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Synthetic studies toward bryostatin 1: preparation of a C_1–C_{16} fragment by pyran annulation

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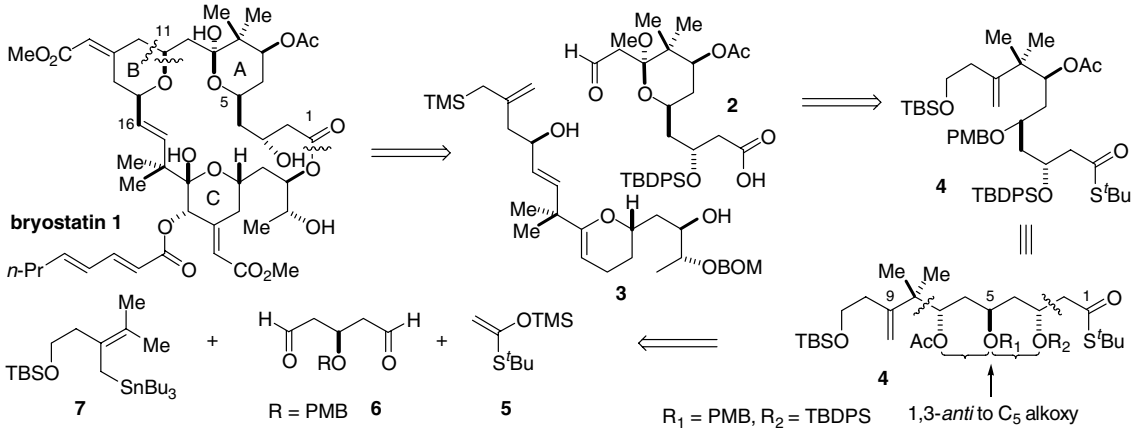
Abstract—An expeditious assembly of a C_1–C_{16} subunit of bryostatin 1 is described. A pyran annulation reaction was utilized to form the B-ring by reaction of a hydroxy-allylsilane with a fully elaborated A-ring subunit. This annulation process proceeded with complete diastereoselectivity and in excellent isolated yield despite the presence of potentially sensitive functionality in the A-ring segment.

Bryostatin 1, isolated by Petit and co-workers from a marine bryozoan in 1982,[1,2] is of great interest as a potential chemotherapeutic agent for cancer, with some 80 clinical trials completed or ongoing.[3] Although bryostatin 1 has shown limited utility as a single agent, remarkable synergies with established chemotherapy regimes have been documented.[4] Recent studies have also revealed a role for this agent in memory and as a potential therapeutic for Alzheimer's disease.[5] Although the exact mode of action of bryostatin with respect to these biological effects remains unknown, it's exceptionally high affinity for protein kinase C (PKC) isozymes is well-established.[6] Structurally, this 20-membered macrolactone with a polyacetate backbone that houses three pyran rings continues to be a daunting challenge as only three completed total syntheses[7–9] of bryostatin have been disclosed despite the many ongoing investigations that are directed toward the total synthesis of this impressive target.[10]

An approach to the synthesis of bryostatin 1 is indicated in Scheme 1. Here, application of our pyran annulation



Scheme 1. Retrosynthetic approach to bryostatin 1.

