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Research paper

One-pot three steps cascade synthesis of novel isoandrographolide analogues and their cytotoxic activity

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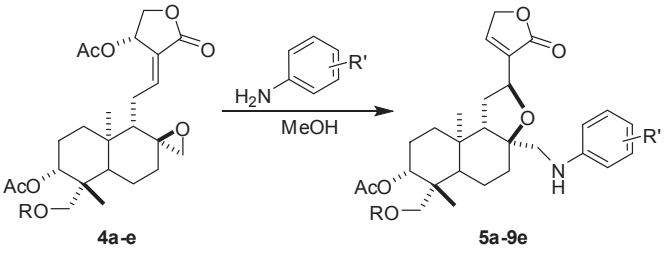
ABSTRACT

An efficient one-pot synthesis of novel andrographolide analogues is reported from a naturally occurring and abundant andrographolide isolated from aerial parts of *Andrographis paniculata*. Reactions in the one-pot proceed through a cascade epoxide ring opening by aniline derivatives/intramolecular ring closing and oxa-conjugate addition-elimination reactions. This methodology produces a new series of 17-amino-8-*epi*-isoandrographolide analogues in fair to excellent yields with high stereoselectivity using an economic and environmental procedure without base or catalyst at room temperature. Twenty-five analogues were obtained and cytotoxicity of all new analogues were evaluated against six cancer cell lines to search for a new lead compound based on andrographolide structure.



1. Introduction

Natural products from medicinal herbs have long been the important sources of therapeutic agents in drug discovery process. With diversity in their structures, the lead compound with promising intrinsic therapeutic property has been employed as the template for chemical transformation which is one of the common approaches to improve their therapeutic properties for discovery of new drug in the pharmaceutical industry. Recently, more attention has been focused on improving the biological activity by chemical modification of the labdane diterpenoid andrographolide, a natural product occurring in the aerial parts of *Andrographis paniculata* Nees [1–5]. Andrographolide is of interest because of its potential as a bioactive pharmacophore, capable of energizing a wide range of biological activities including antibacterial, antihepatotoxic, anti-HIV, anticancer, hypoglycemic and hypotensive activities [6–11]. Isolation and purification of andrographolide from *A. paniculata* may be accomplished by simple chromatographic techniques with 2% over all yields [12,13].

Modification of natural andrographolide into a library of new complex analogues with the appropriate structural diversity to improve their bioactivity continues to represent a challenge in drug discovery and drug development. Recently, new andrographolide analogues have been designed, synthesized and evaluated for their biological activity [14–17]. Structural scaffold modification of natural andrographolide has led to improved and diverse biological activities, especially with regard to cytotoxic as well as anticancer activity [18–21].

The present study designed and synthesized andrographolide-based derivatives from the perspective of their effectiveness as cytotoxic agents, specifically as anti-cancer agents. In an earlier

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study we discovered some semi-synthetic compounds derived from the andrographolide framework demonstrated higher bioactivity than the original natural product [22–24]. Andrographolide modification at C-19 of andrographolide has indicated actively and the cytotoxic potential towards cancer [25]. However, the modification of the core structure of *ent*-labdane diterpenoid has been rarely reported. Therefore, a series of *epi*-isoandrographolide were designed and synthesized by one-pot procedure as novel structural type for searching new potential cytotoxic agents. This one pot method is a suitable procedure for further drug development and an effective approach for scale-up, minimize purification steps and reduce chemical waste are utilized.

In the present study, we explored the modification of andrographolide *via* tandem three steps epoxide ring opening by aniline derivatives followed by intramolecular ring closing and oxa-conjugate addition-elimination reactions leading to a series of 17-amino-8-*epi*-isoandrographolide analogues.

