Total Synthesis

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Total Synthesis of Bryostatin 1: A Short Route

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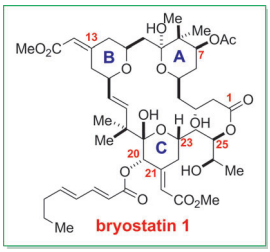
antitumor agents · β-hydroxyalkyl allylsilanes · macrolides · Prins cyclization · total synthesis

Dedicated to Professor Leslie Hough

Molecules of the bryostatin family[1,2] remain popular synthetic targets almost three decades after their initial discovery, mainly because of their remarkable biological properties and their unusual structures, which continue to



pose enormous challenges and tests for efficient stereocontrolled chemical synthesis.[2] The first total synthesis of a bryostatin ever to be accomplished was by Masamune and coworkers at MIT in 1990 with their landmark conquest of bryostatin 7.[3] Their approach served as a guiding beacon for all future synthetic efforts in the area. This synthesis was followed in 1998 by a superb total synthesis of bryostatin 2 by Evans et al. at Harvard University,[4] and two years later by Nishiyama and Yamamura's mammoth effort on bryostatin 3 at Keio University which, significantly, yielded more than 25 mg of the synthetic natural product.[5] In 2006, Hale and Manaviazar successfully recorded a new formal asymmetric total synthesis of bryostatin 7 for the purpose of analogue construction,[6] and in 2008, Trost and Dong announced their total synthesis of bryostatin 16 through a stunning palladium-mediated macrocyclization.[7] One of the most recent synthetic entrants to the bryostatin hall of fame is Gary Keck, with his breathtakingly short asymmetric total synthesis of bryostatin 1.[8] His route was completed in late 2010, and it majestically showcased and exalted many powerful new synthetic reaction technologies invented in his laboratory, and that of his Utah colleague, Jon Rainier.[9]

In his synthesis, Keck initially set out to prepare the A-ring allylsilane **13** (Scheme 1), which was to partner the southern hemisphere enal **29** (Scheme 2) in a novel Lewis acid mediated intermolecular Prins union performed at low temperature (Scheme 3).[10] Keck's route to **13** began with a catalytic asymmetric allylstannation reaction on aldehyde **1** mediated by the complex derived from (*S*)-binol and titanium tetraisopropoxide (Scheme 1);[11] a reaction that performed in an outstanding manner to install the lone asymmetric centre of **2** (93% *ee*). The next key step was the chelation-controlled asymmetric aldol union of aldehyde **3** with the silyl ketene thioacetal **4** that provided alcohol **5** with 41:1 selectivity. Subsequent conversion to the aldehyde **6** and reaction with the allylstannane **7** then afforded **8** which was converted into **12** through another allylstannation reaction, on this occasion, involving **10** and **11**. The resulting 1:1 mixture at C11 was then further manipulated to give a 4:1 mixture enriched in **13**.

Keck's pathway to the C-ring coupling partner **29** (Scheme 2) exploited isobutyl-D-lactate **14** as the starting material and only required 16 steps (20 steps overall) to reach the final destination point. A series of Keck allylstannation reactions set the stereogenic centers at C23 and C25 of alcohol **18** with high stereocontrol (d.r. > 95:5). Esterification then ensued between **18** and **19** and was followed by a homologation that set up a Rainier titanium-induced ring-closing metathesis (RCM) reaction[9] on **24** for the construction of glycal **25**. The synthesis progressed towards **29** using Wender's[12a] and Evans'[4] earlier glycal epoxide ring-opening/oxidation and methyl glyoxalate aldol addition tactics for C-ring exocyclic enoate elaboration at C21.

