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Award Accounts

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Evolution of Synthetic Strategies for Highly Functionalized Natural Products: A Successful Route to Bryostatin 3

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A convergent asymmetric synthesis of the antineoplastic marine macrolide, bryostatin 3 (**1**), has been achieved. This synthesis relied upon stereo-controlled construction of two major fragments, the top-half fragment **2** and the bottom half fragment **3**, and their coupling by the Julia–Lythgoe olefination and Yamaguchi macrolactonization. The top-half fragment **2** could successfully be synthesized by tandem connection of the three key fragments. The bottom-half fragment **3** was prepared by the union of vinyl iodide **39** and α-alkoxy aldehyde **30**.

Total synthesis of architecturally complex natural products remains as a formidable challenge in organic chemistry. In parallel with evolving technologies of analysis and bioassays, target molecules are explosively increasing in number, and becoming more complex and larger in size. These situations often make present synthetic approaches less accessible for the targets, and so more direct and efficient methodologies are in demand. Faced with this issue, synthetic chemists focused their attention to discover and establish new synthetic methodologies with a hope of enabling the construction of complicated structures and of performing unique and unprecedented transformations.

A recent landmark in organic chemistry is the total synthesis of palytoxin by Kishi,[1] which was efficiently achieved by the assembly of highly functionalized fragments by employing the $NiCl_2/CrCl_2$-mediated carbon–carbon bond forming reaction.[2] Thus, development of this new synthetic way resulted in the major leap forward in the complexity and size of the molecules.

My own interest in the natural product synthesis stimulated me to set several synthetic programs. An important objective of these undertakings was identifying and projecting the important synthetic reactions in each total synthesis discussed, which would allow direct access to complex molecules in a shorter time with good atom economy. This personal account will highlight a synthetic work on bryostatin 3 (**1**),[3a] a bioactive marine natural product. The author has participated in the early stage of this successful effort as a graduate student at Keio University, which, at last, was brought to fruition by our successors.[4]

1. Background

The bryostatins constitute a class of twenty related macrolides, isolated from the marine bryozoan *Bugula neritina Linnaeus* and *Amathia convuluta*.[3] They are known to possess exceptional antineoplastic activities against the murine P388 lympocytic leukemia, B16 melanoma, ovarian sarcoma and others, and the potential to activate protein kinase C without tumor promotion similarly to the activities of phorbol and aplysiatoxin.[3b] In particular, bryostatin 1, the most abundant congener in the family, is in clinical development as a chemotherapeutic agent for various forms of cancer.[5]

All bryostatins possess the unique 20-menbered macrolactone framework (bryopyran), which comprise three pyran rings bridged by tethers together, two exocyclic enoates, and a (*E*)-disubstituted olefin moiety (Chart 1).

The synthesis of the bryostatins is of considerable interest at present because of their biological activities, unique structures, and limited availability from natural sources. Although many groups have contributed towards the synthesis of bryostatins,[6] only two types of family members have been synthesized, i.e., bryostatin 7 by Masamune[7] and bryostatin 2 by Evans.[8] Under this situation, the author set up a program aimed at the development of a convergent synthetic pathway toward bryostatin 3, the most complex congener possessing an additional stereocenter at C(22)[9] and the densely functionalized a pyran–butenolide framework. This complexity made its stereocontrolled construction an even more challenging task than that for other family members.

2. Synthetic Plan

The remarkably tough structure of the target molecule offers many synthetic challenges:

1) The stereochemical challenge to construct twelve stereogenic centers.
2) The need for efficient processes for assembling highly functionalized fragments and formation of macrocyclic structure.

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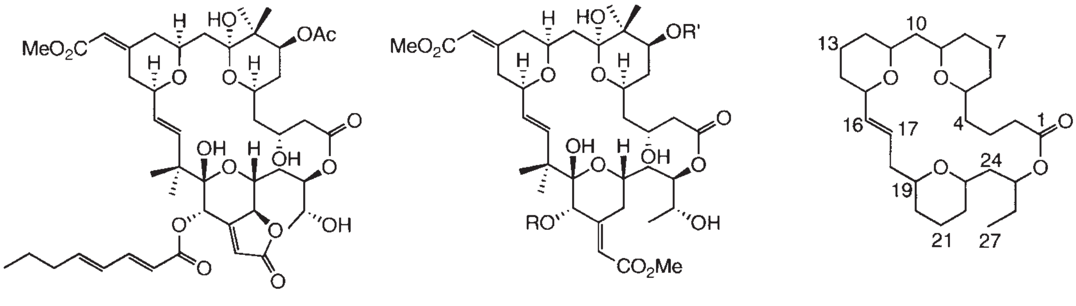
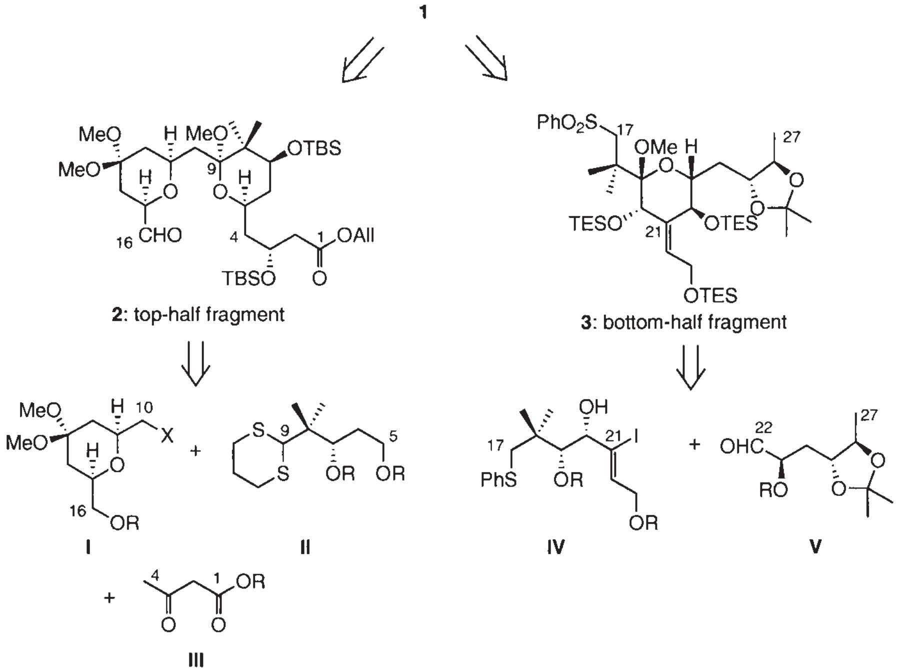


bryostatin 3 (**1**)

bryostatin 1: R=CO(CH)$_4$C$_3$H$_7$, R'=Ac
bryostatin 2: R=CO(CH)$_4$C$_3$H$_7$, R'=H
bryostatin 7: R=Ac, R'=Ac

bryopyran framework

Chart 1.



