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ORIGINAL ARTICLE

Practical synthesis of methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptanoate

Xinpeng Jiang [a], Xueyan Wang [b], Xing Huang [b], Guizhou Li [b], Chuanming Yu [a,b,*]

[a] *College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, PR China*
[b] *Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, PR China*

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KEYWORDS

Misoprostol;
Dehydrate cyclization;
Friedel-Crafts acylation;
Piancatelli rearrangement

Abstract The key intermediate of misoprostol, methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptanoate was prepared from commercially available suberic acid in 40% yield over five steps. The key step involved a $ZnCl_2$ catalyzed Friedel-Crafts reaction between furan and 2,9-oxonanedione. Sulfuric acid catalyzed methylation of 8-(furan-2-yl)-8-oxooctanoic acid followed by sequential reduction and $ZnCl_2$ catalyzed Piancatelli rearrangement resulted in the formation of the key intermediate of misoprostol.

1. Introduction

Misoprostol, a 15-deoxy-16-hydroxy-16-methyl prostaglandin E_1 (PGE_1) methyl ester, is developed for the treatment of peptic ulcer disease [1,2] and for labor induction with Mifepristone [3,4]. As a synthetic analog of prostaglandin E_1, misoprostol can avoid the major side effects caused by PGE_1, including fetal bradycardia, pregnant women's emesis, somnolence, and headache. Therefore the synthesis of misoprostol has attracted lot of attention in recent years (Fig. 1).

The two-component coupling strategy is one of the most efficient routes to assemble misoprostol [5–7]. The essential feature of this approach (Fig. 1) is the conjugate addition of 1-indo-4-methyloct-1-en-4-ol **3** [8] to methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptanoate **2**. To date, a series of researches have been devoted to preparing the key intermediate **2**. In 1976, Kobayash and co-workers [9] found **2** could be prepared mainly by reduction of lactone following selective epoxidation of the olefin in the ring of cyclopentenol giving epoxyalcohol with a double bond in the side chain of the molecule (Scheme 1-a). In 1977, a route developed by Collins et al. [10] revealed an eight-step synthesis of **2** from monomethyl azelate in 12% overall yield (Scheme 1-b). The same year, Kieczykowski et al. [11] employed lithium tert-butyl acetate, 1,5-dibromopentane and lithium imine salts synthesized ketone ester, after sequential three-step transforming intermediate **2** could be obtained in 30% yield (Scheme 1-c). Alternatively, Naora and co-workers [12] used cyclooctanone to do the transformation (Scheme 1-d). In 1994, Holland et al. [13] synthesized of **2** using 2-ethyl-cyclopentanone and methyl-7-