Thereafter, TMSOTf was found to be the optimal Lewis acid for effecting the key Prins union between **13** and **29** (Scheme 3) to obtain tricycle **32**. Further functional group interconversion followed, and Yamaguchi macrolactonization on **33** gave **34**. Then, rather than resorting to a potentially tricky ozonolysis step at C13, as had been done earlier by Wender in a related synthesis of a bryostatin ABC macrolide,[12b] Keck instead opted to perform a Sharpless asymmetric dihydroxylation[13] and a 1,2-diol oxidative cleavage on alkene **34** to obtain ketone **35**. It was then subjected to Fuji olefination (4:1 selectivity),[14] before being selectively O-deacetylated at O20, O-acylated, and globally deprotected with $LiBF_4$ to give bryostatin 1 by a very short route (60 steps overall; longest linear sequence of 31 steps).

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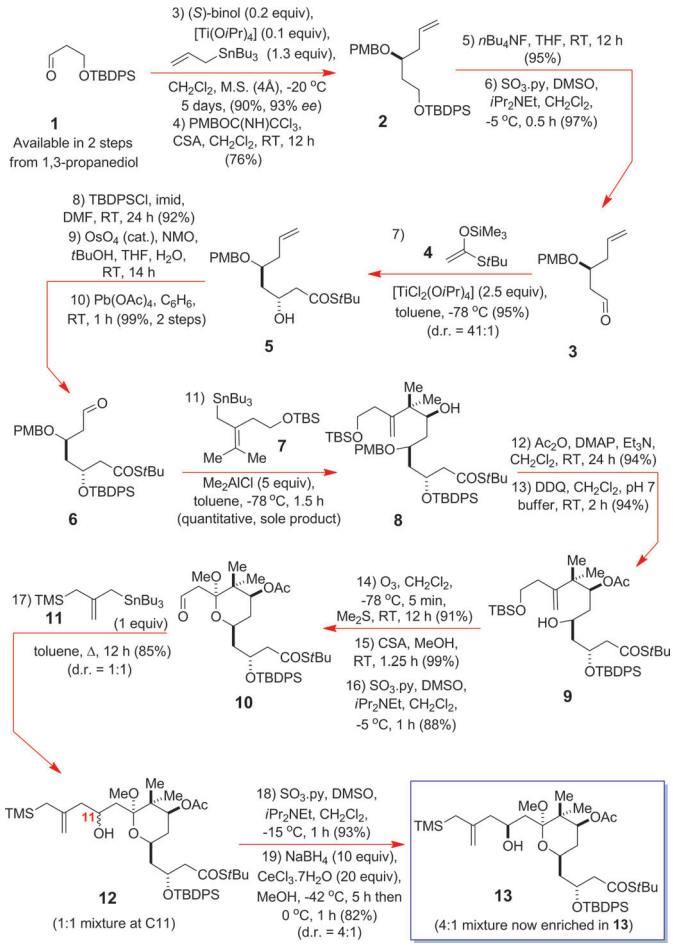
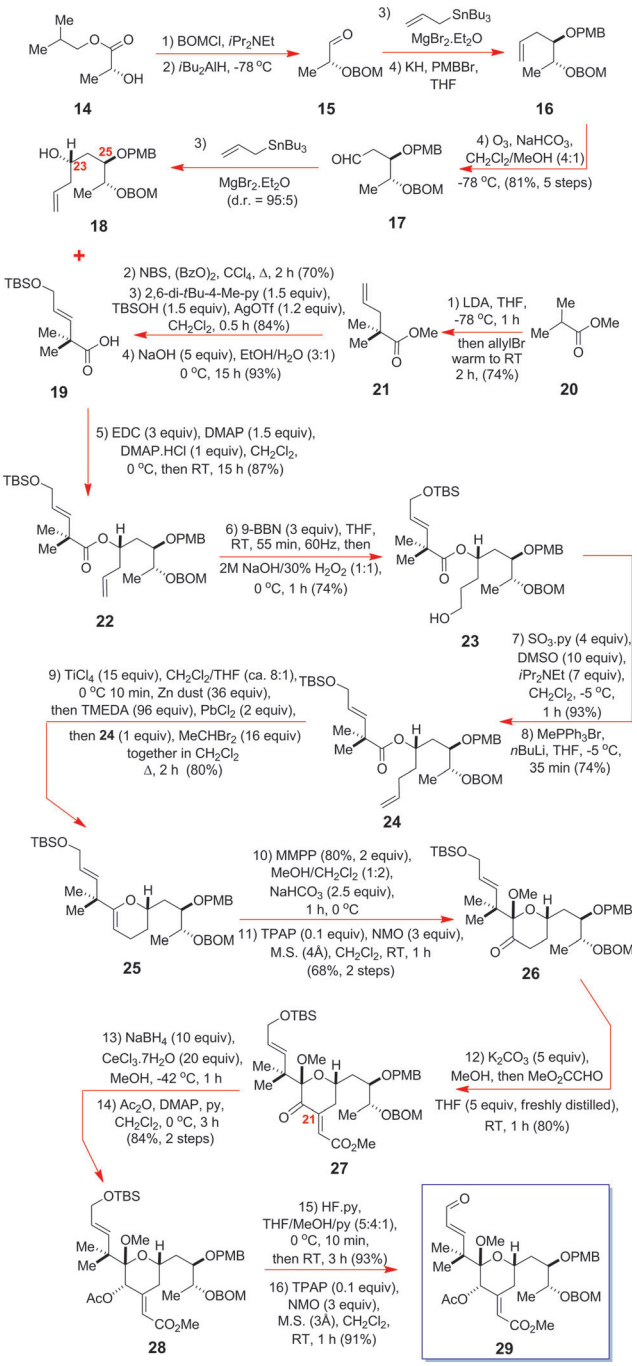
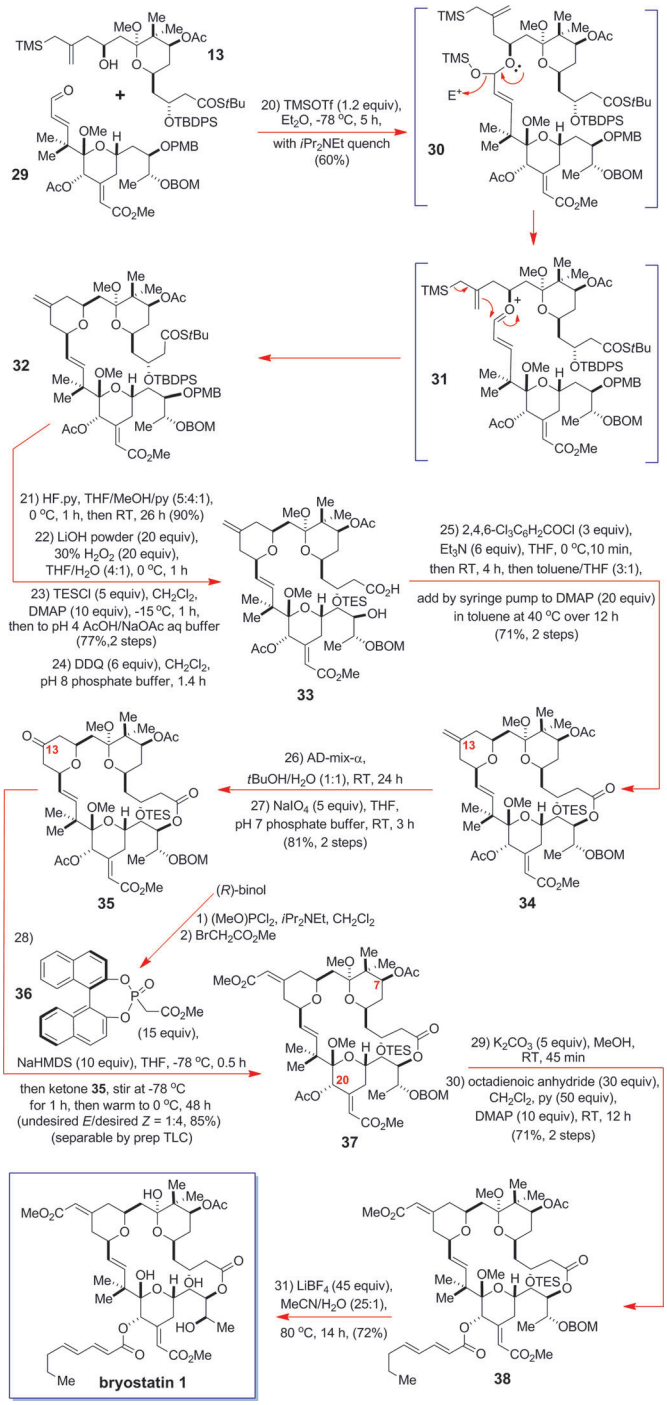


