



Full paper/Mémoire

Structural diversity-guided convenient construction of functionalized polysubstituted butenolides and lactam derivatives

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ABSTRACT

A molecular diversity-oriented convenient access to multi-substituted butenolides and lactam scaffolds via four different methods from various phenylacetic acid derivatives is described. The target molecules have been identified on the basis of analytical spectra data, and are useful synthons in the fields of medicine and agrochemicals.

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1. Introduction

Many heterocyclic compounds bearing butenolides and lactam scaffolds are of synthetic interest, since they display extensive biological activities [1,2], and constitute an important class of natural (Fig. 1) [3–6] or unnatural products [7–10]. Moreover, they are extremely versatile building blocks for the manufacture of bioactive compounds in pharmaceutical drug design and the agrochemical industry. Nowadays, more and more natural products containing butenolides and lactam ring systems have been isolated from a variety of marine and terrestrial organisms, such as bacteria, moulds, algae, fungi, lichens, and sponges [11,12]. On the other hand, many butenolides and lactam derivatives featuring 3-acyl substituents are novel ligands for their strong ability to chelate biologically important metal cations and to mimic phosphate groups in the

binding site of phosphatases and kinases [13–15]. Very recently, some butenolides and lactam derivatives are also widely applied as versatile building blocks for the construction of novel heterocycles and fused heterocycle system [16–19].

Thus, development of novel functionalized multi-substituted butenolides and lactam heterocyclic derivatives as pharmaceuticals is still an important area of interest in life sciences, and the search for an efficient method for the construction of these heterocyclic derivatives under mild conditions is not only highly desirable but also necessary. The promising bioactive and structural diversity of these classes of heteroaryl compounds urged us to conveniently construct a series of novel structural variants of multi-substituted butenolides and lactam derivatives and their related intermediates. In this short communication, we would like to present a molecular diversity-oriented convenient procedure for large-scale access to construct bioactive butenolides or lactam units (Fig. 2) that exploit mild ring-closure methods and cheap raw materials, which will have widely applied prospects because of its easy to obtain raw material and its convenient operation.

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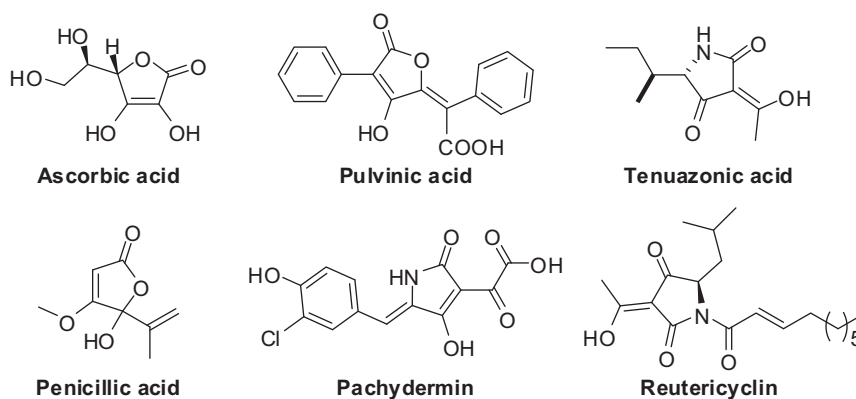


Fig. 1. Representative structures of naturally occurring butenolides and lactam derivatives.

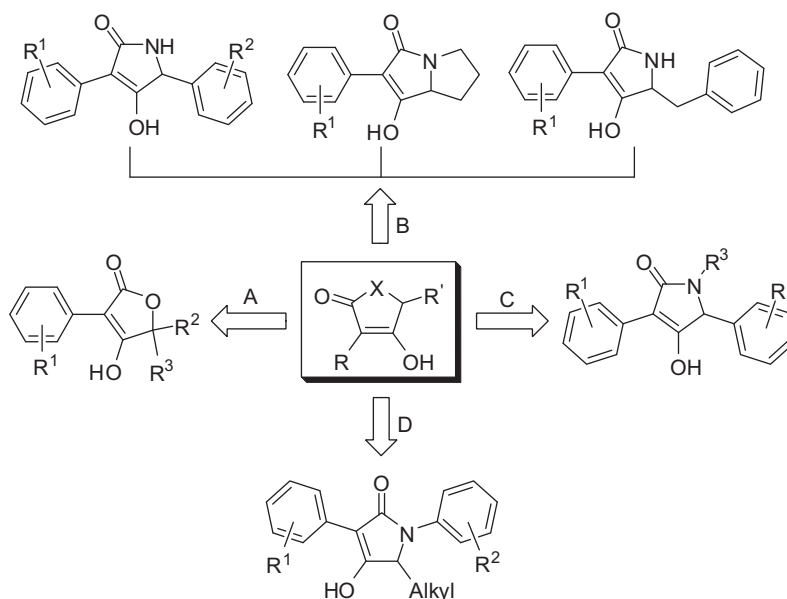


Fig. 2. Design strategy for polysubstituted butenolides and lactams.

2. Results and discussion

2.1. Synthesis of multi-substituted butenolides derivatives

Considering the convenient synthesis to construct the structural diversity of multi-substituted butenolides and lactam scaffolds, various amino-acids, α -hydroxy acids and suitable phenylacetic acids were selected as raw materials. Polysubstituted butenolides derivatives **5** were

prepared in a simplified and more efficient method, which is outlined in [Scheme 1](#).

For the sake of structural diversity, various easily available α -hydroxy acids such as lactic acid, 1-hydroxycyclohexanecarboxylic acid, mandelic acid and their analogues can be selected as raw materials. As shown in [Scheme 1](#), the target butenolides derivatives **5** were conveniently obtained via two steps including esterification, one-pot heterocyclization reactions. The cyclization

Table 1

Synthesis of multi-substituted butenolides derivatives **5**.

Entry	Compd.	Substituents			Appearance	Yield (%) ^a
		R ¹	R ²	R ³		
1	5a	4-MeO	-(CH ₂) ₅ -		White powder	75
2	5b	4-F	H	Ph	Light yellow powder	75
3	5c	2,4-Cl ₂	H	Ph	Light yellow powder	78
4	5d	4-MeO	H	Ph	White powder	71

^a Yields refer to isolated products.

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