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Studies directed towards the synthesis of Bryostatin

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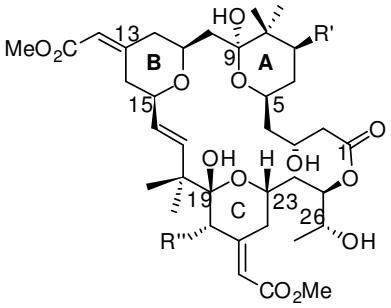
ABSTRACT

Thesis is structured in two different parts. The first part deals with the convergent and stereo selective synthesis of the C1-C10 fragment **3** of cytostatic macrolide bryostatin. Two of the three chiral centers were established *via* Sharpless Kinetic resolution on racemic allylic alcohol **10** followed by reduction with Red-Al. Diastereoselective transformation of the aldehyde **18** moiety to β-hydroxy ester **20** *via* an Aldol reaction, which is transformed to pyran ring **3** *via* chemical transformations, are the key steps. The second part discuss the stereo-controlled asymmetric synthesis of C7-C16 fragment **4** of Bryostatin. The key steps involved in this synthesis are the Jacobsen's hydrolytic kinetic resolution and Reformatsky reaction to build the C11-C16 fragment. The vinyl Grignard has been used to construct the C7-C10 fragment. Cross-metathesis was successfully used to couple both the fragments, C7-C10 and C11-C16 to produce a key component **46**. Oxa-Michael reaction has been employed to construct the pyran ring system **4.**

Keywords: Bryostatin, Antineoplastic activitity, Aldol reaction, Lactonization, Jacobsen's kinetic resolution, Reformatsky reaction, Cross-methathesis

Introduction

The bryostatins are an architecturally intringuing family of 20 antitumor macrolides[1-5] antibiotics that have shown considerable clinical promise or the treatment of various human cancers.[6,7] In 1968, the search for new bioactive marine natural products resulted bryostatins, which were isolated from the bryozoans *Bugula neritina, Linnaeus* and *Amathia convolute* . The discovery of bryostatins (**1**) and its structure determination was first reported by Pettit[8,9] in 1982 (Figure 1). Bryostatin exhibits significant in vivo antineoplastic activity against lymphocytic leukemia, B-cell lymphoma, reticulum cell sarcoma, ovarian carcinoma, and melanoma. The bryostatins also display a diverse range of other biological effects *in vitro* and *in vivo*, including stimulation of T-cells and the immune system, and inhibition of the tumor promotion of phorbols related to protein kinase C.[10] Additionally, the highly oxygenated macrolide structure is the challenging target for synthetic chemists, however, until now only four examples of total synthesis by Masamune,[11,12] Evans,[13] Nishiyama, Yamamura[14] and Trost[15,16] of bryostatins are known , although many approaches towards bryostatin have been reported.[17-22] As part of our ongoing research programme, on the synthesis of biologically active marine anticancer natural products, we have focused on the total synthesis of this rare and costly substance.



Bryostatin

Bryostatin 1: R' = OAc, R'' = OCO(CH)4n-Pr
Bryostatin 2: R' = OH, R'' = OCO(CH)4n-Pr
Bryostatin 7: R' = OAc, R'' = OAc
Bryostatin 11: R' = OAc, R'' = H
Bryostatin 14: R' = OCO(CH3)3, R'' = OH

Figure 1

Retrosynthetic Analysis of Bryostatin

The disconnection approach provides two major fragments **3** and **4** as the key intermediates for the total synthesis of Bryostatin **1** (Scheme 1).

