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Synthesis of the C17-C27 Fragment of Bryostatin 3

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Abstract: The key synthetic intermediate corresponding to the C17 - C27 positions of bryostatin 3, has successfully been synthesized. The newly constructed stereogenic centers were unambiguously confirmed by X-ray crystallographic analysis. © 1998 Elsevier Science Ltd. All rights reserved.

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Bryostatins isolated from the marine bryozoan *Bugula neritina* Linnaeus and *Amathia convoluta*, have met expectations as leads for new potent antineoplastic agents.¹ Actually, bryostatin 1 which is the most abundant congener (2.4 x10⁻⁵%) in the family, is known to be in Phase II of clinical trials. Additionally, several biologically potential features such as the strong interaction with PKC and the antagonism to phorbol ester have been observed, although the mode of action of this natural product is still under investigation. In addition to such interesting biological properties, insufficient amounts of the natural product, have motivated synthetic studies to obtain samples for further evaluations.² Against this background, we have carried out extensive synthetic study on bryostatins.³ We describe herein synthesis of the bottom half of bryostatin 3,4 which is a unique member of the family, for the additional γ -lactone moiety.^{1a,5}



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Scheme 1. reagents: a. i) DIBAL-H / PhMe, -78 °C; ii) Ph₃P-CBr₄ / CH₂Cl₂, 0 °C (88% in 2steps); iii) n-BuLi / THF, then $(CH_2O)_n$ (87%). b. Red-Al / THF, then I₂ (86%). c. TBDPSCl, Imd (95%). d. i) TFA-H₂O / THF; ii) TBDPSCl, Imd; iii) MeOC₆H₄CH(OMe)₂, PPTS / CH₂Cl₂ (77% in 3 steps); iv) DIBAL-H / PhMe, 0 °C (79%). e. MOMCl, i-Pr₂NEt / CH₂Cl₂ (84%).



The synthesis was commenced with reduction of the known ester $1,^{3c}$ followed by usual manipulation to give the corresponding propargyl alcohol 2 in good overall yield. Upon hydroalumination and concomitant iodination, 2 was transformed into vinyl iodide 3 (86%), derivatization of which afforded 4a - 4c, as shown in Scheme 1. Coupling of these vinyl iodides with aldehyde 5⁶ under CrCl₂ - NiCl₂, was unsuccessful, probably owing to low reactivities. Accordingly, our attention was turned to a halogen - metal exchange procedure to generate the corresponding vinyl anions, which would facilitate the desired coupling with 5. The MeLi - t-BuLi conditions were proved to be the method of choice from the extensive assessment of deuterium introduction, as can be seen in Table 1. Actually, successive treatment of 4b with the corresponding bases, followed by the addition of aldehyde 5 provided a 3:1 mixture of the 1,3-diols (6\alpha and 6\beta) in 53% yield, whereas the halogen - metal exchange of 4a and 4c provided considerable amounts of undesired by-products such as arene derivatives. The stereochemistry of both isomers (6\alpha and 6\beta) was determined by the N.O.E. experiments of the corresponding cyclic carbonate derivatives 7 α and 7 β .

The major isomer 6α was converted in five steps into lactol 8, which on acetalization afforded 9 in 91% yield ($\alpha:\beta = 1:10$). The stereochemistry of this compound could be unambiguously confirmed by a single X-ray crystallographic analysis of the major isomer.^{7,8} Exhaustive deprotection of the siloxy groups provided the corresponding triol 10. Reactivity difference among the three hydroxyl groups in 10 allowed the following reactions. Thus, selective oxidation with TPAP effected the one-pot construction of the γ -lactone structure, leading to 11, the acetonide group of which could be removed under several acid-hydrolytic conditions, to the triol 12 involving a hydroxyl group at the C₂₅ position required for macrolactonization. On the other hand, exposure of 10 to TESCI - Imd. afforded the disiloxy ether 13 in 94% yield, while exhaustive etherification under TESOTf - 2,6-lutidine conditions produced 14 (83%), which could also be obtained from 13 under the