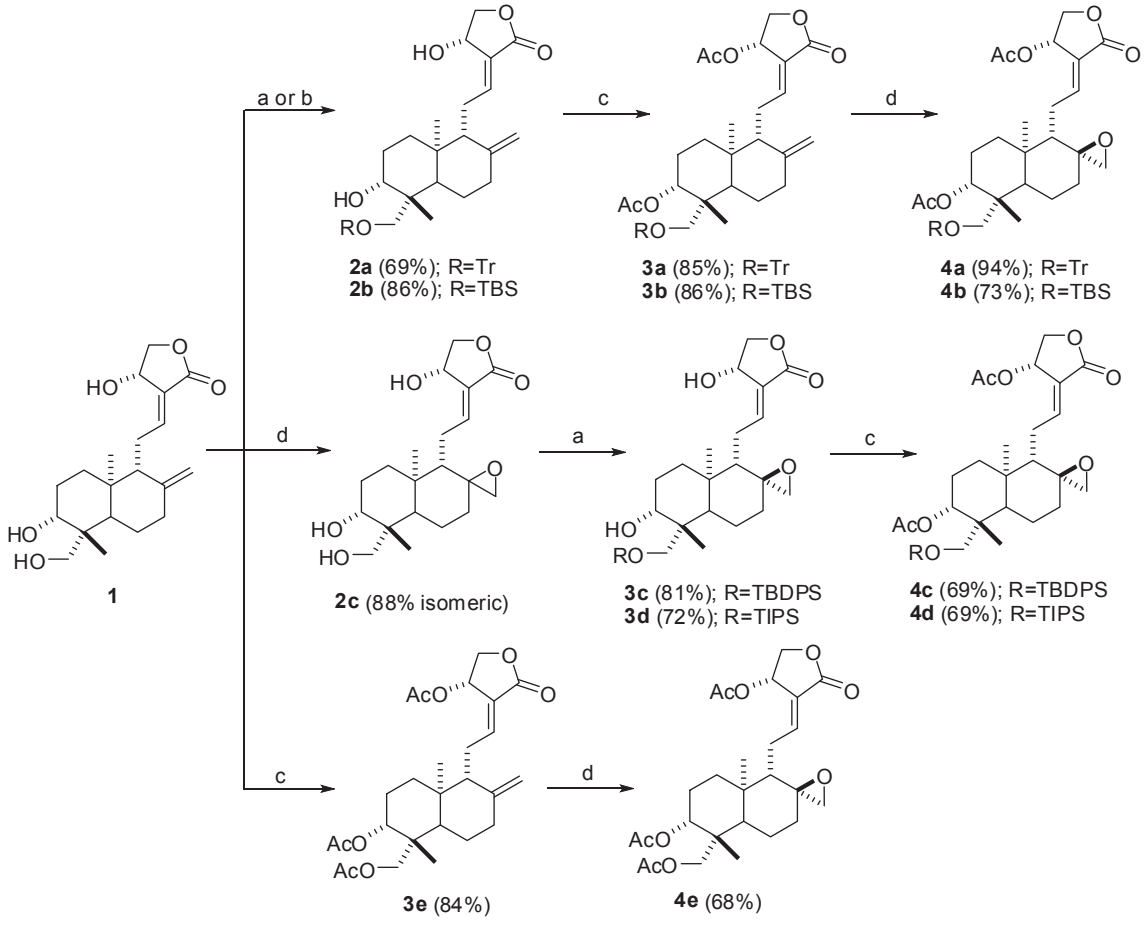
2. Results and discussion

2.1. Chemistry

C-8-epoxy-andrographolide analogues **4a-4e** were synthesized from natural available andrographolide as starting material for the one-pot synthesis of *epi*-isoandrographolide analogues (Scheme 1). First, introducing of trityl and TBS groups at C-19 were carried out in the presence of triphenylmethylchloride, *tert*-butyldimethylsilyl-chloride and pyridine followed by acetylation at 70 °C and epoxidation with MCPBA to afford the desired compounds **4a** and **4b** in high yields. Preparation of C-19 Silyl-precursors **4c** and **4d**, commenced with epoxidation followed by silylation with TBDPSCl and TIPSCl in the presence of pyridine and acetylation to produce the designed products in good yields. C-19 Silyl-precursors **4c** and **4d** can be prepared as per reaction sequence **4a** and **4b**. However, we found that in the preparation of C-19 TBDPS and TIPS-analogues, epoxidation before silyl protection gave higher yield of designed compounds than initial C-19 protection.

A series of 17-amino-8-*epi*-isoandrographolide analogues were synthesized *via* tandem three steps *N*-alkylation-epoxide ring opening reaction followed by intramolecular ring closing and oxa-conjugate addition-elimination reactions. The reaction was first conducted with C-19-trityl epoxyandrographolide analogue **4a** and aniline in methanol without any base or catalyst to give the cyclized product **5a** in fair yield. In a previous study we found the introduction of halogenated and dimethoxy-aniline to the andrographolide framework led to the enhancing of cytotoxic activity.[6a] Therefore, anilines bearing halogenated groups (*ortho*-, *meta*-fluoro and *para*-bromo) and 3,4-dimethoxy groups were investigated under the present condition to give the corresponding cyclized product 17-amino-8-*epi*-isoandrographolide **6a-9a** in moderate to good yields as shown in Table 1.

When 2-fluoro-, 3-fluro- and 4-bromo-aniline were employed as nucleophiles, the reactions were performed more than one days to complete the reactions due to the decreased nucleophilicity of aniline bearing electron withdrawing. Reactions of 3,4-dimethoxyaniline gave the corresponding products **9a**-**9e** in short



Scheme 1. Reagents and Conditions; a) R_3SiCl, pyridine, rt, b) TrCl, pyridine, reflux, for **2a**; c) Ac_2O, 145 °C; d) *m*-CPBA,CH_2Cl_2/MeOH.