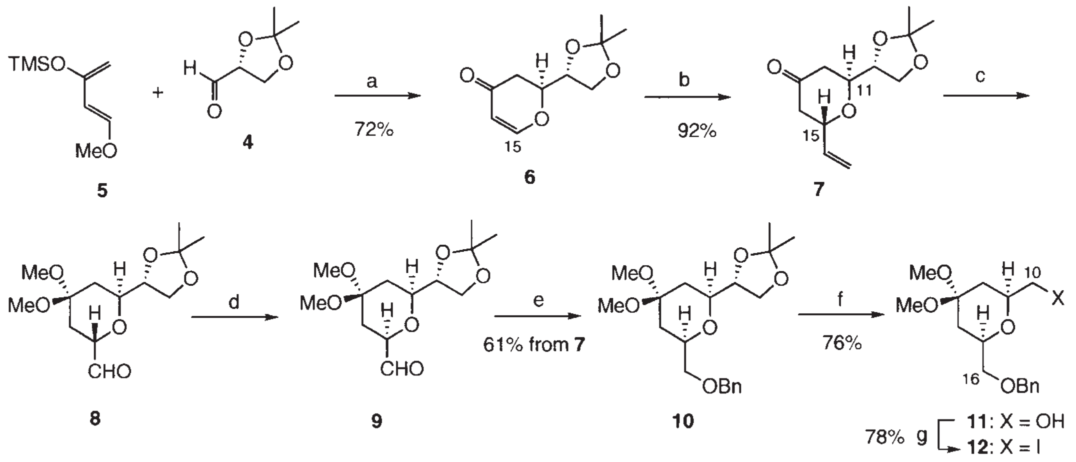
Scheme 1. Synthetic plan.

3) The judicious choice of protecting group arrangements for poly-oxygenated structures.
4) The requirement for the stereo-controlled formation of di- and tri-substituted double bonds.

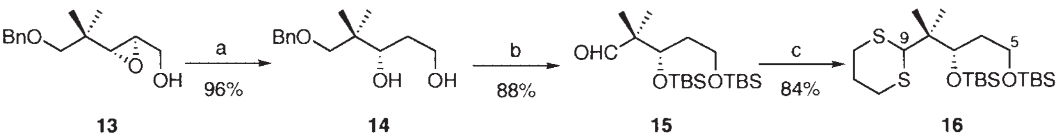
With these considerations in mind, a synthetic strategy for **1** was analyzed as illustrated in Scheme 1. Key features of this approach are the Julia–Lythgoe olefination reaction[10] to assemble two major fragments, the top-half fragment **2** and the bottom-half fragment **3**; macrolactonization to construct the bryopyran framework; the implementation of reagent-controlled aldol reaction of dioxinone derivative; the use of the chiral phosphonate to construct a exocyclic enoate moiety. The top-half fragment **2**, being shared by all bryostatins, can be assembled from more simple compounds **I**–**III**. As for the bottom-half fragment **3**, it can be derived from vinyliodide **IV** and aldehyde **V**. The former would be prepared from the commercially available 2,2-dimethyl-propane-1,3-diol, while the latter can be conveniently prepared from D-glucose.

3. Synthesis of Top-Half Fragment

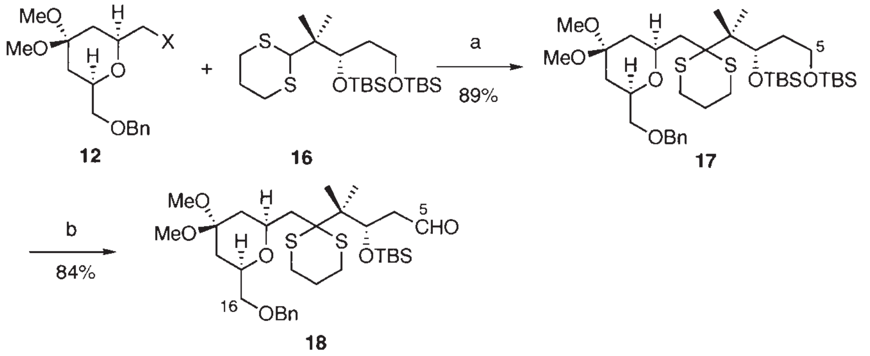
3.1 Construction of the C(10)–C(16) and C(5)–(9) Frameworks. The first stage of the top-half fragment synthesis was the elaboration of the C(10)–C(16) framework (Scheme 2). The hetero-Diels–Alder reaction of **4** with **5** by Danishefsky's protocol[11] was employed to give optically active enone **6** as the sole product in 72% yield. Copper-mediated conjugate addition with vinylmagnesium bromide delivered a vinyl group to C(15) position, thereby giving **7** with high stereoselectivity. The stereochemistry of the product was unambiguously determined by ^{1}H NMR, which turned out to have the undesired *trans*-relationship between C(15) and C(11), which was probably made via kinetically controlled axial attack at C(15). After mild acetalization that preserved the *O*-isopropylidene acetal moiety, ozonolysis of the C–C double bond followed by reductive workup (Me$_2$S) gave aldehyde **8**. At this stage, epimerization at C(15) position to give desired *cis*-isomer **9** was required.



Scheme 2. Preparation of the C(10)–C(16) fragment. a) $ZnCl_2$, PhH, rt; b) $H_2C{=}CHMgBr$, CuI, TMSCl, DMPU, THF; c) i. $Me_2C(OMe)_2$, PPTS, MeOH, ii. O_3 then Me_2S; d) K_2CO_3, MeOH; e) i. $NaBH_4$, ii. BnBr, NaH, DMF; f) Amberlite IR-120B (H^+ form), MeOH, ii. $NaIO_4$, $NaHCO_3$ aq., iii. $NaBH_4$; g) i. TsCl, pyridine, ii. NaI, acetone. TMS = trimethylsilyl, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.



Scheme 3. Preparation of the C(5)–C(9) fragment. a) Red-Al, toluene; b) i. TBSCl, imidazole, DMF, ii. H_2, Pd-black, MeOH, iii. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; c) Propane-1,3-dithiol, $MgBr_2{\cdot}OEt_2$, Et_2O. Red-Al = $NaAlH_2(OCH_2CH_2OCH_3)_2$, TBS = *t*-butyldimethylsilyl.



