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Improved and large-scale synthesis of 10-methyl-aplog-1, a potential lead for an anticancer drug

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ABSTRACT

10-Methyl-aplog-1 (**1**), a simplified analog of tumor-promoting aplysiatoxin, is a potential lead for cancer therapy that exhibits marked and selective growth inhibitory effects against several human cancer cell lines and negligible tumor-promoting activity in vivo. However, more detailed evaluations of its toxicity and anticancer activity in vivo are hampered by supply problems associated with a non-optimal synthetic method. We here addressed this issue through a more practical and reliable synthetic method that afforded several hundred milligrams of **1** with high purity (>98%) in 23 steps from commercially available *m*-hydroxycinnamic acid with an overall yield of 1.1%. The utilization of two key reactions, substrate-controlled epoxidation and the oxidative cleavage of alkene with a free hydroxyl group, successfully reduced the existing five synthetic steps and markedly improved the handling of large amounts of intermediates. We also demonstrated for the first time that such an analog was synthetically accessible in reliable quantities and also that this large supply could advance in vivo trials for the treatment of cancer.

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1. Introduction

The family of enzymes known as protein kinase C (PKC) has been widely recognized as an attractive target for treating intractable diseases such as cancer,[1] Alzheimer's disease (AD),[2] and acquired immune deficiency syndrome (AIDS)[3] because of its pivotal role in many cellular events including differentiation, proliferation, and apoptosis. Thus, natural PKC activators such as phorbol esters, ingenol esters, teleocidins, and aplysiatoxins may serve as therapeutic leads (Fig. 1). Although 12-*O*-tetradecanoylphorbol 13-acetate (TPA) and ingenol 3-angelate have already been evaluated in clinical trials for several cancers,[4,5] their therapeutic use has been impeded by low natural abundance, structural complexity, difficulties associated with their synthesis and modification, as well as their undesired side effects such as tumor-promoting and severe inflammatory activities.

Bryostatin 1 (bryo-1), a lead member of this family, is a fascinating and mysterious PKC activator without tumor-promoting activity in vivo. Bryo-1 has been investigated for anticancer activity in at least 43 phase I and phase II clinical trials,[6,7] where it demonstrated an ability to enhance the effects of some anticancer drugs at remarkably low doses (~50 μg/m^2, or ~1–1.5 mg per 8-week treatment cycle). Moreover, bryo-1 improved learning and memory in animal models,[8] and its therapeutic potential for Alzheimer's disease and other neurodegenerative disorders attracted much attention. Despite the promising biological properties of bryo-1, further studies on its unique mode of action and the clinical development have been hampered by its limited availability. Recently, function oriented synthesis of the simplified analogs of bryo-1 have been carried out to address these problems.[9,10]

As an alternative approach, we developed 10-methyl-aplog-1 (**1**, Scheme 1), a simplified analog of aplysiatoxin that exhibits significant anti-proliferative activity against several human cancer cell lines and negligible tumor-promoting activity in mouse skin.[11] Extensive growth inhibitory assays against 39 human cancer cell lines revealed that its anti-proliferative activity was cell line selective and also that its efficacy profile (fingerprint) was completely different from that of any type of anticancer agent available today, thereby supporting its unique mode of action and a new aspect of anticancer drug development (Fig. 2).

The analog **1** lacked the chiral methyl groups at positions 4, 12, and 30, the methoxy group at position 15 as well as the bromine atom at position 21 to decrease hydrophobicity, and replaced the labile hemiacetal hydroxyl group at position 3 with a hydrogen atom to increase chemical stability. This structural simplification successfully eliminated over 20 synthetic steps and reduced

