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Asymmetric Synthesis of the C(17)-C(27) Segment of the Antineoplastic Macrolide Bryostatin 1

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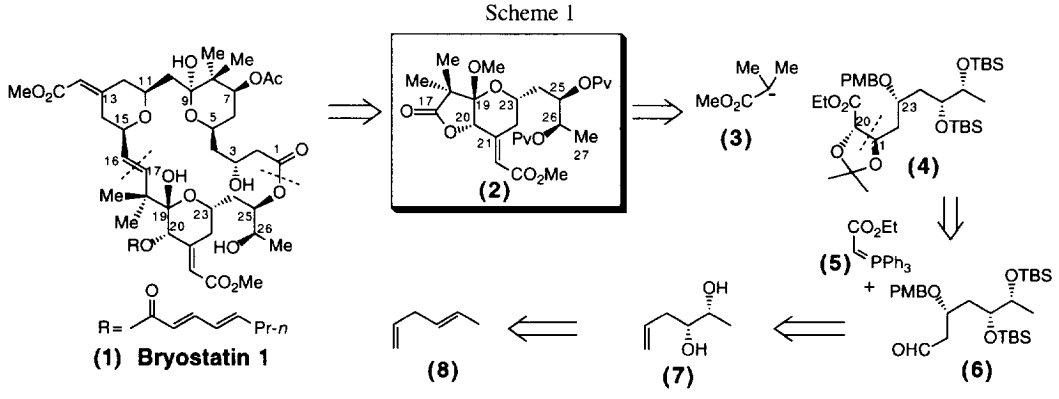
Abstract: An asymmetric synthesis of the C(17)-C(27) segment of bryostatin 1 is described.

Bryostatin 1 is a recently discovered antineoplastic macrolide isolated from the marine organism *Bugula neritina*.[1,2] Bryostatin 1 displays potent antitumour activity against a range of liquid and solid animal tumours, that include the murine P388 lymphocytic leukaemia, where it leads to a 96% life extension at 70 μg/kg,[1] and the murine M531 ovarian sarcoma where it produces a 68% life extension when administered at 40 μg/kg.[2] The exact sequence of biological events by which bryostatin 1 induces tumour regression remains unknown. One hypothesis[3,4] is that bryostatin 1 synergises with interleukin 4 (IL-4) and interleukin-2 (IL-2) to activate protein kinase C, and that this stimulates the maturation of cytotoxic T-lymphocytes from naive, resting T-lymphocytes. Bryostatin 1 then cooperatively activates the newly primed cytotoxic T-cells, along with IL-4 and IL-2, to promote the non-specific lysis of tumour cells. While this mechanism of antitumour action for bryostatin 1 is very appealing,[3,4] further studies are going to be necessary before it is conclusively proven *in vivo*. Such investigations might be facilitated by the availability of bryostatin 1 analogues for use as biological probes. As a result, we have initiated a total synthesis programme[5,6] on bryostatin 1 (**1**), and herein, describe our asymmetric synthesis of **2**, an advanced intermediate corresponding to the C(17)-C(27) sector.

