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Synthetic Studies on Bryostatins, Potent Antineoplastic Agents: Synthesis of the C17-C27 Fragment of C20 Deoxybryostatins

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Abstract: Synthetic process toward the bottom-half portion of C_{20} deoxygenated series of bryostatins is described. It is noted that the neighboring group participation consisting of a six-membered ring enabled introduction of an unsaturated bond required for the characteristic α,β-unsaturated ester of the bryostatins.

Bryostatins isolated from the marine bryozoan *Bugula neritina* Linnaeus and *Amathia convoluta* constitute a family of 17 related macrocyclic polyethers.[1] This class of natural products is known to possess powerful antineoplastic activities against the murine P388 lymphocytic leukemia, and the potential to activate protein kinase C without tumor promotion as the activities of phorbol ester and aplysiatoxin do.[1a] While bryostatin 1 which is obtainable as the most abundant congener (2.4×10^{-5}%) is now in phase II of clinical trial, the much lesser yields of other minor series have precluded detailed evaluation of their biological activities. In this context, extensive efforts have been made to supply sufficient amounts of samples by an improved isolation method[2] or by synthesis.[3] Among the latter approach, no total synthesis of these natural products has been reported with the exception of Masamune's synthesis of bryostatin 7.[4] Against this background, we reported an efficient synthesis of the top-half fragment (C_1-C_{16}) shared by the entire family.[3g] As part of our further investigation of the synthesis of bryostatins, we disclose herein efficient construction of the bottom-half

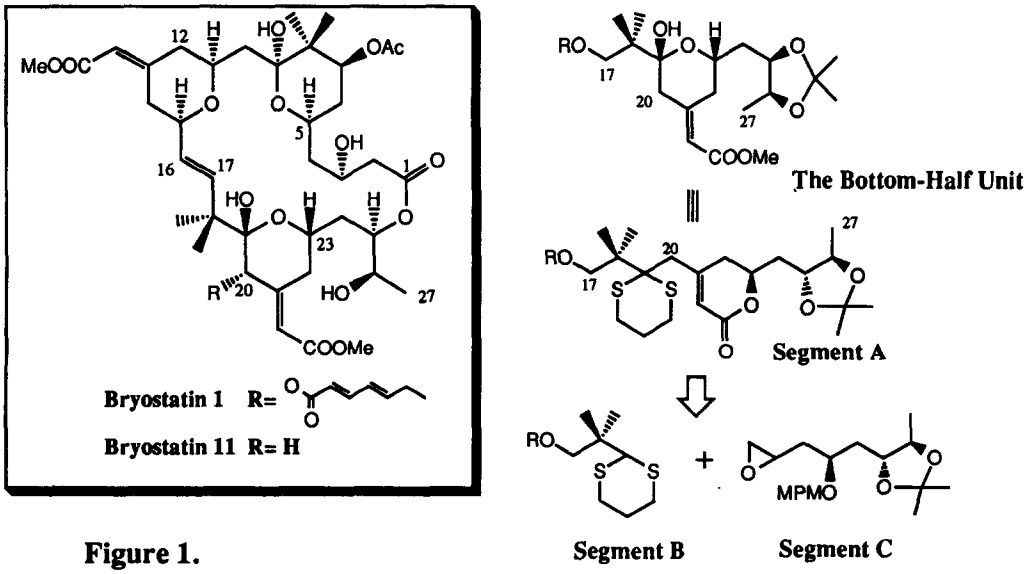
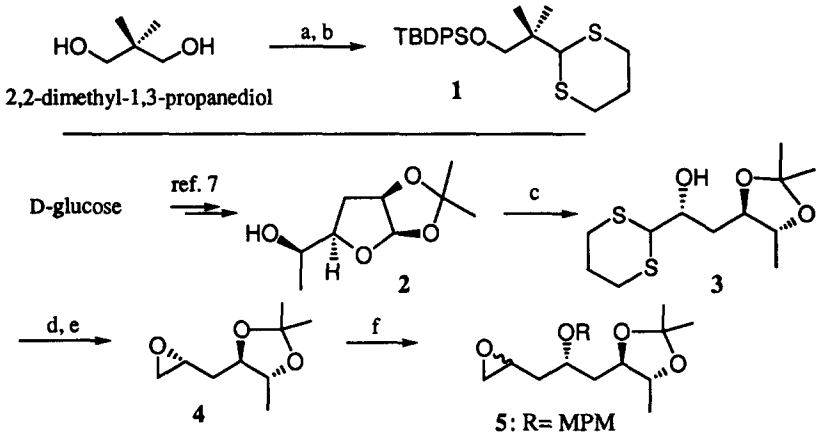