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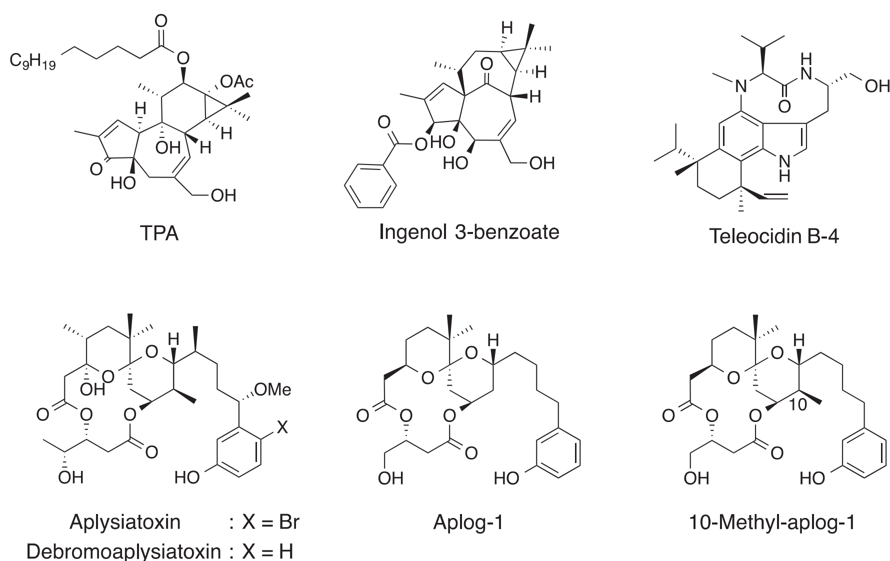
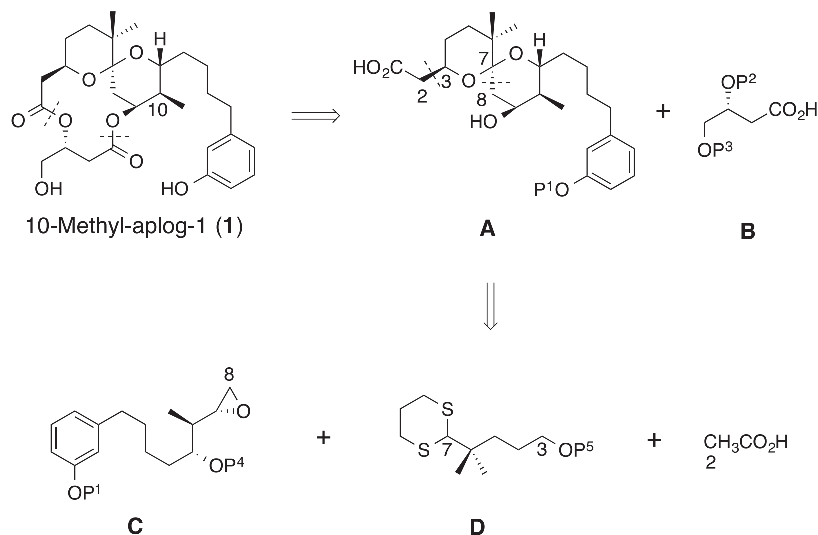


Fig. 1. Structures of naturally occurring tumor promoters and simplified analogs of aplysiatoxin.



Scheme 1. Retrosynthetic analysis of **1**.

barriers against its practical synthesis without attenuating its marked anti-proliferative activities and ability to activate PKCs.[12] Despite these prospective features as a future therapeutic candidate, the inefficiency of our first-generation synthesis of **1** prevented further experiments on animals and structural optimization for clinical use. To satisfy these needs, we attempted to develop a more practical synthetic method for **1** for the preparation of sufficient amounts of the sample in order to examine its toxicity and anticancer effects in an animal model.

2. Results and discussion

From a synthetic perspective, we maintained the triply convergent route applied in our first-generation synthesis, dissecting **1** at two ester linkages to generate subunits A and B. The further division of fragment A provided two subunits, C and D (Scheme 1). Our previous attempt to construct an anti, anti-stereotriad in subunit C using Smith's iodocarbonate cyclization strategy[13] required three steps from a homoallyl alcohol (**5**) (Scheme 2) and also gave unsatisfactory results with poor stereoselectivity and a low yield. Moreover, subsequent methanolysis of the carbonate moiety required careful control of the reaction temperature in order to prevent opening of the epoxide ring.[11] This inefficient and complicated process severely disturbed the large-scale preparation of **1**; thus, its improvement was inevitable. We decided to utilize the one-step hydroxyl-directed epoxidation of **5**. Such an approach could facilitate the handling of large-scale intermediates.

The synthesis of **1** started with the hydrogenation of *m*-hydroxycinnamic acid (**2**), followed by esterification, protection of the phenol group as a benzyl ether, reduction, and bromination to provide a known bromide (**3**) in 91% yield from **2** (Scheme 2). In practice, the first four intermediates of this sequence could be carried forward without purification, and the bromide was purified by column chromatography before the next step. This procedure could be performed routinely on a 20-g scale. The substitution of the known bromide with diethyl malonate gave a diester, which was decarbalkoxylated without purification to produce an ester (**4**) in 62% yield. Partial reduction of **4** to an aldehyde was accomplished on a 5-g scale, and the aldehyde was immediately used for asymmetric Brown crotylation[14] to furnish a homoallyl alcohol (**5**) in 56–84%

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