Scheme 1

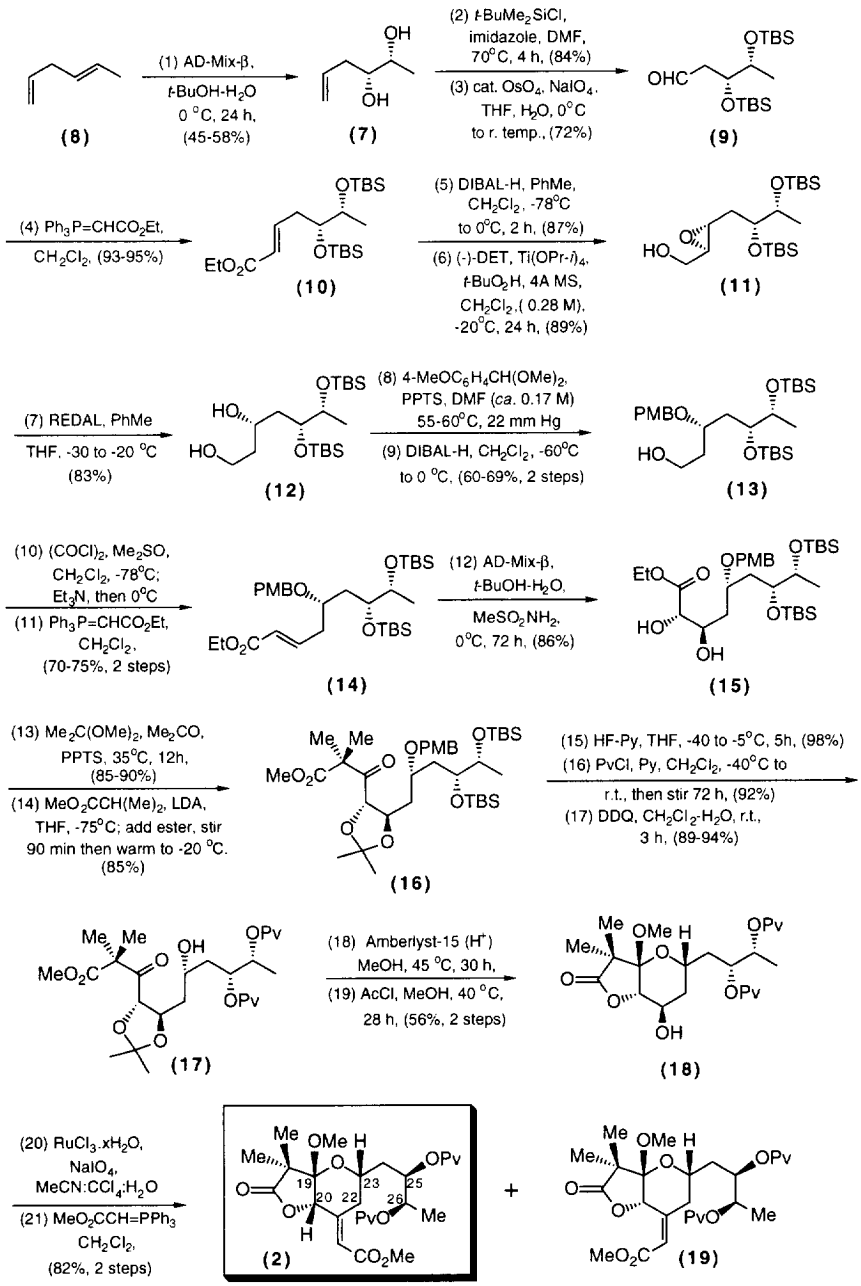


Our retrosynthetic analysis of bryostatin 1 is outlined in Scheme 1. The key steps in our plan were a Claisen condensation between anion **3** and ester **4** to establish the C(18)-C(19) bond, subsequent unmasking of the C(20), C(21) and C(23) hydroxyl protecting groups, a Fischer glycosidation to introduce the axial methyl glycoside at C(19), and a butyrolactonisation between the C(17)-ester and the C(20)-hydroxy group. This would expose the secondary alcohol at C(21) for oxidation and Wittig olefination to install the exocyclic α,β-unsaturated ester of **2**. Ester **4** would be obtainable from aldehyde **6** through a Wittig olefination/Sharpless asymmetric dihydroxylation (AD) tactic. AD technology[7] could also be used to stereoselectively introduce the two hydroxy stereocentres in **7**, if chemoselectively applied on diene **8**.[8] Homologation of the double bond in **7** to give an allylic alcohol might then allow the C(23)-hydroxyl group to be installed through a Sharpless epoxidation/REDAL reduction sequence.