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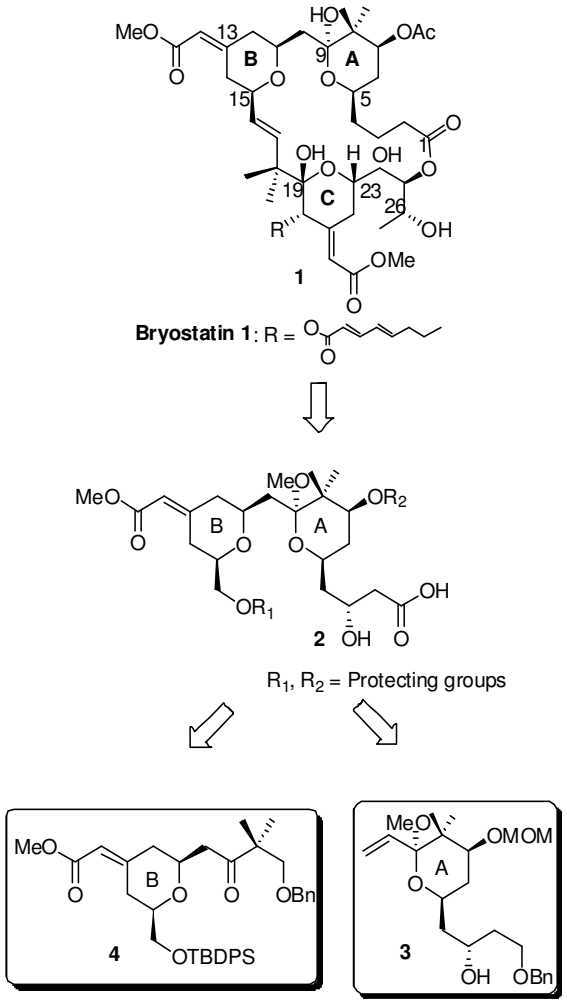
Highlights

1. We have accomplished a convergent and stereselective synthesis of C1-C10 fragment **3** of bryostatin from the known and the commercially available homoproparzyl alcohol, 1,3-propane diol and methyl isobutyrate.
2. The present synthesis features an efficient route to **3** using sharpless kinetic resolution/Red-Al reduction sequence to produce the C3 and C5 chiral.
3. We have demonstrated a convergent and stereoselective synthesis of C7-C16 fragment of bryostatin **1** from a commercially available, but-3-en-1-ol and 2,2-dimethyl-1,3-propane diol.
4. The present synthesis involves Jacobsen's hydrolytic kinetic resolution to install C15 chiral center and cross-metathesis reaction between fragments **40** and **44** to construct the C10-C11 bond. Oxa-Michael cyclization has been utilized to construct the tetrahydropyran ring system.



Scheme 1. Reterosynthetic Analysis of Bryostatin

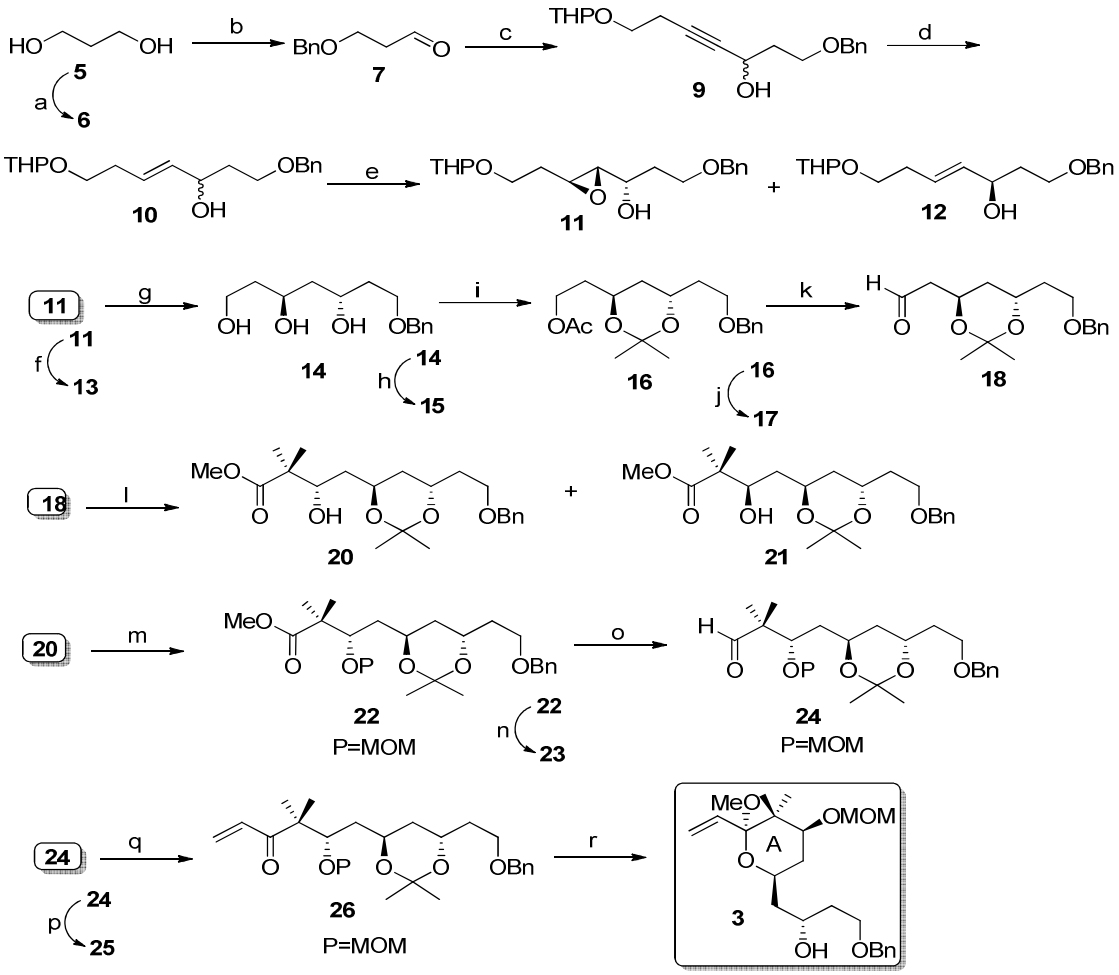
Section-I: Stereoselective Synthesis of C1-C10 fragment of Bryostatin (3)