Figure 1.

fragment suitable for the C_{17}-C_{27} backbone of the C_{20} deoxygenated series (bryostatins 10, 11 and 13).

Synthesis of C_{17}-C_{19} and C_{20}-C_{27} fragments. Based on our retrosynthetic analysis (Figure 1), the α,β-unsaturated lactone (**A**) might be a synthetic equivalent of the bottom half obtained by disconnection of bryostatin 11 at the lactone linkage and the C_{16}-C_{17} double bond. It would be further divided into segments **B** and **C**. Along these lines, the synthesis was initiated by construction of dithioacetal **1**[5] corresponding to the C_{17}-C_{19} portion: the commercially available 2,2-dimethyl-1,3-propanediol was submitted to a three-step sequence involving monosilylation (65%), Swern oxidation (93%) and protection of the corresponding aldehyde by employing 1,3-propanedithiol in the presence of $MgBr_2{\cdot}OEt_2$[6] (99%).

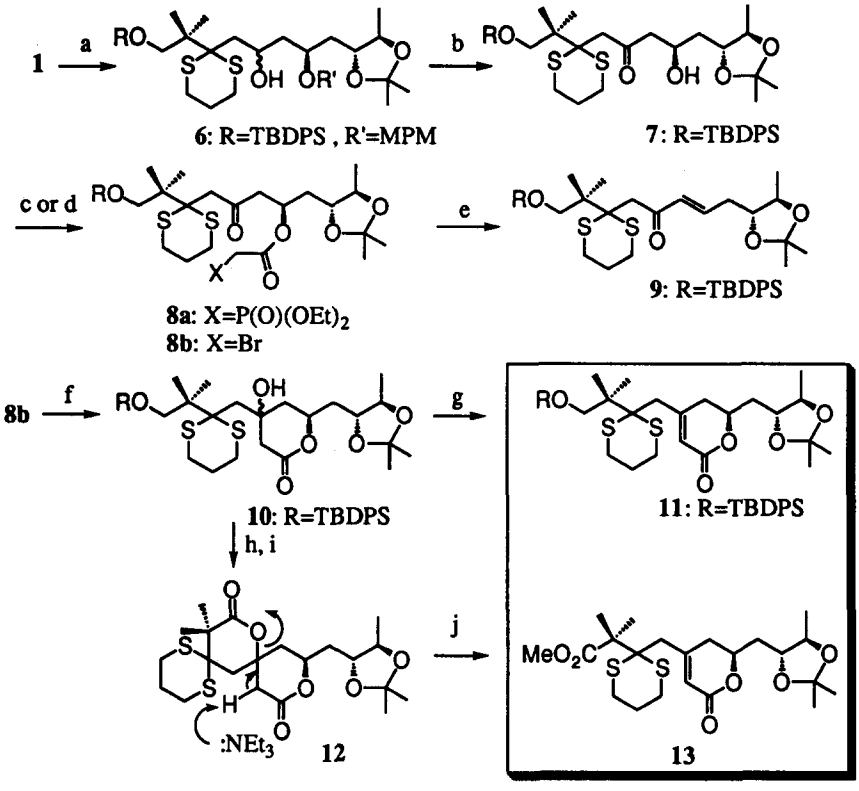
In the next stage, preparation of the coupling partner (**5**) of **1** was realized by using the stereogenic centers of D-glucose, which was derivatized by the known procedure to give the furanose derivative (**2**).[7] Compound **2** was quantitatively converted into **3** by a stepwise functional group protection. Treatment of **3** with MeI-$NaHCO_3$,[8] followed by $NaBH_4$ reduction (73% in 2 steps) provided the corresponding diol, which was transformed into epoxide **4** in 80% yield by the one-pot procedure employing TsCl and NaH. Carbon-chain homologation was achieved in three steps involving Grignard reaction in the presence of catalytic amounts of CuI, followed by alcohol protection as a MPM ether (79% in 2 steps), and mCPBA epoxidation to yield diastereomeric **5** (88%).[9] The mixture could be used for the next step without separation, since the C_{21} position would be oxidized in the later step.