Scheme 1. Keck's synthesis of the A-ring allylsilane **13**. Binol = 1,1′-bi-2-naphthyl, CSA = camphorsulfonic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, imid = imidazole, M.S. = molecular sieves, NMO = 4-methylmorpholine *N*-oxide, PMB = *para*-methoxybenzyl, py = pyridine, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, TMS = trimethylsilyl.



Scheme 2. Keck's synthesis of the C-ring enal **29**. 9-BBN = 9-borabicyclo[3.3.1]nonane, BOM = benzyloxymethyl, Bz = benzoyl, EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, LDA = lithium diisopropylamide, MMPP = magnesium monoperoxyphthalate, NBS = *N*-bromosuccinimide, Tf = trifluoromethanesulfonyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TPAP = tetra-*n*-propylammonium perruthenate.

Although Keck's total synthesis of bryostatin 1 did capitalize on much previous art[2] that had been developed for the fabrication of these molecules, such as Evans' Fuji asymmetric olefination[4,14] for control of the bryostatin B-ring olefin geometry, Wender's chemoselective oxidative cleavage of a B-ring exocyclic methylene group in the presence of other alkenes to obtain a ketone at C13,[12b] and Wender's C-ring olefination tactics,[12a] it also applied many new concepts that Keck's team had independently conceived. In this respect, Keck's synthetic strategy for assembly of the bryostatin ABC-ring system considerably expanded the scope of a new B-ring construction method that had been pioneered in his laboratory for the synthesis of simplified bryostatin analogues;[15] namely, the intermolecular Prins pyran ring-annulation of aldehydes with β-hydroxyalkyl allylsilanes. Indeed, now, in the bryostatin 1 synthetic venture, Keck applied this chemistry on a much more complex and fully adorned C-ring enal **29** that collectively possessed the methyl glycoside at C19, an OAc group at C20, an exocyclic methyl enoate at C21 and an electron-rich PMB group at C25, all within the same substrate (Scheme 3). Given the tremendous range of functionality present in this region, as well in the final product, this reaction is a true marvel to behold, for it relied on the efficient intermolecular hemiacetalization of **29** with **13**, the subsequent trimethylsilanoxide elimination from **30**,

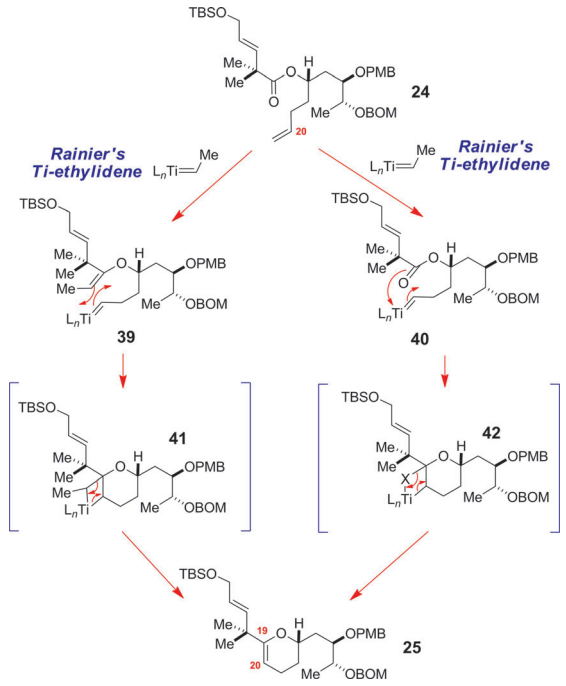


Scheme 3. Keck's intermolecular Prins union of **13** and **29** to obtain **32** and its subsequent conversion through to bryostatin 1. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TES = triethylsilyl.

and the tandem intramolecular allylsilane trapping of oxonium ion **31** to obtain alkene **32** (Scheme 3), which was then taken forward and macrolactonized through the Yamaguchi mixed-anhydride method.