Synthesis of C_1-C_{10} fragment begins with 1,3-propanediol as a starting material (Scheme 2). Protection of 1,3-propane diol (**5**) with benzyl bromide followed by the oxidation with PCC-Celite yielded an aldehyde **7**. This was alkylated[23] with THP protected homoproparzyl alcohol **8** in THF. The resulting proparzyl alcohol **9** was reduced with LAH[24,25] to give the desired (E)-allylic alcohol **10**. Sharpless kinetic resolution of alcohol **10** with (+)-DET as the chiral additive resulted epoxy alcohol **11** $[\alpha]_D^{25}$: –8.9 (*c* = 1.00, $CHCl_3$) in 38% yield and > 98% ee. It underwent regioselective reduction with Red-Al (5.0 equiv) in THF(ca. 0.68 M) between -30 to -10 ^oC to afford diol **13** in 93% yield. The diol **13** was subjected to THP deprotection to afford triol **14** $[\alpha]_D^{25}$: + 7.6 (*c* = 1.0, $CHCl_3$) in 90% yield. The primary hydroxyl group of the triol **14** was selectively protected with acetyl group using Ac_2O in the presence of TEA in DCM. After protection of primary alcohol of triol, the 1,3-diol unit in acetylated compound **15** was protected as an isopropylidene acetal **16**, and O-acetylation was deprotected with K_2CO_3 in MeOH.

This furnished primary alcohol **17** in quantitative yield. Then compound was oxidized to aldehyde **18**, and an Aldol reaction executed with the lithium enolate obtained from treating methyl isobutyrate **19** (7.4 equiv) with LDA[26-28] (7.0 equiv) in THF at -78 ^oC and delivered dia-stereo selectively β-hydroxy ester **20** $[\alpha]_D^{25}$: + 1.9 (*c* = 1.00, $CHCl_3$) as major isomer in 59% yield. Convertion of the alcohol (**20**) to MOM ether **22** was accomplished by reaction with MOMCl and in the presence of $EtN(^iPr)_2$ (unique base) in DCM. The ester group of compound **22** was reduced with DIBAL-H (2.2 equiv), this furnished primary alcohol **23**. Oxidation of alcohol with Dess-Martin periodinane[29] (DMP) yielded aldehyde **24**, and a Grignard reaction[30] performed using vinylmagnesium bromide in THF and subsequent oxidation with DMP in DCM afforded enone **26** in 89% yield. The best conditions for removing the acetonide group from **26** involved the use of trimethyl orthoformate with PTSA as catalyst[31,32] (Scheme 2) in methanol at room temparature accomplished compound **3**. This is not only instigated acetonide deprotection but also induced ring-closure of the pyran hemiketal ring system.

Section-II: Stereoselective Synthesis of C7-C16 fragment of Bryostatin (4)

We began our synthesis with but-3-en-1-ol **27** which was protected as its benzyl ether **28** in 91% yield using benzyl bromide and NaH in THF. Epoxidation of olefin **28** with *m*-CPBA gave the racemic epoxide[33] **29** in 86% yield. The racemic epoxide **29** was then subjected to Jacobsen's hydrolytic kinetic resolution[34] with (*S,S*)-*N,N*-bis-(3,5-di-tert-butylsalicylidene)-1,2-cyclohexane-diamino-Co(III)-acetate to give the stereochemically pure diol **31** in 42% yield with ee >93%. For the determination of enantiomeric excess (ee), the diol **31** was converted to its dibenzoate. Then, the enantiomeric purity of this dibenzoate was determined to be 93.6% by chiral HPLC analysis (Chiralcel ODH; 250 x 4.6 mm, 5 µ, 95:5 petrolium ether – ^iPrOH as eluent). Protection



