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Graphical Abstract

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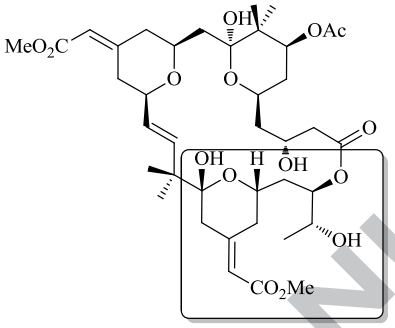

Bryostatin 11

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Stereoselective synthesis of C19-C27 fragment of bryostatin 11

J. S. Yadav,*[a] T. Swamy,[a,b] B. V. Subba Reddy,[a] V. Ravinder[b]
[a]*Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India*
[b]Department of Chemistry, Kakatiya University, Warangal-506 009, India

Fax: 91-40-27160512; E-mail:yadavpub@iict.res.in

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ABSTRACT

A convergent synthesis of C19-C27 fragment (**2**) of bryostatin-11 is described. The key steps involved in this approach are kinetic resolution, Grignard reaction and Sharpless dihydroxylation. AIBN catalyzed radical cyclization strategy has been used for the first time to construct the six-membered pyran system.

Bryostatins are a family of 20 structurally different complex marine natural products that display a wide range of biological activities, most notably anticancer activity.[1] Bryostatins were originally isolated from the marine *Bryozoan bugula neritina Linnaeus* by Pettit and co-workers in 1968 and was fully characterized in 1982.[2] These bryostatins are biologically active marine macrolides, which are found to exhibit an exceptional antineoplastic activity against lymphocytic leukaemia, β-cell lymphoma, reticulum cell sarcoma, ovarian carcinoma, and melanoma and are presently undergoing phase II clinical trials. This effect is attributed to their ability to modulate the functions of protein kinase C isozymes within the cells. As a result, bryostatins are evaluated as chemotherapeutic candidates for the treatment of different types of cancer[3] owing to their low toxicity and prominent antineoplastic activity. Furthermore, bryostatins are very promising in enhancing memory in animal models. They were able to increase the duration of memory retention of the marine slug *Hermissenda crassicornis* by over 500%.[4] These features make them as possible drug candidates for the treatment of Alzheimer's disease.[5]

Low abundance of bryostatins in nature makes the extraction unsuitable for large-scale production. Due to their structural complexity and difficulty in total synthesis, only a few approaches have been reported so far.[6] A number of structurally simple synthetic analogs have been reported to evaluate their efficiency. Interestingly, some of them are found to exhibit greater potency, which may provide a practical supply for clinical use (Figure 1).

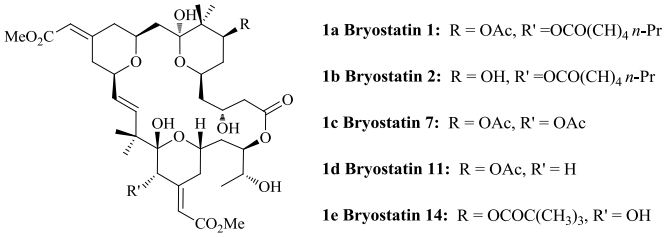
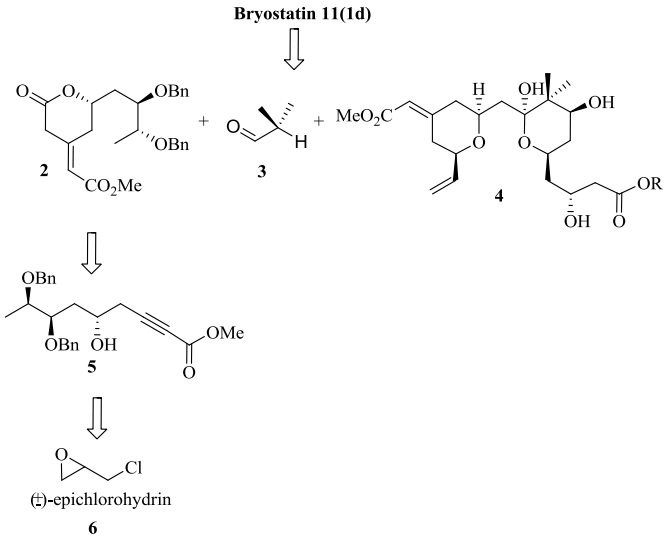