Scheme 4. Preparation of the C(5)–C(16) fragment. a) **16**, *t*-BuLi, HMPA, THF, −78 °C then **12**; b) i. PPTS, MeOH, ii. $SO_3{\cdot}$pyr., DMSO, Et_3N. HMPA = hexamethylphosphoric triamide, PPTS = pyridinium *p*-toluenesulfonate.

Thus, upon exposure of **8** with K_2CO_3 in MeOH, complete equilibration to the thermodynamically more stable *cis*-isomer **9** occurred. Reduction of a formyl group followed by benzylation of the resulting hydroxy group provided **10**. Selective removal of isopropylidene acetal and subsequent glycol cleavage followed by reduction afforded alcohol **11**. Finally, **11** was *O*-tosylated and displaced with iodide to give **12**.

Meanwhile, elaboration of the C(5)–C(9) region began with diol **14**, derived from the known epoxy alcohol **13** (Scheme 3).[12] After silylation of the two hydroxy groups in **14**, removal of the benzyl group followed by Swern oxidation gave **15** in 92% yield. Thioacetal formation of **15** with propane-1,3-dithiol in the presence of $MgBr_2{\cdot}OEt_2$[13] provided the requisite C(5)–C(9) fragment **16** without loss of any silyl group.

The next stage focused on the critical union of sterically encumbered dithioacetal **16** and iodide **12**. Fortunately, a clean coupling reaction was attained by using the combination of *t*-BuLi and HMPA, thereby giving the coupling product **17** in 89% yield (Scheme 4). Lithiations of **16** by using *n*-BuLi or *t*-BuLi in various solvents without additives had been uniformly sluggish, and the coupling reaction had proved fruitless. The requisite C(5)–C(16) fragment **17** in hand was then converted to aldehyde **18** for further stereoselective carbon chain extension. Thus, after selective cleavage of the C(5)-silyl ether, successive oxidation of the resulting alcohol under Swern conditions gave **18** in 91% yield.

3.2 Stereoselective Aldol Reaction of Acetoacetate Derivative. Next to be considered was introduction of a four-carbon unit, which constitutes a 1,3-diol array. This subunit is an ubiquitous structural motif of biogenetic origins from acetic acid, which, in fact, is found in many types of natural products, such as compactin, amphotericin B, and spongestatins.[14–16] One of the basic ideas for attaining the stereoselective construction of this subunit was to employ the aldol addition of acetoacetate dienolates to aldehydes, although, to my knowledge, it had little precedence at that time. In this context, experiments to test this idea were undertaken. Through preliminary experiments, the author soon became interested in the dioxinone derivative **A**, a protected form of acetoacetic acid, as a dienolate precursor (Fig. 1). The reasons for this choice are as follows:

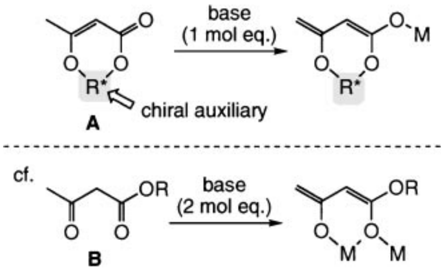
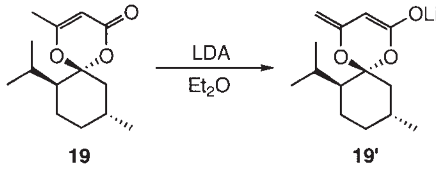


Fig. 1.

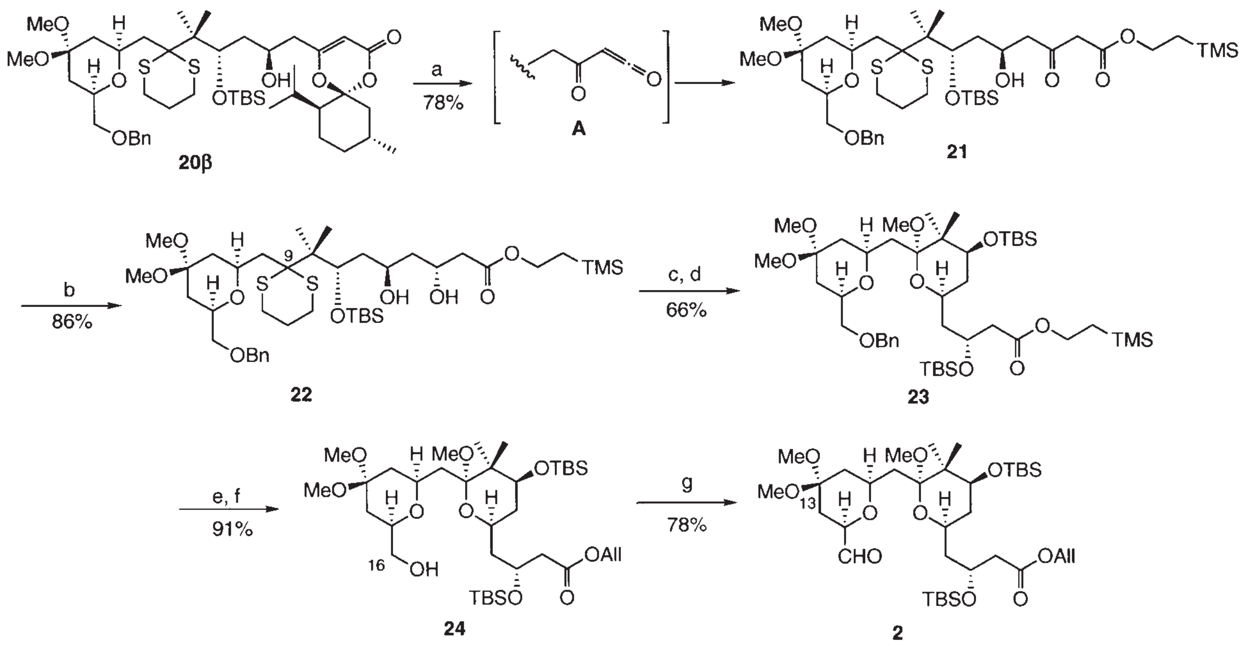
1) Potential utility of the dioxinone unit, which would serve versatile precursors for the preparation of the corresponding *β*-keto esters, amides, and lactones.
2) The chance to introduce a chiral source on the dioxinone ring, which would take part in the stereoselective reaction.
3) In comparison with unprotected acetoacetates, dioxinone **A** requires only one mole equivalent of the base to generate a dienolate, so the reaction system is a simple asymmetric process.