Scheme 2. reagents: a. MeLi / Et₂O, -30 °C, t-BuLi, -90 °C, then 5 (53%). b. triphosgene, pyr. / CH₂Cl₂, -45 °C (71%). c. i) TBSOTf, 2,6-litidine (99%); ii) m-CPBA, Na₂HPO₄ (99%); iii) DDQ / 10% aq.CH₂Cl₂ (99%); iv) Dess - Martin reagent (99%); v) H₂, Pd(OH)₂-C / EtOH, then Me₂C(OMe)₂, PPTS / acetone (89%). d. TBSOTf, TMSOMe, Me₂C(OMe)₂, MS4Å /CH₂Cl₂ (91%). e. TBAF / THF (quant). f. TPAP, NMO, MS4Å /CH₂Cl₂ (86%). g. CSA / MeOH, or PPTS / MeOH, 60 °C, or Amberlyst 15E / MeOH. 50 °C, or 60% aq.AcOH. h. TESCI, Imd. (94%). i. TESOTf, 2,6-lutidine (83%). j. TESOTf, 2,6-lutidine (86%). k. TBAF - AcOH (1:1) (quant). 1. TPAP (100%), or MnO₂ / CH₂Cl₂ (90%). m. (2*E*,4*E*)-octa-2,4-dienoic acid, EDCI, DMAP / CH₂Cl₂ (76%). n. CSA / MeOH (60%).

same TESOTf conditions. Selective removal of the silvl protective group in 14 was effected under TBAF -AcOH conditions to give diol 15 in quantitative yield, which on TPAP or MnO_2 oxidation provided lactone 16 in high yields. Additionally, introduction of the characteristic acyl group at the C₂₀ position could be demonstrated by acylation of 11 with (2*E*,4*E*)-octa-2,4-dienoic acid under the EDCI-DMAP conditions, leading to 17⁹ in good yield, which on acid hydrolysis afforded the corresponding diol 18.9

In conclusion, the bottom half fragment ($C_{17} - C_{27}$) of bryostatin 3 has been successfully synthesized through the halogen-metal exchange reaction. Manipulation of reactivities of the corresponding hydroxyl groups could demonstrate the selective construction of the γ -lacton ring, as well as the feasibility of the acylation at the C_{20} position.