In his synthetic end-game, Keck also beautifully overcame the new and potentially show-stopping obstacle of having to chemoselectively cleave the OAc group at C20 from **37** with retention of the OAc group at C7. Not an easy task by any means! However, Keck took the view that the C20-OAc group would be substantially more electrophilic and less sterically hindered than the one at C7 because of its proximity to the nearby C-ring anomeric center. The great success of this chemoselective cleavage played an absolutely pivotal role in the eventual completion of this total synthesis.

Keck's scintillating demonstration of the enormous utility of Rainier's new titanium-mediated RCM reaction for assembling highly functionalized glycals from olefinic esters (and dienes), using a new highly reduced Takai-type titanium–ethylidene species, of presently undefined structure, is yet another item of exceptional note (Scheme 4).[9,16,17] The Rainier RCM protocol critically underpinned Keck's efforts to synthesize the C-ring glycal **25** in just a mere nine linear steps (13 steps overall) and it set the stage for a 20-step synthesis of the C-ring enal **29** itself.



Scheme 4. Rainier's new titanium–ethylidene RCM reaction of ene-esters.

For any research group to complete an asymmetric total synthesis of a bryostatin macrolide is a major achievement, but to complete the synthesis of a bryostatin that is oxygenated at C20 by a pathway that is only 60 steps overall is even more impressive. In essence, it cut more than 20 steps off the original Masamune,[3] Evans,[4] Nishiyama/Yamamura[5] and Hale/Manaviazar[6] strategies to these natural products, and it did so while maintaining a generally good level of stereocontrol throughout, and exploiting much valuable new synthetic methodology from the Keck group. With his group's latest triumph, Keck has very beautifully demonstrated the enormous worth of his novel intermolecular β-hydroxyalkyl allylsilane Prins pyran-annulation technology[15] for the synthesis of complex pyran rings, and he has also further underscored the utility of many other asymmetric reactions

that have been pioneered in his laboratory, most notably the catalytic asymmetric allylstannation of aldehydes.[11] Keck's efforts have also nobly highlighted the elegant Takai titanium–alkylidene RCM work of his talented Utah colleague, Jon Rainier[9] who, himself, has recently used this reaction technology iteratively in a rather exquisite total synthesis of brevenal.[9b] Overall, this crowned masterpiece of synthetic elegance beautifully graces the rich bryostatin total synthesis tapestry that now exists, and it rightly deserves the numerous plaudits and accolades it is presently receiving, including here. Undoubtedly this recent synthetic pathway to the bryostatins[2,18] will further expedite efforts to construct analogues for future neurological drug development, now that members of this natural product family are no longer considered to be promising as single-agent antitumor drugs for man.[19]

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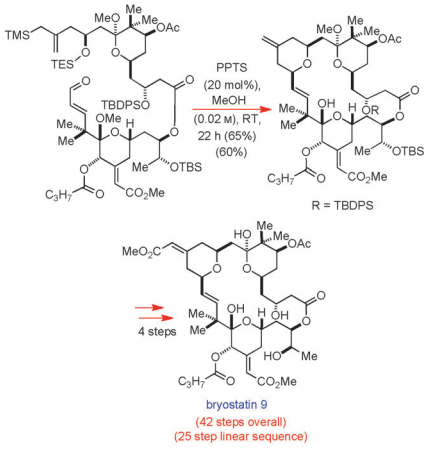

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