90% *ee*, 90% (2 steps). TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, PMB = 4-methoxybenzyl, CBS = Corey–Bakshi–Shibata.

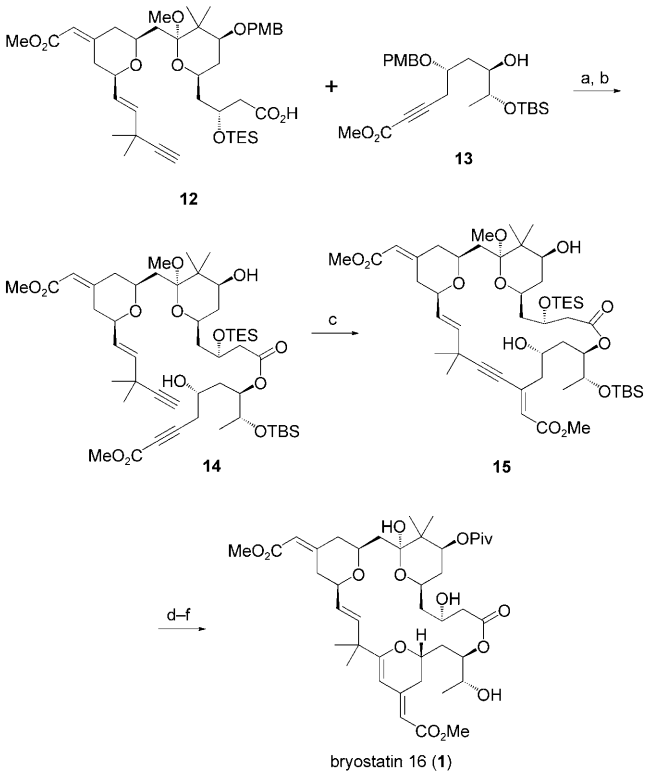
(all and only the atoms in the two starting materials end up in the product) of alkyne **7** and alkene **8** to give pyran **11** (Scheme 3). This impressive transformation generates the



Scheme 3. Ruthenium(II)-catalyzed coupling of alkyne **7** and alkene **8**. a) $[CpRu(MeCN)_3]PF_6$ (13 mol%), CH_2Cl_2, 34% (80% based on recovered starting material). Cp = cyclopentadienyl.

required carbon–carbon bond, creates the B tetrahydropyran ring with the appropriate relative stereochemistry, and properly sets the configuration of the resulting exocyclic trisubstituted double bond in one step, presumably through the intermediacy of ruthenacycle **9** and hydroxyenone **10**. The ability of this tandem alkyne–enone coupling/Michael addition to set the exocyclic double bond as a single stereoisomer is noteworthy, as the installation of this functional group in previous bryostatin syntheses had proven problematic.[9b,c] While the 34% yield obtained is less than optimal, this fact is offset by the powerful convergence of the approach to quickly build up the complexity embedded within the natural product. In addition, a significant quantity of the two starting materials could be recovered, allowing sufficient throughput of material.

Through a series of functional-group transformations that also established ring A, ketone **11** was then advanced to carboxylic acid **12**. Coupling of **12** with alcohol **13** using Yamaguchi's conditions provided, after removal of the two benzyl protecting groups, ester **14** (Scheme 4). With all the carbons of bryostatin 16 in place, the stage was set for the key macrocyclization. In the event, catalytic amounts of $Pd(OAc)_2$ and tris(2,6-dimethoxyphenyl)phosphine in toluene at room temperature led to a 56% yield of enyne **15**. This highly chemoselective reaction, which is actually an isomerization, closes the 26-membered lactone while leaving both the potentially sensitive remote enoate and acetal intact. And much like the reaction in Scheme 3, a crucial carbon–carbon bond is formed, with concomitant stereoselective formation of a challenging trisubstituted enoate, through the action of a catalyst. Perhaps most compelling, however, is the overall simplicity of the reaction: *syn* addition of a terminal alkyne over an alkynoate. The retron for this macrocyclization—a 2,2-disubstituted enoate with one alkynyl residue—has three functional handles for further elaboration. Combined with the fact that alkynes and alkynoates are relatively easy to prepare,



Scheme 4. Macrocyclization and completion of the synthesis. a) **12**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then **13**, DMAP, 92%; b) DDQ, pH 7.0 buffer, CH_2Cl_2, 75%; c) $Pd(OAc)_2$ (12 mol%), TDMPP (15 mol%), toluene, 56%; d) $[AuCl(PPh_3)]$ (20 mol%), $AgSbF_6$ (20 mol%), $NaHCO_3$, CH_2Cl_2/MeCN, 0°C→RT, 73%; e) Piv_2O, DMAP, CH_2Cl_2, 50°C, 62%; f) TBAF, THF, ≈52%. DMAP = *N*,*N*-4-dimethylaminopyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TDMPP = tris(2,6-dimethoxyphenyl)phosphine, TBAF = tetrabutylammonium fluoride.

this reaction should prove useful in the synthesis of many other macrocyclic substances.

At this point the last major hurdle in the synthesis was to close the C ring. While the Trost group had success in the past initiating similar 6-*endo*-dig cyclizations on nonmacrocyclic substrates with Pd^{II} catalysts,[11] the same catalysts in combination with **15** were found to give inseparable mixtures of 5-*exo*-dig and 6-*endo*-dig cyclization products. Fortunately, $[Au(PPh_3)]SbF_6$ was found to be a highly selective catalyst for the desired product. Finally, pivalation of the secondary hydroxy group on the A ring followed by global deprotection completed the synthesis.

Trost and Dong's total synthesis of bryostatin 16 is concise (28-step longest linear sequence, 42 total steps from diol **4**), particularly when compared to previous bryostatin syntheses (over 40-step longest linear sequences and over 70 total steps). They were able to accomplish this feat through an insightful retrosynthetic analysis that allowed them to use conceptually simple reactions, developed within the Trost lab, that don't require "activating" or "leaving" groups. Highlighted by a ruthenium-catalyzed tandem alkyne–enone coupling/Michael addition and a spectacular palladium-catalyzed alkyne–ynoate macrocyclization addition, this synthesis substantially raises the bar for any future bryostatin syntheses. Perhaps these will come from the Trost lab itself. Trost and Dong's stated reason for targeting bryostatin 16 over other members of the family is that it can, in principle, be converted to almost all of the other bryostatins as well as many unnatural analogues. It will be interesting to see if they will attempt to accomplish that goal.

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