Insight into these features was of considerable assistance in the design of a newer and more efficient method for the stereoselective reaction. After surveying a number of dioxinone derivatives, I chose menthonide **19**[17] for the reaction (Eq. 1). Thus, in situ generation of lithium enolate **19′** (1 mol equiv. of LDA, Et_2O, 0 °C, 1 h) and successive addition of LiI and aldehyde **18** underwent a highly diastereoselective reaction, thereby giving the aldol adduct **20*β*** with the correct stereochemistry at C(5) (71%, 96% d.s.) (Eq. 2). Note that, in absence of the additive, the reaction changed the sense of stereoselection, providing **20*α*** as a major diastereomer. Although the rationale of these stereochemical outcomes is still not clarified, the formation of a lithium chelate between dienolate and aldehyde is no doubt essential to the success of the reaction.

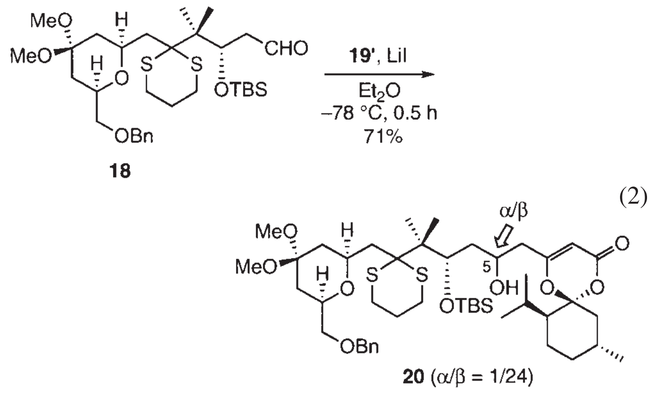
By contrast, several groups have recently reported the asymmetric aldol reaction of achiral acetoacetate-derived *O*-silyl dienolate by using chiral catalyst.[18–20]



(1)



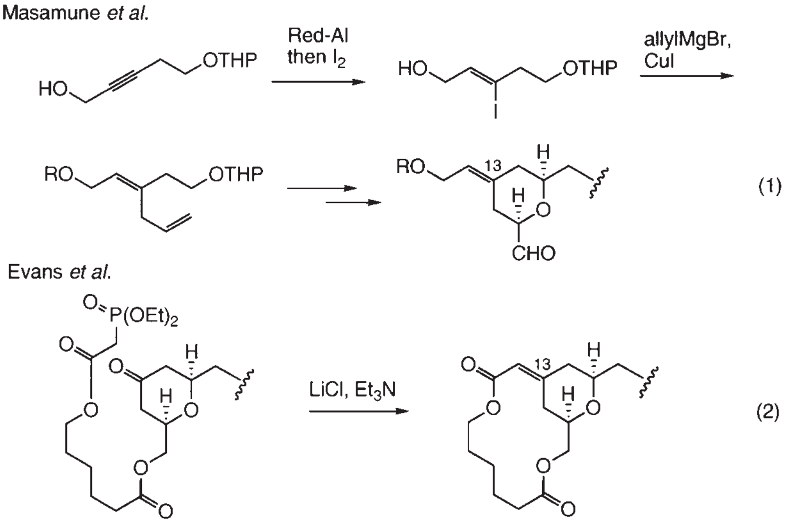
Scheme 5. Synthesis of the top-half fragment **2**. a) $(CH_3)_3Si(CH_2)_2OH$, toluene, reflux; b) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, −20 °C; c) i. $HgCl_2$, HgO, CH_3CN/H_2O (9/1); ii. PPTS, MeOH; d) TBSOTf, 2,6-lutidine, CH_2Cl_2; e) H_2, $Pd(OH)_2/C$, MeOH; f) i. $LiOH{\cdot}H_2O$, THF/MeOH/H_2O (1/2/1), ii. Allyl bromide, $NaHCO_3$, DMF; g) TPAP, NMO, MS 4A, CH_2Cl_2. TMS = trimethylsilyl, TBS = *t*-butyldimethylsilyl, All = allyl, TPAP = tetrapropylammonium perruthenate.



3.3 Completion of the Top-Half Fragment 2 Synthesis. With the requisite stereoisomer in hand, next to be considered was the conversion of **20*β*** to the coupling precursor **2** (Scheme 5). Thus, upon heating of **20*β*** with 2-trimethylsilylethanol in toluene (reflux, 2 h), departure of the chiral auxiliary and concomitant formation of *β*-keto ester **21** via acyl ketene **A** occurred. Evans hydroxy-directed reduction[21] of **21** set the correct C(3)-stereogenic center, thereby giving 1,3-*trans*-diol **22** in 90% yield. After dithioacetal hydrolysis to regenerate the C(9)-carbonyl group, acid treatment (PPTS, MeOH) followed by silylation gave the desired compound **23**, which was converted into allyl ester **24** in a three-step sequence. Finally, adjustment of oxidation level at C(16) by TPAP-oxidation[22] gave **2**.

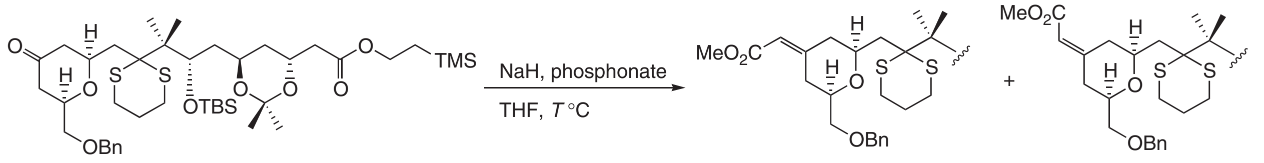
3.4 Model Study for Stereoselective Introduction of the Exocyclic Enoate Unit. Selective introduction of a methoxycarbonylmethylene unit into the C(13) position is one of key issues in bryostatin synthesis. In the Masamune total synthesis, the key intermediate bearing a trisubstituted olefin moiety has been selectively constructed by application of Corey's methodology, which includes the hydroxy-directed hydroalumination of propargyl alcohol and subsequent iodination, followed by the copper-mediated cross coupling reaction with Grignard reagent (reaction 1, Scheme 6).[7] An alternative way of Evans synthesis has demonstrated intramolecular delivery of exocyclic enoate unit via the Horner–Wadsworth–Emmons (HWE) reaction of the tethered phosphonate (reaction 2, Scheme 6).[8d] However, this protocol was not eventually applied in their subsequent work for bryostatin synthesis.

