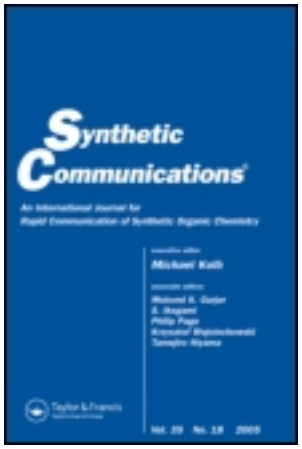

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TOWARD THE TOTAL SYNTHESIS OF BRYOSTATIN 11: STEREOSELECTIVE CONSTRUCTION OF THE C13-EXOCYCLIC ENOATE IN THE C1–C16 FRAGMENT

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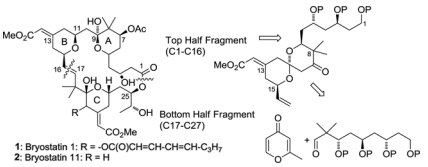
GRAPHICAL ABSTRACT



Abstract *We have utilized a spiroketal template in an approach to the C1–C16 fragment of bryostatin. The stereoselective construction of an exocyclic enoate at C13 and insertion of a vinyl group on C15 were accomplished by using Peterson–Yamamoto olefination and copper-catalyzed addition of vinyl magnesium bromide, respectively.*

Keywords Bryostatin 11; spiroketal chemistry; stereoselective exocyclic enoation

INTRODUCTION

The bryostatin family[1] (Fig. 1) of marine macrolides contains well-known antitumor drug candidates with low toxicity and a unique mode of action against protein kinase C.[2] Bryostatin 1 (**1**) is under investigation in human clinical trials for use alone or in combination with other chemotherapies.[3] Furthermore, **1** improves memory and learning in animal models, indicating a potential for the treatment of neurological disorders such as depression and Alzheimer's disease.[4] Because of their structural complexity as well as potent biological activity, the bryostatins are challenging synthetic targets. Four total syntheses of a bryostatin have been completed until 2010,[5] and many partial preparations have been reported.[6] Simplified analogs have also been designed and studied for biological activities by Wender, Keck, and Hale et al.[7] However, the development of an effective synthetic route is still required for continued and productive biological study, because of the limited supply of these compounds from natural sources. Our synthetic target,

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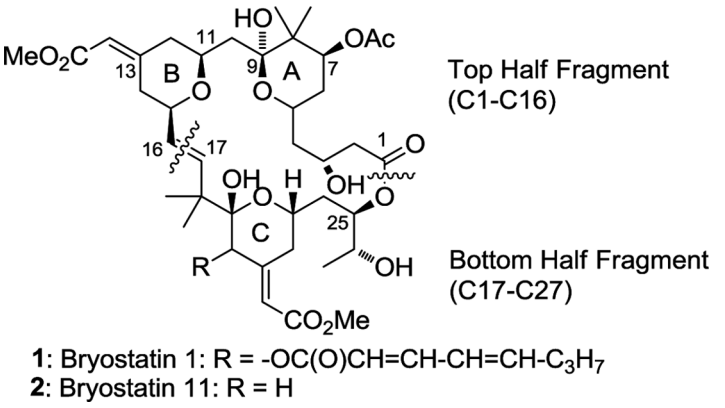


Figure 1. Structure of bryostatins.

bryostatin 11 (**2**), has the simplest structure of the family of structures. Our synthetic efforts toward **2** began with disconnection of both the C16–C17 olefin and the ester-linkage to divide the molecule into two fragments, a C1–C16 fragment and a C17–C25 fragment.

Retrosynthetic analysis of the C1–C16 fragment using our established spiroketal chemistry[8] is shown in Fig. 2. We have previously accomplished a chelation-controlled stereoselective reductive spiroketal cleavage[9] and a copper-catalyzed stereoselective addition of a vinyl group to an unsaturated spiroketal.[10] Herein, we describe an approach to the synthesis of the C1–C16 fragment of bryostatin 11 using a spiroketal as a stereochemical template as well as the stereoselective construction of an exocyclic enoate on C15.