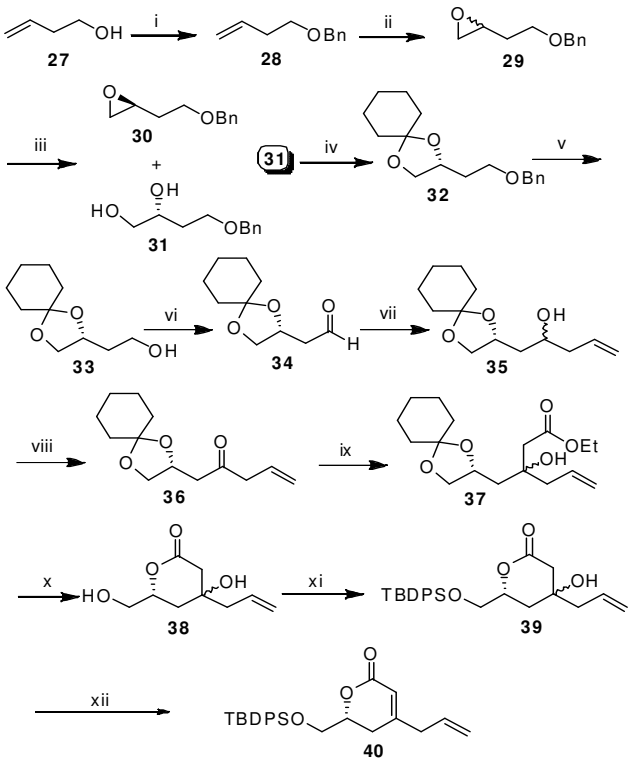
Scheme 2. Reagents and conditions: a) NaH, BnBr, TBAI, THF, 4 h, 66%; b) PCC, Celite, DCM, 3 h, 84%; c) EtMgBr, then **8**, THF, 83%; d) LAH, THF, 96%; e) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, -20 ^oC, DCM, 79%; f) Red-Al, THF, 96%; g) p-TsOH, MeOH,91%; h) Et_3N, Ac_2O, DCM, 75%; i) 2,2-DMP, p-TsOH, DCM, 93%; j) K_2CO_3, MeOH, quantitative yield; k) Dess-Martin periodinane, $NaHCO_3$, DCM, 87%; l) LDA, -78 ^oC, Methylisobutyrate **19**, THF, 94%; m) MOM-Cl, $^iPr_2NEt$, DCM, 92%; n) DIBAL-H, DCM, 0 ^oC, 93%; o) DMP, $NaHCO_3$, DCM, 0 ^oC, 94%; p) CH_2=CHMgBr, THF, 0 ^oC, 86%; q)) DMP, $NaHCO_3$, DCM, 0 ^oC, 89%; r) PPTS, $CH(CH_3O)_3$, MeOH, 73%.

of diol **31** with cyclohexanone using a catalytic amount of *p*-TSA followed by deprotection of primary benzyl ether **32** with Na/liq.NH_3 afforded the primary alcohol **33**. Subsequent oxidation of **33** with Dess-Martin periodinane in dichloromethane afforded the aldehyde **34** in 73% yield.[35] Allylation of aldehyde 3**4** with zinc/allylbromide gave the homoallylic alcohol **35** which was then subjected to DMP oxidation to yield the ketone **36**. Reformatsky reaction[36] of ketone **36** with zinc/ethyl bromoacetate afforded the β-hydroxy ester **37** in 90% yield. Deprotection of *O*-cyclohexylidene acetal **37** followed by an intramolecular lactonization with ester gave the lactone **38**. Protection of the primary alcohol **38** with TBDPSCl in the presence of imidazole and a catalytic amount of DMAP in dichloromethane gave the corresponding TBDPS ether **39**. Subsequent dehydration of **39** with MsCl/Et_3N gave the desired α,β-unsaturated lactone **40** in 86% yield (Scheme 3).

Next we attempted the synthesis of C7-C10 fragment **44** from a known 1,3-propanediol **41**. Protection of alcohol **41** with benzyl bromide in the presence of NaH gave the benzyl ether **42** in 70% yield. Oxidation of mono-benzyl ether **42** using PCC/Celite in DCM gave the aldehyde **43**. Subsequent vinylation of aldehyde **43** with vinyl magnesium bromide[37,38] afforded the allylic alcohol **44** in 88% yield (Scheme 4).