In contrast to these approaches, the synthetic challenge of selective olefination stemmed from the requirement of more simple and direct means (Table 1). As a initial study, simple HWE

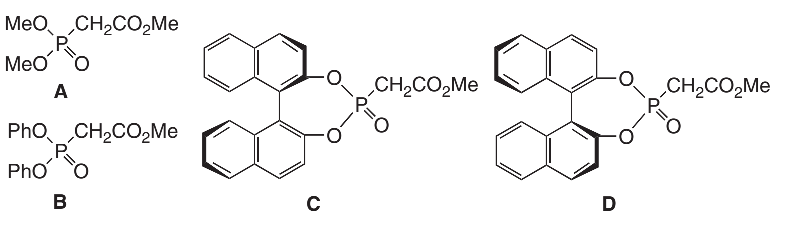


Scheme 6. Strategies for the construction of the exocyclic enoate moiety at C(13).

Table 1. Horner–Wadsworth–Emmons Reaction of **25**



Run	Phosphonate	T/°C	Yield/%	Z/E
1	**A**	25	94	1.6/1
2	**B**	0	90	2.0/1
3	**C**	−78 → 0	92	4.0/1
4	**D**	−78 → 0	85	2.3/1



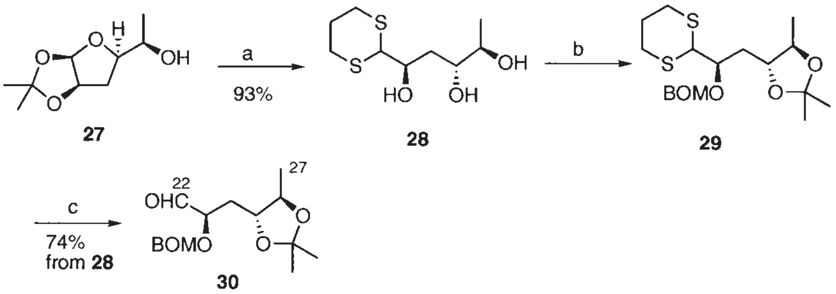
reaction of ketone **25** with trimethyl phosphonatoacetate (**A**) was attempted (run 1).[4e]

Thus, treatment of **25** with **A** and NaH at 25 °C for 12 h gave the corresponding α,β-unsaturated ester **26** in favor of the desired stereochemistry (94% yield, $Z/E = 1.6/1$), suggesting a possibility of selective construction of the *Z*-olefin. For further pursuit of the selective reactions, other phosphonates were examined.[4a,23] Interestingly, all of these attempts performed *Z*-selective reaction. In the case of Ando's reagent **B**,[24] the reaction was faster than that of **A** even at lower temperature (−15 °C, 4 h) with a slight enhancement of *Z*-selectivity (run 2). This result suggested that the *Z*-product preferentially forms under kinetic conditions. From this speculation, cyclic phosphonates were employed for the reaction because these are known to possess higher reactivity than their acyclic counterparts due to the pronounced release of ring strain in conversion from the tetrahedral to the pentacoordinate at phosphorous.[25] Clearly, Fuji's chiral reagent **C**,[26] bearing a strained seven-membered ring, was the more suitable for the *Z*-isomer formation (run 3). Similar observations have appeared in the recent investigation of Evans group.[8a] Interestingly, in comparison with **C**, the antipodal reagent **D** showed less selective reaction, probably due to the mismatched situation around the reaction site (run 4).

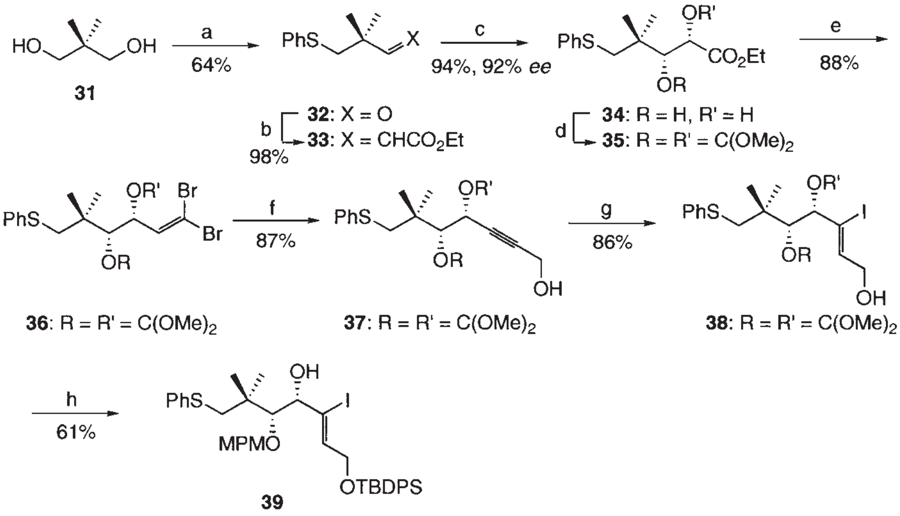
4. Synthesis of the Bottom-Half Fragment 3

4.1 Construction of the C(17)–C(21) and C(22)–C(27) Fragments. The route to the bottom-half fragment **3**, the C(17)–C(27) region including six chiral centers, was started with alcohol **27**,[27] derived from D-glucose (Scheme 7). Treatment of **27** with propane-1,3-dithiol under acidic conditions effected the cleavage of the *O*-isopropylidene group and concomitant thioacetal formation, thereby giving triol **28**. Selective acetal formation was effected with 2,2-dimethoxy propane in the presence of catalytic amount of CSA. A further two-step sequence converted **29** into aldehyde **30**, ready for the coupling with vinyl iodide **39**, which was efficiently prepared from **31** via the route shown in Scheme 8.

A five-step sequence from 1,3-propandiol secured aldehyde **32**, which was subjected to the HWE reaction to give α,β-unsaturated ester **33**. Asymmetric dihydroxylation according to the Sharpless protocol[28] was selected with potassium osmate in the presence of DHQ-PHN ligand. Thus, the corresponding



Scheme 7. Preparation of the C(22)–C(27) fragment. a) 1,3-Propanedithiol, conc. HCl, $CHCl_3$; b) i. $Me_2C(OMe)_2$, CSA, DMF, ii. $BnOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2; c) MeI, $NaHCO_3$, 10% aq. CH_3CN. CSA = camphorsulfonic acid.