Monoprotection of 2,2-dimethyl-1,3-propanediol (**8**) using two methods [NaH, MOMCl or $(MeO)_3CH$, and then diisobutylaluminumhydride (DIBAL)[11]] provided the mono-MOM ether (Scheme 1). The remaining alcohol was oxidized under Swern conditions to an aldehyde. Brown's asymmetric allylation[12] of this aldehyde was

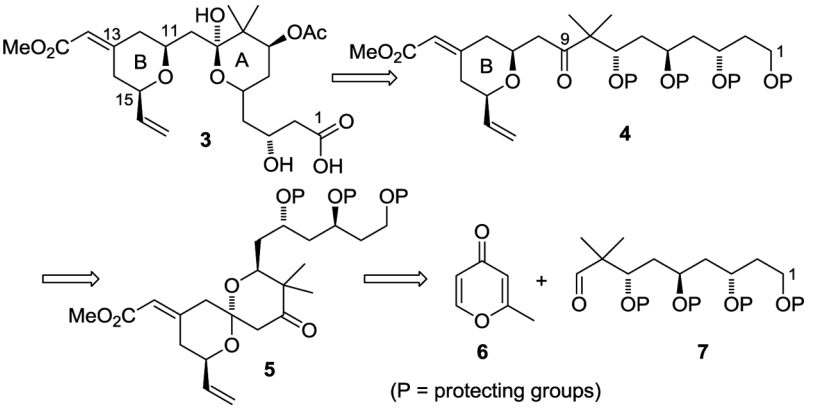
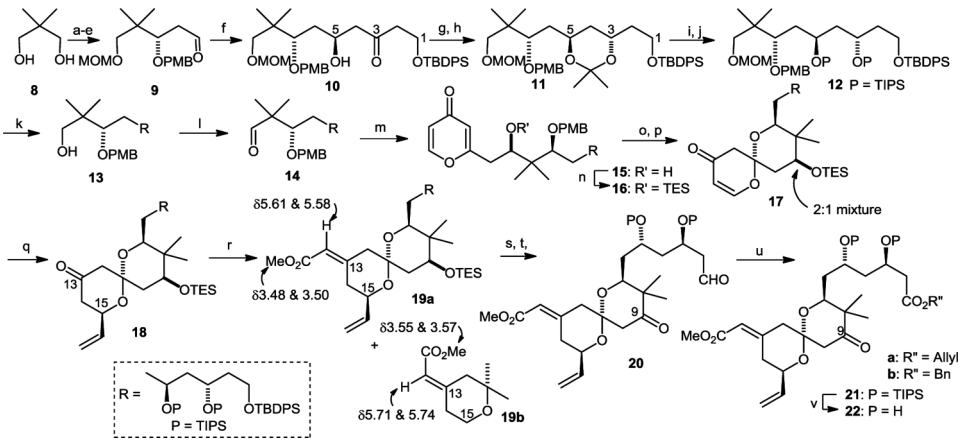


Figure 2. Retrosynthetic analysis of top half fragment.

