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Synthetic studies toward potent cytostatic macrolide bryostatin: an expedient synthesis of C1–C10 fragment

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ABSTRACT

The stereoselective synthesis of C1–C10 fragment of cytostatic macrolide bryostatin is described. Two of the three chiral centers have been established via the Sharpless kinetic resolution of racemic allylic alcohol **15** followed by regioselective reduction of epoxy alcohol **8** with Red-Al. Diastereoselective Aldol reaction of an aldehyde **7** with methyl isobutyrate affords the corresponding β-hydroxyester **23** which is then transformed into tetrahydropyran ring system **3** via an intramolecular hemi-ketalization.

The bryostatins are important class of 20 antitumor macrolides[1–3] which have shown considerable clinical application for the treatment of various human cancers.[4] Bryostatins are bioactive marine natural products which were isolated from the bryozoans Bugula neritina, Linnaeus, and Amathia convolute. The discovery and structural determination of bryostatins (1) were first reported by Pettit in 1982.[5] Bryostatins (1) are found to exhibit a significant in vivo antineoplastic activity against lymphocytic leukemia, B-cell lymphoma, reticulum cell sarcoma, ovarian carcinoma, and melanoma. They also display a diverse range of other biological effects such as the stimulation of T-cells and the immune system,[3] and the inhibition of tumor promoting phorbols related to protein kinase C.[6] As a result, many attempts have been made for the formal synthesis of brayostatins.[7,8] until now only six approaches have been reported for the total synthesis of bryostatins.[9–12] A similar fragment of bryostatins has been reported earlier by our group.[8c] Inspired by their potential application as drug candidates, we attempted the total synthesis of these natural products.

Our retrosynthetic analysis of bryostatin (1) is outlined in Scheme 1. The construction of C1–C10 fragment, a common unit in all bryostatins, was achieved via the Sharpless kinetic resolution[13] of 15 followed by regioselective reduction of epoxy alcohol.[14] Our group has made a significant effort to explore the synthetic utility of Sharpless kinetic resolution for the synthesis of various intermediates in total synthesis of some natural products.

As a part of our interest on the total synthesis of biologically active molecules, we herein report the synthesis of C1–C10 fragment of bryostatin. Out of three stereogenic centers, two were constructed by means of Sharpless kinetic resolution of allylic alcohol and regioselective reduction of epoxy alcohol and the third one was obtained through the diastereoselective Aldol reaction[15] The following reagents such as homopropargyl alcohol, 1,3-propanediol, and methyl isobutyrate were used as starting materials.

The synthesis of C1–C10 fragment was proposed to be obtained by means of Aldol reaction between methyl isobutyrate and C1–C7 aldehyde. Our next plan was to synthesize the C1–C7 aldehyde, which could be prepared from (*E*)-allylic alcohol via the Sharpless kinetic resolution and regioselective reduction of epoxy alcohol with Red-Al.

Mono-protection of 1,3-propanediol (**11**) with benzyl bromide followed by oxidation with PCC on Celite gave the aldehyde **13** in 75% overall yield. Alkynylation of **13** with homopropargyl ether (**14**) in THF[16] gave the propargyl alcohol (**9**) which was then reduced with LAH[17] to give the desired (*E*)-allylic alcohol (**15**). The Sharpless kinetic resolution of alcohol (**15**) with (+)-DET gave the epoxy alcohol (**8**) $[\alpha]_D^{25}$ −8.9 (*c* = 1.0, $CHCl_3$) in 38% yield with >98% ee. Regioselective reduction of epoxy alcohol (**8**) with Red-Al (5.0 equiv) in THF (ca. 0.68 M) between −30 and −10 °C afforded the diol which was then subjected to THP deprotection to yield the triol **19** $[\alpha]_D^{25}$ +7.6 (*c* = 1.0, $CHCl_3$) in quantitative yield. Selective protection of primary hydroxyl group of the triol **19** with Ac_2O in the presence of TEA in DCM gave the acetate **20** in 75% yield. After protection of primary alcohol of the triol as acetate, the resulting