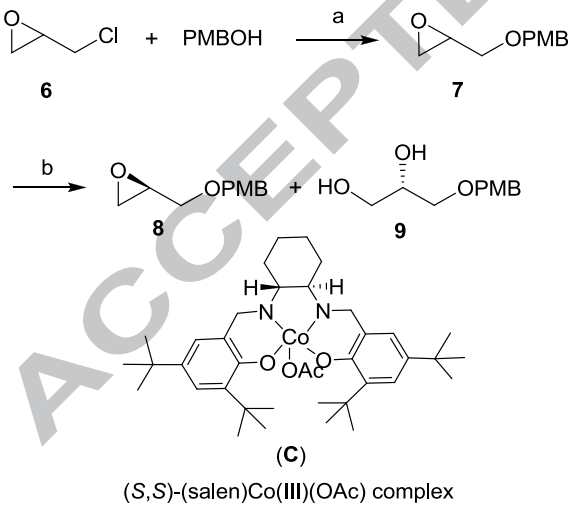
Figure 1. Naturally occurring bryostatins **(1a-e)**

As a part of our ongoing research program on the total synthesis of biologically active marine anticancer natural products,[7] we attempted the total synthesis of these rare and biologically inspiring bryostatins.[8] We herein report a concise and efficient synthesis of C19-C27 fragment (**2**) of bryostatin 11, starting from easily accessible starting materials. Our strategy utilizes a readily available and inexpensive (±)-epichlorohydrin **6** as the starting material. The target fragment **2** could be synthesized from a key intermediate **5**, which in turn could be prepared from the kinetic resolution of racemic oxirane **7**. Retrosynthetic analysis of the target fragment **2** is outlined in Scheme 1.



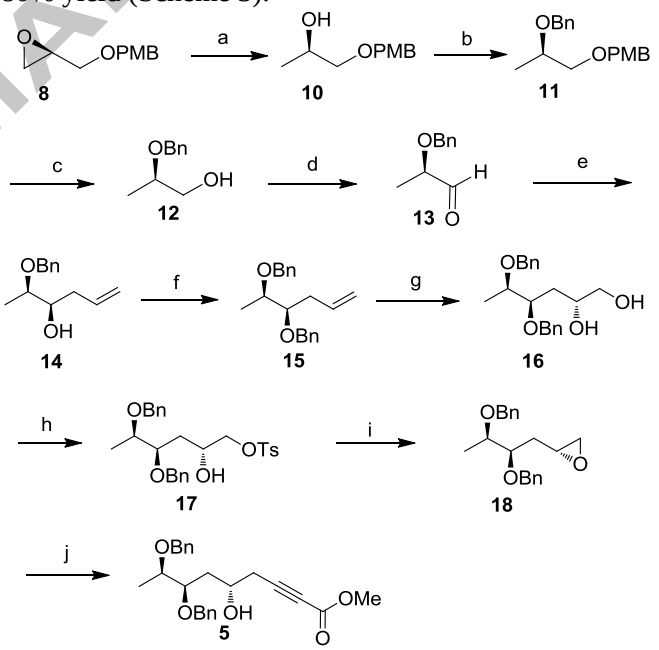
Scheme 1. Retrosynthesis of C19-C27 fragment **2** of bryostatin 11**(1d)**

Accordingly, (±)-epichlorohydrin **6** was converted into *p*-methoxybenzyl glycidol ether (±)-**7** in 81% yield using *p*-methoxybenzyl alcohol. Kinetic resolution of the racemic epoxide (±)-**7** in the presence of 0.2 mol% (salen)-Co(III)(OAc) complex [(*S,S*)-*N,N-bis*-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-Co(III)-acetate] under solvent-free conditions afforded the enantioenriched epoxide **8** in 45% yield (Scheme 2). The optical purity of the epoxide **8** was also confirmed by comparing the optical rotation with the reported value.[9]



Scheme 2. Reagents and conditions: (a) NaH, THF, 0 °C-rt, 16h, 81%; (b) **C**, H_2O, 25 °C, 36h, 45%.