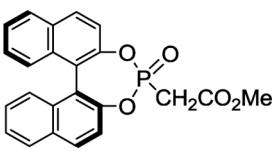


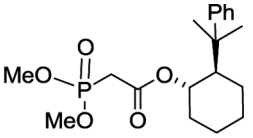
Scheme 1. Reagents and conditions: (a) NaH, MOMCl (78%), or $(MeO)_3CH$, then DIBALH (72%); (b) $(COCl)_2$, DMSO, then Et_3N; (c) 4-ICr_2B-allyl, then 30% H_2O_2, NaOH; (d) PMBCl, KH, THF (66% from **9**); (e) OsO_4, NMO, $NaIO_4$ (86%); (f) $CH_3C(O)CH_2CH_2OTBDPS$ (**23**), LDA, (71%); (g) $Me_4NHB(OAc)_3$, $CH_3CN/AcOH$, −30 °C, 22 h (98%, *anti*/*syn* = 7.8:1); (h) $Me_2C(OMe)_2$, pTsOH, THF (96%), then separation; (i) 70% HOAc (93%); (j) TIPSOTf, 2,6- lutidine (93%); (k) 0.5% cHCl/*i*PrOH, 70 °C, 6 h (69%. two recycle yield); (l) $(COCl)_2$, DMSO, then Et_3N (92%); (m) LiHMDS, 2-methylpyrone, −78 °C, 1 h (41%, rsm 58%); (n) TESOTf, 2,6-lutidine (98%); (o) DDQ, CH_2Cl_2/H_2O (19:1, v/v), rt, 1 h (94%); (p) 0.2% TFA/PhH, rt, 3 d, (79%); (q) vinyl MgBr, $[(nBu_3P)CuI]_4$, −45 °C, 0.5 h, (85%); (r) see Table 1; (s) HF · Py, Py, Py, THF, rt, 3 d (76%, rsm 20%); (t) $(COCl)_2$, DMSO, then Et_3N (90%); (u) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene then BnBr, $CsCO_3$ for **a** or allyl Br, $CaCO_3$ for **b** (80%, 2 steps); (v) TASF, DMF, rt, 1 d (63%, rsm 10%). Rsm, recovered starting material.

followed by protection of the resulting alcohol as the *p*-methoxybenzyl (PMB) ether and oxidative cleavage of the terminal olefin to give aldehyde **9**. The chelation-controlled aldol addition between **9** and ketone **22**[13] afforded β-hydroxyketone **10** with the required configuration at C5 in 71% yield. Evans–Saksena reduction[14] of **10** induced a 7.6:1 ratio in favor of *anti*-diol, which was inseparable from the *syn*-diol. In contrast, the reduction of **10** with $LiAl(OtBu)_3$ in the presence of LiI[13] showed only a low preference for the *anti*-isomer. The mixture of *anti*/*syn*-C3, C5-diol was protected as the acetonide, which could be separated from the undesired *syn*-diol. The stereochemical assignments of C3 and C5 were supported by the ^{13}C NMR spectroscopic data of **11,** which showed the acetonide carbons at 25.98 and 25.71 ppm.[15] Deprotection of the acetonide with HOAc, followed by reprotection of the diol hydroxyl groups as triisopropylsilyl (TIPS) ethers, gave the fully protected C1–C9 linear subunit **12**. Careful treatment of **12** with 0.5% HCl in *i*-PrOH[16] selectively removed only the MOM ether to give primary alcohol **13** along with recovered starting material, which was recycled under the same conditions to supply **13** in 69% yield after two cycles. Lithiation of 2-methylpyrone with LiHMDS followed by addition of aldehyde **14**, obtained by Swern oxidation of **13**, produced **15** in 41% yield along with 58% of recovered starting material, which is reusable. Because protection of the secondary alcohol as the TBS ether produced only the conjugated olefin resulting from dehydration, alcohol **15** was protected as the TES ether to provide **16**. Oxidative cleavage of the PMB ether with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded the secondary alcohol, which upon exposure

Table 1. Steroselective construction of exocyclic olefin on C13 (**18** to **19**)

Reagents
A) $TMSCH_2CO_2Me$
B) $(MeO)_2P(O)CH_2CO_2Me$
C) $(iPrO)_2P(O)CH_2CO_2Me$
D) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$