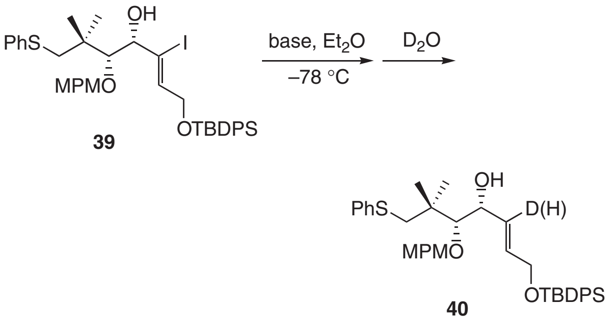


Scheme 8. Preparation of the C(17)–C(21) fragment. a) i. TsCl, pyridine, CH_2Cl_2, ii. DHP, TsOH, CH_2Cl_2, iii. PhSNa, 18-crown-6, DMF, 90 °C, iv. AcOH, THF, H_2O (4:2:1), 60 °C, v. $SO_3\cdot$pyridine, DMSO, Et_3N, CH_2Cl_2; b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, toluene; c) DHQPHN (2 mol%), $K_2OsO_2(OH)_4$ (0.4 mol%), $K_3Fe(CN)_6$, K_2CO_3, $Me_2SO_2NH_2$, *t*-BuOH, H_2O, 0 °C, 18 h; d) $Me_2C(OMe)_2$, TsOH, CH_2Cl_2; e) i. DIBAL-H, toluene, ii. Ph_3P, CBr_4, CH_2Cl_2, 0 °C; f) *n*-BuLi, THF, then $(CHO)_n$; g) i. Red-Al, THF then I_2; h) i. CF_3CO_2H, H_2O, THF, ii. TBDPSCl, imidazole, iii. *p*-$MeOC_6H_4CH(OMe)_2$, PPTS, CH_2Cl_2, iv. DIBAL-H, toluene, 0 °C. TBDPS = *t*-butyldiphenylsilyl, MPM = *p*-methoxybenzyl, Ms = methanesulfonyl, DHP = 3,4-dihydro-2*H*-pyran, Red-Al = $NaAlH_2(OCH_2CH_2OCH_3)_2$, DIBAL-H = *i*-$Bu_2AlH$, PPTS = pyridinium *p*-toluenesulfonate.

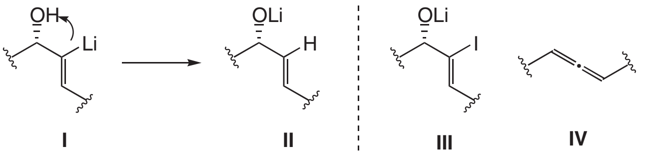
1,2-diol **34** was obtained in 90% ee. After masking of diol moiety, partial reduction of ester to aldehyde with DIBAL-H followed by Corey–Fuchs olefination[29] was employed to give dibromoolefin **36**. Lithium acetylide, generated from **36** with 2 molar equivalents of *n*-BuLi, cleanly reacted with paraformaldehyde to give the corresponding propargylic alcohol **37**. At this stage, recrystallization was operated to yield the optically pure **37** (>99% ee). The latter readily engaged in a hydroxy group-directed hydroalumination of C–C triple bond[30] and the following in situ trapping of the resulting aluminate by iodine to give the iodoalkene **38**. A four-step sequence involving protecting group arrangements occurred to prepare vinyl iodide **39**.

4.2 Model Study for the Halogen–Metal Exchange Reaction of 39. With the above results in hand, the author now focused his attention on a means for the coupling of vinyl iodide **39** with aldehyde **30**. Given the dianion species from **39**, *n*-BuLi was employed for the halogen–metal exchange and concomitant deprotonation of hydroxy group (Table 2). Thus, upon treatment of **39** with 2.5 molar equivalents of *n*-BuLi, formation of the vinyllithium species was assessed by its D_2O quenching. However, the respective product **40** gave only 40% yield with partial recovery of the starting material (45%) (run 1). Surprisingly, no deuterium was incorporated in the product. A further attempt with 3.5 molar equivalents of *t*-BuLi also resulted in less incorporation of deuterium, albeit a high yield of **40** was observed (run 2). These results suggested that the *C*-lithiation was faster than the *O*-lithiation, which made the internal delivery of the proton from the adjacent hydroxy group (**I** → **II**) immediate. On the other hand, the halogen–metal exchange of *O*-protected derivatives of **39** consistently provided considerable amounts of allene derivative **IV**.

Table 2. Attempts for the Halogen–Lithium Exchange

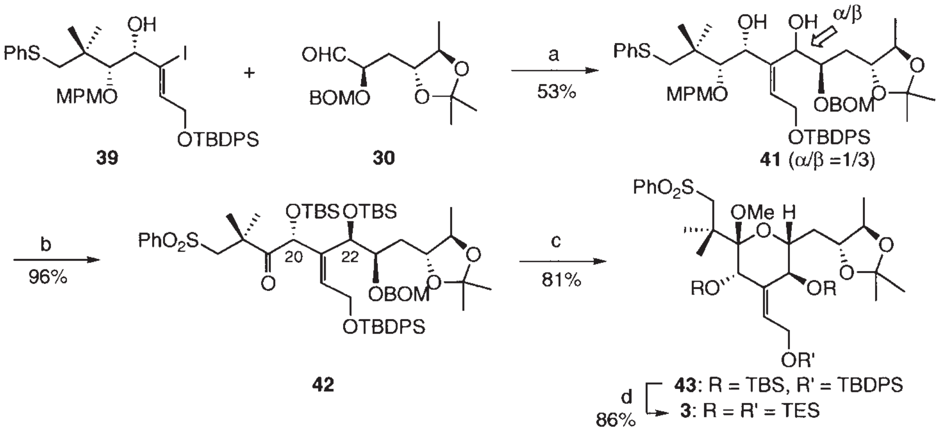


Run	Base (mol equiv.)	Yield/% (Ratio of D/H)
1	*n*-BuLi (2.5)	40 (<1:>99)
2	*t*-BuLi (3.5)	90 (10:90)
3	MeLi (1.0), *t*-BuLi (2.0)	70 (>99:<1)



To circumvent these annoying problems, stepwise lithiation of **39** was attempted. Thus, upon successive treatment of **39** with 1.0 molar equivalent of MeLi, a less reactive agent for halogen–metal exchange, and 2.0 molar equivalents of *t*-BuLi, the reaction was stopped by adding D_2O to give **40** in good yield (run 3). Delightfully, a complete incorporation of one deuterium atom was observed.

