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The Synthesis of α-DDB, β-DDB and Theoretical Study with AM1

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Abstract: The present paper reports the synthesis of two analogs of *Schzandrin* C α-DDB, β-DDB with the gallic acid as the starting material. The key step is the synthesis of monomer of β-DDB and α-DDB for coupling. α-DDB, β-DDB have different yields in Ullmann coupling reaction under the same condition. The yield of α-DDB is little lower than that of β-DDB. The AM1 calculation demonstrates that ΔH of the Ullmann coupling reaction of α-DDB and β–DDB are different. The former is −175.76966KJ/mol and the later is -203.21246KJ/mol. This is in agreement with the fact that β-DDB has higher yield than α-DDB.

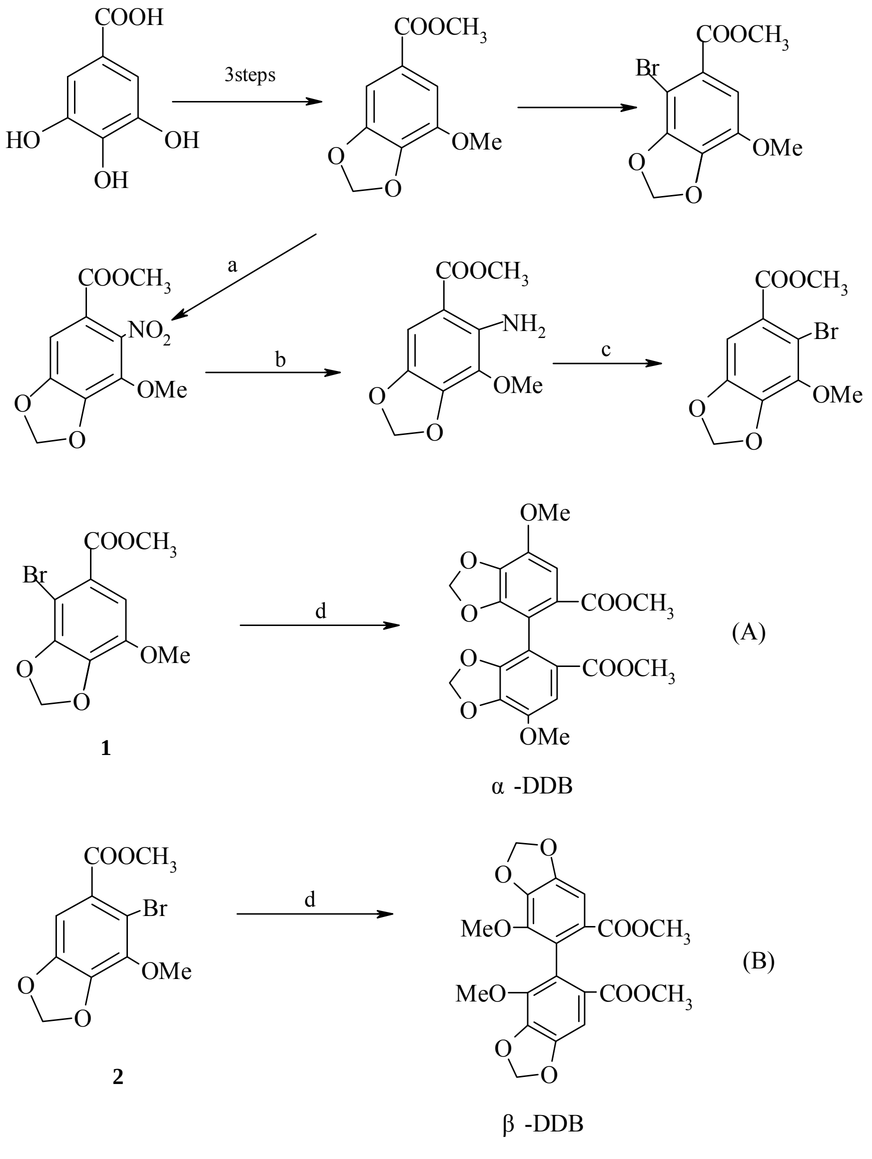
Keywords: Analogs of *Schzandrin* C, biphenyl, dimenthoxy dicarboxylate biphenyl, AM1 calculation

Biphenyl units are present in a wide range of compounds both natural and synthetic, and many of them have pharmacological activity[1]. Xie Jingxi *et al.* found that dimethyl 4,4'-dimethoxy-5,6,5',6'-dimethylenedioxybiphenyl-2,2'-dicarboxylate(α-DDB) as an important intermediate for the synthesis of *Schizandrin* C analogue which is effective in lowering elevated SGPT level[2-3]. Two isomers dimethyl 6,6'-dimethoxy-4,5,4',5'-dimethylenedioxybiphenyl-2,2'-dicarboxylate (β-DDB) and 6,4,-dimethoxy-4,5,5',6'-dimethylenedioxybiphenyl-2,2'-dicarboxylate (γ-DDB) were synthesized by using corresponding monomers for Ullmann coupling reaction. These monomers were separated from the mother liquid of Ullmann reaction. We report in this paper the synthesis of β-DDB through eight steps. The synthesis of γ-DDB has been accomplished[5]. The key step to synthesize the β-DDB is to synthesize the methyl 6-bromo-3,4-methylenedioxy-5-methoxybenzoate (compound **2**) (**Scheme 1**).