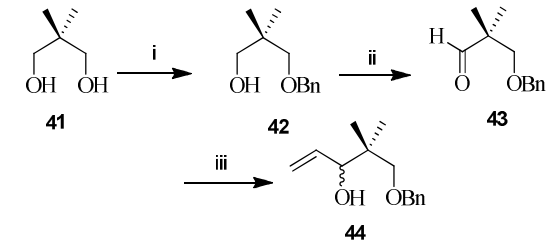
The synthesis of C7-C16 fragment **4**, was achieved by means of cross-metathesis coupling[39,40] between compounds **40** and **44** with 1:2 ratio using the Grubb's 2nd generation catalyst. The resulting olefin **45** was subjected to Dess-Martin periodinane (DMP) oxidation to give the corresponding *α,β*-unsaturated ketone **46** in 83% yield. The stereochemistry in compound **46** was established according to the known intra-molecular oxa-Michael protocol[41,42] by the treatment of compound **46** with CSA/MeOH, followed by the protection of resultant primary hydroxyl group with TBDPSCl/Imidazole. Furthermore, its stereochemistry was determined by nOe experiments. Dehydration of compound **47** with MsCl/Et_3N

and a catalytic amount of DMAP afforded the target C7-C16 fragment **4** in 67% yield (Scheme 5). The structure of compound **4** was further confirmed by a known procedure reported by Trost.[43,44]



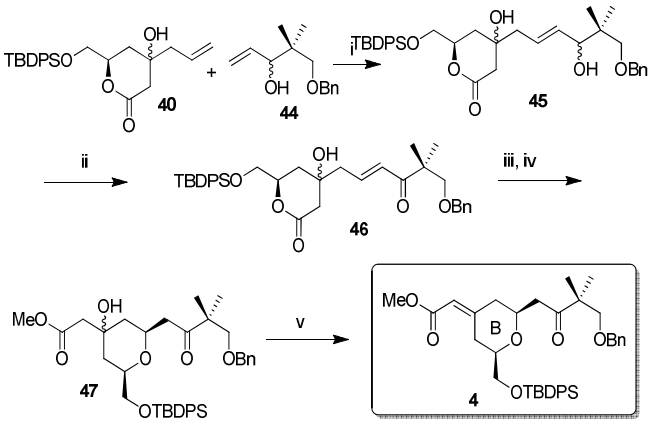
Scheme 3. Stereoselective synthesis of C11-C16 fragment

Reagents and conditions: i) NaH, BnBr, THF, 4h, 91%. ii) *m*-CPBA, CH_2Cl_2, 3h, 86%. iii) (*S*,*S*)-Salen-Co(III)-OAc Complex, 0.5eq. H_2O, 42%, 12h. iv) Cyclohexanone, *p*-TSA, CH_2Cl_2, 2h, 78%. v) Na/Liq.NH_3, THF, 86%. vi) DMP, CH_2Cl_2, 2h, 73%. vii) Zn/CH_2=CH-CH_2Br, THF, 2h, 86%. viii) DMP, CH_2Cl_2, 2h, 72%. ix) Zn/ethyl bromoacetate, Et_2O, 4h, 90%. x) PPTS, MeOH, 60 ^oC, 8h, 78%. xi) TBDPSCl, imidazole, DMAP, CH_2Cl_2, 2h, 88%. xii) MsCl, Et_3N, DMAP, CH_2Cl_2, 6h, 86%.



Scheme 4. Synthesis of C7-C10 fragment

Reagents and conditions: i) NaH, TBAI, BnBr, THF, 4h, 70%. ii) PCC, Celite, CH_2Cl_2, 4h, 84%. iii) CH_2=CHMgBr, THF, 2h, 88%.



Scheme 5. Synthesis of C7-C16 fragment

Reagents and conditions: i) Grubb's 2nd generation catalyst (G-II), DCM, 40 ^oC, 8h, 62%. ii) DMP, $NaHCO_3$, DCM, 2h, 83%. iii) CSA, MeOH, 3h, 84%. iv) TBDPSCl, imidazole, DCM, 2h, 86%. v) MsCl, Et_3N, DMAP, DCM, 1.5h, 67%.

In summary, we have accomplished highly efficient stereoselective synthesis of C1-C10 fragment **3** and C7-C16 fragment **4** of bryostatin.[45,46]

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Thesis Details

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