Keywords: Bryostatin; Chelation; Allylation; Stannane.
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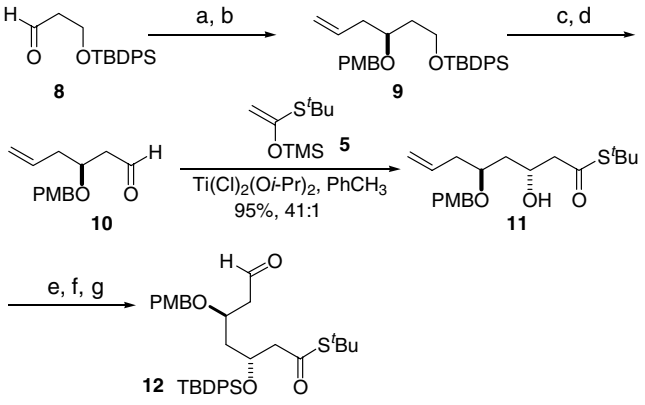
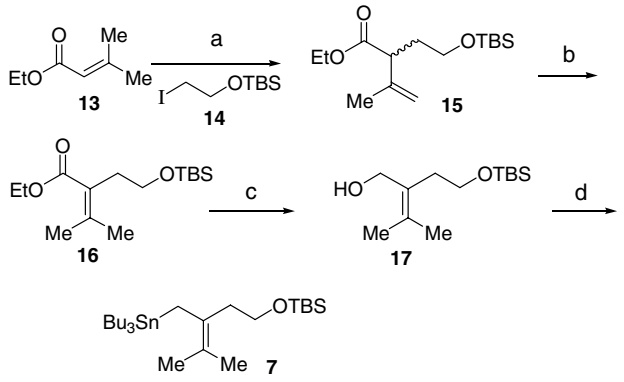
methodology,[11] which has found success in our bryostatin analogue program,[12] was envisioned to unite a C-ring β-hydroxy allylsilane such as **3** with an A-ring subunit **2**, with concurrent formation of the B-ring (Scheme 1). However, the presence of the lactol methyl ether in **2**, and its disposition β to the aldehyde carbonyl, was regarded as a potentially disastrous liability due to the strong Lewis acidic conditions (TMSOTf) required to promote the annulation process. We expected that the A-ring aldehyde **2** would be available from acyclic precursor **4**, which can be seen to possess an *anti*,*anti* relationship of the C_3–C_5–C_7 stereotriad. Thus the C_5 stereocenter could potentially be employed to control the stereoselective introduction of the C_3 and the C_7 stereocenters in sequential chelation-controlled additions at both ends of a β-alkoxy dialdehyde such as **6**.[13,14] The formation of the initial C_5 stereocenter with high stereoselectivity would thus be imperative. It was hoped that our catalytic asymmetric allylation (CAA)[15] reaction would satisfy this requirement. The *p*-methoxybenzyl group was regarded as an ideal protecting group for the C_5 hydroxyl based upon its compatibility with chelating Lewis acids.

The synthesis of the requisite C_1–C_7 aldehyde fragment along these lines has been recently disclosed and is summarized in Scheme 2.[16] This route affords **12** in 57% yield over the eight-step sequence.

In the most critical operation required to prepare the A-ring intermediate 2, allylstannane **7** was to be employed to introduce the *gem*-dimethyl group in a stereoselective addition reaction with an aldehyde such as **6**. We have found the preparation of such allylstannanes incorporating the tetrasubstituted olefin structural motif to be a challenging proposition. Ultimately, we devised a route to such intermediates via a sequence utilizing the vinylogous alkylation of ester enolates. (Scheme 3). Thus, alkylation of the extended lithium enolate of commercially available ethyl 2,2-dimethylacrylate with iodide **14** derived from iodo-ethanol proceeded in 79%



Scheme 2. Reagents and conditions: (a) (*S*)-(−)-1,1′-bi-2-napthol, Ti(O*i*-Pr)$_4$, 4 Å MS, CH_2Cl_2, −20 °C, 5 days, 90%, 93% ee; (b) PMBOC(NH)CCl$_3$, CSA, CH_2Cl_2, rt, 12 h, 76%; (c) TBAF, THF, rt, 12 h, 95%; (d) SO_3·py, Et(*i*-Pr)$_2$NH, DMSO, CH_2Cl_2, −5 °C, 30 min, 97%; (e) TBDPSCl, imidazole, DMF, rt, 24 h, 92%; (f) OsO_4, NMO, *t*-BuOH/THF/H_2O, rt, 14 h; (g) Pb(OAc)$_4$, PhH, rt, 1 h, 99% (two steps).