The only difference between α-DDB and β-DDB is the substituted positions on biphenyl ring. β-DDB has the same substituted positions as the natural product Schizadrin C. The steric hindrance of β-DDB is higher than that of α-DDB. But our experiment result showed that the yield of β-DDB is higher than α-DDB. This result is contrast to their steric hindrance.

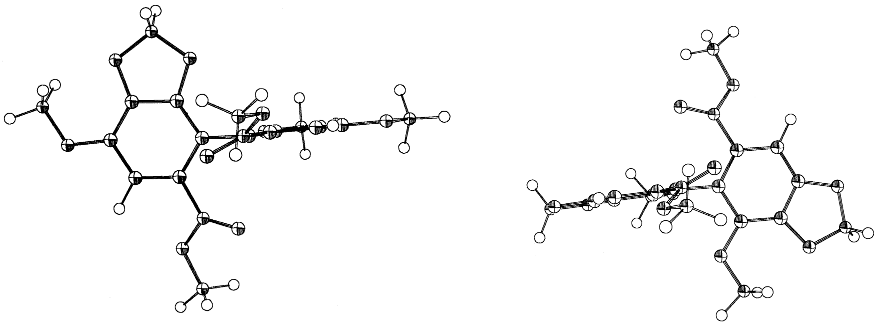
In order to seek some explanations for this phenomenon, we have employed the AM1 semi-empirical method as implemented in 1996 PCMODEL V6-serena to calculate ΔH of β-DDB and α-DDB. The results confirmed the steric structures of α-DDB, β-DDB and their monomers **1** and **2**. The diploe moments and the heat formation of these two monomers and their Ullmann reaction products were obtained. The results show that the phenyl ring and methylenedioxy ring were in co-planar. For α-DDB, β-DDB, the angle of two benzene rings bonded in vertical each other. The compounds are in the thermodynamical state and it is the most stable state (**Figure 1** and **Figure 2**).

Scheme 1 The synthesis route of α-DDB, β-DDB



a, HNO_3; b, Sn/HCl; c, $NaNO_2$/HBr, CuBr/HBr; d, Cu/DMF, refluxing

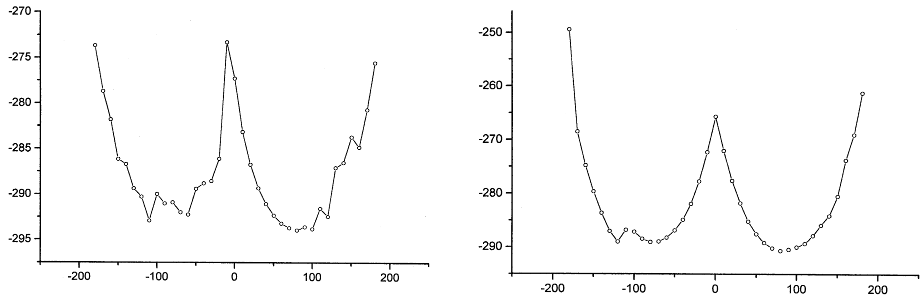
Figure 1 The steric structure of α-DDB(**A**) and β-DDB(**B**)



α-DDB β-DDB

Figure 2 The correlation of the H_f of α -DDB and β -DDB with their rotate angle

α-DDB β-DDB



For this reason the steric hindrance of the monomers may have little influence upon the Ullmann coupling reaction. The ΔH_f of Δ-DDB, monomer **1**, β-DDB and monomer **2** are -595.83637 KJ/mol, -1229.0844 KJ/mol, -575.47047 KJ/mol and -1215.7954 KJ/mol respectively. For the ΔH_f of $CuBr_2$ was –138.358 KJ/mol[6], so the ΔH of the Ullmann coupling reaction of α-DDB is –175.76966 KJ/mol , β-DDB is –203.21246 KJ/mol.

This result might be give us some explanation of above mentioned phenomenon.

Experimental

The Synthesis of β-DDB:

The synthesis of β-DDB is accomplished with methyl 6-bromo-3,4-methy-lenedioxy-5-methoxybenzate **2** under the same condition as that for preparation of α-DDB[4,5] in yield 87%. mp 207~208°C.

Acknowledgment

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