Synthesis of the First Members of a New Class of Biologically Active Bryostatin Analogues

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The bryostatins are a novel family of emerging cancer chemotherapeutic candidates isolated from marine bryozoa on the basis of their significant activity against murine P388 lymphocytic leukemia.1 These macro lactones have been shown to exhibit remarkable and unique activities,2 leading to the recent entry of bryostatin 1 (Figure 1) into Phase II clinical trials for the treatment of melanoma, non-Hodgkins lymphoma, and renal cancer.3 While their molecular mode of action is not known, the bryostatins potently inhibit the binding of the tumor-promoting phorbol esters to protein kinase C (PKC) and stimulate enzymatic activity both in vitro and in vivo.4 However, they induce only a subset of phorbol ester responses and block those actions of phorbol esters which they themselves do not initiate, most notably tumor promotion.5 Efforts to identify the structural basis for these and related activities and to develop more effective clinical candidates have been hampered by the low natural abundance6b of the bryostatins and difficulties associated with their modification. As an alternative approach to these goals, we describe here the first class of simplified, synthetic bryostatin analogues which exhibit a high affinity for PKC and potent growth inhibitory activity related to substituents at C1, C19, and C26 (boxed in Figure 1), whose analogy to diacylglycerol, the endogenous activator of PKC, which they themselves do not initiate, most notably tumor promotion.6 Efforts to identify the structural basis for these and related activities and to develop more effective clinical candidates have been hampered by the low natural abundance6b of the bryostatins and difficulties associated with their modification. As an alternative approach to these goals, we describe here the first class of simplified, synthetic bryostatin analogues which exhibit a high affinity for PKC and potent growth inhibitory activity against several human cancer cell lines.

Computational studies,6 limited structure—activity data,6b,6c7 and analogy to diaclylglycerol, the endogenous activator of PKC, suggest that the binding of bryostatin to PKC could be attributed to substituents at C1, C19, and C26 (boxed in Figure 1), whose orientations are remotely controlled by a lipophilic spacer (shaded in Figure 1). Macrocycles of the general structure 1 were designed to test this hypothesis. These systems retain the putative recognition domain of the bryostatins but incorporate a simplified spacer domain to facilitate their synthesis. This design allows access to 1 through a novel, convergent esterification—macrotransacetalization strategy involving coupling of the recognition domain (2) with variable spacers (3), an approach which has potential for the creation of analogue libraries.

Our first objective in this study was the synthesis of the bryostatin C-ring and its attendant functionality (C15—C27).8 Scheme 1 depicts a first-generation sequence which has readily delivered gram quantities of the target fragment 15. Condensation of the dienolate of 4 with aldehyde 55 followed by acid-catalyzed


(3) Current information on the scope and status of bryostatin clinical trials covering bryostatin synthesis through the end of 1994, including work from the groups of Evans, Hale, Roy, Vandewalle, and Yamamura and Masamune’s Department of Chemistry, Stanford University, V.


dehydration gave pyranones 6a,b (1:1). The β-isomer (6a) was easily separated and reduced under Luche conditions, and the resulting glycal was epoxidized with m-CPBA in the presence of MeOH to afford a C19-methoxylated C20,C21-diol (71% from 6a). Selective benzylation of the C21 equatorial alcohol followed by oxidation of the remaining C20 hydroxyl group with Dess–Martin periodinane (DMP) provided benzoate 7 (90%, two steps). Treatment of 7 with SmI₂ (2 equiv) selectively deoxygenated C21 to give ketone 8 (95%). From 8, a straightforward aldol condensation/elimination sequence with OHCCO₂Me was sufficient to install the desired E-exocyclic unsaturated ester at C21, providing enone 9. Luche reduction of 9 gave exclusively the C20 axial alcohol which was esterified with octanoic acid to afford compound 10 (93%, two steps). Completion of the target fragment, requiring a demanding two carbon homologation at C17, proceeded with removal of the TBS group with HF/pyridine and oxidation of the resulting alcohol with DMP to give aldehyde 12 (86%, two steps). After much experimentation, this hindered aldehyde was found to react with allyl-BEt2 followed by Ac₂O to generate an inconsequential mixture of acetates in high yield (95%, two steps). Dihydroxylation of the terminal olefin with catalytic OsO₄ (NMO co-oxidant) mixture of acetates in high yield (95%, two steps). Dihydroxylation of the terminal olefin with catalytic OsO₄ (NMO co-oxidant) provided benzoate 7 (90%, two steps). Treatment of 7 with SmI₂ (2 equiv) selectively deoxygenated C21 to give ketone 8 (95%). From 8, a straightforward aldol condensation/elimination sequence with OHCCO₂Me was sufficient to install the desired E-exocyclic unsaturated ester at C21, providing enone 9. Luche reduction of 9 gave exclusively the C20 axial alcohol which was esterified with octanoic acid to afford compound 10 (93%, two steps). Exposure of 10 to DDQ selectively liberated the C25 alcohol to give 14 (79%), which, when treated with aqueous HF, gave the target hemiketal 15 in >95% yield.

With an efficient route to the C15–C27 segment of the bryostatins established, attention turned toward installing our first series of C1–C14 inserts. Molecular modeling indicated that B-ring acet/α-ring pyrans of type 24a (Scheme 2) would closely mimic the configuration of bryostatin, allowing for the proper display of putative PKC recognition elements. Accordingly, menthene-derived spacer segments 16 and 17 were prepared independently and coupled by Yamaguchi esterification with alcohol 15 to provide ester adducts 18 (81%) and 19 (81%), respectively. For 19, the C3 TES group was removed with HF/pyridine (81%). At this point, a remarkable macrotransacetalization was initiated by stirring 18 and 20 independently in a dilute (0.004 M) solution of Amberlyst-15 acidic resin with 4-Å molecular sieves in CH₂Cl₂. This pivotal reaction served to close the 20-membered macrocycle via acetal formation. In each case, a single isomer of cyclized product was detected in the crude macrocyclic mixture; a result consistent with a thermodynamically controlled acetalization establishing the equatorial configuration at C15. The cyclized products were independently hydrogenated over Pd(OH)₂ to afford bryostatin analogues 23 (56% from 18) and 24a (88% from 20).

9 Prepared in four steps from commercially available methyl isopropyl ketone (see the Supporting Information).
10 Synthesized in five steps from (R)-(+)-methyl lactate according to minor modifications of a closely related sequence. See ref 8a.
15 Prepared in seven (16) and eleven (17) steps from the 1,3-menthene acetal of 1,3,5-pentanetriol (see the Supporting Information).
16 To our knowledge, there is only a single report of a related transformation: Li, G.; Still, W. C. J. Am. Chem. Soc. 1993, 115, 3804–3805.
17 The all-equatorial configuration of 24a was confirmed by 2D-NOESY 1H-NMR analysis. See ref 6a.