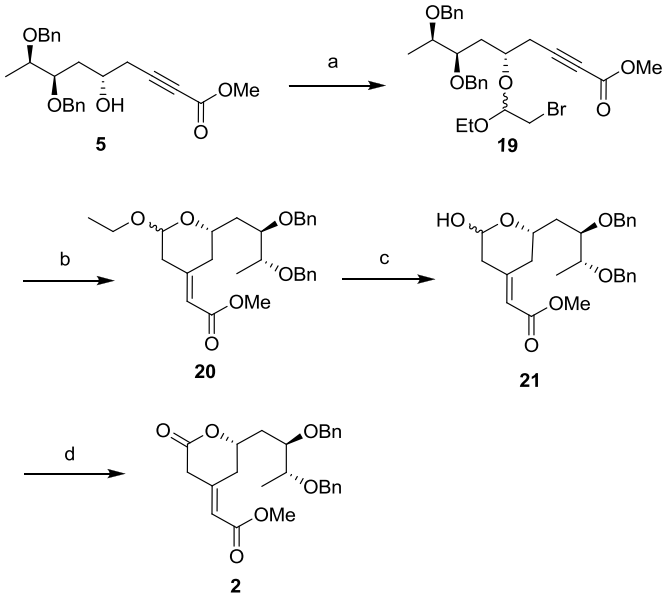
The enantioenriched epoxide **8** was converted into the corresponding alcohol **10** using $LiAlH_4$ in THF. Protection of the alcohol **10** with BnBr in the presence of NaH afforded the benzyl ether **11** in 93% yield. Deprotection of the *p*-methoxybenzyl group of **11** using ceric ammonium nitrate (CAN) in acetonitrile:water (9:1) gave the alcohol **12**. [9] Oxidation of the alcohol under Swern oxidation[9] conditions afforded the aldehyde **13** in 85% yield. The aldehyde **13** was further treated with allylmagnesium bromide after chelating with $MgBr_2.OEt_2$ to afford the compound **14** in 85% yield.[10] The exclusive formation of *erythro*-isomer was observed due to *Re*-face attack of the allyl nucleophile. However, in the absence of a chelating agent, the diastereomers were formed in 1:1 ratio, which was confirmed by ^{1}H NMR spectrum of the crude reaction mixture. Protection of **14** with BnBr in the presence of NaH afforded the benzyl ether **15**. Sharpless asymmetric dihydroxylation[11] of **15** with AD-mix-β gave the diol **16** in 85% yield as a major diastereomer (dr 88:12), which was confirmed by ^{1}H NMR spectrum of the crude reaction mixture. Treatment of **16** with *p*-TsCl in the presence of TEA in CH_2Cl_2 for 16h afforded the *mono*-tosylate **17** in 71% yield, which was then converted into epoxide **18** in 75% yield using K_2CO_3 in MeOH. Metallation of the methyl propiolate (*n*-BuLi, THF, at -78 °C) followed by addition to epoxide **18** in the presence of $BF_3.OEt_2$ afforded the desired alcohol **5** in 80% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) LAH, THF, 0-25 °C, 1h, 83%; (b) NaH, BnBr, THF, 0 °C-reflux, 93%; (c) CAN, MeCN:H_2O (9:1), 0 °C-rt, 1h, 90%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 2h, 85%; (e) Allyl bromide, $MgBr_2.Et_2O$, Mg, -78 °C, 1h, 85%; (f) NaH, BnBr, THF, 0 °C-reflux, 16h, 85%; (g) AD-mix β, *t*-BuOH-H_2O, 0 °C, 18h, 85%; (h) *p*-TsCl, TEA, CH_2Cl_2, rt, 16h, 71%; (i) K_2CO_3, MeOH, 0 °C, 1h, 75%; (j) Methyl propionate, *n*BuLi, $BF_3.Et_2O$, CH_2Cl_2, -78 °C, 1h, 80%.

Further treatment of **5** with NBS and ethyl vinyl ether afforded the bromoacetal[12] **19**, which was then subjected to radical cyclization using a freshly distilled nBu_3SnH in the presence of a catalytic amount of

azobisisobutyronitrile (AIBN) to afford the cyclic ether **20** in 92% yield.[13] Deprotection of the ethyl group from **20** using 80% aqueous acetic acid at 55-60 ºC afforded the free lactol **21** in 82% yield, which was further oxidized under Dess-Martin periodinane conditions to afford the required fragment **2** in 85% yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) Ethyl vinyl ether, NBS, CH_2Cl_2, 0 ^oC, 16h, 88%; (b) $n$$Bu_3SnH$, AIBN, toluene, reflux, 2h, 92%; (c) 80% aq. AcOH, 55 ^oC, 1h, 82%; (d) Dess-Martin periodinane, CH_2Cl_2, 0 ^oC-rt, 2h, 85%.

In 2D NOESY spectrum of the C19-C27 fragment **2,** the olefinic proton shows a strong nOe correlation with CH_2 protons adjacent to the carbonyl group of the lactone (Figure 2).[13] In the absence of nOe cross-peak between the olefinic proton and the CH_2 protons adjacent to alkyl side chain clearly indicates the geometry of the double bond as an E-configuration.