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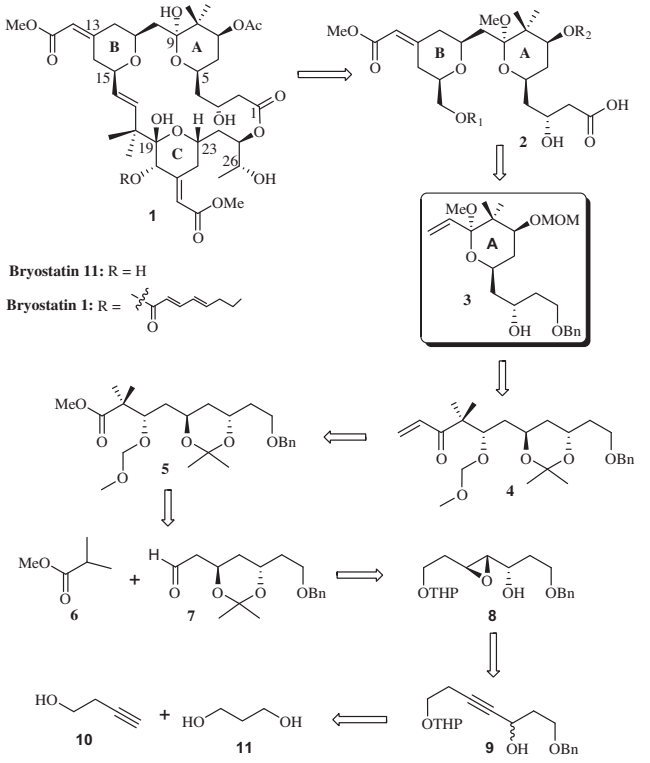
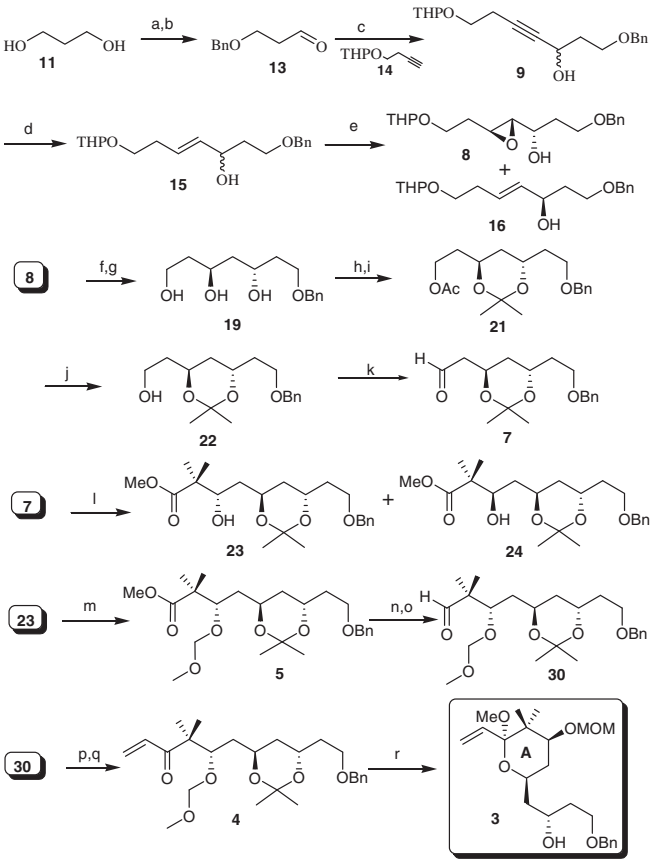
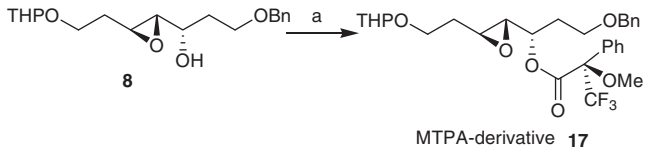


Scheme 1. Retrosynthetic analysis of bryostatin.