Asymmetric dihydroxylation[7] of diene **8** with AD-mix-β (0.6 equiv) occurred selectively across the (*E*)-disubstituted olefin, to deliver known diol **7** in 45-58% yield.[8] The two hydroxy groups in **7** were protected as *t*-butyldimethylsilyl ethers by treatment with *t*-butyldimethylsilyl chloride (2.4 equiv) and imidazole (3.0 equiv) in DMF (*ca.* 1M) at 70°C, and the double bond oxidatively cleaved with catalytic osmium tetroxide (1.8 mol %) and sodium periodate (6.5 equiv) in aqueous THF. The resulting aldehyde **9** reacted readily with stabilised ylid **5** (3.0 equiv) in CH_2Cl_2 (*ca.* 1M) to provide alkene **10** as essentially one geometrical isomer. After reduction of the ester group with DIBAL-H (2.2 equiv), a Sharpless asymmetric epoxidation[9] was carried out on the (*E*)-allylic alcohol with (-)-DET as the chiral additive. Epoxy alcohol **11** {$[\alpha]_D$ +48.4° (*c* 0.5, CH_2Cl_2)}was obtained in 89% yield and >96% ee; it underwent regioselective reduction[10] with REDAL (5.0 equiv) in THF (*ca.* 0.68 M) between -30 and -20 °C to afford diol **12** {$[\alpha]_D$ +18.4° (*c* 0.5, CH_2Cl_2)} in 83% yield. After protection of the 1,3-diol as its *p*-methoxybenzylidene acetal, reductive cleavage[11] was performed with DIBAL-H (2.4 equiv) in CH_2Cl_2 (*ca.* 1M). This furnished primary alcohol **13** in 60-69% yield for the two steps. Compound **13** was then oxidised to aldehyde **6**,[12] and a Wittig reaction performed to obtain **14** as the major geometrical isomer. The Sharpless AD reaction on alkene **14** with AD-mix-β (3.85 equiv) and methanesulfonamide (3.8 equiv) proved rather slow, taking 3 days at 0°C to reach completion. However, it did successfully install the C(20)-hydroxy stereocentre with total stereocontrol in 86% yield. The diol unit in **15** was next protected as an isopropylidene acetal, and a Claisen condensation executed with the lithium enolate obtained from treating methyl isobutyrate (7.4 equiv) with LDA (7.0 equiv) in THF at -75°C. The Claisen condensation was essentially complete after 90 min at -75°C and delivered β-keto ester **16** {$[\alpha]_D$ +38.4° (*c* 0.5, CH_2Cl_2)} in 85% yield. *O*-Desilylation was accomplished with HF-pyridine complex (2.4 equiv) in THF (*ca.* 0.14 M) at -5°C. The resulting diol was then *O*-pivaloylated, and the *p*-methoxybenzyl ether removed[13] with DDQ (1.5 equiv) in CH_2Cl_2-H_2O (17:1, *ca.* 0.14 M) to give alcohol **17**. The best conditions for removing the acetonide group from **17** involved the use of Amberlyst-15 (H^+) resin in methanol at 45°C for 30 h. This not only instigated cyclisation to the butyrolactone[14] but also induced ring-closure of the pyran hemiketal ring system. Fischer glycosidation[15] of the bicyclic lactol proceeded slowly with acetyl chloride (18.5 equiv) in methanol (*ca* 0.16 M) at 40°C for 28 h, but did produce methyl glycoside **18** {$[\alpha]_D$ +28.5° (*c* 0.2, CH_2Cl_2)} in 56% yield from **17**. All that now remained to complete the synthesis of **2** was oxidation of alcohol **18** with ruthenium trichloride (8 mol%) and sodium periodate (2.0 equiv) in MeCN:CCl_4:H_2O (2:2:3),[16] followed by a Wittig reaction with $MeO_2CCH{=}PPh_3$ (2.8 equiv) in dichloromethane. Somewhat surprisingly, this olefination proved to be non-stereoselective, delivering a 1:1 mixture of (*E*)- and (*Z*)-isomers in 82 % yield; the latter were successfully separated by multiple-elution preparative TLC. The double-bond geometry in alkene **2** was apparent from the 400 MHz ^1H NMR NOESY

spectrum in C_6D_6. This revealed a strong NOE between the equatorial hydrogen at C(20), which resonated as a singlet at δ 4.07, and the olefinic hydrogen at δ 5.85 which resonated as a narrow doublet (J = 1.8 Hz). In addition, the equatorial allylic hydrogen at C(22) resonated as a double-doublet at δ 3.91 (J = 1.8, 14.1 Hz); its

Scheme 2



chemical shift was indicative of it residing in the deshielding cone of the α,β-unsaturated ester carbonyl group. The axial hydrogen at C(22) resonated as a doublet of double-doublets at δ 2.09 (J = 1.8, 11.7, 14.0 Hz). As one would expect, the C(22) equatorial hydrogen also showed a strong NOE with the axial hydrogen at C(23), which indicated that both these hydrogens were *syn*-related. The C(23) hydrogen appeared as a multiplet at δ 3.70 and gave rise to a significant NOE with the methoxy group of the methyl glycoside (s, δ 3.11), confirming their 1,3-diaxial relationship. The low-field positions of the C(25) hydrogen (δ 5.38, m) and the C(26) hydrogen (δ 5.01, m) corroborated the presence of *O*-pivaloate esters at these positions. Evidence for the γ-butyrolactone ring system was provided by the IR spectrum of **2** (KBr) which displayed an intense C=O stretching absorption at 1793 cm^{-1}; its high frequency position was suggestive of significant angular strain within the lactone ring. Compound **2** also gave a satisfactory microanalysis for $C_{27}H_{42}O_{10}$ (Calcd.: C, 61.58; H, 8.04%. Found: C, 61.42; H, 8.40%). Further synthetic studies on bryostatin 1 will be reported in due course.

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17. All new compounds gave satisfactory 400 MHz ^{1}H and 100 MHz ^{13}C NMR and IR spectra, as well as appropriate parent ion identification by HRMS and/or C and H combustion microanalyses within 0.4%.

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