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- 6. Essentially the same synthetic method as that for this compound has been published in ref. 3b.
- 7. Crystal data: $C_{53}H_{84}O_9SSi_3$ (FW=981.56), monoclinic, P2₁, a=8.779 (3), b=26.794 (5), c=12.682 (3) Å, β =92.29 (2)°,V=2980.7 (14) Å³, Z=2, Dx=1.094 Mg m⁻³, T=297 K. X-ray intensities were measured on a Rigaku AFC-5 diffractometer with Mo K α radiation (λ = 0.71073 Å), and final R=0.060 for 3961 observed reflections. The details have been deposited at the Cambridge Crystallographic Data Center.
- 9b: mp 110 111 °C (EtOH); [α]_D²² +20.6° (c 1.00, CHCl₃); IR (film) 1588 cm⁻¹; δ_H (CDCl₃) -0.04 (3H, s), 0.03 (3H, s), 0.08 (6H, s), 0.82 (6H, s), 0.88 (9H, s), 1.14 (3H, d, J= 3.6 Hz), 1.18 (9H, s), 1.29 (3H, s), 1.34 (3H, s), 1.65 1.72 (2H, complex), 1.81 (3H, s), 1.86 (3H, s), 3.40 (1H, m), 3.41 (3H, s), 3.53 (1H, m), 3.82 (1H, br t, J= 9.6 Hz), 3.91 (1H, d, J= 14.8 Hz), 3.98 (1H, d, J= 14.8 Hz), 4.02 (1H, br d, J= 7.2 Hz), 4.15 (1H, br t, J= 8.4 Hz), 4.51 4.55 (2H, complex), 4.92 (1H, br s), 6.25 (1H, m), 6.91 6.94 (3H, complex), 7.23 7.32 (6H, complex), 7.81 7.85 (4H, complex); δ_C (CDCl₃) -5.1, -4.6, -3.9, -3.7, 17.0, 18.5, 19.4, 23.0, 25.9, 26.3, 27.0, 27.4, 37.0, 46.8, 50.8, 61.0, 64.2, 71.4, 72.2, 75.7, 77.4, 77.6, 78.6, 103.4, 108.1, 127.9, 128.1, 128.3, 128.5, 128.6, 129.0, 130.1, 130.2, 132.6, 136.0, 138.9, 144.0.
- 9. **17**: $[\alpha]_D^{20} 30.8^{\circ}$ (*c* 1.00, CHCl₃); IR (film): 1795, 1760, 1735, 1650 cm⁻¹; δ_H (CDCl₃) 0.95 (3H, t, J= 7.4 Hz), 1.29 (3H, s), 1.30 (3H, s), 1.34 (3H, s), 1.35 (3H, s), 1.46 (3H, s), 1.50 (2H, ddd, J= 15.8, 7.4, 7.2 Hz), 1.94 (1H, ddd, J= 13.8, 10.8, 2.4 Hz), 2.05 (1H, ddd, J= 13.6, 10.4, 2.4 Hz), 2.19 (2H, dd, J= 14, 6.8 Hz), 3.38 (1H, d, J= 14.4 Hz), 3.40 (3H, s), 3.64 (1H, dt, 10, 1.6 Hz), 3.65 (1H, d, J= 14.4 Hz), 3.73 (1H, ddd, J= 16.6, 6, 2.2 Hz), 3.82 (1H, ddd, J= 10, 8, 2.4 Hz), 4.59 (1H, dd, J= 9.2, 2 Hz), 5.68 (1H, d, J= 15.8 HZ), 5.84 (1H, s), 6.08 (1H, d, J= 1.6 Hz), 6.18 (1H, dd, J= 15.6, 10 Hz), 6.25 (1H, dt, J= 15.6, 6.4 Hz), 7.31 (1H, dt, J= 7.6, 1.2 Hz), 7.54 (2H, t, J= 7.6 Hz), 7.64 (1H, dt, J= 7.6, 1.2 Hz), 7.89 (2H, dt, J= 7.6, 1.2 Hz); δ_C (CDCl₃) 13.7, 17.0, 21.8, 22.5, 24.0, 27.1, 35.1, 35.4, 45.2, 53.5, 62.8, 68.7, 74.8, 77.2, 78.1, 103.1, 108.1, 116.7, 117.3, 127.5, 128.0, 129.2, 133.4, 142.2, 147.5, 148.0, 162.0, 164.7, 172.0. **18**: IR (film): 3506, 1782, 1750, 1722, 1639 cm⁻¹; δ_H (CDCl₃) 0.92 (3H, t, J= 7.4 Hz), 1.19 (3H, d, J= 6.4 Hz), 1.26 (3H, s), 1.33 (3H, s), 1.30 1.45 (2H, complex), 1.86 (1H, m), 2.01 (1H, m), 2.15 (1H, dd, J= 14, 7.2 Hz), 2.30 (1H, m), 3.37 (3H, s), 3.40 (1H, s), 3.57 (1H, s), 3.58 3.73 (3H, complex), 4.58 (1H, dd, J= 9.2, 1.6 Hz), 5.66 (1H, d, J= 15.6 Hz), 5.87 (1H, s), 6.06 (1H, d, J= 1.6 Hz), 6.09 6.19 (2H, complex), 7.13 (1H, m), 7.46 7.53 (3H, complex), 7.86 (2H, dd, J= 6.8, 1.6 Hz).