Scheme 2. Reagents and conditions: (a) NaH, BnBr, TBAI, THF, 4 h, 66%; (b) PCC, Celite, DCM, 3 h, 84%; (c) EtMgBr generation followed by **14,** then **13**, THF, 83%; (d) LAH, THF, 96%; (e) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, −20 °C, DCM, (**8**/**16** = 38:41); (f) Red-Al, THF, 93%; (g) *p*-TsOH, MeOH, 90%; (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 °C, Methyl isobutyrate, THF, (**23**/**24** = 59:35); (m) MOMCl, $^iPr_2NEt$, DCM, 89%; (n) DIBAL-H, DCM, 0 °C, 91%; (o) DMP, $NaHCO_3$, DCM, 0 °C, 94%; (p) CH_2=CHMgBr, THF, 0 °C, 86%; (q) DMP, $NaHCO_3$, DCM, 0 °C, 89%; (r) PPTS, $CH(OCH_3)_3$, MeOH, 73%.



Scheme 3. Reagents and conditions: EDCI, MTPA, DMAP, DCM, 77%.

1,3-diol **20** was then protected as its isopropylideneacetal **21.** Deacetylation of **21** with K_2CO_3 in MeOH gave the primary alcohol **22** in quantitative yield. Oxidation of primary alcohol **22** gave the aldehyde **7**. Aldol reaction of an aldehyde **7** with the lithium enolate derived from methyl isobutyrate (**6**) (7.4 equiv) and LDA[15] (7.0 equiv) in THF at −78 °C afforded the β-hydroxyester **23** $[\alpha]_D^{25}$ +1.9 (c = 1, $CHCl_3$) as a major isomer in 59% yield. Protection of alcohol (**23**) with MOMCl in the presence of EtN^iPr_2 in DCM gave the MOM ether. Reduction of ester functionality **5** with DIBAL-H (2.2 equiv) furnished the primary alcohol in 91% yield, which was then subjected to oxidation with Dess–Martin periodinane[18] (DMP) to yield the aldehyde **30**. Grignard reaction[16] of aldehyde **30** with vinylmagnesium bromide in THF gave the allylic alcohol which was then oxidized with DMP in DCM to afford the enone **4** in 88% overall yield. Deprotection of acetonide from compound **4** with trimethylorthoformate in the presence of PTSA[19] (Scheme 2) in methanol at room temperature gave the target fragment **3**. The above conditions affect not only the cleavage of acetonide but also induce the ring-closure via hemi-ketalization.

The enantiomeric excess of epoxy alcohol **8** was measured by converting into its MTPA derivative,[20] using EDCI, methoxy trifluoromethylphenylacetic acid (MTPA) and a catalytic amount of DMAP in dry DCM. The MTPA derivative **17** was obtained in 77% yield. ^{1}H NMR spectrum of compound **17** showed predominantly one singlet (integration 22:0.2) at 3.53 ppm corresponds to methoxy protons in MTPA group, which confirms the presence of one enantiomer predominantly (>98% ee) in compound **8** (Scheme 3).

The diastereomeric mixture of β-hydroxyesters (**23**,**24**)[15] was separated by column chromatography **23** as a major isomer and **24** as a minor isomer. In order to confirm the exact stereochemistry of the newly generated hydroxyl center at C7, the following series of reactions were performed as shown in Scheme 4.