4.3 Completion of the Bottom-Half Fragment 3 Synthesis. As the coupling of **39** with **30** thus appeared to be feasible, addition of lithiodianion to aldehyde **30** at −90 °C was attempted, giving the product **41** in favor of the desired β-isomer ($\mathbf{41\alpha}/\mathbf{41\beta} = 1/3$) (Scheme 9). With all of the stereogenic centers in the bottom-half fragment now installed, $\mathbf{41\beta}$ was converted to the coupling precursor **3**. Thus, after silylation of diol moiety, oxidation of the phenylthio group by using *m*-CPBA gave the corresponding sulfone. It is noteworthy that the sensitive tri-substituted olefin moiety survived under the reaction conditions, presumably due to steric hindrance offered by the proximal silyl groups at C(20) and C(22). Removal of MPM group followed by oxidation of the resulting alcohol under Dess–Martin conditions[31] smoothly proceeded to give ketone **42**. Selective detachment of the BOM group in **42** was achieved by catalytic hydrogenation without saturation of the trisubstituted double bond with concomitant partial cleavage of the *O*-isopro-



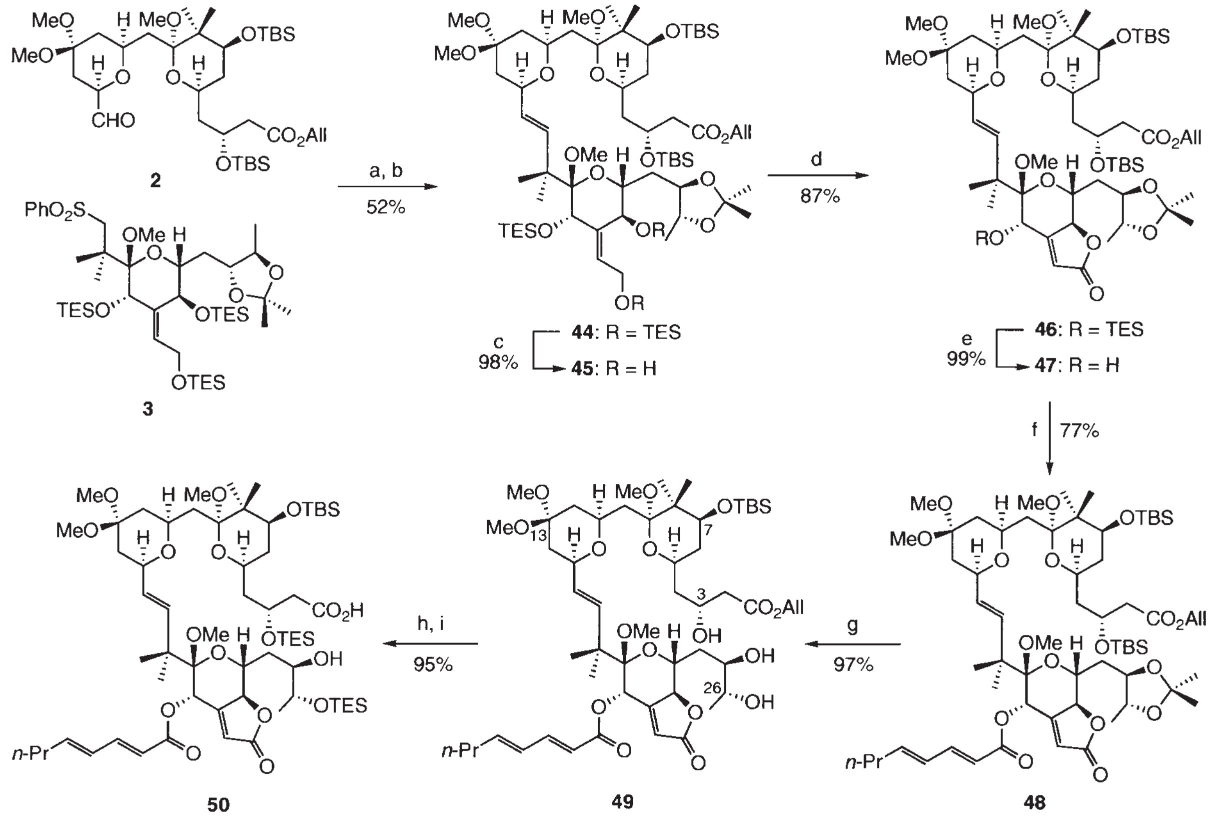
Scheme 9. Synthesis of bottom-half fragment **3**. a) MeLi, Et_2O, −30 °C, *t*-BuLi, −90 °C, then **30**; b) i. TBSOTf, 2,6-lutidine, ii. *m*-CPBA, Na_2HPO_4, CH_2Cl_2, iii. DDQ, H_2O, CH_2Cl_2, iv. Dess–Martin periodinane; c) i. H_2, $Pd(OH)_2/C$, EtOH then $Me_2C(OMe)_2$, PPTS, acetone, ii. TBSOTf, TMSOMe, $Me_2C(OMe)_2$, MS 4A, CH_2Cl_2; d) i. TBAF, THF, ii. TESOTf, 2,6-lutidine, CH_2Cl_2.

pylidene group, which was restored by treatment with 2,2-dimethoxypropane in the presence of catalytic amount of PPTS in acetone. Formation of acetal **43** was accomplished by reacting the ketone with TBSOTf, TMSOMe, and 2,2-dimethoxypropane in favor of β-stereochemistry. Finally, protecting group interchange from TBS group to TES provided the fully protected bottom-half fragment **3**, in readiness for the Julia–Lythgoe coupling with the top-half fragment **2**. Note that this transformation would permit selective removal of silyl groups later in the synthesis, as required.

