

0040-4039(94)02477-4

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

Karl J. Hale,\* J. A. Lennon, Soraya Manaviazar, Muhammad H. Javaid

The Christopher Ingold Laboratories, Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK.

and

## Christopher J. Hobbs

Roche Products Limited, Welwyn Garden City, Herts AL7 3AY, UK.

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*.<sup>1,2</sup> 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  $\mu$ g/kg,<sup>1</sup> and the murine M531 ovarian sarcoma where it produces a 68% life extension when administered at 40  $\mu$ g/kg.<sup>2</sup> The exact sequence of biological events by which bryostatin 1 induces tumour regression remains unknown. One hypothesis<sup>3,4</sup> 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,<sup>3,4</sup> 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<sup>5,6</sup> on bryostatin 1 (1), and herein, describe our asymmetric synthesis of **2**, an advanced intermediate corresponding to the C(17)-C(27) sector.



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  $\alpha$ , $\beta$ -unsaturated ester of **2**. Ester **4** would be obtainable from aldehyde **6** through a Wittig olefination/Sharpless asymmetric dihydroxylation (AD) tactic. AD technology<sup>7</sup> could also be used to stereoselectively introduce the two hydroxy stereocentres in **7**, if chemoselectively applied on diene **8**.<sup>8</sup> 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<sup>7</sup> of diene 8 with AD-mix- $\beta$  (0.6 equiv) occurred selectively across the (E)disubstituted olefin, to deliver known diol 7 in 45-58% yield.<sup>8</sup> The two hydroxy groups in 7 were protected as tbutyldimethylsilyl 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 vlid 5 (3.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (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<sup>9</sup> 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<sub>2</sub>Cl<sub>2</sub>)}was obtained in 89% yield and >96% ee; it underwent regioselective reduction<sup>10</sup> 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<sub>2</sub>Cl<sub>2</sub>)} in 83% yield. After protection of the 1.3-diol as its p-methoxybenzylidene acetal, reductive cleavage<sup>11</sup> was performed with DIBAL-H (2.4 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (ca. 1M). This furnished primary alcohol 13 in 60-69% yield for the two steps. Compound 13 was then oxidised to aldehvde  $6.1^2$  and a Wittig reaction performed to obtain 14 as the major geometrical isomer. The Sharpless AD reaction on alkene 14 with AD-mix- $\beta$  (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  $\beta$ -keto ester 16 {[ $\alpha$ ]<sub>D</sub> +38.4° (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>)} in 85% yield. O-Desilvlation was accomplished with HF-pyridine complex (2.4 equiv) in THF (ca. 0.14 M) at -5°C. The resulting diol was then O-pivalovlated, and the p-methoxybenzyl ether removed<sup>13</sup> with DDO (1.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O (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<sup>+</sup>) resin in methanol at 45°C for 30 h. This not only instigated cyclisation to the butyrolactone<sup>14</sup> but also induced ring-closure of the pyran hemiketal ring system. Fischer glycosidation<sup>15</sup> 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<sub>2</sub>Cl<sub>2</sub>)} 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<sub>4</sub>:H<sub>2</sub>O (2:2:3),<sup>16</sup> followed by a Wittig reaction with MeO<sub>2</sub>CCH=PPh<sub>3</sub> (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 <sup>1</sup>H NMR NOESY spectrum in C<sub>6</sub>D<sub>6</sub>. This revealed a strong NOE between the equatorial hydrogen at C(20), which resonated as a singlet at  $\delta$  4.07, and the olefinic hydrogen at  $\delta$  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  $\delta$  3.91 (J = 1.8, 14.1 Hz); its



chemical shift was indicative of it residing in the deshielding cone of the  $\alpha$ , $\beta$ -unsaturated ester carbonyl group. The axial hydrogen at C(22) resonated as a doublet of double-doublets at  $\delta$  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  $\delta$  3.70 and gave rise to a significant NOE with the methoxy group of the methyl glycoside (s,  $\delta$  3.11), confirming their 1,3-diaxial relationship. The low-field positions of the C(25) hydrogen ( $\delta$  5.38, m) and the C(26) hydrogen ( $\delta$  5.01, m) corroborated the presence of *O*-pivaloate esters at these positions. Evidence for the  $\gamma$ -butyrolactone ring system was provided by the IR spectrum of **2** (KBr) which displayed an intense C=O stretching absorption at 1793 cm<sup>-1</sup>; its high frequency position was suggestive of significant angular strain within the lactone ring. Compound **2** also gave a satisfactory microanalysis for C<sub>27</sub>H<sub>42</sub>O<sub>10</sub> (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.