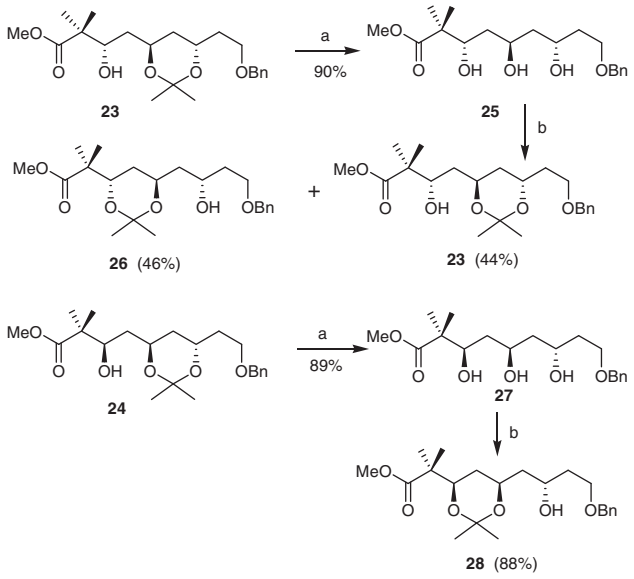
The major isomer **23** was treated with a catalytic amount of *p*-TsOH in MeOH to afford the triol (**25**) in 90% yield. The compound **25** was then subjected to acetonide protection employing the standard conditions with 2,2-DMP to yield the two possible regioisomers **26** and **23** in 1:1 ratio, which were easily separated through column chromatography. As we already have the authentic compound **23**, the newly obtained isomer **26** was easily distinguished by TLC and isolated in 46% yield by column chromatography. ^{13}C NMR spectrum of compound **26** showed the *gem*-dimethyl carbon of dioxolane ring at 23.99 ppm, which confirms the *anti*-stereochemistry between the two hydroxyl groups.[15] Thus the stereochemistry at C7 and C5 was found to be *anti*, in major diastereomer **23**.

Similarly, the minor isomer **24** was treated with *p*-TsOH in MeOH to afford the triol (**27**) in 89% yield. Compound **27** was then protected as its acetonide employing the standard conditions with 2,2-DMP. The *syn* isomer **28** was obtained exclusively in 88% yield. The ^{13}C NMR of compound **28** showed the *gem*-dimethyl carbon of dioxolane ring at 30.07 ppm, which confirms the *syn*-stereochemistry between two hydroxyl groups.[13] Thus, the stereochemistry at C7 and C5 was found to be *syn*, in minor diastereomer **24**.

In summary, we have accomplished a stereoselective synthesis of C1–C10 fragment **3** of bryostatin from a commercially available homopropargyl alcohol, 1,3-propanediol and methyl isobutyrate.[21] The present synthesis demonstrates an efficient route to the synthesis of fragment **3** using Sharpless kinetic resolution/Red-Al reduction to produce the C3 and C5 chiral centers. Aldol reaction between anion **6** and aldehyde **7** was successfully utilized to establish the C7 chiral center.

Acknowledgement

S.A. thanks CSIR, New Delhi for the award of Fellowship.



Scheme 4. Reagents and conditions: (a) *p*-TsOH, MeOH; (b) 2,2-DMP, *p*-TsOH, DCM.