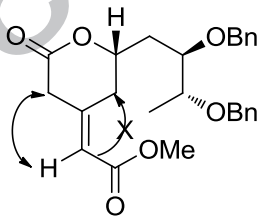


Figure 2. Characteristic nOe cross peaks of **2**

In conclusion, we have developed an efficient stereo- and enantioselective approach for the synthesis of C19-C27 fragment **2** of bryostatin-11 (**1d**). The geometry of the olefin at C21 position and the chirality at C23, C25, and C26 were successfully established through the highly stereo- and enantioselective pathways. The pyran ring system has been constructed through AIBN catalyzed radical cyclization, which is an interesting feature of this approach. The chelate-controlled addition of allylmagnesium bromide to aldehyde **13** in the presence of $MgBr_2.OEt_2$ afforded the *erythro*-isomer exclusively due to *Re*-face attack of the allyl-nucleophile, which is also an interesting aspect of this approach.

Acknowledgement

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14. Spectral data for selected compounds. **2-(4-Methoxybenzyloxymethyl)-(*R*)-oxirane (8)**: $[\alpha]_D^{20}$ +3.2 (*c* = 3.5, $CHCl_3$); IR (neat): υ_{max} 2922, 1610, 1245 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 4.45 (brs, 2H), 3.81 (s, 3H), 3.69-3.63 (m, 1H), 3.45-3.34 (m, 1H), 3.23-3.18 (m, 1H), 2.76-2.69 (m, 1H), 2.57-2.54 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 132.2, 130.0, 129.5, 113.5, 74.2, 70.5, 55.3, 50.7, 44.1. ESI-MS: *m/z*: 194 (M^+).

(2*R*,3*R*)-2-(Benzyloxy)hex-5-en-3-ol (14): $[\alpha]_D^{20}$ -17.58 (*c* = 3, $CHCl_3$); IR (neat): υ_{max} 3420, 2927, 1638, 1453, 1377, 1091, 748, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.31-7.20 (m, 5H), 5.85-5.73 (m, 1H), 5.12-5.02 (m, 2H), 4.54 (d, *J* = 6.7 Hz, 2H), 3.74-3.68 (m, 1H), 3.51-3.45 (m, 1H), 2.22 (t, *J* = 6.5 Hz, 2H), 2.04 (brs, 1H), 1.15 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.5, 135.2, 128.5, 128.0, 117.1, 77.4, 74.5, 71.2, 37.8, 15.5; ESI-MS: *m/z*: 229 (*M*+Na).

(*R*)-2-((2*R*,3*R*)-2,3-*Bis*(benzyloxy)butyl)oxirane (18): $[\alpha]_D^{20}$ +18.4 (*c* = 3.5, $CHCl_3$); IR (neat): υ_{max} 3031, 2864, 1733, 1617, 1496, 1453, 1352, 1093, 737, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.32-7.25 (m, 10H), 4.62-4.52 (m, 4H), 3.74-3.65 (m, 2H), 3.05-2.95 (m, 1H), 2.80-2-65 (m, 1H), 2.52-2.45 (m, 1H), 1.65-1.31 (m, 2H), 1.15 (d, *J* = 6.0 Hz, 3H); ESI-MS: *m/z*: 313 (*M*+1).

(5*S*,7*R*,8*R*)-Methyl 7,8-*bis*(benzyloxy)-5-hydroxynon-2-ynoate (5): $[\alpha]_D^{20}$ +14.28 (*c* = 2, $CHCl_3$); IR (neat): υ_{max} 3555, 3031, 2953, 2238, 1714, 1435, 1260, 1075, 1027, 947, 771, 753, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35-7.22 (m, 10H), 4.65-4.50 (m, 4H), 3.95-3.91 (m, 1H), 3.72 (s, 3H), 3.71-3.65 (m, 2H), 2.45 (t, *J* = 6.0 Hz, 2H), 1.75 (t, *J* = 6.0 Hz, 2H), 1.16 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.5, 138.5, 129.0, 128.1, 86.5, 78.5, 78.0, 77.2, 75.1, 72.5, 71.3, 67.5, 53.1, 36.5, 27.4, 14.7; ESI-MS: *m/z)*: 397 (*M*+1).

(*E*)-Methyl 2-((*S*)-2-((2*R*,3*R*)-2,3-*bis*(benzyloxy)butyl)tetrahydro-6-oxopyran-4-ylidene)acetate (2): $[\alpha]_D^{20}$ +30.0 (*c* = 0.3, $CHCl_3$); IR (neat): υ_{max} 3442, 3015, 2915, 1636, 1151, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25-7.32 (m, 10H), 5.85 (s, 1H), 4.45-4.65 (m, 4H), 3.95-3.99 (m, 1H), 3.72 (s, 3H), 3.62-3.70 (m, 2H), 3.22 (s, 2H), 2.32-2.40 (m, 2H), 1.95-2.02 (m, 1H), 1.65-1.74 (m, 1H), 1.16 (d, *J* = 6.0 Hz, 3H); ESI-MS: *m/z*: 456 (*M*+18).