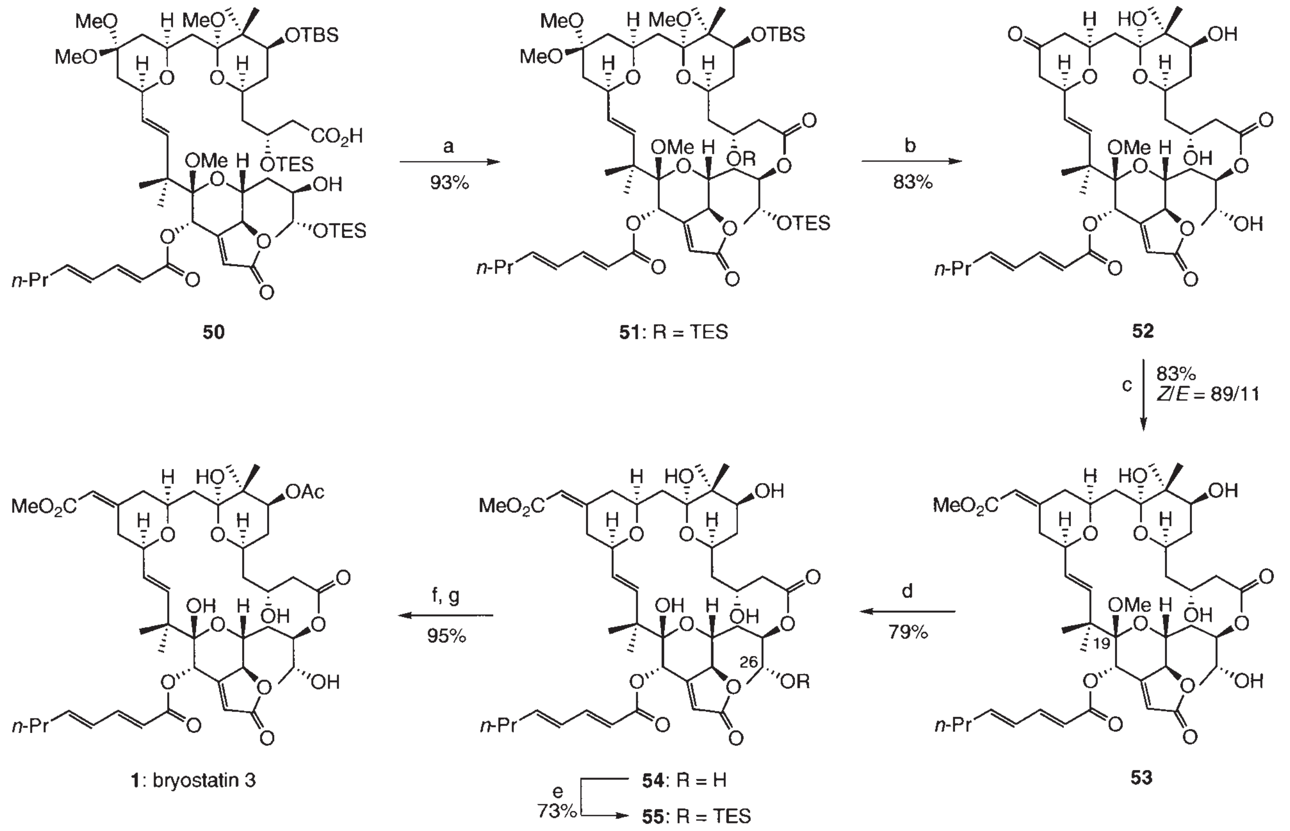
5. End Game toward 1

With the successful access to two major fragments, **2** and **3**, this project arrived at two pivotal stages of the bryostatin synthesis, i.e., the Julia–Lythgoe olefination and macrolactonization. As the first key reaction, union of **2** with **3** was successively effected by using PhLi as base,[7] followed by treatment with BzCl and DMAP (Scheme 10). Reductive elimination reaction of the resulting coupling product with 5% Na–Hg in the presence of Na_2HPO_4 gave *trans*-olefin **44** ($J_{H(16),H(17)} = 16.1$ Hz). Fortunately, selective detachment of two TES groups was successful by treatment with TBAF and AcOH (1:1) in THF, thereby giving diol **45** in almost quantitative yield.

Selective oxidation of the liberated primary alcohol with TPAP and NMO provided the desired α,β-unsaturated γ-lactone **46**. Once again, selective deprotection under the TBAF–AcOH (2:1) conditions was conducted to give **47**, which was attached with 2,4-octadienoic acid according to the Yamaguchi conditions,[32] thereby providing ester **48**. Detachment of isopropylidene acetal and C(3)-TBS group with CSA in MeOH gave triol **49** without loss of other potentially-sensitive functionalities such as C(7)-silyl group and C(13) acetal center. At this stage, careful treatment of **49** with TESCl and Et_3N enabled differential protection of the C(3) and C(26) hydroxy groups, which were successively treated with morpholine in the presence of $Pd[PPh_3]_4$ as a catalyst, giving seco acid **50**. As the second key transformation, macrolactonization of **50** was successfully accomplished by using the Yamaguchi protocol[32] to give **51** in 93% yield (Scheme 11). This was submitted to the detachment of all silyl groups with 46% HF aq. in CH_3CN to give ketone **52** in high yield. At this stage, we carried out Horner–Wadsworth–Emmons reaction with an anion generated from the reagent **C** and NaH in THF to give a mixture of α,β-unsaturated esters in 83% yield. Notably, in the case of the reaction with ketone **52**, a high selectivity was observed (**53*Z***:**53*E*** = 89:11). After chromatographic separation, great efforts to cleave the methyl acetal bond at the C(19) position were unsuccessful. When extremely drastic conditions were used for hydrolysis, the pyran part, including the unsaturated γ-lactone, was decomposed. These phenomena were quite different from those of other bryostatins. Finally, the compound **53** was hydrolyzed with TFA and H_2O (10:1) in CH_2Cl_2 to afford the desired compound **54** in 79% yield. Based on the ^1H and ^{13}C NMR spectra and ROESY experiments, **54** adopts the same confor-



Scheme 10. Synthesis of the seco acid **50**. a) **3**, PhLi, THF, −78 °C; then **2**, −78 °C; then BzCl, DMAP, −78 → 0 °C; b) 5% Na–Hg, MeOH/EtOAc (2/1), −35 °C; c) TBAF, AcOH, THF, 0 °C; d) TPAP, NMO, MS 4A, CH_2Cl_2; e) TBAF, AcOH, THF, 0 °C; f) 2,4-octadienoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene; g) CSA, MeOH; h) TESCl, Et_3N, DMF, −30 °C; i) $Pd[PPh_3]_4$, morpholine, THF.



Scheme 11. Synthesis of bryostatin 3 (**1**). a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, toluene; then DMAP, toluene; b) 46% HFaq., CH_3CN; c) NaH, phosphonate **C**, THF, 0 °C, −50 → −10 °C; d) TFA, H_2O, CH_2Cl_2; e) TESCl, DMAP, CH_2Cl_2, −10 °C; f) Ac_2O, pyridine; g) 46% HFaq., CH_3CN/H_2O.

mation as those of other bryostatins.[33] Furthermore, **54** was treated with TESCl and DMAP selectively to protect the OH group at the C(26) position giving silyl ether **55**. This was acetylated and then desilylated with 46% HF aq. in CH_3CN to give rise to bryostatin 3 (**1**) in almost quantitative yield. The synthetic compound is completely identical with the natural source of **1** in all respects of the spectral data (HR-FABMS, IR, ^1H and ^{13}C NMR).

6. Conclusion

The highly convergent total synthesis of bryostatin 3 (**1**) was accomplished through use of novel, highly stereo- and chemoselective reactions, and efficient coupling strategies. This synthetic route provides great practical utility for preparation of **1**. Up to now, the Keio's group has been able to prepare 25 mg of bryostatin 3. This will be used for a variety of biological tests as well as for studies on some interactions with protein kinase C and others.

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