* Corresponding author at: College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, PR China. Fax: +86 571 88320867.
E-mail address: ycm@zjut.edu.cn (C. Yu).
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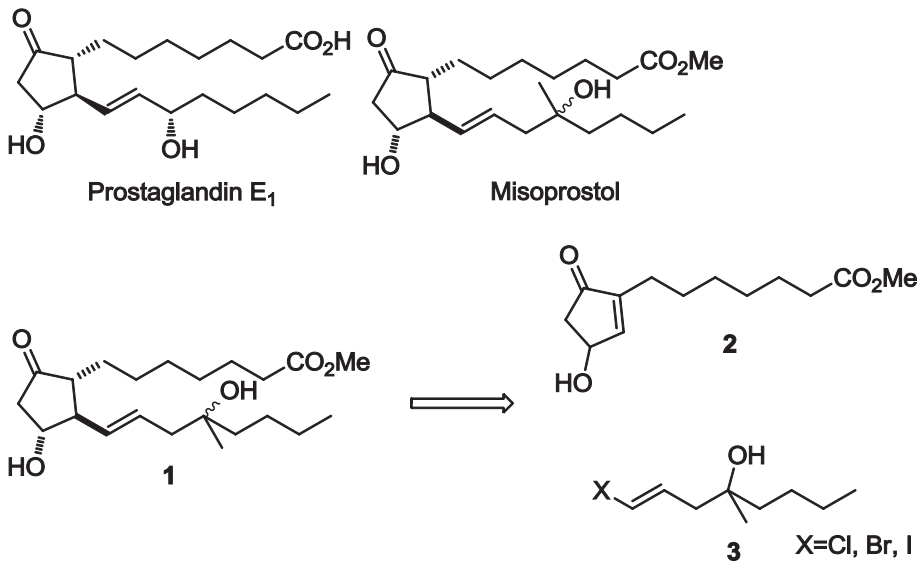
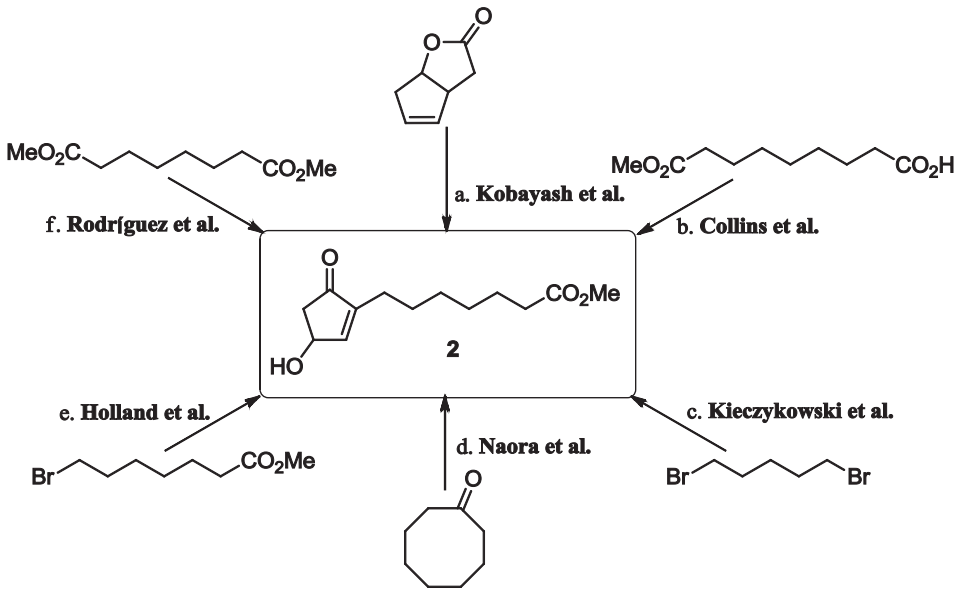


Figure 1 Prostaglandin E_1, misoprostol and two-component coupling retrosynthetic analysis for misoprostol.



Scheme 1 Different protocols for the synthesis of methyl 7-(3-hydroxy-5-oxo-1- cyclopenten-1-yl)-heptanoate **2**.

bromoheptanoate as starting materials in six steps with an overall yield of 23% (Scheme 1-e). Later, Rodríguez et al. [14] reported enzymatic cleavage of dimethyl suberate with porcine pancreatic lipase (PPL) gave a half ester, which was then converted into a mixed anhydride. After reaction with furan, it was reduced with $NaBH_4$ and isomerization to afford **2** (Scheme 1-f). Nevertheless, the majority of these current composite methods bear some disadvantages, including low yields, uneconomic and environmental unfriendly reaction conditions. Herein, we present a practical and efficient synthesis of methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptano ate from readily available suberic acid, which is not only more environmental friendly, but also can shorten synthesis steps and enhance overall yields.

The synthetic roadmap toward methyl 7-(3-hydroxy-5-oxo cyclopent-1-en-1-yl)-heptanoate **2** was designed on the basis of retrosynthetic analysis shown in Fig. 2. According to Rodríguez's synthesis, **2** could be prepared through a $ZnCl_2$ catalyzed Piancatelli isomerization of methyl 8-(furan-2-yl)-8-hydroxyoctanoate **8** [15], which could be obtained by reduction with $NaBH_4$ from methyl 8-(furan-2-yl)-8-oxooctanoate **7**. Disconnection of the C—C bond linking furan with carbon chain revealed 2,9-oxonanedione **5** as potential intermediates in the synthetic direction. 2,9-oxonanedione itself could be easily prepared from dehydrate cyclization of suberic acid **4**.

2. Experimental

All reagents were purchased from commercial sources and used without purification.