- 1. Pettit, G.R.; Herald, C.L.; Clardy, J.; Arnold, E.; Doubek, D.L.; Herald, D.L., J. Am. Chem. Soc., 1982, 104, 6846.
- 2. Pettit, G.R.; Kamano, Y.; Herald, C.L.; Tozawa, M., J. Am. Chem. Soc., 1984, 106, 6768.
- 3. Trenn, G.; Pettit, G.R.; Takayama, H.; Hu-Li, J.; Sitkovsky, M.V., J. Immunol., 1988, 140, 433.
- 4. Hess, A.D.; Silanskis, M.K.; Esa, A.H.; Pettit, G.R.; Stratford May, W., J. Immunol., 1988, 141, 3263.
- Total synthesis of bryostatin 7: Blanchette, M.A.; Malamas, M.A.; Nantz, M.H.; Roberts, J.C.; Somfai, P.; Whritenour, D.C.; Masamune, S.; Kageyama, M.; Tamura, T., J. Org. Chem., 1989, 54, 2817; Masamune, S., Pure Appl. Chem., 1988, 60, 1587; Kageyama, M.; Tamura, T.; Nantz, M.H; Roberts, J.C.; Somfai, P.; Whritenour, D.C.; Masamaune, S., J. Am. Chem. Soc., 1990, 112, 7407.
- Synthetic Studies on the bryostatins: Roy, R.; Rey, A.W.; Charron, M.; Molino, R., J. Chem. Soc. Chem. Commun., 1989, 1308; Munt, S.P.; Thomas, E.J., J. Chem. Soc. Chem. Commun., 1989, 480; Evans, D.A.; Carreira, E.M., Tetrahedron Lett., 1990, 31, 4703; Roy, R.; Rey, A.W., Synlett, 1990, 448; Evans, D.A.; Gauchet-Prunet, J.A.; Carreira, E.M.; Charette, A.B., J. Org. Chem., 1991, 56, 741; De Brabander, J.; Vanhessche, K.; Vandewalle, M., Tetrahedron Lett., 1991, 32, 2821; Ohmori, K.; Suzuki, T.; Miyazawa, K.; Nishiyama, S.; Yamamura, S., Tetrahedron Lett., 1993, 34, 4981; De Brabander, J.; Vandewalle, M., Synthesis, 1994, 855.
- Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L., J. Org. Chem., 1992, 57, 2768.
- 8. Xu, D.; Crispino, G.A.; Sharpless, K.B., J. Am. Chem. Soc., 1992, 114, 7570.
- 9. Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B., J. Am. Chem. Soc., 1987, 109, 5765.
- 10. Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Viti, S.M., J. Org. Chem., 1982, 47, 1378.
- 11. Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K., Chem. Lett., 1983, 1593.
- 12. Mancuso, A.J.; Huang, S.-L.; Swern, D., J. Org. Chem., 1978, 43, 2480.
- 13. Horita, K; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O., Tetrahedron, 1986, 42, 3021.
- 14. Tanimoto, N.; Gerritz, S.W.; Sawabe, A.; Noda, T.; Filla, S.A.; Masamune, S., Angew. Chem. Int.Edn.Engl., 1994, 33, 673.
- 15. Caldwell, C.G.; Rupprecht, K.M.; Bondy, S.; Davis, A.A., J. Org. Chem., 1990, 55, 2355.
- 16. Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B., J. Org. Chem., 1981, 46, 3936.
- 17. All new compounds gave satisfactory 400 MHz <sup>1</sup>H and 100 MHz <sup>13</sup>C NMR and IR spectra, as well as appropriate parent ion identification by HRMS and/or C and H combustion microanalyses within 0.4%.

(Received in UK 29 November 1994; accepted 21 December 1994)

Acknowledgements: We are very grateful to the University of London Central Research Fund, Roche Products, Rohm & Haas (Philadelphia), and Pfizer (Sandwich) for their generous financial support of this investigation. We thank Roche Products and the SERC for the award of a CASE studentship (JL), and the ULIRS for HRMS and high-field NMR measurements. References and Notes