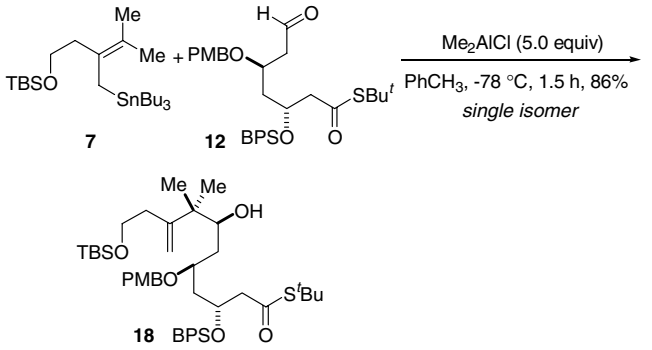


Scheme 3. Reagents and conditions: (a) LDA, THF, −78 °C, 30 min; 2-iodo-1-(*t*-butyldimethylsilanoxy)ethane, −78 °C to rt, 15 h, 79%; (b) *t*-BuOK, THF, 0 °C, 2 h, 93%; (c) DIBAL, CH_2Cl_2, 0 °C, 2 h, 94%; (d) *n*-BuLi, THF, −78 °C, 45 min; MsCl, −78 °C, 1.25 h; Bu_3SnLi, −78 °C to rt, 20 h, 72%.

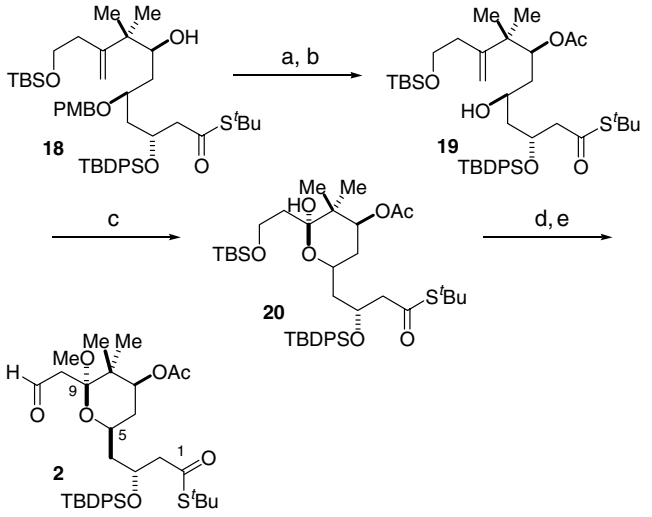
yield.[17] Migration of the olefin to give the thermodynamically favored α,β-unsaturated ester **16** was effected by exposure to *t*-BuOK in THF in 93% yield. Here, it was found that rigorous exclusion of oxygen during the isomerization was necessary to prevent autoxidation of the potassium enolate.[18] Full-reduction of the ester proceeded uneventfully to give the allylic alcohol **17**.

This set the stage for introduction of the stannyl moiety, which unexpectedly proved to be rather difficult. Our initial intention was to convert the alcohol to the corresponding bromide or chloride and effect a displacement reaction with tributyltinlithium.[19] However, attempted conversion of the alcohol to the corresponding chloride or bromide yielded compounds that proved unstable with respect to isolation and purification. It was critical that pure materials be obtainable here to preclude extensive purification of the desired allylstannane. It was thus necessary to convert the hydroxyl functionality to a suitable leaving group followed by direct exposure, without workup, to the tin nucleophile. This in turn required that the reaction used to activate the hydroxyl group be free of byproducts which could interfere with the use of tributyltinlithium. The most efficient manner devised to accomplish this proceeded via in situ formation of the mesylate at −78 °C (reaction of the alcohol with 1 equiv of *n*-BuLi followed by the addition of mesyl chloride) followed by addition of tributyltinlithium and slow warming of the mixture to room temperature.[18] This afforded allylstannane **7** in 50% overall yield for the sequence (from ester **13**).

Consistent with our previous observations,[16] the nucleophilic addition of stannane **7** to aldehyde **12** required the use of a strongly activating Lewis acid with the ability to chelate, as neither $MgBr_2$·OEt_2 nor Ti(Cl)$_2$(O*i*-Pr)$_2$ provided sufficient activation to promote this reaction (Scheme 4). In the event, precomplexation of the aldehyde **12** with excess Me_2AlCl in toluene at −78 °C followed by the addition of stannane **7** afforded the coupled product **18** in 86% yield and as a single diastereomer as judged by ^1H and ^{13}C NMR spectroscopy.[20]



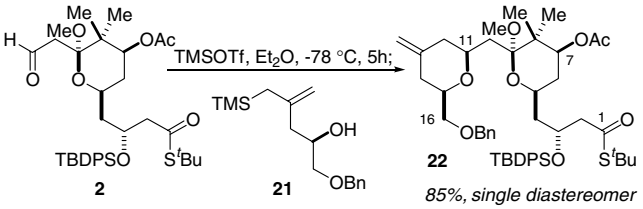
Scheme 4. C_7–C_8 bond construction and installation of the *gem*-dimethyl moiety.