Entry	Reagents	Bases	Additive	Solvents	Conditions	Yields (%) (**19a/19b**[b])	Rsm
1	A	LDA	—	THF	−78 °C, 1.5 h	77 (12:1)	—
2	B	NaH	—	THF	−30 °C to rt, 45 h	51 (2.3:1)	39
3		NaH	15-Crown-5[a]	$PhCH_3$	−45 °C to rt, 25 h	46 (1.4:1)	29
4		*t*BuOK	—	THF	−45 °C to rt, 44 h	57 (5:1)	14
5		LiCl/DBU	—	CH_3CN	rt, 3 h	27 (1.5:1)	49
6		Triton B	—	THF	−78 °C to rt, 41 h	12 (4:1)	46
7	C	NaH	15-Crown-5[a]	$PhCH_3$	−45 °C to rt, 25 h	17 (3.8:1)	77
8		*t*BuOK	—	THF	−45 °C to rt, 42 h	28 (4:1)	60
9	D	NaHMDS	—	THF	−78 °C to −35 °C, 26 h	—	70
10	E	*t*BuOK	—	THF	−45 °C to rt, 48 h	28 (3.8:1)	21
11	F	*n*BuLi	—	THF	−30 °C, 7 d	—	72
12		*t*BuOK	—	THF	−45 °C to rt, 48 h	65[d] (?)[c]	<20

[a]No reaction was observed when performed without crown ether.
[b]Determined by ^1H NMR spectroscopy.
[c]The ratio of compounds was hard to determine because of the complex NMR spectra.
[d]The resulting compound was (−)-*trans*-2-(α-cumyl)cyclohexanoate instead of methyl ester **19**.

to trifluoroacetic acid in benzene resulted in the spiroenone **17** in 79% yield. Copper-catalyzed addition of vinyl magnesium bromide to the enone gave **18** in 85% yield with excellent stereoselectivity at C15. With the desired spiroketal **18** in hand, we turned to the stereoselective incorporation of the C13 enoate. Numerous studies have reported stereoselective construction of the exocyclic olefin for bryostatin synthesis.[17] However, various Horner–Wadsworth–Emmons reagents, including

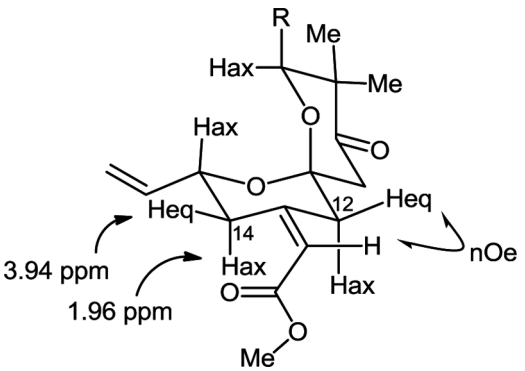


Figure 3. Stereochemistry of **20**.

chiral phosphonates, and reaction conditions resulted in poor yield or selectivity of products as shown in Table 1. Finally, Peterson–Yamamoto olefination[18] effectively afforded a favorable 11.5:1 mixture of isomers (**19a**/**19b**) in 77% yield (entry 1). A similar selective exocyclic olefination under Peterson–Yamamoto conditions was reported by Evans.[19] Both studies indicated that the selectivity might be supported by an *axial*-alcohol or alkoxy group at the β-position to the cyclic ketone. Subsequently, the triethylsilyl (TES) and *tert*-butyldiphenylsilyl (TBDPS) groups were cleaved simultaneously by treating **19** with buffered HF · py in tetrahydrofuran (THF) solution. The resulting diol was oxidized to a keto-akdehyde **20**, which was converted to the allyl or benzyl ester **21a** or **21b**, respectively. Treatment of **21a/b** with TASF in dimethylformamide (DMF) generated the desired diol **22**. Lewis acid–promoted chelation-controlled stereoselective reductive cleavage of **22** to give **4** is currently in progress.

The relative stereochemistry of the C13 enoate of **20** was assigned by ^{1}H NMR, which showed a significant downfield shift of the C14 equatorial proton (1.96 ppm) resulting from the electronic effect of the carbonyl group of the α,β-unsaturated ester. The assignment was also supported by a nuclear Overhauser effect spectroscopy (NOESY) experiment, in which the nuclear Overhauser effect (nOe) was observed between the C12 equatorial proton and the olefin proton as shown in Fig. 3.

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