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21. Analytical and Spectral data/Selected physical data of compounds:
    Experimental section
    All the reactions were carried out under inert atmosphere, unless *mention*ed, following standard syringe septa techniques. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions were monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F254 to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh) and neutral alumina using diethyl ether, ethyl acetate, and hexane as eluents. Optical rotation values were measured with a Perkin–Elmer P241 polarimeter and JASCO DIP-360 digital polarimeter at 25 °C and IR spectra were recorded on Perkin–Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200 MHz, Bruker Avance 300 MHz, Varian Unity 400 MHz, or Varian Inova 500 MHz spectrometer using trimethylsilane as an internal standard in $CDCl_3$. Mass spectra were recorded on Micro mass VG-7070H for ESI–MS and HRMS, VG Autospec M for FABMS.
    Compound **8**: Colorless liquid; $R_f = 0.4$ (SiO_2, 40% EtOAc in hexane); $[\alpha]_D^{25}$ −8.9 ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.14 (m, 5H), 4.53–4.45 (m, 1H) 4.42 (s, 2H), 3.84–3.51 (m, 5H), 3.49–3.34 (m, 2H), 3.18–3.06 (brs, 1H), 3.06–2.95 (m, 1H), 2.75–2.67 (m, 1H), 1.92–1.56 (m, 6H), 1.55–1.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 128.2, 127.4, 98.8, 72.9, 68.5, 68.3, 67.4, 64.0, 63.8, 62.3, 62.1, 60.4, 53.9, 53.6, 33.3, 33.2, 31.9, 30.4, 25.2, 19.4; IR (neat): υ_{max} 3447, 2925, 2858, 1451, 1360, 1118, 1075, 1029, 977, 740, 698 cm^{-1}; ESI–MS: *m/z* 359 [M+Na]; HRMS (ESI) calcd for $C_{19}H_{28}O_5Na$: 359.1834. Found: 359.1820. Compound **23** Major isomer: Colorless viscous liquid; $R_f = 0.4$ (SiO_2, 50% EtOAc in hexane); $[\alpha]_D^{25}$ +1.9 ($c = 1.0$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 4.46 (s, 2H), 4.17–4.04 (m, 1H), 4.04–3.90 (m, 1H), 3.85 (dd, 1H, $J = 6.8$, 4.5 Hz), 3.69 (s, 3H), 3.56–3.44 (m, 2H), 2.92–2.66 (brs, –OH), 1.79–1.63 (m, 3H), 1.62–1.38 (m, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.87, 138.42, 128.24, 127.57, 100.37, 72.99, 72.49, 66.53, 64.01, 63.83, 51.73, 46.81, 37.82, 37.01, 35.90 26.91, 24.70 (2C), 21.88, 20.28; IR (neat): υ_{max} 3056, 1729 cm^{-1}; ESI–MS: *m/z* 417 [M+Na]; HRMS (ESI) calcd for $C_{22}H_{34}O_6Na$: 417.2253. Found: 417.2242. *Compound* **4**: Colorless liquid; $R_f = 0.4$ (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{25}$ −4.8 ($c = 1.0$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34–7.22 (m, 5H), 6.86–6.75 (m, 1H), 6.29 (dd, 1H, $J = 16.6$, 2.2 Hz), 5.60 (dd, 1H, $J = 9.8$, 2.2 Hz), 4.61 (d, 1H, $J = 6.7$ Hz), 4.56 (d, 1H, $J = 6.7$ Hz), 4.46 (s, 2H), 4.01–3.87 (m, 2H), 3.85–3.78 (m, 1H), 3.57–3.43 (m, 2H), 3.30 (s, 3H), 1.72 (dd, 2H, $J = 12.8$, 6.0 Hz), 1.63–1.36 (m, 4H), 1.32 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.8, 138.4, 131.9, 128.2, 127.7, 127.5, 127.4, 100.2, 98.4, 80.7, 73.0, 66.5, 64.9, 63.5, 63.0, 55.6, 38.7, 38.6, 35.9, 25.0, 24.9, 20.3, 20.5; IR (neat): υ_{max} 2924, 2854, 1735, 1694, 1459, 1377, 1223, 1101, 1032, 748, 699 cm^{-1}; ESI–MS: *m/z* 457 [M+Na]; HRMS (ESI) calcd for $C_{25}H_{38}O_6Na$: 457.2720. Found: 457.2722. *Compound* **3**: Colorless viscous liquid; $R_f = 0.6$ (SiO_2, 30% EtOAc in hexane). $[\alpha]_D^{25}$ +16.5 ($c = 0.5$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42-7.16 (m, 5H), 5.69–5.55 (m, 1H), 5.37–5.23 (m, 2H), 4.65 (d, 1H, $J = 6.7$ Hz), 4.57 (d, 1H, $J = 6.7$ Hz), 4.50 (s, 2H), 4.15–3.97 (m, 1H), 3.97–3.79 (m, 2H), 3.72–3.54 (m, 2H), 3.32 (s, 3H), 3.08 (s, 3H), 1.79–1.67 (m, 3H), 1.66–1.38 (m, 3H), 0.99 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.3, 129.6, 128.2, 127.5, 127.4, 118.5, 95.8, 95.7, 76.7, 73.0, 68.5, 67.3, 65.1, 48.8, 42.9, 42.7, 41.4, 37.1, 33.8, 29.6.,20.7, 16.9; IR (neat): υ_{max} 3446, 2925, 2855, 1097, 1040 cm^{-1}; ESI–MS: *m/z* 456 [M+Na]; HRMS (ESI) calcd for $C_{24}H_{39}O_6Na$: 456.2725. Found: 456.2727.