



Synthesis of 1,3-dihydroxy-5-(tridec-4',7'-dienyl)benzene, a new compound with important cytotoxic properties isolated from *Lithraea molleoides*

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Introduction

Dichloromethane extract from *Lithraea molleoides* (Anacardiaceae) leaves, an Argentine medicinal plant (Toursarkissian, 1980; Muñoz, 1990), which has been collected in the Province of Entre Ríos, Argentina, showed important biological activities (Chaturvedula *et al.*, 2002), e.g., antiviral (Kott *et al.*, 1998), antimicrobial (Penna *et al.*, 2001), and cytotoxicity (Ruffa *et al.*, 2002) on human carcinoma cells. Different bioassays carried out on this extract led to the isolation of a new active 5-alkylsubstituted resorcinol, 1,3-dihydroxy-5-(tridec-4',7'-dienyl)-benzene. The chemical structure of the compound was established on the basis of spectroscopic data (UV, IR, ^1H - and ^{13}C -NMR, COSY) (López *et al.*, 2005).

This compound showed cytotoxic activity on three human tumor cell lines, such as hepatic carcinoma-Hep G2 cell line, mucoepidermoid lung carcinoma-H292 cell line, and mammary

gland adenocarcinoma-MCF7 (Kozubek *et al.*, 2001).

However, the isolation of this natural compound was very tedious, and yields were very poor. These facts together with the promising antitumor activity and the need for new bioassays led us to propose possible routes of synthesis for obtaining this natural compound as well as that of stereoisomers.

Methodology

Several syntheses have been used to obtain this type of resorcinols, and have been reviewed (Baylis *et al.*, 1981; Sargent and Wangchareontrakul, 1989; Kozubek and Tyman, 1999). Based on reported syntheses we proposed those for obtaining the stereoisomers.

The first aim is the synthesis of alcohol **1**, which by a linear synthesis or a convergent synthesis will lead to the searched product **4** (Fig. 1).

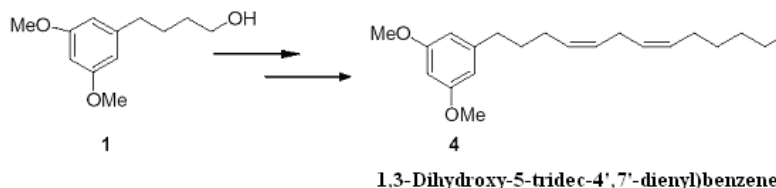


Figure 1

**Results**

The synthesis of alcohol **1** was outlined from a commercial product, 3,5-dimethoxybenzaldehyde, *via* two routes (Fig. 2).

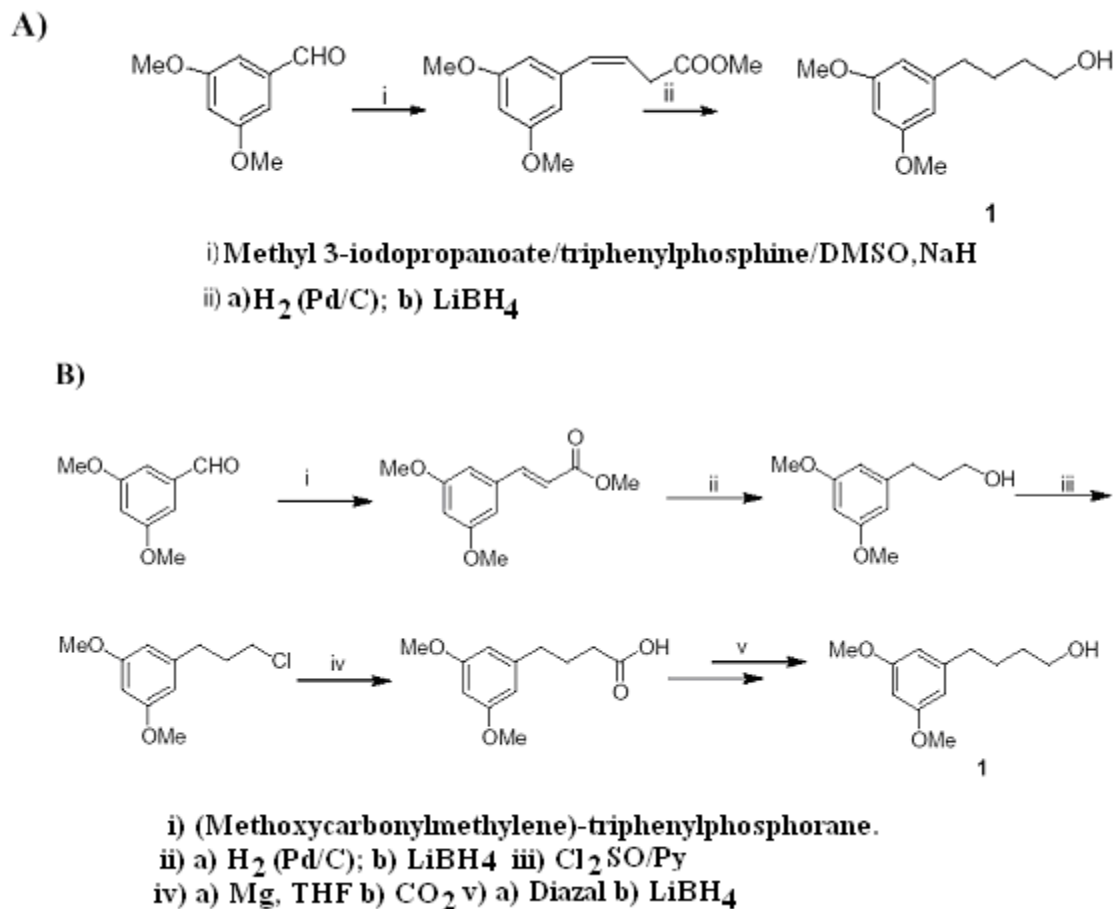


Figure 2

Route B showed a series of problems, thereby being discarded. On the other hand, alkene **3** was synthesized by the following sequence of reactions (Fig. 3).