Scheme 1. *Reagents* a) i. TBDPSCl, Imd. (65%); ii. Swern oxid. (93%). b) 1,3-propanedithiol, $MgBr_2{\cdot}OEt_2$ /Et_2O (99%). c) i. 1,3-propanedithiol, conc.HCl/$CHCl_3$ (93%); ii. $Me_2C(OMe)_2$, CSA/DMF (99%). d) i. MeI, $NaHCO_3$; ii. $NaBH_4$ (73% in 2 steps). e) p-TsCl, NaH/THF (80%). f) i. $CH_2CHMgBr$, CuI/Et_2O; ii. MPMCl, NaH (79% in 2 steps); iii. mCPBA/CH_2Cl_2 (88%).

Construction of the C_{17}-C_{27} framework. Anion-generation of the sterically hindered thioacetal position of **1** was evaluated to execute a coupling condition with **5**. Among the basic conditions attempted, the optimized result was acquired by treatment with tBuLi (2eq.) - TMEDA (3eq.) in THF at -45°C, 2 hr. Indeed, an anion generated by this procedure gave rise to the expected coupling with **5**, leading to **6** as a sole product in 97% yield. Although such oxidation conditions as Swern, SO_3-pyr-DMSO, Ac_2O-DMSO, PCC, Dess-Martin periodate and iPr_4NRuO_4 were troublesome, only Moffatt's method effected the desired oxidation (87%) of the secondary alcohol of **6**, followed by oxidative removal of a MPM group with DDQ[10] (96%) to afford aldol derivative **7**.[12] The stage was set for introduction of an α,β-unsaturated lactone moiety. Unfortunately,

intramolecular Horner-Emmons reaction to construct the *E*-trisubstituted olefin was unsuccessful, probably owing to basic conditions that caused β-elimination of the hydroxyl function at the C_{23} position to yield **9** (scheme 2). Based on this result, our interest was turned to Molander's protocol for SmI_2-mediated intramolecular Reformasky reaction under neutral conditions.[11] Eventually, treatment of α-bromoacetate **8b** with SmI_2 underwent a critical C-C bond formation to introduce a two-carbon unit at the C_{21} position to give **10** (86%) as a 3:1 diastereomeric mixture. Lactone **10** in hand provided two possibilities of derivatization aimed at coupling with the top-half segment in the latter step. Thus, treatment of **10** with Ac_2O-DMAP-pyridine effected a β-elimination to provide **11**[12] possessing a siloxy ether at C_{17} position. On the other hand, deprotection of a silyl protective group of **10** followed by oxidation afforded the spirobislactone **12** via a lactol intermediate, which on treatment with NEt_3 underwent spontaneous β-elimination and ring opening to furnish C_{17}-methyl ester **13**[12] after esterification with CH_2N_2.



Scheme 2. *Reagents* a) tBuLi, TMEDA/THF, -45 °C, 2 h, then **5** (97%). b) i. Moffatt oxid. (87%); ii. DDQ/10%aq.- CH_2Cl_2 (96%). c) $(EtO)_2P(O)CH_2COCl$, pyr/CH_2Cl_2 (89%). d) $BrCH_2COBr$, pyr/CH_2Cl_2 (99%). e) usual conditions for Horner-Emmons reaction. f) SmI_2/THF, -78 °C (86%). g) Ac_2O, DMAP, pyr/PhH, reflux (95%). h) nBu_4NF/THF (85%). i) DMSO, Ac_2O (92%). j) i. Et_3N (98%); ii. CH_2N_2/MeOH (100%).