Scheme 5. Reagents and conditions: (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 24 h, 94%; (b) DDQ, 2:1 CH_2Cl_2/pH 7.0 buffer, rt, 2 h, 94%; (c) O_3, CH_2CH_2, −78 °C, 5 min; DMS, rt, 12 h, 91%; (d) CSA, MeOH, rt, 1.25 h, 99%; (e) SO_3·py, Et(*i*-Pr)$_2$NH, DMSO, CH_2Cl_2, −5 °C, 1 h, 88%.

Conversion of this acyclic material to the A-ring of bryostatin 1 first required acetylation of the C_7 hydroxyl group, which proceeded uneventfully under standard conditions to give acetate **19** in 94% yield (Scheme 5). Subsequent oxidative PMB removal was realized in 94% yield under buffered DDQ conditions. Ozonolysis with reductive work-up proceeded in 91% yield to give lactol **20** as the sole product; none of the open-chain keto-alcohol isomer was detected by ^{1}H NMR of the crude reaction product. The stereochemistry about the A-ring was established unambiguously at this stage by an NOE experiment which revealed interactions between the C_5, C_7, and lactol OH protons, thereby confirming the suspected stereochemical outcome of the key fragment coupling reaction. Deprotection of the TBS ether with simultaneous formation of the methyl ketal was carried out in a single operation by treatment with acidic methanol to give the corresponding primary alcohol. Subsequent Parikh–Doering oxidation then afforded the desired aldehyde A-ring subunit **2** in 88% yield.

In the critical event, subjection of an ether solution of aldehyde **2** and the known β-hydroxy allylsilane **21**[11]



Scheme 6. Formation of the B-ring by pyran annulation.

to the action of TMSOTf at −78 °C yielded the AB bicycle **22** in 85% yield and as a single diastereomer, thus confirming the viability of **2** as a suitable substrate for the pyran annulation. The expected stereochemistry of the newly formed pyran was corroborated by diagnostic NOE transfers from the C_{11} proton to the C_{15} and C_9 methoxy protons. Our concerns regarding the potential Lewis acid lability of the mixed acetal β to the aldehyde during the pyran annulation were not totally unfounded, however. It was noted that aldehyde **2** was quite acid sensitive in that it proved unstable in $CDCl_3$ as NMR solvent unless the $CDCl_3$ was pretreated with K_2CO_3. Moreover, it was found that monitoring of the pyran annulation reaction itself by TLC gave misleading results using aliquots spotted directly from the reaction mixture, as products other than **22** were observed as the major materials. Only the disappearance of starting materials could be reliably monitored in this way. After completion of the reaction and quenching at low temperature, however, **2** is observed as essentially the only product. It should be noted that the pyran annulation reaction was best quenched cold (at −78 °C) initially by addition of Hünigs base followed by the addition of aqueous $NaHCO_3$ solution.

The success of the pyran annulation to form the B-ring (Scheme 6) with the model allylsilane suggests that A-ring aldehyde **2** could be joined with a more complex C-ring β-hydroxy allylsilane, as proposed in our retrosynthetic analysis (Scheme 1). It worth noting that the AB bicyclic material **22** was accessed in 26% overall yield, over a 17-step sequence that began with commercially available 1,3-propanediol. This represents, to the best of our knowledge, the most expedient route to an AB bicyclic system of bryostatin 1 reported to date. In this regard, it should be noted that both Evans and Yamamura have documented that the exocyclic enoate at C_{13} in bryostatin 1 can be introduced in advanced intermediates (with the entire macrocylic skeleton in place) using the BINOL based phosophonate reagent developed by Fuji.[21] Thus introduction of the unsaturated ester is anticipated to require two additional steps of oxidative olefin cleavage and Emmons reaction. Efforts to extend the strategy and methodology described herein to the total synthesis of bryostatin 1 and analogues are in progress.

Acknowledgments

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Supplementary data

Complete experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for compounds described herein. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.094.

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