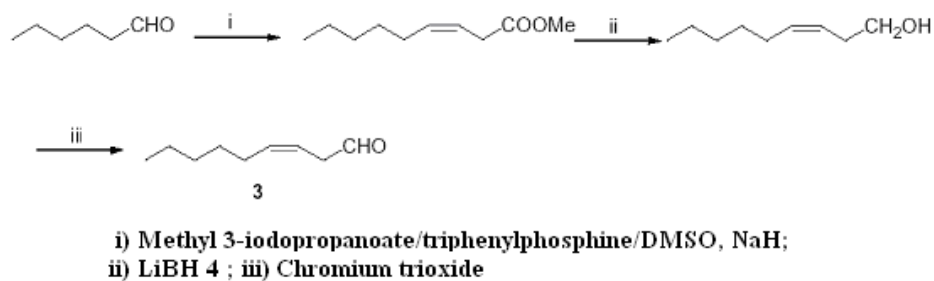
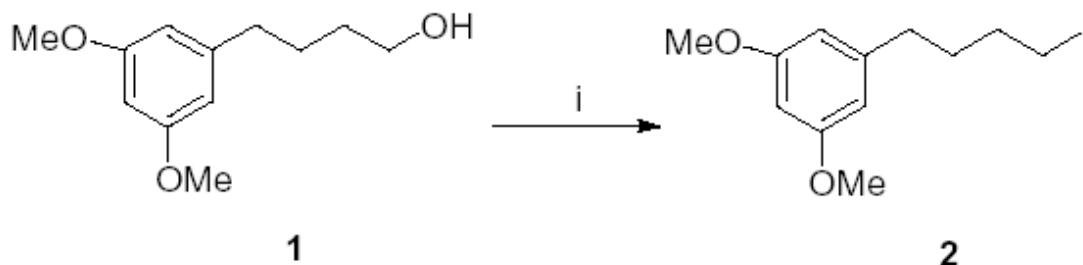


Figure 3



The subsequent substitution of the alcohol function of compound **1** with iodine would lead to **2** (Fig. 4).



i) P/I_2

Figure 4

Considering a *convergent synthesis*, Wittig reaction between compounds **2** and **3** would give rise finally to one of the target compounds, the *cis*-stereoisomer (all bonds are *cis*) (Fig. 5).

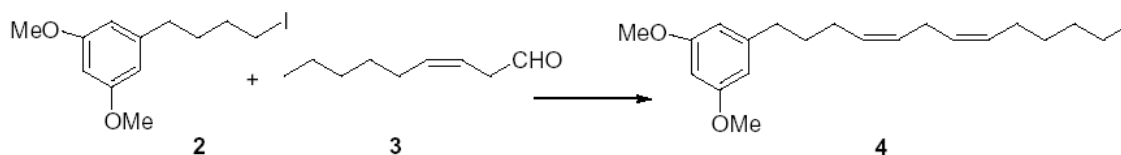
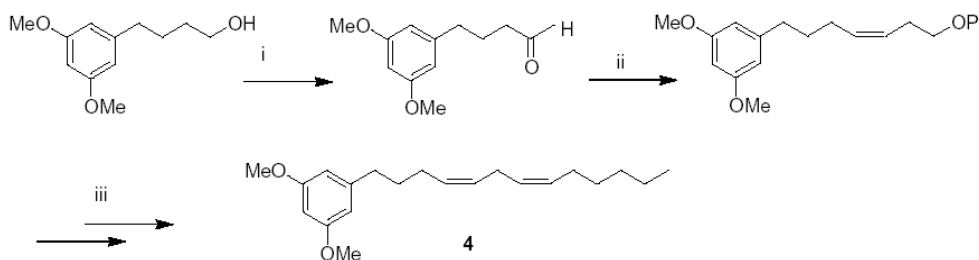


Figure 5

Another alternative route to obtain **4** by a linear synthesis from **1** would be that shown in Fig. 6.



i) CR_3O/Py ii) a) WITTIG b) $Ph_3P/ClCH_2CH_2CH_2OP$ iii) $Bu_4N^+F^-$, THF, 25°C b) P/I_2 c) $Ph_3P/ DMSO, NaH/ Hexanal$

Figure 6

The structures of the intermediates were determined by proton magnetic resonance spectroscopy, and analysis of coupling constants.



Conclusions

Route B for obtaining alcohol **1** displayed several difficulties. On one hand, a low yield (21%) for obtaining the corresponding chloride and, on the other hand, the lack of reactivity of the latter in Grignard reaction. Consequently, the convergent synthesis was addressed.

Note: This study was presented at the "XXVI Congreso Argentino de Química", San Luis, Argentina, 2006

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