In conclusion, we have successfully synthesized the bottom-half fragments (**11**, **13**) of bryostatins 10, 11 and 13, and further investigation toward the total synthesis of these natural products is now in progress.

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5. **1**: IR (film): 2990, 2960, 2940, 2860 cm^{-1}; ^1H NMR (90MHz , $CDCl_3$): δ 1.05 (6H, s), 1.06 (9H, s), 1.50-2.16 (2H, complex), 2.89 (4H, dd, J= 7.5, 3.3 Hz), 3.52 (2H, s), 4.36 (1H, s), 7.33-7.40 (6H, complex), 7.63-7.75 (4H, complex).
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9. **5**: IR (film): 2980, 2930, 2870, 1610, 1515 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$): δ 1.23 (3H, d, J= 5.3 Hz), 1.38 (6H, s), 1.60-2.08 (4H, complex), 2.50 (1H, m), 2.77 (1H, m), 3.04 (1H, m), 3.58-3.92 (2H, complex), 3.80 (3H, s), 4.52-4.56 (2H, complex), 6.82-6.92 (2H, complex).
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12. **7**: $[\alpha]_D^{27}$ -7.1° (*c* 0.94, $CHCl_3$); IR (film) 3500, 1700 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 1.07 (9H, s), 1.21 (6H, s), 1.25 (3H, d, J= 5.8Hz), 1.38 (3H, s), 1.39 (3H, s), 1.51 (1H, m), 1.69 (1H, m), 1.80 (1H, m), 1.94 (1H, m), 2.66-2.86 (5H, complex), 2.93 (1H, dd, J=18.1, 2.9Hz), 3.18 (1H, d, J= 14.7Hz), 3.25 (1H, d, J= 14.7Hz), 3.32 (1H, d, J= 3.4Hz, overlapped OH signal), 3.71-3.74 (2H, complex), 3.80 (2H, s), 4.21 (1H, m), 7.37-7.45 (6H, complex), 7.66-7.68 (4H, complex). **11**: $C_{36}H_{49}O_5S_2Si$ [*m/z* 653.2754 (M^+-CH_3)]; $[\alpha]_D^{27}$ -16.0° (*c* 0.92, $CHCl_3$); IR (film) 1720, 1625, 1585, 1425 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 1.06 (9H, s), 1.23 (3H, d, J= 5.8Hz), 1.27 (3H, d, J= 5.8Hz), 1.36 (3H, s), 1.38 (3H, s), 1.69 (1H, ddd, J= 14.2, 10.0, 3.9Hz), 1.78-1.95 (3H, complex), 2.50 (1H, ddd, J= 18.0, 12.3, 1.8Hz), 2.64-2.79 (4H, complex), 2.83 (1H, dd, J= 18.0, 3.7Hz), 2.87 (1H, d, J= 14.2Hz), 2.99 (1H, d, J= 14.2Hz), 3.69 (1H, qd, J= 8.3, 5.8Hz), 3.75-3.84 (3H, complex), 4.47 (1H, m), 6.02 (1H, d, J= 1.8Hz), 7.37-7.46 (4H, complex), 7.65-7.67 (6H, complex). **13**: $C_{22}H_{34}O_6S_2$ [*m/z* 458.1804 (M^+)]; $[\alpha]_D^{19}$ -12.8° (*c* 0.15, $CHCl_3$); IR (film) 2930, 1715, 1440, 1385, 1255 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 1.28 (3H, d, J= 6.0 Hz), 1.37 (3H, s), 1.39 (3H, s), 1.48 (3H,s), 1.49(3H, s), 1.75 (1H, ddd, J= 14.0, 10.0, 3.6Hz), 1.89-2.02 (2H, complex), 2.62 (1H, ddd, J= 18.0, 12.0, 2.4Hz), 2.75-2.93 (5H, complex), 3.02 (2H, s), 3.69 (3H, s), 3.67-3.74 (1H, m), 3.86 (1H, ddd, J= 10.0, 8.4, 2.4Hz), 4.61 (1H, ddt, J= 12.0, 9.2, 3.6Hz), 6.11 (1H, d, J= 4.0Hz).

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